(12) STANDARD PATENT (11) Application No. **AU 2022204581 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Binding proteins recognizing HA-2 antigen and uses thereof

(51) International Patent Classification(s)
C07K 16/28 (2006.01)

(21) Application No: **2022204581** (22) Date of Filing: **2022.04.14**

(87) WIPO No: **WO22/221478**

(30) Priority Data

(31) Number	(32) Date	(33) Country
63/174,818	**2021.04.14**	**US**
63/215,760	**2021.06.28**	**US**
63/288,078	**2021.12.10**	**US**
63/329,560	**2022.04.11**	**US**

(43) Publication Date: **2022.11.03**
(43) Publication Journal Date: **2022.11.03**
(44) Accepted Journal Date: **2023.04.13**

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(56) Related Art
van Buuren et al "HLA Micropolymorphisms Strongly Affect Peptide–MHC Multimer–Based Monitoring of Antigen-Specific CD8+ T Cell Responses"; The Journal of Immunology (2014) Vol: 192, pp 641-648
Nakatsugawa et al "Specific Roles of Each TCR Hemichain in Generating Functional Chain-Centric TCR"; The Journal of Immunology (2015), Vol 194, pp 3487-3500
Heemskerk et al "Reprogramming of Virus-specific T Cells into Leukemia-reactive T Cells Using T Cell Receptor Gene Transfer"; J. Exp. Med (2004), Vol: 199; No: 7; pp 885-894

Abstract

Provided herein are binding proteins recognizing HA-2 antigen and uses thereof.

BINDING PROTEINS RECOGNIZING HA-2 ANTIGEN AND USES THEREOF

Cross-Reference to Related Applications

This application claims the benefit of U.S. Provisional Application No. 63/174,818, filed on 14 April 2021, U.S. Provisional Application No. 63/215,760, filed on 28 June 2021, U.S. Provisional Application No. 63/288,078, filed on 10 December 2021, and U.S. Provisional Application No. 63/329,560, filed on 11 April 2022; the entire contents of each of said applications are incorporated herein in their entirety by this reference.

Background of the Invention

Approximately 50% of AML patients relapse following allogeneic hematopoietic stem cell transplant therapy, leaving them with very few treatment options (Rautenberg *et al.* (2019) *Int. J. Mol. Sci.* 20:228). Rare patients who naturally develop a minor antigen-specific graft-versus-leukemia T cell response show substantially lower relapse rates (Marijt *et al.* (2003) *Proc. Natl. Acad. Sci. U.S.A.* 100:2742-2747; Spierings *et al.* (2013) *Biol. Blood Marrow Transplant.* 19:1244-1253). HA-2 (YIGEVLVSV, genotype RS_61739531 C/C or T/C) is an HLA-A*02:01- and hematopoietically-restricted minor histocompatibility antigen (derived from the class I myosin protein, MYO1G; Pierce *et al.* (2001) *J. Immunol.* 167:3223-3230), making it an ideal candidate for TCR immunotherapy of liquid tumors. Patients receiving donor lymphocyte infusion from HA-2 mismatched donors who develop HA-2-specific T cells show a graft vs leukemia response and experience long-term remission (Marijt *et al.* (2003) *Proc. Natl. Acad. Sci. U.S.A.* 100:2742-2747). There is a need for developing HA-2-specific TCR immunotherapy, such as to treat disorders characterized by expression of an HA-2 antigen.

Summary of the Invention

The present invention is based, at least in part, on the discovery of binding proteins, including T cell receptors (TCRs), that recognize an HA-2 antigen (*e.g.*, YIGEVLVSV and/or YIGEVLVSM).

In one aspect, a binding protein comprising: a) a T cell receptor (TCR) alpha chain CDR sequence with at least about 80% identity to a TCR alpha chain CDR sequence selected from the group consisting of TCR alpha chain CDR sequences listed in Table 1; and/or b) a TCR beta chain CDR sequence with at least about 80% identity to a TCR beta chain CDR sequence selected from the group consisting of TCR beta chain CDR sequences

listed in Table 1, wherein the binding protein is capable of binding to an HA-2 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about $5x10^{-4}$ M, is provided.

In another aspect, a binding protein comprising: a) a TCR alpha chain variable (V_α) domain sequence with at least about 80% identity to a TCR V_α domain sequence selected from the group consisting of TCR V_α domain sequences listed in Table 1; and/or b) a TCR beta chain variable (V_β) domain sequence with at least about 80% identity to a TCR V_β domain sequence selected from the group consisting of TCR V_β domain sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-2 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about $5x10^{-4}$ M, is provided.

In still another aspect, a binding protein comprising: a) a TCR alpha chain sequence with at least about 80% identity to a TCR alpha chain sequence selected from the group consisting of TCR alpha chain sequences listed in Table 1; and/or b) a TCR beta chain sequence with at least about 80% identity to a TCR beta chain sequence selected from the group consisting of TCR beta chain sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-2 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about $5x10^{-4}$ M, is provided.

In yet another aspect, a binding protein comprising: a) a TCR alpha chain CDR sequence selected from the group consisting of TCR alpha chain CDR sequences listed in Table 1; and/or b) a TCR beta chain CDR sequence selected from the group consisting of TCR beta chain CDR sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-2 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about $5x10^{-4}$ M, is provided.

In another aspect, a binding protein comprising: a) a TCR alpha chain variable (V_α) domain sequence selected from the group consisting of TCR V_α domain sequences listed in Table 1; and/or b) a TCR beta chain variable (V_β) domain sequence selected from the group consisting of TCR V_β domain sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-2 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about $5x10^{-4}$ M, is provided.

In still another aspect, a binding protein comprising: a) a TCR alpha chain sequence selected from the group consisting of TCR alpha chain sequences listed in Table 1; and/or b) a TCR beta chain sequence selected from the group consisting of TCR beta chain

sequences listed in Table 1, wherein the binding protein is capable of binding to an HA-2 immunogenic peptide-MHC (pMHC) complex, optionally wherein the binding affinity has a K_d less than or equal to about $5x10^{-4}$ M, is provided.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment described herein. For example, in one embodiment, 1) a TCR alpha chain CDR, TCR V_α domain, and/or TCR alpha chain is encoded by a TRAV, TRAJ, and/or TRAC gene or fragment thereof selected from the group of TRAV, TRAJ, and TRAC genes listed in Table 1, and/or 2) a TCR beta chain CDR, TCR V_β domain, and/or TCR beta chain is encoded by a TRBV, TRBJ, and/or TRBC gene or fragment thereof selected from the group of TRBV, TRBJ, and TRBC genes listed in Table 1, and/or 3) each CDR of the binding protein has up to five amino acid substitutions, insertions, deletions, or a combination thereof as compared to the cognate reference CDR sequence listed in Table 1, is provided. In another embodiment, an HA-2 immunogenic peptide comprises the amino acid sequence YIGEVLVSV or YIGEVLVSM. In still another embodiment, a binding protein is chimeric, humanized, or human. In yet another embodiment, a binding protein is a TCR, an antigen-binding fragment of a TCR, a single chain TCR (scTCR), a chimeric antigen receptor (CAR), or a fusion protein comprising a TCR and an effector domain, optionally wherein the binding domain comprises a transmembrane domain and an effector domain that is intracellular. In yet another embodiment, a TCR alpha chain and a TCR beta chain are covalently linked, optionally wherein the TCR alpha chain and the TCR beta chain are covalently linked through a linker peptide. In another embodiment, a TCR alpha chain and/or a TCR beta chain are covalently linked to a moiety, optionally wherein the covalently linked moiety comprises an affinity tag or a label. In still another embodiment, an affinity tag is selected from the group consisting of CD34 enrichment tag, Glutathione-S-Transferase (GST), calmodulin binding protein (CBP), protein C tag, Myc tag, HaloTag, HA tag, Flag tag, His tag, biotin tag, and V5 tag, and/or wherein the label is a fluorescent protein. In yet another embodiment, a covalently linked moiety is selected from the group consisting of an inflammatory agent, cytokine, toxin, cytotoxic molecule, radioactive isotope, or antibody or antigen-binding fragment thereof. In another embodiment, a binding protein binds to a pMHC complex on a cell surface. In still another embodiment, an MHC is a MHC multimer, optionally wherein the MHC multimer is a tetramer. In yet another embodiment, an MHC is a MHC class I molecule. In another embodiment, an

MHC comprises an MHC alpha chain that is an HLA serotype HLA-A*02. In still another embodiment, an HLA allele is selected from the group consisting of HLA-A*0201, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele. In yet another embodiment, binding of a binding protein described herein to an HA-2 peptide-MHC (pMHC) complex elicits an immune response, optionally wherein the immune response is a T cell response. In another embodiment, a T cell response is selected from the group consisting of T cell expansion, cytokine release, and/or cytotoxic killing. In still another embodiment, a binding protein is capable of specifically binding to the HA-2 immunogenic peptide-MHC (pMHC) complex with a $K_d$less than or equal to about $1x10^{-4}$ M, less than or equal to about $5x10^{-5}$ M, less than or equal to about $1x10^{-5}$ M, less than or equal to about $5x10^{-6}$ M, less than or equal to about $1x10^{-6}$ M, less than or equal to about $5x10^{-7}$ M, less than or equal to about $1x10^{-7}$ M, less than or equal to about $5x10^{-8}$ M, less than or equal to about $1x10^{-8}$ M, less than or equal to about $5x10^{-9}$ M, less than or equal to about $1x10^{-9}$ M, less than or equal to about $5x10^{-10}$ M, less than or equal to about $1x10^{-10}$ M, less than or equal to about $5x10^{-11}$ M, less than or equal to about $1x10^{-11}$ M, less than or equal to about $5x10^{-12}$ M, or less than or equal to about $1x10^{-12}$ M. In yet another embodiment, a binding protein has a higher binding affinity to the peptide-MHC (pMHC) than does a known T-cell receptor. In another embodiment, a binding protein has at least 1.05-fold higher binding affinity to the peptide-MHC (pMHC) than does a known T-cell receptor. In still another embodiment, a binding protein induces higher T cell expansion, cytokine release, and/or cytotoxic killing than does a known T-cell receptor when contacted with target cells with a heterozygous expression of HA-2. In yet another embodiment, a binding protein induces at least 1.05-fold increase in T cell expansion, cytokine release, and/or cytotoxic killing than does a known T-cell receptor when contacted with target cells with a heterozygous expression of HA-2. As used herein, references to fold changes, in some embodiments, may be in comparison to any reference modality of interest, such as comparison to a different binding protein; comparison tothe same bindng protein under different context like expression of the same binding protein in a different immune cell, at a different level, in combination with other agents described herein; and the like. In another embodiment, a target cell is a DEL, THP-1, or TF-1 cell line. In still another embodiment, a target cell is a cancer cell. In yet another embodiment, a cancer is a hematological malignancy. In another embodiment, a hematological malignancy is a leukemia, a lymphoma, a myelodysplastic disorder, a myeloproliferative neoplasm, or a myeloma.

In yet another aspect, a TCR alpha chain and/or beta chain selected from the group consisting of TCR alpha chain and beta chain sequences listed in Table 1, is provided.

In another aspect, an isolated nucleic acid molecule that hybridizes, under stringent conditions, with the complement of a nucleic acid encoding a polypeptide selected from the group consisting of polypeptide sequences listed in Table 1, or a sequence with at least about 80% homology to a nucleic acid encoding a polypeptide selected from the group consisting of the polypeptide sequences listed in Table 1, optionally wherein the isolated nucleic acid molecule comprises 1) a TRAV, TRAJ, and/or TRAC gene or fragment thereof selected from the group of TRAV, TRAJ, and TRAC genes listed in Table 1 and/or 2) a TRBV, TRBJ, and/or TRBC gene or fragment thereof selected from the group of TRBV, TRBJ, and TRBC genes listed in Table 1, is provided.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment described herein. For example, in one embodiment, a nucleic acid is codon optimized for expression in a host cell.

In still another aspect, a vector comprising an isolated nucleic acid described herein, is provided.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment described herein. For example, in one embodiment, a vector is a cloning vector, expression vector, or viral vector. In another embodiment, a vector further comprises nucleic acid sequence encoding CD8α and/or CD8β. In still another embodiment, a nucleic acid sequence encoding CD8α or CD8β is operably linked to a nucleic acid encoding a tag. In **yet another embodiment, a nucleic acid encoding a tag is at the 5' upstream of the nucleic** acid sequence encoding CD8α or CD8β such that the tag is fused to the N-terminus of CD8α or CD8β. In another embodiment, a tag is a CD34 enrichment tag. In still another embodiment, an isolated nucleic acid described herein, and the nucleic acid sequence encoding CD8α and/or CD8β are interconnected with an internal ribosome entry site or a nucleic acid sequence encoding a self-cleaving peptide. In yet another embodiment, a self-cleaving peptide is P2A, E2A, F2A or T2A.

In yet another aspect, a host cell which comprises an isolated nucleic acid described herein, comprises a vector described herein, and/or expresses a binding protein described herein, optionally wherein the cell is genetically engineered, is provided.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment described herein. For example, in one embodiment, a host cell comprises a chromosomal gene knockout of a TCR gene, an HLA gene, or both. In still another embodiment, a host cell comprises a knockout of an HLA gene selected from an α1 macroglobulin gene, α2 macroglobulin gene, α3 macroglobulin gene, β1 microglobulin gene, β2 microglobulin gene, and combinations thereof. In yet another embodiment, a host cell comprises a knockout of a TCR gene selected from a TCR α variable region gene, TCR β variable region gene, TCR constant region gene, and combinations thereof. In another embodiment, a host cell expresses CD8α and/or CD8β. In still another embodiment, a CD8α and/or CD8β is fused to a CD34 enrichment tag. In yet another embodiment, host cells are enriched using a CD34 enrichment tag. In another embodiment, a host cell is a hematopoietic progenitor cell, peripheral blood mononuclear cell (PBMC), cord blood cell, or immune cell. In another embodiment, an immune cell is a cytotoxic lymphocyte, cytotoxic lymphocyte precursor cell, cytotoxic lymphocyte progenitor cell, cytotoxic lymphocyte stem cell, $CD4^+$ T cell, $CD8^+$ T cell, CD4/CD8 double negative T cell, gamma delta (γδ) T cell, natural killer (NK) cell, NK-T cell, dendritic cell, or combination thereof. In still another embodiment, a T cell is a naive T cell, central memory T cell, effector memory T cell, or a combination thereof. In yet another embodiment, a T cell is a primary T cell or a cell of a T cell line. In another embodiment, a T cell does not express or has a lower surface expression of an endogenous TCR. In still another embodiment, a host cell is capable of producing a cytokine or a cytotoxic molecule when contacted with a target cell that comprises a peptide-MHC (pMHC) complex comprising the HA-2 peptide epitope in the context of an MHC molecule. In yet another embodiment, a host cell is contacted with the target cell *in vitro*, *ex vivo*, or *in vivo*. In another embodiment, a cytokine is TNF-α, IL-2, and/or IFN-γ. In still another embodiment, a cytotoxic molecule is perforins and/or granzymes, optionally wherein the cytotoxic molecule is granzyme B. In yet another embodiment, a host cell is capable of producing a higher level of cytokine or a cytotoxic molecule when contacted with a target cell with a heterozygous expression of HA-2. In another embodiment, a host cell is capable of producing an at least 1.05-fold higher level of cytokine or a cytotoxic molecule. In still another embodiment, a host cell is capable of killing a target cell that comprises a peptide-MHC (pMHC) complex comprising the HA-2 peptide epitope in the context of an MHC molecule. In yet another embodiment, killing is

determined by a killing assay. In another embodiment, a ratio of a host cell and a target cell in a killing assay is from 20:1 to 0.625:1. In still another embodiment, a target cell is a T2 cell pulsed with 1 μg/mL to 50 pg/mL of HA-2 peptide. In yet another embodiment, a host cell is capable of killing a higher number of target cells when contacted with target cells with a heterozygous expression of HA-2. In another embodiment, a host cell is capable of killing an at least 1.05-fold higher number of target cells. In still another embodiment, a target cell is a DEL, THP-1, or TF-1 cell line. In yet another embodiment, an HA-2 immunogenic peptide comprises the amino acid sequence YIGEVLVSV or YIGEVLVSM. In another embodiment, an MHC molecule is a MHC class I molecule. In still another embodiment, an MHC molecule comprises an MHC alpha chain that is an HLA serotype HLA-A*02. In yet another embodiment, an HLA allele is selected from the group consisting of HLA-A*02:01, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele. In another embodiment, a target cell is a cell line selected from the group consisting of Del, THP-1, and TF-1 cell lines, is a hematopoietic cancer cell expressing HA-2, or is not NB4. In still another embodiment, a cancer cell is of a hematological malignancy selected from the group consisting of a leukemia, a lymphoma, a myelodysplastic disorder, a myeloproliferative neoplasm, or myeloma. In yet another embodiment, a host cell does not express HA-2 antigen, is not recognized by a binding protein described herein, is not of serotype HLA-A*02, and/or does not express an HLA-A*02 allele.

In another aspect, a population of host cells described herein, is provided.

In still another aspect, a composition comprising: a) a binding protein described herein, b) an isolated nucleic acid described herein, c) a vector described herein, d) a host cell described herein, and/or e) a population of host cells described herein, and a carrier, is provided.

In yet another aspect, a device or kit comprising: a) a binding protein described herein, b) an isolated nucleic acid described herein, c) a vector described herein, d) a host cell described herein, and/or e) a population of host cells described herein, said device or kit optionally comprising a reagent to detect binding of a), d) and/or e) to a pMHC complex, is provided.

In another aspect, a method of producing a binding protein described herein, wherein the method comprises the steps of: (i) culturing a transformed host cell which has been transformed by a nucleic acid comprising a sequence encoding a binding protein

described herein under conditions suitable to allow expression of said binding protein; and (ii) recovering the expressed binding protein, is provided.

In still another aspect, a method of producing a host cell expressing a binding protein described herein, wherein the method comprises the steps of: (i) introducing a nucleic acid comprising a sequence encoding a binding protein described herein into the host cell; (ii) culturing the transformed host cell under conditions suitable to allow expression of said binding protein, is provided.

In yet another aspect, a method of detecting the presence or absence of an HA-2 antigen and/or a cell expressing HA-2, optionally wherein the cell is a hyperproliferative cell, comprising detecting the presence or absence of said HA-2 antigen in a sample by use of at least one binding protein described herein, or at least one host cell described herein, wherein detection of the HA-2 antigen is indicative of the presence of an HA-2 antigen and/or cell expressing HA-2, is provided.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment described herein. For example, in one embodiment, at least one binding protein described herein, or at least one host cell described herein, forms a complex with an HA-2 peptide in the context of an MHC molecule, and the complex is detected in the form of fluorescence activated cell sorting (FACS), enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemically, Western blot, or intracellular flow assay. In another embodiment, a method further comprises obtaining a sample from a subject. In still another embodiment, a method further comprises confirming cells expressing HA-2 by bone marrow biopsy.

In another aspect, a method of detecting the level of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen in a subject, comprising: a) contacting a sample obtained from the subject with at least one binding protein described herein, at least one host cell described herein, or a population of host cells described herein; and b) detecting the level of reactivity, wherein a higher level of reactivity compared to a control level indicates the level of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen in the subject.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment

described herein. For example, in one embodiment, a control level is a reference number. In another embodiment, a control level is a level of a subject without a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen.

In still another aspect, a method for monitoring the progression of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen in a subject, the method comprising: a) detecting in a subject sample at a first point in time the level of the HA-2 antigen or the cell of interest expressing HA-2 , as described herein; b) repeating step a) at a subsequent point in time; and c) comparing the level of the HA-2 antigen or the cell of interest expressing HA-2 detected in steps a) and b) to monitor the progression of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen in the subject, wherein an absent or reduced level of the HA-2 antigen or the cell of interest expressing HA-2 detected in step b) compared to step a) indicates an inhibited progression of the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen in the subject, is provided.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment described herein. For example, in one embodiment, a subject has undergone treatment to treat the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen between the first point in time and the subsequent point in time.

In yet another aspect, a method of assessing the efficacy of a therapy for a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen comprising: a) determining the presence or level of reactivity between a sample obtained from a subject and at least one binding protein described herein, at least one host cell described herein, or a population of host cells described herein, in a first sample obtained from the subject prior to providing at least a portion of the therapy for the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen to the subject, and b) determining the presence or level of reactivity between a sample obtained from the subject and at least one binding protein described

herein, at least one host cell described herein, or a population of host cells describged herein, in a second sample obtained from the subject following provision of the portion of the therapy for the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen, wherein the absence or a reduced level of reactivity in the second sample, relative to the first sample, is an indication that the therapy is efficacious for treating the non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen in the subject, is provided.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment described herein. For example, in one embodiment, a level of reactivity is indicated by a) the presence of binding and/or b) T cell activation and/or effector function, optionally wherein the T cell activation or effector function is T cell proliferation, killing, or cytokine release. In another embodiment, a T cell activation or effector function is T cell proliferation, killing, or cytokine release. In still another embodiment, a T cell binding, activation, and/or effector function is detected using fluorescence activated cell sorting (FACS), enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemically, Western blot, or intracellular flow assay.

In another aspect, a method of preventing and/or treating a non-malignant disorder, a hyperproliferative disorder or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen in a subject comprising administering to the subject a therapeutically effective amount of a composition comprising cells expressing at least one binding protein described herein.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment described herein. For example, in one embodiment, a cell is an allogeneic cell, syngeneic cell, or autologous cell. In another embodiment, a cell is genetically modified. In still another embodiment, a cell comprises a chromosomal gene knockout of a TCR gene, an HLA gene, or both a TCR gene and an HLA gene. In still another embodiment, a cell comprises a knockout of an HLA gene selected from an αl macroglobulin gene, α2 macroglobulin gene, **α3 macroglobulin gene, β1 microglobulin gene, β2 microglobulin** gene, and a combination thereof. In yet another embodiment, a cell comprises a knockout of a TCR gene selected from a TCR **α variable region gene, TCR β variable region gene,**

TCR constant region gene, and combinations thereof. In another embodiment, a cell expresses CD8α and/or CD8β, optionally wherein the CD8α and/or CD8β is fused to a CD34 enrichment tag. In still another embodiment, cells are enriched using the CD34 enrichment tag. In yet another embodiment, a cell is a hematopoietic progenitor cell, peripheral blood mononuclear cell (PBMC), cord blood cell, or immune cell. In another embodiment, an immune cell is a cytotoxic lymphocyte, cytotoxic lymphocyte precursor cell, cytotoxic lymphocyte progenitor cell, cytotoxic lymphocyte stem cell, $CD4^+$ T cell, $CD8^+$ T cell, CD4/CD8 double negative T cell, gamma delta (γδ) T cell, natural killer (NK) cell, NK-T cell, dendritic cell, or combination thereof. In another embodiment, a T cell is a naive T cell, central memory T cell, effector memory T cell, or combination thereof. In still another embodiment, a T cell is a primary T cell or a cell of a T cell line. In yet another embodiment, a T cell does not express or has a lower surface expression of an endogenous TCR. In another embodiment, a cell is capable of producing a cytokine or a cytotoxic molecule when contacted with a target cell that comprises a peptide-MHC (pMHC) complex comprising the HA-2 in the context of an MHC molecule. In still another embodiment, a cytokine is TNF-α, IL-2, and/or IFN-γ. In yet another embodiment, a cytotoxic molecule is perforins and/or granzymes, optionally wherein the cytotoxic molecule is granzyme B. In another embodiment, a cell is capable of producing a higher level of cytokine or a cytotoxic molecule when contacted with a target cell with a heterozygous expression of HA-2. In still another embodiment, a cell is capable of producing an at least 1.05-fold higher level of cytokine or a cytotoxic molecule. In yet another embodiment, a host cell is capable of killing a target cell that comprises a peptide–MHC (pMHC) complex comprising an HA-2 in the context of an MHC molecule. In another embodiment, a host cell is capable of killing a higher number of target cells when contacted with target cells with a heterozygous expression of HA-2. In still another embodiment, a host cell is capable of killing an at least 1.05-fold higher number of target cells. In yet another embodiment, an HA-2 immunogenic peptide comprises the amino acid sequence YIGEVLVSV or YIGEVLVSM. In another embodiment, an MHC molecule is an MHC class I molecule. In still another embodiment, an MHC molecule comprises an MHC alpha chain that is an HLA serotype HLA-A*02. In yet another embodiment, an HLA allele is selected from the group consisting of HLA-A*02:01, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele. In another embodiment, a target cell is a non-malignant cell or a hyperproliferating cell expressing the HA-2 antigen

in a subject. In still another embodiment, a composition further comprises a pharmaceutically acceptable carrier. In yet another embodiment, a composition induces an immune response against the non-malignant cells or the hyperproliferating cells expressing the HA-2 antigen in a subject. In another embodiment, a composition induces an antigen-specific T cell immune response against non-malignant cells or hyperproliferating cells expressing HA-2 antigen in a subject. In still another embodiment, an antigen-specific T cell immune response comprises at least one of a $CD4^+$ helper T lymphocyte (Th) response and a CD8+ cytotoxic T lymphocyte (CTL) response. In yet another embodiment, a hyperproliferative disorder comprises a hematological malignancy. In another embodiment, a hematological malignancy comprises a leukemia, a lymphoma, a myelodysplastic disorder, a myeloproliferative neoplasm, or a myeloma. In still another embodiment, a hematological malignancy comprises a leukemia. In yet another embodiment, a leukemia is selected from acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), mixed phenotype acute leukemia (MPAL), chronic myeloid leukemia (CML), B cell prolymphocytic leukemia, hairy cell leukemia, or chronic lymphocytic leukemia (CLL). In yet another embodiment, a hematological disorder comprises a lymphoma. In another embodiment, a lymphoma is selected from Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), a central nervous system lymphoma, small lymphocytic lymphoma (SLL), CD37+ dendritic cell lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated (MALT) lymphoid tissue, nodal marginal zone B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, precursor B-lymphoblastic lymphoma, immunoblastic large cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, or Burkitt's lymphoma. In another embodiment, a hematological malignancy comprises a myelodysplastic disorder (MDS), optionally wherein the MDS is selected from refractory cytopenia with unilineage dysplasia (refractory anemia, refractory neutropenia, and refractory thrombocytopenia), refractory anemia with ring sideroblasts (RARS), refractory anemia with ring sideroblasts - thrombocytosis (RARS-t), refractory cytopenia with multinieage dysplasia (RCMD), refractory cytopenia with multinieage dysplasia and ring sideroblasts (RCMD-RS), refractory anemia with excess blasts (RAEB), myelodysplasia unclassifiable, refractory cytopenia of childhood, or MDS with isolated del(5q). In still another embodiment, a non-malignant disorder is an immune deficiency disorder,

optionally wherein the immune deficiency disorder is selected from the group consisting of severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, chronic granulomatous disease, leukocyte adhesion deficiency, DiGeorge syndrome, and indications for hematopoietic stem cell transplantation (HCT). In yet another embodiment, a non-malignant disorder is a non-malignant hematology disorder, optionally wherein the non-malignant hematology disorder is selected from the group consisting of sickle cell anemia, thalassemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), severe aplastic anemia, marrow failure syndromes, Fanconi anemia, Diamond-Blackfan anemia, and Shwachman Diamond syndrome. In another embodiment, a non-malignant disorder is an autoimmune disorder, optionally wherein the autoimmune disorder is systemic sclerosis or multiple sclerosis. In still another embodiment, a subject is receiving or previously received a hematopoietic cell transplant (HCT), optionally wherein the HCT comprises cells that do not express HA-2 antigen, are not recognized by a binding protein described herein, are not of serotype HLA-A*02, and/or do not express an HLA-A*02:01 allele. In yet another embodiment, an HCT comprises a donor hematopoeitic cell comprising a chromosomal knockout of a gene that encodes an HLA component, a chromosomal knockout of a gene that encodes a TCR component, or both. In another embodiment, a subject had previously received lymphodepleting chemotherapy. In still another embodiment, a lymphodepleting chemotherapy comprised cyclophosphamide, fludarabine, anti-thymocyte globulin, or a combination thereof. In yet another embodiment, a method further comprises administering at least one additional treatment for the non-malignant disorder, the hyperproliferative disorder or the relapse of a hyperproliferative disorder to a subject. In another embodiment, at least one additional treatment for the non-malignant disorder, the hyperproliferative disorder or the relapse of a hyperproliferative disorder is administered concurrently or sequentially with the composition. In still another embodiment, a subject is an animal model of disorder characterized by HA-2 antigen and/or the subject is a mammal, optionally wherein the mammal is a human, a primate, or a rodent.

In still another aspect, an expression vector comprising a promoter operably linked to a nucleic acid sequence encoding CD8α and/or CD8β, is provided.

Numerous embodiments are further provided that may be applied to any aspect encompassed by the present invention and/or combined with any other embodiment described herein. For example, in one embodiment, a nucleic acid sequence encoding

CD8α or CD8β is operably linked to a nucleic acid encoding a tag such that the tag is fused to the CD8α or CD8β. **In another embodiment, a nucleic acid encoding a tag is at the 5'** upstream of the nucleic acid sequence encoding CD8α or CD8β such that the tag is fused to the N-terminal of CD8α or CD8β. In still another embodiment, a tag is a CD34 enrichment tag. In yet another embodiment, a vector further comprises a nucleic sequence encoding a TCRα and/or TCRβ. In another embodiment, a TCRα and/or TCRβ comprises a mutated transmembrane domain and/or a mutated constant domain. In still another embodiment, a mutated transmembrane domain and/or mutated constant domain enhance cellular surface expression of TCRα and/or TCRβ while decreasing expression of endogenous TCRα and/or TCRβ. In yet another embodiment, a nucleic acid sequence encoding CD8α and/or CD8β and the nucleic sequence encoding TCRα and/ TCRβ, are interconnected with an internal ribosome entry site or a nucleic acid sequence encoding a self-cleaving peptide. In another embodiment, a self-cleaving peptide is P2A, E2A, F2A or T2A. In still another embodiment, a vector further comprises a nucleic sequence encoding a polypeptide selected from the group consisting of polypeptide sequences listed in Table 1, or a sequence with at least about 80% homology to a nucleic acid encoding a polypeptide selected from the group consisting of the polypeptide sequences listed in Table 1, optionally wherein the isolated nucleic acid molecule comprises 1) a TRAV, TRAJ, and/or TRAC gene or fragment thereof selected from the group of TRAV, TRAJ, and TRAC genes listed in Table 1 and/or 2) a TRBV, TRBJ, and/or TRBC gene or fragment thereof selected from the group of TRBV, TRBJ, and TRBC genes listed in Table 1. In yet another embodiment, a vector has a nucleic sequence set forth in Table 2.

Brief Description of the Drawings

Figure 1 shows a schematic diagram of TCR discovery platform. The TCR discovery platform identified 1,302 novel HA-2 TCRs. $CD14^+$ monocytes were isolated from PBMCs of six HA-2 negative healthy donors on day -4 and differentiated to mature DCs. On day -1, naïve CD8 T cells were isolated from autologous PBMCs and rested overnight. Co-culture of CD8 T cells and DCs was performed following 3 h pulsing of DCs with 1 μg/mL HA-2 REF peptide (YIGEVLVSV), followed by an 11-day cell expansion phase. Dextramer staining was performed with A*02:01-specific HA-2 REF (YIGEVLVSV) and HA-2 SNP (YIGEVLVSM) dextramers to identify clones, which were then sorted for single cell TCR sequencing.

Figure 2 shows results of a DexScan performed on 380 TCRs identified as shown in Figure 1 for functional assessment using a library of individually cloned HA-2 TCR viruses. Briefly, pan T cells isolated from HLA-A*01:01/A*03:01-positive healthy donor PBMCs were transduced to express a pool of HA-2-specific TCRs and stained with various dilutions of A*02:01-specific HA-2 REF (YIGEVLVSV) dextramer. Dextramer-bound cells were sorted and sequenced. TCR enrichment (*i.e.*, change in the proportion of TCR in sorted samples versus input) was used to nominate TCRs for functional evaluation. The figure indicates TCRs selected by DexScan for advancement into functional evaluation.

Figure 3 shows that HA-2 TCRs are expressed on the surface of engineered T cells. Pan-T cells were transduced to express 15 HA-2-specific TCRs that were selected from the DexScan screen. Dot plots show surface expression of the TCRs as assessed by A*02:01-specific HA-2 REF (YIGEVLVSV) dextramer staining.

Figure 4A - Figure 4D show HA-2 TCR functional evaluation results. Pan T cells isolated from HLA-A*01:01/A*03:01-positive healthy donor PBMCs were transduced to express HA-2-specific TCRs, and assessed for functional responses to target cells expressing HA-2 and HLA-A*02:01. Figure 4A shows dot plots demonstrating representative expression of three HA-2-specific TCRs as assessed by A*02:01-specific HA-2 REF (YIGEVLVSV) dextramer staining. Figure 4B - Figure 4D show functional responses of HA2-specific TCRs to HLA-A*02:01$^+$ HA-2$^+$ target cell lines, DEL (high MHC, high HA-2), THP-1 (medium MHC, low HA-2), TF-1 (low MHC, low HA-2), and a negative control cell line, NB4 (irrelevant MHC). Figure 4B shows results of engineered T cells co-cultured with IncuCyte® NucLight™ Red-labeled target cell lines at indicated E:T ratios. Cell survival was quantified on an IncuCyte® machine as a readout of cytotoxicity of the T cells. Figure 4C shows production of IFN-γ, IL-2, TNF-α and granzyme B in co-culture supernatants at 24 h (E:T 1:1). A T cell-only condition was used to determine background level of cytokine production. The dotted line represents the highest levels of cytokine in the T cell-only condition. Figure 4D shows proliferation of the HA-2-specific TCR-expressing T cells. Engineered T cells were labeled with a proliferation dye and co-cultured with target cell lines for 96 h (E:T 1:1). Dye dilution was used to assess proliferation of CD8$^+$ and CD4$^+$ T cells. Counting beads were added to the samples prior to analysis by flow cytometry and absolute numbers of divided CD8$^+$ and CD4$^+$ T cells were enumerated. A T cell-only condition was used to determine background level of proliferation. The dotted line represents the highest levels of proliferation in T cell only

condition. TCRs were compared by one-way ANOVA followed by Tukey's multiple comparison test. * P<0.05, ** P<0.005, *** P<0.0005, **** P<0.0001. These experiments were performed in 2-3 donors and representative data from 1 donor is shown.

Figure 5 shows alloreactivity landscape results for MJ2-DP8 and MJ7-DP19 TCRs tested in an alloreactivity assay. Endogenous MHCs were knocked out of HEK293T cells using CRISPR/Cas9-gRNA ribonucleoprotein delivery. MHC-null HEK293T cells were transduced with IncuCyte® NucLight™ Red and individual MHCs representing the 110 most prevalent HLA types using lentiviral transduction. A cell line that stably expresses A*02:01 and a 90-residue protein fragment that includes the HA-2 REF (YIGEVLVSV) sequence was used as a positive control. Cells in 96-well format were incubated with human primary $CD8^+$ T cells expressing MJ2-DP8 and MJ7-DP19 TCRs for 48 h. Target cell numbers were measured over time using an IncuCyte® machine by measuring the number of IncuCyte® NucLight™ Red-positive cells. Cell inhibition at 48 h of each TCR on each MHC in the assay was calculated as 1- (Target cell doubling[Incubated with TCR-expressing T cells]/ Target cell doubling[Incubated with T cell media]). To subtract the effect of non-MHC-related target cell growth inhibition such as competition for nutrition from T cells or non-specific cell killing from donor T cells and to correct for batch effect of each 96-well plate, the cell inhibition value of each well (each MHC) on each 96-well plate were subtracted by the median of cell inhibition of the wells on each 96-well plate.

Figure 6 shows results of a DexScan performed on 1,174 TCRs identified as shown in Figure 1 for functional assessment using a library pool of HA-2 TCR viruses. Briefly, pan T cells isolated from HLA-A*01:01/A*03:01-positive healthy donor PBMCs were transduced with a library pool of HA-2 TCR viruses and stained A*02:01-specific HA-2 REF (YIGEVLVSV) dextramer. Dextramer-bound cells were sorted and sequenced. TCR enrichment (*i.e.*, change in the proportion of TCR in sorted samples versus input) was used to nominate TCRs for functional evaluation. The figure indicates TCRs selected by DexScan for advancement into functional evaluation.

Figure 7A - **Figure 7M** show HA-2 TCR functional evaluation results shown using mean with standard error of the mean (SEM) indications. Pan T cells isolated from HLA-A*01:01/A*03:01-positive healthy donor PBMCs were transduced to express HA-2-specific TCRs, and assessed for functional responses to target cells expressing HA-2 and HLA-A*02:01. Figure 7A shows dot plots demonstrating representative expression of fifteen HA-2-specific TCRs as assessed by A*02:01-specific HA-2 REF (YIGEVLVSV)

dextramer staining. Figure 7B - Figure 7M show functional responses of HA2-specific TCRs to the followng HLA-A*02:01$^+$ HA-2$^+$ target cell lines: DEL (high MHC, high HA-2) (Figure 7B - Figure 7D), THP-1 (medium MHC, low HA-2) (Figure 7E - Figure 7G), TF1 (low MHC, low HA-2) (Figure 7H - Figure 7J), and the negative control cell line, NB4 (irrelevant MHC) (Figure 7K - Figure 7M). Engineered T cells were co-cultured with IncuCyte® NucLight™ Red-labeled target cell lines at indicated E:T ratios, and their survival was quantified on an IncuCyte® machine as a readout of cytotoxicity of the T cells. Production of IFN-γ, IL-2, TNF-α and granzyme B in co-culture supernatants at 24 h (E:T 1:1). A T cell-only condition was used to determine background level of cytokine production. The dotted line represents the highest levels of cytokine in the T cell-only condition. To determine proliferation of the HA-2-specific TCR-expressing T cells, engineered T cells were labeled with a proliferation dye and co-cultured with target cell lines for 96 h (E:T 1:1). Dye dilution was used to assess proliferation of CD8$^+$ and CD4$^+$ T cells. Counting beads were added to the samples prior to analysis by flow cytometry and absolute numbers of divided CD8$^+$ and CD4$^+$ T cells were enumerated. A T cell-only condition was used to determine background level of proliferation. As described above, the dotted line represents the highest levels of proliferation in T cell-only condition. TCRs were compared by one-**way ANOVA followed by Tukey's multiple comparison test.** $P<0.05$ indicates statistical significance and key statistics are reported with each figure as follows: a) the left panel bar graph of Figure 7B shows that the results for each of MJ2-DP22, MJ9-DP5, and MJ7-DP19 were significantly different from the results for each of MJ14-SP4, MJ13-SP43, MJ14-DP162, and NTD ($P<0.05$); b) the right panel bar graph of Figure 7B shows that the results for each of MJ14-DP317, MJ2-DP8, and MJ7-DP19 were significantly different from the results for each of MJ14-DP33, MJ13-DP32, and NTD ($P<0.05$); c) the interferon-γ bar graph of Figure 7C shows that the results for each of MJ2-DP22, MJ14-DP317, and MJ2-DP8 were significantly different from the results for each of MJ14-SP4, MJ13-SP43, MJ14-DP137, MJ14-DP162, MJ14-DP33, MJ2-DP24, MJ13-DP148, MJ13-DP32, and NTD ($P<0.05$), while the results for each of MJ9-DP5 and MJ7-DP19 were significantly different from the results for each of all TCRs, except MJ14-DP137 ($P<0.05$); d) the IL-2 and TNF-α bar graphs of Figure 7C show that the results for each of MJ2-DP22, MJ9-DP5, MJ14-DP317, MJ2-DP8, and MJ7-DP19 were significantly different from the results for each of MJ14-SP4, MJ13-SP43, MJ14-DP137, MJ14-DP162, MJ14-DP33, MJ2-DP24, MJ13-DP148, MJ13-DP32, and NTD ($P<0.05$); e) the granzyme

B bar graph of Figure 7C shows that the results for each of MJ2-DP22, MJ14-DP317, MJ2-DP8, and MJ7-DP19 were significantly different from the results for each of MJ14-SP4, MJ13-SP43, MJ14-DP137, MJ14-DP162, MJ14-DP33, MJ2-DP24, MJ13-DP148, MJ13-DP32, and NTD ($P<0.05$), while the result for MJ9-DP5 was significantly different from the result for each of all TCRs, except MJ14-DP137 ($P<0.05$); f) the CD8 T cell proliferation bar graph of Figure 7D shows that the results for each of MJ14-DP317, MJ9-DP5, MJ2-DP8, and MJ7-DP19 were significantly different from the results for each of MJ14-SP4, MJ13-SP43, MJ14-DP137, MJ14-DP162, MJ14-DP33, MJ2-DP24, MJ13-DP148, MJ13-DP32, and NTD ($P<0.05$), while the result for MJ2-DP22 was significantly different from the results for each of all TCRs, except MJ14-DP137; g) the CD4 T cell proliferation bar graph of Figure 7D shows that the results for each of MJ14-DP317 and MJ2-DP8 were significantly different from the results for each of MJ14-SP4, MJ13-SP43, MJ14-DP137, MJ14-DP162, MJ14-DP33, MJ2-DP24, MJ13-DP148, MJ13-DP32, and NTD ($P<0.05$), while the results for each of MJ2-DP22, MJ9-DP5, and MJ7-DP19 were significantly different from the results for each of all TCRs, except MJ14-DP137 ($P<0.05$); h) the left panel bar graph of Figure 7E shows that the results for each of MJ2-DP22, MJ9-DP5, and MJ7-DP19 were significantly different from the results for each of MJ14-SP4, MJ13-SP43, MJ14-DP137, MJ14-DP162, and NTD ($P<0.05$); i) the right panel bar graph of Figure 7E shows that the results for each of MJ14-DP317, MJ2-DP8, and MJ7-DP19 were significantly different from the results for each of MJ14-DP33, MJ12-DP24, MJ13-DP148, MJ13-DP32, and NTD ($P<0.05$); j) the interferon-γ, TNF-α and granzyme B bar graphs of Figure 7F show that the results for each of MJ2-DP22, MJ9-DP5, MJ14-DP317, MJ2-DP8, and MJ7-DP19 were significantly different from the results for each of MJ14-SP4, MJ13-SP43, MJ14-DP137, MJ14-DP162, MJ14-DP33, MJ2-DP24, MJ13-DP148, MJ13-DP32, and NTD ($P<0.05$) and only MJ9-DP5, MJ14-DP317, and MJ2-DP8 produced IL-2 above background levels; k) the CD8 T cell proliferation graph and CD4 T cell proliferation graph of Figure 7G each show that the results for each of MJ2-DP22, MJ14-DP317, MJ9-DP5, MJ2-DP8, and MJ7-DP19 were significantly different from the results for MJ14-SP4, MJ13-SP43, MJ14-DP137, MJ14-DP162, MJ14-DP33, MJ2-DP24, MJ13-DP148, MJ13-DP32, and NTD ($P<0.05$); l) the left panel bar graph of Figure 7H shows that the results for each of MJ2-DP22, MJ9-DP5, and MJ7-DP19 were significantly different from the results for each of MJ14-SP4, MJ13-SP43, MJ14-DP137, MJ14-DP162, and NTD ($P<0.05$); and m) the right panel bar graph of Figure 7H shows that the results for each of MJ14-DP317,

MJ2-DP8, and MJ7-DP19 were significantly different from the results for each of MJ14-DP33, MJ12-DP24, MJ13-DP148, MJ13-DP32, and NTD ($P<0.05$).

Figure 8A - **Figure 8M** similarly show HA-2 TCR functional evaluation results for seven HA-2 TCRs in two unique donors selected based on data from Figure 7A - Figure 7M. Bar graphs indicate mean with standard error of the mean (SEM). Pan T cells isolated from HLA-A*01:01/A*03:01-positive healthy donor PBMCs were transduced to express HA-2-specific TCRs, and assessed for functional responses to target cells expressing HA-2 and HLA-A*02:01. Figure 8A shows dot plots demonstrating expression of seven HA-2-specific TCRs as assessed by A*02:01-specific HA-2 REF (YIGEVLVSV) dextramer staining in two unique donors. Figure 8B - Figure 8M show functional responses of the HA2-specific TCRs to the following HLA-A*02:01$^+$ HA-2$^+$ target cell lines: DEL (high MHC, high HA-2) (Figure 8B - Figure 8D), THP-1 (medium MHC, low HA-2) (Figure 8E - Figure 8G), TF1 (low MHC, low HA-2) (Figure 8H - Figure 8J), and the negative control cell line, NB4 (irrelevant MHC; HLA-A*02:01- (*i.e.*, negative)) (Figure 8K - Figure 8M). Engineered T cells were co-cultured with IncuCyte® NucLight™ Red-labeled target cell lines at indicated E:T ratios, and their survival was quantified on an IncuCyte® machine as a readout of cytotoxicity of the T cells. Production of IFN-γ, IL-2, TNF-α and granzyme B in co-culture supernatants at 24 h (E:T 1:1). A T cell-only condition was used to determine background level of cytokine production. The dotted line represents the highest levels of cytokine in the T cell-only condition. To determine proliferation of the HA-2-specific TCR-expressing T cells, engineered T cells were labeled with a proliferation dye and co-cultured with target cell lines for 96 h (E:T 1:1). Dye dilution was used to assess proliferation of CD8$^+$ and CD4$^+$ T cells. Counting beads were added to the samples prior to analysis by flow cytometry and absolute numbers of divided CD8$^+$ and CD4$^+$ T cells were enumerated. A T cell-only condition was used to determine background level of proliferation. As described above, the dotted line represents the highest levels of proliferation in the T cell-only condition. TCRs were compared by one-way ANOVA **followed by Tukey's multiple comparison test.** $P<0.05$ indicates statistical significance and key statistics are reported with each figure as follows: a) the left panel and right panel bar graphs of Figure 8B show that the results for each of MJ14-DP317, MJ9-DP5, MJ2-DP22, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-SP4 and NTD ($P<0.05$); b) bar graphs of Figure 8C show that results for each of MJ14-DP317, MJ9-DP5, MJ2-DP22, MJ7-DP19, and MJ2-DP8 were significantly different from

the results for each of MJ14-DP137, MJ14-SP4, and NTD for all cytokines in both donors ($P<0.05$), except that only the result for MJ14-DP317 was not different from the result for MJ14-DP137 for TNF-α in donor 3; c) the CD8 T cell proliferation panel for donor 2 of Figure 8D shows that the results for each of MJ14-DP317, MJ9-DP5, and MJ2-DP22 were significantly different from the results for each of MJ14-SP4 and NTD ($P<0.05$), while the results for each of MJ7-DP19 and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD ($P<0.05$); d) the CD4 T cell proliferation panel for donor 2 of Figure 8D shows that the results for each of MJ14-DP317, MJ2-DP22, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD ($P<0.05$), while the result for MJ9-DP5 was significantly different from the results for each of MJ14-SP4 and NTD ($P<0.05$); e) the CD8 T cell proliferation panel and the CD4 T cell proliferation panel for donor 3 of Figure 8D each shows that the results for each of MJ14-DP317, MJ9-DP5, MJ2-DP22, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD ($P<0.05$); f) the left panel and right panel bar graphs of Figure 8E show that the results for each of MJ14-DP317, MJ9-DP5, MJ2-DP22, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD for each donor ($P<0.05$); g) bar graphs of Figure 8F show that results for each of MJ14-DP317, MJ9-DP5, MJ2-DP22, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD for IFN-γ, IL-2 and TNF-α in both donors ($P<0.05$), the results for each of MJ14-DP317, MJ9-DP5, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD in donor 2 for granzyme B ($P<0.05$), and the results for each of MJ9-DP5, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD in donor 3 for granzyme B ($P<0.05$); h) bar graphs of Figure 8G show that the results for each of MJ14-DP317, MJ9-DP5, MJ2-DP22, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD for each of CD8 T cell proflieration and CD4 T cell proliferation for both donors ($P<0.05$); i) the bar graph for donor 2 of Figure 8H shows that the results for each of MJ14-DP317, MJ9-DP5, MJ2-DP22, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD ($P<0.05$); j) the bar graph for donor 3 of Figure 8H shows that the results for each of MJ9-DP5, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD

($P<0.05$), while the result for MJ2-DP22 was significantly different from the results for each of MJ14-DP137 and NTD ($P<0.05$); k) the CD8 T cell proliferation bar graph for donor 2 of Figure 8J shows that the results for each of MJ14-DP317, MJ9-DP5, MJ2-DP22, MJ7-DP19, and MJ2-DP8 were significantly different from the results for each of MJ14-DP137, MJ14-SP4, and NTD ($P<0.05$), while the CD4 T cell proliferation bar graph for donor 2 of Figure 8J di not show significant differences between the TCRs; and l) the CD8 T cell proliferation and the CD4 T cell proliferation bar graphs for donor 3 of Figure 8J each show that the result for MJ2-DP8 was significantly different from each of the results for MJ14-DP137, MJ14-SP4, and NTD ($P<0.05$) and that the result for MJ2-DP22 was significantly different from each of the results for MJ14-DP137 and NTD ($P<0.05$).

Figure 9 shows alloreactivity landscape results for MJ9-DP5, MJ2-DP22, and MJ14-DP317 tested in an alloreactivity assay. Endogenous MHCs were knocked out of HEK293T cells using CRISPR/Cas9-gRNA ribonucleoprotein delivery. MHC-null HEK293T cells were transduced with IncuCyte® **NucLight™ Red and individual MHCs** representing the 110 most prevalent HLA types using lentiviral transduction. A cell line was prepared that stably expresses A*02:01 and a 90-residue protein fragment that includes the HA-2 REF (YIGEVLVSV) as positive control. Cells in 384-well format were incubated with human primary $CD8^+$ T cells expressing MJ9-DP5, MJ2-DP22, and MJ14-DP317 for 48 h. Target cell numbers were measured over time using IncuCyte® machine by measuring the number of **IncuCyte® NucLight™ Red positive cells.** Cell inhibition at 48 h of each TCR on each MHC in the assay was calculated as 1- (Target cell doubling[Incubated with TCR-expressing T cells]/ Target cell doubling[Incubated with untransduced donor T cells]). To correct for batch effect of each 384-well plate, the cell inhibition value of each well (each MHC) on each 384-well plate were subtracted by the median of cell inhibition of the wells on each 384-well plate.

Figure 10A and **Figure 10B** show strategies for conducting and results from off-target screen assays. Figure 10A shows a schematic overview of the genome-wide safety screen assay used. In this genome-wide safety screen, T cells expressing HA2-MJ14-DP317 were co-cultured with a library of HLA-A*02:01^+ target cells, wherein each such target cell expresses a different 90-amino acid (90-aa) protein fragment. Collectively, the library includes fragments that tile across every protein in 22-amino acid steps. Fragments are processed naturally by the target cells and the resulting peptides are displayed on cell-surface MHCs. If a T cell recognizes its target, it attempts to kill the target cell, thereby

activating a fluorescent reporter. By isolating fluorescent cells and sequencing their expression cassettes, the natural target(s) of the TCR are revealed. The screen is designed to overpredict off-targets by overexpressing 90-aa protein fragments, which are more efficiently processed than full-length proteins, such that identified hits may not be expected to be physiologically relevant off-targets. Kula *et al.* (2019) *Cell* 178:1016-1028 provide additional details. Figure 10B shows that multiple tiles containing the HA-2 epitope were significantly enriched in the screens with HA2-MJ14-DP317 (TCR-101) and further shows that multiple genes were identified as potential off-targets. The x-axis represents protein fragments in the peptidome library and the Y-axis represents fold enrichment of individual tiles over input library.

Figure 11A and **Figure 11B** show that TSC-101 displays as least 100-3,000 fold lower affinity for putative off-target peptides as compared to target HA-2 peptide. The cytotoxic activity of TSC-101 TCR-T cells was tested against T2 cells pulsed with different on- and off-target peptides. Figure 11A shows that affinity of TCR-101 for on- and off-target peptides was measured by calculating area under the curve (AUC) for growth of the T2 target cells co-cultured with TSC-101 T cells was measured over 72h as a function of the dose of peptide. Figure 10B shows individual EC_{50} for the 8-point titration of the HA-2^{+}peptide, HA-2^{-} peptide, putative off-target MYO3A/B peptide, putative off-target MALT1 peptide. Note that the determination of EC50 for the remaining peptides (MTA1, KLHL30 and HUWE1) is not displayed as their 3-point titration did not enable the calculation of the EC_{50}.

Figure 12A and **Figure 12B** show that TSC-101 exhibits robust cytotoxicity against primary hematologic tumor samples, including acute myeloid leukemia (AML) and acute lympocytic leukemia (ALL) tumor samples. TSC-101 and non-engineered control (NC) T cells were co-cultured for 20 h with HLA-A*02:01-positive PBMCs or BMMCs from AML (Figure 12A) or ALL (Figure 12B) patients at an E:T of 10:1. The viability of targets upon co-culture with TSC-101 T cells was then assessed by flow cytometry and normalized to the viability of targets upon co-culture with NC T cells. Data are representative of 3 donors.

Figure 13 provides summary data.

Figure 14A and **Figure 14B** show that TSC-101 lacks reactivity to non-hematopoietic primary human cells. The data show IFN-γ concentrations measured in the supernatant of TSC-101 co-cultured during 48 h with different target cells corrected for

background (background IFN-γ was measured with effector cells alone (Figure 14A). Target cells included NB-4 (negative control) and THP-1 (positive control) and HLA-A*02:01 positive primary human cells, including PBMCs (green bars), endothelial cells (HUVEC), skeletal muscle cells (SKMC), keratinocytes (NHEK), bronchial epithelial cells (HBEC), melanocytes (NHEM), retina pigmented epithelial cells (RPEC) small intestine epithelial cells (SIEC), Gaba neurons, hepatocytes, gastric epithelial cells (GEC), astrocytes, cardiomyocytes (HCM), cardiac fibroblasts (HCF), dermal fibroblasts (HDF), and pulmonary fibroblasts (HPF). Each run of co-culture is presented and separated by a dashed line. The non-hematopoietic were pulsed with 100 ng/mL of HA-2^{+} peptide prior to the co-culture (Figure 14B).

Detailed Description of the Invention

The present invention is based, at least in part, on the discovery of binding proteins, including T cell receptors (TCRs), that recognize HA-2 antigen (*e.g.*, immunogenic peptide comprising the amino acid sequence YIGEVLVSV or YIGEVLVSM).

Accordingly, the present invention relates, in part, to the identified binding proteins (*e.g.,* TCRs), host cells expressing binding proteins (*e.g.,* TCRs), compositions comprising binding proteins (*e.g.,* TCRs) and host cells expressing binding proteins (*e.g.,* TCRs), methods of diagnosing, prognosing, and monitoring T cell response to cells expressing the HA-2 antigen, and methods for preventing and/or treating a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of the HA-2 antigen by administering host cells expressing binding proteins (*e.g.,* TCRs).

I. Definitions

For convenience, certain terms employed in the specification, examples, and appended claims are collected here.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.,* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "administering" means providing a pharmaceutical agent or composition to a subject, and includes, but is not limited to, administering by a medical professional and self-administering. This involves the physical introduction of a composition comprising a

therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. In some embodiments, routes of administration for binding proteins described herein include intravenous, intraperitoneal, intramuscular, subcutaneous, spinal or other parenteral routes of administration, for example by injection or infusion. The phrase "parenteral administration" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intraperitoneal, intramuscular, intraarterial, intrathecal, intralymphatic, intralesional, intracapsular, intraorbital, intracardiac, intradermal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection and infusion, as well as *in vivo* electroporation. Alternatively, a binding protein described herein may be administered via a non-parenteral route, such as a topical, epidermal or mucosal route of administration, for example, intranasally, orally, vaginally, rectally, sublingually or topically. Administering may also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

As used herein, the term "antigen" refers to any natural or synthetic immunogenic substance, such as a protein, peptide, or hapten. An antigen may be an HA-2antigen, or a fragment thereof, against which protective or therapeutic immune responses are desired.

The term "adjuvant" as used herein refers to substances, which when administered prior, together or after administration of an antigen accelerates, prolong and/or enhances the quality and/or strength of an immune response to the antigen in comparison to the administration of the antigen alone. Adjuvants can increase the magnitude and duration of the immune response induced by vaccination.

The term "antibody" as used to herein includes whole antibodies and any antigen binding fragments (*i.e.,* "antigen-binding portions") or single chains thereof. An "antibody" refers, in one embodiment, to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. In certain naturally occurring antibodies, the heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. In certain naturally occurring antibodies, each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The V_H and V_L regions may be

further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.,* effector cells) and the first component (Clq) of the classical complement system.

The term "antigen presenting cell" or "APC" includes professional antigen presenting cells (*e.g.,* B lymphocytes, monocytes, dendritic cells, Langerhans cells), as well as other antigen presenting cells (*e.g.,* keratinocytes, endothelial cells, astrocytes, fibroblasts, and oligodendrocytes).

The term "antigen-binding portion" of a binding protein, such as a TCR, as used herein, refers to one or more portions of a TCR that retain the ability to bind (*e.g.*, specifically and/or selectively) to an antigen (*e.g.,* an HA-2 antigen). Such portions are, for example, between about 8 and about 1500 amino acids in length, suitably between about 8 and about 745 amino acids in length, suitably about 8 to about 300, for example about 8 to about 200 amino acids, or about 10 to about 50 or 100 amino acids in length. It has been shown that the antigen-binding function of a TCR can be performed by fragments of a full-length TCR. Examples of binding portions **encompassed within the term "antigen**-binding **portion" of a TCR, include (i) a Fv fragment consisting of the** V_α and V_β domains of a TCR, (ii) an isolated complementarity determining region (CDR) or (iii) a combination of two or more isolated CDRs which may optionally be joined by a synthetic linker. Furthermore, although V_α and V_β, are coded by separate genes, they may be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_α and V_β regions pair to form monovalent molecules (known as single chain TCR (scTCR)). Such single chain TCRs are also intended to be encompassed within **the term "antigen-binding portion" of a TCR**. These TCR fragments can be obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are complete binding proteins. Antigen-binding portions may be produced by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact immunoglobulins.

The terms "complementarity determining region" and "CDR" are synonymous with "hypervariable region" or "HVR" and are known in the art to refer to non-contiguous sequences of amino acids within certain binding proteins, such as TCR variable regions, which confer antigen specificity and/or binding affinity. For TCRs, in general, there are three CDRs in each α-chain variable region (αCDR1, αCDR2, and αCDR3) and three CDRs in each β-chain variable region (βCDR1, βCDR2, and βCDR3). CDR3 is believed to be the main CDR responsible for recognizing processed antigen. CDR1 and CDR2 mainly interact with the MHC.

The term "body fluid" refers to fluids that are excreted or secreted from the body as well as fluids that are normally not excreted or secreted from the body (*e.g.,* amniotic fluid, aqueous humor, bile, blood and blood plasma, cerebrospinal fluid, cerumen and earwax, cowper's fluid or pre-ejaculatory fluid, chyle, chyme, stool, female ejaculate, interstitial fluid, intracellular fluid, lymph, menses, breast milk, mucus, pleural fluid, pus, saliva, sebum, semen, serum, sweat, synovial fluid, tears, urine, vaginal lubrication, vitreous humor, vomit). In some embodiments, the body fluid comprises immune cells, optionally wherein the immune cells are cytotoxic lymphocytes such as cytotoxic T cells and/or NK cells, CD4+ T cells, and the like.

The term "coding region" refers to regions of a nucleotide sequence comprising codons that are translated into amino acid residues, whereas the term "non-coding region" refers to regions of a nucleotide sequence that are not translated into amino acids (*e.g.,* 5' and 3' untranslated regions).

The term "complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is anti-parallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is anti-parallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. In some embodiments, the first region comprises a first portion and the second region comprises a second portion, whereby, when

the first and second portions are arranged in an antiparallel fashion, at least about 50%, and, in other embodiments, at least about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more, or any range in between, inclusive, such as at least about 80%-100%, of the nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion. In some embodiments, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

As used herein, the term "costimulate" with reference to activated immune cells includes the ability of a costimulatory molecule to provide a second, non-activating **receptor mediated signal (a "costimulatory signal") that induces proliferation or effector** function. For example, a costimulatory signal may result in cytokine secretion, *e.g.,* in a T cell that has received a T cell-receptor-mediated signal. Immune cells that have received a cell-receptor mediated signal, *e.g.,* via an activating receptor are referred to herein as **"activated immune cells."**

"CD3" is known in the art as a multi-protein complex of six chains (see, Abbas and Lichtman, Cellular and Molecular Immunology (9^{th} Edition) (2018); Janeway *et al.* (Immunobiology) (9^{th} Edition) (2016)). In mammals, the complex comprises a CD3γ chain, a CD3δ chain, two CD3ε chains, and a homodimer of CD3ζ chains. The CD3γ, CD3δ, and CD3ε chains are related cell surface proteins of the immunoglobulin superfamily containing a single immunoglobulin domain. The transmembrane regions of the CD3γ, CD3δ, and CD3ε chains are negatively charged, which is a characteristic that is believed to allow these chains to associate with positively charged regions or residues of T cell receptor chains. The intracellular tails of the CD3γ, CD3δ, and CD3ε chains each contain a single conserved motif known as an immunoreceptor tyrosine-based activation motif or IT AM, whereas each CD3ζ chain has three ITAMs. Without wishing to be bound by theory, it is believed that the IT AMs are important for the signaling capacity of a TCR complex. CD3 used in accordance with the present invention may be from various animal species, including human, mouse, rat, or other mammals.

A "component of a TCR complex," as used herein, refers to a TCR chain (i.e ., TCRα, TCRβ, TCRγ or TCRδ), a CD3 chain (*i.e.,* CD3γ, CD3δ, CD3ε or CD3ζ), or a complex formed by two or more TCR chains or CD3 chains (*e.g.,* a complex of TCRα and TCRβ, a complex of TCRγ and TCRδ, a complex of CD3ε and CD3δ, a complex of CD3γ and CD3ε, or a sub-TCR complex of TCRα, TCRβ, CD3γ, CD3δ, and two CD3ε chains).

The term "chimeric antigen receptor" or "CAR" refers to a fusion protein that is engineered to contain two or more amino acid sequences linked together in a way that does not occur naturally or does not occur naturally in a host cell, which fusion protein can function as a receptor when present on a surface of a cell. CARs encompassed by the present invention include an extracellular portion comprising an antigen-binding domain (*i.e.,* obtained or derived from an immunoglobulin or immunoglobulin-like molecule, such as a TCR specific for an HA-2 antigen, a single chain TCR-derived binding protein, an scFv derived from an antibody, an antigen binding domain derived or obtained from a killer immunoreceptor from an NK cell, and the like) linked to a transmembrane domain and one or more intracellular signaling domains (such as an effector domain, optionally containing co-stimulatory domain(s)) (see, *e.g.,* Sadelain *et al.* (2013) *Cancer Discov.* 3:388; see also Harris and Kranz (2016) *Trends Pharmacol. Sci.* 37: 220; Stone *et al.* (2014) *Cancer Immunol. Immunother.* 63:1163).

As used herein, the term "cytotoxic T lymphocyte (CTL) response" refers to an immune response induced by cytotoxic T cells. CTL responses are mediated primarily by $CD8^+$ T cells.

The term "consisting essentially of is not equivalent to "comprising" and refers to the specified materials or steps of a claim, or to those that do not materially affect the basic characteristics of a claimed subject matter. For example, a protein domain, region, or module (*e.g.,* a binding domain, hinge region, linker module) or a protein (which may have one or more domains, regions, or modules) "consists essentially of a particular amino acid sequence when the amino acid sequence of a domain, region, module, or protein includes extensions, deletions, mutations, or a combination thereof (*e.g.,* amino acids at the amino- or carboxy -terminus or between domains) that, in combination, contribute to at most 20% (*e.g.,* at most 15%, 10%, 8%, 6%, 5%, 4%, 3%, 2% or 1%) of the length of a domain, region, module, or protein and do not substantially affect (*i.e.,* do not reduce the activity by more than 50%, such as no more than 40%, 30%, 25%, 20%, 15%, 10%, 5%, or 1%) the activity of the domain(s), region(s), module(s), or protein (*e.g.,* the target binding affinity of a binding protein).

The term "determining a suitable treatment regimen for the subject" is taken to mean the determination of a treatment regimen (*i.e.,* a single therapy or a combination of different therapies that are used for the prevention and/or treatment of the viral infection in the subject) for a subject that is started, modified and/or ended based or essentially based or

at least partially based on the results of the analysis according to the present invention. One example is starting an adjuvant therapy after surgery whose purpose is to decrease the risk of recurrence, another would be to modify the dosage of a particular chemotherapy. The determination can, in addition to the results of the analysis according to the present invention, be based on personal characteristics of the subject to be treated. In most cases, the actual determination of the suitable treatment regimen for the subject will be performed by the attending physician or doctor.

As used herein, a "hematopoietic progenitor cell" is a cell that can be derived from hematopoietic stem cells or fetal tissue and is capable of further differentiation into mature cells types (*e.g.,* immune system cells). Exemplary hematopoietic progenitor cells include those with a $CD24^{Lo}$ Lin- $CD117^{+}$ phenotype or those found in the thymus (referred to as progenitor thymocytes).

"Homologous" as used herein, refers to nucleotide sequence similarity between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. In some embodiments, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and, in other embodiments, at least about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more, or any range in between, inclusive, such as at least about 80%-100%, of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. In some embodiments, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

As used herein, the term "HA-2 antigen" or "HA-2 peptide antigen" or "HA-2-containing peptide antigen" or "HA-2 epitope" or "HA-2 peptide epitope" or "HA-2 peptide" refers to a naturally or synthetically produced peptide portion of a member of the class I myosin family known as MYO1G (Pierce *et al.* (2001) *J. Immunol.* 167:3223-3230).

The gene is located on the short arm of chromosome 7 in humans and its expression is limited to cells of hematopoietic origin. MYO1G is a diallelic gene encoding two genetic variants, designated MYO1G(V) and MYO1G(M). MYO1G(V) encodes the YIGEVLVSV HA-2 epitope and MYO1G(M) encodes the YIGEVLVSM HA-2 epitope. The single amino acid change between the two peptides has only a modest effects on peptide binding to the class I MHC-restricted element HLA-A (*e.g.*, HLA-A*0201) and on recognition by T cells when added exogenously to target cells. However, the peptide encoded by MYO1G(M) is believed not to be presented at the surface of cells that endogenously express the MYO1G(M) allele. HA-2 antigen protein can range in length from about 7 amino acids, about 8 amino acids, about 9 amino acids, about 10 amino acids, up to about 20 amino acids, and can form a complex with a MHC (*e.g.*, HLA) molecule such that a binding protein of this disclosure specific for an HA-2 peptide:MHC (*e.g.*, HLA) complex can bind (*e.g.*, specifically and/or selectively) to such as complex. An exemplary HA-2 peptide antigen comprises a peptide having the amino acid YIGEVLVSV or YIGEVLVSM. In some embodiments, the YIGEVLVSV peptide sequence is referred to as "HA-2 REF" and the YIGEVLVSM peptide sequence is referred to as "HA-2 SNP".

The term "hyperproliferative disorder characterized by expression of an HA-2 antigen" can be any hyperproliferative disorder where the HA-2 antigen is present in a MHC (*e.g.*, HLA) complex expressed by at least some hyperproliferating cells in the subject. Examples of hyperproliferative disorders characterized by HA-2:HLA complexes include hematological malignancies. In certain embodiments, the hematological malignancy comprises a leukemia (*e.g.*, an acute leukemia or a chronic leukemia). In specific embodiments, the leukemia comprises acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), mixed phenotype acute leukemia (MPAL), chronic myeloid leukemia (CML), B cell prolymphocytic leukemia, hairy cell leukemia, or chronic lymphocytic leukemia (CLL). In certain embodiments, the hematological malignancy comprises a lymphoma. In certain embodiments, the lymphoma comprises Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), a central nervous system lymphoma, small lymphocytic lymphoma (SLL), CD37+ dendritic cell lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, extraosseous plasmacytoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated (MALT) lymphoid tissue, nodal marginal zone B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma,

precursor B-lymphoblastic lymphoma, immunoblastic large cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, Burkitt's lymphoma/leukemia, B-cell proliferations of uncertain malignant potential, lymphomatoid granulomatosis, and post-transplant lymphoproliferative disorder. In certain embodiments, the hematological malignancy comprises a myelodysplastic disorder (MDS), such as, for example, refractory cytopenia with unilineage dysplasia (refractory anemia, refractory neutropenia, and refractory thrombocytopenia), refractory anemia with ring sideroblasts (RARS), refractory anemia with ring sideroblasts - thrombocytosis (RARS-t), refractory cytopenia with multinieage dysplasia (RCMD), refractory cytopenia with multinieage dysplasia and ring sideroblasts (RCMD-RS), refractory anemia with excess blasts (RAEB), myelodysplasia unclassifiable, refractory cytopenia of childhood, MDS with isolated del(5q), and other well-known MDS subtypes (see, for example, 2016 World Health Organization MDS classification available on the World Wide Web at nbci.nlm.nih.gov/pmc/articles/PMC655460/). In certain embodiments, the hematological malignancy comprises a myeloproliferative neoplasms (MPN), such as for example, myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myelomonocytic leukemia, chronic myeloproliferative disease-unclassifiable, chronic neutrophilic leukemia, chronic eosinophilic leukemia and MPN-not otherwise specified. In further embodiments, the hematological malignancy comprises a myeloma.

The term "immune response" includes T cell mediated and/or B cell mediated immune responses. Exemplary immune responses include T cell responses, *e.g.,* cytokine production and cellular cytotoxicity. In addition, the term immune response includes immune responses that are indirectly effected by T cell activation, *e.g.,* antibody production (humoral responses) and activation of cytokine responsive cells, *e.g.,* macrophages.

An increased ability to stimulate an immune response or the immune system, can result from an enhanced agonist activity of T cell costimulatory receptors and/or an enhanced antagonist activity of inhibitory receptors. An increased ability to stimulate an immune response or the immune system may be reflected by a fold increase of the EC_{50} or maximal level of activity in an assay that measures an immune response, *e.g.,* an assay that measures changes in cytokine or chemokine release, cytolytic activity (determined directly on target cells or indirectly via detecting CD107a or granzymes) and proliferation. The ability to stimulate an immune response or the immune system activity may be enhanced by at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%,

140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 500%, or more.

The term "immunotherapeutic agent" may include any molecule, peptide, antibody or other agent which can stimulate a host immune system to generate an immune response to a viral infection in the subject. Various immunotherapeutic agents are useful in the compositions and methods described herein.

The term "immune cell" refers to any cell of the immune system that originates from a hematopoietic stem cell in the bone marrow, which gives rise to two major lineages: a myeloid progenitor cell (which give rise to myeloid cells such as monocytes, macrophages, dendritic cells, megakaryocytes and granulocytes); and a lymphoid progenitor cell (which give rise to lymphoid cells such as T cells, B cells and natural killer (NK) cells). Exemplary immune system cells include a $CD4^+$ T cell, a $CD8^+$ T cell, a CD4 CD8 double negative T cell, a gd T cell, a regulatory T cell, a natural killer cell, and a dendritic cell. Macrophages and dendritic cells may be referred to as "antigen presenting cells" or "APCs," which are specialized cells that can activate T cells when a major histocompatibility complex (MHC) receptor on the surface of the APC complexed with a peptide interacts with a TCR on the surface of a T cell.

An "isolated protein" refers to a protein that is substantially free of other proteins, cellular material, separation medium, and culture medium when isolated from cells or produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the binding protein, antibody, polypeptide, peptide or fusion protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of a biomarker polypeptide or fragment thereof, in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. In one embodiment, the language "substantially free of cellular material" includes preparations of a biomarker protein or fragment thereof, having less than about 30% (by dry weight) of non-biomarker protein (also referred to herein as a "contaminating protein"), or, in some embodiments, less than about 25%, 20%, 15%, 10%, 5%, 1%, or less, or any range in between inclusive, such as less than about 1% to 5%, of non-biomarker protein. When binding protein, antibody, polypeptide, peptide or fusion

protein or fragment thereof, *e.g.,* a biologically active fragment thereof, is recombinantly produced, it may be substantially free of culture medium, *i.e.,* culture medium represents less than about 20%, 15%, 10%, 5%, 1%, or less, or any range in between inclusive, such as less than about 1% to 5%, of the volume of the protein preparation.

As used herein, the term "isotype" refers to the antibody class (*e.g.,* IgM, IgG1, IgG2C, and the like) that is encoded by heavy chain constant region genes.

As used herein, the term "K_D" is intended to refer to the dissociation equilibrium constant of a particular binding protein-antigen interaction. The binding affinity of binding proteins encompassed by the present invention may be measured or determined by standard binding protein-target binding assays, for example, competitive assays, saturation assays, or standard immunoassays, such as ELISA or RIA. A relatively lower Kd value indicates a relatively higher binding affinity (*e.g.*, Kd values of less than or equal to about $5x10^{-4}$ M (500 uM) include a Kd value of $1x10^{-4}$ M (100 uM) and a 100 uM Kd indicates a relatively higher binding affinity as compared to a 500 uM Kd).

A "kit" is any manufacture (*e.g.,* a package or container) comprising at least one reagent, *e.g.,* a probe or small molecule, for specifically detecting and/or affecting the expression of a marker encompassed by the present invention. The kit may be promoted, distributed, or sold as a unit for performing the methods encompassed by the present invention. The kit may comprise one or more reagents necessary to express a composition useful in the methods encompassed by the present invention. In some embodiments, the kit may further comprise a reference standard, *e.g.,* a nucleic acid encoding a protein that does not affect or regulate signaling pathways controlling cell growth, division, migration, survival or apoptosis. One skilled in the art can envision many such control proteins, including, but not limited to, common molecular tags (*e.g.,* green fluorescent protein and beta-galactosidase), proteins not classified in any of pathway encompassing cell growth, division, migration, survival or apoptosis by GeneOntology reference, or ubiquitous housekeeping proteins. Reagents in the kit may be provided in individual containers or as mixtures of two or more reagents in a single container. In addition, instructional materials which describe the use of the compositions within the kit may be included.

As used herein, the term "linked" refers to the association of two or more molecules. The linkage may be covalent or non-covalent. The linkage also may be genetic (*i.e.,* recombinantly fused). Such linkages may be achieved using a wide variety of art recognized techniques, such as chemical conjugation and recombinant protein production.

A "linker," in some embodiments, may refer to an amino acid sequence that connects two proteins, polypeptides, peptides, domains, regions, or motifs and may provide a spacer function compatible with interaction of the two sub-binding domains so that the resulting polypeptide retains a specific binding affinity *(e.g.,* scTCR) to a target molecule or retains signaling activity *(e.g.,* TCR complex). In some embodiments, a linker is comprised of about two to about 35 amino acids, for instance, or about four to about 20 amino acids or about eight to about 15 amino acids or about 15 to about 25 amino acids.

"Major histocompatibility complex" (MHC) refers to glycoproteins that deliver peptide antigens to a cell surface. MHC class I molecules are heterodimers having a membrane spanning a chain (with three a domains) and a non-covalently associated b2 microglobulin. MHC class II molecules are composed of two transmembrane glycoproteins, a and b, both of which span the membrane. Each chain has two domains. MHC class I molecules deliver peptides originating in the cytosol to the cell surface, where a peptide antigen-MHC (pMHC) complex is recognized by $CD8^+$ T cells. MHC class II molecules deliver peptides originating in the vesicular system to the cell surface, where they are recognized by $CD4^+$ T cells. Human MHC is referred to as human leukocyte antigen (HLA).

The terms "prevent," "preventing," "prevention," "prophylactic treatment," and the like refer to reducing the probability of developing a disease, disorder, or condition in a subject, who does not have, but is at risk of or susceptible to developing a disease, disorder, or condition.

The term "prognosis" includes a prediction of the probable course and outcome of a viral infection or the likelihood of recovery from the disease. In some embodiments, the use of statistical algorithms provides a prognosis of a viral infection in an individual. For example, the prognosis may be surgery, development of a clinical subtype of a viral infection, development of one or more clinical factors, or recovery from the disease.

As used herein, "percent identity" between amino acid sequences is synonymous with "percent homology," which can be determined using the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified by Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. The noted algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches are performed with the NBLAST program, score=100, wordlength=12, to obtain nucleotide sequences homologous to a polynucleotide described

herein. BLAST protein searches are performed with the XBLAST program, score=50, wordlength=3, to obtain amino acid sequences homologous to a reference polypeptide. To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul *et al.* (1997) *Nuc. Acids Res.* 25:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.,* XBLAST and NBLAST) may be used.

The phrase "pharmaceutically-acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body.

The term "recombinant host cell" (or simply "host cell") refers to a cell that comprises a nucleic acid that is not naturally present in the cell, such as a cell into which a recombinant expression vector has been introduced. It should be understood that cells according to the present invention is intended to refer not only to the particular subject cell, but also encompasses progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term cell according to the present invention.

The term "cancer response," "response to immunotherapy," or "response to modulators of T-cell mediated cytotoxicity/immunotherapy combination therapy" relates to any response of the hyperproliferative disorder (*e.g.,* cancer) to a cancer agent, such as a modulator of T-cell mediated cytotoxicity, and an immunotherapy, preferably to a change in tumor mass and/or volume after initiation of neoadjuvant or adjuvant therapy. The term "neoadjuvant therapy" refers to a treatment given before the primary treatment. Examples of neoadjuvant therapy may include chemotherapy, radiation therapy, and hormone therapy. Hyperproliferative disorder response may be assessed, for example for efficacy or in a neoadjuvant or adjuvant situation, where the size of a tumor after systemic intervention may be compared to the initial size and dimensions as measured by CT, PET, mammogram, ultrasound or palpation. Responses may also be assessed by caliper measurement or pathological examination of the tumor after biopsy or surgical resection. Response may be recorded in a quantitative fashion like percentage change in tumor volume or in a qualitative fashion like "pathological complete response" (pCR), "clinical complete remission" (cCR), "clinical partial remission" (cPR), "clinical stable disease" (cSD),

"clinical progressive disease" (cPD) or other qualitative criteria. Assessment of hyperproliferative disorder response may be done early after the onset of neoadjuvant or adjuvant therapy, *e.g.,* after a few hours, days, weeks or preferably after a few months. A typical endpoint for response assessment is upon termination of neoadjuvant chemotherapy or upon surgical removal of residual tumor cells and/or the tumor bed. This is typically three months after initiation of neoadjuvant therapy. In some embodiments, clinical efficacy of the therapeutic treatments described herein may be determined by measuring the clinical benefit rate (CBR). The clinical benefit rate is measured by determining the sum of the percentage of patients who are in complete remission (CR), the number of patients who are in partial remission (PR) and the number of patients having stable disease (SD) at a time point at least 6 months out from the end of therapy. The shorthand for this formula is CBR=CR+PR+SD over 6 months. In some embodiments, the CBR for a particular cancer therapeutic regimen is at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, or more. Additional criteria for evaluating the response to cancer therapies are related to "survival," which includes all of the following: survival until mortality, also known as overall survival (wherein said mortality may be either irrespective of cause or tumor related); "recurrence-free survival" (wherein the term recurrence shall include both localized and distant recurrence); metastasis free survival; disease free survival (wherein the term disease shall include cancer and diseases associated therewith). The length of said survival may be calculated by reference to a defined start point (*e.g.,* time of diagnosis or start of treatment) and end point (*e.g.,* death, recurrence or metastasis). In addition, criteria for efficacy of treatment may be expanded to include response to chemotherapy, probability of survival, probability of metastasis within a given time period, and probability of tumor recurrence. For example, in order to determine appropriate threshold values, a particular cancer therapeutic regimen may be administered to a population of subjects and the outcome may be correlated to biomarker measurements that were determined prior to administration of any cancer therapy. The outcome measurement may be pathologic response to therapy given in the neoadjuvant setting. Alternatively, outcome measures, such as overall survival and disease-free survival may be monitored over a period of time for subjects following cancer therapy for which biomarker measurement values are known. In certain embodiments, the doses administered are standard doses known in the art for cancer therapeutic agents. The period of time for which subjects are monitored may vary. For example, subjects may be monitored for at least 2, 4,

6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 45, 50, 55, or 60 months. Biomarker measurement threshold values that correlate to outcome of a cancer therapy may be determined using well-known methods in the art, such as those described in the Examples section.

As indicated, the terms may also refer to an improved prognosis, for example, as reflected by an increased time to recurrence, which is the period to first recurrence censoring for second primary cancer as a first event or death without evidence of recurrence, or an increased overall survival, which is the period from treatment to death from any cause. To respond or to have a response means there is a beneficial endpoint attained when exposed to a stimulus. Alternatively, a negative or detrimental symptom is minimized, mitigated or attenuated on exposure to a stimulus. It will be appreciated that evaluating the likelihood that a tumor or subject will exhibit a favorable response is equivalent to evaluating the likelihood that the tumor or subject will not exhibit favorable response (*i.e.*, will exhibit a lack of response or be non-responsive).

The term "resistance" refers to an acquired or natural resistance of a cancer sample or a mammal to a cancer therapy (*i.e.*, being nonresponsive to or having reduced or limited response to the therapeutic treatment), such as having a reduced response to a therapeutic treatment by 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or more, such 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 15-fold, 20-fold or more, or any range in between, inclusive. The reduction in response may be measured by comparing with the same cancer sample or mammal before the resistance is acquired, or by comparing with a different cancer sample or a mammal that is known to have no resistance to the therapeutic treatment. A typical acquired resistance to chemotherapy is called "multidrug resistance." The multidrug resistance may be mediated by P-glycoprotein or may be mediated by other mechanisms, or it may occur when a mammal is infected with a multi-drug-resistant microorganism or a combination of microorganisms. The determination of resistance to a therapeutic treatment is routine in the art and within the skill of an ordinarily skilled clinician, for example, may be measured by cell proliferative assays and cell death assays as described herein as "sensitizing." In some embodiments, the term "reverses resistance" means that the use of a second agent in combination with a primary cancer therapy (*e.g.,* chemotherapeutic or radiation therapy) is able to produce a significant decrease in tumor volume at a level of statistical significance (*e.g.,* $p<0.05$) when compared to tumor volume of untreated tumor in the circumstance

where the primary cancer therapy (*e.g.,* chemotherapeutic or radiation therapy) alone is unable to produce a statistically significant decrease in tumor volume compared to tumor volume of untreated tumor. This generally applies to tumor volume measurements made at a time when the untreated tumor is growing logarithmically.

The term "sample" used for detecting or determining the absence, presence, or level of at least one biomarker is typically brain tissue, cerebrospinal fluid, whole blood, plasma, serum, saliva, urine, stool (*e.g.,* feces), tears, and any other bodily fluid (*e.g.,* as described above under the definition of "body fluids"), or a tissue sample (*e.g.,* biopsy) such as a small intestine, colon sample, or surgical resection tissue. In some embodiments, methods encompassed by the present invention further comprises obtaining the sample from the individual prior to detecting or determining the absence, presence, or level of at least one marker in the sample.

The term "sensitize" means to alter cancer cells or tumor cells in a way that allows for more effective treatment of the associated cancer with a cancer therapy (*e.g.,* anti-immune checkpoint, chemotherapeutic, and/or radiation therapy). In some embodiments, normal cells are not affected to an extent that causes the normal cells to be unduly injured by the therapies. An increased sensitivity or a reduced sensitivity to a therapeutic treatment is measured according to a known method in the art for the particular treatment and methods described herein below, including, but not limited to, cell proliferative assays (Tanigawa *et al.* (1982) *Cancer Res.* 42:2159-2164) and cell death assays (Weisenthal *et al.* (1984) *Cancer Res.* 94:161-173; Weisenthal *et al.* (1985) *Cancer Treat Rep.* 69:615-632; Weisenthal *et al.*, In: Kaspers G J L, Pieters R, Twentyman P R, Weisenthal L M, Veerman A J P, eds. Drug Resistance in Leukemia and Lymphoma. Langhorne, P A: Harwood Academic Publishers, 1993:415-432; Weisenthal (1994) *Contrib. Gynecol. Obstet.* 19:82-90). The sensitivity or resistance may also be measured in animal by measuring the tumor size reduction over a period of time, for example, 6 month for human and 4-6 weeks for mouse. A composition or a method sensitizes response to a therapeutic treatment if the increase in treatment sensitivity or the reduction in resistance is 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, or more, such 2-fold, 3-fold, 4-fold, 5-fold, 10-fold, 15-fold, 20-fold or more, or any range in between, inclusive, compared to treatment sensitivity or resistance in the absence of such composition or method. The determination of sensitivity or resistance to a therapeutic treatment is routine in the art and within the skill of an ordinarily skilled clinician. It is to

be understood that any method described herein for enhancing the efficacy of a cancer therapy may be equally applied to methods for sensitizing hyperproliferative or otherwise cancerous cells (*e.g.,* resistant cells) to the cancer therapy.

The term "small molecule" is a term of the art and includes molecules that are less than about 1000 molecular weight or less than about 500 molecular weight. In one embodiment, small molecules do not exclusively comprise peptide bonds. In another embodiment, small molecules are not oligomeric. Exemplary small molecule compounds which may be screened for activity include, but are not limited to, peptides, peptidomimetics, nucleic acids, carbohydrates, small organic molecules (*e.g.,* polyketides) (Cane *et al.* (1998) *Science* 282:63-68), and natural product extract libraries. In another embodiment, the compounds are small, organic non-peptidic compounds. In a further embodiment, a small molecule is not biosynthetic.

The term "specific binding" refers to binding protein binding to a predetermined antigen. Typically, the binding protein binds with an affinity (K_D) of approximately less than or equal to about $5x10^{-4}$ M, less than or equal to about $1x10^{-4}$ M, less than or equal to about $5x10^{-5}$ M, less than or equal to about $1x10^{-5}$ M, less than or equal to about $5x10^{-6}$ M, less than or equal to about $1x10^{-6}$ M, less than or equal to about $5x10^{-7}$ M, less than or equal to about $1x10^{-7}$ M, less than or equal to about $5x10^{-8}$ M, less than or equal to about $1x10^{-8}$ M, less than or equal to about $5x10^{-9}$ M, less than or equal to about $1x10^{-9}$ M, less than or equal to about $5x10^{-10}$ M, less than or equal to about $1x10^{-10}$ M, less than or equal to about $5x10^{-11}$ M, less than or equal to about $1x10^{-11}$ M, less than or equal to about $5x10^{-12}$ M, less than or equal to about $1x10^{-12}$ M, or even lower, or any range in between, inclusive, such as between about 1-50 micromolar, 1-100 micromolar, 0.1-500 micromolar, and the like,when determined by a binding assay, such as surface plasmon resonance (SPR) technology in a BIAcore™ assay instrument using an antigen of interest as the analyte and the binding protein as the ligand. In some embodiments, the binding protein binds to the predetermined antigen with an affinity that is at least 1.1-, 1.2-, 1.3-, 1.4-, 1.5-, 1.6-, 1.7-, 1.8-, 1.9-, 2.0-, 2.5-, 3.0-, 3.5-, 4.0-, 4.5-, 5.0-, 6.0-, 7.0-, 8.0-, 9.0-, or 10.0-fold or greater than its affinity for binding to a non-specific antigen (*e.g.,* BSA, casein) other than the predetermined antigen or a closely-related antigen. The phrases "a binding protein recognizing an antigen" and "a binding protein specific for an antigen" are used interchangeably herein with the term "a binding protein which binds specifically to an antigen." Selective binding is a relative term referring to the ability of a binding protein to discriminate the binding of

one antigen over another, such as a particular family member or antigen target over a related family member or antigen target. For example, analytical data provided in the Examples section demonstrate that binding proteins described herein specifically bind HA-2 immunogenic epitopes and/or selectively bind a number of related epitopes (*e.g.*, HA-2 immunogenic epitopes and closely related sequences) discriminating such targets from the vast majority of other possible epitopes available in the human genome.

The term "subject" refers to any healthy animal, mammal or human, or any animal, mammal or human afflicted with a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen. **The term "subject" is interchangeable with "patient."**

The term "survival" includes all of the following: survival until mortality, also known as overall survival (wherein said mortality may be either irrespective of cause or tumor related); "recurrence-free survival" (wherein the term recurrence shall include both localized and distant recurrence); metastasis free survival; disease free survival (wherein the term disease shall include cancer and diseases associated therewith). The length of said survival may be calculated by reference to a defined start point (*e.g.,* time of diagnosis or start of treatment) and end point (*e.g.,* death, recurrence or metastasis). In addition, criteria for efficacy of treatment may be expanded to include response to chemotherapy, probability of survival, probability of metastasis within a given time period, and probability of tumor recurrence.

The term "synergistic effect" refers to the combined effect of two or more agents (*e.g.,* an HA-2-related agent described herein and another therapy for treating a disorder characterized by HA-2 expression) that is greater than the sum of the separate effects of the cancer agents/therapies alone.

As used herein, the term "T cell-mediated response" refers to a response mediated by T cells, including effector T cells (*e.g.,* $CD8^+$ cells) and helper T cells (*e.g.,* $CD4^+$ cells). T cell mediated responses include, for example, T cell cytotoxicity and proliferation.

A "transcribed polynucleotide" or "nucleotide transcript" is a polynucleotide (*e.g.,* an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a biomarker nucleic acid and normal post-transcriptional processing (*e.g.,* splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

A "T cell" is an immune system cell that matures in the thymus and produces T cell receptors (TCRs). T cells may be naive (not exposed to antigen; increased expression of CD62L, CCR7, CD28, CD3, CD 127, and CD45RA, and decreased expression of CD45RO as compared to T_{CM}), memory T cells (T_M) (antigen-experienced and long-lived), and effector cells (antigen-experienced, cytotoxic). T_M may be further divided into subsets of central memory T cells (T_{CM}, increased expression of CD62L, CCR7, CD28, CD127, CD45RO, and CD95, and decreased expression of CD54RA as compared to naive T cells) and effector memory T cells (T_{EM}, decreased expression of CD62L, CCR7, CD28, CD45RA, and increased expression of CD127 as compared to naive T cells or T_{CM}). Effector T cells (T_E) refers to antigen-experienced CD8+ cytotoxic T lymphocytes that have decreased expression of CD62L ,CCR7, CD28, and are positive for granzyme and perforin as compared to T_{CM}. Other exemplary T cells include regulatory T cells, such as $CD4^+$ $CD25^+$ ($Foxp3^+$) regulatory T cells and Tregl7 cells, as well as Trl, Th3, $CD8^+CD28$, and Qa-1 restricted T cells.

Conventional T cells, also known as Tconv or Teffs, have effector functions (*e.g.,* cytokine secretion, cytotoxic activity, anti-self-recognition, and the like) to increase immune responses by virtue of their expression of one or more T cell receptors. Tcons or Teffs are generally defined as any T cell population that is not a Treg and include, for example, **naïve T cells, acti**vated T cells, memory T cells, resting Tcons, or Tcons that have differentiated toward, for example, the Th1 or Th2 lineages. In some embodiments, Teffs are a subset of non-Treg T cells. In some embodiments, Teffs are CD4+ Teffs or CD8+ Teffs, such as CD4+ helper T lymphocytes (*e.g.,* Th0, Th1, Tfh, or Th17) and CD8+ cytotoxic T lymphocytes. As described further herein, cytotoxic T cells are CD8+ T lymphocytes. **"Naïve Tcons" are $CD4^+$** T cells that have differentiated in bone marrow, and successfully underwent a positive and negative processes of central selection in a thymus, but have not yet been activated by exposure to an antigen. **Naïve Tcons are commonly** characterized by surface expression of L-selectin (CD62L), absence of activation markers such as CD25, CD44 or CD69, and absence of memory markers such as CD45RO. **Naïve** Tcons are therefore believed to be quiescent and non-dividing, requiring interleukin-7 (IL-7) and interleukin-15 (IL- 15) for homeostatic survival (see, at least WO 2010/101870). The presence and activity of such cells are undesired in the context of suppressing immune responses. Unlike Tregs, Tcons are not anergic and can proliferate in response to antigen-

based T cell receptor activation (Lechler *et al.* (2001) *Philos. Trans. R. Soc. Lond. Biol. Sci.* 356:625-637).

"T effector" ("T_{eff}" or "T_E") cells refers to T cells (*e.g.,* CD4+ and CD8+ T cells) with cytolytic activities as well as T helper (Th) cells, which secrete cytokines and activate and direct other immune cells, but does not include regulatory T cells (Treg cells).

"T cell receptor" or "TCR" refers to an immunoglobulin superfamily member (having a variable binding domain, a constant domain, a transmembrane region, and a short cytoplasmic tail; *see, e.g.,* Janeway *et al.* (1997*) Curr. Biol. Publ.* 4:33) that is capable of binding (*e.g.*, specifically and/or selectively) to an antigen peptide bound to a MHC receptor. A TCR can be found on the surface of a cell or in soluble form and generally is comprised of a heterodimer having alpha and beta chains (also known as TCRα and TCRβ, respectively), or γ and δ chains (also known as TCRγ and TCRδ, respectively). Like immunoglobulins (*e.g.,* antibodies), the extracellular portion of TCR chains (*e.g.,* α-chain and β-chain) contain two immunoglobulin domains: a variable domain (*e.g.,* α-chain variable domain or V_α and β-chain variable domain or V_β; typically amino acids 1 to 116 based on Kabat numbering (Kabat *et al.* (1991) "Sequences of Proteins of lmmunological Interest, US Dept. Health and Human Services, Public Health Service National Institutes of Health, 5th ed.) at the N-terminal end, and one constant domain (*e.g.,* α-chain constant domain or C_α, typically amino acids 117 to 259 based on Kabat, β-chain constant domain or C_β, typically amino acids 117 to 295 based on Kabat) at the C-terminal end and adjacent to the cell membrane. Also like immunoglobulins, the variable domains contain complementary determining regions ("CDRs", also called hypervariable regions or "HVRs") separated by framework regions ("FRs") *(see, e.g.,* Fores *et al.* (1990) *Proc. Natl. Acad Sci. US.A.* 87:9138; Chothia *et al.* (1988) *EMBO J.* 7:3745; Lefranc *et al.* (2003) *Dev. Comp. Immunol.* 27:55). In some embodiments, a TCR is found on the surface of a T cell (or T lymphocyte) and associates with the CD3 complex. The source of a TCR encompassed by the present invention may be from various animal species, such as a human, mouse, rat, rabbit or other mammal.

The term "T cell receptor" or "TCR" should be understood to encompass full TCRs as well as antigen-binding portions or antigen-binding fragments thereof. In some embodiments, the TCR is an intact or full-length TCR, including TCRs in the αβ form or γδ form. In some embodiments, the TCR is an antigen-binding portion that is less than a full-length TCR but that binds to a specific peptide bound in an MHC molecule, such as binds

to an MHC-peptide complex. In some cases, an antigen-binding portion or fragment of a TCR may contain only a portion of the structural domains of a full-length or intact TCR, but yet is able to bind the peptide epitope, such as MHC-peptide complex, to which the full TCR binds. In some cases, an antigen-binding portion contains the variable domains of a TCR, such as variable α chain and variable β chain of a TCR, sufficient to form a binding site for binding to a specific MHC-peptide complex. Generally, the variable chains of a TCR contain complementarity determining regions (CDRs) involved in recognition of the peptide, MHC and/or MHC-peptide complex.

Nomenclature established by the International Immunogenetics Information System (IMGT) (see also Scaviner and Lefranc (2000) *Exp. Clin. Immunogenet.* 17:83-96 and 97-106; Folch and Lefranc (2000) *Exp. Clin. Immunogenet,* 17:107-114; T Cell Receptor Factsbook", (2001) LeFranc and LeFranc, Academic Press, ISBN 0-12-441352-8). The IMGT provides unique sequences used to describe a TCR, and sequences described herein may be identified by reference to such unique sequences provided herein. TCR sequences are publicly available at the IMGT database at imgt.org.

As described above, native alpha/beta heterodimeric TCRs have an alpha chain and a beta chain. Broadly, each chain comprises variable, joining and constant regions, and the beta chain also usually contains a short diversity region between the variable and joining regions, but this diversity region is often considered as part of the joining region. Each variable region comprises three hypervariable CDRs (Complementarity Determining Regions) embedded in a framework sequence. CDR3 is well-known to be the main mediator of antigen recognition. There are several types of alpha chain variable (Vα) regions and several types of beta chain variable (Vβ) regions distinguished by their framework, CDR1 and CDR2 sequences, and by a partly defined CDR3 sequence. The Vα types are referred to in IMGT nomenclature by a unique TRAV number. For example, "TRAV4" defines a TCR Vα region having unique framework and CDR1 and CDR2 sequences, and a CDR3 sequence which is partly defined by an amino acid sequence which is preserved from TCR to TCR but which also includes an amino acid sequence which varies from TCR to TCR. Similarly, "TRBV2" defines a TCR Vβ region having unique framework and CDR1 and CDR2 sequences, but with only a partly defined CDR3 sequence. It is known that there are 54 alpha variable genes, of which 44 are functional, and 67 beta variable genes, of which 42 are functional, within the alpha and beta loci, respectively.

The joining regions of the TCR are similarly defined by the unique IMGT TRAJ and TRBJ nomenclature, and the constant regions by the IMGT TRAC and TRBC nomenclature. The beta chain diversity region is referred to in IMGT nomenclature by the abbreviation TRBD, and, as mentioned, the concatenated TRBD/TRBJ regions are often considered together as the joining region.

The gene pools that encode the TCR alpha and beta chains are located on different chromosomes and contain separate V, (D), J and C gene segments, which are brought together by rearrangement during T cell development. This leads to a very high diversity of T cell alpha and beta chains due to the large number of potential recombination events that occur between the 54 TCR alpha variable genes and 61 alpha J genes or between the 67 beta variable genes, two beta D genes and 13 beta J genes. The recombination process is not precise and introduces further diversity within the CDR3 region. Each alpha and beta variable gene may also comprise allelic variants, designated in IMGT nomenclature as TRAVxx*01 and *02, or TRBVx-x*01 and *02 respectively, thus further increasing the amount of variation. In the same way, some of the TRBJ sequences have two known variations. (Note that the absence of a "*" qualifier means that only one allele is known for the relevant sequence). The natural repertoire of human TCRs resulting from recombination and thymic selection has been estimated to comprise approximately 10^6 unique beta chain sequences, determined from CDR3 diversity (Arstila *et al.* (1999) *Science* 286:958-961) and could be even higher (Robins *et al.* (2009) *Blood* 114:4099-4107). Each beta chain is estimated to pair with at least 25 different alpha chains, thus generating further diversity (Arstila *et al.* (1999) Science 286:958-961).

The term "TCR alpha variable domain" therefore refers to the concatenation of TRAV and TRAJ regions; a TRAV region only; or TRAV and a partial TRAJ region, and the term TCR alpha constant domain refers to the extracellular TRAC region, or to a C-terminal truncated or full length TRAC sequence. Likewise the term "TCR beta variable domain" refers to the concatenation of TRBV and TRBD/TRBJ regions; to the TRBV and TRBD regions only; to the TRBV and TRBJ regions only; or to the TRBV and partial TRBD and/or TRBJ regions, and the term TCR beta constant domain refers to the extracellular TRBC region, or to a C-terminal truncated or full length TRBC sequence. These TCR alpha variable domain and TCR beta variable domain nomenclature similarly applies to the variable domains of TCR gamma and TCR delta chains, respectively, for

gamma/delta TCRs. An ordinarily skilled artisan can obtain TRAV, TRAJ, TRAC, TRBV, TRBJ, and TRBC gene sequences, such as through the publicly available IMGT database.

The term "TCR complex" refers to a complex formed by the association of CD3 with TCR. For example, a TCR complex may be composed of a CD3γ chain, a CD3δ chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRα chain, and a TCRβ chain. Alternatively, a TCR complex may be composed of a CD3γ chain, a CD3δ chain, two CD3ε chains, a homodimer of CD3ζ chains, a TCRγ chain, and a TCRδ chain.

The term "therapeutic effect" refers to a local or systemic effect in animals, particularly mammals, and more particularly humans, caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and conditions in an animal or human.

The terms "therapeutically effective amount" and "effective amount" means that amount of a substance that produces some desired effect, such as a desired local or systemic therapeutic effect, in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any treatment. In some embodiments, a therapeutically effective amount of a substance will depend on the substance's therapeutic index, solubility, pharmacokinetics, half-life, and the like. Toxicity and therapeutic efficacy of subject compounds may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.,* for determining the LD_{50} and the ED_{50}. In some embodiments, compositions that exhibit large therapeutic indices are used. In some embodiments, the LD_{50} (lethal dosage) may be measured and may be, for example, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more reduced for the agent relative to no administration of the agent. Similarly, the ED_{50} (*i.e.,* the concentration which achieves a half-maximal inhibition of symptoms) may be measured and may be, for example, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more increased for the agent relative to no administration of the agent. Also, similarly, the IC_{50} may be measured and may be, for example, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900%, 1000% or more increased for the agent relative to no administration of the agent. In some embodiments, T cell immune response in an assay may be increased by at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%,

85%, 90%, 95%, or even 100%. In another embodiment, at least about a 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or even 100% decrease in a viral load may be achieved.

The term "treat" refers to the therapeutic management or improvement of a condition (*e.g.,* a disease or disorder) of interest. Treatment may include, but is not limited to, administering an agent or composition (*e.g.,* a pharmaceutical composition) to a subject. Treatment is typically undertaken in an effort to alter the course of a disease (which term is used to indicate any disease, disorder, syndrome or undesirable condition warranting or potentially warranting therapy) in a manner beneficial to the subject. The effect of treatment may include reversing, alleviating, reducing severity of, delaying the onset of, curing, inhibiting the progression of, and/or reducing the likelihood of occurrence or recurrence of the disease or one or more symptoms or manifestations of the disease. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. A therapeutic agent may be administered to a subject who has a disease or is at increased risk of developing a disease relative to a member of the general population. In some embodiments, a therapeutic agent may be administered to a subject who has had a disease but no longer shows evidence of the disease. The agent may be administered *e.g.,* to reduce the likelihood of recurrence of evident disease. A therapeutic agent may be administered prophylactically, *i.e.*, before development of any symptom or manifestation of a disease. "Prophylactic treatment" refers to providing medical and/or surgical management to a subject who has not developed a disease or does not show evidence of a disease in order, *e.g.,* to reduce the likelihood that the disease will occur or to reduce the severity of the disease should it occur. The subject may have been identified as being at risk of developing the disease (*e.g.,* at increased risk relative to the general population or as having a risk factor that increases the likelihood of developing the disease.

The term "unresponsiveness" includes refractivity of cancer cells to therapy or refractivity of therapeutic cells, such as immune cells, to stimulation, *e.g.,* stimulation via an activating receptor or a cytokine. Unresponsiveness may occur, *e.g.,* because of exposure to immunosuppressants or exposure to high doses of antigen. As used herein, the term "anergy" or "tolerance" includes refractivity to activating receptor-mediated

stimulation. Such refractivity is generally antigen-specific and persists after exposure to the tolerizing antigen has ceased. For example, anergy in T cells (as opposed to unresponsiveness) is characterized by lack of cytokine production, *e.g.,* IL-2. T cell anergy occurs when T cells are exposed to antigen and receive a first signal (a T cell receptor or CD-3 mediated signal) in the absence of a second signal (a costimulatory signal). Under these conditions, reexposure of the cells to the same antigen (even if reexposure occurs in the presence of a costimulatory polypeptide) results in failure to produce cytokines and, thus, failure to proliferate. Anergic T cells may, however, proliferate if cultured with cytokines (*e.g.,* IL-2). For example, T cell anergy may also be observed by the lack of IL-2 production by T lymphocytes as measured by ELISA or by a proliferation assay using an indicator cell line. Alternatively, a reporter gene construct may be used. For example, anergic T cells fail to initiate IL-2 gene transcription induced by a heterologous promoter under the control of the 5' IL-2 gene enhancer or by a multimer of the AP1 sequence that may be found within the enhancer (Kang *et al.* (1992) *Science* 257:1134).

The term "variable region" or "variable domain" refers to the domain of an immunoglobulin superfamily binding protein (*e.g.,* a TCR α-chain or β-chain (or γ chain and δ chain for γδ TCRs)) that is involved in binding of the immunoglobulin superfamily binding protein (*e.g.,* TCR) to antigen. The variable domains of the α-chain and β-chain (V_α and V_β, respectively) of a native TCR generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three CDRs. The V_α domain is encoded by two separate DNA segments, the variable gene segment and the joining gene segment (V-J); the V_β domain is encoded by three separate DNA segments, the variable gene segment, the diversity gene segment, and the joining gene segment (V-D-J). A single V_α or V_β domain may be sufficient to confer antigen-binding specificity. Furthermore, TCRs that bind a particular antigen may be isolated using a V_α or V_β domain from a TCR that binds the antigen to screen a library of complementary V_α or V_β domains, respectively.

The term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. In some embodiments, a vector is an episome, *i.e.,* a nucleic acid capable of extra-chromosomal replication. In some embodiments, vectors are those capable of autonomous replication and/or expression of nucleic acids to which they are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors". In general, expression

vectors of utility in recombinant DNA techniques are often in the form of "plasmids" which refer generally to circular double stranded DNA loops, which, in their vector form are not bound to the chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, as will be appreciated by those skilled in the art, the present invention is intended to include such other forms of expression vectors that serve equivalent functions and which become subsequently known in the art.

There is a known and definite correspondence between the amino acid sequence of a particular protein and the nucleotide sequences that can code for the protein, as defined by the genetic code (shown below). Likewise, there is a known and definite correspondence between the nucleotide sequence of a particular nucleic acid and the amino acid sequence encoded by that nucleic acid, as defined by the genetic code.

GENETIC CODE

Alanine (Ala, A)	GCA, GCC, GCG, GCT
Arginine (Arg, R)	AGA, ACG, CGA, CGC, CGG, CGT
Asparagine (Asn, N)	AAC, AAT
Aspartic acid (Asp, D)	GAC, GAT
Cysteine (Cys, C)	TGC, TGT
Glutamic acid (Glu, E)	GAA, GAG
Glutamine (Gln, Q)	CAA, CAG
Glycine (Gly, G)	GGA, GGC, GGG, GGT
Histidine (His, H)	CAC, CAT
Isoleucine (Ile, I)	ATA, ATC, ATT
Leucine (Leu, L)	CTA, CTC, CTG, CTT, TTA, TTG
Lysine (Lys, K)	AAA, AAG
Methionine (Met, M)	ATG
Phenylalanine (Phe, F)	TTC, TTT
Proline (Pro, P)	CCA, CCC, CCG, CCT
Serine (Ser, S)	AGC, AGT, TCA, TCC, TCG, TCT
Threonine (Thr, T)	ACA, ACC, ACG, ACT
Tryptophan (Trp, W)	TGG
Tyrosine (Tyr, Y)	TAC, TAT
Valine (Val, V)	GTA, GTC, GTG, GTT

Termination signal (end) TAA, TAG, TGA

An important and well-known feature of the genetic code is its redundancy, whereby, for most of the amino acids used to make proteins, more than one coding nucleotide triplet may be employed (illustrated above). Therefore, a number of different nucleotide sequences may code for a given amino acid sequence. Such nucleotide sequences are considered functionally equivalent since they result in the production of the same amino acid sequence in all organisms (although certain organisms may translate some sequences more efficiently than they do others). Moreover, occasionally, a methylated variant of a purine or pyrimidine may be found in a given nucleotide sequence. Such methylations do not affect the coding relationship between the trinucleotide codon and the corresponding amino acid.

In view of the foregoing, the nucleotide sequence of a DNA or RNA encoding a biomarker nucleic acid (or any portion thereof) may be used to derive the polypeptide amino acid sequence, using the genetic code to translate the DNA or RNA into an amino acid sequence. Likewise, for polypeptide amino acid sequence, corresponding nucleotide sequences that can encode the polypeptide can be deduced from the genetic code (which, because of its redundancy, will produce multiple nucleic acid sequences for any given amino acid sequence). Thus, description and/or disclosure herein of a nucleotide sequence which encodes a polypeptide should be considered to also include description and/or disclosure of the amino acid sequence encoded by the nucleotide sequence. Similarly, description and/or disclosure of a polypeptide amino acid sequence herein should be considered to also include description and/or disclosure of all possible nucleotide sequences that can encode the amino acid sequence.

II. Binding Proteins

In an aspect encompassed by the present invention, provided herein are binding proteins that bind (*e.g.*, specifically and/or selectively) to a peptide-MHC (pMHC) complex (*e.g.*, MHC complex that stably presents a peptide) comprising an HA-2 immunogenic peptide in the context of an MHC molecule (*e.g.,* a MHC class I molecule). In some embodiments, the binding protein is capable of binding (*e.g.*, specifically and/or selectively) to an HA-2 peptide-MHC (pMHC) complex with a K_d less than or equal to about $5x10^{-4}$ M, less than or equal to about $1x10^{-4}$ M, less than or equal to about $5x10^{-5}$ M, less than or equal to about $1x10^{-5}$ M, less than or equal to about $5x10^{-6}$ M, less than or equal

to about $1x10^{-6}$ M, less than or equal to about $5x10^{-7}$ M, less than or equal to about $1x10^{-7}$ M, less than or equal to about $5x10^{-8}$ M, less than or equal to about $1x10^{-8}$ M, less than or equal to about $5x10^{-9}$ M, less than or equal to about $1x10^{-9}$ M, less than or equal to about $5x10^{-10}$ M, less than or equal to about $1x10^{-10}$ M, less than or equal to about $5x10^{-11}$ M, less than or equal to about $1x10^{-11}$ M, less than or equal to about $5x10^{-12}$ M, less than or equal to about $1x10^{-12}$ M, or any range in between, inclusive, such as between about 1-50 micromolar, 1-100 micromolar, 0.1-500 micromolar, and the like. In some embodiments, the MHC molecule comprises an MHC alpha chain that is an HLA serotype HLA-A*02. In some embodiments, the HLA allele is selected from the group consisting of HLA-A*0201, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele. In a specific embodiment, the HLA allele is HLA-A*0201. In some embodiments, the binding proteins provided herein are genetically engineered, isolated, and/or purified.

In some embodiments, the binding proteins have a higher binding affinity to the HA-2 peptide-MHC (pMHC) than does a known T-cell receptor (*e.g.*, a TCR from van Loenen *et al.* (2010) *Proc. Natl. Acad. Sci. U.S.A.* 107:10972-10977 or others described herein). For example, the binding proteins may have at least 1.2 fold, 1.5 fold, 1.8 fold, 2.0 fold, 2.2 fold, 2.5 fold, 2.8 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 5.5 fold, 6 fold, 6.5 fold, 7 fold, 7.5 fold, 8 fold, 8.5 fold, 9 fold, 9.5 fold, 10 fold, 11 fold, 12 fold, 13 fold, 14 fold, 15 fold, 16 fold, 17 fold, 18 fold, 19 fold, 20 fold, 25 fold, 30 fold, 35 fold, 40 fold, 45 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 1000 fold, 5000 fold, 10000 fold, 50000 fold, 100000 fold, 500000 fold, 1000000 fold, or more, or any range in between, inclusive, such as 1.2 fold to 2 fold, higher binding affinity to the HA-2 peptide-MHC (pMHC) than does a known T-cell receptor.

In some embodiments, the binding protein induces higher T cell expansion, cytokine release, and/or cytotoxic killing than does a known T-cell receptor when contacted with target cells with expression of HA-2 at a certain level or below (*e.g.*, see Table 4 for representative cell lines expressing HA-2 at varying levels). For example, in some embodiments of any aspect described herein, HA-2 level can be expressed in terms of transcripts per million and may be, for example, less than or equal to about 1,000 transcript per million transcripts (TPM), 950 TPM, 900 TPM, 850 TPM, 800 TPM, 750 TPM, 700 TPM, 650 TPM, 600 TPM, 550 TPM, 500 TPM, 450 TPM, 400 TPM, 350 TPM, 300 TPM, 250 TPM, 200 TPM, 150 TPM, 100 TPM, 95 TPM, 90 TPM, 85 TPM, 80 TPM, 75 TPM, 70 TPM, 65 TPM, 60 TPM, 55 TPM, 50 TPM, 45 TPM, 40 TPM, 35 TPM, 34 TPM, 33

TPM, 32 TPM, 31 TPM, 30 TPM, 29 TPM, 28 TPM, 27 TPM, 26 TPM, 25 TPM, 24 TPM, 23 TPM, 22 TPM, 21 TPM, 20 TPM, 19 TPM, 18 TPM, 17 TPM, 16 TPM, 15 TPM, 14 TPM, 13 TPM, 12 TPM, 11 TPM, 10 TPM, 9 TPM, 8 TPM, 7 TPM, 6 TPM, 5 TPM, 4 TPM, 3 TPM, 2 TPM, and 1 TPM, or any range in between, inclusive, such as less than or equal to about 1,000 TPM to less than or equal to about 16 TPM). In some embodiments, the low HA-2 expression level is termed "heterozygous expression" meaning between about 1 TPM and about 35 TPM, or any range in between, inclusive, such as 32 TPM or 1-32 TPM. A higher expression is 36 TPM and higher. As described further herein, TPM is measured according to well-known techniques, such as RNA-Seq, and gene expression TPM data are well known in the art for a variety of cell lines, tissue types, and the like (see, for example, the Broad Institute Cancer Cell Line Encyclopedia (CCLE) on the World Wide Web at portals.broadinstitute.org). In some embodiment, the binding protein induces at least 1.2 fold, 1.5 fold, 1.8 fold, 2.0 fold, 2.2 fold, 2.5 fold, 2.8 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 5.5 fold, 6 fold, 6.5 fold, 7 fold, 7.5 fold, 8 fold, 8.5 fold, 9 fold, 9.5 fold, 10 fold, 11 fold, 12 fold, 13 fold, 14 fold, 15 fold, 16 fold, 17 fold, 18 fold, 19 fold, 20 fold, 25 fold, 30 fold, 35 fold, 40 fold, 45 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 1000 fold, or more, or any range in between, inclusive, such as 1.2 fold to 2 fold, increase in T cell expansion, cytokine release, and/or cytotoxic killing than does a known T-cell receptor when contacted with target cells with heterozygous expression of HA-2.

In some embodiments, the expression of HA-2 is detected using RNA-sequencing (RNA-seq). RNA-seq generally comprises the following steps: obtaining a sample containing genetic material, isolating total RNA from the sample obtained, preparing an amplified cDNA library from the total RNA, sequencing the amplified cDNA library, and analyzing and profiling the amplified cDNA to assess the expression level of different transcripts. The sample can be a population of cells, a tissue sample, a bioposy sample, a cell culture, or a single cell. Total RNA can be isolated from the biological sample using any method known in the art. In certain embodiments, total RNA is extracted from plasma. Plasma RNA **extraction is described in Enders et al., "The Concentration of Circulating** Corticotropin-Releasing Homer m**RNA in Material Plasma Is Inclined in Preclampsia,"** Clinr. As described therein, the plasma collected after the centrifugation step is mixed with Trizol LS reagent (Invitrogen) and chloroform. The mixture is centrifuged and the aqueous layer is transferred to a new tube. Ethanol is added to this aqueous layer. The mixture is

then placed in an RNeasy mini column (Qiagen) and processed according to the manufacturer's recommendations.

In some embodiments, RNA-seq described herein includes the step of preparing amplified cDNA from total RNA. For example, cDNA is prepared and the isolated RNA sample is randomly amplified without dilution, or the mixture of genetic material in the isolated RNA is dispersed into individual reaction samples. In certain embodiments, amplification is initiated randomly at the 3 'end and throughout the entire transcriptome in the sample to amplify both mRNA and non-polyadenylated transcripts. In this way, double-stranded cDNA amplification products are optimized for the generation of sequencing libraries for next generation sequencing platforms. A kit suitable for amplification of cDNA by the method encompassedy by the present invention includes, for example, Ovation® RNA-Seq System.

In some embodiments, RNA-seq described herein includes the step of sequencing the amplified cDNA. Any known sequencing method can be used to sequence the amplified cDNA mixture including the single molecule sequencing method. In certain embodiments, the amplified cDNA is sequenced by whole transcriptome shotgun sequencing. Whole transcriptome shotgun sequencing can be performed using various next generation sequencing platforms such as Illumina® Genome Analyzer platform, ABI SOLiD™ Sequencing platform, or Life Science's 454 Sequencing platform.

In some embodiments, RNA-seq described herein further comprises performing digital counting and analysis on the cDNA. The number of amplified sequences for each transcript in the amplified sample can be quantified by sequence reading (one reading per amplified strand). In some embodiments, transcript per million (TPM) is used to quantify the expression level of a particular transcript. TPM may be calculated as shown in Wagner *et al.* (2012) *Theory in Biosciences* 131:281-285, the content of which is incorporated by reference herein in its entirety.

In some embodiments, the binding proteins provided herein include (*e.g.,* comprise, consist essentially of, or consist of): a) a TCR alpha chain sequence with at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR alpha chain sequence selected from the group consisting of the TCR alpha sequences listed in Table 1; and/or b) a TCR beta chain sequence with at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR

beta chain sequence selected from the group consisting of the TCR beta chain sequences listed in Table 1.

In some embodiments, the binding proteins provided herein include (*e.g.,* comprise, consist essentially of, or consist of): a) a TCR alpha chain sequence selected from the group consisting of the TCR alpha chain sequences listed in Table 1; and/or b) a TCR beta chain sequence selected from the group consisting of the TCR beta chain sequences listed in Table 1.

In some embodiments, the binding proteins provided herein include (*e.g.,* comprise, consist essentially of, or consist of): a) a TCR alpha chain variable (V_α) domain sequence with at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR alpha chain variable (V_α) domain sequence selected from the group consisting of the TCR V_α domain sequences listed in Table 1; and/or b) a TCR beta chain variable (V_β) domain sequence with at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR beta chain variable (V_β) domain sequence selected from the group consisting of the TCR V_β domain sequences listed in Table 1.

In some embodiments, the binding proteins provided herein include (*e.g.,* comprise, consist essentially of, or consist of): a) a TCR alpha chain variable (V_α) domain sequence selected from the group consisting of the TCR V_α domain sequences listed in Table 1; and/or b) a TCR beta chain variable (V_β) domain sequence selected from the group consisting of the TCR V_β domain sequences listed in Table 1.

In some embodiments, the binding proteins provided herein include (*e.g.,* comprise, consist essentially of, or consist of at least one (*e.g.,* one, two or three, such as CDR3 alone or in combination with a CDR1 and CDR2)) TCR alpha chain complementarity determining region (CDR) sequence with at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR alpha chain CDR sequence selected from the group consisting of the TCR alpha chain CDR sequences listed in Table 1. CDR3 is believed to be the main CDR responsible for recognizing processed antigen and CDR1 and CDR2 mainly interact with the MHC, so, in some embodiments, binding protein comprising a CDR3 alone from a TCR alpha chain and/or a CDR3 alone from a TCR beta chain listed in Table 1, each CDR3 having a sequence homology as recited in this paragraph, are provided.

In some embodiments, the binding proteins provided herein may also include (*e.g.,* comprise, consist essentially of, or consist of at least one (*e.g.,* one, two or three, such as CDR3 alone or in combination with a CDR1 and CDR2)) TCR beta chain complementarity determining region (CDR) sequence with at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR beta chain CDR sequence selected from the group consisting of the TCR beta chain CDR sequences listed in Table 1. As described above, CDR3 is believed to be the main CDR responsible for recognizing processed antigen and CDR1 and CDR2 mainly interact with the MHC, so, in some embodiments, binding protein comprising a CDR3 alone from a TCR beta chain and/or a CDR3 alone from a TCR alpha chain listed in Table 1, each CDR3 having a sequence homology as recited in this paragraph, are provided.

In some embodiments, the binding proteins provided herein include (*e.g.,* comprise, consist essentially of, or consist of at least one (*e.g.,* one, two or three)) TCR alpha chain complementarity determining region (CDR) listed in Table 1.

In some embodiments, the binding proteins provided herein may also include (*e.g.,* comprise, consist essentially of, or consist of at least one (*e.g.,* one, two or three)) TCR beta chain complementarity determining region (CDR) listed in Table 1.

In some embodiments, the binding proteins provided herein include (*e.g.,* comprise, consist essentially of, or consist of) a TCR alpha chain constant region (C_α) sequence with at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR $C\alpha$ sequence listed in Table 1.

In some embodiments, the binding proteins provided herein may also include (*e.g.,* comprise, consist essentially of, or consist of) a TCR beta chain constant region (C_β) sequence with at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR C_β sequence listed in Table 1.

In some embodiments, the binding proteins provided herein include (*e.g.,* comprise, consist essentially of, or consist of) a TCR alpha chain constant region (C_α) sequence selected from the group consisting of the TCR $C\alpha$ sequences listed in Table 1.

In some embodiments, the binding proteins provided herein may also include (*e.g.,* comprise, consist essentially of, or consist of) a TCR beta chain constant region (C_β) sequence selected from the group consisting of the TCR C_β sequences listed in Table 1.

In some embodiments, the binding proteins provided herein comprise a constant region that is chimeric, humanized, human, primate, or rodent (*e.g.*, rat or mouse). For example, a human variable region may be chimerized with a murine constant region or a murine variable region may be humanized with a human constant region and/or human framework regions. In some embodiments, the constant regions may be mutated to modify functionality (*e.g.*, introduction of non-naturally occurring cysteine substitutions in opposing residue locations in TCR alpha and beta chains to provide disulfide bonds useful for increasing affinity between the TCR alpha and beta chains). Similarly, mutations may be made in the transmembrane domain of the constant region to modify functionality (*e.g.*, increase hydrophobicity by introducing a non-naturally occurring substitution of a residue with a hydrophobic amino acid). In some embodiments, mutations may be made to the constant region to increase cell surface expression.

Table 1

HA2-MJ1-DP1 wild type sequence:

Alpha chain:
TRAV34/TRAJ42/TRAC
METVLQVLLGILGFQAAWVSSQELEQSPQSLIVQEGKNLTINCTSS**KTLYG**LYWYK
QKYGEGLIFLMM**LQKGGEE**KSHEKITAKLDEKKQQSSLHITASQPRHAGIYL**CGA**
RKKNYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitd
ktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnll
mtlrlws

Beta chain:
TRBV7-8/TRBJ1-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSSGPTSPQHFGDGTRLSILEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngke
vhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgfts
vsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ1-DP1 MGTM sequence:

Alpha chain:
TRAV34/TRAJ42/TRAC
METVLQVLLGILGFQAAWVSSQELEQSPQSLIVQEGKNLTINCTSS**KTLYG**LYWYK
QKYGEGLIFLMM**LQKGGEE**KSHEKITAKLDEKKQQSSLHITASQPRHAGIYL**CGA**
RKKNYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitd
ktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnll
mtlrlws

Beta chain:
TRBV7-8/TRBJ1-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL

CASSSGPTSPQHFGDGTRLSILEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngke
vhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgits
asyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ1-DP57 wild type sequence:
Alpha chain:
TRAV12-2/TRAJ52/TRAC
MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYS**DRGSQS**FF
WYRQYSGKSPELIMF**IYSNGD**KEDGRFTAQLNKASQYVSLLIRDSQPSDSATYL**CA**
VNKGGGTSYGKLTFGQGTILTVHPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitd
ktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnll
mtlrlws

Beta chain:
TRBV27/TRBJ1-1/TRBC1
MGPQLLGYVVLCLLGAGPLEAQVTQNPRYLITVTGKKLTVTCSQN**MNHEY**MSWY
RQDPGLGLRQIYY**SMNVEV**TDKGDVPEGYKVSRKEKRNFPLILESPSPNQTSLYF**C**
ASSWTLNTEAFFGQGTRLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngk
evhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgft
svsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ1-DP57 MGTM sequence:
Alpha chain:
TRAV12-2/TRAJ52/TRAC
MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYS**DRGSQS**FF
WYRQYSGKSPELIMF**IYSNGD**KEDGRFTAQLNKASQYVSLLIRDSQPSDSATYL**CA**
VNKGGGTSYGKLTFGQGTILTVHPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitd
ktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnll
mtlrlws

Beta chain:
TRBV27/TRBJ1-1/TRBC1
MGPQLLGYVVLCLLGAGPLEAQVTQNPRYLITVTGKKLTVTCSQN**MNHEY**MSWY
RQDPGLGLRQIYY**SMNVEV**TDKGDVPEGYKVSRKEKRNFPLILESPSPNQTSLYF**C**
ASSWTLNTEAFFGQGTRLTVVEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngk
evhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgit
sasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ1-DP2 wild type sequence:
Alpha chain:
TRAV3/TRAJ26/TRAC
MASAPISMLAMLFTLSGLRAQSVAQPEDQVNVAEGNPLTVKCTYS**VSGNPY**LFWY
VQYPNRGLQFLLK**YITGDNLV**KGSYGFEAEFNKSQTSFHLKKPSALVSDSALYF**CA**
VRDPGNYGQNFVFGPGTRLSVLPYiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-9/TRBJ2-5/TRBC1
MGTSLLCWMALCLLGADHADTGVSQDPRHKITKRGQNVTFRCDPI**SEHNR**LYWY

RQTLGQGPEFLTY**FQNEAQ**LEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYL
CASSLLGHTQETQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ1-DP2 MGTM sequence:
Alpha chain:
TRAV3/TRAJ26/TRAC
MASAPISMLAMLFTLSGLRAQSVAQPEDQVNVAEGNPLTVKCTYS**VSGNPY**LFWY
VQYPNRGLQFLLK**YITGDNLV**KGSYGFEAEFNKSQTSFHLKKPSALVSDSALYF**CA**
VRDPGNYGQNFVFGPGTRLSVLPYiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-9/TRBJ2-5/TRBC1
MGTSLLCWMALCLLGADHADTGVSQDPRHKITKRGQNVTFRCDPI**SEHNR**LYWY
RQTLGQGPEFLTY**FQNEAQ**LEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYL
CASSLLGHTQETQYFGPGTRLLVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelsww
vngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgra
dcgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ1-DP37 wild type sequence:
Alpha chain:
TRAV36DV7/TRAJ42/TRAC
MMKCPQALLAIFWLLLSWVSSEDKVVQSPLSLVVHEGDTVTLNCSYE**VTNFRS**LL
WYKQEKKAPTFLFM**LTSSGIE**KKSGRLSSILDKKELFSILNITATQTGDSAIYL**CAV**
EAGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm
tlrlws

Beta chain:
TRBV18/TRBJ1-3/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPRTGGIGNTIYFGEGSWLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelsww
vngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgra
dcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ1-DP37 MGTM sequence:
Alpha chain:
TRAV36DV7/TRAJ42/TRAC
MMKCPQALLAIFWLLLSWVSSEDKVVQSPLSLVVHEGDTVTLNCSYE**VTNFRS**LL
WYKQEKKAPTFLFM**LTSSGIE**KKSGRLSSILDKKELFSILNITATQTGDSAIYL**CAV**
EAGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV18/TRBJ1-3/TRBC1

MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPRTGGIGNTIYFGEGSWLTVVEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelsw
wvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawg
radcgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP9 wild type sequence:

Alpha chain:

TRAV19/TRAJ28/TRAC

MLTASLLRAVIASICVVSSMAQKVTQAQTEISVVEKEDVTLDCVYE**TRDTTYY**LF
WYKQPPSGELVFLIR**RNSFDEQN**EISGRYSWNFQKSTSSFNFTITASQVVDSAVYF**C**
ALSELAYSGAGSYQLTFGKGTKLSVIPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdv
yitdktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkva
gfnllmtlrlws

Beta chain:

TRBV11-2/TRBJ2-3/TRBC1

MGTRLLCWAALCLLGAELTEAGVAQSPRYKIIEKRQSVAFWCNPI**SGHAT**LYWYQ
QILGQGPKLLIQ**FQNNGV**VDDSQLPKDRFSAERLKGVDSTLKIQPAKLEDSAVYL**C**
ASSLQGLPDTDTQYFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP9 MGTM sequence:

Alpha chain:

TRAV19/TRAJ28/TRAC

MLTASLLRAVIASICVVSSMAQKVTQAQTEISVVEKEDVTLDCVYE**TRDTTYY**LF
WYKQPPSGELVFLIR**RNSFDEQN**EISGRYSWNFQKSTSSFNFTITASQVVDSAVYF**C**
ALSELAYSGAGSYQLTFGKGTKLSVIPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdv
yitdktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkva
gfnllmtlrlws

Beta chain:

TRBV11-2/TRBJ2-3/TRBC1

MGTRLLCWAALCLLGAELTEAGVAQSPRYKIIEKRQSVAFWCNPI**SGHAT**LYWYQ
QILGQGPKLLIQ**FQNNGV**VDDSQLPKDRFSAERLKGVDSTLKIQPAKLEDSAVYL**C**
ASSLQGLPDTDTQYFGPGTRLTVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP25 wild type sequence:

Alpha chain:

TRAV21/TRAJ42/TRAC

METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVRS**
GYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrl
ws

Beta chain:

TRBV7-8/TRBJ2-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSFSGSTQETQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP25 MGTM sequence:
Alpha chain:
TRAV21/TRAJ42/TRAC
METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVRS**
GYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrl
ws

Beta chain:
TRBV7-8/TRBJ2-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSFSGSTQETQYFGPGTRLLVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP17 wild type sequence:
Alpha chain:
TRAV21/TRAJ42/TRAC
METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVR**
WGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktv
ldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtl
rlws

Beta chain:
TRBV7-8/TRBJ2-3/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSSSAGFTDTQYFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP17 MGTM sequence:
Alpha chain:
TRAV21/TRAJ42/TRAC
METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVR**
WGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktv
ldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtl
rlws

Beta chain:
TRBV7-8/TRBJ2-3/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSSSAGFTDTQYFGPGTRLTVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ1-DP33 wild type sequence:
Alpha chain:
TRAV35/TRAJ42/TRAC
MLLEHLLIILWMQLTWVSGQQLNQSPQSMFIQEGEDVSMNCTSS**SIFNT**WLWYKQ
EPGEGPVLLIA**LYKAGEL**TSNGRLTAQFGITRKDSFLNISASIPSDVGIYF**CAGPPM**
NYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrl
ws

Beta chain:
TRBV7-8/TRBJ2-1/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSLFSRHEQFFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngk
evhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgft
svsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ1-DP33 MGTM sequence:
Alpha chain:
TRAV35/TRAJ42/TRAC
MLLEHLLIILWMQLTWVSGQQLNQSPQSMFIQEGEDVSMNCTSS**SIFNT**WLWYKQ
EPGEGPVLLIA**LYKAGEL**TSNGRLTAQFGITRKDSFLNISASIPSDVGIYF**CAGPPM**
NYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrl
ws

Beta chain:
TRBV7-8/TRBJ2-1/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSLFSRHEQFFGPGTRLTVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngk
evhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgit
sasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ3-DP12 wild type sequence:
Alpha chain:
TRAV27/TRAJ42/TRAC
MVLKFSVSILWIQLAWVSTQLLEQSPQFLSIQEGENLTVYCNSS**SVFSS**LQWYRQEP
GEGPVLLVT**VVTGGEV**KKLKRLTFQFGDARKDSSLHITAAQTGDTGLYL**CAGAG**
MNYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvl
dmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlr
lws

Beta chain:
TRBV18/TRBJ2-1/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSLTSGRLNEQFFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ3-DP12 MGTM sequence:
Alpha chain:
TRAV27/TRAJ42/TRAC
MVLKFSVSILWIQLAWVSTQLLEQSPQFLSIQEGENLTVYCNSS**SVFSS**LQWYRQEP
GEGPVLLVT**VVTGGEV**KKLKRLTFQFGDARKDSSLHITAAQTGDTGLYL**CAGAG**
MNYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvl
dmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlr
lws

Beta chain:
TRBV18/TRBJ2-1/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSLTSGRLNEQFFGPGTRLTVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ3-DP20 wild type sequence:

Alpha chain:
TRAV39/TRAJ42/TRAC
MKKLLAMILWLQLDRLSGELKVEQNPLFLSMQEGKNYTIYCNYS**TTSDR**LYWYR
QDPGKSLESLFV**LLSNGAV**KQEGRLMASLDTKARLSTLHITAAVHDLSATYF**CAV**
PMGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-8/TRBJ2-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSRGPGTQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngke
vhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgfts
vsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ3-DP20 MGTM sequence:
Alpha chain:
TRAV39/TRAJ42/TRAC
MKKLLAMILWLQLDRLSGELKVEQNPLFLSMQEGKNYTIYCNYS**TTSDR**LYWYR
QDPGKSLESLFV**LLSNGAV**KQEGRLMASLDTKARLSTLHITAAVHDLSATYF**CAV**
PMGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt

vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-8/TRBJ2-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSRGPGTQYFGPGTRLLVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngke
vhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgits
asyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-BG3-DP15 wild type sequence:
Alpha chain:
TRAV21/TRAJ42/TRAC
METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVR**
PGDYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-8/TRBJ2-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSFFQGETQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngk
evhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgft
svsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-BG3-DP15 MGTM sequence:
Alpha chain:
TRAV21/TRAJ42/TRAC
METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVR**
PGDYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-8/TRBJ2-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSFFQGETQYFGPGTRLLVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvng
kevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgi
tsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-BG3-DP42 wild type sequence:
Alpha chain:
TRAV6/TRAJ13/TRAC
MAFWLRSLGLHFRPHLGRRMESFLGGVLLILWLQVDWVKSQKIEQNSEALNIQEG
KTATLTCNYT**NYSPAY**LQWYRQDPGRGPVFLLL**IRENEKE**KRKERLKVTFDTTLK

QSLFHITASQPADSATYL**CALVGGGYQKVTF**GTGTKLQVIPNiqnpdpavyqlrdskssdks
vclftdfdsqtnvsqskdsdvyitdktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfet
dtnlnfqnlsvigfrilllkvagfnllmtlrlws

Beta chain:
TRBV6-2/TRBJ2-1/TRBC1
MSLGLLCCGAFSLLWAGPVNAGVTQTPKFRVLKTGQSMTLLCAQD**MNHEY**MYW
YRQDPGMGLRLIHY**SVGEGT**TAKGEVPDGYNVSRLKKQNFLLGLESAAPSQTSVY
F**CATLTERSSYNEQFF**GPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelsww
vngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgra
dcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-BG3-DP42 MGTM sequence:
Alpha chain:
TRAV6/TRAJ13/TRAC
MAFWLRSLGLHFRPHLGRRMESFLGGVLLILWLQVDWVKSQKIEQNSEALNIQEG
KTATLTCNYT**NYSPAY**LQWYRQDPGRGPVFLLL**IRENEKE**KRKERLKVTFDTTLK
QSLFHITASQPADSATYL**CALVGGGYQKVTF**GTGTKLQVIPNiqnpdpavyqlrdskssdks
vclftdfdsqtnvsqskdsdvyitdktvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfe
tdtnlnfqnllvivlrilllkvagfnllmtlrlws

Beta chain:
TRBV6-2/TRBJ2-1/TRBC1
MSLGLLCCGAFSLLWAGPVNAGVTQTPKFRVLKTGQSMTLLCAQD**MNHEY**MYW
YRQDPGMGLRLIHY**SVGEGT**TAKGEVPDGYNVSRLKKQNFLLGLESAAPSQTSVY
F**CATLTERSSYNEQFF**GPGTRLTVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelsww
vngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgra
dcgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-BG3-DP67 wild type sequence:
Alpha chain:
TRAV26-1/TRAJ42/TRAC
MRLVARVTVFLTFGTIIDAKTTQPTSMDCAEGRAANLPCNHS**TISGNEY**VYWYRQI
HSQGPQYIIH**GLKNN**ETNEMASLIITEDRKSSTLILPHATLRDTAVYY**CIVRPRNYG**
GSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrsm
dfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrlws

Beta chain:
TRBV7-9/TRBJ1-4/TRBC1
MGTSLLCWMALCLLGADHADTGVSQDPRHKITKRGQNVTFRCDPI**SEHNR**LYWY
RQTLGQGPEFLTY**FQNEAQ**LEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYL
CASSLDFDLGQTRRANEKLFFGSGTQLSVLEdlnkvfppevavfepseaeishtqkatlvclatgffpd
hvelswwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivs
aeawgradcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-BG3-DP67 MGTM sequence:
Alpha chain:
TRAV26-1/TRAJ42/TRAC
MRLVARVTVFLTFGTIIDAKTTQPTSMDCAEGRAANLPCNHS**TISGNEY**VYWYRQI
HSQGPQYIIH**GLKNN**ETNEMASLIITEDRKSSTLILPHATLRDTAVYY**CIVRPRNYG**

GSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrsm
dfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlws

Beta chain:
TRBV7-9/TRBJ1-4/TRBC1
MGTSLLCWMALCLLGADHADTGVSQDPRHKITKRGQNVTFRCDPI**SEHNR**LYWY
RQTLGQGPEFLTY**FQNEAQ**LEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYL
CASSLDFDLGQTRRANEKLFFGSGTQLSVLEdlnkvfppevavfepskaeiahtqkatlvclatgffp
dhvelswwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqi
vsaeawgradcgitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP8 wild type sequence (same CDRs as "TCR-101a"):
Alpha chain:
TRAV41/TRAJ50/TRAC
MVKIRQFLLAILWLQLSCVSAAKNEVEQSPQNLTAQEGEFITINCSYS**VGISA**LHWL
QQHPGGGIVSLFM**LSSGK**KKHGRLIATINIQEKHSSLHITASHPRDSAVYI**CAVDGT**
GGTKKTSYDKVIFGPGTSLSVIPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvl
dmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlr
lws

Beta chain:
TRBV5-1/TRBJ2-1/TRBC1
MGSRLLCWVLLCLLGAGPVKAGVTQTPRYLIKTRGQQVTLSCSPI**SGHRS**VSWYQ
QTPGQGLQFLFE**YFSETQ**RNKGNFPGRFSGRQFSNSRSEMNVSTLELGDSALYL**CA**
SSLRGLAAYNEQFFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvn
gkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradc
gftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP8 MGTM sequence (also known as "TCR-101a"):
Alpha chain:
TRAV41/TRAJ50/TRAC
MVKIRQFLLAILWLQLSCVSAAKNEVEQSPQNLTAQEGEFITINCSYS**VGISA**LHWL
QQHPGGGIVSLFM**LSSGK**KKHGRLIATINIQEKHSSLHITASHPRDSAVYI**CAVDGT**
GGTKKTSYDKVIFGPGTSLSVIPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvl
dmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlr
lws

Beta chain:
TRBV5-1/TRBJ2-1/TRBC1
MGSRLLCWVLLCLLGAGPVKAGVTQTPRYLIKTRGQQVTLSCSPI**SGHRS**VSWYQ
QTPGQGLQFLFE**YFSETQ**RNKGNFPGRFSGRQFSNSRSEMNVSTLELGDSALYL**CA**
SSLRGLAAYNEQFFGPGTRLTVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvn
gkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradc
gitsasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ7-DP19 wild type sequence (same CDRs as "TCR-101b"):
Alpha chain:
TRAV39/TRAJ43/TRAC
MKKLLAMILWLQLDRLSGELKVEQNPLFLSMQEGKNYTIYCNYS**TTSDR**LYWYR
QDPGKSLESLFV**LLSNGAV**KQEGRLMASLDTKARLSTLHITAAVHDLSATYF**CAV**

DTNMRFGAGTRLTVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrsmdfk
snsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrlws

Beta chain:
TRBV6-1/TRBJ1-4/TRBC1
MSIGLLCCVAFSLLWASPVNAGVTQTPKFQVLKTGQSMTLQCAQD**MNHNS**MYW
YRQDPGMGLRLIYY**SASEGT**TDKGEVPNGYNVSRLNKREFSLRLESAAPSQTSVYF
CASSEIQGEKLFFGSGTQLSVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngk
evhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgft
svsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ7-DP19 MGTM sequence (also known as "TCR-101b"):
Alpha chain:
TRAV39/TRAJ43/TRAC
MKKLLAMILWLQLDRLSGELKVEQNPLFLSMQEGKNYTIYCNYS**TTSDR**LYWYR
QDPGKSLESLFV**LLSNGAV**KQEGRLMASLDTKARLSTLHITAAVHDLSATYF**CAV**
DTNMRFGAGTRLTVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrsmdfk
snsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlws

Beta chain:
TRBV6-1/TRBJ1-4/TRBC1
MSIGLLCCVAFSLLWASPVNAGVTQTPKFQVLKTGQSMTLQCAQD**MNHNS**MYW
YRQDPGMGLRLIYY**SASEGT**TDKGEVPNGYNVSRLNKREFSLRLESAAPSQTSVYF
CASSEIQGEKLFFGSGTQLSVLEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngk
evhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgit
sasyhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP1 wild type sequence:
Alpha chain:
TRAV39/TRAJ42/TRAC
MKKLLAMILWLQLDRLSGELKVEQNPLFLSMQEGKNYTIYCNYS**TTSDR**LYWYR
QDPGKSLESLFV**LLSNGAV**KQEGRLMASLDTKARLSTLHITAAVHDLSATYF**CAV**
RMGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-8/TRBJ1-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSFASQPQHFGDGTRLSILEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngkev
hsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgftsv
syqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP1 MGTM sequence:
Alpha chain:
TRAV39/TRAJ42/TRAC
MKKLLAMILWLQLDRLSGELKVEQNPLFLSMQEGKNYTIYCNYS**TTSDR**LYWYR
QDPGKSLESLFV**LLSNGAV**KQEGRLMASLDTKARLSTLHITAAVHDLSATYF**CAV**
RMGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt

vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-8/TRBJ1-5/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSFASQPQHFGDGTRLSILEdlnkvfppevavfepskaeiahtqkatlvclatgffpdhvelswwvngkev
hsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgitsa
syhqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ13-DP32 sequence:
Alpha chain:
TRAV22/TRAJ26/TRAC
MKRILGALLGLLSAQVCCVRGIQVEQSPPDLILQEGANSTLRCNFS**DSVNN**LQWFH
QNPWGQLINLFY**IPSGT**KQNGRLSATTVATERYSLLYISSSQTTDSGVYF**CAVEGG**
SYNYGQNFVFGPGTRLSVLPYiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmr
smdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrlws

Beta chain:
TRBV7-9/TRBJ2-1/TRBC1
MGTSLLCWMALCLLGADHADTGVSQDPRHKITKRGQNVTFRCDPI**SEHNR**LYWY
RQTLGQGPEFLTY**FQNEAQ**LEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYL
CASSLVRERERGNEQFFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvels
wwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeaw
gradcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ13-DP32 MGTM Sequence:
Alpha chain:
TRAV22/TRAJ26/TRAC
MKRILGALLGLLSAQVCCVRGIQVEQSPPDLILQEGANSTLRCNFS**DSVNN**LQWFH
QNPWGQLINLFY**IPSGT**KQNGRLSATTVATERYSLLYISSSQTTDSGVYF**CAVEGG**
SYNYGQNFVFGPGTRLSVLPYiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmr
smdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlws

Beta chain:
TRBV7-9/TRBJ2-1/TRBC1
MGTSLLCWMALCLLGADHADTGVSQDPRHKITKRGQNVTFRCDPI**SEHNR**LYWY
RQTLGQGPEFLTY**FQNEAQ**LEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYL
CASSLVRERERGNEQFFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvels
wwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeaw
gradcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ13-DP148 sequence:
Alpha chain:
TRAV21/TRAJ42/TRAC
METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVR**
VRDYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm

tlrlws

Beta chain:
TRBV18/TRBJ1-4/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPPGGQGEKLFFGSGTQLSVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ13-DP148 MGTM Sequence:
Alpha chain:
TRAV21/TRAJ42/TRAC
METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVR**
VRDYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV18/TRBJ1-4/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPPGGQGEKLFFGSGTQLSVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ13-SP43 sequence:
Alpha chain:
TRAV12-2/TRAJ11/TRAC
MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYS**DRGSQS**FF
WYRQYSGKSPELIMF**IYSNGD**KEDGRFTAQLNKASQYVSLLIRDSQPSDSATYL**CA**
VKGAGYSTLTFGKGTMLLVSPDiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrl
ws

Beta chain:
TRBV6-5/TRBJ2-3/TRBC1
MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQD**MNHEY**MSW
YRQDPGMGLRLIHY**SVGAGI**TDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYF
CASSDGGALAYFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngke
vhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgfts
vsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ13-SP43 MGTM Sequence:
Alpha chain:
TRAV12-2/TRAJ11/TRAC
MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYS**DRGSQS**FF
WYRQYSGKSPELIMF**IYSNGD**KEDGRFTAQLNKASQYVSLLIRDSQPSDSATYL**CA**
VKGAGYSTLTFGKGTMLLVSPDiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld

mrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrl
ws

Beta chain:
TRBV6-5/TRBJ2-3/TRBC1
MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQD**MNHEY**MSW
YRQDPGMGLRLIHY**SVGAGI**TDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYF
CASSDGGALAYFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngke
vhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgfts
vsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP33 sequence:
Alpha chain:
TRAV36DV7/TRAJ42/TRAC
MMKCPQALLAIFWLLLSWVSSEDKVVQSPLSLVVHEGDTVTLNCSYE**VTNFRS**LL
WYKQEKKAPTFLFM**LTSSGIE**KKSGRLSSILDKKELFSILNITATQTGDSAIYL**CAV**
ESGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktv
ldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtl
rlws

Beta chain:
TRBV18/TRBJ1-3/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPRTGGDGNTIYFGEGSWLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelsw
wvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawg
radcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP33 MGTM Sequence:
Alpha chain:
TRAV36DV7/TRAJ42/TRAC
MMKCPQALLAIFWLLLSWVSSEDKVVQSPLSLVVHEGDTVTLNCSYE**VTNFRS**LL
WYKQEKKAPTFLFM**LTSSGIE**KKSGRLSSILDKKELFSILNITATQTGDSAIYL**CAV**
ESGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktv
ldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtl
rlws

Beta chain:
TRBV18/TRBJ1-3/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPRTGGDGNTIYFGEGSWLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelsw
wvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawg
radcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP45 sequence:
Alpha chain:
TRAV20/TRAJ42/TRAC
MEKMLECAFIVLWLQLGWLSGEDQVTQSPEALRLQEGESSSLNCSYT**VSGLRG**LF
WYRQDPGKGPEFLFT**LYSAGEE**KEKERLKATLTKKESFLHITAPKPEDSATYL**CAV**

QASYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm
tlrlws

Beta chain:
TRBV18/TRBJ2-5/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPVPVPLPTTQETQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvel
swwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaea
wgradcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP45 MGTM Sequence:
Alpha chain:
TRAV20/TRAJ42/TRAC
MEKMLECAFIVLWLQLGWLSGEDQVTQSPEALRLQEGESSSLNCSYT**VSGLRG**LF
WYRQDPGKGPEFLFT**LYSAGEE**KEKERLKATLTKKESFLHITAPKPEDSATYL**CAV**
QASYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV18/TRBJ2-5/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPVPVPLPTTQETQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvel
swwvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaea
wgradcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP137 sequence:
Alpha chain:
TRAV27/TRAJ42/TRAC
MVLKFSVSILWIQLAWVSTQLLEQSPQFLSIQEGENLTVYCNSS**SVFSS**LQWYRQEP
GEGPVLLVT**VVTGGEV**KKLKRLTFQFGDARKDSSLHITAAQTGDTGLYL**CAGAPS**
NYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrl
ws

Beta chain:
TRBV18/TRBJ2-1/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPPGQNNEQFFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvn
gkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradc
gftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP137 MGTM Sequence:
Alpha chain:
TRAV27/TRAJ42/TRAC
MVLKFSVSILWIQLAWVSTQLLEQSPQFLSIQEGENLTVYCNSS**SVFSS**LQWYRQEP

GEGPVLLVT**VVTGGEV**KKLKRLTFQFGDARKDSSLHITAAQTGDTGLYL**CAGAPS**
NYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrl
ws

Beta chain:
TRBV18/TRBJ2-1/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPPGQNNEQFFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvn
gkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradc
gftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-SP4 sequence:
Alpha chain:
TRAV12-2/TRAJ11/TRAC
MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYS**DRGSQS**FF
WYRQYSGKSPELIMF**IYSNGD**KEDGRFTAQLNKASQYVSLLIRDSQPSDSATYL**CA**
VRRSGYSTLTFGKGTMLLVSPDiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrl
ws

Beta chain:
TRBV6-5/TRBJ1-1/TRBC1
MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQD**MNHEY**MSW
YRQDPGMGLRLIHY**SVGAGI**TDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYF
CASSLGAEAFFGQGTRLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngkev
hsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgftsv
syqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-SP4 MGTM Sequence:
Alpha chain:
TRAV12-2/TRAJ11/TRAC
MKSLRVLLVILWLQLSWVWSQQKEVEQNSGPLSVPEGAIASLNCTYS**DRGSQS**FF
WYRQYSGKSPELIMF**IYSNGD**KEDGRFTAQLNKASQYVSLLIRDSQPSDSATYL**CA**
VRRSGYSTLTFGKGTMLLVSPDiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrl
ws

Beta chain:
TRBV6-5/TRBJ1-1/TRBC1
MSIGLLCCAALSLLWAGPVNAGVTQTPKFQVLKTGQSMTLQCAQD**MNHEY**MSW
YRQDPGMGLRLIHY**SVGAGI**TDQGEVPNGYNVSRSTTEDFPLRLLSAAPSQTSVYF
CASSLGAEAFFGQGTRLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngkev
hsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgftsv
syqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP162 sequence:
Alpha chain:
TRAV8-2/TRAJ42/TRAC

MLLLLVPVLEVIFTLGGTRAQSVTQLDSHVSVSEGTPVLLRCNYS**SSYSPS**LFWYV
QHPNKGLQLLLK**YTSAATLV**KGINGFEAEFKKSETSFHLTKPSAHMSDAAEYF**CV**
VMRGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrl
ws

Beta chain:
TRBV20-1/TRBJ2-5/TRBC1
MLLLLLLLGPGSGLGAVVSQHPSWVICKSGTSVKIECRSL**DFQATT**MFWYRQFPK
QSLMLMAT**SNEGSKA**TYEQGVEKDKFLINHASLTLSTLTVTSAHPEDSSFYI**CSAK**
RGDAFGETQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngkev
hsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgftsv
syqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP162 MGTM Sequence:
Alpha chain:
TRAV8-2/TRAJ42/TRAC
MLLLLVPVLEVIFTLGGTRAQSVTQLDSHVSVSEGTPVLLRCNYS**SSYSPS**LFWYV
QHPNKGLQLLLK**YTSAATLV**KGINGFEAEFKKSETSFHLTKPSAHMSDAAEYF**CV**
VMRGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvld
mrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrl
ws

Beta chain:
TRBV20-1/TRBJ2-5/TRBC1
MLLLLLLLGPGSGLGAVVSQHPSWVICKSGTSVKIECRSL**DFQATT**MFWYRQFPK
QSLMLMAT**SNEGSKA**TYEQGVEKDKFLINHASLTLSTLTVTSAHPEDSSFYI**CSAK**
RGDAFGETQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvngkev
hsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcgftsv
syqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP317 sequence (same CDRs as "TCR-101"):
Alpha chain:
TRAV38-2DV8/TRAJ11/TRAC
MACPGFLWALVISTCLEFSMAQTVTQSQPEMSVQEAETVTLSCTYD**TSESDYY**LF
WYKQPPSRQMILVIR**QEAYKQQN**ATENRFSVNFQKAAKSFSLKISDSQLGDAAMY
F**CAYRSERYSTLTF**GKGTMLLVSPDiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdk
tvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnll
mtlrlws

Beta chain:
TRBV30/TRBJ2-3/TRBC1
MLCSLLALLLGTFFGVRSQTIHQWPATLVQPVGSPLSLECTVE**GTSNPN**LYWYRQA
AGRGLQLLFY**SVGIG**QISSEVPQNLSASRPQDRQFILSSKKLLLSDSGFYL**CAWSVP**
YLAGGKRPDTQYFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvng
kevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcg
ftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP317 MGTM Sequence (also known as "TCR-101" and "MJ14-DP317"):
Alpha chain:

TRAV38-2DV8/TRAJ11/TRAC
MACPGFLWALVISTCLEFSMAQTVTQSQPEMSVQEAETVTLSCTYD**TSESDYY**LF
WYKQPPSRQMILVIR**QEAYKQQN**ATENRFSVNFQKAAKSFSLKISDSQLGDAAMY
F**CAYRSERYSTLTF**GKGTMLLVSPDiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdk
tvldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnll
mtlrlws

Beta chain:
TRBV30/TRBJ2-3/TRBC1
MLCSLLALLLGTFFGVRSQTIHQWPATLVQPVGSPLSLECTVE**GTSNPN**LYWYRQA
AGRGLQLLFY**SVGIG**QISSEVPQNLSASRPQDRQFILSSKKLLLSDSGFYL**CAWSVP**
YLAGGKRPDTQYFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvng
kevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradcg
ftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP331 sequence:
Alpha chain:
TRAV36DV7/TRAJ42/TRAC
MMKCPQALLAIFWLLLSWVSSEDKVVQSPLSLVVHEGDTVTLNCSYE**VTNFRS**LL
WYKQEKKAPTFLFM**LTSSGIE**KKSGRLSSILDKKELFSILNITATQTGDSAIYL**CAV**
EAGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm
tlrlws

Beta chain:
TRBV18/TRBJ1-3/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPRTGRGGNTIYFGEGSWLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelsw
wvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawg
radcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ14-DP331 MGTM Sequence:
Alpha chain:
TRAV36DV7/TRAJ42/TRAC
MMKCPQALLAIFWLLLSWVSSEDKVVQSPLSLVVHEGDTVTLNCSYE**VTNFRS**LL
WYKQEKKAPTFLFM**LTSSGIE**KKSGRLSSILDKKELFSILNITATQTGDSAIYL**CAV**
EAGYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV18/TRBJ1-3/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSPRTGRGGNTIYFGEGSWLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelsw
wvngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawg
radcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP22 sequence:

Alpha chain:
TRAV35/TRAJ42/TRAC
MLLEHLLIILWMQLTWVSGQQLNQSPQSMFIQEGEDVSMNCTSS**SIFNT**WLWYKQ
EPGEGPVLLIA**LYKAGEL**TSNGRLTAQFGITRKDSFLNISASIPSDVGIYF**CAGPFGY**
GGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrs
mdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllmtlrlws

Beta chain:
TRBV7-8/TRBJ1-2/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSLIGRGWDGYTFGSGTRLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelsww
vngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgra
dcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP22 MGTM Sequence:
Alpha chain:
TRAV35/TRAJ42/TRAC
MLLEHLLIILWMQLTWVSGQQLNQSPQSMFIQEGEDVSMNCTSS**SIFNT**WLWYKQ
EPGEGPVLLIA**LYKAGEL**TSNGRLTAQFGITRKDSFLNISASIPSDVGIYF**CAGPFGY**
GGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdktvldmrs
mdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllmtlrlws

Beta chain:
TRBV7-8/TRBJ1-2/TRBC1
MGTRLLCWVVLGFLGTDHTGAGVSQSPRYKVAKRGQDVALRCDPI**SGHVS**LFWY
QQALGQGPEFLTY**FQNEAQ**LDKSGLPSDRFFAERPEGSVSTLKIQRTQQEDSAVYL
CASSLIGRGWDGYTFGSGTRLTVVEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelsww
vngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgra
dcgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP24 sequence:
Alpha chain:
TRAV8-2/TRAJ13/TRAC
MLLLLVPVLEVIFTLGGTRAQSVTQLDSHVSVSEGTPVLLRCNYS**SSYSPS**LFWYV
QHPNKGLQLLLK**YTSAATLV**KGINGFEAEFKKSETSFHLTKPSAHMSDAAEYF**CV**
VTGGSGGYQKVTFGTGTKLQVIPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-9/TRBJ2-5/TRBC1
MGTSLLCWMALCLLGADHADTGVSQDPRHKITKRGQNVTFRCDPI**SEHNR**LYWY
RQTLGQGPEFLTY**FQNEAQ**LEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYL
CASSPLGTDQETQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ2-DP24 MGTM Sequence:
Alpha chain:

TRAV8-2/TRAJ13/TRAC
MLLLLVPVLEVIFTLGGTRAQSVTQLDSHVSVSEGTPVLLRCNYS**SSYSPS**LFWYV
QHPNKGLQLLLK**YTSAATLV**KGINGFEAEFKKSETSFHLTKPSAHMSDAAEYF**CV**
VTGGSGGYQKVTFGTGTKLQVIPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV7-9/TRBJ2-5/TRBC1
MGTSLLCWMALCLLGADHADTGVSQDPRHKITKRGQNVTFRCDPI**SEHNR**LYWY
RQTLGQGPEFLTY**FQNEAQ**LEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYL
CASSPLGTDQETQYFGPGTRLLVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwv
ngkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgrad
cgftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ9-DP5 sequence:
Alpha chain:
TRAV21/TRAJ42/TRAC
METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVR**
PKNYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpspesscdvklveksfetdtnlnfqnlsvigfrilllkvagfnllm
tlrlws

Beta chain:
TRBV18/TRBJ2-1/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSLTSGSSNEQFFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvn
gkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradc
gftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

HA2-MJ9-DP5 MGTM Sequence:
Alpha chain:
TRAV21/TRAJ42/TRAC
METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFT**DSAIYN**LQWFR
QDPGKGLTSLLL**IQSSQRE**QTSGRLNASLDKSSGRSTLYIAASQPGDSATYL**CAVR**
PKNYGGSQGNLIFGKGTKLSVKPNiqnpdpavyqlrdskssdksvclftdfdsqtnvsqskdsdvyitdkt
vldmrsmdfksnsavawsnksdfacanafnnsiipedtffpssdvpcdvklveksfetdtnlnfqnllvivlrilllkvagfnllm
tlrlws

Beta chain:
TRBV18/TRBJ2-1/TRBC1
MDTRLLCCAVICLLGAGLSNAGVMQNPRHLVRRRGQEARLRCSPM**KGHSH**VYW
YRQLPEEGLKFMVY**LQKENI**IDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYF
CASSLTSGSSNEQFFGPGTRLTVLEdlnkvfppevavfepseaeishtqkatlvclatgffpdhvelswwvn
gkevhsgvstdpqplkeqpalndsryclssrlrvsatfwqnprnhfrcqvqfyglsendewtqdrakpvtqivsaeawgradc
gftsvsyqqgvlsatilyeillgkatlyavlvsalvlmamvkrkdf

* Table 1 providing representative TCR sequences are grouped according to MHC serotype presentation and sub-grouped according to different peptides presented by the MHC serotype and bound by the sub-grouped TCRs. Individual TCRs, such as those representatively exemplified in the tables, are described and claimed, as well as the genus of binding proteins that bind a peptide epitope sequence described herein either alone or in a complex with an MHC, such as those grouped in the tables provided herein. In addition, TRAV, TRAJ, and TRAC genes for each TCR alpha chain described herein, and TRBV, TRBJ, and TRBC genes for each TCR beta chain described herein, are provided. Sequences for each TCR described herein are provided as pairs of cognate alpha chain and beta chains for each named TCR. TCR sequences described herein are annotated. Variable domain sequences are capitalized. Constant domain sequences are in lower case. CDR1, CDR2, and CDR3 sequences are annotated using bold and underlined text. CDR1, CDR2, and CDR3 are shown in standard order of appearance from left (N-terminus) to right (C-terminus). TRAV, TRAJ, and TRAC genes for each TCR alpha chain described herein, and TRBV, TRBJ, and TRBC genes for each TCR beta chain described herein, are annotated according to well-known IMGT nomenclature described herein. The designation "DP" in a clone name identifies a TCR that recognizes both SNP peptide-loaded and REF peptide-loaded MHC dextramers. The designation "SP" in a clone name identifies a TCR that only recognizes REF peptide-loaded MHC dextramers

Table 2

Vector: pTSLV101-MSCV-MGTMA-QQ-CD8

tggaagggctaattcactcccaaagaagacaagatatccttgatctgtggatctaccacacacaaggctacttccctgattagcagaa
ctacacaccagggccaggggtcagatatccactgacctttggatggtgctacaagctagtaccagttgagccagataaggtagaag
aggccaataaaggagagaacaccagcttgttacaccctgtgagcctgcatgggatggatgacccggagagagaagtgttagagtg
gaggtttgacagccgcctagcatttcatcacgtggcccgagagctgcatccggagtacttcaagaactgctgatatcgagcttgctac
aagggactttccgctggggactttccagggaggcgtggcctgggcgggactggggagtggcgagccctcagatcctgcatataa
gcagctgctttttgcctgtactgggtctctctggttagaccagatctgagcctgggagctctctggctaactagggaacccactgctta
agcctcaataaagcttgccttgagtgcttcaagtagtgtgtgcccgtctgttgtgtgactctggtaactagagatccctcagacccttta
gtcagtgtggaaaatctctagcagtggcgcccgaacagggacttgaaagcgaaagggaaaccagaggagctctctcgacgcagg
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* MSCV promoter is in bold. MGTM-alpha is annotated using bold and italic text. Q-tag 1 is annotated using bold and underlined text. Q-tag 2 is annotated using italic and underlined text. CD8-alpha is in italic. CD8-beta is underlined.

Vector: pTSLV102-MSCV-MGTM-Q-CD8

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GTGATTCCTCTGAATTATTTTCATTTTAAAGAAATTGTATTTGTTAAATATGTAC
TACAAACTtagtagt

* MSCV promoter is in bold. Alpha chain constant domain is annotated using bold and italic text. Q-tag is annotated using bold and underlined text. CD8-alpha is in italic. CD8-beta is underlined.

Vector: TSC-101 npDNA Transposon:

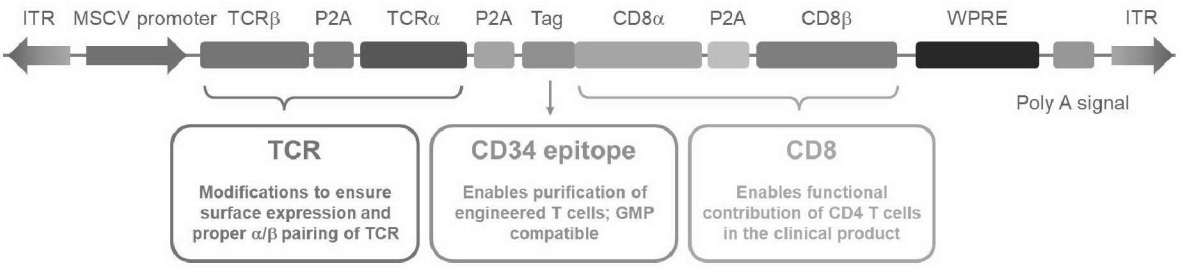
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TAAACATGAGAGCTTAGTACATACTATCAACAGGTTGAACTGCTGATCTGTACAGTAG
AATTGGTAAAGAGAGTTGTGTAAAATATTGAGTTCGCACATCTTGTTGTCTGATTATTG
ATTTTTGGCGAAACCATTTGATCATATGACAAGATGTGTATCTACCTTAACTTAATGAT
TTTGATAAAAATCATTAGGTACC

Schematic of the TSC-101 npDNA Transposon Vector Cassette



Key: CD: Cluster of Differentiation, ITR: Inverted Terminal Repeat, npDNA: Nanoplasmid DNA, MSCV: Murine Stem Cell Virus, TCR: T Cell Receptor, WPRE: Woodchuck Hepatitis Virus Post-Transcriptional Regulatory Element

Map of the TSC-101 npDNA Transposon Vector Cassette:



Virus, TCR: T Cell Receptor, TIR: Terminal Inverted Repeat, QBend: Mouse anti Human CD34 Antibody, WPRE: Woodchuck Hepatitis Virus Post-Transcriptional Regulatory Element

The TSC-101 npDNA Transposon is a 5,721-bp supercoiled, Nanoplasmid™ DNA (npDNA) carrying the minimal R6K bacterial replication origin and anti-sense RNA-based antibiotic-free selection marker (RNA-OUT). The inverted terminal repeats (ITRs) of the armyworm *Spodoptera frugiperda* transposon (required for transposase-mediated integration) are connected to the two ends of the exogenous DNA sequence. The TSC-101 HA-2-specific TCR α- and β-chain genes and the codon-diversified CD8 α- and β-chain

genes are placed under the control of the murine stem cell virus (MSCV) promoter. The constant regions of the TCR α- and β-chains contain amino-acid substitutions that stabilize their expression on the surface of engineered T cells and help prevent mispairing with the α- and β-chains of the endogenous TCRs. These four open reading frames (TCRβ, TCRα, CD8α, and CD8β) are encoded on a single mRNA molecule along with the open reading frame-disabled woodchuck post-transcriptional regulatory element (WPRE), which is known to enhance gene expression (Loeb, 1999). The ribosomal skipping that takes places on the self-cleaving peptide P2A leads to production of the four separate polypeptides. The 16-amino acid CD34 epitope recognized by the mouse monoclonal antibody QBend/10 is fused to the N-terminus of the exogenous CD8 α-chain, allowing for purification of transgene-expressing cells to increase the safety and potency of the drug substance. The Nanoplasmid vector backbone (<500 base pairs) is substantially smaller than conventional plasmids (>1500 base pairs). It contains no antibiotic-resistant gene, and its replication origin (R6K) necessary for plasmid preparation supports propagation in a narrower range of bacterial species than the commonly used origin pUC.

* Included in Table 1 is peptide epitopes, as well as polypeptide molecules comprising an amino acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or more identity across their full length with an amino acid sequence of any sequences listed in Table 1, or a portion thereof. Such polypeptides may have a function of the full-length peptide or polypeptide as described further herein.

* Included in Table 2 are RNA nucleic acid molecules (*e.g.*, thymines replaced with uredines), nucleic acid molecules encoding orthologs of the encoded proteins, as well as DNA or RNA nucleic acid sequences comprising a nucleic acid sequence having at least 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, or more identity across their full length with the nucleic acid sequence of any sequence listed in Table 2, or a portion thereof. Such nucleic acid molecules can have a function of the full-length nucleic acid as described further herein.

In some embodiments, the binding proteins disclosed herein may comprise a T cell receptor (TCR), an antigen-binding fragment of a TCR, or a chimeric antigen receptor

(CAR). In some embodiments, the binding protein disclosed herein may comprise two polypeptide chains, each of which comprises a variable region comprising a CDR3 of a TCR alpha chain and a CDR3 of a TCR beta chain, or a CDR1, CDR2, and CDR3 of both a TCR alpha chain and a TCR beta chain. In some embodiments, a binding protein comprises a single chain TCR (scTCR), which comprises both the TCR V_α and TCR V_β domains, but only a single TCR constant domain (C_α or C_β). **The term "chimeric antigen receptor" (CAR) refers to a fusion protein that is engineered to contain two or** more naturally-occurring amino acid sequences linked together in a way that does not occur naturally or does not occur naturally in a host cell, which fusion protein can function as a receptor when present on a surface of a cell. CARs encompassed by the present invention may include an extracellular portion comprising an antigen-binding domain (*i.e.,* obtained or derived from an immunoglobulin or immunoglobulin-like molecule, such as an antibody or TCR, or an antigen binding domain derived or obtained from a killer immunoreceptor from an NK cell) linked to a transmembrane domain and one or more intracellular signaling domains (optionally containing co-stimulatory domain(s)) (see, *e.g.,* Sadelain *et al.* (2013*) Cancer Discov.* 3:388, Harris and Kranz (2016) *Trends Pharmacol. Sci.* 37:220, and Stone *et al.* (2014) *Cancer Immunol. Immunother.* 63:1163).

In some embodiments, 1) the TCR alpha chain CDR, TCR V_α domain, and/or TCR alpha chain is encoded by a TRAV, TRAJ, and/or TRAC gene or fragment thereof selected from the group of TRAV, TRAJ, and TRAC genes listed in Table 1, and/or 2) the TCR beta chain CDR, TCR V_β domain, and/or TCR beta chain is encoded by a TRBV, TRBJ, and/or TRBC gene or fragment thereof selected from the group of TRBV, TRBJ, and TRBC genes listed in Table 1, and/or 3) each CDR of the binding protein has up to five amino acid substitutions, insertions, deletions, or a combination thereof as compared to the cognate reference CDR sequence listed in Table 1.

In some embodiments, the binding proteins (*e.g.,* the TCR, antigen-binding fragment of a TCR, or chimeric antigen receptor (CAR)) disclosed herein is chimeric (*e.g.,* comprises amino acid residues or motifs from more than one donor or species), humanized (*e.g.,* comprises residues from a non-human organism that are altered or substituted so as to reduce the risk of immunogenicity in a human), or human.

Methods for producing engineered binding proteins, such as TCRs, CARs, and antigen-binding fragments thereof, are well-known in the art (*e.g.*, Bowerman *et al.* (2009) *Mol. Immunol.* 5:3000; U.S. Pat. No. 6,410,319; U.S. Pat. No. 7,446,191; U.S. Pat. Publ.

No. 2010/065818; U.S. Pat. No. 8,822,647; PCT Publ. No. WO 2014/031687; U.S. Pat. No. 7,514,537; and Brentjens *et al.* (2007) *Clin. Cancer Res.* 73:5426).

In some embodiments, the binding protein described herein is a TCR, or antigen-binding fragment thereof, expressed on a cell surface, wherein the cell surface-expressed TCR is capable of more efficiently associating with a CD3 protein as compared to endogenous TCR. A binding protein encompassed by the present invention, such as a TCR, when expressed on the surface of a cell like a T cell, may also have higher surface expression on the cell as compared to an endogenous binding protein, such as an endogenous TCR. In some embodiments, provided herein is a CAR, wherein the binding domain of the CAR comprises an antigen-specific TCR binding domain (see, *e.g.,* Walseng *et al.* (2017) *Scientific Reports* 7:10713).

Also provided are modified binding proteins (*e.g.,* TCRs, antigen-binding fragments of TCRs, or CARs) that may be prepared according to well-known methods using a binding protein having one or more of the V_α and/or V_β sequences disclosed herein as starting material to engineer a modified binding protein that may have altered properties from the starting binding protein. A binding protein may be engineered by modifying one or more residues within one or both variable regions (*i.e.,* V_α and/or V_β), for example within one or more CDR regions and/or within one or more framework regions. Additionally or alternatively, a binding protein may be engineered by modifying residues within the constant region(s).

Another type of variable region modification is to mutate amino acid residues within the V_α and/or V_β CDR1, CDR2 and/or CDR3 regions to thereby improve one or more binding properties (*e.g.,* affinity) of the binding protein of interest. Site-directed mutagenesis or PCR-mediated mutagenesis may be performed to introduce the mutation(s) and the effect on protein binding, or other functional property of interest, may be evaluated in *in vitro*, *ex vivo*, or *in vivo* assays as described herein and provided in the Examples. In some embodiments, conservative modifications (as discussed above) may be introduced. The mutations may be amino acid substitutions, additions or deletions. In some embodiments, the mutations are substitutions. Moreover, typically no more than one, two, three, four or five residues within a CDR region are modified.

In some embodiments, binding proteins (*e.g.,* TCRs, antigen-binding fragments of TCRs, or CARs) described herein may possess one or more amino acid substitutions, deletions, or additions relative to a naturally occurring TCR. In some embodiments, each

CDR of the binding protein has up to five amino acid substitutions, insertions, deletions, or a combination thereof as compared to the cognate reference CDR sequence listed in Table 1. Conservative substitutions of amino acids are well-known and may occur naturally or may be introduced when the binding protein is recombinantly produced. Amino acid substitutions, deletions, and additions may be introduced into a protein using mutagenesis methods known in the art (see, *e.g.,* Sambrook *et al.* (2001) *Molecular Cloning: A Laboratory Manual*, 3d ed., Cold Spring Harbor Laboratory Press, NY). Oligonucleotide-directed site-specific (or segment specific) mutagenesis procedures may be employed to provide an altered polynucleotide that has particular codons altered according to the substitution, deletion, or insertion desired. Alternatively, random or saturation mutagenesis techniques, such as alanine scanning mutagenesis, error prone polymerase chain reaction mutagenesis, and oligonucleotide-directed mutagenesis may be used to prepare immunogen polypeptide variants (see, *e.g.,* Sambrook *et al.* supra).

A variety of criteria known to the ordinarily skilled artisan indicate whether an amino acid that is substituted at a particular position in a peptide or polypeptide is conservative (or similar). For example, a similar amino acid or a conservative amino acid substitution is one in which an amino acid residue is replaced with an amino acid residue having a similar side chain. Similar amino acids may be included in the following categories: amino acids with basic side chains (*e.g.,* lysine, arginine, histidine); amino acids with acidic side chains (*e.g.,* aspartic acid, glutamic acid); amino acids with uncharged polar side chains (*e.g.,* glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, histidine); amino acids with nonpolar side chains (*e.g.,* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan); amino acids with beta-branched side chains (*e.g.,* threonine, valine, isoleucine), and amino acids with aromatic side chains (*e.g.,* tyrosine, phenylalanine, tryptophan). Proline, which is considered more difficult to classify, shares properties with amino acids that have aliphatic side chains (*e.g.,* leucine, valine, isoleucine, and alanine). In some embodiments, substitution of glutamine for glutamic acid or asparagine for aspartic acid may be considered a similar substitution in that glutamine and asparagine are amide derivatives of glutamic acid and aspartic acid, respectively. As understood in the art "similarity" between two polypeptides is determined by comparing the amino acid sequence and conserved amino acid substitutes thereto of the polypeptide to the sequence of a second polypeptide (*e.g.,* using GENEWORKS™, Align, the BLAST algorithm, or other algorithms described herein and practiced in the art).

In some embodiments, an encoded binding protein (*e.g.,* TCR, antigen-binding fragment of a TCR, or CAR) may comprise a "signal peptide" (also known as a leader sequence, leader peptide, or transit peptide). Signal peptides target newly synthesized polypeptides to their appropriate location inside or outside the cell. A signal peptide may be removed from the polypeptide during or once localization or secretion is completed. Polypeptides that have a signal peptide are referred to herein as a "pre-protein" and polypeptides having their signal peptide removed are referred to herein as "mature" proteins or polypeptides. In some embodiments, a binding protein (*e.g.,* TCR, antigen-binding fragment of a TCR, or CAR) described herein comprises a mature V_α domain, a mature V_β domain, or both. In some embodiments, a binding protein (*e.g.,* TCR, antigen-binding fragment of a TCR, or CAR) described herein comprises a mature TCR β-chain, a mature TCR α-chain, or both.

In some embodiments, the binding proteins are fusion proteins comprising: (a) an extracellular component comprising a TCR or antigen-binding fragment thereof; (b) an intracellular component comprising an effector domain or a functional portion thereof; and (c) a transmembrane domain connecting the extracellular and intracellular components. In some embodiments, the fusion protein is capable of binding (*e.g.*, specifically and/or selectively) to a peptide-MHC (pMHC) complex comprising an HA-2 immunogenic peptide in the context of an MHC molecule (*e.g.,* a MHC class I molecule). In some embodiments, the MHC molecule comprises an MHC alpha chain that is an HLA serotype HLA-A*02. In some embodiments, the HLA allele is selected from the group consisting of HLA-A*0201, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele. In specific embodiments, the HLA allele is HLA-A*0201.

As used herein, an "effector domain" or "immune effector domain" is an intracellular portion or domain of a fusion protein or receptor that can directly or indirectly promote an immune response in a cell when receiving an appropriate signal. In some embodiments, an effector domain is from an immune cell protein or portion thereof or immune cell protein complex that receives a signal when bound (*e.g.,* CD3ζ), or when the immune cell protein or portion thereof or immune cell protein complex binds directly to a target molecule and triggers signal transduction from the effector domain in an immune cell.

An effector domain may directly promote a cellular response when it contains one or more signaling domains or motifs, such as an intracellular tyrosine-based activation

motif (ITAM), such as those found in costimulatory molecules. Without wishing to be bound by theory, it is believed that ITAMs are useful for T cell activation following ligand engagement by a T cell receptor or by a fusion protein comprising a T cell effector domain. In some embodiments, the intracellular component or functional portion thereof comprises an ITAM. Exemplary immune effector domains include but are not limited to those from, CD3ε, CD3δ, CD3ζ, CD25, CD79A, CD79B, CARD11, DAP10, FcRα, FcRβ, FcRγ, Fyn, HVEM, ICOS, Lck, LAG3, LAT, LRP, NKG2D, NOTCH1, NOTCH2, NOTCH3, NOTCH4, Wnt, ROR2, Ryk, SLAMF1, Slp76, pTα, TCRα, TCRβ, TRIM, Zap70, PTCH2, or any combination thereof. In some embodiments, an effector domain comprises a lymphocyte receptor signaling domain (*e.g.,* CD3ζ or a functional portion or variant thereof).

In further embodiments, the intracellular component of the fusion protein comprises a costimulatory domain or a functional portion thereof selected from CD27, CD28, 4-1BB (CD137), OX40 (CD134), CD2, CD5, ICAM-l (CD54), LFA-l (CD11a/CD18), ICOS (CD278), GITR, CD30, CD40, BAFF-R, HVEM, LIGHT, MKG2C, SLAMF7, NKp80, CD160, B7-H3, a ligand that binds (*e.g.*, specifically and/or selectively) with CD83, or a functional variant thereof, or any combination thereof. In some embodiments, the intracellular component comprises a CD28 costimulatory domain or a functional portion or variant thereof (which may optionally include a LL-GG mutation at positions 186-187 of the native CD28 protein (*e.g.*, Nguyen *et al*. (2003) *Blood* 702:4320), a 4-1BB costimulatory domain or a functional portion or variant thereof, or both.

In some embodiments, an effector domain comprises a CD3ε endodomain or a functional (*e.g.,* signaling) portion thereof, or a functional variant thereof. In further embodiments, an effector domain comprises a CD27 endodomain or a functional (*e.g.,* signaling) portion thereof, or a functional variant thereof. In further embodiments, an effector domain comprises a CD28 endodomain or a functional (*e.g.,* signaling) portion thereof, or a functional variant thereof. In still further embodiments, an effector domain comprises a 4-1BB endodomain or a functional (*e.g.,* signaling) portion thereof, or a functional variant thereof. In further embodiments, an effector domain comprises an OX40 endodomain or a functional (*e.g.,* signaling) portion thereof, or a functional variant thereof. In further embodiments, an effector domain comprises a CD2 endodomain or a functional (*e.g.,* signaling) portion thereof, or a functional variant thereof. In further embodiments, an effector domain comprises a CD5 endodomain or a functional (*e.g.,* signaling) portion

thereof, or a functional variant thereof. In further embodiments, an effector domain comprises an ICAM-l endodomain or a functional (*e.g.,* signaling) portion thereof, or a functional variant thereof. In further embodiments, an effector domain comprises a LFA-l endodomain or a functional (*e.g.,* signaling) portion thereof, or a functional variant thereof. In further embodiments, an effector domain comprises an ICOS endodomain or a functional (*e.g.,* signaling) portion thereof, or a functional variant thereof.

An extracellular component and an intracellular component encompassed by the present invention are connected by a transmembrane domain. A "transmembrane domain," as used herein, is a portion of a transmembrane protein that can insert into or span a cell membrane. Transmembrane domains have a three-dimensional structure that is thermodynamically stable in a cell membrane and generally range in length from about 15 amino acids to about 30 amino acids. The structure of a transmembrane domain may comprise an alpha helix, a beta barrel, a beta sheet, a beta helix, or any combination thereof. In some embodiments, the transmembrane domain comprises or is derived from a known transmembrane protein (*e.g.,* a CD4 transmembrane domain, a CD8 transmembrane domain, a CD27 transmembrane domain, a CD28 transmembrane domain, or any combination thereof).

In some embodiments, the extracellular component of the fusion protein further comprises a linker disposed between the binding domain and the transmembrane domain. As used herein when referring to a component of a fusion protein that connects the binding **and transmembrane domains, a "linker" may be an amino acid sequence having from about** two amino acids to about 500 amino acids, which can provide flexibility and room for conformational movement between two regions, domains, motifs, fragments, or modules connected by the linker. For example, a linker encompassed by the present invention can position the binding domain away from the surface of a host cell expressing the fusion protein to enable proper contact between the host cell and a target cell, antigen binding, and activation (Patel *et al.* (1999) *Gene Therapy* 6:412-419). Linker length may be varied to maximize antigen recognition based on the selected target molecule, selected binding epitope, or antigen binding domain seize and affinity (see, *e.g.,* Guest *et al.* (2005) *Immunother.* 28:203-11 and PCT Publ. No. WO 2014/031687). Exemplary linkers include those having a glycine-serine amino acid chain having from one to about ten repeats of Gly_xSer_y, wherein x and y are each independently an integer from 0 to 10, provided that x

and y are not both 0 (*e.g.,* $(Gly_4Ser)_2$, $(Gly_3Ser)_2$, Gly_2Ser, or a combination thereof, such as $((Gly_3Ser)_2Gly_2Ser)$).

Binding proteins encompassed by the present invention may, in some embodiments, be covalently linked to a moiety. In some embodiments, the covalently linked moiety comprises an affinity tag or a label. The affinity tag may be selected from the group consisting of Glutathione-S-Transferase (GST), calmodulin binding protein (CBP), protein C tag, Myc tag, HaloTag, HA tag, Flag tag, His tag, biotin tag, and V5 tag. The label may be a fluorescent protein. In some embodiments, the covalently linked moiety is selected from the group consisting of an inflammatory agent, an anti-inflammatory agent, a cytokine, a toxin, a cytotoxic molecule, a radioactive isotope, or an antibody such as a single-chain Fv.

A binding protein may be conjugated to an agent used in imaging, research, therapeutics, theranostics, pharmaceuticals, chemotherapy, chelation therapy, targeted drug delivery, and radiotherapy. In some embodiments, a binding protein may be conjugated to or fused with detectable agents, such as a fluorophore, a near-infrared dye, a contrast agent, a nanoparticle, a metal-containing nanoparticle, a metal chelate, an X-ray contrast agent, a PET agent, a metal, a radioisotope, a dye, radionuclide chelator, or another suitable material that can be used in imaging. In some embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more detectable moieties may be linked to a binding protein. Non-limiting examples of radioisotopes include alpha emitters, beta emitters, positron emitters, and gamma emitters. In some embodiments, the metal or radioisotope is selected from the group consisting of actinium, americium, bismuth, cadmium, cesium, cobalt, europium, gadolinium, iridium, lead, lutetium, manganese, palladium, polonium, radium, ruthenium, samarium, strontium, technetium, thallium, and yttrium. In some embodiments, the metal is actinium, bismuth, lead, radium, strontium, samarium, or yttrium. In some embodiments, the radioisotope is actinium-225 or lead-212. In some embodiments, the near-infrared dyes are not easily quenched by biological tissues and fluids. In some embodiments, the fluorophore is a fluorescent agent emitting electromagnetic radiation at a wavelength between 650 nm and 4000 nm, such emissions being used to detect such agent. Non-limiting examples of fluorescent dyes that may be used as a conjugating molecule include DyLight-680, DyLight-750, VivoTag-750, DyLight-800, IRDye-800, VivoTag-680, Cy5.5, ZQ800, or indocyanine green (ICG). In some embodiments, near infrared dyes often include cyanine dyes (*e.g.,* Cy7, Cy5.5, and Cy5). Additional, non-limiting examples of fluorescent dyes

for use as a conjugating molecule in accordance with present invention include acradine orange or yellow, Alexa Fluors® (*e.g.,* Alexa Fluor® 790, 750, 700, 680, 660, and 647) and any derivative thereof, 7-actinomycin D, 8-anilinonaphthalene-1-sulfonic acid, ATTO® dye and any derivative thereof, auramine-rhodamine stain and any derivative thereof, bensantrhone, bimane, 9-10-bis(phenylethynyl)anthracene, 5,12-bis(phenylethynyl)naththacene, bisbenzimide, brainbow, calcein, carbodyfluorescein and any derivative thereof, 1-chloro-9,10-bis(phenylethynyl)anthracene and any derivative thereof, DAPI, DiOC6, DyLight® Fluors® and any derivative thereof, epicocconone, ethidium bromide, FlAsH-EDT2®, Fluo dye and any derivative thereof, FluoProbe® and any derivative thereof, fluorescein and any derivative thereof, Fura® and any derivative thereof, GelGreen® and any derivative thereof, GelRed® and any derivative thereof, fluorescent proteins and any derivative thereof, m isoform proteins and any derivative thereof such as for example mCherry, hetamethine dye and any derivative thereof, hoeschst stain, iminocoumarin, indian yellow, indo-1 and any derivative thereof, laurdan, lucifer yellow and any derivative thereof, luciferin and any derivative thereof, luciferase and any derivative thereof, mercocyanine and any derivative thereof, nile dyes and any derivative thereof, perylene, phloxine, phyco dye and any derivative thereof, propium iodide, pyranine, rhodamine and any derivative thereof, ribogreen, RoGFP, rubrene, stilbene and any derivative thereof, sulforhodamine and any derivative thereof, SYBR and any derivative thereof, synapto-pHluorin, tetraphenyl butadiene, tetrasodium tris, Texas Red, Titan Yellow, TSQ, umbelliferone, violanthrone, yellow fluorescent protein and YOYO-1. Other suitable fluorescent dyes include, but are not limited to, fluorescein and fluorescein dyes (*e.g.,* fluorescein isothiocyanine or FITC, naphthofluorescein, 4', 5'-dichloro-2',7'-dimethoxyfluorescein, 6-carboxyfluorescein or FAM, *etc.*), carbocyanine, merocyanine, styryl dyes, oxonol dyes, phycoerythrin, erythrosin, eosin, rhodamine dyes (*e.g.,* carboxytetramethyl-rhodamine or TAMRA, carboxyrhodamine 6G, carboxy-X-rhodamine (ROX), lissamine rhodamine B, rhodamine 6G, rhodamine Green, rhodamine Red, tetramethylrhodamine (TMR), *etc.*), coumarin and coumarin dyes (*e.g.,* methoxycoumarin, dialkylaminocoumarin, hydroxycoumarin, aminomethylcoumarin (AMCA), *etc.*), Oregon Green™ dyes (*e.g.,* Oregon Green™ 488, 500, 514., *etc.*), Texas Red®, Texas Red®-X, SPECTRUM RED®, SPECTRUM GREEN®, cyanine dyes (*e.g.,* CY-3, Cy-5, CY-3.5, CY-5.5, *etc.*), Alexa Fluor® dyes (*e.g.,* Alexa Fluor® 350, 488, 532, 546, 568, 594, 633, 660, 680, *etc.*), BODIPY® dyes (*e.g.,* BODIPY® FL, R6G, TMR, TR, 530/550, 558/568,

564/570, 576/589, 581/591, 630/650, 650/665, *etc.*), IRD dyes (*e.g.,* IRD40™, IRD700™, IRD800™, *etc.*), and the like. Additional suitable detectable agents are well-known in the art (*e.g.*, PCT Publ. No. PCT/US14/56177). Non-limiting examples of radioisotopes include alpha emitters, beta emitters, positron emitters, and gamma emitters. In some embodiments, the metal or radioisotope is selected from the group consisting of actinium, americium, bismuth, cadmium, cesium, cobalt, europium, gadolinium, iridium, lead, lutetium, manganese, palladium, polonium, radium, ruthenium, samarium, strontium, technetium, thallium, and yttrium. In some embodiments, the metal is actinium, bismuth, lead, radium, strontium, samarium, or yttrium. In some embodiments, the radioisotope is actinium-225 or lead-212.

Binding proteins may be conjugated to a radiosensitizer or photosensitizer. Examples of radiosensitizers include but are not limited to: ABT-263, ABT-199, WEHI-539, paclitaxel, carboplatin, cisplatin, oxaliplatin, gemcitabine, etanidazole, misonidazole, tirapazamine, and nucleic acid base derivatives (*e.g.,* halogenated purines or pyrimidines, such as 5-fluorodeoxyuridine). Examples of photosensitizers include but are not limited to: fluorescent molecules or beads that generate heat when illuminated, nanoparticles, porphyrins and porphyrin derivatives (*e.g.,* chlorins, bacteriochlorins, isobacteriochlorins, phthalocyanines, and naphthalocyanines), metalloporphyrins, metallophthalocyanines, angelicins, chalcogenapyrrillium dyes, chlorophylls, coumarins, flavins and related compounds such as alloxazine and riboflavin, fullerenes, pheophorbides, pyropheophorbides, cyanines (*e.g.,* merocyanine 540), pheophytins, sapphyrins, texaphyrins, purpurins, porphycenes, phenothiaziniums, methylene blue derivatives, naphthalimides, nile blue derivatives, quinones, perylenequinones (*e.g.,* hypericins, hypocrellins, and cercosporins), psoralens, quinones, retinoids, rhodamines, thiophenes, verdins, xanthene dyes (*e.g.,* eosins, erythrosins, rose bengals), dimeric and oligomeric forms of porphyrins, and prodrugs such as 5-aminolevulinic acid. Advantageously, this approach allows for highly specific targeting of cells of interest (*e.g.,* immune cells) using both a therapeutic agent (*e.g.,* drug) and electromagnetic energy (*e.g.,* radiation or light) concurrently. In some embodiments, the binding protein is fused with, or covalently or non-covalently linked to the agent, for example, directly or via a linker.

In some embodiments, the binding protein may be chemically modified. For example, a binding protein may be mutated to modify peptide properties such as detectability, stability, biodistribution, pharmacokinetics, half-life, surface charge,

hydrophobicity, conjugation sites, pH, function, and the like. N-methylation is one example of methylation that can occur in a binding protein encompassed by the present invention. In some embodiments, a binding protein may be modified by methylation on free amines such as by reductive methylation with formaldehyde and sodium cyanoborohydride.

A chemical modification may comprise a polymer, a polyether, polyethylene glycol, a biopolymer, a zwitterionic polymer, a polyamino acid, a fatty acid, a dendrimer, an Fc region, a simple saturated carbon chain such as palmitate or myristolate, or albumin. The chemical modification of a binding protein with an Fc region may be a fusion Fc-protein. A polyamino acid may include, for example, a poly amino acid sequence with repeated single amino acids (*e.g.,* poly glycine), and a poly amino acid sequence with mixed poly amino acid sequences that may or may not follow a pattern, or any combination of the foregoing.

In some embodiments, the binding proteins encompassed by the present invention may be modified. In some embodiments, the modifications having substantial or significant sequence identity to a parent binding protein to generate a functional variant that maintains one or more biophysical and/or biological activities of the parent binding protein (*e.g.*, maintain pMHC binding specificity). In some embodiments, the mutation is a conservative amino acid substitution.

In some embodiments, binding proteins encompassed by the present invention may comprise synthetic amino acids in place of one or more naturally-occurring amino acids. Such synthetic amino acids are well-known in the art, and include, for example, aminocyclohexane carboxylic acid, norleucine, a-amino n-decanoic acid, homoserine, S-acetylaminomethyl-cysteine, trans-3- and trans-4-hydroxyproline, 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-**carboxyphenylalanine, β-phenylserine β-**hydroxyphenylalanine, phenylglycine, a-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, a-aminocyclopentane carboxylic acid, oc-aminocyclohexane carboxylic acid, a-aminocycloheptane carboxylic acid, a-(2-amino-2-norbornane)-**carboxylic acid, α,γ-diaminobutyric acid, ,β**-diaminopropionic acid, homophenylalanine, and oc-tert-butylglycine.

Binding proteins encompassed by the present invention may be glycosylated, amidated, carboxylated, phosphorylated, esterified, N-acylated, cyclized (*e.g.*, via a disulfide bridge), or converted into an acid addition salt and/or optionally dimerized or polymerized, or conjugated.

In some embodiments, the attachment of a hydrophobic moiety, such as to the N-terminus, the C-terminus, or an internal amino acid, may be used to extend half-life of a peptide encompassed by the present invention. In other embodiments, a binding protein may include post-translational modifications (*e.g.,* methylation and/or amidation), which can affect, for example, serum half-life. In some embodiments, simple carbon chains (*e.g.,* by myristoylation and/or palmitylation) may be conjugated to the binding proteins. In some embodiments, the simple carbon chains may render the binding proteins easily separable from the unconjugated material. For example, methods that may be used to separate the binding proteins from the unconjugated material include, but are not limited to, solvent extraction and reverse phase chromatography. The lipophilic moieties can extend half-life through reversible binding to serum albumin. The conjugated moieties may be lipophilic moieties that extend half-life of the peptides through reversible binding to serum albumin. In some embodiments, the lipophilic moiety may be cholesterol or a cholesterol derivative, including cholestenes, cholestanes, cholestadienes and oxysterols. In some embodiments, the binding proteins may be conjugated to myristic acid (tetradecanoic acid) or a derivative thereof. In other embodiments, a binding protein may be coupled (*e.g.,* conjugated) to a half-life modifying agent. Examples of half-life modifying agents include but are not limited to: a polymer, a polyethylene glycol (PEG), a hydroxyethyl starch, polyvinyl alcohol, a water soluble polymer, a zwitterionic water soluble polymer, a water soluble poly(amino acid), a water soluble polymer of proline, alanine and serine, a water soluble polymer containing glycine, glutamic acid, and serine, an Fc region, a fatty acid, palmitic acid, or a molecule that binds to albumin. In some embodiments, a spacer or linker may be coupled to a binding protein, such as 1, 2, 3, 4, or more amino acid residues that serve as a spacer or linker in order to facilitate conjugation or fusion to another molecule, as well as to facilitate cleavage of the peptide from such conjugated or fused molecules. In some embodiments, binding proteins may be conjugated to other moieties that, for example, can modify or effect changes to the properties of the binding proteins.

A binding protein may be produced recombinantly or synthetically, such as by solid-phase peptide synthesis or solution-phase peptide synthesis. Polypeptide synthesis

may be performed by known synthetic methods, such as using fluorenylmethyloxycarbonyl (Fmoc) chemistry or by butyloxycarbonyl (Boc) chemistry. Polypeptide fragments may be joined together enzymatically or synthetically.

In an aspect encompassed by the present invention, provided herein are methods of producing a binding protein described herein, comprising the steps of: (i) culturing a transformed host cell which has been transformed by a nucleic acid comprising a sequence encoding a binding protein described herein under conditions suitable to allow expression of said binding protein; and (ii) recovering the expressed binding protein.

Methods useful for isolating and purifying recombinantly produced binding protein, by way of example, may include obtaining supernatants from suitable host cell/vector systems that secrete the binding protein into culture media and then concentrating the media using a commercially available filter. Following concentration, the concentrate may be applied to a single suitable purification matrix or to a series of suitable matrices, such as an affinity matrix or an ion exchange resin. One or more reverse phase HPLC steps may be employed to further purify a recombinant polypeptide. These purification methods may also be employed when isolating an immunogen from its natural environment. Methods for large scale production of one or more of binding proteins described herein include batch cell culture, which is monitored and controlled to maintain appropriate culture conditions. Purification of the binding protein may be performed according to methods described herein and known in the art.

In any of the herein disclosed embodiments, the encoded binding protein is capable of bind to a peptide–MHC (pMHC) complex comprising an HA-2 immunogenic peptide in the context of an MHC molecule (*e.g.,* a MHC class I molecule). In some embodiments, the MHC molecule comprises an MHC alpha chain that is an HLA serotype HLA-A*02. In some embodiments, the HLA allele is selected from the group consisting of HLA-A*0201, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele.

A variety of assays are well-known for assessing binding affinity and/or determining whether a binding molecule binds (*e.g.*, specifically and/or selectively) to a particular ligand (*e.g.,* peptide antigen-MHC complex). It is within the level of a skilled artisan to determine the binding affinity of a binding protein for a target, such as a T cell peptide epitope of a target polypeptide, such as by using any of a number of binding assays that are well-known in the art. For example, in some embodiments, a Biacore™ machine may be used to determine the binding constant of a complex between two proteins. The

dissociation constant (K_D) for the complex may be determined by monitoring changes in the refractive index with respect to time as buffer is passed over the chip. Other suitable assays for measuring the binding of one protein to another include, for example, immunoassays such as enzyme linked immunosorbent assays (ELISA) and radioimmunoas says (RIA), or determination of binding by monitoring the change in the spectroscopic or optical properties of the proteins through fluorescence, UV absorption, circular dichroism, or nuclear magnetic resonance (NMR). Other exemplary assays include, but are not limited to, Western blot, ELISA, analytical ultracentrifugation, spectroscopy and surface plasmon resonance (Biacore™) analysis (see, *e.g.,* Scatchard *et al.* (1949) *Ann. N.Y. Acad. Sci.* 51:660, Wilson (2002) *Science* 295:2103, Wolff *et al.* (1993) *Cancer Res.* 53:2560, and U.S. Pat. Nos. 5,283,173 and 5,468,614), flow cytometry, sequencing and other methods for detection of expressed nucleic acids. In one example, apparent affinity for a target is measured by assessing binding to various concentrations of tetramers, for example, by flow cytometry using labeled multimers, such as MHC-antigen tetramers. In one representative example, apparent K_D of a binding protein is measured using 2-fold dilutions of labeled tetramers at a range of concentrations, followed by determination of binding curves by non-linear regression, apparent K_D being determined as the concentration of ligand that yielded half-maximal binding.

III. Nucleic Acids and Vectors

In an aspect encompassed by the present invention, provided herein are nucleic acid molecules that encode binding proteins (*e.g.,* TCRs, antigen-binding fragments of the TCRs, CARs, and the like), peptides, and fragments thereof described herein.

In some embodiments, the nucleic acid molecule hybridizes, under stringent conditions, with the complement of a sequence with at least about at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity, such as over the full length, to a nucleic acid encoding a polypeptide selected from the group consisting of the polypeptide sequences listed in Table 1.

In some embodiments, the nucleic acid molecule hybridizes, under stringent conditions, with the complement of a nucleic acid encoding a polypeptide selected from the group consisting of polypeptide sequences listed in Table 1.

In some embodiments, the nucleic acid molecule comprises (*e.g.,* comprises, consists essentially of, or consists of) a nucleotide sequence encoding a polypeptide selected from the group consisting of polypeptide sequences listed in Table 1.

In some embodiments, the nucleic acids comprise (*e.g.,* comprise, consist essentially of, or consist of) a nucleotide sequence encoding at least one (*e.g.,* one, two, or three) TCR α-chain CDR set forth in Table 1. In some embodiments, the nucleic acids comprise (*e.g.,* comprise, consist essentially of, or consist of) a nucleotide sequence encoding a TCR V_α domain having an amino acid sequence that is at least about at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR V_α domain sequence set forth in Table 1. In some embodiments, the nucleic acids comprise (*e.g.,* comprise, consist essentially of, or consist of) a nucleotide sequence encoding a TCR α-chain having an amino acid sequence that is at least about at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR α-chain sequence set forth in Table 1.

In some embodiments, the nucleic acids comprise (*e.g.,* comprise, consist essentially of, or consist of) a nucleotide sequence encoding at least one (*e.g.,* one, two, or three) TCR β-chain CDR set forth in Table 1. In some embodiments, the nucleic acids comprise (*e.g.,* comprise, consist essentially of, or consist of) a nucleotide sequence encoding a TCR V_β domain having an amino acid sequence that is at least about at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR V_β domain sequence set forth in Table 1. In some embodiments, the nucleic acids comprise (*e.g.,* comprise, consist essentially of, or consist of) a nucleotide sequence encoding a TCR β-chain having an amino acid sequence that is at least about at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identity to a TCR β-chain sequence set forth in Table 1.

The term "nucleic acid" includes "polynucleotide," "oligonucleotide," and "nucleic acid molecule," and generally means a polymer of DNA or RNA, which may be single-stranded or double-stranded, synthesized or obtained (*e.g.,* isolated and/or purified) from natural sources, which may contain natural, non-natural or altered nucleotides, and which may 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).

In some embodiments, the nucleic acids encompassed by the present 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 may replicate in a living cell, or (ii) molecules that result from the replication of those described in (i) above. For purposes herein, the replication may be *in vitro*/*ex vivo* replication or *in vivo* replication.

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 may 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 may be used to generate the nucleic acids include, but are not limited to, 5-fiuorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N^6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N^6-substituted adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N^6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, 3-(3-amino-3-N-2-carboxypropyl) uracil, and 2,6-diaminopurine. Alternatively, one or more of the nucleic acids encompassed by the present invention can be purchased from companies, such as Integrated DNA Technologies (Coralville, IA).

In one embodiment, the nucleic acid comprises a codon-optimized nucleotide sequence. Without being bound to a 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. In some embodiments, the nucleotide sequences described herein are codon-optimized for expression in a host cell (*e.g.,* an immune cell, such as a T cell).

The present 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.

The nucleotide sequence which hybridizes under stringent conditions may hybridize 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 may be rendered more stringent by the addition of increasing amounts of formamide.

The present invention also provides a nucleic acid comprising a nucleotide sequence that is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identical to any of the nucleic acids described herein.

Typically, said nucleic acid is a DNA or RNA molecule, which may be included in a suitable vector, such as a plasmid, cosmid, episome, artificial chromosome, phage or a viral vector.

The terms "vector", "cloning vector" and "expression vector" mean the vehicle by which a DNA or RNA sequence (*e.g.,* a foreign gene) can be introduced into a host cell, so as to transform the host and promote expression (*e.g.,* transcription and translation) of the introduced sequence. Thus, a further object encompassed by the present invention relates to a vector comprising a nucleic acid encompassed by the present invention. In some embodiments, the vector is selected from the group of vectors shown in Table 2.

Such vectors may comprise regulatory elements, such as a promoter, enhancer, terminator and the like, to cause or direct expression of said polypeptide upon administration to a subject. Examples of promoters and enhancers used in the expression vector for animal cell include early promoter and enhancer of SV40 (Mizukami T. *et al.* 1987), LTR promoter and enhancer of Moloney mouse leukemia virus (Kuwana Y *et al.* 1987), promoter (Mason J O *et al.* 1985) and enhancer (Gillies S D *et al.* 1983) of immunoglobulin H chain and the like.

Any expression vector for animal cell may be used. Examples of suitable vectors include pAGE107 (Miyaji H *et al.* 1990), pAGE103 (Mizukami T *et al.* 1987), pHSG274 (Brady G *et al.* 1984), pKCR (O'Hare K *et al.* 1981), pSG1 beta d2-4-(Miyaji H *et al.* 1990) and the like. Other representative examples of plasmids include replicating plasmids comprising an origin of replication, or integrative plasmids, such as for instance pUC, pcDNA, pBR, and the like. Representative examples of viral vector include adenoviral, retroviral, lentiviral, herpes virus and AAV vectors. Such recombinant viruses may be produced by techniques known in the art, such as by transfecting packaging cells or by transient transfection with helper plasmids or viruses. Typical examples of virus packaging cells include PA317 cells, PsiCRIP cells, GPenv-positive cells, 293 cells, *etc.* Detailed protocols for producing such replication-defective recombinant viruses are well-known in the art and may be found, for instance, in PCT Publ. WO 95/14785, PCT. Publ. WO 96/22378, U.S. Pat. No. 5,882,877, U.S. Pat. No. 6,013,516, U.S. Pat. No. 4,861,719, U.S. Pat. No. 5,278,056, and PCT Publ. WO 94/19478.

In some embodiments, the composition comprises an expression vector comprising an open reading frame encoding a binding protein or a polypeptide described herein or a fragment thereof. In some embodiments, the nucleic acid includes regulatory elements necessary for expression of the open reading frame. Such elements may include, for example, a promoter, an initiation codon, a stop codon, and a polyadenylation signal. In

addition, enhancers may be included. These elements may be operably linked to a sequence that encodes the binding protein, polypeptide or fragment thereof.

In some embodiments, the vector further comprises nucleic acid sequence encoding CD8α and/or CD8β. In certain embodiments, the nucleic acid sequence encoding CD8α or CD8β is operably linked to a nucleic acid encoding a tag (*e.g.*, a CD34 enrichment tag). In specific embodiments, the nucleic acid sequence encoding CD8α and/or CD8β are interconnected with an internal ribosome entry site or a nucleic acid sequence encoding a self-cleaving peptide, such as P2A, E2A, F2A or T2A, etc.

In some embodiments, the expression vector provided herein comprises a nucleotide sequence that is at least about 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more identical to any of the nucleic acids set forth in Table 2.

Examples of promoters include, but are not limited to, promoters from Simian Virus 40 (SV40), Mouse Mammary Tumor Virus (MMTV) promoter, Human Immunodeficiency Virus (HIV) such as the HIV Long Terminal Repeat (LTR) promoter, Moloney virus, Cytomegalovirus (CMV) such as the CMV immediate early promoter, Epstein Barr Virus (EBV), Rous Sarcoma Virus (RSV) as well as promoters from human genes such as human actin, human myosin, human hemoglobin, human muscle creatine, and human metalothionein. Examples of suitable polyadenylation signals include but are not limited to SV40 polyadenylation signals and LTR polyadenylation signals.

In addition to the regulatory elements required for expression, other elements may also be included in the nucleic acid molecule. Such additional elements include enhancers. Enhancers include the promoters described herein. In some embodiments, enhancers/promoters include, for example, human actin, human myosin, human hemoglobin, human muscle creatine and viral enhancers such as those from CMV, RSV and EBV.

In some embodiments, the nucleic acid may be operably incorporated in a carrier or delivery vector as described further below. Useful delivery vectors include but are not limited to biodegradable microcapsules, immuno-stimulating complexes (ISCOMs) or liposomes, and genetically engineered attenuated live carriers such as viruses or bacteria.

In some embodiments, the vector is a viral vector, such as lentiviruses, retroviruses, herpes viruses, adenoviruses, adeno-associated viruses, vaccinia viruses, baculoviruses,

Fowl pox, AV-pox, modified vaccinia Ankara (MVA) and other recombinant viruses. For example, a lentivirus vector may be used to infect T cells.

In some embodiments, the recombinant expression vector is capable of delivering a polynucleotide to an appropriate host cell, for example, a T cell or an antigen-presenting cell, *i.e.,* a cell that displays a peptide/MHC complex on its cell surface (*e.g.*, a dendritic cell) and lacks CD8. In some embodiments, the host cell is a hematopoietic progenitor cell or a human immune system cell. For example, the immune system cell may be a $CD4^+$ T cell, a $CD8^+$ T cell, a CD4/CD8 double negative T cell, a gd T cell, a natural killer cell, a dendritic cell, or any combination thereof. In some embodiments, wherein a T cell is the host, the T cell may be naive, a central memory T cell, an effector memory T cell, or any combination thereof. The recombinant expression vectors may therefore also include, for example, lymphoid tissue-specific transcriptional regulatory elements (TREs), such as a B lymphocyte, T lymphocyte, or dendritic cell specific TREs. Lymphoid tissue specific TREs are known in the art (see, *e.g.,* Thompson *et al.* (1992) *Mol. Cell. Biol.* 72:1043, Todd *et al.* (1993) *J. Exp. Med.* 777:1663, and Penix *et al.* (1993) *J. Exp. Med.* 775:1483).

In some embodiments, a recombinant expression vector comprises a nucleotide sequence encoding a TCR α chain, a TCR β chain, and/or a linker peptide. For example, in some embodiments, the recombinant expression vector comprises a nucleotide sequence encoding the full-length TCR alpha and TCR beta chains of the binding protein with a linker positioned between them, wherein the nucleotide sequence encoding the beta chain is positioned 5' of the nucleotide sequence encoding the alpha chain. In some embodiments, the nucleotide sequence encodes the full-length TCR alpha and TCR beta chains with a linker positioned between them, wherein the nucleotide sequence encoding the TCR beta chain is positioned 3 ' of the nucleotide sequence encoding the TCR alpha chain. In some embodiments, the full-length TCR alpha and/or TCR beta chains are replaced with fragments thereof.

As described further below, another aspect encompassed by the present invention relates to a cell which has been transfected, infected or transformed by a nucleic acid and/or a vector in accordance with the present invention. A host cell may include any individual cell or cell culture which may receive a vector or the incorporation of nucleic acids and/or proteins, as well as any progeny cells. The term also encompasses progeny of the host cell, whether genetically or phenotypically the same or different. Suitable host cells may depend on the vector and may include mammalian cells, animal cells, human cells, simian cells,

insect cells, yeast cells, and bacterial cells. These cells may be induced to incorporate the vector or other material by use of a viral vector, transformation via calcium phosphate precipitation, DEAE-dextran, electroporation, microinjection, or other methods (see, *e.g.*, Sambrook *el al.* (1989) *Molecular Cloning: A Laboratory Manual 2d ed.* (Cold Spring Harbor Laboratory)). The term "transformation" means the introduction of a "foreign" (*i.e.*, extrinsic or extracellular) gene, DNA or RNA sequence to a host cell, so that the host cell will express the introduced gene or sequence to produce a desired substance, typically a protein or enzyme coded by the introduced gene or sequence. A host cell that receives and expresses introduced DNA or RNA has been "transformed."

The nucleic acids encompassed by the present invention may be used to produce a recombinant polypeptide encompassed by the present invention in a suitable expression system. The term "expression system" means a host cell and compatible vector under suitable conditions, *e.g.,* for the expression of a protein coded for by foreign DNA carried by the vector and introduced to the host cell.

Common expression systems include *E. coli* host cells and plasmid vectors, insect host cells and *Baculovirus* vectors, and mammalian host cells and vectors. Other examples of host cells include, without limitation, prokaryotic cells (such as bacteria) and eukaryotic cells (such as yeast cells, mammalian cells, insect cells, plant cells, *etc.*). Specific examples include *E. coli*, *Kluyveromyces* or *Saccharomyces* yeasts, mammalian cell lines (*e.g.,* Vero cells, CHO cells, 3T3 cells, COS cells, *etc.*) as well as primary or established mammalian cell cultures (*e.g.,* produced from lymphoblasts, fibroblasts, embryonic cells, epithelial cells, nervous cells, adipocytes, *etc.*). Examples also include mouse SP2/0-Ag14 cell (ATCC CRL1581), mouse P3X63-Ag8.653 cell (ATCC CRL1580), CHO cell in which a dihydrofolate reductase gene (hereinafter referred to as "DHFR gene") is defective (Urlaub G *et al* (1980), rat YB2/3HL.P2.G11.16Ag.20 cell (ATCC CRL 1662, hereinafter referred to as "YB2/0 cell"), and the like. In some embodiments, the YB2/0 cell is used since ADCC activity of chimeric or humanized binding proteins is enhanced when expressed in this cell.

The present invention also encompasses methods of producing a recombinant host cell expressing binding proteins, peptides and fragments thereof encompassed by the present invention, said method comprising the steps consisting of (i) introducing *in vitro* or *ex vivo* a recombinant nucleic acid or a vector as described above into a competent host cell, (ii) culturing *in vitro* or *ex vivo* the recombinant host cell obtained and (iii), optionally,

selecting the cells which express said binding proteins, peptides and fragments thereof. Such recombinant host cells may be used for the diagnostic, prognostic, and/or therapeutic method encompassed by the present invention.

In another aspect, the present invention provides isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein. Thus, the polynucleotides of this embodiment may be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides. For example, polynucleotides encompassed by the present invention may be used to identify, isolate, or amplify partial or full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated, or otherwise complementary to, a cDNA from a human or mammalian nucleic acid library. In some embodiments, the cDNA library comprises at least about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more, or any range in between, inclusive, such as at least about 80%-100%, full-length sequences. The cDNA libraries may be normalized to increase the representation of rare sequences. Low or moderate stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative to complementary sequences. Moderate and high stringency conditions may optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 70% sequence identity and may be employed to identify orthologous or paralogous sequences. Optionally, polynucleotides encompassed by the present invention will encode at least a portion of a binding protein encoded by the polynucleotides described herein. The polynucleotides encompassed by the present invention embrace nucleic acid sequences that may be employed for selective hybridization to a polynucleotide encoding a binding protein encompassed by the present invention (see, *e.g.,* Ausubel, supra and Colligan, supra).

IV. Host Cells

In an aspect encompassed by the present invention, provided herein are host cells that express the binding proteins (*e.g.,* TCRs, antigen-binding fragments of TCRs, CARs, or fusion proteins comprising a TCR and an effector domain) described herein. In some embodiments, the host cells comprise the nucleic acids or vectors described herein.

In some embodiments, a polynucleotide encoding a binding protein is used to transform, transfect, or transduce a host cell (*e.g.*, a T cell) for use in adoptive transfer therapy. Advances in nucleic acid sequencing and particular TCR sequencing have been described (*e.g.,* Robins *et al.* (2009) *Blood* 114:4099; Robins *et al.* (2010) *Sci. Translat. Med.* 2:47ra64, Robins *et al.* (2011) *J. Imm. Meth.*, and Warren *et al.* (2011) *Genome Res.* 21:790) and may be employed in the course of practicing embodiments encompassed by the present invention. Similarly, methods for transfecting or transducing T cells with desired nucleic acids are well-known in the art (*e.g.,* U.S. Pat. Publ. No. US 2004/0087025) as have adoptive transfer procedures using T cells of desired antigen-specificity (*e.g.,* Schmitt *et al.* (2009) *Hum. Gen.* 20:1240, Dossett *et al.* (2009) *Mol. Ther.* 77:742, Till *et al.* (2008) *Blood* 772:2261, Wang *et al.* (2007) *Hum. Gene Ther.* 18:112, Kuball *et al.* (2007) *Blood* 709:2331, U.S. Pat. Publ. 2011/0243972, U.S. Pat. Publ. 2011/0189141, and Leen *et al.* (2007) *Ann. Rev. Immunol.* 25:243).

Any suitable immune cell may be modified to include a heterologous polynucleotide encompassed by the present invention, including, for example, a T cell, a NK cell, or a NK-T cell. In some embodiments, the cell may be a primary cell or a cell of a cell line. In some embodiments, a modified immune cell comprises a $CD4^+$T cell, a $CD8^+$ T cell, or both. For purposes herein, the T cell may 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 may be obtained from numerous sources, including but not limited to blood, bone marrow, lymph node, the thymus, or other tissues or fluids. T cells may also be enriched for or purified. In some embodiments, the T cell is a human T cell. In some embodiments, the T cell is a T cell isolated from a human. The T cell may be any type of T cell and may be of any developmental stage, including but not limited to, cytotoxic lymphocyte, cytotoxic lymphocyte precursor cell, cytotoxic lymphocyte progenitor cell, cytotoxic lymphocyte stem cell, $CD4^+/CD8^+$ 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), naive T cells, and the like.

Any appropriate method may be used to transfect or transduce the cells, for example, T cells, or to administer the nucleotide sequences or compositions encompassed by methods described herein. Methods for delivering polynucleotides to host cells include,

for example, use of cationic polymers, lipid-like molecules, and certain commercial products such as, for example, in vivo-jetPEI®. Other methods include *ex vivo* transduction, injection, electroporation, DEAE-dextran, sonication loading, liposome-mediated transfection, receptor-mediated transduction, microprojectile bombardment, transposon-mediated transfer, and the like. Still further methods of transfecting or transducing host cells employ vectors, described in further detail herein.

Modified immune cells as described herein may be functionally characterized using methodologies for assaying T cell activity, including determination of T cell binding, activation or induction and also including determination of T cell responses that are antigen-specific. Examples include determination of T cell proliferation, T cell cytokine release, antigen-specific T cell stimulation, MHC restricted T cell stimulation, CTL activity (*e.g.,* by detecting ^{51}Cr release from pre-loaded target cells), changes in T cell phenotypic marker expression, and other measures of T-cell functions.

Procedures for performing these and similar assays may be found, for example, in Lefkovits (Immunology Methods Manual: Hie Comprehensive Sourcebook of Techniques, 1998), as well as Current Protocols in Immunology, Weir, (1986) Handbook of Experimental Immunology, Blackwell Scientific, Boston, MA; Mishell and Shigii (eds.) (1979) Selected Methods in Cellular Immunology, Freeman Publishing, San Francisco, CA; Green and Reed (1998) *Science* 281:1309, and references cited therein.

In some embodiments, apparent affinity for a binding protein, such as a TCR or antigen-binding portion thereof, may be measured by assessing binding to various concentrations of MHC multimers. "MHC-peptide multimer staining" refers to an assay used to detect antigen-specific T cells, which, in some embodiments, features a tetramer of MHC molecules, each comprising an identical peptide having an amino acid sequence that is cognate (*e.g.,* identical or related to) at least one antigen (*e.g.,* an HA-2 immunogenic peptide), wherein the complex is capable of binding to a binding protein, such as a TCR or antigen-binding portion thereof, that recognizes the cognate antigen. Each of the MHC molecules may be tagged with a biotin molecule. Biotinylated MHC/peptides may be multimerized (*e.g.*, tetramerized) by the addition of streptavidin, which may be fluorescently labeled.

The multimer may be detected by flow cytometry via the fluorescent label. In some embodiments, a pMHC multimer assay is used to detect or select enhanced affinity binding protein, such as a TCR or antigen-binding portion thereof, encompassed by the present

invention. In some examples, apparent K_D of a binding protein, such as a TCR or antigen-binding portion thereof, is measured using 2-fold dilutions of labeled multimers at a range of concentrations, followed by determination of binding curves by non-linear regression, apparent K_D being determined as the concentration of ligand that yielded half-maximal binding.

Levels of cytokines may be determined using methods described herein, such as ELISA, ELISPOT, intracellular cytokine staining, and flow cytometry and combinations thereof (*e.g.,* intracellular cytokine staining and flow cytometry).

Immune cell proliferation and clonal expansion resulting from an antigen-specific elicitation or stimulation of an immune response may be determined by isolating lymphocytes, such as circulating lymphocytes in samples of peripheral blood cells or cells from lymph nodes, stimulating the cells with antigen, and measuring cytokine production, cell proliferation and/or cell viability, such as by incorporation of tritiated thymidine or non-radioactive assays, such as MTT assays and the like. The effect of an immunogen described herein on the balance between a Thl immune response and a Th2 immune response may be examined, for example, by determining levels of Thl cytokines, such as IFN-g, IL-12, IL-2, and TNF-b, and Type 2 cytokines, such as IL-4, IL-5, IL-9, IL-10, and IL-l3.

A host cell encompassed by the present invention may comprise a single polynucleotide that encodes a binding protein as described herein, or the binding protein may be encoded by more than one polynucleotide. In other words, components or portions of a binding protein may be encoded by two or more polynucleotides, which may be contained on a single nucleic acid molecule or may be contained on two or more nucleic acid molecules.

In some embodiments, a polynucleotide encoding two or more components or portions of a binding protein encompassed by the present invention comprises the two or more coding sequences operatively associated in a single open reading frame. Such an arrangement can advantageously allow coordinated expression of desired gene products, such as, for example, contemporaneous expression of alpha- and beta-chains of a TCR, such that they are produced in about a 1:1 ratio. In some embodiments, two or more substituent gene products of a binding protein encompassed by the present invention, such as a TCR (*e.g.,* alpha- and beta-chains) or CAR, are expressed as separate molecules and associate post-translationally. In further embodiments, two or more substituent gene

products of a binding protein encompassed by the present invention are expressed as a single peptide with the parts separated by a cleavable or removable segment. For instance, self-cleaving peptides useful for expression of separable polypeptides encoded by a single polynucleotide or vector are known in the art and include, for example, a porcine teschovirus-1 2 A (P2A) peptide, a thoseaasigna virus 2A (T2A) peptide, an equine rhinitis A virus (ERAV) 2A (E2A) peptide, and a foot-and-mouth disease vims 2A (F2A) peptide.

In some embodiments, a binding protein encompassed by the present invention comprises one or more junction amino acids. "Junction amino acids" or "junction amino acid residues" refer to one or more (*e.g.,* 2 to about 10) amino acid residues between two adjacent motifs, regions or domains of a polypeptide, such as between a binding domain and an adjacent constant domain or between a TCR chain and an adjacent self-cleaving peptide. Junction amino acids can result from the design of a construct that encodes a fusion protein (*e.g.,* amino acid residues resulting from the use of a restriction enzyme site during the construction of a nucleic acid molecule encoding a fusion protein), or from cleavage of, for example, a self-cleaving peptide adjacent one or more domains of an encoded binding protein encompassed by the present invention (*e.g.,* a P2A peptide disposed between a TCR a-**chain and a TCR** β-chain, the self-cleavage of which can leave one or more junction amino acids in the a-**chain, the TCR** β-chain, or both).

Engineered immune cells encompassed by the present invention may be administered as therapies for, *e.g.,* a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen. In some circumstances, it may be desirable to reduce or stop the activity associated with a cellular immunotherapy. Thus, in some embodiments, an engineered immune cell encompassed by the present invention comprises a heterologous polynucleotide encoding a binding protein and an accessory protein, such as a safety switch protein, which can be targeted using a cognate drug or other compound to selectively modulate the activity (*e.g.,* lessen or ablate) of such cells when desirable. Safety switch proteins used in this regard include, for example, a truncated EGF receptor polypeptide (huEGFRt) that is devoid of extracellular N-terminal ligand binding domains and intracellular receptor tyrosine kinase activity but retains the native amino acid sequence, type I transmembrane cell surface localization, and a conformationally intact binding epitope for pharmaceutical-grade anti-EGFR monoclonal antibody, cetuximab (Erbitux) tEGF receptor (tEGFr; Wang *et al.* (2011) *Blood* 118:1255-1263), a caspase polypeptide

(*e.g.,* iCasp9; Straathof *et al.* (2005) *Blood* 105:4247-4254, Di Stasi *et al.* (2011) *N. Engl. J. Med.* 365:1673-1683, Zhou and Brenner (2016) *Hematol.* pii:S0301-472X:30513-30516), RQR8 (Philip *et al.* (2014) *Blood* 124:1277-1287), and a human c-myc protein tag (Kieback *et al.* (2008) *Proc. Natl. Acad. Sci. USA* 105:623-628)

Other accessory components useful for therapeutic cells comprise a tag or selection marker (*e.g.*, a CD34 enrichment tag) that allows the cells to be identified, sorted, isolated, enriched, or tracked. For example, marked immune cells having desired characteristics (*e.g.,* an antigen-specific TCR and a safety switch protein) may be sorted away from unmarked cells in a sample and more efficiently activated and expanded for inclusion in a therapeutic product of desired purity.

As used herein, the term "selection marker" comprises a nucleic acid construct that confers an identifiable change to a cell permitting detection and positive selection of immune cells transduced with a polynucleotide comprising a selection marker. For example, RQR is a selection marker that comprises a major extracellular loop of CD20 and two minimal CD34 binding sites. In some embodiments, an RQR-encoding polynucleotide comprises a polynucleotide that encodes the 16 amino acid CD34 minimal epitope. In some embodiments, such as certain embodiments provided in the examples herein, the CD34 minimal epitope is incorporated at the amino terminal position of the CD8 stalk domain (Q8). In further embodiments, the CD34 minimal binding site sequence may be combined with a target epitope for CD20 to form a compact marker/suicide gene for T cells (RQR8) (Philip *et al.* 2014). This construct allows for the selection of immune cells expressing the construct, with for example, CD34-specific antibody bound to magnetic beads (Miltenyi) and that utilizes clinically accepted pharmaceutical antibody, rituximab, that allows for the selective deletion of a transgene expressing engineered T cell (*e.g.*, Philip *et al.* (2014) *Blood* 124:1277-1287, U.S. Pat. Publ. 2015-0093401, and U.S. Pat. Publ. 2018-0051089).

Further exemplary selection markers include several truncated type I transmembrane proteins normally not expressed on T cells: the truncated low-affinity nerve growth factor, truncated CD19, and truncated CD34 (*e.g.*, Di Stasi *et al.* (2011) *N. Engl. J. Med.* 365:1673-1683, Mavilio *et al.* (1994) *Blood* 83:1988-1997, and Fehse *et al.* (2000) *Mol. Ther.* 7:448-456). A particularly attractive feature of CD19 and CD34 is the availability of the off-the-**shelf Miltenyi CliniMACs™ selection system that can target** these markers for clinical-grade sorting. However, CD19 and CD34 are relatively large

surface proteins that may tax the vector packaging capacity and transcriptional efficiency of an integrating vector. Surface markers containing the extracellular, non-signaling domains or various proteins (*e.g.,* CD19, CD34, LNGFR, etc.) also may be employed. Any selection marker may be employed and should be acceptable for good manufacturing practices. In some embodiments, selection markers are expressed with a polynucleotide that encodes a gene product of interest (*e.g.,* a binding protein encompassed by the present invention, such as a TCR or CAR, or antigen-binding fragment thereof). Further examples of selection markers include, for example, reporters such as GFP, EGFP, β-gal or chloramphenicol acetyltransferase (CAT). In some embodiments, a selection marker, such as, for example, CD34 is expressed by a cell and the CD34 may be used to select enrich for, or isolate (*e.g.,* by immunomagnetic selection) the transduced cells of interest for use in the methods described herein. As used herein, a CD34 marker is distinguished from an anti-CD34 antibody, or, for example, a scFv, TCR, or other antigen recognition moiety that binds to CD34.

In some embodiments, a selection marker comprises an RQR polypeptide, a truncated low-affinity nerve growth factor (tNGFR), a truncated CD19 (tCD19), a truncated CD34 (tCD34), or any combination thereof.

By way of background, inclusion of $CD4^+$ T cells in an immunotherapy cell product can provide antigen-induced IL-2 secretion and augment persistence and function of transferred cytotoxic $CD8^+$ T cells (*e.g.,* Kennedy *et al.* (2008) *Immunol. Rev.* 222:129 and Nakanishi *et al. Nature* (2009) 52:510). In some embodiments, a class I-restricted TCR in $CD4^+$ T cells may require the transfer of a CD8 co-receptor to enhance sensitivity of the TCR to class I HLA peptide complexes. CD4 co-receptors differ in structure to CD8 and cannot effectively substitute for CD8 co-receptors (*e.g.,* Stone & Kranz (2013) *Front. Immunol.* 4:244 and Cole *et al.* (2012) *Immunology* 737:139). Thus, another accessory protein for use in the compositions and methods encompassed by the present invention comprises a CD8 co-receptor or component thereof. Engineered immune cells comprising a heterologous polynucleotide encoding a binding protein encompassed by the present invention may, in some embodiments, further comprise a heterologous polynucleotide encoding a CD8 co-receptor protein, or a beta-chain or alpha-chain component thereof.

A host cell may be efficiently transduced to contain, and may efficiently express, a single polynucleotide that encodes the binding protein, safety switch protein, selection marker, and CD8 co-receptor protein.

In one embodiment, the host cell encompassed by the present invention further includes a nucleic acid encoding a co-stimulatory molecule, such that the modified T cell expresses the co-stimulatory molecule. In some embodiments, the co-stimulatory domain is selected from CD3, CD27, CD28, CD83, CD86, CD127, 4-1BB, 4-1BBL, PD1 and PD1L.

In any of the foregoing embodiments, a host cell that express the binding protein described herein may be a universal immune cell. A "universal immune cell" comprises an immune cell that has been modified to reduce or eliminate expression of one or more endogenous genes that encode a polypeptide product selected from PD-l, LAG-3, CTLA4, TIM3, TIGIT, an HLA molecule, a TCR molecule, or any combination thereof. Without wishing to be bound by theory, certain endogenously expressed immune cell proteins may downregulate the immune activity of the modified immune cells (*e.g.*, PD-l, LAG-3, CTLA4, TIGIT), or may interfere with the binding activity of a heterologously expressed binding protein encompassed by the present invention (*e.g.,* an endogenous TCR that binds a non-HA-2 antigen and interferes with the modified immune cell binding to a target cell that expresses an HA-2 antigen such as an HA-2 immunogenic peptide comprising the amino acid sequence YIGEVLVSV or YIGEVLVSM in the context of a MHC molecule. Further, endogenous proteins (*e.g.,* immune cell proteins, such as an HLA allele) expressed on a donor immune cell may be recognized as foreign by an allogeneic host, which may result in elimination or suppression of the modified donor immune cell by the allogeneic host.

Accordingly, decreasing or eliminating expression or activity of such endogenous genes or proteins can improve the activity, tolerance, or persistence of the modified immune cells in an autologous or allogeneic host setting, and allows universal administration of the cells (*e.g.,* to any recipient regardless of HLA type). In some embodiments, cells in accordance with the present invention are syngeneic, meaning that they are genetically identical or sufficiently identical and immunologically compatible as to allow for transplantation. In some embodiments, a universal immune cell is a donor cell (*e.g.,* allogeneic) or an autologous cell. In some embodiments, a modified immune cell (*e.g.,* a universal immune cell) encompassed by the present invention comprises a chromosomal gene knockout of one or more of a gene that encodes PD-l, LAG-3, CTLA4, TIM3, TIGIT, an HLA component (*e.g.,* a gene that encodes an αl macroglobulin, an α2 macroglobulin, an α3 macroglobulin, a β1 microglobulin, or a β2 microglobulin), or a TCR component (*e.g.,* a gene that encodes a TCR variable region or a TCR constant region) (see,

e.g., Torikai *el al.* (2016) *Nature Sci. Rep.* 6:21757; Torikai *et al.* (2012) *Blood* 179:5697; and Torikai *et al.* (2013) *Blood* 722:1341, which also provide representative, exemplary gene editing techniques, compositions, and adoptive cell therapies useful according to the present invention).

As used herein, the term "chromosomal gene knockout" refers to a genetic alteration or introduced inhibitory agent in a host cell that prevents (*e.g.*, reduces, delays, suppresses, or abrogates) production, by the host cell, of a functionally active endogenous polypeptide product. Alterations resulting in a chromosomal gene knockout may include, for example, introduced nonsense mutations (including the formation of premature stop codons), missense mutations, gene deletion, and strand breaks, as well as the heterologous expression of inhibitory nucleic acid molecules that inhibit endogenous gene expression in the host cell.

In some embodiments, a chromosomal gene knock-out or gene knock-in may be made by chromosomal editing of a host cell. Chromosomal editing may be performed using, for example, endonucleases. As used herein "endonuclease" refers to an enzyme capable of catalyzing cleavage of a phosphodiester bond within a polynucleotide chain. In some embodiments, an endonuclease is capable of cleaving a targeted gene thereby inactivating or "knocking out" the targeted gene. An endonuclease may be a naturally occurring, recombinant, genetically modified, or fusion endonuclease. The nucleic acid strand breaks caused by the endonuclease are commonly repaired through the distinct mechanisms of homologous recombination or non-homologous end joining (NHEJ). During homologous recombination, a donor nucleic acid molecule may be used for a donor gene "knock-in", for target gene "knock-out", and optionally to inactivate a target gene through a donor gene knock in or target gene knock out event. NHEJ is an error-prone repair process that often results in changes to the DNA sequence at the site of the cleavage, *e.g.,* a substitution, deletion, or addition of at least one nucleotide. NHEJ may be used to "knock-out" a target gene. Examples of endonucleases include zinc finger nucleases, TALE-nucleases, CRISPR-Cas nucleases, meganucleases, and megaTALs.

As used herein, a "zinc finger nuclease" (ZFN) refers to a fusion protein comprising a zinc finger DNA-binding domain fused to a non-specific DNA cleavage domain, such as a FokI endonuclease. Each zinc finger motif of about 30 amino acids binds to about 3 base pairs of DNA, and amino acids at certain residues may be changed to alter triplet sequence specificity (*e.g.,* Desjarlais *et al.* (1993) *Proc. Natl. Acad. Sci.* 90:2256-2260 and Wolfe *et*

al. (1999) J. *Mol. Biol.* 255:1917-1934). Multiple zinc finger motifs may be linked in tandem to create binding specificity to desired DNA sequences, such as regions having a length ranging from about 9 to about 18 base pairs. By way of background, ZFNs mediate genome editing by catalyzing the formation of a site-specific DNA double strand break (DSB) in the genome, and targeted integration of a transgene comprising flanking sequences homologous to the genome at the site of DSB is facilitated by homology directed repair. Alternatively, a DSB generated by a ZFN can result in knock out of target gene via repair by non-homologous end joining (NHEJ), which is an error-prone cellular repair pathway that results in the insertion or deletion of nucleotides at the cleavage site. In some embodiments, a gene knockout comprises an insertion, a deletion, a mutation or a combination thereof, made using a ZFN molecule.

As used herein, a "transcription activator-like effector nuclease" (TALEN) refers to a fusion protein comprising a TALE DNA-binding domain and a DNA cleavage domain, such as a FokI endonuclease. A "TALE DNA binding domain" or "TALE" is composed of one or more TALE repeat domains/units, each generally having a highly conserved 33-35 amino acid sequence with divergent 12th and 13th amino acids. The TALE repeat domains are involved in binding of the TALE to a target DNA sequence. The divergent amino acid residues, referred to as the repeat variable diresidue (RVD), correlate with specific nucleotide recognition. The natural (canonical) code for DNA recognition of these TALEs has been determined such that an HD (histine-aspartic acid) sequence at positions 12 and 13 of the TALE leads to the TALE binding to cytosine (C), NG (asparagine-glycine) binds to a T nucleotide, NI (asparagine-isoleucine) to A, NN (asparagine-asparagine) binds to a G or A nucleotide, and NG (asparagine-glycine) binds to a T nucleotide. Non-canonical (atypical) RVDs are also well-known in the art (*e.g.,* U.S. Pat. Publ. No. US 2011/0301073, which atypical RVDs are incorporated by reference herein in their entirety). TALENs may be used to direct site-specific double-strand breaks (DSB) in the genome of T cells. Non-homologous end joining (NHEJ) ligates DNA from both sides of a double-strand break in which there is little or no sequence overlap for annealing, thereby introducing errors that knock out gene expression. Alternatively, homology directed repair can introduce a transgene at the site of DSB providing homologous flanking sequences are present in the transgene. In some embodiments, a gene knockout comprises an insertion, a deletion, a mutation or a combination thereof, and made using a TALEN molecule.

As used herein, a "clustered regularly interspaced short palindromic repeats/Cas" (CRISPR/Cas) nuclease system refers to a system that employs a CRISPR RNA (crRNA)-guided Cas nuclease to recognize target sites within a genome (known as protospacers) via base-pairing complementarity and then to cleave the DNA if a short, conserved protospacer associated motif (PAM) immediately follows 3' of the complementary target sequence. CRISPR/Cas systems are classified into three types (*i.e.,* type I, type II, and type III) based on the sequence and structure of the Cas nucleases. The crRNA-guided surveillance complexes in types I and III need multiple Cas subunits. Type II system, the most studied, comprises at least three components: an RNA-guided Cas9 nuclease, a crRNA, and a trans-acting crRNA (tracrRNA). The tracrRNA comprises a duplex forming region. A crRNA and a tracrRNA form a duplex that is capable of interacting with a Cas9 nuclease and guiding the Cas9/crRNA:tracrRNA complex to a specific site on the target DNA via Watson-Crick base-pairing between the spacer on the crRNA and the protospacer on the target DNA upstream from a PAM. Cas9 nuclease cleaves a double-stranded break within a region defined by the crRNA spacer. Repair by NHEJ results in insertions and/or deletions which disrupt expression of the targeted locus. Alternatively, a transgene with homologous flanking sequences may be introduced at the site of DSB via homology directed repair. The crRNA and tracrRNA may be engineered into a single guide RNA (sgRNA or gRNA) (*e.g.,* Jinek *et al.* (2012) *Science* 337:816-821). Further, the region of the guide RNA complementary to the target site may be altered or programed to target a desired sequence (Xie *et al.* (2014) *PLOS One* 9:el00448, U.S. Pat. Publ. No. US 2014/0068797, U.S. Pat. Publ. No. US 2014/0186843, U.S. Pat. No. 8,697,359, and PCT Publ. No. WO 2015/071474). In some embodiments, a gene knockout comprises an insertion, a deletion, a mutation or a combination thereof, and made using a CRISPR/Cas nuclease system.

Exemplary gRNA sequences and methods of using the same to knock out endogenous genes that encode immune cell proteins include those described in Ren *et al.* (2017) *Clin. Cancer Res.* 23:2255-2266, which provides representative, exemplary gRNAs, CAS9 DNAs, vectors, and gene knockout techniques.

As used herein, a "meganuclease," also referred to as a "homing endonuclease," refers to an endodeoxyribonuclease characterized by a large recognition site (double stranded DNA sequences of about 12 to about 40 base pairs). Meganucleases may be divided into five families based on sequence and structure motifs: LAGLIDADG, GIY-

YIG, HNH, His-Cys box, and PD-(D/E)XK. Exemplary meganucleases include I-SceI, I-CeuI, PI-PspI, RI-Sce, I-SceIV, I-CsmI, I-PanI, I-SceII, I-PpoI, I-SceIII, I-CreI, I-TevI, I-TevII and I-TevIII, whose recognition sequences are well-known (*e.g.,* U.S. Pat. Nos. 5,420,032 and 6,833,252, Belfort *et al.* (1997) *Nucl. Acids Res.* 25:3379-3388, Dujon *et al.* (1989) *Gene* 52:115-118, Perler *et al.* (1994) *Nucl. Acids Res.* 22:1125-1127, Jasin (1996) *Trends Genet.* 72:224-228, Gimble *et al.* (1996) *J. Mol. Biol.* 263:163-180, and Argast *et al.* (1998) *J. Mol. Biol.* 280: 345-353).

In some embodiments, naturally-occurring meganucleases may be used to promote site-specific genome modification of a target of interest, such as an immune checkpoint, an HLA-encoding gene, or a TCR component-encoding gene.

In other embodiments, an engineered meganuclease having a novel binding specificity for a target gene is used for site-specific genome modification (see, *e.g.,* Porteus *et al.* (2005) *Nat. Biotechnol.* 23:967-73, Sussman *et al.* (2004) *J. Mol. Biol.* 342:31-41, Epinat *et al.* (2003) *Nucl. Acids Res.* 37:2952-2962, Chevalier *et al.* (2002) *Mol. Cell* 70:895-905, Ashworth *et al.* (2006) *Nature* 441:656-659, Paques *et al.* (2007) *Curr. Gene Ther.* 7:49-66, and U.S. Pat. Publ. Nos. US 2007/0117128, US 2006/0206949, US 2006/0153826, US 2006/0078552, and US 2004/0002092). In further embodiments, a chromosomal gene knockout is generated using a homing endonuclease that has been modified with modular DNA binding domains of TALENs to make a fusion protein known as a megaTAL. MegaTALs may be utilized to not only knock-out one or more target genes, but to also introduce (knock in) heterologous or exogenous polynucleotides when used in combination with an exogenous donor template encoding a polypeptide of interest.

In some embodiments, a chromosomal gene knockout comprises an inhibitory nucleic acid molecule that is introduced into a host cell (*e.g.*, an immune cell) comprising a heterologous polynucleotide encoding an antigen-specific receptor that binds (*e.g.*, specifically and/or selectively) to an HA-2 antigen, wherein the inhibitory nucleic acid molecule encodes a target-specific inhibitor and wherein the encoded target-specific inhibitor inhibits endogenous gene expression (*i.e.,* of an immune checkpoint, an HLA component, or a TCR component, or any combination thereof) in the host immune cell.

A chromosomal gene knockout may be confirmed directly by DNA sequencing of the host immune cell following use of the knockout procedure or agent.

Chromosomal gene knockouts may also be inferred from the absence of gene expression (*e.g.,* the absence of an mRNA or polypeptide product encoded by the gene) following the knockout.

In some embodiments, a host cell encompassed by the present invention is capable of specifically and/or selectively killing 50% or more of target cells that comprise a peptide–MHC (pMHC) complex comprising an HA-2 immunogenic peptide in the context of an MHC molecule.

In some embodiments, the modified immune cell is capable of producing a cytokine when contacted with target cells that comprise a peptide–MHC (pMHC) complex comprising an HA-2 immunogenic peptide in the context of an MHC molecule.

In some embodiments, the cytokine comprises IFN-γ or IL2. In some embodiments, the cytokine comprises TNF-α.

In some embodiments, the host cell is capable of producing a higher level of cytokine or a cytotoxic molecule when contacted with a target cell with expression of HA-2 at a level of less than or equal to about 1,000 transcript per million transcripts (TPM), 950 TPM, 900 TPM, 850 TPM, 800 TPM, 750 TPM, 700 TPM, 650 TPM, 600 TPM, 550 TPM, 500 TPM, 450 TPM, 400 TPM, 350 TPM, 300 TPM, 250 TPM, 200 TPM, 150 TPM, 100 TPM, 95 TPM, 90 TPM, 85 TPM, 80 TPM, 75 TPM, 70 TPM, 65 TPM, 60 TPM, 55 TPM, 50 TPM, 45 TPM, 40 TPM, 35 TPM, 34 TPM, 33 TPM, 32 TPM, 31 TPM, 30 TPM, 29 TPM, 28 TPM, 27 TPM, 26 TPM, 25 TPM, 24 TPM, 23 TPM, 22 TPM, 21 TPM, 20 TPM, 19 TPM, 18 TPM, 17 TPM, 16 TPM, 15 TPM, 14 TPM, 13 TPM, 12 TPM, 11 TPM, 10 TPM, 9 TPM, 8 TPM, 7 TPM, 6 TPM, 5 TPM, 4 TPM, 3 TPM, 2 TPM, and 1 TPM, or any range in between, inclusive, such as less than or equal to about 1,000 TPM to less than or equal to about 35 TPM). In some embodiments, the low HA-2 expression level is termed "heterozygous expression" meaning between about 1 TPM and about 35 TPM, or any range in between, inclusive, such as 1-32 TPM. For example, the host cell is capable of producing an at least 1.2 fold, 1.5 fold, 1.8 fold, 2.0 fold, 2.2 fold, 2.5 fold, 2.8 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 5.5 fold, 6 fold, 6.5 fold, 7 fold, 7.5 fold, 8 fold, 8.5 fold, 9 fold, 9.5 fold, 10 fold, 11 fold, 12 fold, 13 fold, 14 fold, 15 fold, 16 fold, 17 fold, 18 fold, 19 fold, 20 fold, 25 fold, 30 fold, 35 fold, 40 fold, 45 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 1000 fold, or more, or any range in between, inclusive, such as 1.2 fold to 2 fold, higher level of cytokine or a cytotoxic molecule.

In some embodiments, the host cell is capable of specifically and/or selectively killing a taget cell expressing HA-2 (*e.g.*, a hyperproliferative cell expressing HA-2). In certain embodiments, the target cell expresses: (i) a polypeptide comprising or consisting of an amino acid sequence YIGEVLVSV or YIGEVLVSM; and (ii) a matched MHC molecule.

In some embodiments, host cells do not express HA-2 antigen, are not recognized by a binding protein of any one of claims 1-30, are not of serotype HLA-A*02, and/or do not express an HLA-A*02 allele, such as HLA-A*02:01, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, or HLA-A*0207 allele. For example, a patient may receive host cells from a healthy donor who is HA-2 REF-negative (*e.g.*, HA-2 SNP/SNP genotype **and/or doesn't express HA**-2 REF) or HLA-A*02:01-negative. Stem cells, such as hematopoietic stem cells, isolated from that donor (or engineered autologous cells) may be used as the source of transplant material. In parallel, T cells isolated from the same donor may be be genetically engineered to recognize HA-2, such as by expressing an HA-2 binding protein described herein. Donor stem cells may be used to engraft cells popultions, such as a reconstituted immune system, into the patient and host cells may be infused into the patient with the goal of eliciting a highly specific anti-tumor effect. The engineered donor T cells may be designed to recognize and eliminate HA-2-expressing cells, such as **all of the patient's native blood cells, including**, for example, cancer cells like residual leukemia cells, which are HA-2-positive, thereby preventing relapse and promoting complete cures. **Because the patient's new healthy blood** cells are derived from the donor and are therefore either HA-2-negative, HLA-A*02 serotype negative, and/or or HLA-A*02:01-negative, engineered cells described herein may have have minimal toxic side effects. Such patient-matched host cells and treatment methods may be used according to therapeutic methods described further below.

In some embodiments, the killing is determined by a killing assay. In some embodiment, the killing assay is carrier out by coculturing the host cell and the target cell at a ratio from 20:1 to 0.625:1, for example, from 15:1 to 1.25:1, from 10:1 to 1.5:1, from 8:1 to 3:1, from 6:1 to 5:1, 20:1 to 5:1, 10:1 to 2.5:1 etc.. In some embodiments, the target cell is pulsed with 1 μg/mL to 50 pg/mL of HA-2 peptide, for example, from 1 ug/mL to 10 ng/mL, 500 ng/mL to 0.5 ng/mL, from 10 ng/mL to 10 pg/mL from 250 ng/mL to 1 ng/mL, from 50 ng/mL to 5 ng/mL, from 20 ng/mL to 10 ng/mL, etc.

In some embodiments, the host cell is capable of killing a higher number of target cells when contacted with target cells with a level of HA-2 less than or equal to about 1,000 transcript per million transcripts (TPM), 950 TPM, 900 TPM, 850 TPM, 800 TPM, 750 TPM, 700 TPM, 650 TPM, 600 TPM, 550 TPM, 500 TPM, 450 TPM, 400 TPM, 350 TPM, 300 TPM, 250 TPM, 200 TPM, 150 TPM, 100 TPM, 95 TPM, 90 TPM, 85 TPM, 80 TPM, 75 TPM, 70 TPM, 65 TPM, 60 TPM, 55 TPM, 50 TPM, 45 TPM, 40 TPM, 35 TPM, 34 TPM, 33 TPM, 32 TPM, 31 TPM, 30 TPM, 29 TPM, 28 TPM, 27 TPM, 26 TPM, 25 TPM, 24 TPM, 23 TPM, 22 TPM, 21 TPM, 20 TPM, 19 TPM, 18 TPM, 17 TPM, 16 TPM, 15 TPM, 14 TPM, 13 TPM, 12 TPM, 11 TPM, 10 TPM, 9 TPM, 8 TPM, 7 TPM, 6 TPM, 5 TPM, 4 TPM, 3 TPM, 2 TPM, and 1 TPM, or any range in between, inclusive, such as less than or equal to about 1,000 TPM to less than or equal to about 16 TPM). In some embodiments, the low HA-2 expression level is termed "heterozygous expression" meaning between about 1 TPM and about 35 TPM, or any range in between, inclusive, such as 1-32 TPM. For example, the host cell may be capable of killing an at least 1.2 fold, 1.5 fold, 1.8 fold, 2.0 fold, 2.2 fold, 2.5 fold, 2.8 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 5.5 fold, 6 fold, 6.5 fold, 7 fold, 7.5 fold, 8 fold, 8.5 fold, 9 fold, 9.5 fold, 10 fold, 11 fold, 12 fold, 13 fold, 14 fold, 15 fold, 16 fold, 17 fold, 18 fold, 19 fold, 20 fold, 25 fold, 30 fold, 35 fold, 40 fold, 45 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, 100 fold, 1000 fold, or more, or any range in between, inclusive, such as 1.2 fold to 2 fold, higher number of target cells.

The present invention further provides a population of cells comprising at least one host cell described herein. The population of cells may 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 may 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 may 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 encompassed by the present invention, the population of cells is a clonal population comprising host cells comprising a recombinant expression vector as described herein.

In an embodiment encompassed by the present invention, the numbers of cells in the population may be rapidly expanded. Expansion of the numbers of T cells may be accomplished by any of a number of methods as are well-known in the art (*e.g.*, U.S. Pat. Nos. 8,034,334 and 8,383,099, U.S. Pat. Publ. No. 2012/0244133, Dudley *et al.* (2003) *J. Immunother*. 26:332-242, and Riddell *et al.* (1990) *J. Immunol. Methods* 128:189-201). For example, expansion of the numbers of T cells may be carried out by culturing the T cells with OKT3 antibody, IL-2, and feeder PBMC (*e.g.,* irradiated allogeneic PBMC).

V. Pharmaceutical Compositions

In another aspect encompassed by the present invention, pharmaceutical compositions are provided herein comprising compositions described herein (*e.g.*, binding proteins, nucleic acids, cells, and the like) and a pharmaceutically acceptable carrier, diluent, or excipient.

The term "pharmaceutically acceptable" refers to those agents, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

Agents and other compositions encompassed by the present invention may be specially formulated for administration in solid or liquid form, including those adapted for various routes of administration, such as (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, boluses, powders, granules, pastes; (2) parenteral administration, for example, by subcutaneous, intramuscular or intravenous injection as, for example, a sterile solution or suspension; (3) topical application, for example, as a cream, ointment or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; or (5) aerosol, for example, as an aqueous aerosol, liposomal preparation or solid particles containing the compound. Any appropriate form factor for an agent or composition described herein, such as, but not limited to, tablets, capsules, liquid syrups, soft gels, suppositories, and enemas, is contemplated.

Pharmaceutical compositions encompassed by the present invention may be presented as discrete dosage forms, such as capsules, sachets, or tablets, or liquids or aerosol sprays each containing a pre-determined amount of an active ingredient as a powder

or in granules, a solution, or a suspension in an aqueous or non- aqueous liquid, an oil-in-water emulsion, a water-in-oil liquid emulsion, powders for reconstitution, powders for oral consumptions, bottles (including powders or liquids in a bottle), orally dissolving films, lozenges, pastes, tubes, gums, and packs. Such dosage forms may be prepared by any of the methods of pharmacy.

Suitable excipients include water, saline, dextrose, glycerol, or the like and combinations thereof. In some embodiments, compositions comprising host cells, binding proteins, or fusion proteins as disclosed herein further comprise a suitable infusion media. Suitable infusion media may be any isotonic medium formulation, typically normal saline, Normosol™-R (Abbott) or Plasma-Lyte™ A (Baxter), 5% dextrose in water, Ringer's lactate may be utilized. An infusion medium may be supplemented with human serum albumin or other human serum components. Unit doses comprising an effective amount of a host cell, or composition are also contemplated.

Also provided herein are unit doses that comprise an effective amount of a host cell or of a composition comprising the host cell. As described herein, host cells include immune cells, T cells ($CD4^+$ T cells and/or CD8+ T cells), cytotoxic lymphocytes (*e.g.,* cytotoxic T cells and/or natural killer (NK) cells), and the like. For example, in some embodiments, a unit dose comprises a composition comprising at least about 30%, at least about 40%, at least about 50%, at least about 60%), at least about 70%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% engineered cells, either alone or in combination with other cells, such as comprising at least about 30%, at least about 40%, at least about 50%, at least about 60%), at least about 70%, at least about 80%, at least about 85%, at least about 90%, or at least about 95% other cells. In some embodiments, undesired cells are present at a reduced amount or substantially not present, such as less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, or less then about 1% the population of cells in the composition.

The amount of cells in a composition or unit dose is at least one cell (for example, at least one engineered $CD8^+$ T cell, engineered $CD4^+$ T cell, and/or NK cell) or is more typically greater than 10^2 cells, for example, up to 10^6, up to 10^7, up to 10^8 cells, up to 10^9 cells, or more than 10^{10} cells. In some embodiments, the cells are administered in a range from about 106 to about 10^{10} cells/m^2, such as in a range of about 10^5 to about 10^9 cells/m^2. The number of cells will depend upon the ultimate use for which the composition is

intended as well the type of cells included therein. For example, cells modified to contain a binding protein specific for a particular antigen will comprise a cell population containing at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more of such cells. For uses provided herein, cells are generally in a volume of a liter or less, 500 ml or less, 250 ml or less, or 100 ml or less. In embodiments, the density of the desired cells is typically greater than 10^4 cells/ml and generally is greater than 10^7 cells/ml, generally 10^8 cells/ml or greater. The cells may be administered as a single infusion or in multiple infusions over a range of time. A clinically relevant number of immune cells may be apportioned into multiple infusions that cumulatively equal or exceed 10^6, 10^7, 10^8, 10^9, 10^{10}, or 10^{11} cells. In some embodiments, a unit dose of the engineered immune cells may be co-administered with (*e.g.,* simultaneously or contemporaneously) hematopoietic stem cells from an allogeneic donor.

Pharmaceutical compositions may be administered in a manner appropriate to the disease or condition to be treated (or prevented) as determined by persons skilled in the medical art. An appropriate dose and a suitable duration and frequency of administration of the compositions will be determined by such factors as the health condition of the patient, size of the patient (*i.e.,* weight, mass, or body area), the type and severity of the patient's condition, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provide the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (such as described herein, including an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity).

An effective amount of a pharmaceutical composition refers to an amount sufficient, at dosages and for periods of time needed, to achieve the desired clinical results or beneficial treatment, as described herein. An effective amount may be delivered in one or more administrations. If the administration is to a subject already known or confirmed to have a disease or disease-state, the term "therapeutically effective amount" may be used in reference to treatment, whereas "prophylactically effective amount" may be used to describe administrating an effective amount to a subject that is susceptible or at risk of developing a disease or disease-state (*e.g.,* recurrence) as a preventative course.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers may be frozen to

preserve the stability of the formulation until infusion into the patient. In some embodiments, a unit dose comprises a host cell as described herein at a dose of about 10^7 cells/m^2 to about 10^{11} cells/m^2. The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.,* parenteral or intravenous administration or formulation.

If the subject composition is administered parenterally, the composition may also include sterile aqueous or oleaginous solution or suspension. Suitable non-toxic parenterally acceptable diluents or solvents include water, Ringer's solution, isotonic salt solution, 1,3-butanediol, ethanol, propylene glycol or polythethylene glycols in mixtures with water. Aqueous solutions or suspensions may further comprise one or more buffering agents, such as sodium acetate, sodium citrate, sodium borate or sodium tartrate. Of course, any material used in preparing any dosage unit formulation should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations. Dosage unit form, as used herein, refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit may contain a predetermined quantity of engineered immune cells or active compound calculated to produce the desired effect in association with an appropriate pharmaceutical carrier.

In some embodiments, the pharmaceutical composition described, when administered to a subject, can elicit an immune response against a cell of interest that expresses HA-2. Such pharmaceutical compositions may be useful as vaccines for prophylactic and/or therapeutic treatment of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen.

In some embodiments, the pharmaceutical composition further comprises a physiologically acceptable adjuvant. In some embodiments, the adjuvant employed provides for increased immunogenicity of the pharmaceutical composition. Such a further immune response stimulating compound or adjuvant may be (i) admixed to the pharmaceutical composition in accordance with the present invention after reconstitution of the peptides and optional emulsification with an oil-based adjuvant as defined above, (ii) may be part of the reconstitution composition encompassed by the present invention defined above, (iii) may be physically linked to the peptide(s) to be reconstituted or (iv) may be administered separately to the subject, mammal or human, to be treated. The

adjuvant may be one that provides for slow release of antigen (*e.g.,* the adjuvant may be a liposome), or it may be an adjuvant that is immunogenic in its own right thereby functioning synergistically with antigens. For example, the adjuvant may be a known adjuvant or other substance that promotes antigen uptake, recruits immune system cells to the site of administration, or facilitates the immune activation of responding lymphoid cells. Adjuvants include, but are not limited to, immunomodulatory molecules (*e.g.,* cytokines), oil and water emulsions, aluminum hydroxide, glucan, dextran sulfate, iron oxide, sodium alginate, bacto-adjuvant, synthetic polymers such as poly amino acids and co-polymers of amino acids, saponin, paraffin oil, and muramyl dipeptide. In some embodiments, the adjuvant is adjuvant 65, α-GalCer, aluminum phosphate, aluminum hydroxide, calcium phosphate, β-glucan peptide, CpG DNA, GM-CSF, GPI-0100, IFA, IFN-γ, IL-17, lipid A, lipopolysaccharide, Lipovant, Montanide™, N-acetyl-muramyl-L-alanyl-D-isoglutamine, pam3CSK4, quil A, trehalose dimycolate, or zymosan.

In some embodiments, the adjuvant is an immunomodulatory molecule. For example, the immunomodulatory molecule may be a recombinant protein cytokine, chemokine, or immunostimulatory agent or nucleic acid encoding cytokines, chemokines, or immunostimulatory agents designed to enhance the immunologic response.

Examples of immunomodulatory cytokines include interferons (*e.g.,* IFNα, IFNβ and IFNγ), interleukins (*e.g.,* IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-17 and IL-20), tumor necrosis factors (*e.g.,* TNFα and TNFβ), erythropoietin (EPO), FLT-3 ligand, gIp10, TCA-3, MCP-1, MIF, MIP-1.alpha., MIP-1β, Rantes, macrophage colony stimulating factor (M-CSF), granulocyte colony stimulating factor (G-CSF), and granulocyte-macrophage colony stimulating factor (GM-CSF), as well as functional fragments of any of the foregoing.

In some embodiments, an immunomodulatory chemokine that binds to a chemokine receptor, *i.e.,* a CXC, CC, C, or CX3C chemokine receptor, also may be included in the compositions provided here. Examples of chemokines include, but are not limited to, Mip1α, Mip-1β, Mip-3α (Larc), Mip-3β, Rantes, Hcc-1, Mpif-1, Mpif-2, Mcp-1, Mcp-2, Mcp-3, Mcp-4, Mcp-5, Eotaxin, Tarc, Elc, I309, IL-8, Gcp-2 Gro-α, Gro-β, Gro-γ, Nap-2, Ena-78, Gcp-2, Ip-10, Mig, I-Tac, Sdf-1, and Bca-1 (Blc), as well as functional fragments of any of the foregoing.

In some embodiments, the composition comprises a binding protein (*e.g.,* a TCR, an antigen-binding fragment of a TCR, a CAR, or a fusion protein comprising a TCR and an

effector domain), a TCRα and/or TCRβ polypeptide described herein. In some embodiments, the composition comprises a nucleic acid encoding a binding protein, a TCRα and/or TCRβ polypeptide described herein, such as a DNA molecule encoding a binding protein, a TCRα and/or TCRβ polypeptide. In some embodiments, the composition comprises an expression vector comprising an open reading frame encoding a binding protein, a TCRα and/or TCRβ polypeptide.

When taken up by a cell (*e.g.,* T cells, NK cells, *etc.*), a DNA molecule may be present in the cell as an extrachromosomal molecule and/or may integrate into the chromosome. DNA may be introduced into cells in the form of a plasmid which may remain as separate genetic material. Alternatively, linear DNAs that may integrate into the chromosome may be introduced into the cell. Optionally, when introducing DNA into a cell, reagents which promote DNA integration into chromosomes may be added.

VI. Uses and Methods

The compositions described herein may be used in a variety of diagnostic, prognostic, and therapeutic applications. In any method described herein, such as a diagnostic method, prognostic method, therapeutic method, or combination thereof, all steps of the method can be performed by a single actor or, alternatively, by more than one actor. For example, diagnosis can be performed directly by the actor providing therapeutic treatment. Alternatively, a person providing a therapeutic agent can request that a diagnostic assay be performed. The diagnostician and/or the therapeutic interventionist can interpret the diagnostic assay results to determine a therapeutic strategy. Similarly, such alternative processes can apply to other assays, such as prognostic assays.

In some uses and methods encompassed by the present invention, subjects or subject samples are utilized. In some embodiments, the subject is an animal. The animal may be of either sex and may be at any stage of development. In some embodiments, the animals is a vertebrate, such as a mammal. In some embodiments, the subject is a non-human mammal. In some embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In some embodiments, the subject is a companion animal, such as a dog or cat. In some embodiments, the subject is a livestock animal, such as a cow, pig, horse, sheep, or goat. In some embodiments, the subject is a zoo animal. In some embodiments, the subject is a research animal, such as a rodent (*e.g.,* mouse or rat), dog, pig, or non-human primate. In some embodiments, the animal is a genetically engineered

animal. In some embodiments, the animal is a transgenic animal (*e.g.,* transgenic mice and transgenic pigs). In some embodiments, the subject is a fish or reptile.

In some embodiments, the subject is a rodent, such as a mouse. In some such embodiments, the mouse is a transgenic mouse, such as a mouse expressing human MHC (*i.e.,* HLA) molecules (*e.g.*, Nicholson *et al.* (2012) *Adv. Hematol.* 2012:404081). In some embodiments, the subject is a transgenic mouse expressing human TCRs or is an antigen-negative mouse (*e.g.*, Li *et al.* (2010) *Nat. Med.* 16:1029-1034 and Obenaus *et al.* (2015) *Nat. Biotechnol.* 33:402-407). In some embodiments, the subject is a transgenic mouse expressing human HLA molecules and human TCRs. In some embodiments, such as where the subject is a transgenic HLA mouse, the identified TCRs are modified, *e.g.,* to be chimeric or humanized. In some embodiments, the TCR scaffold is modified, such as analogous to known binding protein humanizing methods.

In some embodiments, the subject is a human. In some embodiments, the subject is an animal model of a disorder characterized by HA-2 expression (*e.g.*, a non-malignant disorder, the hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen). For example, the animal model may be an orthotopic xenograft animal model of a human-derived cancer.

In some embodiments, the subject is a human, such as a human with a disorder characterized by HA-2 expression.

The methods described herein may be used to treat a subject in need thereof. As used herein, a "subject in need thereof" includes any subject who has a disorder characterized by HA-2 expression, a relapse of a disorder characterized by HA-2 expression, and/or who is predisposed to a disorder characterized by HA-2 expression. As described herein, a disorder characterized by HA-2 expression may be a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen.

In some embodiments of the methods encompassed by the present invention, the subject has not undergone treatment for a disorder characterized by HA-2 expression, such as chemotherapy, radiation therapy, targeted therapy, and/or immunotherapies. In some embodiments, the subject has undergone treatment for a disorder characterized by HA-2 expression, such as chemotherapy, radiation therapy, targeted therapy, and/or immunotherapies.

In some embodiments, the subject has had surgery to remove cancerous or precancerous tissue. In some embodiments, the cancerous tissue has not been removed, *e.g.,* the cancerous tissue may be located in an inoperable region of the body, such as in a tissue that is essential for life, or in a region where a surgical procedure would cause considerable risk of harm to the patient.

In some embodiments, the subject or cells thereof are resistant to a therapy of relevance, such as resistant to standard of care therapy, immune checkpoint inhibitor therapy, and the like. For example, modulating one or more biomarkers encompassed by the present invention may overcome resistance to immune checkpoint inhibitor therapy.

In some embodiments, the subjects are in need of modulation according to compositions and methods described herein, such as having been identified as having an unwanted absence, presence, or aberrant HA-2 expression.

a. Diagnostic Methods

In an aspect encompassed by the present invention, provided herein are diagnostic methods for detecting the presence or absence of an HA-2 antigen and/or a cell of interest expressing HA-2, comprising detecting the presence or absence of said HA-2 antigen in a sample by use of at least one binding protein, or at least one host cell described herein. In some embodiments, the method further comprising obtaining the sample (*e.g.*, from a subject). In some embodiments, the at least one binding protein or the at least one host cell, forms a complex with an HA-2 peptide epitope in the context of an MHC molecule, and the complex is detected in the form of fluorescence activated cell sorting (FACS), enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemically, Western blot, or intracellular flow assay.

In an aspect encompassed by the present invention, provided herein are diagnostic methods for detecting the level of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen in a subject, comprising: a) contacting a sample obtained from the subject with at least one binding protein, at least one host cell, or a population of host cells described herein; and b) detecting the level of reactivity, wherein a higher level of reactivity compared to a control level indicates that the level of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen in the subject.

In some embodiments, the level of reactivity is indicated by T cell activation or effector function, such as, but not limited to, T cell proliferation, killing, or cytokine release. The control level may be a reference number or a level of a healthy subject who has no exposure to a non-alignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen.

A biological sample may be obtained from a subject for determining the presence and level of an immune response to a peptide antigen (*e.g.,* an HA-2 antigen) as described herein. **A "biological sample" as used herein may be a blood sample (from which serum or** plasma may be prepared), biopsy specimen, body fluids (*e.g.,* blood, isolated PBMCs, isolated T cells, lung lavage, ascites, mucosal washings, synovial fluid, etc.), bone marrow, lymph nodes, tissue explant, organ culture, or any other tissue or cell preparation from the subject or a biological source. Biological samples may also be obtained from the subject prior to receiving any pharmaceutical composition, which biological sample is useful as a control for establishing baseline data.

Antigen-specific T cell responses are typically determined by comparisons of observed T cell responses according to any of the herein described T cell functional parameters (*e.g.,* proliferation, cytokine release, CTL activity, altered cell surface marker phenotype, *etc.*) that may be made between T cells that are exposed to a cognate antigen in an appropriate context (*e.g.,* the antigen used to prime or activate the T cells, when presented by immunocompatible antigen-presenting cells) and T cells from the same source population that are exposed instead to a structurally distinct or irrelevant control antigen. A response to the cognate antigen that is greater, with statistical significance, than the response to the control antigen signifies antigen-specificity.

The level of an immune response, such as a cytotoxic T lymphocyte (CTL) immune response may be determined by any one of numerous immunological methods described herein and routinely practiced in the art. For example, the level of a CTL immune response may be determined prior to and following administration of any one of the herein described binding proteins expressed by, for example, a T cell. Cytotoxicity assays for determining CTL activity may be performed using any one of several techniques and methods routinely practiced in the art (*e.g.,* Henkart el al., "Cytotoxic T-Lymphocytes" in Fundamental Immunology, Paul (ed.) (2003 Lippincott Williams & Wilkins, Philadelphia, PA), pages 1127-50, and references cited therein).

The present invention provides, in part, methods, systems, and code for accurately classifying whether a biological sample is associated with an output of interest, such as expression of a target of interest, such as HA-2. In some embodiments, the present invention is useful for classifying a sample (*e.g.,* from a subject) as associated with or at risk for responding to or not responding to therapy for a disorder characterized by HA-2 expression using a statistical algorithm and/or empirical data.

An exemplary method for detecting the amount or activity of HA-2, and thus useful for classifying whether a sample is likely or unlikely to respond to a therapy for a disorder characterized by HA-2 expression involves contacting a biological sample with an agent, such as an HA-2 immunogenic peptide or binding agent described herein, capable of detecting the amount or activity of HA-2 in the biological sample. In some embodiments, the method further comprises obtaining a biological sample, such as from a test subject. In some embodiments, at least one agent is used, wherein two, three, four, five, six, seven, eight, nine, ten, or more such agents may be used in combination (*e.g.,* in sandwich ELISAs) or in serial. In certain instances, the statistical algorithm is a single learning statistical classifier system. For example, a single learning statistical classifier system may be used to classify a sample as a based upon a prediction or probability value and the presence or level of the biomarker. The use of a single learning statistical classifier system typically classifies the sample with a sensitivity, specificity, positive predictive value, negative predictive value, and/or overall accuracy of at least about 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%.

Other suitable statistical algorithms are well-known to those of skill in the art. For example, learning statistical classifier systems include a machine learning algorithmic technique capable of adapting to complex data sets (*e.g.,* panel of markers of interest) and making decisions based upon such data sets. In some embodiments, a single learning statistical classifier system such as a classification tree (*e.g.,* random forest) is used. In other embodiments, a combination of 2, 3, 4, 5, 6, 7, 8, 9, 10, or more learning statistical classifier systems are used, preferably in tandem. Examples of learning statistical classifier systems include, but are not limited to, those using inductive learning (*e.g.,* decision/classification trees such as random forests, classification and regression trees (C&RT), boosted trees, etc.), Probably Approximately Correct (PAC) learning, connectionist learning (*e.g.,* neural networks (NN), artificial neural networks (ANN), neuro

fuzzy networks (NFN), network structures, perceptrons such as multi-layer perceptrons, multi-layer feed-forward networks, applications of neural networks, Bayesian learning in belief networks, etc.), reinforcement learning (*e.g.,* passive learning in a known environment such as naive learning, adaptive dynamic learning, and temporal difference learning, passive learning in an unknown environment, active learning in an unknown environment, learning action-value functions, applications of reinforcement learning, etc.), and genetic algorithms and evolutionary programming. Other learning statistical classifier systems include support vector machines (*e.g.,* Kernel methods), multivariate adaptive regression splines (MARS), Levenberg-Marquardt algorithms, Gauss-Newton algorithms, mixtures of Gaussians, gradient descent algorithms, and learning vector quantization (LVQ). In certain embodiments, the method encompassed by the present invention further comprises sending the sample classification results to a clinician, *e.g.,* an oncologist.

In some embodiments, the diagnosis of a subject is followed by administering to the individual a therapeutically effective amount of a defined treatment based upon the diagnosis.

In some embodiments, the methods further involve obtaining a control biological sample (*e.g.,* biological sample from a subject who does not have a disorder characterized by HA-2 expression, a subject who is in remission, a subject whose disorder is susceptible to therapy, a subject whose disorder is progressing, or other subjects of interest).

In some embodiments of analytical methods described herein, HA-2 expression (*e.g.*, in a sample from a subject) is compared to a pre-determined control (standard) sample. The sample from the subject is typically from a diseased tissue, such as cancer cells or tissues. The control sample may be from the same subject or from a different subject. The control sample is typically a normal, non-diseased sample. However, in some embodiments, such as for staging of disease or for evaluating the efficacy of treatment, the control sample may be from a diseased tissue. The control sample may be a combination of samples from several different subjects. In some embodiments, the HA-2 expression measurement(s) from a subject is compared to a pre-determined level. This pre-determined level is typically obtained from normal samples. As described herein, a "pre-determined" expression may be used to, by way of example only, evaluate a subject that may be selected for treatment, evaluate a response to cancer, and/or evaluate a response to a combination cancer therapy. A pre-determined biomarker amount and/or activity measurement(s) may be determined in populations of patients with or without a disorder characterized by HA-2

expression. The pre-determined biomarker amount and/or activity measurement(s) may be a single number, equally applicable to every patient, or the pre-determined biomarker amount and/or activity measurement(s) may vary according to specific sub-populations of patients. Age, weight, height, and other factors of a subject may affect the pre-determined biomarker amount and/or activity measurement(s) of the individual. Furthermore, the pre-determined biomarker amount and/or activity may be determined for each subject individually. In one embodiment, the amounts determined and/or compared in a method described herein are based on absolute measurements.

In another embodiment, the amounts determined and/or compared in a method described herein are based on relative measurements, such as ratios (*e.g.,* biomarker copy numbers, level, and/or activity before a treatment vs. after a treatment, such biomarker measurements relative to a spiked or man-made control, such biomarker measurements relative to the expression of a housekeeping gene, and the like). For example, the relative analysis may be based on the ratio of pre-treatment biomarker measurement as compared to post-treatment biomarker measurement. Pre-treatment biomarker measurement may be made at any time prior to initiation of a therapy. Post-treatment biomarker measurement may be made at any time after initiation of therapy. In some embodiments, post-treatment biomarker measurements are made 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 weeks or more after initiation of therapy, and even longer toward indefinitely for continued monitoring. Treatment may comprise therapy to treat the disorder characterized by HA-2 expression, either alone or in combination with other agents, such as anti-cancer agents like chemotherapy or immune checkpoint inhibitors.

The pre-determined HA-2 expression may be any suitable standard. For example, the pre-determined HA-2 expression may be obtained from the same or a different subject for whom a subject selection is being assessed. In one embodiment, the pre-determined biomarker amount and/or activity measurement(s) may be obtained from a previous assessment of the same patient. In such a manner, the progress of the selection of the patient may be monitored over time. In addition, the control may be obtained from an assessment of another human or multiple humans, *e.g.,* selected groups of humans, if the subject is a human. In such a manner, the extent of the selection of the human for whom selection is being assessed may be compared to suitable other humans, *e.g.,* other humans who are in a similar situation to the human of interest, such as those suffering from similar or the same condition(s) and/or of the same ethnic group.

In some embodiments, the change of HA-2 expression from the pre-determined level is about 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0 fold or greater, or any range in between, inclusive. Such cut-off values apply equally when the measurement is based on relative changes, such as based on the ratio of pre-treatment biomarker measurement as compared to post-treatment biomarker measurement.

In some embodiments, HA-2 expression may be detected and/or quantified by detecting or quantifying HA-2 polypeptide or antigen thereof, such as by using a composition described herein. The polypeptide may be detected and quantified by any of a number of means well-known to those of skill in the art, such as by immunodiffusion, immunoelectrophoresis, radioimmunoassay (RIA), enzyme-linked immunosorbent assays (ELISAs), immunofluorescent assays, Western blotting, binder-ligand assays, immunohistochemical techniques, agglutination, complement assays, high performance liquid chromatography (HPLC), thin layer chromatography (TLC), hyperdiffusion chromatography, and the like (*e.g.,* Basic and Clinical Immunology, Sites and Terr, eds., Appleton and Lange, Norwalk, Conn. pp 217-262, 1991).

b. Therapeutic Methods

In an aspect encompassed by the present invention, provided herein are methods for preventing and/or treating a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen, and/or for inducing an immune response against a cell of interest, such as a hyperproliferative cell, expressing an HA-2 antigen. In some embodiments, the method comprises administering to a subject a therapeutically effective amount of a composition comprising cells expressing at least one binding protein described herein. The methods encompassed by the present invention also may be used to determine the responsiveness to therapy for many different disorders characterized by HA-2 expression in subjects, such as those described herein.

In some embodiments, provided herein are methods for preventing and/or treating certain hyperproliferative disorders (*e.g.*, hematological malignancies). In certain embodiments, the hematological malignancy comprises a leukemia (*e.g.*, an acute leukemia or a chronic leukemia). In specific embodiments, the leukemia comprises acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), mixed phenotype acute leukemia (MPAL), chronic myeloid leukemia (CML), B cell prolymphocytic leukemia, hairy cell leukemia, or chronic lymphocytic leukemia (CLL). In certain embodiments, the

hematological malignancy comprises a lymphoma. In certain embodiments, the lymphoma comprises Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), a central nervous system lymphoma, small lymphocytic lymphoma (SLL), CD37+ dendritic cell lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, extraosseous plasmacytoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated (MALT) lymphoid tissue, nodal marginal zone B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, mediastinal (thymic) large B-cell lymphoma, precursor B-lymphoblastic lymphoma, immunoblastic large cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, Burkitt's lymphoma/leukemia, B-cell proliferations of uncertain malignant potential, lymphomatoid granulomatosis, and post-transplant lymphoproliferative disorder. In certain embodiments, the hematological malignancy comprises a myelodysplastic disorder (MDS), such as, for example, refractory cytopenia with unilineage dysplasia (refractory anemia, refractory neutropenia, and refractory thrombocytopenia), refractory anemia with ring sideroblasts (RARS), refractory anemia with ring sideroblasts - thrombocytosis (RARS-t), refractory cytopenia with multinieage dysplasia (RCMD), refractory cytopenia with multinieage dysplasia and ring sideroblasts (RCMD-RS), refractory anemia with excess blasts (RAEB), myelodysplasia unclassifiable, refractory cytopenia of childhood, MDS with isolated del(5q), and other well-known MDS subtypes (see, for example, 2016 World Health Organization MDS classification available on the World Wide Web at nbci.nlm.nih.gov/pmc/articles/PMC655460/). In certain embodiments, the hematological malignancy comprises a myeloproliferative neoplasms (MPN), such as for example, myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myelomonocytic leukemia, chronic myeloproliferative disease-unclassifiable, chronic neutrophilic leukemia, chronic eosinophilic leukemia and MPN-not otherwise specified. In further embodiments, the hematological malignancy comprises a myeloma.

In some embodiments, provided herein are methods for preventing and/or treating a non-malignant disorder. In certain embodiments, subjects affilicted with these non-malignant disorders have undergone or are undergoing hematopoietic cell transplantation. In some embodiments, the non-malignant disorder is selected from the group consisting of non-malignant hematology (*e.g.,* sickle cell anemia, thalassemia, aplastic anemia, hemophagocytic lymphohistiocytosis (HLH), severe aplastic anemia, marrow failure syndromes (including Fanconi anemia, Diamond-Blackfan anemia, Shwachman Diamond

syndrome ,and others); immune deficiency disorders (*e.g.*, severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, Omenn syndrome, X-linked lymphoproliferative syndrome, chronic granulomatous disease, leukocyte adhesion deficiency, DiGeorge syndrome and other well-known disorders, such as indications for hematopoietic stem cell transplantation (HCT) like those listed at bethematchclinical.org/workarea/downloadasset.aspx?id-3545); and autoimmune disorder (*e.g.*, systemic sclerosis, glomerular nephritis, arthritis, dilated cardiomyopathy-like disease, ulceous colitis, Sjogren syndrome, Crohn disease, systemic erythematodes, chronic rheumatoid arthritis, multiple sclerosis, psoriasis, allergic contact dermatitis, polymyosiis, pachyderma, periarteritis nodosa, rheumatic fever, vitiligo vulgaris, insulin dependent diabetes mellitus, Behcet disease, Hashimoto disease, Addison disease, dermatomyositis, myasthenia gravis, Reiter syndrome, Graves' disease, anaemia perniciosa, Goodpasture syndrome, sterility disease, chronic active hepatitis, pemphigus, autoimmune thrombopenic purpura, and autoimmune hemolytic anemia, active chronic hepatitis, Addison's disease, anti-phospholipid syndrome, atopic allergy, autoimmune atrophic gastritis, achlorhydra autoimmune, celiac disease, Cushing's syndrome, dermatomyositis, discoid lupus, erythematosis, Goodpasture's syndrome, Hashimoto's thyroiditis, idiopathic adrenal atrophy, idiopathic thrombocytopenia, insulin-dependent diabetes, Lambert-Eaton syndrome, lupoid hepatitis, some cases of lymphopenia, mixed connective tissue disease, pemphigoid, pemphigus vulgaris, pernicious anema, phacogenic uveitis, polyarteritis nodosa, polyglandular autosyndromes, primary biliary cirrhosis, primary sclerosing cholangitis, Raynaud's syndrome, relapsing polychondritis, Schmidt's syndrome, limited scleroderma (or crest syndrome), sympathetic ophthalmia, systemic lupus erythematosis, Takayasu's arteritis, temporal arteritis, thyrotoxicosis, type b insulin resistance, ulcerative colitis and Wegener's granulomatosis). In specific embodiments, the autoimmune disorder is systemic sclerosis or multiple sclerosis.

In addition, the compositions described herein may also be administered in combination therapy to further modulate a desired activity. Additional agents include, without limitations, chemotherapeutic agents, hormones, antiangiogens, radiolabelled, compounds, or with surgery, cryotherapy, and/or radiotherapy. The preceding treatment methods may be administered in conjunction with other forms of conventional therapy (*e.g.,* standard-of-care treatments for cancer well-known to the skilled artisan), either consecutively with, pre- or post-conventional therapy. For example, these modulatory

agents may be administered with a therapeutically effective dose of chemotherapeutic agent. In another embodiment, these modulatory agents are administered in conjunction with chemotherapy to enhance the activity and efficacy of the chemotherapeutic agent. The Physicians' Desk Reference (PDR) discloses dosages of chemotherapeutic agents that have been used in the treatment of various cancers. The dosing regimen and dosages of these aforementioned chemotherapeutic drugs that are therapeutically effective will depend on the particular melanoma, being treated, the extent of the disease and other factors familiar to the physician of skill in the art and may be determined by the physician.

Therapy using one or more compositions described herein, either alone or in combination with other therapies, such as cancer therapies, may be used to contact HA-2-expressing cells and/or administered to a desired subject, such as a subject that is indicated as being a likely responder to therapy. In another embodiment, such therapy may be avoided once a subject is indicated as not being a likely responder to the therapy (*e.g.*, as assessed according to a diagnostic or prognostic method described herein) and an alternative treatment regimen, such as targeted and/or untargeted cancer therapies, may be recommended and/or administered.

The term "targeted therapy" refers to administration of agents that selectively interact with a chosen biomolecule to thereby treat cancer. For example, targeted therapy regarding the inhibition of immune checkpoint inhibitor is useful in combination with the methods encompassed by the present invention.

The term "immunotherapy" or "immunotherapies" generally refers to any strategy for modulating an immune response in a beneficial manner and encompasses the treatment of a subject afflicted with, or at risk of contracting or suffering a recurrence of, a disease by a method comprising inducing, enhancing, suppressing or otherwise modifying an immune response, as well as any treatment that uses certain parts of a subject's immune system to fight diseases, such as cancer. The subject's own immune system is stimulated (or suppressed), with or without administration of one or more agent for that purpose. Immunotherapies that are designed to elicit or amplify an immune response are referred to as "activation immunotherapies." Immunotherapies that are designed to reduce or suppress an immune response are referred to as "suppression immunotherapies." In some embodiments, an immunotherapy is specific for cells of interest, such as cancer cells. In some embodiments, immunotherapy may be "untargeted," which refers to administration of agents that do not selectively interact with immune system cells, yet modulates immune

system function. Representative examples of untargeted therapies include, without limitation, chemotherapy, gene therapy, and radiation therapy.

Some forms of immunotherapy are targeted therapies that may comprise, for example, the use of cancer vaccines and/or sensitized antigen presenting cells. For example, an oncolytic virus is a virus that is able to infect and lyse cancer cells, while leaving normal cells unharmed, making them potentially useful in cancer therapy. Replication of oncolytic viruses both facilitates tumor cell destruction and also produces dose amplification at the tumor site. They may also act as vectors for anticancer genes, allowing them to be specifically delivered to the tumor site. The immunotherapy may involve passive immunity for short-term protection of a host, achieved by the administration of pre-formed antibody directed against a cancer antigen or disease antigen (*e.g.,* administration of a monoclonal antibody, optionally linked to a chemotherapeutic agent or toxin, to a tumor antigen). Immunotherapy may also focus on using the cytotoxic lymphocyte-recognized epitopes of cancer cell lines. Alternatively, antisense polynucleotides, ribozymes, RNA interference molecules, triple helix polynucleotides and the like, may be used to selectively modulate biomolecules that are linked to the initiation, progression, and/or pathology of a tumor or cancer. Similarly, immunotherapy may take the form of cell-based therapies. For example, adoptive cellular immunotherapy is a type of immunotherapy using immune cells, such as T cells, that have a natural or genetically engineered reactivity to a patient's cancer are generated and then transferred back into the cancer patient. The injection of a large number of activated tumor-specific T cells may induce complete and durable regression of cancers.

Immunotherapy may involve passive immunity for short-term protection of a host, achieved by the administration of pre-formed antibody directed against a cancer antigen or disease antigen (*e.g.,* administration of a monoclonal antibody, optionally linked to a chemotherapeutic agent or toxin, to a tumor antigen). Immunotherapy may also focus on using the cytotoxic lymphocyte-recognized epitopes of cancer cell lines. Alternatively, antisense polynucleotides, ribozymes, RNA interference molecules, triple helix polynucleotides and the like, may be used to selectively modulate biomolecules that are linked to the initiation, progression, and/or pathology of a tumor or cancer.

In some embodiments, an immunotherapeutic agent is an agonist of an immune-stimulatory molecule; an antagonist of an immune-inhibitory molecule; an antagonist of a chemokine; an agonist of a cytokine that stimulates T cell activation; an agent that

antagonizes or inhibits a cytokine that inhibits T cell activation; and/or an agent that binds to a membrane bound protein of the B7 family. In some embodiments, the immunotherapeutic agent is an antagonist of an immune-inhibitory molecule. In some embodiments, the immunotherapeutic agents may be agents for cytokines, chemokines and growth factors, for examples, neutralizing antibodies that neutralize the inhibitory effect of tumor associated cytokines, chemokines, growth factors and other soluble factors, including IL-10, TGF-β and VEGF.

In some embodiments, immunotherapy comprises inhibitors of one or more immune checkpoints. The term "immune checkpoint" refers to a group of molecules on the cell surface of CD4+ and/or CD8+ T cells that fine-tune immune responses by modulating anti-cancer immune responses, such as down-modulating or inhibiting an anti-tumor immune response. Immune checkpoint proteins are well-known in the art and include, without limitation, CTLA-4, PD-1, VISTA, B7-H2, B7-H3, PD-L1, B7-H4, B7-H6, ICOS, HVEM, PD-L2, CD200R, CD160, gp49B, PIR-B, KRLG-1, KIR family receptors, TIM-1, TIM-3, TIM-4, LAG-3 (CD223), IDO, GITR, 4-IBB, OX-40, BTLA, SIRPalpha (CD47), CD48, 2B4 (CD244), B7.1, B7.2, ILT-2, ILT-4, TIGIT, HHLA2, butyrophilins, and A2aR (see, for example, WO 2012/177624). The term further encompasses biologically active protein fragments, as well as nucleic acids encoding full-length immune checkpoint proteins.

Some immune checkpoints are "immune-inhibitory immune checkpoints" encompassing molecules (*e.g.*, proteins) that inhibit, down-regulate, or suppress a function of the immune system (*e.g.*, an immune response). For example, PD-L1 (programmed death-ligand 1), also known as CD274 or B7-H1, is a protein that transmits an inhibitory signal that reduces proliferation of T cells to suppress the immune system. CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), also known as CD152, is a protein receptor on the surface of antigen-presenting cells that serves as an immune checkpoint ("off" switch) to downregulate immune responses. TIM-3 (T-cell immunoglobulin and mucin-domain containing-3), also known as HAVCR2, is a cell surface protein that serves as an immune checkpoint to regulate macrophage activation. VISTA (V-domain Ig suppressor of T cell activation) is a type I transmembrane protein that functions as an immune checkpoint to inhibit T cell effector function and maintain peripheral tolerance. LAG-3 (lymphocyte-activation gene 3) is an immune checkpoint receptor that negatively regulates proliferation, activation, and homeostasis of T cells. BTLA (B- and T-lymphocyte attenuator) is a protein that displays T cell inhibition via interactions with tumor necrosis family receptors (TNF-

R). KIR (killer-cell immunoglobulin-like receptor) is a family of proteins expressed on NK cells, and a minority of T cells, that suppress the cytotoxic activity of NK cells. In some embodiments, immunotherapeutic agents may be agents specific to immunosuppressive enzymes such as inhibitors that may block the activities of arginase (ARG) and indoleamine 2,3-dioxygenase (IDO), an immune checkpoint protein that suppresses T cells and NK cells, which change the catabolism of the amino acids arginine and tryptophan in the immunosuppressive tumor microenvironment. The inhibitors may include, but are not limited to, *N*-hydroxy-L-Arg (NOHA) targeting to ARG-expressing M2 macrophages, nitroaspirin or sildenafil (Viagra®), which blocks ARG and nitric oxide synthase (NOS) simultaneously; and IDO inhibitors, such as 1-methyl-tryptophan. The term further encompasses biologically active protein fragment, as well as nucleic acids encoding full-length immune checkpoint proteins and biologically active protein fragments thereof. In some embodiment, the term further encompasses any fragment according to homology descriptions provided herein.

By contrast, other immune checkpoints are "immune-stimulatory" encompassing molecules (*e.g.*, proteins) that activate, stimulate, or promote a function of the immune system (*e.g.*, an immune response). In some embodiments, the immune-stimulatory molecule is CD28, CD80 (B7.1), CD86 (B7.2), 4-1BB (CD137), 4-1BBL (CD137L), CD27, CD70, CD40, CD40L, CD122, CD226, CD30, CD30L, OX40, OX40L, HVEM, **BTLA, GITR and its ligand GITRL, LIGHT, LTβR, LTαβ, ICOS (CD278), ICOSL (B7-**H2), and NKG2D. CD40 (cluster of differentiation 40) is a costimulatory protein found on antigen presenting cells that is required for their activation. OX40, also known as tumor necrosis factor receptor superfamily member 4 (TNFRSF4) or CD134, is involved in maintenance of an immune response after activation by preventing T-cell death and subsequently increasing cytokine production. CD137 is a member of the tumor necrosis factor receptor (TNF-R) family that co-stimulates activated T cells to enhance proliferation and T cell survival. CD122 is a subunit of the interleukin-2 receptor (IL-2) protein, which promotes differentiation of immature T cells into regulatory, effector, or memory T cells. CD27 is a member of the tumor necrosis factor receptor superfamily and serves as a co-stimulatory immune checkpoint molecule. CD28 (cluster of differentiation 28) is a protein expressed on T cells that provides co-stimulatory signals required for T cell activation and survival. GITR (glucocorticoid-induced TNFR-related protein), also known as TNFRSF18 and AITR, is a protein that plays a key role in dominant immunological self-tolerance

maintained by regulatory T cells. ICOS (inducible T-cell co-stimulator), also known as CD278, is a CD28-superfamily costimulatory molecule that is expressed on activated T cells and play a role in T cell signaling and immune responses.

Immune checkpoints and their sequences are well-known in the art and representative embodiments are described further below. Immune checkpoints generally relate to pairs of inhibitory receptors and the natural binding partners (*e.g.*, ligands). For example, PD-1 polypeptides are inhibitory receptors capable of transmitting an inhibitory signal to an immune cell to thereby inhibit immune cell effector function, or are capable of promoting costimulation (*e.g.,* by competitive inhibition) of immune cells, *e.g.,* when present in soluble, monomeric form. Preferred PD-1 family members share sequence identity with PD-1 and bind to one or more B7 family members, *e.g.,* B7-1, B7-2, PD-1 ligand, and/or other polypeptides on antigen presenting cells. The term "PD-1 activity," includes the ability of a PD-1 polypeptide to modulate an inhibitory signal in an activated immune cell, *e.g.,* by engaging a natural PD-1 ligand on an antigen presenting cell. Modulation of an inhibitory signal in an immune cell results in modulation of proliferation of, and/or cytokine secretion by, an immune cell. Thus, the term "PD-1 activity" includes the ability of a PD-1 polypeptide to bind its natural ligand(s), the ability to modulate immune cell inhibitory signals, and the ability to modulate the immune response. The term "PD-1 ligand" refers to binding partners of the PD-1 receptor and includes both PD-L1 (Freeman *et al.* (2000) *J. Exp. Med.* 192:1027-1034) and PD-L2 (Latchman *et al.* (2001) *Nat. Immunol.* 2:261). The term "PD-1 ligand activity" includes the ability of a PD-1 ligand polypeptide to bind its natural receptor(s) (*e.g.,* PD-1 or B7-1), the ability to modulate immune cell inhibitory signals, and the ability to modulate the immune response.

As used herein, the term "immune checkpoint therapy" refers to the use of agents that inhibit immune-inhibitory immune checkpoints, such as inhibiting their nucleic acids and/or proteins. Inhibition of one or more such immune checkpoints may block or otherwise neutralize inhibitory signaling to thereby upregulate an immune response in order to more efficaciously treat cancer. Exemplary agents useful for inhibiting immune checkpoints include antibodies, small molecules, peptides, peptidomimetics, natural ligands, and derivatives of natural ligands, that may either bind and/or inactivate or inhibit immune checkpoint proteins, or fragments thereof; as well as RNA interference, antisense, nucleic acid aptamers, etc. that may downregulate the expression and/or activity of immune checkpoint nucleic acids, or fragments thereof. Exemplary agents for upregulating an

immune response include antibodies against one or more immune checkpoint proteins that block the interaction between the proteins and its natural receptor(s); a non-activating form of one or more immune checkpoint proteins (*e.g.,* a dominant negative polypeptide); small molecules or peptides that block the interaction between one or more immune checkpoint proteins and its natural receptor(s); fusion proteins (*e.g.,* the extracellular portion of an immune checkpoint inhibition protein fused to the Fc portion of an antibody or immunoglobulin) that bind to its natural receptor(s); nucleic acid molecules that block immune checkpoint nucleic acid transcription or translation; and the like. Such agents may directly block the interaction between the one or more immune checkpoints and its natural receptor(s) (*e.g.,* antibodies) to prevent inhibitory signaling and upregulate an immune response. Alternatively, agents may indirectly block the interaction between one or more immune checkpoint proteins and its natural receptor(s) to prevent inhibitory signaling and upregulate an immune response. For example, a soluble version of an immune checkpoint protein ligand such as a stabilized extracellular domain may binding to its receptor to indirectly reduce the effective concentration of the receptor to bind to an appropriate ligand. In one embodiment, anti-PD-1 antibodies, anti-PD-L1 antibodies, and/or anti-PD-L2 antibodies, either alone or in combination, are used to inhibit immune checkpoints. Therapeutic agents used for blocking the PD-1 pathway include antagonistic antibodies and soluble PD-L1 ligands. The antagonist agents against PD-1 and PD-L1/2 inhibitory pathway may include, but are not limited to, antagonistic antibodies to PD-1 or PD-L1/2 (*e.g.*, 17D8, 2D3, 4H1, 5C4 (also known as nivolumab or BMS-936558), 4A11, 7D3 and 5F4 disclosed in U.S. Pat. No. 8,008,449; AMP-224, pidilizumab (CT-011), pembrolizumab, and antibodies disclosed in U.S. Pat. Numbers 8,779,105; 8,552,154; 8,217,149; 8,168,757; 8,008,449; 7,488,802; 7,943,743; 7,635,757; and 6,808,710. Similarly, additional representative checkpoint inhibitors may be, but are not limited to, antibodies against inhibitory regulator CTLA-4 (anti-cytotoxic T-lymphocyte antigen 4 anti-cytotoxic T-lymphocyte antigen 4), such as ipilimumab, tremelimumab (fully humanized), anti-CD28 antibodies, anti-CTLA-4 adnectins, anti-CTLA-4 domain antibodies, single chain anti-CTLA-4 antibody fragments, heavy chain anti-CTLA-4 fragments, light chain anti-CTLA-4 fragments, and other antibodies, such as those disclosed in U.S. Pat. Numbers 8,748, 815; 8,529,902; 8,318,916; 8,017,114; 7,744,875; 7,605,238; 7,465,446; 7,109,003; 7,132,281; 6,984,720; 6,682,736; 6,207,156; and 5,977,318, as well

as EP Pat. No. 1212422, U.S. Pat Publ. Numbers 2002/0039581 and 2002/086014, and Hurwitz *et al.* (1998) *Proc. Natl. Acad. Sci. U.S.A.* 95:10067-10071.

The representative definitions of immune checkpoint activity, ligand, blockade, and the like exemplified for PD-1, PD-L1, PD-L2, and CTLA-4 apply generally to other immune checkpoints.

The term "untargeted therapy" refers to administration of agents that do not selectively interact with a chosen biomolecule yet treat cancer. Representative examples of untargeted therapies include, without limitation, chemotherapy, gene therapy, and radiation therapy.

In one embodiment, chemotherapy is used. Chemotherapy includes the administration of a chemotherapeutic agent. Such a chemotherapeutic agent may be, but is not limited to, those selected from among the following groups of compounds: platinum compounds, cytotoxic antibiotics, antimetabolities, anti-mitotic agents, alkylating agents, arsenic compounds, DNA topoisomerase inhibitors, taxanes, nucleoside analogues, plant alkaloids, and toxins; and synthetic derivatives thereof. Exemplary agents include, but are not limited to, alkylating agents: nitrogen mustards (*e.g.,* cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, estramustine, and melphalan), nitrosoureas (*e.g.,* carmustine (BCNU) and lomustine (CCNU)), alkylsulphonates (*e.g.,* busulfan and treosulfan), triazenes (*e.g.,* dacarbazine, temozolomide), cisplatin, treosulfan, and trofosfamide; plant alkaloids: vinblastine, paclitaxel, docetaxol; DNA topoisomerase inhibitors: teniposide, crisnatol, and mitomycin; anti-folates: methotrexate, mycophenolic acid, and hydroxyurea; pyrimidine analogs: 5-fluorouracil, doxifluridine, and cytosine arabinoside; purine analogs: mercaptopurine and thioguanine; DNA antimetabolites: 2'-deoxy-5-fluorouridine, aphidicolin glycinate, and pyrazoloimidazole; and antimitotic agents: halichondrin, colchicine, and rhizoxin. Similarly, additional exemplary agents including platinum-ontaining compounds (*e.g.,* cisplatin, carboplatin, oxaliplatin), vinca alkaloids (*e.g.,* vincristine, vinblastine, vindesine, and vinorelbine), taxoids (*e.g.,* paclitaxel or a paclitaxel equivalent such as nanoparticle albumin-bound paclitaxel (ABRAXANE), docosahexaenoic acid bound-paclitaxel (DHA-paclitaxel, Taxoprexin), polyglutamate bound-paclitaxel (PG-paclitaxel, paclitaxel poliglumex, CT-2103, XYOTAX), the tumor-activated prodrug (TAP) ANG1005 (Angiopep-2 bound to three molecules of paclitaxel), paclitaxel-EC-1 (paclitaxel bound to the erbB2-recognizing peptide EC-1), and glucose-conjugated paclitaxel, *e.g.,* 2'-paclitaxel methyl 2-glucopyranosyl succinate; docetaxel, taxol), epipodophyllins (*e.g.,*

etoposide, etoposide phosphate, teniposide, topotecan, 9-aminocamptothecin, camptoirinotecan, irinotecan, crisnatol, mytomycin C), anti-metabolites, DHFR inhibitors (*e.g.,* methotrexate, dichloromethotrexate, trimetrexate, edatrexate), IMP dehydrogenase inhibitors (*e.g.,* mycophenolic acid, tiazofurin, ribavirin, and EICAR), ribonuclotide reductase inhibitors (*e.g.,* hydroxyurea and deferoxamine), uracil analogs (*e.g.,* 5-fluorouracil (5-FU), floxuridine, doxifluridine, ratitrexed, tegafur-uracil, capecitabine), cytosine analogs (*e.g.,* cytarabine (ara C), cytosine arabinoside, and fludarabine), purine analogs (*e.g.,* mercaptopurine and Thioguanine), Vitamin D3 analogs (*e.g.,* EB 1089, CB 1093, and KH 1060), isoprenylation inhibitors (*e.g.,* lovastatin), dopaminergic neurotoxins (*e.g.,* 1-methyl-4-phenylpyridinium ion), cell cycle inhibitors (*e.g.,* staurosporine), actinomycin (*e.g.,* actinomycin D, dactinomycin), bleomycin (*e.g.,* bleomycin A2, bleomycin B2, peplomycin), anthracycline (*e.g.,* daunorubicin, doxorubicin, pegylated liposomal doxorubicin, idarubicin, epirubicin, pirarubicin, zorubicin, mitoxantrone), MDR inhibitors (*e.g.,* verapamil), Ca^{2+} ATPase inhibitors (*e.g.,* thapsigargin), imatinib, thalidomide, lenalidomide, tyrosine kinase inhibitors (*e.g.,* axitinib (AG013736), bosutinib (SKI-606), cediranib (RECENTIN™, AZD2171), dasatinib (SPRYCEL®, BMS-354825), erlotinib (TARCEVA®), gefitinib (IRESSA®), imatinib (Gleevec®, CGP57148B, STI-571), lapatinib (TYKERB®, TYVERB®), lestaurtinib (CEP-701), neratinib (HKI-272), nilotinib (TASIGNA®), semaxanib (semaxinib, SU5416), sunitinib (SUTENT®, SU11248), toceranib (PALLADIA®), vandetanib (ZACTIMA®, ZD6474), vatalanib (PTK787, PTK/ZK), trastuzumab (HERCEPTIN®), bevacizumab (AVASTIN®), rituximab (RITUXAN®), cetuximab (ERBITUX®), panitumumab (VECTIBIX®), ranibizumab (Lucentis®), nilotinib (TASIGNA®), sorafenib (NEXAVAR®), everolimus (AFINITOR®), alemtuzumab (CAMPATH®), gemtuzumab ozogamicin (MYLOTARG®), temsirolimus (TORISEL®), ENMD-2076, PCI-32765, AC220, dovitinib lactate (TKI258, CHIR-258), BIBW 2992 (TOVOK™), SGX523, PF-04217903, PF-02341066, PF-299804, BMS-777607, ABT-869, MP470, BIBF 1120 (VARGATEF®), AP24534, JNJ-26483327, MGCD265, DCC-2036, BMS-690154, CEP-11981, tivozanib (AV-951), OSI-930, MM-121, XL-184, XL-647, and/or XL228), proteasome inhibitors (*e.g.,* bortezomib (VELCADE®)), mTOR inhibitors (*e.g.,* rapamycin, temsirolimus (CCI-779), everolimus (RAD-001), ridaforolimus, AP23573 (Ariad), AZD8055 (AstraZeneca), BEZ235 (Novartis), BGT226 (Norvartis), XL765 (Sanofi Aventis), PF-4691502 (Pfizer), GDC0980 (Genentech), SF1126 (Semafoe) and OSI-027 (OSI)), oblimersen, gemcitabine,

carminomycin, leucovorin, pemetrexed, cyclophosphamide, dacarbazine, procarbizine, prednisolone, dexamethasone, campathecin, plicamycin, asparaginase, aminopterin, methopterin, porfiromycin, melphalan, leurosidine, leurosine, chlorambucil, trabectedin, procarbazine, discodermolide, carminomycin,, aminopterin, and hexamethyl melamine. Compositions comprising one or more chemotherapeutic agents (*e.g.,* FLAG, CHOP) may also be used. FLAG comprises fludarabine, cytosine arabinoside (Ara-C) and G-CSF. CHOP comprises cyclophosphamide, vincristine, doxorubicin, and prednisone. In another embodiment, PARP (*e.g.,* PARP-1 and/or PARP-2) inhibitors are used and such inhibitors are well-known in the art (*e.g.,* Olaparib, ABT-888, BSI-201, BGP-15 (N-Gene Research Laboratories, Inc.); INO-1001 (Inotek Pharmaceuticals Inc.); PJ34 (Soriano *et al.*, 2001; Pacher *et al.*, 2002b); 3-aminobenzamide (Trevigen); 4-amino-1,8-naphthalimide; (Trevigen); 6(5H)-phenanthridinone (Trevigen); benzamide (U.S. Pat. Re. 36,397); and NU1025 (Bowman *et al.*). The mechanism of action is generally related to the ability of PARP inhibitors to bind PARP and decrease its activity. PARP catalyzes the conversion of beta-nicotinamide adenine dinucleotide (NAD+) into nicotinamide and poly-ADP-ribose (PAR). Both poly (ADP-ribose) and PARP have been linked to regulation of transcription, cell proliferation, genomic stability, and carcinogenesis (Bouchard et.al. (2003) *Exp. Hematol.* 31:446-454); Herceg (2001) *Mut. Res.* 477:97-110). Poly(ADP-ribose) polymerase 1 (PARP1) is a key molecule in the repair of DNA single-strand breaks (SSBs) (de Murcia J. *et al.* (1997) *Proc. Natl. Acad. Sci. U.S.A.* 94:7303-7307; Schreiber *et al.* (2006) *Nat. Rev. Mol. Cell Biol.* 7:517-528; Wang *et al.* (1997) *Genes Dev.* 11:2347-2358). Knockout of SSB repair by inhibition of PARP1 function induces DNA double-strand breaks (DSBs) that may trigger synthetic lethality in cancer cells with defective homology-directed DSB repair (Bryant *et al.* (2005) *Nature* 434:913-917; Farmer *et al.* (2005) *Nature* 434:917-921). The foregoing examples of chemotherapeutic agents are illustrative and are not intended to be limiting.

In another embodiment, radiation therapy is used. The radiation used in radiation therapy may be ionizing radiation. Radiation therapy may also be gamma rays, X-rays, or proton beams. Examples of radiation therapy include, but are not limited to, external-beam radiation therapy, interstitial implantation of radioisotopes (I-125, palladium, iridium), radioisotopes such as strontium-89, thoracic radiation therapy, intraperitoneal P-32 radiation therapy, and/or total abdominal and pelvic radiation therapy. For a general overview of radiation therapy, see Hellman, Chapter 16: Principles of Cancer Management:

Radiation Therapy, 6th edition, 2001, DeVita *et al.*, eds., J. B. Lippencott Company, Philadelphia. The radiation therapy may be administered as external beam radiation or teletherapy wherein the radiation is directed from a remote source. The radiation treatment may also be administered as internal therapy or brachytherapy wherein a radioactive source is placed inside the body close to cancer cells or a tumor mass. Also encompassed is the use of photodynamic therapy comprising the administration of photosensitizers, such as hematoporphyrin and its derivatives, Vertoporfin (BPD-MA), phthalocyanine, photosensitizer Pc4, demethoxy-hypocrellin A; and 2BA-2-DMHA.

In another embodiment, hormone therapy is used. Hormonal therapeutic treatments may comprise, for example, hormonal agonists, hormonal antagonists (*e.g.,* flutamide, bicalutamide, tamoxifen, raloxifene, leuprolide acetate (LUPRON), LH-RH antagonists), inhibitors of hormone biosynthesis and processing, and steroids (*e.g.,* dexamethasone, retinoids, deltoids, betamethasone, cortisol, cortisone, prednisone, dehydrotestosterone, glucocorticoids, mineralocorticoids, estrogen, testosterone, progestins), vitamin A derivatives (*e.g.,* all-trans retinoic acid (ATRA)); vitamin D3 analogs; antigestagens (*e.g.,* mifepristone, onapristone), or antiandrogens (*e.g.,* cyproterone acetate).

In one aspect, provided herein is a method of eliciting in a subject an immune response to a cell that expresses an HA-2 antigen. In some embodiments, the method comprises administering to the subject a pharmaceutical composition described herein, wherein the pharmaceutical composition, when administered to the subject, elicits an immune response to the cell that expresses an HA-2 antigen.

In some embodiments, the immune response can include a cell-mediated immune response. A cellular immune response is a response that involves T cells and may be determined *in vitro*, *ex vivo*, or *in vivo*. For example, a general cellular immune response may be determined as the T cell proliferative activity in cells (*e.g.,* peripheral blood leukocytes (PBLs)) sampled from the subject at a suitable time following the administering of a pharmaceutical composition. Following incubation of *e.g.,* PBMCs with a stimulator for an appropriate period, [^{3}H]thymidine incorporation may be determined. The subset of T cells that is proliferating may be determined using flow cytometry.

In another aspect encompassed by the present invention, the methods provided herein include administering to both human and non-human mammals as described above. Veterinary applications also are contemplated. In some embodiments, the subject may be any living organism in which an immune response may be elicited.

In some embodiments, the pharmaceutical composition may be administered at any time that is appropriate. For example, the administering may be conducted before or during treatment of a subject having a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen, and continued after the non-malignant disorder, hyperproliferative disorder, or the relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen becomes clinically undetectable. The administering also may be continued in a subject showing signs of recurrence.

In some embodiments, the pharmaceutical composition may be administered in a therapeutically or a prophylactically effective amount. Administering the pharmaceutical composition to the subject may be carried out using known procedures, and at dosages and for periods of time sufficient to achieve a desired effect.

In some embodiments, the pharmaceutical composition may be administered to the subject at any suitable site. Administration may be accomplished using methods generally known in the art. Agents, including cells, may be introduced to the desired site by direct injection, or by any other means used in the art including, but are not limited to, intravascular, intracerebral, parenteral, intraperitoneal, intravenous, epidural, intraspinal, intrasternal, intra-articular, intra-synovial, intrathecal, intra-arterial, intracardiac, or intramuscular administration. For example, subjects of interest may be engrafted with the transplanted cells by various routes. Such routes include, but are not limited to, intravenous administration, subcutaneous administration, administration to a specific tissue (*e.g.*, focal transplantation), injection into the femur bone marrow cavity, injection into the spleen, administration under the renal capsule of fetal liver, and the like. In certain embodiment, the cancer vaccine encompassed by the present invention is injected to the subject intratumorally or subcutaneously. Cells may be administered in one infusion, or through successive infusions over a defined time period sufficient to generate a desired effect. Exemplary methods for transplantation, engraftment assessment, and marker phenotyping analysis of transplanted cells are well-known in the art (see, for example, Pearson *et al.* (2008) *Curr. Protoc. Immunol.* 81:15.21.1-15.21.21; Ito *et al.* (2002) *Blood* 100:3175-3182; Traggiai *et al.* (2004) *Science* 304:104-107; Ishikawa *et al. Blood* (2005) 106:1565-1573; Shultz *et al.* (2005) *J. Immunol.* 174:6477-6489; and Holyoake *et al.* (1999) *Exp. Hematol.* 27:1418-1427). In some embodiments, the dose may be administered in an amount and for a period of time effective in bringing about a desired response, be it

eliciting the immune response or the prophylactic or therapeutic treatment of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen and/or symptoms associated therewith.

The pharmaceutical composition may be given subsequent to, preceding, or contemporaneously with other therapies including therapies that also elicit an immune response in the subject. For example, the subject may previously or concurrently be treated by other forms of immunomodulatory agents, such other therapies may be provided in such a way so as not to interfere with the immunogenicity of the compositions described herein.

Administering may be properly timed by the care giver (*e.g.,* physician, veterinarian), and may depend on the clinical condition of the subject, the objectives of administering, and/or other therapies also being contemplated or administered. In some embodiments, an initial dose may be administered, and the subject monitored for an immunological and/or clinical response. Suitable means of immunological monitoring include using patient's peripheral blood lymphocyte (PBL) as responders and immunogenic peptides or peptide-MHC complexes described herein as stimulators. An immunological reaction also may be determined by a delayed inflammatory response at the site of administering. One or more doses subsequent to the initial dose may be given as appropriate, typically on a monthly, semimonthly, or a weekly basis, until the desired effect is achieved. Thereafter, additional booster or maintenance doses may be given as required, particularly when the immunological or clinical benefit appears to subside.

In general, an appropriate dosage and treatment regimen provides the active molecules or cells in an amount sufficient to provide a benefit. Such a response may be monitored by establishing an improved clinical outcome (*e.g.,* more frequent remissions, complete or partial, or longer disease-free survival) in treated subjects as compared to non-treated subjects. Increases in preexisting immune responses to a viral protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which are routine.

For prophylactic use, a dose should be sufficient to prevent, delay the onset of, or diminish the severity of a disease associated with disease or disorder. Prophylactic benefit of the immunogenic compositions administered according to the methods described herein can be determined by performing pre-clinical (including *in vitro*, *ex vivo*, and *in vivo* animal studies) and clinical studies and analyzing data obtained therefrom by appropriate

statistical, biological, and clinical methods and techniques, all of which can readily be practiced by an ordinarily skilled artisan.

As used herein, administration of a composition refers to delivering the same to a subject, regardless of the route or mode of delivery. Administration may be effected continuously or intermittently, and parenterally. Administration may be for treating a subject already confirmed as having a recognized condition, disease or disease state, or for treating a subject susceptible to or at risk of developing such a condition, disease or disease state. Co-administration with an adjunctive therapy may include simultaneous and/or sequential delivery of multiple agents in any order and on any dosing schedule (*e.g.,* engineered immune cells with one or more cytokines; immunosuppressive therapy such as calcineurin inhibitors, corticosteroids, microtubule inhibitors, low dose of a mycophenolic acid prodrug, or any combination thereof).

In some embodiments, a plurality of doses of a host cell (*e.g.,* an engineered immune cell) described herein is administered to the subject, which may be administered at intervals between administrations of about two to about four weeks.

Treatment or prevention methods encompassed by the present invention may be administered to a subject as part of a treatment course or regimen, which may comprise additional treatments prior to, or after, administration of the instantly disclosed unit doses, cells, or compositions. For example, in some embodiments, a subject receiving a unit dose of the host cell (*e.g.,* an engineered immune cell) is receiving or had previously received a hematopoietic cell transplant (HCT; including myeloablative and non-myeloablative HCT). In any of the foregoing embodiments, a hematopoietic cell used in an HCT may be a "universal donor" cell that is modified to reduce or eliminate expression of one or more endogenous genes that encode a polypeptide product selected from an MHC, antigen, and a binding protein (*e.g.,* by a chromosomal gene knockout according to the methods described herein).

Techniques and regimens for performing cell transplantation are known in the art and may comprise transplantation of any suitable donor cell, such as a cell derived from umbilical cord blood, bone marrow, or peripheral blood, a hematopoietic stem cell, a mobilized stem cell, or a cell from amniotic fluid. Accordingly, in some embodiments, a host cell (*e.g.,* an engineered immune cell) encompassed by the present invention may be administered with or shortly after stem cell therapy.

Methods encompassed by the present invention may, in some embodiments, further include administering one or more additional agents to treat the disease or disorder (*e.g.,* a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen) in a combination therapy. For example, in some embodiments, a combination therapy comprises administering host cell or binding protein encompassed by the present invention with (concurrently, simultaneously, or sequentially) an antiviral agent. In some embodiments, a combination therapy comprises administering a host cell or binding protein encompassed by the present invention with lopinavir/ritonavir, chloroquine, ribavirin, steroid drugs, hydroxychloroquine, and/or interferon α. In some embodiments, a combination therapy comprises administering a host cell, composition, or unit dose of the host cells encompassed by the present invention with a secondary therapy, such as a surgery, an antibody, a vaccine, or any combination thereof.

In some embodiments, the subject is a human, such as a human with a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen. In some embodiments, the subject is a rodent, such as a mouse. In some such embodiments, the mouse is a transgenic mouse, such as a mouse expressing human MHC (*i.e.,* HLA) molecules, such as HLA-A2 (*e.g.*, Nicholson *et al.* (2012) *Adv. Hematol.* 2012:404081).

In some embodiments, the subject is a transgenic mouse expressing human TCRs or is an antigen-negative mouse (*e.g.*, Li *et al.* (2010) *Nat. Med.* 16:1029-1034 and Obenaus *et al.* (2015) *Nat. Biotechnol.* 33:402-407). In some embodiments, the subject is a transgenic mouse expressing human HLA molecules and human TCRs.

In some embodiments, such as where the subject is a transgenic HLA mouse, the identified TCRs are modified, *e.g.,* to be chimeric or humanized. In some embodiments, the TCR scaffold is modified, such as analogous to known binding protein humanizing methods.

c. Screening Methods

Another aspect encompassed by the present invention encompasses screening assays.

The present invention encompasses assays for screening agents, such as test proteins, that bind to, or modulate the activity of, HA-2 or an antigen thereof. Such agents include, without limitation, antibodies, proteins, fusion proteins, small molecules, and nucleic acids. In some embodiments, a method for identifying an agent which modulates

an immune response entails determining the ability of the candidate agent to modulate HA-2 activity and further modulate an immune response of interest, such as modulated cytotoxic T cell activation and/or activity, sensitivity of cancer cells to immune checkpoint therapy, and the like.

In some embodiments, an assay is a cell-free or cell-based assay, comprising contacting a target, with a test agent, and determining the ability of the test agent to modulate (*e.g.,* upregulate or downregulate) the amount and/or activity of the target, such as by measuring direct or indirect parameters as described below.

In some embodiments, an assay is a cell-based assay, such as one comprising contacting (a) a cell of interest with a test agent and determining the ability of the test agent to modulate the amount and/or activity of the target, such as binding characteristics. Determining the ability of the polypeptides to bind to, or interact with, each other may be accomplished, *e.g.*, by measuring direct binding or by measuring a parameter of immune cell activation or function.

In another embodiment, an assay is a cell-based assay, comprising contacting a cell such as a cancer cell with immune cells (*e.g.*, cytotoxic T cells) and a test agent, and determining the ability of the test agent to modulate the amount and/or activity of the target, and/or modulated immune responses, such as by measuring direct or indirect parameters as described below.

The methods described above and herein may also be adapted to test one or more agents that are already known to modulate the amount and/or activity of one or more biomarkers described herein to confirm modulation of the one or more biomarkers and/or to confirm the effects of the agents on readouts of a desired phenotype, such as modulated immune responses, sensitivity to immune checkpoint blockade, and the like.

In some embodiments, determining the ability of a test agent (*e.g.* antibodies, fusion proteins, peptides, or small molecules) to modulate the interaction between a given set of polypeptides may be accomplished by determining the activity of one or more members of the set of polypeptides. For example, the activity of a protein and/or one or more binding partners may be determined by detecting induction of a cellular second messenger (*e.g.*, intracellular signaling), detecting catalytic/enzymatic activity of an appropriate substrate, detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*, chloramphenicol acetyl transferase), or detecting a cellular response regulated by the

protein and/or the one or more binding partners. Determining the ability of the test agent to bind to or interact with said polypeptide may be accomplished, for example, by measuring the ability of a compound to modulate immune cell costimulation or inhibition in a proliferation assay, or by interfering with the ability of said polypeptide to bind to antibodies that recognize a portion thereof.

Agents that modulate target amount and/or activity, such as interactions with one or more binding partners, may be identified by their ability to inhibit immune cell proliferation, and/or effector function, or to induce anergy, clonal deletion, and/or exhaustion when added to an *in vitro* assay. For example, cells may be cultured in the presence of an agent that stimulates signal transduction via an activating receptor. A number of recognized readouts of cell activation may be employed to measure, cell proliferation or effector function (*e.g.*, antibody production, cytokine production, phagocytosis) in the presence of the agent. The ability of a test agent to block this activation may be readily determined by measuring the ability of the agent to effect a decrease in proliferation or effector function being measured, using techniques known in the art.

For example, agents encompassed by the present invention may be tested for the ability to inhibit or enhance costimulation in a T cell assay, as described in Freeman *et al.* (2000) *J. Exp. Med.* 192:1027 and Latchman *et al.* (2001) *Nat. Immunol.* 2:261. CD4+ T cells may be isolated from human PBMCs and stimulated with activating anti-CD3 antibody. Proliferation of T cells may be measured by ^{3}H thymidine incorporation. An assay may be performed with or without CD28 costimulation in the assay. Similar assays may be performed with Jurkat T cells and PHA-blasts from PBMCs.

Alternatively, agents encompassed by the present invention may be tested for the ability to modulate cellular production of cytokines which are produced by or whose production is enhanced or inhibited in immune cells in response to modulation of the one or more biomarkers. Indicative cytokines released by immune cells of interest may be identified by ELISA or by the ability of an antibody which blocks the cytokine to inhibit immune cell proliferation or proliferation of other cell types that is induced by the cytokine, such as those described in the Examples section. An *in vitro* immune cell costimulation assay may also be used in a method for identifying cytokines which may be modulated by modulation of the one or more biomarkers. For example, if a particular activity induced upon costimulation, *e.g.,* immune cell proliferation, cannot be inhibited by addition of

blocking antibodies to known cytokines, the activity may result from the action of an unknown cytokine. Following costimulation, this cytokine may be purified from the media by conventional methods and its activity measured by its ability to induce immune cell proliferation. To identify cytokines which may play a role the induction of tolerance, an *in vitro* T cell costimulation assay as described above may be used. In this case, T cells would be given the primary activation signal and contacted with a selected cytokine, but would not be given the costimulatory signal. After washing and resting the immune cells, the cells would be rechallenged with both a primary activation signal and a costimulatory signal. If the immune cells do not respond *(e.g.,* proliferate or produce cytokines) they have become tolerized and the cytokine has not prevented the induction of tolerance. However, if the immune cells respond, induction of tolerance has been prevented by the cytokine. Those cytokines which are capable of preventing the induction of tolerance may be targeted for blockage *in vivo* in conjunction with reagents which block B lymphocyte antigens as a more efficient means to induce tolerance in transplant recipients or subjects with autoimmune diseases.

In some embodiments, an assay encompassed by the present invention is a cell-free assay for screening for agents that modulate the interaction between a biomarker and/or one or more binding partners, comprising contacting a polypeptide and one or more natural binding partners, or biologically active portion thereof, with a test agent and determining the ability of the test compound to modulate the interaction between the polypeptide and one or more natural binding partners, or biologically active portion thereof. Binding of the test compound may be determined either directly or indirectly as described above. In one embodiment, the assay includes contacting the polypeptide, or biologically active portion thereof, with its binding partner to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test agent to interact with the polypeptide in the assay mixture, wherein determining the ability of the test agent to interact with the polypeptide comprises determining the ability of the test agent to preferentially bind to the polypeptide or biologically active portion thereof, as compared to the binding partner.

In some embodiments, whether for cell-based or cell-free assays, a test agent may further be assayed to determine whether it affects binding and/or activity of the interaction between the polypeptide and the one or more binding partners, with other binding partners. Other useful binding analysis methods include the use of real-time Biomolecular Interaction

Analysis (BIA) (Sjolander and Urbaniczky (1991) *Anal. Chem.* 63:2338-2345 and Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, Biacore®). Changes in the optical phenomenon of surface plasmon resonance (SPR) may be used as an indication of real-time reactions between biological polypeptides. Polypeptides of interest may be immobilized on a Biacore® chip and multiple agents (blocking antibodies, fusion proteins, peptides, or small molecules) may be tested for binding to the polypeptide of interest. An example of using the BIA technology is described by Fitz *et al.* (1997) *Oncogene* 15:613.

The cell-free assays encompassed by the present invention are amenable to use of both soluble and/or membrane-bound forms of proteins. In the case of cell-free assays in which a membrane-bound form protein is used it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)$_n$, 3-[(3-cholamidopropyl)dimethylamminio]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylamminio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl=N,N-dimethyl-3-ammonio-1-propane sulfonate.

In one or more embodiments of the above described assay methods, it may be desirable to immobilize either polypeptides to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a polypeptide, may be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein may be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase-based polypeptide fusion proteins, or glutathione-S-transferase/target fusion proteins, may be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then combined with the test compound, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to remove any unbound components, the matrix immobilized in the case of beads, complex determined

either directly or indirectly, for example, as described above. Alternatively, the complexes may be dissociated from the matrix, and the level of polypeptide binding or activity determined using standard techniques.

The present invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of the present invention to further use an agent identified as described herein in an appropriate model system. For example, an agent identified as described herein may be used in a model system to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein may be used in a model system to determine the mechanism of action of such an agent. Furthermore, the present invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

d. Monitoring of Effects During Clinical Trials

Monitoring the influence of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen therapy (*e.g.,* compounds, drugs, vaccines, cell therapies, and the like) on immune responses, such as T cell reactivity (*e.g.,* the presence of binding and/or T cell activation and/or effector function), may be applied not only in basic candidate HA-2 antigen binding molecule screening, but also in clinical trials. For example, the effectiveness of binding proteins and related compositions described herein, such as nucleic acids, host cells, pharmaceutical formulations, and the like, to increase immune response (*e.g.,* T cell immune response) against cells of interest, such as hyperproliferative cells, expressing an HA-2 antigen, may be monitored in clinical trials of subjects afflicted with a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen. In such clinical trials, the presence of binding and/or T cell activation and/or effector function (*e.g.,* T cell proliferation, killing, and/or cytokine release), may **be used as a "read out" or marker of the phenotype of a** particular cell, tissue, or system. Similarly, the effectiveness of an adaptive T cell therapy with T cells engineered to express a binding protein (*e.g.,* a TCR, an antigen-binding fragment of a TCR, a CAR, or a fusion protein comprising a TCR and an effector domain) as described herein to increase immune response to cells of interest, such as hyperproliferative cells, that are expressing an HA-2 antigen, may be monitored in clinical trials of subjects having a non-malignant disorder, a hyperproliferative disorder, or a relapse

of a hyperproliferative disorder characterized by expression of an HA-2 antigen. In such clinical trials, the presence of binding and/or T cell activation and/or effector function (*e.g.,* T cell proliferation, killing, or cytokine release), may **be used as a "read out" or marker of** the phenotype of a particular cell, tissue, or system.

For example, increased administration of a non-malignant disorder, the hyperproliferative disorder, or the relapse of the hyperproliferative disorder characterized by expression of an HA-2 antigen therapy may be desirable to increase the presence or level of reactivity between a sample obtained from the subject and one or more binding proteins or related composition, such as to increase the effectiveness of the non-malignant disorder, the hyperproliferative disorder, or the relapse of the hyperproliferative disorder characterized by expression of an HA-2 antigen therapy. According to such an embodiment, the presence or level of reactivity between a sample obtained from the subject and one or more binding proteins or related composition may be used as an indicator of the effectiveness of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen therapy, even in the absence of an observable phenotypic response. Similarly, analysis of the presence or level of reactivity between a sample obtained from the subject and one or more binding proteins or related composition, such as by a direct binding assay, fluorescence activated cell sorting (FACS), enzyme linked immunosorbent assay (ELISA), radioimmune assay (RIA), immunochemically, Western blot, or intracellular flow assay, may also be used to select patients who will receive the non-malignant disorder, the hyperproliferative disorder, or the relapse of the hyperproliferative disorder characterized by expression of an HA-2 antigen therapy.

For example, in a direct binding assay, immunogenic peptides or antigen peptide-MHC (pMHC) complexes may be coupled with a radioisotope or enzymatic label such that binding may be determined by detecting the labeled immunogenic peptides or pMHC complexes. For example, the immunogenic peptides or pMHC complexes may be labeled with ^{125}I, ^{35}S, ^{14}C, or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, the immunogenic peptides or pMHC complexes may be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. Determining the interaction between immunogenic peptides or pMHC complexes and immune cells, such as

T cells and/or NK cells, may also be accomplished using standard binding or enzymatic analysis assays. In one or more embodiments of the above described assay methods, it may be desirable to immobilize immunogenic peptides or pMHC complexes to accommodate automation of the assay.

It is also within the scope of the present invention to determine the ability of an agent to modulate a parameter of interest without the labeling of any of the interactants. For example, a microphysiometer may be used to detect interaction between polypeptides without the labeling of polypeptides to be monitored (McConnell *et al.* (1992) *Science* 257:1906-1912). As used herein, a "microphysiometer" (*e.g.*, Cytosensor®) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate may be used as an indicator of the interaction between compound and receptor.

Binding of immunogenic peptides or pMHC complexes to immune cells, such as T cells and/or NK cells, may be accomplished in any vessel suitable for containing the reactants. Non-limiting examples of such vessels include microtiter plates, test tubes, and micro-centrifuge tubes. Immobilized forms of the immunogenic peptides or pMHC complexes may also include immunogenic peptides or pMHC complexes bound to a solid phase like a porous, microporous (with an average pore diameter less than about one micron) or macroporous (with an average pore diameter of more than about 10 microns) material, such as a membrane, cellulose, nitrocellulose, or glass fibers; a bead, such as that made of agarose or polyacrylamide or latex; or a surface of a dish, plate, or well, such as one made of polystyrene.

In some embodiments, the reactivity of a sample obtained from the subject to one or more binding proteins or to one or more host cells described herein may be measured by detecting the presence of binding and/or T cell activation and/or effector function. The term "T cell activation" refers to T lymphocytes selected from proliferation, differentiation, cytokine secretion, release of cytotoxic effector molecules, cytotoxic activity, and expression of activation markers, particularly refers to one or more cellular responses of cytotoxic T lymphocytes.

Cytokine production and/or release may be measured by methods well-known in the art, for example, ELISA, enzyme-linked immune absorbent spot (ELISPOT), Luminex® assay, intracellular cytokine staining, and flow cytometry, and combinations

thereof (*e.g.,* intracellular cytokine staining and flow cytometry). It may be determined according to the method implemented.

The term "cytokine" as used herein refers to a molecule that mediates and/ r regulates a biological or cellular function or process (*e.g.,* immunity, inflammation, and hematopoiesis). The term "cytokine" as used herein includes "lymphokines", "chemokines", "monokines", and "interleukins". Examples of useful cytokines are GM-CSF, IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-15, IFN-α, IFN-β, IFN-γ, MIP-1α, MIP-1β, TGF-β, TNF-α, and TNF-β.

The proliferation and clonal expansion of T cells resulting from antigen-specific induction or stimulation of an immune response may be determined, for example, through incorporation of a non-radioactive assay such as a tritiated thymidine assay or MTT assay.

Cytotoxicity assays to determine CTL activity may be performed using any one of several techniques and methods routinely practiced in the art (*e.g.,* Henkart *et al.* (2003) *Fund. Immunol.* 1127-1150). Additional description of methods for measuring antigen-specific T cell reactivity can be found in, for example, U.S. Pat. No. 10,208,086 and U.S. Pat. Publ. No. 2017/0209573.

e. Predictive Medicine

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect encompassed by the present invention encompasses diagnostic assays for determining (*e.g.*, detecting) the presence, absence, amount, and/or activity level of HA-2 or reactivity to HA-2 in the context of a biological sample (*e.g.,* blood, serum, cells, or tissue) to thereby determine whether an individual afflicted with a disorder characterized by HA-2 expression is likely to respond to therapy, whether in an original state or as a recurrence. Such assays may be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset or after recurrence of a disorder characterized by HA-2 expression.

The diagnostic methods described herein may furthermore be utilized to identify subjects having or at risk of developing a disorder associated with expression or lack thereof of HA-2. As used herein, the term "aberrant" includes an upregulation or downregulation of HA-2 from normal levels. Aberrant expression or activity includes increased or decreased expression or activity, as well as expression or activity which does

not follow the normal developmental pattern of expression or the subcellular pattern of expression. For example, aberrant levels is intended to include the cases in which a mutation in the biomarker gene or regulatory sequence, or amplification of the chromosomal gene, thereof causes upregulation or downregulation of the biomarker of interest. As used herein, the term "unwanted" includes an unwanted phenomenon involved in a biological response, such as immune cell activity.

The assays described herein, such as the preceding diagnostic assays or the following assays, may be utilized to identify a subject having or at risk of developing a disorder associated with HA-2 misregulation. Thus, the present invention provides a method for identifying a disorder associated with aberrant or unwanted HA-2 regulation in which a test sample is obtained from a subject and HA-2 expression is detected, wherein the presence of HA-2 expression is diagnostic for a subject having or at risk of developing the disorder associated with aberrant or unwanted HA-2 expression. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample may be a biological fluid (*e.g.*, cerebrospinal fluid or serum), cell sample, or tissue, such as a histopathological slide of the tumor microenvironment, peritumoral area, and/or intratumoral area.

Furthermore, the prognostic assays described herein may be used to determine whether a subject may be administered an agent described herein to treat such a disorder associated with aberrant or unwanted HA-2 expression. For example, such methods may be used to determine whether a subject may be effectively treated with one or a combination of agents. Thus, the present invention provides methods for determining whether a subject may be effectively treated with one or more agents described herein for treating a disorder associated with aberrant or unwanted HA-2 expression.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one antibody reagent described herein, which may be conveniently used, *e.g.*, in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving the biomarker of interest.

Furthermore, any cell type or tissue in which the biomarker of interest is expressed may be utilized in the prognostic assays described herein.

In addition, the prognostic methods described herein may be used to determine whether a subject may be administered a therapeutic agent to treat a disorder characterized by HA-2 expression.

f. Clinical Efficacy

Clinical efficacy may be measured by any method known in the art. For example, the response to a therapy relates to any response of the disorder characterized by HA-2 expression, *e.g.,* a tumor, to the therapy, preferably to a change in the number of cancer cells, tumor mass, and/or tumor volume, such as after initiation of neoadjuvant or adjuvant chemotherapy. Tumor response may be assessed in a neoadjuvant or adjuvant situation where the size of a tumor after systemic intervention may be compared to the initial size and dimensions as measured by CT, PET, mammogram, ultrasound or palpation and the cellularity of a tumor may be estimated histologically and compared to the cellularity of a tumor biopsy taken before initiation of treatment. Response may also be assessed by caliper measurement or pathological examination of the tumor after biopsy or surgical resection. Response may be recorded in a quantitative fashion such as percentage change in tumor volume or cellularity or by using a semi-quantitative scoring system such as residual cancer burden (Symmans *et al.* (2007) *J. Clin. Oncol.* 25:4414-4422) or Miller-Payne score (Ogston *et al.* (2003) *Breast* (Edinburgh, Scotland) 12:320-327) in a qualitative fashion like "pathological complete response" (pCR), "clinical complete remission" (cCR), "clinical partial remission" (cPR), "clinical stable disease" (cSD), "clinical progressive disease" (cPD) or other qualitative criteria. Assessment of tumor response may be performed early after the onset of neoadjuvant or adjuvant therapy (*e.g.,* after a few hours, days, weeks or preferably after a few months). A typical endpoint for response assessment is upon termination of neoadjuvant chemotherapy or upon surgical removal of residual tumor cells and/or the tumor bed. Additional guidance is provided in definitions of terms listed in Section I above.

VII. Cell Therapy

In another aspect encompassed by the present invention, the methods include adoptive cell therapy, whereby genetically engineered cells expressing the provided molecules targeting an MHC-restricted epitope (*e.g.,* cells expressing a binding protein (*e.g.,* a TCR or CAR) or antigen-binding fragment thereof) are administered to subjects. Such administration may promote activation of immune cells (*e.g.,* T cell activation) in an antigen-targeted manner, such that the cells of interest such as hyperproliferative cells, express an HA-2 antigen are targeted for destruction.

Thus, the provided methods and uses include methods and uses for adoptive cell therapy. In some embodiments, the methods include administration of the cells or a composition containing the cells to a subject, tissue, or cell, such as one having, at risk for, or suspected of having the disease, condition or disorder. In some embodiments, the cells, populations, and compositions are administered to a subject having the particular disease or condition to be treated (*e.g.,* via adoptive cell therapy, such as by adoptive T cell therapy). In some embodiments, the cells or compositions are administered to the subject, such as a subject having or at risk for the disease or condition. In some embodiments, the methods thereby treat, *e.g.,* ameliorate one or more symptom of the disease or condition.

Methods for administration of cells for adoptive cell therapy are known and may be used in connection with the provided methods and compositions (*e.g.*, U.S. Pat. Publ. No. 2003/0170238, U.S. Pat. No. 4,690,915, Rosenberg (2011) *Nat. Rev. Clin. Oncol.* 8:577-585, Themeli *et al.* (2013) *Nat. Biotechnol.* 31:928-933, Tsukahara *et al.* (2013) *Biochem. Biophys. Res. Commun.* 438:84-89, and Davila *et al.* (2013) *PLoS ONE* 8:e61338).

In some embodiments, cell therapy (*e.g.,* adoptive cell therapy, such as adoptive T cell therapy) may be carried out by autologous transfer, in which the cells are isolated and/or otherwise prepared from the subject who is to receive the cell therapy, or from a sample derived from such a subject. Thus, in some embodiments, the cells are derived from a subject, *e.g.,* patient, in need of a treatment and the cells, following isolation and processing are administered to the same subject.

In some embodiments, the cell therapy (*e.g.,* adoptive cell therapy, such as adoptive T cell therapy) may be carried out by allogeneic transfer, in which the cells are isolated and/or otherwise prepared from a subject other than a subject who is to receive or who ultimately receives the cell therapy, *e.g.,* a first subject. In such embodiments, the cells then are administered to a different subject, *e.g.,* a second subject, of the same species. In some embodiments, the first and second subjects are genetically identical (syngeneic). In some embodiments, the first and second subjects are genetically similar. In some embodiments, the second subject expresses the same HLA class or supertype as the first subject.

In some embodiments, the subject, to whom the cells, cell populations, or compositions are administered is a primate, such as a human. In some embodiments, the primate is a monkey or an ape. The subject may be male or female and may be any suitable age, including infant, juvenile, adolescent, adult, and geriatric subjects. In some

embodiments, the subject is a non-primate mammal, such as a rodent. In some examples, the patient or subject is a validated animal model for disease, adoptive cell therapy, and/or for assessing toxic outcomes such as cytokine release syndrome (CRS).

The binding molecules, such as TCRs, antigen-binding fragments of TCRs (*e.g.,* scTCRs) and chimeric receptors (*e.g.,* CARs) containing the TCR, and cells expressing the same, may be administered by any suitable means, for example, by injection, *e.g.,* intravenous or subcutaneous injections, intraocular injection, periocular injection, subretinal injection, intravitreal injection, trans-septal injection, subscleral injection, intrachoroidal injection, intracameral injection, subconjectval injection, subconjuntival injection, sub-Tenon's injection, retrobulbar injection, peribulbar injection, or posterior juxtascleral delivery. In some embodiments, they are administered by parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing and administration may depend in part on whether the administration is brief or chronic. Various dosing schedules include but are not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion.

For the prevention or treatment of disease, the appropriate dosage of the binding molecule or cell may depend on the type of disease to be treated, the type of binding molecule, the severity and course of the disease, whether the binding molecule is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the binding molecule, and the discretion of the attending physician. The compositions and molecules and cells are in some embodiments suitably administered to the patient at one time or over a series of treatments.

In some embodiments, cells may be administered at 0.1×10^6, 0.2×10^6, 0.3×10^6, 0.4×10^6, 0.5×10^6, 0.6×10^6, 0.7×10^6, 0.8×10^6, 0.9×10^6, 1.0×10^6, 5.0×10^6, 1.0×10^7, 5.0×10^7, 1.0×10^8, 5.0×10^8, or more, or any range in between or any value in between, cells per kilogram of subject body weight. The number of cells transplanted may be adjusted based on the desired level of engraftment in a given amount of time. Generally, 1×10^5 to about 1×10^9 cells/kg of body weight, from about 1×10^6 to about 1×10^8 cells/kg of body weight, or about 1×10^7 cells/kg of body weight, or more cells, as necessary, may be transplanted. In some embodiment, transplantation of at least about $0.1x10^6$, $0.5x10^6$, 1.0×10^6, 2.0×10^6, 3.0×10^6, 4.0×10^6, or 5.0×10^6 total cells relative to an average size mouse

is effective. For example, in some embodiments, cells, or individual populations of sub-types of cells, may be administered to the subject at a range of about one million to about 100 billion cells and/or that amount of cells per kilogram of body weight, such as, *e.g.,* 1 million to about 50 billion cells (*e.g.,* about 5 million cells, about 25 million cells, about 500 million cells, about 1 billion cells, about 5 billion cells, about 20 billion cells, about 30 billion cells, about 40 billion cells, or a range defined by any two of the foregoing values), such as about 10 million to about 100 billion cells (*e.g.,* about 20 million cells, about 30 million cells, about 40 million cells, about 60 million cells, about 70 million cells, about 80 million cells, about 90 million cells, about 10 billion cells, about 25 billion cells, about 50 billion cells, about 75 billion cells, about 90 billion cells, or a range defined by any two of the foregoing values), and in some cases about 100 million cells to about 50 billion cells (*e.g.,* about 120 million cells, about 250 million cells, about 350 million cells, about 450 million cells, about 650 million cells, about 800 million cells, about 900 million cells, about 3 billion cells, about 30 billion cells, about 45 billion cells) or any value in between these ranges and/or per kilogram of body weight. Dosages may vary depending on attributes particular to the disease or disorder and/or patient and/or other treatments.

Engraftment of transplanted cells may be assessed by any of various methods, such as, but not limited to, tumor volume, cytokine levels, time of administration, flow cytometric analysis of cells of interest obtained from the subject at one or more time points following transplantation, and the like. For example, a time-based analysis of waiting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 days or may signal the time for tumor harvesting. Any such metrics are variables that may be adjusted according to well-known parameters in order to determine the effect of the variable on a response to anti-cancer immunotherapy. In addition, the transplanted cells may be co-transplanted with other agents, such as cytokines, extracellular matrices, cell culture supports, and the like.

Cells may also be administered before, concurrently with, or after, other anti-cancer agents.

Two or more cell types may be combined and administered, such as cell-based therapy and adoptive cell transfer of stem cells, cancer vaccines and cell-based therapy, and the like. For example, adoptive cell-based immunotherapies may be combined with the cell-based therapies encompassed by the present invention. In some embodiments, the cell-based agents may be used alone or in combination with additional cell-based agents, such

as immunotherapies like adoptive T cell therapy (ACT). For example, T cells genetically engineered to recognize CD19 used to treat follicular B cell lymphoma. Immune cells for ACT may be dendritic cells, T cells such as $CD8^+$ T cells and $CD4^+$ T cells, natural killer (NK) cells, NK T cells, cytotoxic T lymphocytes (CTLs), tumor infiltrating lymphocytes (TILs), lymphokine activated killer (LAK) cells, memory T cells, regulatory T cells (Tregs), helper T cells, cytokine-induced killer (CIK) cells, and any combination thereof. Well-known adoptive cell-based immunotherapeutic modalities, including, without limitation, irradiated autologous or allogeneic tumor cells, tumor lysates or apoptotic tumor cells, antigen-presenting cell-based immunotherapy, dendritic cell-based immunotherapy, adoptive T cell transfer, adoptive CAR T cell therapy, autologous immune enhancement therapy (AIET), cancer vaccines, and/or antigen presenting cells. Such cell-based immunotherapies may be further modified to express one or more gene products to further modulate immune responses, such as expressing cytokines like GM-CSF, and/or to express tumor-associated antigen (TAA) antigens, such as Mage-1, gp-100, and the like. The ratio of an agent encompassed by the present invention, such as cancer cells, to another agent encompassed by the present invention or other composition may be 1:1 relative to each other (*e.g.*, equal amounts of 2 agents, 3 agents, 4 agents, etc.), but may modulated in any amount desired (*e.g.*, 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 2:1, 2.5:1, 3:1, 3.5:1, 4:1, 4.5:1, 5:1, 5.5:1, 6:1, 6.5:1, 7:1, 7.5:1, 8:1, 8.5:1, 9:1, 9.5:1, 10:1, or greater).

In some embodiments, for example, where the subject is a human, the dose includes fewer than about $1x10^8$ total binding protein (*e.g.,* TCR or CAR)-expressing cells, T cells, or peripheral blood mononuclear cells (PBMCs), *e.g.,* in the range of about $1x10^6$ to $1x10^8$ such cells, such as $2x10^6$, $5x10^6$, $1x10^7$, $5x10^7$, or $1x10^8$ or total such cells, or the range between any two of the foregoing values.

In some embodiments, the cells or related compositions described herein, such as nucleic acids, host cells, pharmaceutical formulations, and the like, may be administered as part of a combination treatment, such as simultaneously with or sequentially with, in any order, another therapeutic intervention, such as another antibody or engineered cell or receptor or agent, such as a cytotoxic or therapeutic agent.

In some embodiments, the cells or related composition may be co-administered with one or more additional therapeutic agents or in connection with another therapeutic intervention, either simultaneously or sequentially in any order. In some contexts, the cells or related composition are co-administered with another therapy sufficiently close in time

such that the cell populations enhance the effect of one or more additional therapeutic agents, or vice versa. In some embodiments, the cells or related composition are administered prior to the one or more additional therapeutic agents. In some embodiments, the cells or related composition are administered after to the one or more additional therapeutic agents.

In some embodiments, the biological activity of the cells or related composition is measured by any of a number of known methods once the cells or related composition are administered to a subject (*e.g.,* a human). Parameters to assess include specific binding of an engineered or natural T cell or other immune cell to antigen, *in vivo*, *e.g.,* by imaging, or *in vitro*/ex *vivo*, *e.g.,* by ELISA or flow cytometry. In some embodiments, the ability of the cells to destroy target cells (cytotoxicity) may be measured using any suitable assay or method known in the art (*e.g.*, Kochenderfer *et al.* (2009) *J. Immunother.* 32: 689-702 and Herman *et al.* (2004) *J. Immunol. Meth.* 285:25-40). In some embodiments, the biological activity of the cells also may be measured by assaying expression and/or secretion of certain cytokines, such as CD107a, IFNγ, IL-2, and TNF alpha. In some embodiments, the biological activity is measured by assessing clinical outcome, such as reduction in viral burden or load.

In some embodiments, cells are modified in any number of ways, such that their therapeutic or prophylactic efficacy is increased. For example, the binding protein (*e.g.*, engineered TCR, CAR, or antigen-binding fragment thereof) expressed by the population may be conjugated either directly or indirectly through a linker to a targeting moiety. The practice of conjugating compounds to targeting moieties is well-known in the art (*e.g.*, Wadwa *et al.* (1995) *J. Drug Targeting* 3:111 and U.S. Pat. No. 5,087,616).

Immune cells, such as cytotoxic lymphocytes, may be obtained from any suitable source such as peripheral blood, spleen, and lymph nodes. The immune cells may be used as crude preparations or as partially purified or substantially purified preparations, which may be obtained by standard techniques, including, but not limited to, methods involving immunomagnetic or flow cytometry techniques using antibodies.

In another aspect encompassed by the present invention, provided herein is a method for eliciting an immune response to a cell that expresses an HA-2 antigen, the method comprising administering to the subject cells described herein expressing a binding protein (*e.g.*, engineered TCR, CAR, or antigen-binding fragment thereof) in effective amounts sufficient to elicit the immune response. In some embodiments, provided herein is

a method for treatment or prophylaxis of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen, the method comprising administering to the subject an effective amount of the cells described herein expressing a binding protein (*e.g.*, engineered TCR, CAR, or antigen-binding fragment thereof). In one embodiment, the cells are administered systemically, such as by injection. Alternately, one may administer locally rather than systemically, for example, via injection directly into tissue, such as in a depot or sustained release formulation.

In some embodiments, the cells described herein expressing a binding protein (*e.g.*, engineered TCR, CAR, or antigen-binding fragment thereof) may be used as active compounds in immunomodulating compositions for prophylactic or therapeutic treatment of a non-malignant disorder, a hyperproliferative disorder, or a relapse of a hyperproliferative disorder characterized by expression of an HA-2 antigen. In some embodiments, HA-2-primed antigen-presenting cells may be used for generating lymphocytes (*e.g.*, $CD8^+$ T lymphocytes, $CD4^+$ T lymphocytes, and/or B lymphocytes), for further use in adoptive transfer to the subject with the cells described herein expressing a binding protein (*e.g.*, engineered TCR, CAR, or antigen-binding fragment thereof).

In some embodiments, the cells described herein expressing a binding protein (*e.g.*, engineered TCR, CAR, or antigen-binding fragment thereof), either alone or in combination with the lymphocytes, may be administered to a subject for eliciting an immune response, particularly for eliciting an immune response to cells are expressing an HA-2 antigen.

As described above, single or multiple administrations of the cells described herein expressing a binding protein (*e.g.*, engineered TCR, CAR, or antigen-binding fragment thereof) cells, either alone or in combination with the lymphocytes, may be carried out with cell numbers and treatment being selected by the care provider *(e.g.,* physician). Similarly, the cells, either alone or in combination with lymphocytes, may be administered in a pharmaceutically acceptable carrier. Suitable carriers may be growth medium in which the cells were grown, or any suitable buffering medium such as phosphate buffered saline. Cells may be administered alone or as an adjunct therapy in conjunction with other therapeutics.

VIII. Kits and Devices

The present invention also encompasses kits and devices. For example, the kit or device may comprise binding proteins, nucleic acids or vectors comprising sequences encoding binding proteins, host cells comprising nucleic acids or vectors and/or expressing the binding proteins as described herein, stable MHC-peptide complexes, adjuvants, detection reagents, and combinations thereof, packaged in a suitable container and may further comprise instructions for using such reagents. The kit or device may also contain other components, such as administration tools packaged in a separate container. The kit or device may be promoted, distributed, or sold as a unit for performing the methods encompassed by the present invention.

The disclosure is further illustrated by the following examples, which should not be construed as limiting.

EXAMPLES

Example 1: Materials and Methods for Example 2

a. Human peripheral blood mononuclear cell collection

HLA-A*02:01-positive healthy donor leukopaks were collected by HemaCare (Los Angeles, CA), StemExpress (Placerville, CA), and Discovery Life Sciences (Huntsville, AL) using their IRB-approved protocols. Peripheral blood mononuclear cells (PBMCs) were isolated from fresh leukopaks from HemaCare and Discovery Life Sciences by density gradient centrifugation using Lymphocyte Separation Medium (Corning, Corning, NY). PBMCs contained in the lymphocyte layer were collected following centrifugation, washed 3 times with DPBS (Cytiva, Marlborough, MA), and counted. PBMCs were isolated from StemExpress leukopaks either by density gradient centrifugation as above, or using a Custom Leukopak PBMC Isolation kit (Miltenyi Biotec, Auburn, CA) on the MultiMACS™ Cell24 Separator Plus instrument, version 3 (Miltenyi Biotec) per the manufacturer's instructions. Isolated PBMCs were frozen in CryoStor® CS10 (StemCell Technologies, Cambridge, MA) and stored in liquid nitrogen.

b. HA-2 genotyping

DNA was extracted from PBMCs of A*02:01-expressing healthy donors using the GeneJET™ Genomic DNA Purification Kit (Thermo Fisher Scientific, Waltham, MA) or

the QIAamp® DNA Mini Kit (Qiagen, Germantown, MD) according to the manufacturer's instructions. PCR was performed using primers (5' GTGACTTGTAGGCCGCATCTACACCTACAT 3' and 5' GTGAGGCTACGAGAGAATCAGCCAGGTTCG 3') to amplify the genomic region containing the HA-2 SNP (RS_61739531) using Phusion® High-Fidelity PCR Master Mix (Thermo Fisher Scientific), with cycling conditions as follows: denaturation at 98°C for 3 minutes, followed by 37 cycles at 98°C for 5 seconds, 68°C for 10 seconds, and 72°C for 30 seconds, and final extension at 72°C for 5 minutes. PCR products were purified using the Monarch® PCR and DNA Cleanup Kit (New England Biolabs, Ipswich, MA) according to the manufacturer's instructions. DNA concentration was determined using a Qubit™ 4 Fluorometer (Invitrogen, Carlsbad, CA), and sequencing of the purified products was performed by GENEWIZ, Inc. (Cambridge, MA).

c. TCR discovery screens

(i) DC culture

Monocyte isolation was performed on day -4 using PBMCs isolated from HLA-A*02:01-positive healthy HA-2-negative (RS_61739531, T/T) donors with the EasySep™ Human CD14 Positive Selection Kit II (StemCell Technologies) according to the manufacturer's instructions. Purity and costimulatory molecule expression were assessed using fluorescently-labeled antibodies specific for CD14 (M5E2, BioLegend, Dedham, MA), HLA-A2 (BB7.2, BioLegend), CD80 (2D10, BioLegend), CD83 (HB15e, BioLegend), and CD86 (IT2.2, BioLegend); CD14 expression was >90%. $CD14^+$ monocytes were resuspended in AIM-V® media (Thermo Fisher Scientific) supplemented with recombinant human GM-CSF and IL-4 (R&D Systems, Minneapolis, MN) at final concentrations of 800 IU/mL and 1000 IU/mL, respectively. On day -2, recombinant human TNF-α (10 ng/mL), IL-6 (1000 IU/mL), and IL-1β (2 ng/mL) (R&D Systems), as well as PGE2 (1 μg/mL, StemCell Technologies), were added to cultured monocytes.

(ii) CD8 naïve T cell isolation

On day -1, autologous CD8 naïve T cells were isolated from PBMCs from HLA-A*02:01-expressing healthy HA-2-negative (RS_61739531, T/T) donors using the EasySep™ Human Naïve CD8+ T Cell Isolation Kit II (StemCell Technologies) according to the manufacturer's instructions. Purity was assessed using fluorescently-labeled antibodies specific for CD8α (HIT8a, BioLegend), CD45RO (UCHL1, BioLegend), CD45RA (HI100, BioLegend), CD56 (5.1H11, BioLegend), CD57 (HCD57, BioLegend),

and CCR7 (G043H7, BioLegend). **Purity of naive CD8α$^+$** T cells was >90%. Cells were rested overnight at 37°C, 5% CO_2 in T cell medium (X-VIVO™ 15 serum-free medium [Lonza, Rockland, MD] containing 10% human serum [Sigma Aldrich, St. Louis, MO], 1% penicillin-streptomycin [Thermo Fisher Scientific], 1% GlutaMAX™ [Thermo Fisher]), supplemented with 10 ng/ml recombinant human IL-7 (R&D Systems).

(iii) Co-culture

On day 0, CD8 T cell purity was reassessed using the identical antibody panel as on day 3, and DC maturation was confirmed by upregulation of HLA-A2, CD80, CD83, and CD86 and downregulation of CD14. DCs were pulsed with 1 μM HA-2 peptide (YIGEVLVSV, GenScript [Piscataway, NJ]) for 3 hours at 37°C, 5% CO_2. Pulsed DCs were co-cultured with rested CD8 naïve T cells in T cell medium supplemented with recombinant human IL-12 (10 ng/mL) and IL-21 (60 ng/mL) (R&D Systems). Co-cultures were supplemented with recombinant human IL-7 and IL-15 (R&D Systems) between days 3 and 10. Dextramer staining for HA-2-specific cells was performed on day 11, using A*02:01 HA-2 REF (YIGEVLVSV) and HA-2 SNP (YIGEVLVSM) dextramers **(Immudex, Copenhagen, Denmark), CD8α and TCRα/β** (IP26, BioLegend), and DAPI **(Thermo Fisher Scientific) according to the manufacturer's instructions.**

(iv) Antigen-specific cell sorting

On day 12, cells were collected and stained with A*02:01 HA-2 REF (YIGEVLVSV) and HA-2 SNP (YIGEVLVSM) dextramers, as well as with antibodies **specific for CD8α and TCRα/β**, and with DAPI as on day 11, and HA-2-positive cells **(CD8α$^+$**, DAPI$^-$**, TCRα/β$^+$**, HA-2$^+$) were sorted using a Sony SH800S cell sorter (Sony Biotechnology, San Jose, CA). Sorted cells were subjected to single cell **TCRα/β** sequencing using the 10x Genomics platform (Pleasanton, CA).

(v) Flow cytometry

Cells were acquired using a CytoFLEX™ flow cytometer (Beckman Coulter, Indianapolis, IN) and analyzed using FlowJo software (version 10, TreeStar, Ashland, OR). Cell sorting was performed using a Sony SH800S cell sorter (Sony Biotechnology).

d. **Single cell TCRα/β** sequencing using the 10x Genomics platform

Single-cell TCR-seq (scTCR-seq) libraries were prepared according to the 10x Genomics Single Cell V(D)J Reagent Kit (v1) protocol (10x Genomics). A target number of 10,000 cells per sample was captured in droplets (GEMs) within the 10x Genomics

Chromium™ instrument before undergoing reverse transcription. Following reverse transcription, GEMs were broken, and barcoded cDNA was purified from the samples using silane magnetic beads. cDNA was amplified as follows: 98°C for 45 seconds; 13 cycles of 98°C for 20 seconds, 67°C for 30 seconds, 72°C for 1 minute; 72°C for 1 minute). Following sample purification with 0.6X SPRIselect beads (Beckman Coulter), 2 uL of each library was used for TCR sequence enrichment. TCR sequence enrichment consisted of 2 rounds of PCR to amplify both the TCRα and TCRβ chain transcripts. TCR-enriched libraries were subsequently fragmented, end-repaired, and amplified with indexing primers. The fully-assembled libraries were sequenced on an Illumina NextSeq™ instrument (Illumina, San Diego, CA) using a High Output v2.5 kit (150 cycles) with read lengths: 26bp (read 1), 8bp (i7 index), and 98bp (read 2). Sequenced scTCRseq reads were processed using the cellranger 3.1.0 pipeline. Reads were aligned to the GRCh38 reference genome, and the cellranger vdj module was used to annotate TCR consensus sequences.

e. Lentiviral packaging and quantification of lentiviral titer

Lenti-X™ cells (Takara Bio USA, Mountain View, CA) were plated at 75% confluency and transfected using jetPRIME® transfection reagent (Polyplus, Illkirch, France). Briefly, HA-2 constructs were mixed with packaging plasmids (pREV/pTAT/pVSVG/pGAGPOL) and incubated with jetPRIME® reagent according to the manufacturer's protocol, and Opti-Pro™ SFM medium was added at 24 hours post-transfection. Viral supernatants were harvested 48 hours after transfection and were concentrated using either Vivaspin® 20 centrifugal concentrators or Vivaflow® 50 cassettes (Sartorius, Bohemia, NY). Lentiviral titer was determined by either GFP or TCRα/β expression using a $TCR^{-/-}$ Jurkat cell line. To quantify viral titers, $TCR^{-/-}$ Jurkat cells were transduced with serial dilutions of HA-2-specific TCR-expressing viruses, and 48 to 72 hours post-transduction, GFP or TCRα/β expression was assessed by flow cytometric analysis. Samples were analyzed using a CytoFLEX™ flow cytometer (Beckman Coulter). Titer was calculated as the percentage of cells expressing GFP or TCRα/β as TU/ml using the formula:

TU/ml = (% $TCR\alpha/\beta^{+}$) x (number of cells used in transduction) x (dilution factor) x 1000

Alternatively, lentiviral titers were determined by RT-qPCR using qPCR Lentivirus Complete Titration Kit (Applied Biological Materials Inc, Richmond, Canada) according to manufacturer protocol. Titer was calculated according to the following formula:

Titer of virus=5 x $10^7/2^{3(Ctx-C11)/(Ct2-Ct1)}$

Ctx =Average of 3 Ct values of the unknown sample

Ct1 = Average of 3 Ct values of the Standard 1

Ct2 = Average of 3 Ct values of the Standard 2

f. DexScan

(i) Engineering T cells to express HA-2-specific TCRs

Pan T cells were isolated from HLA-A*01:01/A*03:01-positive healthy donor PBMCs using the EasySep™ Human T Cell isolation (StemCell Technologies) per the manufacturer's instructions. Isolated T cells were activated with ImmunoCult™ CD3/CD28/CD2 T cell activator cocktail (StemCell Technologies) and cultured overnight in complete T cell media (X-VIVO™ 15 [Lonza] supplemented with 5% human serum [Sigma Aldrich], 1% penicillin-streptomycin [Thermo Fisher Scientific], 1X GlutaMax™ supplement [Thermo Fisher Scientific], 5 ng/mL IL-7 [R&D Systems] and 50 IU/mL IL-2 [Sigma Aldrich]). 24 hours post-activation, T cells were transduced with either a library of individually cloned HA-2 TCR viruses or a library pool of HA-2 TCR viruses. 24 hours post-transduction, T cells were washed and transferred to G-Rex® plates (Wilson Wolf, New Brighton, MN) and expanded for a total of 7-8 days post-activation. T cell cultures were supplemented with fresh IL-2 (50 IU/mL) and IL-7 (5 ng/mL) every 2-3 days. Three days prior to cell sorting, T cells engineered with the library pool of HA-2 TCRs were enriched with the CD34 Microbead kit (Miltenyi Biotec) according to manufacturer instructions.

(ii) Sorting of engineered HA-2 TCR-transduced pan T cells

Engineered pan T cells were stained with HA-2 REF (YIGEVLVSV) dextramer, TCR α/β PE-Cy™7 (IP26, BioLegend), CD8 PerCP-Cy™5.5 (HIT8a, BioLegend) and CD4 APC-Cy™7 (OKT4, Biolegend), CD34 Alexa Fluor® 488 (QBEND/10, R&D Systems) and DAPI per the manufacturers' instructions. HA-2-expressing cells were then sorted into two samples of 25,000 cells on the MoFlo® Astrios™ Cell Sorter (Beckman Coulter). Two additional input samples representing an unsorted population, was also reserved for comparison against enriched samples.

(iii) Genomic DNA isolation and sequencing library preparation

Genomic DNA (gDNA) was extracted from sorted cells using the GeneJET™ Genomic DNA Purification Kit (Thermo Fisher Scientific). The antigen cassette was amplified from the extracted gDNA by PCR using Q5® High-Fidelity 2x Master Mix

(NEB, MA) using Human Constant region forward primer, (TCR P2A F Rd2, GACTGGAGTTCAGACGTGTGCTCTTCCGATCTACGTTGAAGAGAACCCCGGACC T, Integrated DNA Technologies (IDT), Coralville, Iowa) and Human constant region reverse primer, TCR_HCA_R, ACACTCTTTCCCTACACGACGCTCTTCCGATCTCTGTCTCTCAGCTGGTACACGG C, IDT) and then appended with sequencing adaptors and sample-specific index sequences in a second PCR reaction using Phusion® High-Fidelity PCR Master Mix (Thermo Fisher Scientific). Amplicons were sequenced on an Illumina MiSeq™ using the standard Illumina sequencing primer.

(iv) Sequencing and data analysis

Amplicons were PCR-amplified from HA-2-specific T cells isolated after staining with fluorescently-conjugated dextramer and sequenced on an Illumina MiSeq™ (Illumina, Inc.) using a 151x8x8 read structure. Reads were trimmed 41bp from 5' end of reads and aligned to a reference containing 1,302 HA-2-specific TCR sequences using Bowtie2 software. TCR counts were obtained by manual python scripts, reads were considered as a count if they had fewer than five mismatches (NM), mapping quality (MAPQ) above 10, and alignment score (AS) greater than -20. Changes in TCR counts, as well as TCR enrichment (*i.e.*, change in the proportion of TCR in sorted samples versus input), were used to nominate TCRs for functional evaluation.

g. Functional evaluation of HA-2-specific TCRs

(i) Engineering T cells to express HA-2-specific TCRs

Pan T cells were isolated from HLA-A*01:01/A*03:01-positive healthy donor PBMCs using the EasySep™ Human T Cell isolation kit (StemCell Technologies) per the manufacturer's instructions. Isolated T cells were activated with ImmunoCult™ CD3/CD28/CD2 T cell activator cocktail (StemCell Technologies) and cultured overnight in complete T cell media (X-VIVO™ 15 [Lonza, Morristown, NJ] supplemented with 5% human serum [Sigma Aldrich], 1% penicillin-streptomycin [Thermo Fisher Scientific], 1X GlutaMax™ supplement [Thermo Fisher Scientific], 5 ng/mL IL-7 [R&D Systems] and 50 IU/mL IL-2 [Sigma Aldrich]). 24 hours post-activation, T cells were transduced with HA-2 TCR viral supernatants at an MOI (multiplicity of infection) of 5 or 10. 24 hours post-transduction, T cells were transferred to G-Rex® plates (Wilson Wolf) and expanded for a total of 7-8 days post-activation. T cell cultures were supplemented with fresh IL-2 (50 IU/mL) and IL-7 (5 ng/mL) every 2-3 days. Where indicated, enrichment of $CD34^+$

transduced cells was performed using the Miltenyi CD34 Microbead Kit per the manufacturer's instructions (Miltenyi Biotec). After enrichment, T cells were further expanded for 3-5 days in complete T cell media followed by flow cytometric analysis for purity and expression of the HA-2-specific TCR.

(ii) Flow cytometry of engineered HA-2 TCR-transduced pan T cells

Engineered pan T cells were stained with HLA-A*02:01 HA-2 (YIGEVLVSV) dextramer and HA-2 (YIGEVLVSM) (Immudex) dextramer, TCR α/β PE-Cy™7 (IP26, BioLegend), CD8 PerCP-Cy™5.5 (HIT8a, BioLegend), CD4 APC-Cy™7 (OKT4, Biolegend), and CD34 Alexa Fluor® 488 (QBEND/10, R&D Systems) and DAPI per the manufacturers' instructions. Cells were then run on the CytoFLEX™ flow cytometer (Beckman Coulter) and analyzed using FlowJo software (version 10, TreeStar).

(iii) Cell lines

The T lymphoblast cell line T2 (ATCC CRL-1992), AML cell lines TF-1 (ATCC CRL-2003) and THP-1 (ATCC TIB202,) were purchased from the American Type Culture Collection (ATCC, Manassas, VA). The anaplastic large cell lymphoma cell line DEL (ACC 338) was purchased from Deutsche Sammlung von Mikroorganismen und Zellkulturen (DSMZ, Braunschweig, Germany). The acute promyelocytic leukemia cell line NB4 (CSC-C0328) was purchased from Creative Bioarray (Shirley, NY). T2 cells were cultured in IMDM containing 20% heat-inactivated FBS. TF-1 cells were cultured in RPMI 1640 containing 10% heat-inactivated FBS and 2 ng/mL recombinant human GM-CSF. THP-1 cells were maintained in RPMI 1640 media containing 10% heat-inactivated FBS and 0.05 mM 2-mercaptoethanol. DEL and NB4 cells were maintained in RPMI 1640 media containing 10% heat-inactivated FBS.

(iv) Generation of stable cell lines expressing Incucyte® NucLight™ Red

T2, TF-1, THP-1, DEL and NB4 cells were transduced with Incucyte® NucLight™ Red Lentivirus Reagent (EF-1α promoter, puromycin selection) (Sartorius) in serum-free media at an MOI between 3 and 5. 24 hours post transduction, cells were washed and resuspended in their respective cell line media and cultured at 37°C, 5% CO_2. 3 days post-transduction, puromycin (Gibco, Waltham, MA) was added to the cultures at a pre-determined concentration (ranging from 0.5 ug/mL to 1 ug/mL) to select for transduced cells. Cultures were expanded under puromycin selection until they were at least 98% Incutye® NucLight™ Red-positive as determined by flow cytometric analysis.

(v) In vitro cytotoxicity assay

In vitro cytotoxicity assays were performed in 96-well flat-bottom tissue culture plates coated with poly-L-ornithine (Sigma Aldrich) for 30 minutes at RT, after which the coating solution was removed, and plates were allowed to dry for another 30 minutes at RT. Where indicated, T cells were co-cultured with Incucyte® NucLight™ Red-expressing THP-1, DEL, TF-1, NB4 or peptide-pulsed T2 cells (pulsed with 100 ng/ml or 1 ng/ml of HA-2 peptide [YIGEVLVSV]) at E:T ratios ranging from 20:1 to 0.625:1. Data were acquired on an Incucyte® S3 instrument (Sartorius), and target cell growth was quantified on the Incucyte® S3 as a readout of T cell cytotoxicity.

(vi) Cytokine production assay

T cells were co-cultured with Incucyte® NucLight™ Red-expressing THP-1, DEL, TF-1, NB4 and peptide-pulsed T2 cells (100 ng/mL or 1 ng/mL HA-2 peptide [YIGEVLVSV, Genscript]) at an E:T of 1:1. Supernatants were harvested 24 hours later and frozen at -80°C. Supernatants were thawed and loaded on a ProteinSimple® multianalyte cartridge (ProteinSimple, San Jose, CA) to evaluate the levels of IFN-γ, TNF-α, IL-2 and granzyme B using the Ella instrument (ProteinSimple).

(vii) Proliferation assay

T cells were labeled with 2.5 μM CellTrace™ Violet (Thermo Fisher Scientific) per the manufacturer's instructions. T cells were co-cultured with Incucyte® NucLight™ Red-expressing THP-1, DEL, TF-1, NB4 and peptide-pulsed T2 cells (100 ng/mL or 1 ng/mL HA-2 peptide [YIGEVLVSV]) at an E:T of 1:1. After 96 hours, cells were harvested and stained with Fixable viability dye eFluor™ 660 (Thermo Fisher Scientific), TCR α/β PE-Cy™7 (IP26, BioLegend), CD4 APC-Cy™7 (OKT4, BioLegend) and CD8 PerCP-Cy™5.5 (HIT8a, BioLegend) antibodies. Cells were washed with EasySep™ buffer and fixed with BD Cytofix™ fixation buffer (BD Biosciences, Franklin Lakes, NJ). CountBright™ Absolute Counting Beads (Thermo Fisher Scientific) were diluted in EasySep™ buffer and added to samples prior to acquisition on the CytoFLEX™ flow cytometer to assess dilution of CellTrace™ Violet as an indicator of T cell proliferation. Data were analyzed using FlowJo software (version 10, TreeStar), and absolute counts of divided CD8 and CD4 T cells were determined using the formula: # CD8 or CD4 T cells in sample = (# CD8 or CD4 T cell events in gate/# bead events in gate) x lot-specific assigned bead count

h. Alloreactivity and safety screens

(i) Engineering T cells to express HA-2-specific TCRs

CD8+ T cells from a A*02:01-negative donor were isolated using the human CD8 Microbead Kit (Miltenyi Biotec) or straight from Whole Blood CD8 Microbeads, human (Miltenyi Biotec) **according to the manufacturer's instructions. Isolated cells were used** immediately or frozen and stored in liquid nitrogen.

Alloreactivity screens, such as for MJ2-DP8 and MJ7-DP19 TCRs, were performed. On day -1, freshly isolated CD8 T cells were rested overnight in T cell medium (RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum [FBS], 100 IU/mL penicillin, 100 µg/mL streptomycin, recombinant human IL-2 [50U/mL, PeproTech, Cranbury, NJ], recombinant human IL-15 [5 ng/mL, R&D Systems], and recombinant human IL-7 [5ng/mL, (R&D Systems]). On day 0, the CD8 T cells were activated using ImmunoCult™ CD3/CD28/CD2 T cell activator cocktail (StemCell Technologies). On day 1, cells were washed and resuspended in T cell medium with IL-2, IL-7, and IL-15 and transduced with lentiviral particles to express HA-2-reactive TCRs. On day 2, cells were washed and resuspended in T cell medium with IL-2, IL-7, and IL-15 for expansion until day 5. On day 5, cells were harvested and resuspended in MACS buffer (Miltenyi Biotec) and incubated with FcR blocking reagent (100 uL/mL, StemCell Technologies) for 5 minutes at room temperature. Cell concentration was adjusted to 60e6 cells/mL and A*0201 HA-2 (YIGEVLVSV) dextramer APC (Immudex) was added at a 1:25 dilution for 10 minutes at room temperature. HA-2 dextramer APC-positive cells were isolated using Anti-**APC Microbeads (Miltenyi Biotec) according to the manufacturer's instructions.** Isolated cells were resuspended in T cell medium with IL-2, IL-7, and IL-15 and expanded until day 12, at which point cells were frozen.

Safety screens (MJ2-DP8 or MJ7-DP19 TCRs, MJ9-DP5, MJ2-DP22 and MJ14-DP317) and alloreactivity screens (MJ9-DP5, MJ2-DP22, MJ14-DP317). On day -1, CD8 T cells were thawed and rested overnight in T cell medium (RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum [FBS], 100 IU/mL penicillin, 100 µg/mL streptomycin, recombinant human IL-2 [50U/mL, PeproTech, Cranbury, NJ], recombinant human IL-15 [5 ng/mL, R&D Systems], and recombinant human IL-7 [5 ng/mL, (R&D Systems]). On day 0, the CD8 T cells were activated using ImmunoCult™ CD3/CD28/CD2 T cell activator cocktail (StemCell Technologies). On day 1, cells were washed and resuspended in T cell medium with IL-2, IL-7, and IL-15 and transduced with lentiviral particles to express HA-2-reactive TCRs. On day 2, cells were washed and resuspended in T cell medium with IL-2, IL-7, and IL-15 for expansion until day 5. On day

5, cells were harvested and resuspended in MACS buffer (Miltenyi Biotec) and incubated with FcR blocking reagent (100 uL/mL, StemCell Technologies) for 5 minutes at room temperature. Cell concentration was adjusted to 60e6 cells/mL and A*0201 HA-2 (YIGEVLVSV) dextramer APC (Immudex) was added at a 1:25 dilution for 20 minutes at room temperature. HA-2 dextramer APC-positive cells were isolated by cell sorting (Beckman Coulter MoFlo Astrios EQ). Sorted cells were resuspended in T cell medium with IL-2, IL-7, and IL-15 and expanded until day 12, at which point cells were frozen.

(ii) Generation of 96-well-based MHC-expressing arrays for alloreactivity screens

Endogenous HLA-A/B/C were knocked out in HEK293T cells using CRISPR. Guide RNAs were designed against sequences conserved across the HLA-A, HLA-B and HLA-C loci using the multicrispr.net tool (Prykhozhij *et al.* (2015) *PLoS One* 10:e0119372). The following guides were selected: CRISPR-ALL-1: CGGCTACTACAACCAGAGCG, CRISPR-ALL-2: AGATCACACTGACCTGGCAG, CRISPR-ALL-3: AGGTCAGTGTGATCTCCGCA. gRNAs were cloned into the LentiCRISPR V2 vector using BsmBI sites. HEK 293T cells were transfected with plasmid guide constructs using Mirus TransIT® (Mirus Bio, Madison, WI). After 7 days, MHC-negative cells were sorted using a pan-MHC antibody (BioLegend). Single cell clones were expanded, and the absence of MHC was verified by flow cytometry and Western blot.

MHC-**null HEK293T cells were transduced with IncuCyte® NucLight™ Red virus. Transduced wells were sorted for NucLight™ Red expression using a Sony SH800 sorter.** To generate an MHC-expressing array, MHC-null Nu**cLight™ Red**- expressing HEK 293T cells were transduced with the most common 110 MHCs (pHAGE-EF1a-MHC-UBC-NAT) in individual wells in 96-well plates. Transduced cells were selected with nourseothricin (400 ng/ ml) for one week. Cells expressing the most common 110 MHCs were passaged and stored in 96-well plates as an array.

To generate the positive control for the assay the A*02:01-expressing cells in the above array were transduced with HA-2 90-mer-expressing construct (pHAGE-CMV-FHA-HA2V-d1-EFS-AmCyan) and sorted for AmCyan expression using a MoFlo® Astrios EQ™.

(iii) Co-culture for alloreactivity screens

On day 0, T cells were restimulated in upright T25 flasks with 1e6 T cells, 20e6 irradiated PBMCs, recombinant human IL-2, and CD3 monoclonal antibody (OKT3)

[0.1ug/mL, eBioscience]. Half the volume of media was exchanged on days 2, 4, and 5 with RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum [FBS], 100 IU/mL penicillin, 100 µg/mL streptomycin, and recombinant human IL-2 [50U/mL, PeproTech, Cranbury, NJ]. Cells were harvested for assay on day 6.

The assay was performed in duplicate for TCRs, MJ2-DP8 and MJ7-DP19. On day 5, target cells in the 96-well array were passaged and seeded in 96-well plates. On day 6, human CD8 T cells expressing the TCRs were added at an E:T of 4:1 and incubated with target cells for 48h. Target cell numbers were measured over time using IncuCyte® by measuring the number of IncuCyte® **NucLight™ Red positive cells. Cell inhibition at 48 h** of each TCR on each MHC in the assay was calculated as 1- (Cell doubling[Incubated with TCR-expressing T cells]/ Cell doubling[Incubated with T cell media]). To subtract the effect of non-MHC-related target cell growth inhibition such as competition for nutrition from T cells or non-specific cell killing from donor T cells and to correct for batch effect of each 96-well plate, the cell inhibition value of each well (each MHC) on each 96-well plate were subtracted by the median of cell inhibition of the wells on each 96-well plate.

The assay was performed in triplicate for TCRs MJ9-DP5, MJ2-DP22, MJ14-DP317. On day 5, target cells in the 96-well array were passaged and seeded in 384-well plates. On day 6, human CD8 T cells expressing the TCRs were added at an E:T of 5:1 and incubated with target cells for 48 hours. Target cell numbers were measured over time using IncuCyte® **by measuring the number of NucLight™ Red**-positive cells. Cell inhibition at 48 h of each TCR on each MHC in the assay was calculated as 1-(Cell doubling[Incubated with TCR-expressing T cells]/Cell doubling[Incubated with untransduced donor T cells]). To correct for batch effect of each 384-well plate, the cell inhibition value of each well (each MHC) on each 384-well plate were subtracted by the median of cell inhibition of the wells on each 384-well plate.

(iv) Transduction of HEK 293T cells with a genome-wide peptide library for safety screens

MHC-null HEK 293T cells were engineered to express HLA-A*02:01, a fluorescent reporter and a cell-surface reporter, both activated by T cell killing. Reporter cells were transduced to express a library comprising >600,000 overlapping tiles of peptides comprised of 90 amino acids each, representative of the human proteome.

(v) Transduction of HEK293 T cells with HA-2-containing constructs for safety screens

HEK 293T cells engineered to express HLA-A*02:01 were transduced to express one of eight tiles, comprised of 90 amino acids each, containing the HA-2 epitope (YIGEVLVSV or YIGEVLVSM). Transduced cells were selected with puromycin.

(vi) Reporter cells for safety screens

HLA-A*02:01 expressing HEK 293T cells expressing individual HA-2 tiles were combined with the transduced with a genome-wide peptide library at a frequency of 1:650,000 each. Cells were expanded and then used in co-culture with engineered CD8+ T cells.

(vii) Sorting of reporter cells following co-culture for safety screens

CD8+ T cells engineered with the relevant TCRs were expanded by co-culturing with irradiated (60Gy) allogeneic PBMCs in the presence of 0.1 µg/mL anti-CD3 (OKT3, eBioscience) and 50 U/mL recombinant IL-2 (Peprotech). After 7 days of expansion, the cells were collected and co-cultured with library-transduced reporter cells and incubated at 37°C for 4 h. After incubation, cells were harvested by trypsinization and labeled with Annexin V magnetic microbeads (Miltenyi Biotec) according to the manufacturer's instructions. Annexin-labeled cells were isolated using an autoMACS® Pro (Miltenyi Biotec), and reporter-positive cells were sorted using a MoFlo® Astrios™ EQ cell sorter (Beckman Coulter).

(viii) Genomic DNA isolation and sequencing library preparation for safety screens

Genomic DNA (gDNA) was extracted from sorted cells using the GeneJET™ Genomic DNA Purification Kit (Thermo Fisher Scientific). The antigen cassette was amplified from the extracted gDNA by PCR then appended with sequencing adaptors and sample-specific index sequences in a second PCR reaction. Amplicons were sequenced on an Illumina NextSeq machine using the standard Illumina sequencing primer.

(ix) Sequence alignment and epitope identification for safety screens

Nucleotide sequences were mapped to individual nucleotide tiles. The proportion of read counts for each tile was calculated for each screen replicate (n=8) and for the input for each pool of transduced reporter cells, and enrichments of each tile were calculated by dividing the proportion of the tile in the screen replicate by the proportion of the tile in the input library. A modified geometric mean of the enrichment of an identical tile across the 8 screen replicates was used to identify reproducible screen hits. Specific MHC-binding epitopes for each tile above the threshold of 1.5-fold enrichment were predicted using

NetMHC4.0. Candidate epitopes for each tile were selected by identifying predicted strong-binding epitopes shared across overlapping adjacent and redundant tiles that were enriched in the screen.

i. Incucyte®-based cytotoxicity assay to assess avidity for putative off-targets

(i) T cells

Clinically representative HA-2 TCR T cells were produced at TScan Therapeutics (Waltham, MA, USA) from the cells of HLA-A*02:01-negative healthy donors using a reduced-scale adaptation of a planned manufacturing protocol for clinical drug product. **The finalized vector used here contained the α and β chains of the** HA-2 TCR with modified constant regions (Mouse Grafting, Trans-Membrane optimization, MGTM); **exogenous CD8 coreceptor (α and β chain); and a tag fused to the N-terminus of the CD8 α** chain (*i.e.*, 16 amino acids encoding the CD34 epitope recognized by the Qbend10 antibody). T cells engineered to express a TCR of **interest are designated as "TSC"** and the **underlying TCRs are designated as "TCR" constructs. For example,** TSC-101 refers to the T cell product engineered using TCR-101 and TCR-101 refers to the TCR only. Briefly, after isolating PBMCs from a fresh apheresis product, transposase mRNA and vector transposon npDNA were delivered by electroporation. T cells were then activated, expanded and purified using the engineered human-CD34-tag (*i.e.*, CD34+ selection). After further expansion, cells were frozen and stored in liquid nitrogen.

(ii) T2 peptide pulsing and Incucyte assay

In vitro cytotoxicity assays were performed in 96-well flat-bottom tissue culture plates (Corning) coated with poly-L-ornithine (Millipore-Sigma) for 40 minutes at room temperature, after which the coating solution was removed, and plates were allowed to dry for 30 minutes at room temperature. Incucyte® NucLight™ Red-expressing T2 cells were pulsed with a titration of various concentrations of seven different peptides for 1 hour: HA-2^+ peptide (YIGEVLVSV), HA-2^- (YIGEVLVSM) peptide or putative off-target peptides derived from MYO3A/MYO3B (YVGDILIAL), MALT1 (AVDEFLLLL), MTA1 (KQIDQFLVV) , KLHL30 (KLEEVLVVV), and HUWE1 (GLTEDMVTV). T cells were co-cultured with peptide-pulsed Incucyte® NucLight™ Red-expressing T2 cells at an E:T ratio of 5:1 for 3 days. Data were acquired and analyzed on an IncuCyte® S3 Live-Cell Analysis system (Sartorius, Goettingen, Germany). Analyzed data (software GUI Version 2021A) were normalized to t=4 h and expressed as a percent of target cell growth. The area under the curve (AUC) of the T2 cell growth for each peptide dose was calculated

using GraphPad Prism software (version 9.1.2[226]). The AUCs were plotted as a function of peptide dose and a nonlinear regression curve (using the equation Sigmoidal, 4PL, X is concentration) was used to calculate the IC50 of T2 cell growth inhibition (designated as EC50 of cytotoxicity in Figure 11B).

j. Flow-based cytotoxicity assay with primary hematological cancer samples

(i) T cells

Clinically representative HA-2 TCR T cells were produced as described in the section above describing Incucyte®-based cytotoxicity assays to assess avidity for putative off-targets.

(ii) Primary AML and ALL samples

Primary samples (PBMCs and BMMCs) from patients diagnosed with ALL or AML were purchased as frozen vials from Tissue Solutions and Discovery Life Science. The cells were genotyped for HA-2 as described in section 2 above describing HA-2 genotyping. HLA genotype was provided by the vendors or was determined by flow cytometry using the antibody, anti-HLA-A2 (clone BB7.2), following a standard flow staining protocol.

(iii) Preparation of T cells and primary AML and ALL samples for coculture

T cells and primary ALL and AML samples were thawed the day before the assay and were allowed to recover overnight at 37°C and 5% CO_2. ALL and AML samples were thawed into target cell medium (RPMI 1640 supplemented with 10% heat-inactivated fetal bovine serum, 100 IU/mL penicillin, 100 μg/mL streptomycin) containing DNAse I (100 U/mL, StemCell Technologies), were incubated 5 minutes at room temperature, and were washed and resuspended in target cell medium at 0.5-1.0E+6 live cells/mL prior to plating in T75 flasks. T cells (TSC-101 or non-transduced control T cells from matched donor) were thawed into cytokine free T cell medium (X-Vivo™ 15 supplemented with 5% human serum, 100 IU/mL penicillin, 100 μg/mL streptomycin and 1x GlutaMAX™), washed once with cytokine-free T cell medium, and were then seeded in a G-Rex® 6-well plate in T cell medium supplemented with 25 ng/mL IL2 (Sigma-Aldrich) and 5 ng/mL IL7 (RD Systems) at a density of 1.0E+6 live cells.

(iv) Co-culture

On the day of the assay, target cells were labeled with CellTrace™ Violet (CTV, Thermofisher), and effector T cells were labeled with CFSE (Thermofisher). To this end, cells were washed once with Easysep™ (StemCell Technologies) and were stained for 7

minutes at room temperature with 2.5 μM dye diluted in Easysep™ at a cell concentration of 2.0E+6/mL. Cells were washed twice following labeling and were resuspended in target cell medium (targets) or cytokine-free T cell medium (T cells) prior to plating. AML and ALL samples displayed variable viabilities (20-60%). Therefore, following CTV labeling, primary tumor samples were enriched for live cells by performing density centrifugation. Briefly, after washing out the CTV dye, primary tumor samples were resuspended in target cell medium at a concentration up to 4.0E+6 live cells/mL. Using 5 mL round bottom tubes, 1 mL of the cell suspension was layered on top of 1 mL Ficoll-Paque™ **PLUS** (Cytiva). Cells were centrifuged at 1,890 rpm for 15 minutes at room temperature with the brake set at 0 (no brake) and acceleration set at 3 (slow acceleration). Subsequently, the buffy coat was collected and washed twice with target cell medium. Target cell density was adjusted to 1.0E+5 live cells/mL and T cell density was adjusted to 1.0E+6 live cells/mL. One hundred μL of CFSE-labeled effector cells were combined with 100 μL of CTV-labeled target cells in 96-well round bottom plates, thereby resulting in an E:T of 10:1 (with 1.0E+5 T cells and 1.0E+4 target cells per well).

(v) Cytotoxicity Analysis by Live-Dead Staining and Flow Cytometry

Cells were washed once with flow staining and wash buffer (*i.e.*, Easysep™, ThermoFisher) and were stained 20 minutes at 4°C with 1/1000 diluted Fixable Near-Infrared **LIVE/DEAD™** dye (ThermoFisher). After washing twice, cells were fixed 20 minutes at 4°C with BD Cytofix™. After washing out the fixative, cells were stored at 4°C until ready for acquisition. Samples were acquired on a CytoFLEX S machine (Beckman-Coulter) using Cytexpert software (v2.4) and were were analyzed with FlowJo Software (v10.72_CL). The percentage of live targets (*i.e.*, live-dead stain negative/CFSE negative/CTV positive cells) upon co-culture with HA-2 TCR T cells was determined and normalized to the percentage of live targets observed upon co-culture with matched non-transduced T cells.

k. T cell reactivity in primary and induced pluripotent stem (iPS)-derived cells

Evaluation of HA-2 TCR T cells reactivity to primary/iPS-derived cells was performed by co-culturing clinically representative HA-2 TCR T cells with primary/iPS-**derived cells for 48 hours and quantifying IFNγ production.**

Primary human cells from 13 different tissues/cell types were purchased from commercial suppliers (**see "target cells" listing below**). HLA-A*02:01 status was either

provided by the supplier, screened by flow cytometry as described in section 2 above describing HA-2 genotyping. Cells were revived and cultured following manufacturer's recommendation.

Prior to co-culture, all primary/iPS-derived cells (except for PBMC) were loaded with HA-2 SNP+ peptide ('HA-2-pulsed'), or left untouched ('Non-pulsed'), for 2 hours. HA-2-pulsed cells represented a positive control to confirm activation of TSC-101 cells by primary/iPS-derived cells expressing cognate peptide-MHC class I complexes. For all TSC-101/iPS-derived co-culture experiments, NB-4 (HA-2 SNP negative, HLA-A*02:01 positive) and THP-1 (HA-2 SNP positive, HLA-A*02:01 positive) cells were co-cultured in parallel as additional negative and positive controls, respectively.

NB-4 & THP-1 cells were seeded at 25,000 or 50,000 cell/well in 96-well plates (Corning) on the day of the co-culture. Similarly, PBMC were seeded at 50,000 cells/well on the day of the co-culture, whilst adherent primary/iPS-derived cells were present at confluency at the point of co-culture. To achieve an adherent, confluent monolayer at the point of co-culture, primary/iPS-derived cells were seeded 24 hours prior to co-culture, unless the supplier's culture guidelines stipulated otherwise. All conditions, including co-culture and TSC-101/primary/iPS-derived alone cultures, were set up in a 50:50 mixture of effector media and the primary/iPS-derived media or NB4 & THP-1 co-culture media.

Clinically representative HA-2 TCR T cells were produced and prepared as described in the section describing Incucyte®-based cytotoxicity assays above to assess avidity for putative off-targets. HA-2 TCR T cells were seeded at 50,000 cells on top of target cells on the day of co-culture.

The IFNγ levels in assay supernatants after 48h of coculture were quantified by TR-FRET. TR-FRET reagents were purchased from Cisbio and used according to the manufacturer's instructions. Following incubation, fluorescence values were acquired using a BMG PHERAStar plate reader. IFNγ levels in supernatants were interpolated from a standard curve with a 4-parameter logistic curve fit using BMG MARS data analysis software. The lower limit of quantification (LLOQ) was defined as the lowest concentration of IFNγ standard that generated a raw value above the blank corrected value.

Target cells:

Tissue	Cell type	N*	vendor
Blood	Human Peripheral blood mononuclear cells	5	NHSBT
Vasculature	Human Umbilical Vein Endothelial Cells	5	Promocell

Heart	Human Cardiac Myocytes	3	Promocell ScienCell Fujifilm
	Human Cardiac Fibroblasts	2	Promocell
Skin	Human Dermal Fibroblasts	2	PromoCell
	Human Epidermal Keratinocytes	4	Promocell
	Normal Human Epidermal Melanocytes	5	Promocell Lonza
Lung	Human Bronchial Epithelial Cells	6	Promocell Lonza ScienCell
	Pulmonary Fibroblasts	2	Promocell
Liver	Human Hepatocytes	4	Fujifilm Zenbio ScienCell
Gastro-intestinal	Human Gastric Epithelial Cells	2	AcceGen/Generon Cell Biologics
	Human Small Intestinal Epithelial Cells	2	Lonza Cell Biologics
CNS	Human GABA neurons	1	Fugifilm
	Human Astrocytes	4	ScienCell Fugifilm
Eye	Human Retinal Pigment Epithelial Cells	2	ScienCell
Muscle	Skeletal Muscle Cells	3	ScienCell

*** "N" indicates the number of primary samples for each condition**

1. Materials

Cell lines

- Lenti-X™: Takara Bio USA, 632180
- Jurkat: ATCC, TIB-152
- HEK293T cells: ATCC, CRL-3216
- T2: ATCC, CRL-1992
- TF-1: ATCC, CRL-2003
- THP-1: ATCC, TIB202
- NB4: Creative Bioarray, CSC-C0328
- DEL: ACC 338, DSMZ
- Primary AML and ALL samples: Tissue Solutions, Discovery Life Science

Media and supplements

- X-VIVO™ 15, serum-free hematopoietic cell medium, with L-Glutamine, gentamycin and phenol red: Lonza, 04-418Q
- Human male AB serum (heat-inactivated): Sigma Aldrich, H3667-100ML

- Penicillin streptomycin: Gibco, 15149-122
- GlutaMAX™ supplement: Fisher Scientific, 35050061
- RPMI-1640 medium: ATCC, 30-2001
- Fetal bovine serum (FBS), heat-inactivated: Gibco, A3840102
- IMDM: ATCC, 30-2005
- RPMI medium 1640 (1x) [+] 4.5 g/L D-glucose, [+] 2.383 g/L HEPES buffer, [+] L-glutamine, [+] 1.5 g/L sodium bicarbonate, [+] 110 mg/L sodium pyruvate: Gibco, A10491-01
- AIM-V® medium: [+] L-glutamine, [+] 50 µg/mL streptomycin sulfate, [+] 10 µg/mL gentamicin sulfate: Gibco, 12055-083
- 30% BSA in PBS: Sigma Aldrich, A9576-50ML
- β-Mercaptoethanol: MP Biomedicals, 02190242
- DMEM medium (1X) [+] 4.5 g/L D-glucose, [+] L-glutamine, [+] 3.7 g/L sodium bicarbonate: Thermo Fisher Scientific, 11965084
- DMEM (1x) [+] 4.5 g/L D-glucose, [+] L-glutamine, [-] Sodium Pyruvate: Gibco, 11965
- OptiPRO™ SFM medium: Thermo Fisher Scientific, 12309019

Buffers

- EasySep™ buffer: StemCell Technologies, 20144
- DPBS (no Ca2+/Mg2+): Gibco, 14190-122
- DPBS (no Ca2+/Mg2+): Cytiva, SH30028.03
- AutoMACS® running buffer: Miltenyi, 130-091-221

Cytokines

- Recombinant human IL-2: Sigma Aldrich, 11147528001
- Recombinant human IL-2: PeproTech, 200-02
- Recombinant IL-7: R&D Systems, 207-IL/CF
- Recombinant human IL-12: R&D Systems, 219-IL-005
- Recombinant human IL-15: R&D Systems, 247-ILB-005
- Recombinant human GM-CSF: R&D Systems, 215-GM-050
- Recombinant human IL-4: R&D Systems, 204-IL-050
- Recombinant human TNF-α: R&D Systems, 210-TA-050
- Recombinant human IL-1β/IL-1F2: R&D Systems, 201-LB-025
- Recombinant human IL-6: R&D Systems, 206-IL-050

- PGE2: StemCell Technologies, 72194

Kits

- **EasySep™ Human T Cell Isolation Kit: StemCell Technologies: 17951**
- **EasySep™ Human Naïve CD8+ T Cell Isolation Kit II: STEMCELL Technologies,** 17968
- **EasySep™ Human CD14 Positive Selection Kit II: STEMCELL Technologies, 17858**
- CD8 microbeads: Miltenyi Biotec, 130-045-201
- CD34 Microbead Kit: Miltenyi Biotec, 130-046-702
- Anti-APC microbeads: Miltenyi Biotec, 130-090-855
- LS columns, Miltenyi Biotec, 130-042-401
- Ella Simple Plex™ kit for 32 samples: ProteinSimple: SPCKC-PS-003027
- qPCR Lentivirus Complete Titration Kit: Applied Biological Materials: LV900-LR

Antibodies and staining reagents

- CD3 monoclonal antibody (OKT), functional grade: eBioscience 16-0037-81
- Anti-**human CD8α PerCp**-Cy™5.5 (clone: HIT8a): BioLegend: 300924
- Anti-human CD4 APC-Cy™7 (Clone: OKT4): BioLegend: 317418
- Anti-human CD56 PE (clone: 5.1H11): BioLegend: 362508
- Anti-human CD57 PE (clone: HCD57): BioLegend: 322312
- Anti-human CD34 Alexa Fluor® 488: (Clone: QBEND/10): R&D Systems, FAB7227G
- Anti-human CD34 APC: (Clone: QBEND/10): RD Systems, FAB7227A
- Anti-human CD45RO FITC (clone: UCHL1): BioLegend, 304204
- Anti-human CD45RA APC (clone: HI100): BioLegend, 304112
- Anti-human CCR7 BV605 (clone: G043H7): BioLegend, 353224
- Anti-Human CD14 Alexa Fluor® 488 (clone: M5E2): BioLegend, 301811
- Anti-human CD83 PE-Cy™7 (clone: HB15e): BioLegend, 305326
- Anti-human HLA-A2 PE (clone: BB7.2): BioLegend, 343306
- Anti-human CD80 APC (clone: 2D10): BioLegend, 305220
- Anti-human CD86 **Brilliant Violet 605™** (clone IT2.2): BioLegend, 305430
- Anti-human TCR**α/β FITC (clone: IP26): BioLegend, 221058**
- Anti-**human TCRα/β PE**-Cy™7 (clone: IP26): BioLegend: 306720
- Anti-human HLA-A,B,C APC Antibody: BioLegend, 311410

- Anti-Human CD32 (Fc gamma RII) Blocker: STEMCELL Technologies, 18520
- CellTrace™ Violet (CTV): Fisher Scientific: C34571
- **Cell Trace™ Violet (CTV): Thermo**Fisher, C34557
- **Cell Trace™ CFSE** (CFSE): ThermoFisher, C34554
- Fixable viability Dye eFluor™ 660 (APC Channel) Thermo Fisher Scientific: 65-0864-14
- LIVE/DEAD™ **Fixable Near**-IR Dead Cell Staining Kit (APC-Cy7 channel): ThermoFisher, L34976
- DAPI: Thermo Scientific: Thermo Scientific, 62248
- **CountBright™ Absolute Counting Beads: Fisher Scientific: C36950**
- Cytofix™: BD Biosciences, 554655

Peptides

- MART1 (ELAGIGILTV): GenScript
- HA-2 REF (YIGEVLVSV): GenScript
- HA-2 SNP (YIGEVLVSM): GenScript
- KLHL30 (KLEEVLVVV): GenScript
- MALT1 (AVDEFLLLL): GenScript
- MTA1 (KQIDQFLVV): GenScript
- MYO3A/MYO3B (YVGDILIAL): GenScript
- HUWE1 (GLTEDMVTV): GenScript

Dextramers

- HLA-A*02:01 YIGEVLVSV HA-2 REF Dextramer: Immudex, WB3704
- HLA-A*02:01 YIGEVLVSM HA-2 SNP dextramer, WB5732
- HLA-A*02:01 ELAGIGILTV MART1 dextramer: Immudex, WB2162

CRISPR-Cas9 and electroporation reagents

- Alt-R® S.p. Cas9 Nuclease V3 (Lot #0000417827): IDT, 1081059
- Alt-R® CRISPR-Cas9 tracrRNA (Lot #0000415438): IDT, 1072534
- 4D-Nucleofector™ Core Unit: Lonza, AAF-1002B
- 4D-Nucleofector™ X Unit: Lonza, AAF-1002X
- SE Cell Line 4D-Nucleofector™ X Kit L: Lonza V4XC-1012

Tissue culture plates

- G-Rex® 24-well plate: Wilson Wolf, 80192M
- G-Rex® 6-well plate: Wilson Wolf, 80240M

- G-Rex® 100: Wilson Wolf, 80500
- T75 cm2 Nunc EasYFlask™: ThermoFisher, 156499
- TC-treated 6-well plate: Corning Costar, 3506
- Non-treated 6-well plate: Corning Costar, 3736
- TC-treated 24-well plates: Corning Costar, 3524
- Non-treated 24-well plate: Corning Costar, 3738
- 96-well flat-bottom plates: Corning Costar, 3595
- 96-well round bottom plates: Corning Costar, 3894
- 384-well flat-bottom plates: Corning Costar, 3764

Leukopak processing reagents:

- Multi-24 Column Block: Miltenyi Biotec, 130-095-692
- Single-well Deep Well Plate: Miltenyi Biotec, 130-114-966
- Custom Leukopak PBMC Isolation Kit, human: Miltenyi Biotec, 120-051-115
- Lymphocyte Separation Medium: Corning, 25-072-CV
- CryoStor® CS10: StemCell Technologies, 07930
- StraightFrom Whole Blood CD8 Microbeads, human: Miltenyi Biotec, 130-090-878

Genotyping and sequencing reagents

- GeneJET™ Genomic DNA Purification Kit: Thermo Fisher Scientific, K0722
- QIAamp® DNA Mini Kit: Qiagen, 51304
- Phusion® High-Fidelity PCR Master Mix with HF Buffer: Thermo Fisher Scientific, F531L
- Monarch® PCR & DNA Cleanup Kit (5 µg): New England Biolabs, T1030L
- Nuclease-Free Water: Ambion, AM9937
- Q5 High-Fidelity 2x Master Mix: NEB, M0492L

10x Genomics reagents

- Chromium™ Single Cell 5' Library & Gel Bead kit v1: 10x Genomics, PN1000006
- Chromium™ Single Cell V(D)J Enrichment Kit, Human T Cell: 10x Genomics, PN1000005
- Chromium™ Chip A Single Cell Kit: 10x Genomics, PN1000152
- Single Index Kit T Set A: 10x Genomics, PN1000213
- SPRIselect reagent kit: Beckman Coulter, B23318
- High Sensitivity D5000 ScreenTape: Agilent Technologies, 5067-5592

- High Sensitivity D5000 Reagents: Agilent Technologies, 5067-5593
- **Qubit™ dsDNA HS Assay Kit: Invitrogen, Q32854**

Packaging and lentivirus production reagents

- jetPRIME® transfection reagent: Polyplus-transfection, 114-75
- Vivaspin® 20: Sartorius, VS2041
- Vivaflow® 50 cassettes: Sartorius, VF05P4

Other reagents

- **ImmunoCult™ Human CD3/CD28/CD2 T cell activator: StemCell Technologies,** 10970
- Poly-L-ornithine solution 0.01%: Millipore-Sigma, P4957-50ML
- ViaStain™ AO/PI staining solution in PBS: Nexcelom Bioscience, CS2-0106-5mL
- Puromycin: Gibco, A11138-03
- Nourseothricin: GoldBio, N-500-1
- Incucyte® NucLight™ Red Lentivirus Reagent (EF-1 Alpha Promoter, Puromycin selection), Sartorius, 4476
- Ficoll-Paque™ **PLUS**: Cytiva, 17144003
- DNAse I: StemCell Technologies, 07474

PCR Primers

- Human Constant region forward primer, TCR P2A F Rd2, GACTGGAGTTCAGACGTGTGCTCTTCCGATCTACGTTGAAGAGAACCCCGG ACCT: Integrated DNA Technologies
- Human constant region reverse primer, TCR_HCA_R, ACACTCTTTCCCTACACGACGCTCTTCCGATCTCTGTCTCTCAGCTGGTACA CGGC: Integrated DNA Technologies

Example 2: Identification of HA-2 Binding Proteins

A high-throughput TCR discovery platform that enables rapid cloning of antigen-specific TCRs from healthy donors was developed (Figure 1). This platform was then used to screen naïve CD8+ T cells from HLA-A*02:01-positive healthy HA-2-negative (RS_61739531, T/T) donors, and 1,302 HA-2-specific TCRs were identified (Figure 1). A subset of these TCRs (380 TCRs- Figure 2 or 1,174 TCRs-Figure 6) were then further screened to identify binding to HA-2 REF (YIFEVLVSV) dextramer (Figure 2 and Figure 6) and clones were selected to undergo additional functional analyses. As described in

Table 1, TCRs were identified that recognize both the SNP and REF (target) peptides of HA-2, such as TCR-10 1, or recognize the REF (target) peptide. Since the SNP peptide has been shown using mass spectrometry in the literature not to be presented at the cell surface, whereas the REF (target) peptide (YIGEVLVSV) is naturally processed, TCRs that bind REF (target) peptide are useful regardless of ability to bind SNP peptide. It has also been determined that 'DP' TCRs that recognized both SNP and REF peptides recognize the REF peptide (target) much better than the SNP peptide when the peptide is added exogenously. For TCRs HA2-MJ1-DP57, HA2-MJ1-DP2, HA2-MJ1-DP37, HA2-MJ7-DP19, HA2-MJ3-DP12, HA2-MJ2-DP8, HA2-MJ2-DP1 and HA2-MJ1-DP1, REF peptide-pulsed cells are killed faster than SNP peptide pulsed cells at the same peptide dose and E:T.

Pan-T cells engineered to express each of the clones listed in Figures 2 and 6 by transduction were generated (Figures 3, 4A, 7A, and 8A) and these engineered T cells were demonstrated to kill target cancer cells across a number of different cancer types, stimulate production of IFN-gamma, IL-2, TNF-alpha, and granzyme B in co-culture experients, and proliferate in response to stimulation by target cells (Figures 4B-4D, 7B-7M, and 8B-8M). In addition, representative alloreactivity landscape analyses indicated that these functionally validated HA-2 TCR clones have minimal or no alloreactivity against other major HLA-I alleles tested (Figures 5 and 9). RNA expression for HA-2 and HLA-A cell lines from CCLE are shown in Table 3 below and demonstrate that cell lines tested have varying levels of target HA2 and HLA-A expression.

The anti-HA-2 TCRs described herein are rare and have unique properites. For example, 1,302 TCRs were identified identified from screening ~268 million naïve T cells from HA2 SNP/SNP genotype human donors. These TCRs were systematically and stringently tested for surface expression when expressed exogenously in T cells using a lentivirus. These TCRs were assayed to further confirm target cell killing, cytokine secretion, and proliferation in response to cell lines that express a wide range of HLA and HA2 REF peptide expression (*e.g.*, high to low levels of HLA and HA2 REF peptide). In addition, TCRs exhibited minimal alloreacitivity to an expansive panel of 110 different HLAs. Safety screens designed to overpredict off-targets by overexpressing 90-aa protein fragments, which are more efficiently processed than full-length proteins and which cover the entire human wild-type proteome (Figure 10A), were applied to the TCRs. For example, several putative off-targets fragments were identified for the HA2-MJ14-DP317 (TCR-101) TCR using the highly sensitive screen (Figure 10B), but the putative off-target

peptides predicted from these fragments exhibited at least 100-3,000-fold lower affinity relative to the target HA-2 peptide (Figures 11A and 11B), which highlights the strong safety profile of the exemplary TCR. In some embodiments, binding proteins encompassed by the present invention have affinities that are at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, 1800, 1850, 1900, 1950, 2000, 2050, 2100, 2150, 2200, 2250, 2300, 2350, 2400, 2450, 2500, 2550, 2600, 2650, 2700, 2750, 2800, 2850, 2900, 2950, 3000, or more fold, or any range in between, such as 100-3,000 fold, 100-1,000 fold, 50-300 fold, etc., stronger for the target peptide than one or more non-target peptides (*e.g.*, one or more putative off-target peptides). Moreover, the TCRs exhibit robust functional activity, such in assays confirming cytotoxicity against primary hematologic tumor samples (Figures 12A and 12B). Figure 13 provides summary data and Figures 14A and 14B confirm that TSC-101 lacks reactivity to non-hematopoietic primary human cells.

Table 3. Reference for cell line expression

Cell line	Type of control	HA2 genotype	HLA-A typnaie	HA2 expression*	HLA-A expression*
DEL	Positive	REF/SNP	A*02:01, A*26:01	373	1040
THP-1	Positive	REF/SNP	A*02:01, A*02:01	23	275
TF-1	Positive	REF/REF	A*02:01, A*33:03	16	55
NB4	Negative	ND	A*11:01 A*11:01	39	35

* HA-2 and HLA-A expression from the Cancer Cell Line Encyclopedia (CCLE) cell line database (available on the World Wide Web at portals.broadinstitute.org/ccle) in transcripts per million (TPM). HLA type from the TRON Cell Line Portal (TCLP) (available on the World Wide Web at celllines.tron-mainz.de).

Incorporation by Reference

All publications, patents, and patent applications mentioned herein are hereby incorporated by reference in their entirety as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Also incorporated by reference in their entirety are any polynucleotide and polypeptide sequences which reference an accession number correlating to an entry in a public database, such as those maintained by The Institute for Genomic Research (TIGR) on the World Wide Web at tigr.org and/or the National Center for Biotechnology Information (NCBI) on the World Wide Web at ncbi.nlm.nih.gov.

Equivalents and Scope

The details of one or more embodiments encompassed by the present invention are set forth in the description above. Although representative, exemplary materials and methods have been described above, any materials and methods similar or equivalent to those described herein may be used in the practice or testing of embodiments encompassed by the present invention. Other features, objects and advantages related to the present invention are apparent from the description. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present invention belongs. In the case of conflict, the present description provided above will control.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments encompassed by the present invention described herein. The scope encompassed by the present invention is not intended to be limited to the description provided herein and such equivalents are intended to be encompassed by the appended claims.

It is also noted that the term "comprising" is intended to be open and permits but does not require the inclusion of additional elements or steps. **When the term "comprising" is used herein, the term "consisting of" is thus also encompassed and disclosed.**

Where ranges are given, endpoints are included. Furthermore, it is to be understood that unless otherwise indicated or otherwise evident from the context and understanding of one of ordinary skill in the art, values that are expressed as ranges may assume any specific value or subrange within the stated ranges in different embodiments encompassed by the

present invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise.

In addition, it is to be understood that any particular embodiment encompassed by the present invention that falls within the prior art may be explicitly excluded from any one or more of the claims. Since such embodiments are deemed to be known to one of ordinary skill in the art, they may be excluded even if the exclusion is not set forth explicitly herein. Any particular embodiment of the compositions encompassed by the present invention (*e.g.,* any antibiotic, therapeutic or active ingredient; any method of production; any method of use; etc.) may be excluded from any one or more claims, for any reason, whether or not related to the existence of prior art.

It is to be understood that the words which have been used are words of description rather than limitation, and that changes may be made within the purview of the appended claims without departing from the true scope and spirit encompassed by the present invention in its broader aspects.

While the present invention has been described at some length and with some particularity with respect to several described embodiments, it is not intended that it should be limited to any such particulars or embodiments or any particular embodiment, but it is to be construed with references to the appended claims so as to provide the broadest possible interpretation of such claims in view of the prior art and, therefore, to effectively encompass the intended scope encompassed by the present invention.

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What is claimed is:

1. An HA-2 (YIGEVLVSV) peptide-MHC (HLA-A*02) (pMHC) complex binding protein comprising:

a) a T cell receptor (TCR) alpha chain variable domain comprising CDR1 having residues 47-53 of SEQ ID NO: 93, CDR2 having residues 71-78 of SEQ ID NO: 93, and CDR3 having residues 112-124 of SEQ ID NO: 93; and

b) a TCR beta chain variable domain comprising CDR1 having residues 44-49 of SEQ ID NO: 92, CDR2 having residues 67-71 of SEQ ID NO: 92, and CDR3 having residues 108-126 of SEQ ID NO: 92.

2. The binding protein of claim 1 comprising:

a) a TCR alpha chain variable (V_α) domain comprising residues 1-135 of SEQ ID NO: 93; and

b) a TCR beta chain variable (V_β) domain comprising residues 1-136 of SEQ ID NO: 92.

3. The binding protein of claim 1 or 2 comprising:

a) a TCR alpha chain variable (V_α) domain comprising residues 1-135 of SEQ ID NO: 93; and

b) a TCR beta chain sequence comprising i) the sequence of SEQ ID NO: 92 or ii) the sequence of SEQ ID NO: 92, except with the following five substitutions: E153K, S157A, F268I, V271A, and Q274H.

4. The binding protein of claim 1 or 2 comprising:

a) a TCR alpha chain sequence comprising the sequence of SEQ ID NO: 93; and

b) a TCR beta chain variable (V_β) domain comprising residues 1-136 of SEQ ID NO: 92.

5. The binding protein of claim 1 or 2 comprising:

a) a TCR alpha chain sequence comprising the sequence of SEQ ID NO: 93; and

b) a TCR beta chain sequence comprising the sequence of SEQ ID NO: 92.

6. The binding protein of claim 1 or 2 comprising:

a) a TCR alpha chain sequence comprising the sequence of SEQ ID NO: 93; and

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b) a TCR beta chain sequence comprising the sequence of SEQ ID NO: 92, except with the following five substitutions: E153K, S157A, F268I, V271A, and Q274H.

7. The binding protein of any one of claims 1-6, wherein the TCR alpha chain or TCR V_α domain is encoded by a TRAV38-2DV8 and TRAJ11 gene.

8. The binding protein of any one of claims 1-7, wherein the TCR beta chain or TCR V_β domain is encoded by a TRBV30 and TRBJ2-3 gene.

9. The binding protein of any one of claims 1-8, wherein the binding protein is chimeric, humanized, or human.

10. The binding protein of any one of claims 1-9, wherein the binding protein is a TCR, an antigen-binding fragment of a TCR, a single chain TCR (scTCR), a chimeric antigen receptor (CAR), or a fusion protein comprising a TCR and an effector domain

11. The binding protein of claim 10, wherein the binding domain comprises a transmembrane domain and an effector domain that is intracellular.

12. The binding protein of any one of claims 1-11, wherein the TCR alpha chain and the TCR beta chain are covalently linked.

13. The binding protein of claim 12, wherein the TCR alpha chain and the TCR beta chain are covalently linked through a linker peptide.

14. The binding protein of any one of claims 1-13, wherein the TCR alpha chain and/or the TCR beta chain are covalently linked to a moiety.

15. The binding protein of claim 14, wherein the covalently linked moiety comprises an affinity tag or a label.

16. The binding protein of claim 15, wherein the affinity tag is selected from the group consisting of CD34 enrichment tag, Glutathione-S-Transferase (GST), calmodulin

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binding protein (CBP), protein C tag, Myc tag, HaloTag, HA tag, Flag tag, His tag, biotin tag, and V5 tag, and/or wherein the label is a fluorescent protein.

17. The binding protein of claim 15 or 16, wherein the covalently linked moiety is selected from the group consisting of an inflammatory agent, cytokine, toxin, cytotoxic molecule, radioactive isotope, and antibody or antigen-binding fragment thereof.

18. The binding protein of any one of claims 1-17, wherein the binding protein binds to the pMHC complex on a cell surface.

19. The binding protein of any one of claims 1-18, wherein the MHC is a MHC multimer.

20. The binding protein of claim 19, wherein the MHC multimer is a tetramer.

21. The binding protein of any one of claims 1-20, wherein the MHC is a MHC class I molecule.

22. The binding protein of any one of claims 1-21, wherein the MHC comprises an MHC alpha chain that is an HLA serotype HLA-A*02.

23. The binding protein of any one of claims 1-22, wherein the HLA allele is selected from the group consisting of HLA-A*0201, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele.

24. The binding protein of claim 23, wherein the HLA allele is HLA-A*0201.

25. The binding protein of any one of claims 1-24, wherein binding of the binding protein to the HA-2 peptide-MHC (pMHC) complex elicits an immune response.

26. The binding protein of claim 25, wherein the immune response is a T cell response.

27. The binding protein of claim 25 or 26, wherein the T cell response is selected from the group consisting of T cell expansion, cytokine release, and cytotoxic killing.

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28. The binding protein of any one of claims 1-27, wherein the binding protein is capable of specifically binding to the HA-2 (YIGEVLVSV)peptide-MHC (HLA-A*02) (pMHC) complex with a K_d less than or equal to about $1x10^{-4}$ M.

29. An isolated nucleic acid molecule that encodes a binding protein of any one of claims 1-28.

30. The isolated nucleic acid of claim 29, wherein the nucleic acid is codon optimized for expression in a host cell.

31. A vector comprising the isolated nucleic acid of claim 29 or 30.

32. The vector of claim 31 comprising the sequence of SEQ ID NO: 106.

33. The vector of claim 31 or 32, wherein the vector is a cloning vector, expression vector, or viral vector.

34. The vector of any one of claims 31-33, wherein the vector further comprises a nucleic acid sequence encoding CD8α and/or CD8β.

35. The vector of claim 34, wherein the nucleic acid sequence encoding CD8α or CD8β is operably linked to a nucleic acid encoding a tag.

36. The vector of claim 35, wherein the nucleic acid encoding a tag is at the 5' upstream of the nucleic acid sequence encoding CD8α or CD8β such that the tag is fused to the N-terminus of CD8α or CD8β.

37. The vector of claim 35 or 36, wherein the tag is a CD34 enrichment tag.

38. The vector of any one of claims 31-37, wherein the isolated nucleic acid of claim 29 or 30, and the nucleic acid sequence encoding CD8α and/or CD8β are interconnected with an internal ribosome entry site or a nucleic acid sequence encoding a self-cleaving peptide.

39. The vector of claim 38, wherein the self-cleaving peptide is P2A, E2A, F2A or T2A.

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40. A host cell which comprises the isolated nucleic acid of claim 29 or 30, comprises the vector of any one of claims 31-39, and/or expresses the binding protein of any one of claims 1-28.

41. The host cell of claim 40, wherein the cell is genetically engineered.

42. The host cell of claim 40 or 41, wherein the host cell comprises a chromosomal gene knockout of a TCR gene, an HLA gene, or both.

43. The host cell of any one of claims 40-42, wherein the host cell comprises a knockout of an HLA gene selected from an α1 macroglobulin gene, α2 macroglobulin gene, α3 macroglobulin gene, β1 microglobulin gene, β2 microglobulin gene, or a combination thereof.

44. The host cell of any one of claims 40-43, wherein the host cell comprises a knockout of a TCR gene selected from a TCR α variable region gene, TCR β variable region gene, TCR constant region gene, or a combination thereof.

45. The host cell of any one claims 40-44, wherein the host cell expresses CD8α and/or CD8β.

46. The host cell of claim 45, wherein the CD8α and/or CD8β is fused to a CD34 enrichment tag.

47. The host cell of any one of claims 40-46, wherein the host cell is a hematopoietic progenitor cell, peripheral blood mononuclear cell (PBMC), cord blood cell, or immune cell.

48. The host cell of claim 47, wherein the immune cell is a cytotoxic lymphocyte, cytotoxic lymphocyte precursor cell, cytotoxic lymphocyte progenitor cell, cytotoxic lymphocyte stem cell, $CD4^+$ T cell, $CD8^+$ T cell, CD4/CD8 double negative T cell, gamma delta (γδ) T cell, natural killer (NK) cell, NK-T cell, dendritic cell, or a combination thereof.

49. The host cell of any one of claims 40-48, wherein the host cell is a naive T cell, central memory T cell, effector memory T cell, or a combination thereof.

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50. The host cell of any one of claims 40-49, wherein the host cell is a primary T cell or a cell of a T cell line.

51. The host cell of any one of claims 40-50, wherein the host cell does not express or has a lower surface expression of an endogenous TCR.

52. The host cell of any one of claims 40-51, wherein the host cell is capable of producing a cytokine or a cytotoxic molecule when contacted with a target cell that comprises a peptide-MHC (pMHC) complex comprising an HA-2 peptide epitope in the context of an MHC molecule.

53. The host cell of claim 52, wherein the cytokine is TNF-α, IL-2, and/or IFN-γ.

54. The host cell of claim 52 or 53, wherein the cytotoxic molecule is perforins and/or granzymes.

55. The host cell of claim 54, wherein the cytotoxic molecule is granzyme B.

56. The host cell of any one of claims 52-55, wherein the host cell is capable of producing a higher level of cytokine or a cytotoxic molecule when contacted with a target cell with a heterozygous expression of HA-2.

57. The host cell of claim 56, wherein the host cell is capable of producing an at least 1.05-fold higher level of cytokine or a cytotoxic molecule.

58. The host cell of any one of claims 52-57, wherein the host cell is capable of killing a target cell that comprises a peptide-MHC (pMHC) complex comprising the HA-2 peptide epitope in the context of an MHC molecule.

59. The host cell of claim 58, wherein the killing is determined by a killing assay.

60. The host cell of claim 58 or 59, wherein the ratio of the host cell and the target cell in the killing assay is from 20:1 to 0.625:1.

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61. The host cell of any one of claims 58-60, wherein the target cell is a T2 cell pulsed with 1 μg/mL to 50 pg/mL of HA-2 peptide.

62. The host cell of any one of claims 58-61, wherein the host cell is capable of killing a higher number of target cells when contacted with target cells with a heterozygous expression of HA-2.

63. The host cell of claim 62, wherein the host cell is capable of killing an at least 1.05-fold higher number of target cells.

64. The host cell of any one of claims 58, 59, 63, and 64, wherein the target cell is a DEL, THP-1, or TF-1 cell line.

65. The host cell of any one of claims 52-64, wherein the HA-2 peptide epitope comprises the amino acid sequence YIGEVLVSV.

66. The host cell of any one of claims 52-64, wherein the HA-2 peptide epitope comprises the amino acid sequence YIGEVLVSM.

67. The host cell of any one of claims 52-66, wherein the MHC molecule is a MHC class I molecule.

68. The host cell of any one of claims 52-67, wherein the MHC molecule comprises an MHC alpha chain that is an HLA serotype HLA-A*02.

69. The host cell of any one of claims 52-68, wherein the HLA allele is selected from the group consisting of HLA-A*0201, HLA-A*0202, HLA-A*0203, HLA-A*0205, HLA-A*0206, and HLA-A*0207 allele.

70. The host cell of claim 69, wherein the HLA allele is HLA-A*0201.

71. The host cell of any one of claims 52-70, wherein the target cell is a cell line selected from the group consisting of Del, THP-1, and TF-1 cell lines, is a hematopoietic cancer cell expressing HA-2, or is not NB4.

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72. The host cell of claim 71, wherein the cancer cell is of a hematological malignancy selected from the group consisting of a leukemia, a lymphoma, a myelodysplastic disorder, a myeloproliferative neoplasm, and myeloma.

73. The host cell of any one of claims 52-72, wherein the host cell does not express HA-2 antigen, is not recognized by a binding protein of any one of claims 1-28, is not of serotype HLA-A*02, and/or does not express an HLA-A*02 allele.

74. A population of host cells of any one of claims 40-73.

75. A composition comprising: a) a binding protein according to any one of claims 1-28, b) an isolated nucleic acid according to claim 29 or 30, c) a vector according to any one of claims 31-39, d) a host cell according to any one of claims 40-73, and/or e) a population of host cells according to claim 74, and a carrier.

76. A device or kit comprising: a) a binding protein according to any one of claims 1-28, b) an isolated nucleic acid according to claim 29 or 30, c) a vector according to any one of claims 31-39, d) a host cell according to any one of claims 40-73, and/or e) a population of host cells according to claim 74.

77. The device or kit of claim 76, wherein said device or kit further comprises a reagent to detect binding of a), d) and/or e) to a pMHC complex.

78. A method of producing a binding protein according to any one of claims 1-28, wherein the method comprises the steps of: (i) culturing a transformed host cell which has been transformed by a nucleic acid comprising a sequence encoding a binding protein according to any one of claims 1-28 under conditions suitable to allow expression of said binding protein; and (ii) recovering the expressed binding protein.

79. A method of producing a host cell expressing a binding protein according to any one of claims 1-28, wherein the method comprises the steps of: (i) introducing a nucleic acid comprising a sequence encoding a binding protein according to any one of claims 1-28 into the

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host cell; (ii) culturing the transformed host cell under conditions suitable to allow expression of said binding protein.

Figure 1

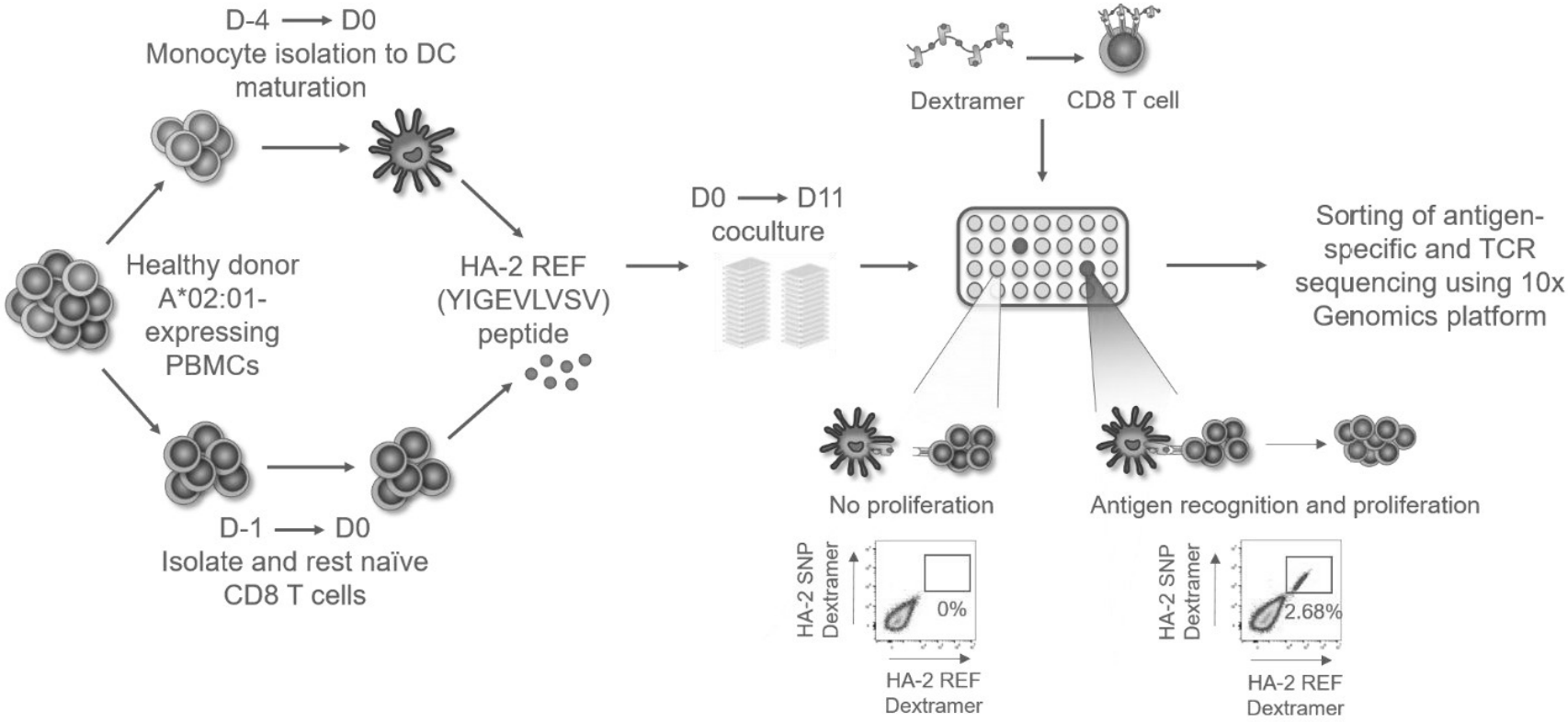

D-4 ⟶ D0
Monocyte isolation to DC maturation
Healthy donor A*02:01-expressing PBMCs
HA-2 REF (YIGEVLVSV) peptide
D-1 ⟶ D0
Isolate and rest naïve CD8 T cells
D0 ⟶ D11
coculture
Dextramer
CD8 T cell
Sorting of antigen-specific and TCR sequencing using 10x Genomics platform
No proliferation
Antigen recognition and proliferation
HA-2 SNP Dextramer
0%
HA-2 REF Dextramer
HA-2 SNP Dextramer
2.68%
HA-2 REF Dextramer

Figure 2

TCR
HA2-MJ1-DP57
HA2-MJ1-DP2
HA2-MJ1-DP37
HA2-MJ2-DP9
HA2-MJ2-DP25
HA2-MJ7-DP19
HA2-MJ3-DP12
HA2-MJ2-DP17
HA2-MJ2-DP8
HA2-BG3-DP67
HA2-BG3-DP42
HA2-BG3-DP15
HA2-MJ1-DP33
HA2-MJ3-DP20
HA2-MJ2-DP1

Figure 3

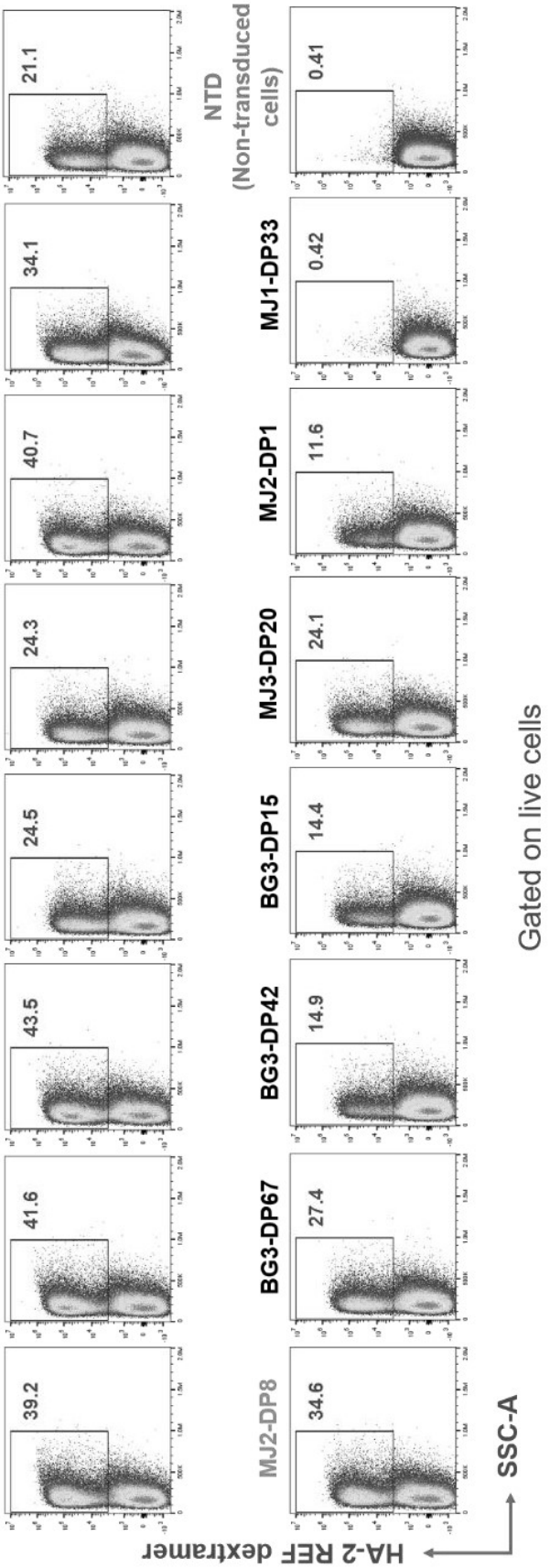

MJ1-DP57
39.2
MJ1-DP2
41.6
MJ1-DP37
43.5
MJ2-DP9
24.5
MJ2-DP25
24.3
MJ7-DP19
40.7
MJ3-DP12
34.1
MJ2-DP17
21.1
NTD
(Non-transduced cells)
MJ2-DP8
34.6
BG3-DP67
27.4
BG3-DP42
14.9
BG3-DP15
14.4
MJ3-DP20
24.1
MJ2-DP1
11.6
MJ1-DP33
0.42
0.41
HA-2 REF dextramer
SSC-A
Gated on live cells

Figure 4A

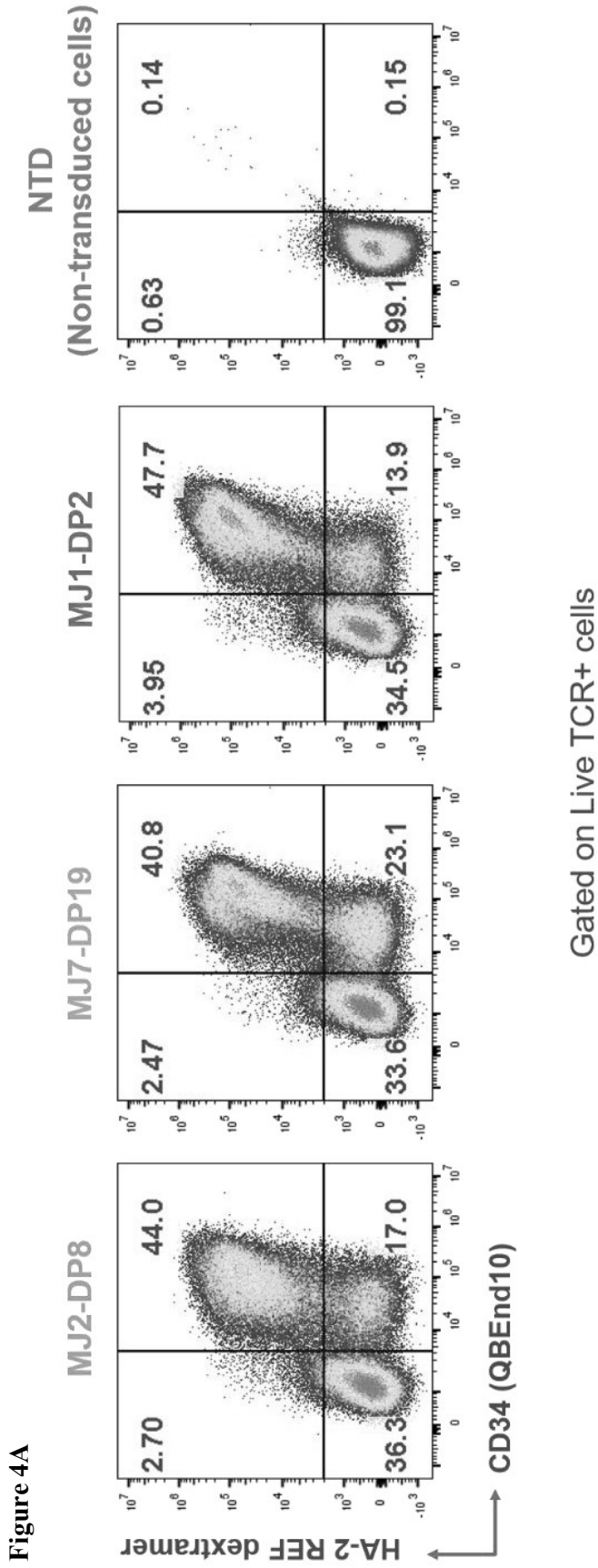

MJ2-DP8
MJ7-DP19
MJ1-DP2
NTD
(Non-transduced cells)
2.70
44.0
36.3
17.0
2.47
40.8
33.6
23.1
3.95
47.7
34.5
13.9
0.63
0.14
99.1
0.15
HA-2 REF dextramer
CD34 (QBEnd10)
Gated on Live TCR+ cells

Figure 4B

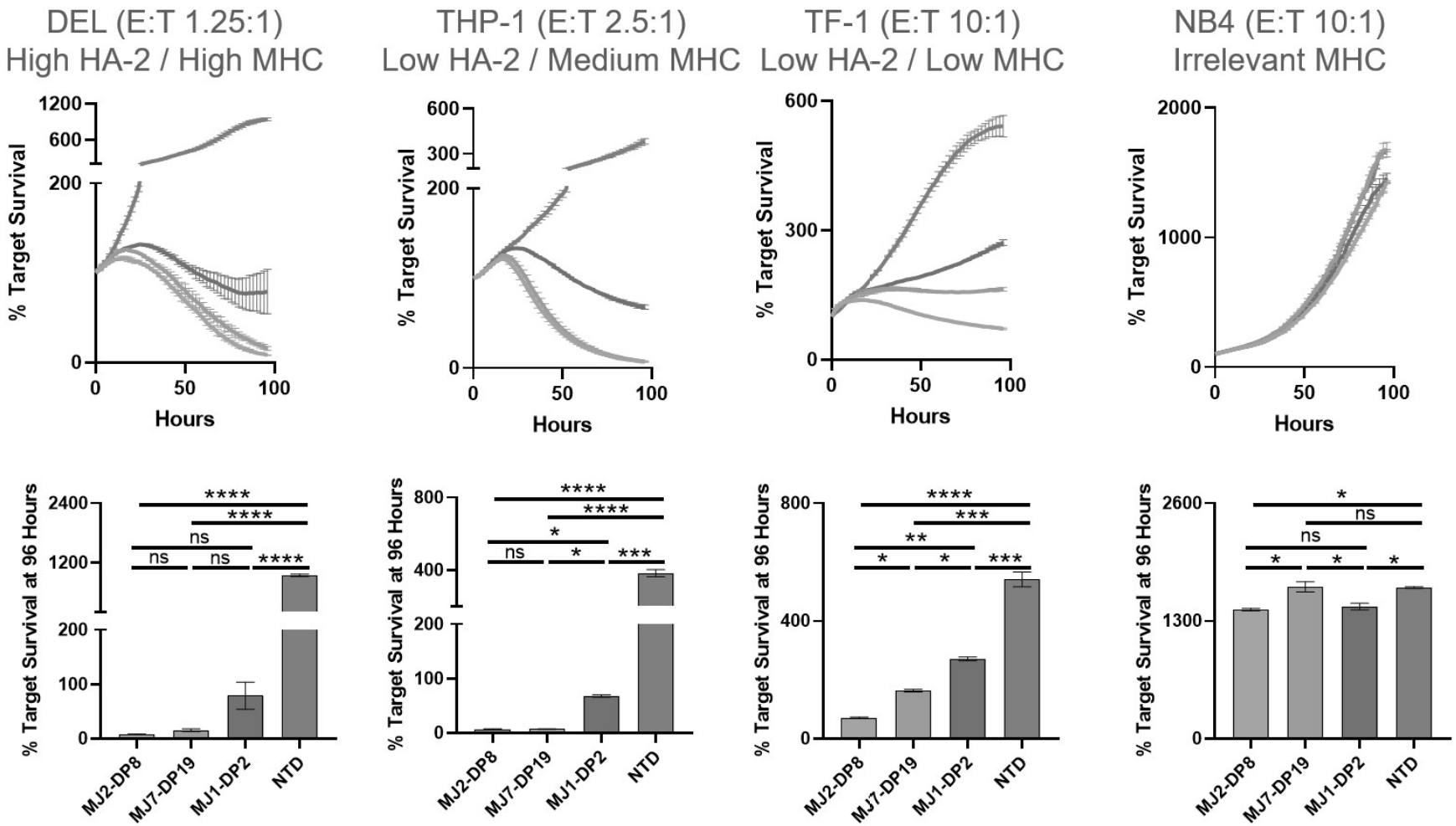

DEL (E:T 1.25:1)
High HA-2 / High MHC
THP-1 (E:T 2.5:1)
Low HA-2 / Medium MHC
TF-1 (E:T 10:1)
Low HA-2 / Low MHC
NB4 (E:T 10:1)
Irrelevant MHC
% Target Survival
Hours
% Target Survival at 96 Hours
MJ2-DP8
MJ7-DP19
MJ1-DP2
NTD
ns
*
**
***
****

Figure 4C

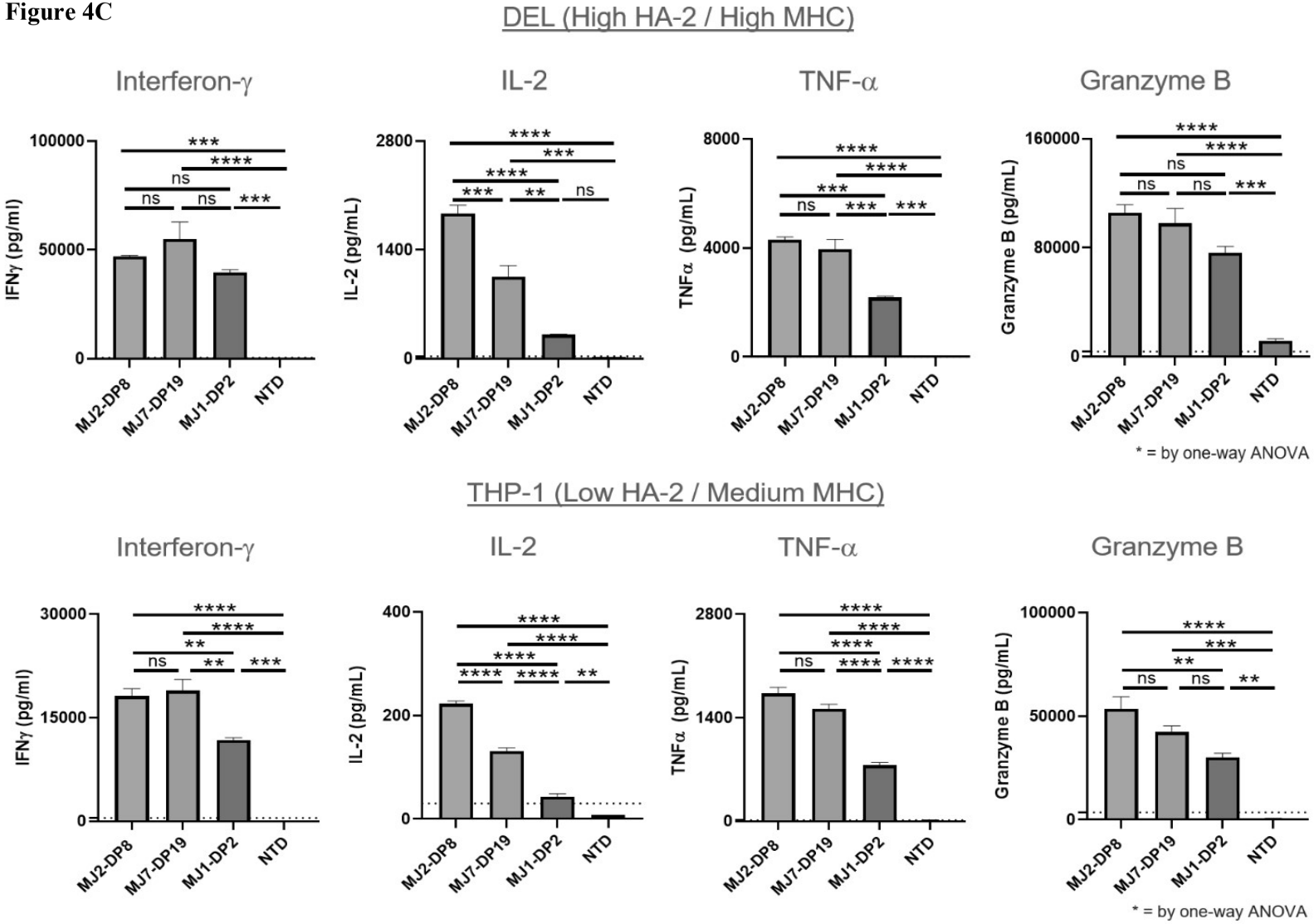

DEL (High HA-2 / High MHC)
Interferon-γ
IL-2
TNF-α
Granzyme B
IFNγ (pg/ml)
IL-2 (pg/mL)
TNFα (pg/mL)
Granzyme B (pg/mL)
MJ2-DP8
MJ7-DP19
MJ1-DP2
NTD
* = by one-way ANOVA
THP-1 (Low HA-2 / Medium MHC)
Interferon-γ
IL-2
TNF-α
Granzyme B
IFNγ (pg/ml)
IL-2 (pg/mL)
TNFα (pg/mL)
Granzyme B (pg/mL)
MJ2-DP8
MJ7-DP19
MJ1-DP2
NTD
* = by one-way ANOVA

Figure 4C (cont.)

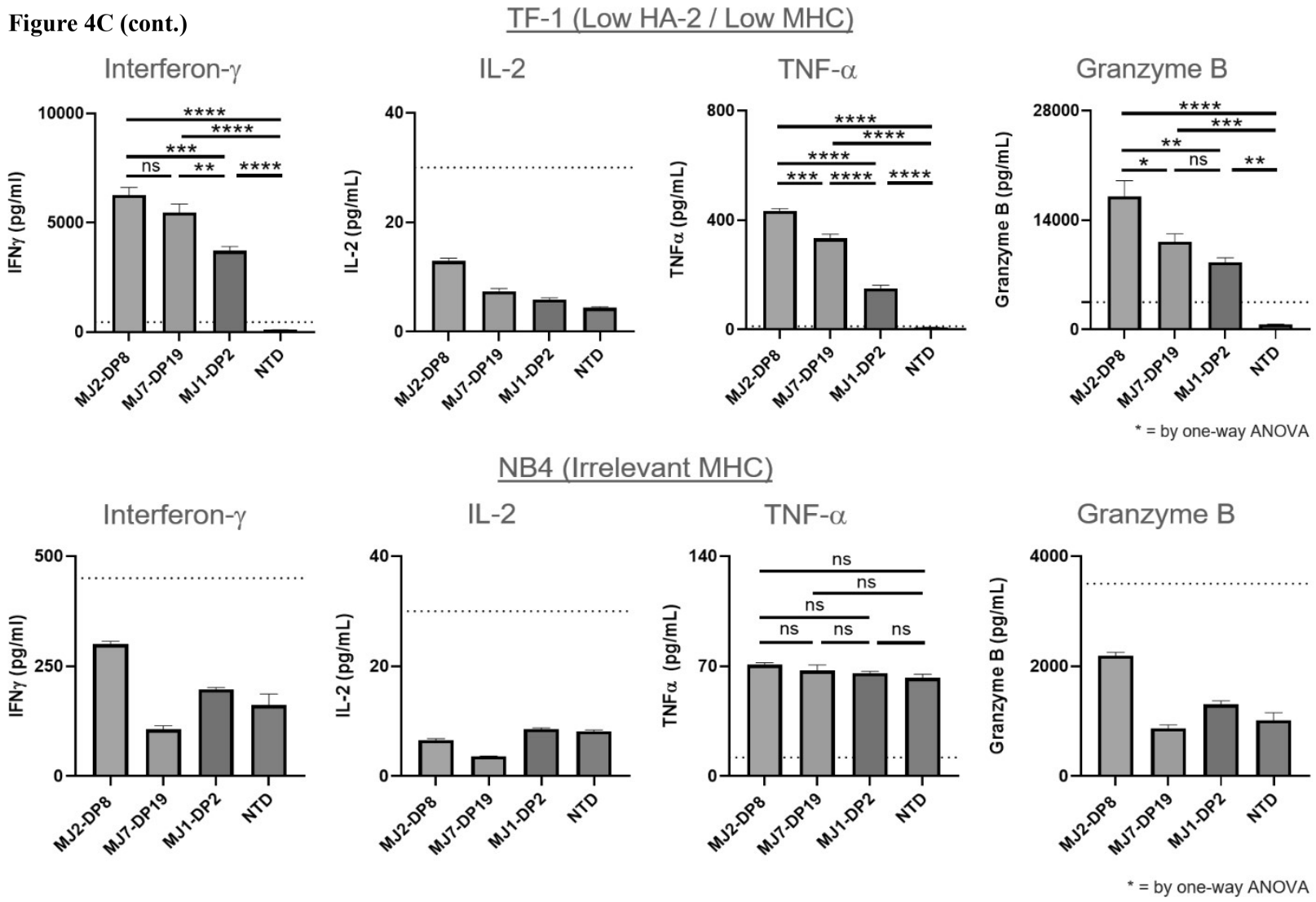


Figure 4D

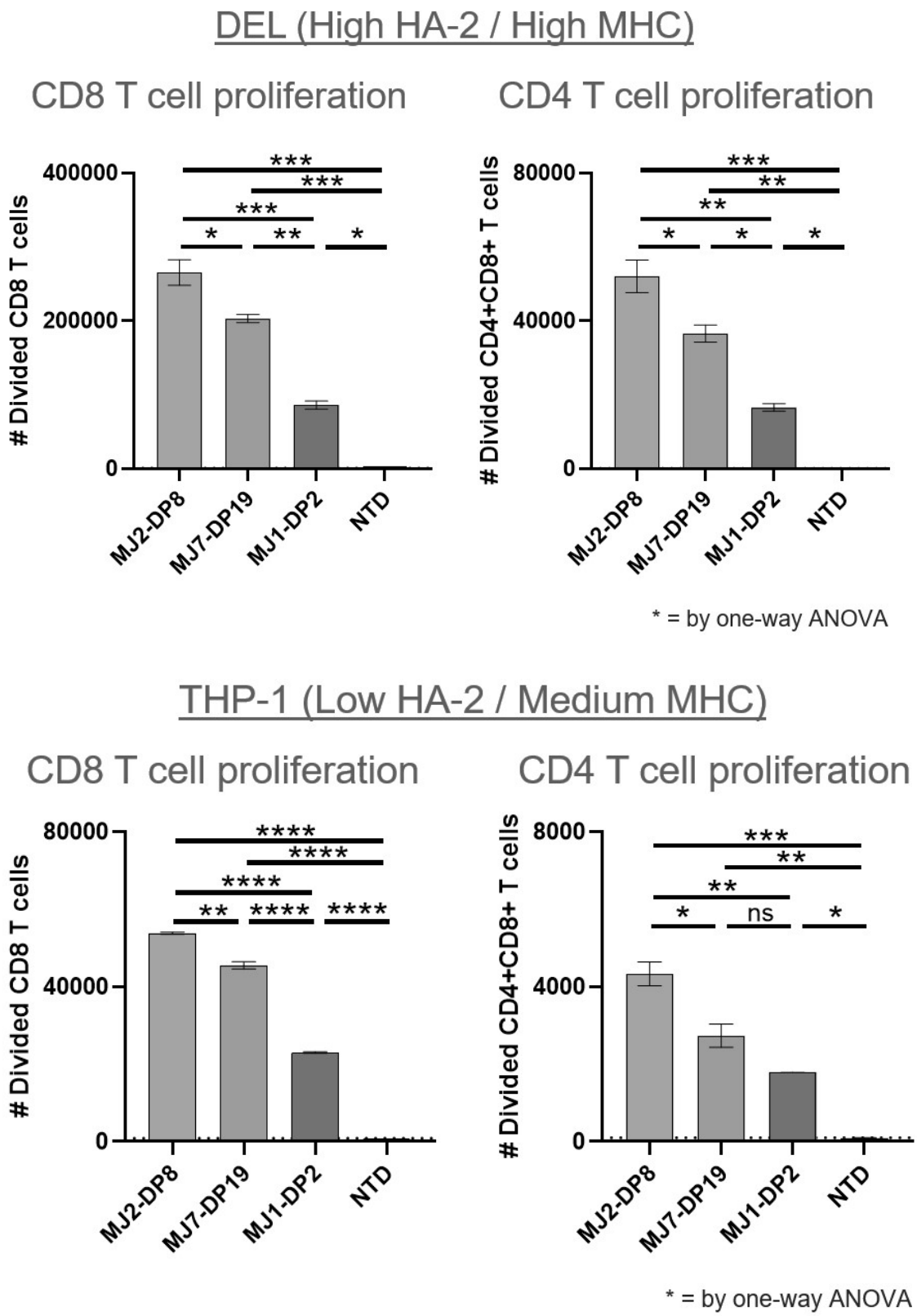

DEL (High HA-2 / High MHC)
CD8 T cell proliferation
CD4 T cell proliferation
Divided CD8 T cells
Divided CD4+CD8+ T cells
400000
200000
0
80000
40000
***
**
*
MJ2-DP8
MJ7-DP19
MJ1-DP2
NTD
* = by one-way ANOVA
THP-1 (Low HA-2 / Medium MHC)
CD8 T cell proliferation
CD4 T cell proliferation
Divided CD8 T cells
Divided CD4+CD8+ T cells
80000
40000
0
8000
4000
****
**
*
ns
MJ2-DP8
MJ7-DP19
MJ1-DP2
NTD
* = by one-way ANOVA

Figure 4D (cont.)

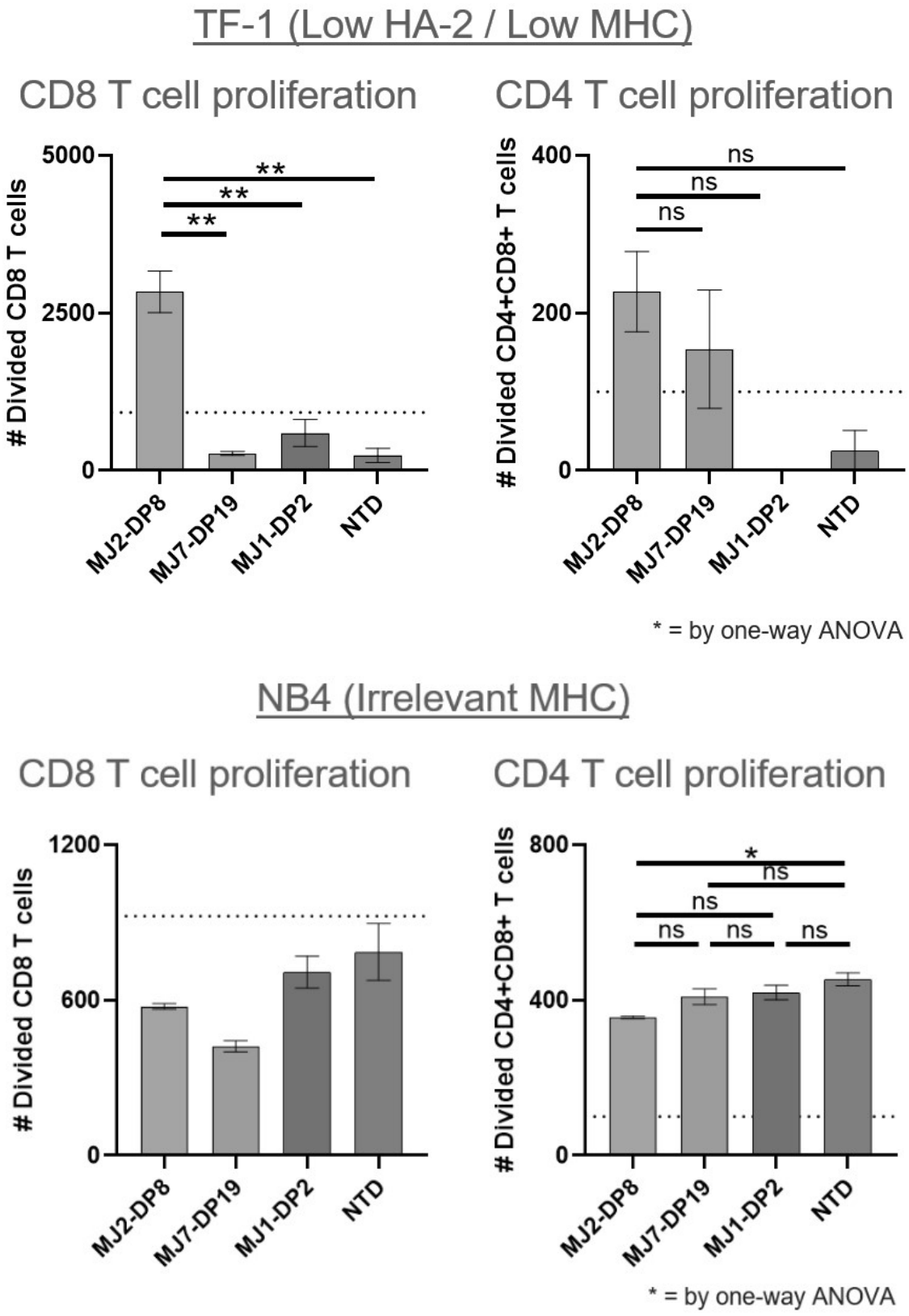


Figure 5

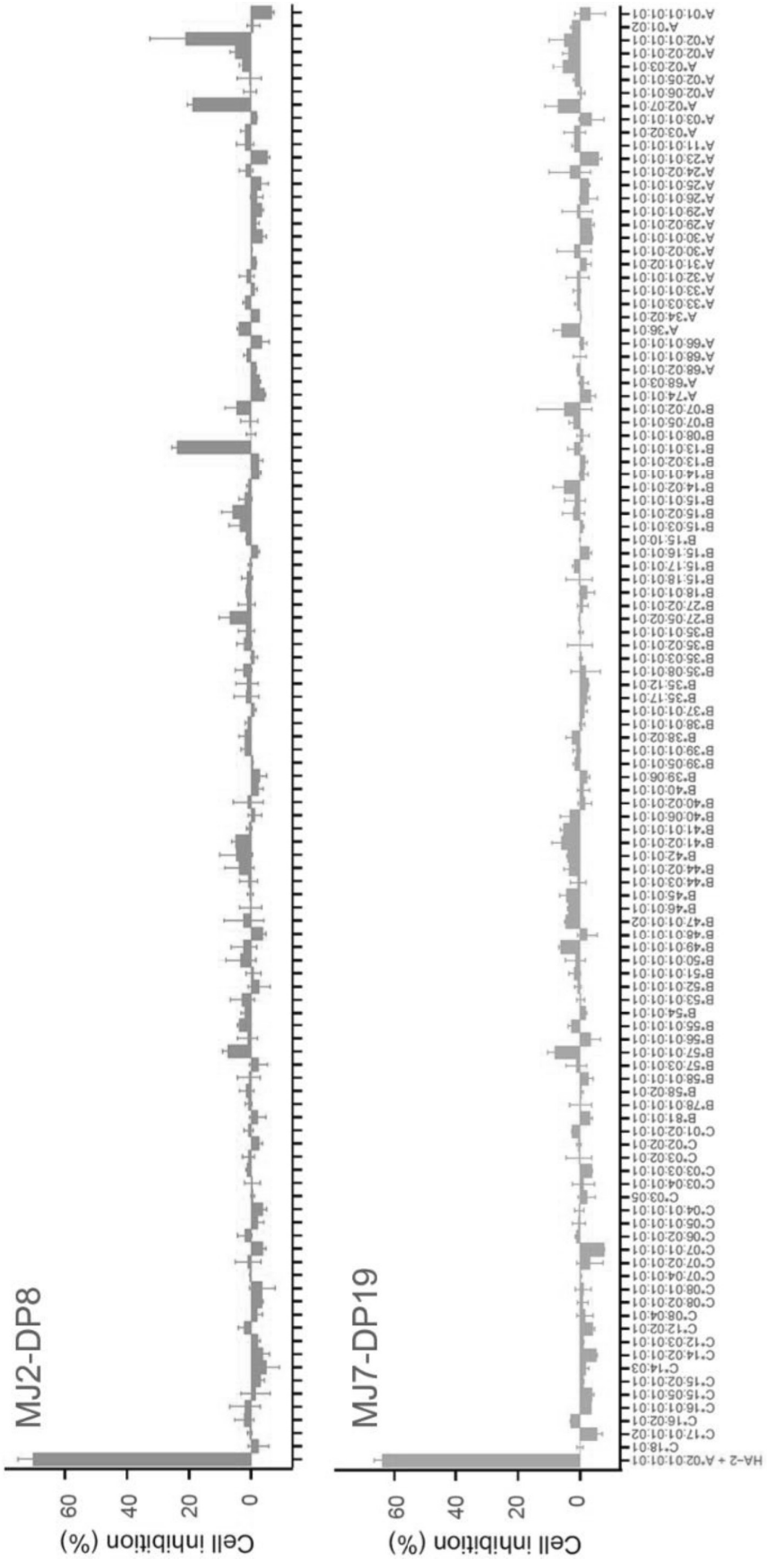

MJ2-DP8
Cell inhibition (%)
0
20
40
60
MJ7-DP19
Cell inhibition (%)
0
20
40
60
HA-2 + A*02:01:01:01

Figure 6

TCR
HA2-MJ7-DP19
HA2-MJ14-SP4
HA2-MJ2-DP8
HA2-MJ13-DP148
HA2-MJ14-DP317
HA2-MJ2-DP22
HA2-MJ14-DP331
HA2-MJ14-DP45
HA2-MJ2-DP24
HA2-MJ14-DP162
HA2-MJ14-DP137
HA2-MJ14-DP33
HA2-MJ9-DP5
HA2-MJ13-SP43
HA2-MJ13-DP32

Figure 7A

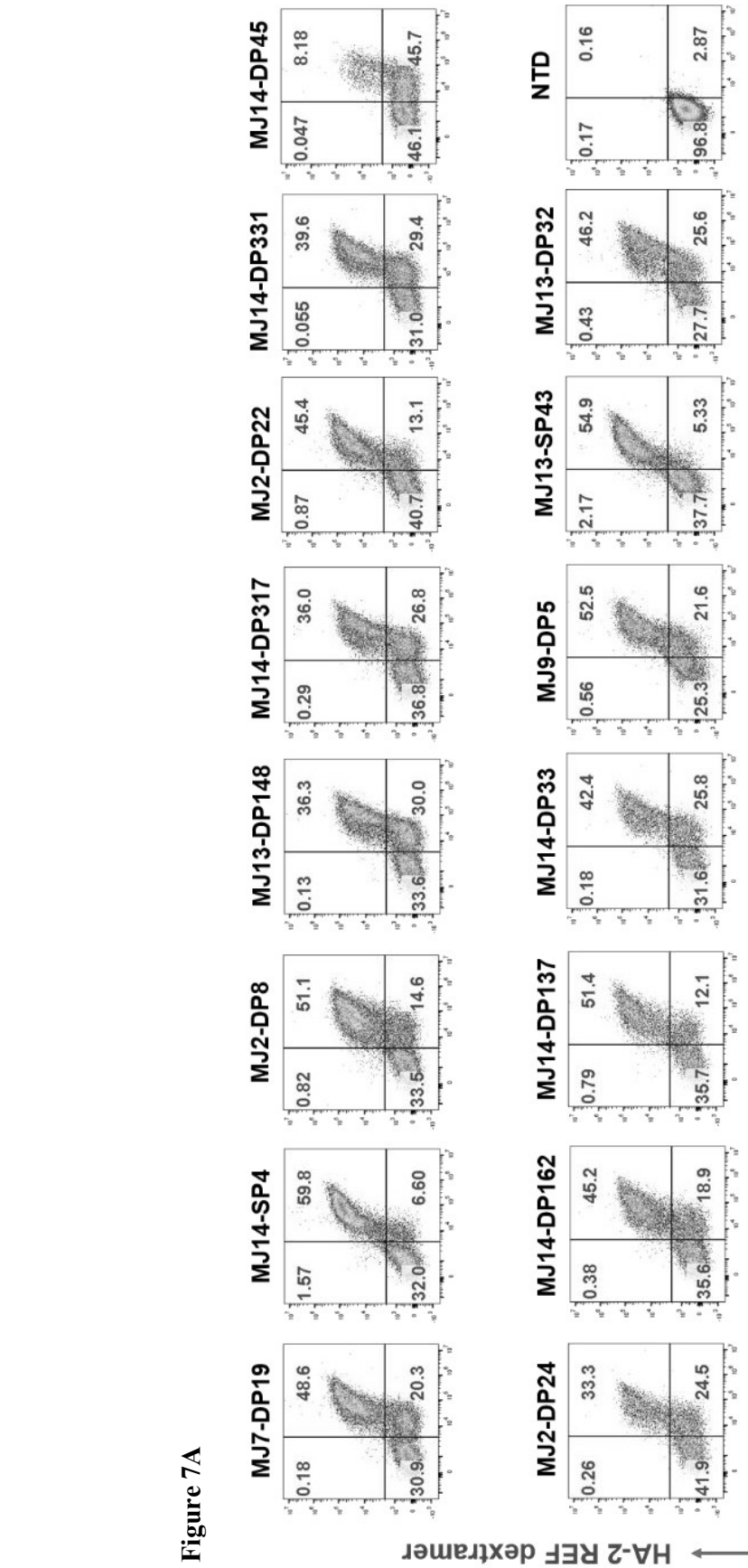
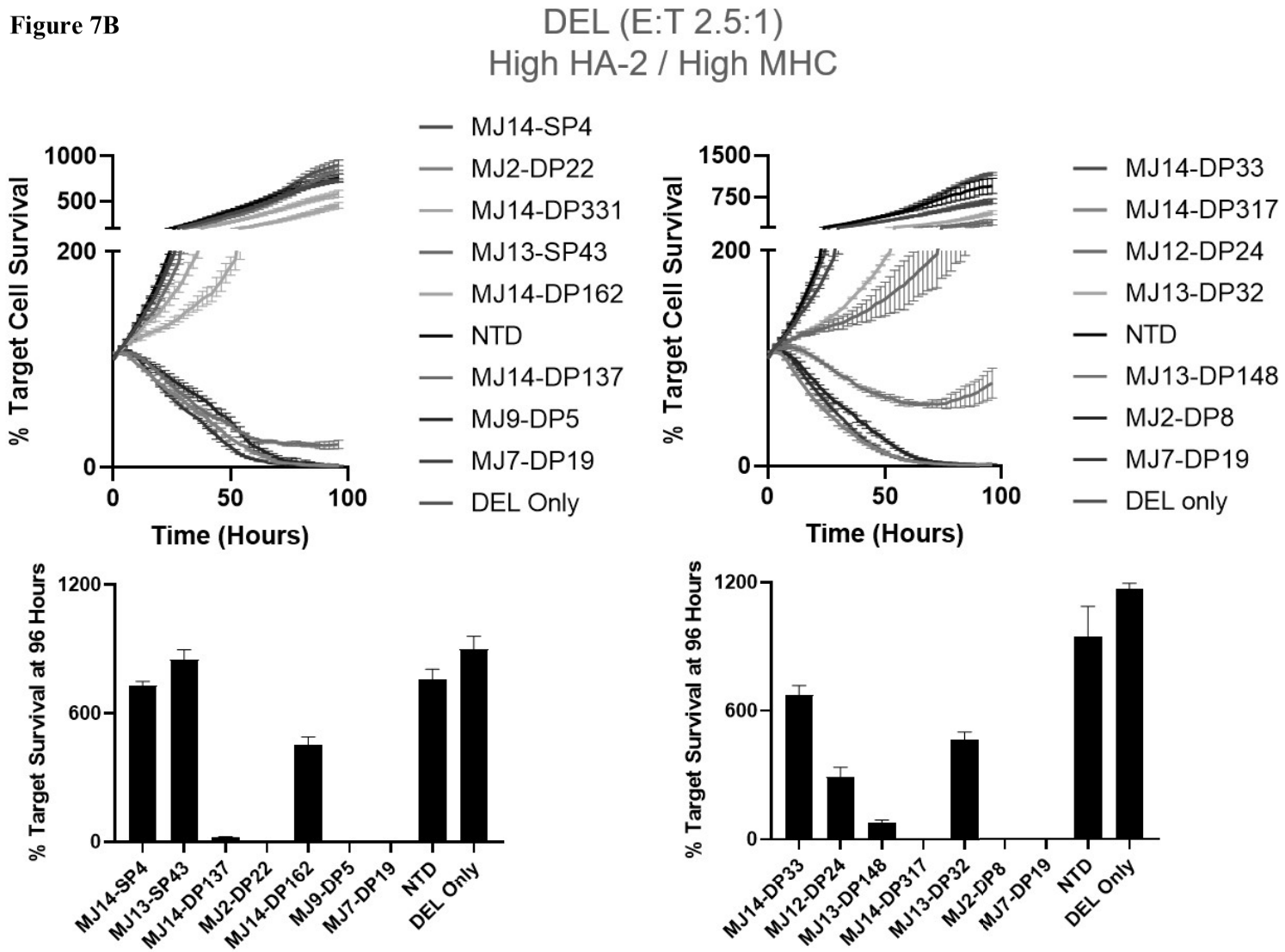

MJ7-DP19
MJ14-SP4
MJ2-DP8
MJ13-DP148
MJ14-DP317
MJ2-DP22
MJ14-DP331
MJ14-DP45
MJ2-DP24
MJ14-DP162
MJ14-DP137
MJ14-DP33
MJ9-DP5
MJ13-SP43
MJ13-DP32
NTD
HA-2 REF dextramer
CD34 (QBEnd10)
Gated on live cells

Figure 7B


DEL (E:T 2.5:1)
High HA-2 / High MHC
% Target Cell Survival
Time (Hours)
MJ14-SP4
MJ2-DP22
MJ14-DP331
MJ13-SP43
MJ14-DP162
NTD
MJ14-DP137
MJ9-DP5
MJ7-DP19
DEL Only
MJ14-DP33
MJ14-DP317
MJ12-DP24
MJ13-DP32
NTD
MJ13-DP148
MJ2-DP8
MJ7-DP19
DEL only
% Target Survival at 96 Hours
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ7-DP19
NTD
DEL Only
MJ14-DP33
MJ12-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD
DEL Only

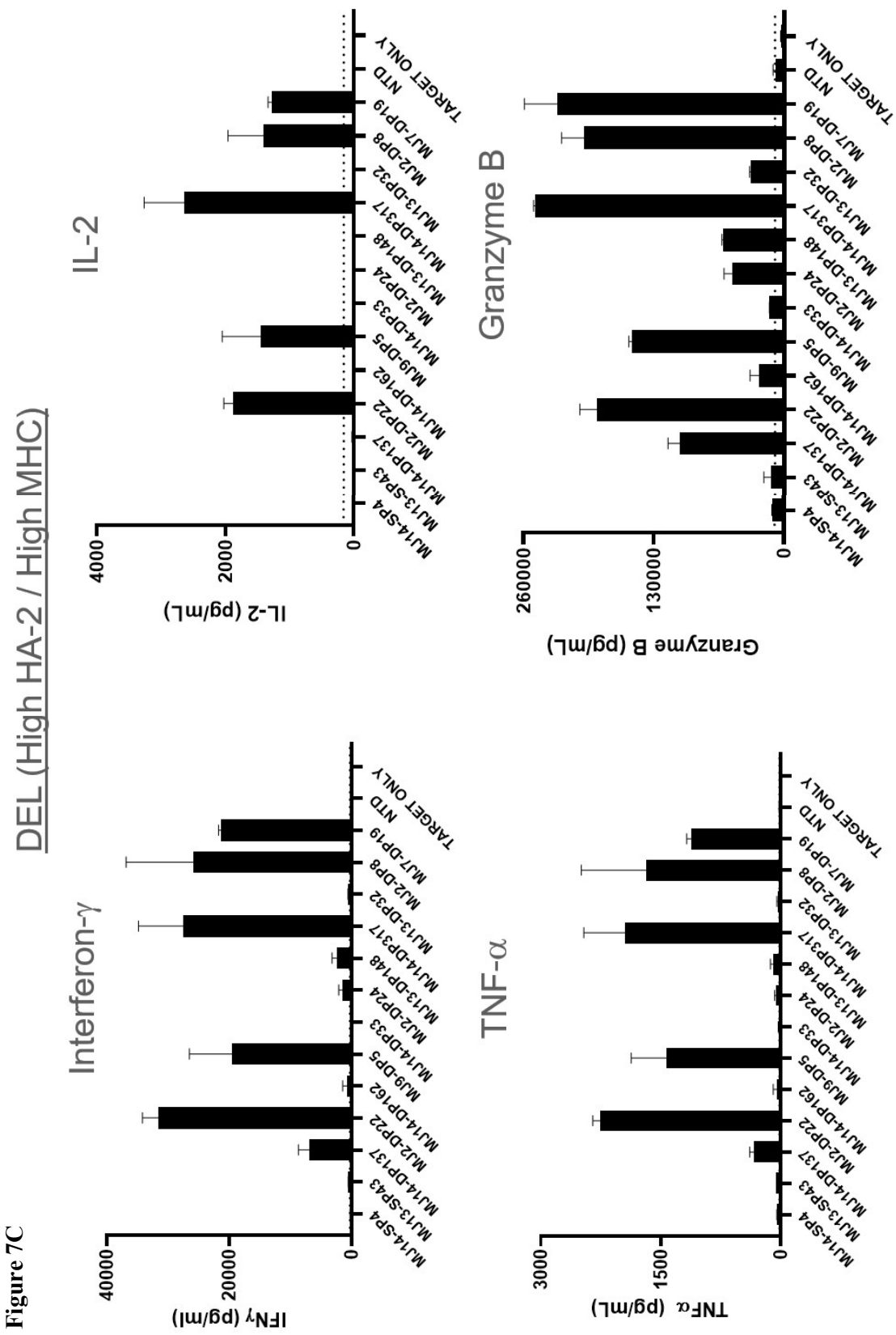

DEL (High HA-2 / High MHC)
Interferon-γ
IFNγ (pg/ml)
40000
20000
0
TNF-α
TNFα (pg/mL)
3000
1500
0
IL-2
IL-2 (pg/mL)
4000
2000
0
Granzyme B
Granzyme B (pg/mL)
260000
130000
0
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ14-DP33
MJ2-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD
TARGET ONLY

Figure 7C

Figure 7D

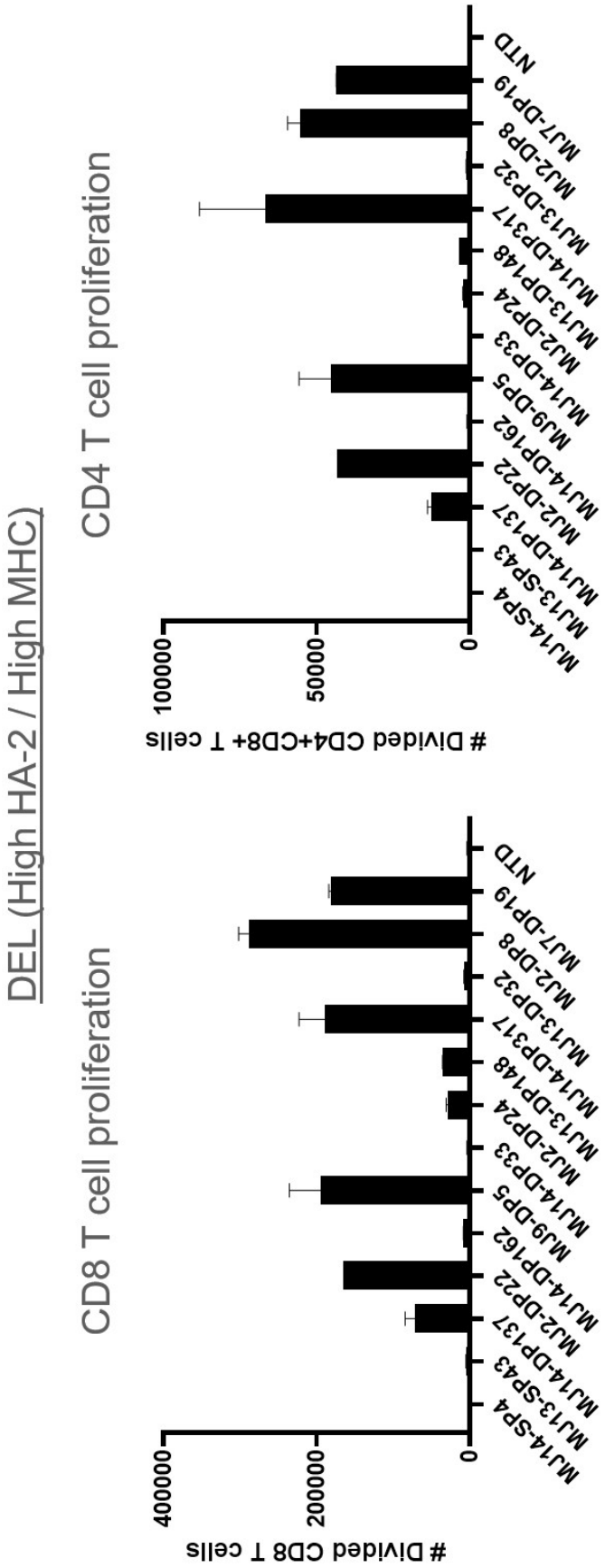
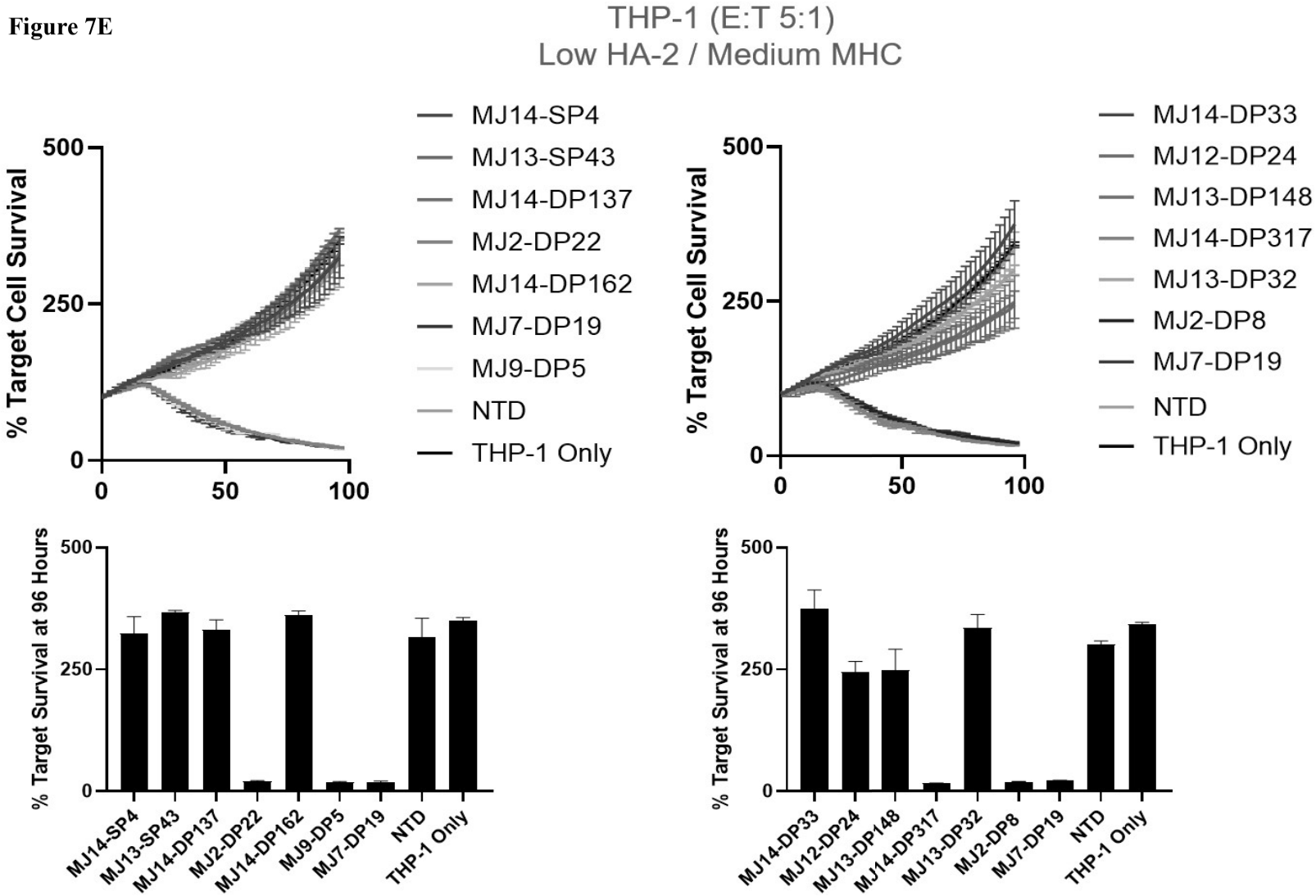

DEL (High HA-2 / High MHC)
CD8 T cell proliferation
Divided CD8 T cells
400000
200000
0
CD4 T cell proliferation
Divided CD4+CD8+ T cells
100000
50000
0
M14-SP4
M13-SP43
M14-DP137
M12-DP22
M14-DP162
M9-DP5
M14-DP33
M12-DP24
M13-DP148
M14-DP317
M13-DP32
M12-DP8
M17-DP19
NTD

Figure 7E


THP-1 (E:T 5:1)
Low HA-2 / Medium MHC
% Target Cell Survival
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ7-DP19
MJ9-DP5
NTD
THP-1 Only
MJ14-DP33
MJ12-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD
THP-1 Only
% Target Survival at 96 Hours

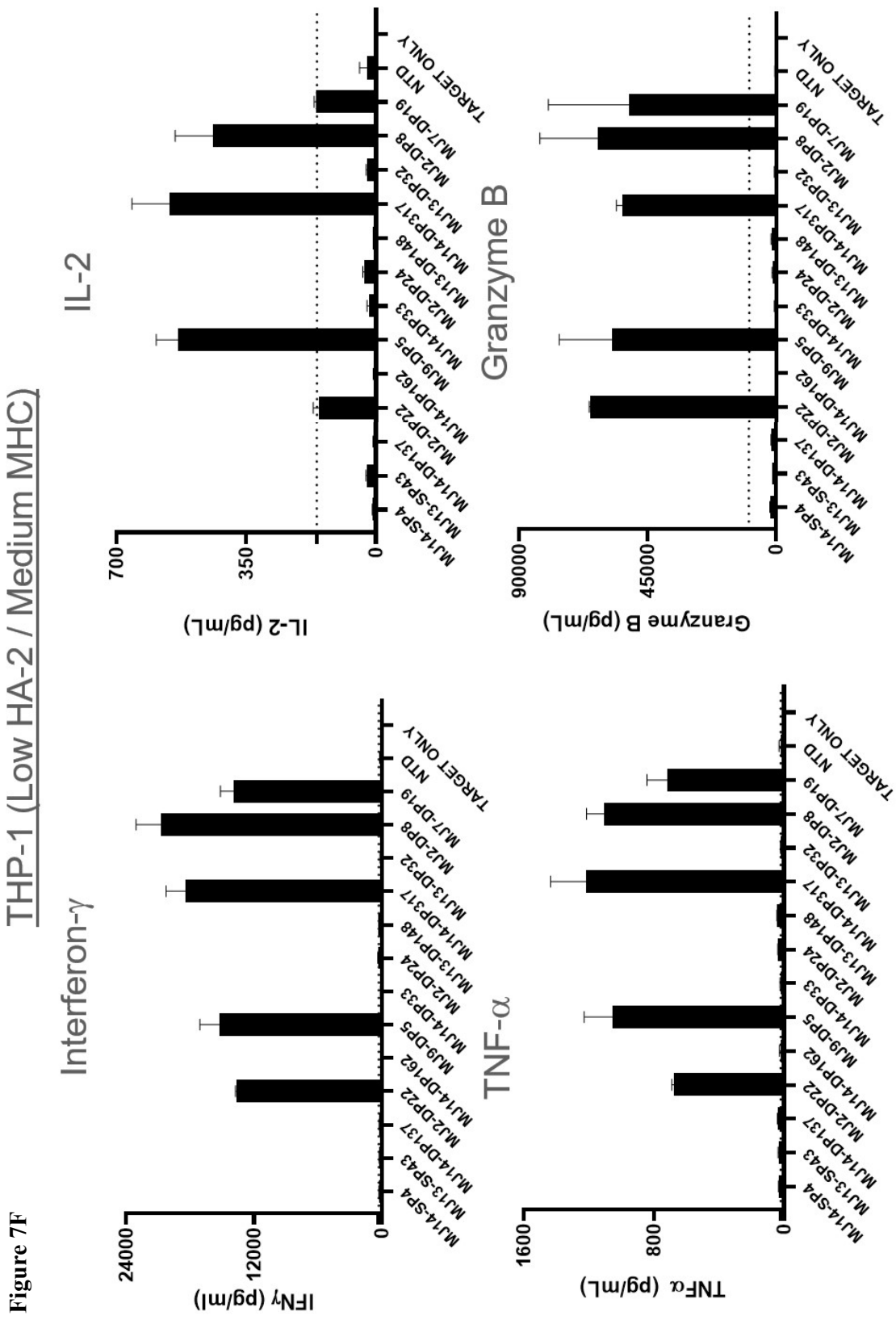

THP-1 (Low HA-2 / Medium MHC)
Interferon-γ
IFNγ (pg/ml)
24000
12000
0
IL-2
IL-2 (pg/mL)
700
350
0
Granzyme B
Granzyme B (pg/mL)
90000
45000
0
TNF-α
TNFα (pg/mL)
1600
800
0
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ14-DP33
MJ2-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD
TARGET ONLY

Figure 7F

Figure 7G

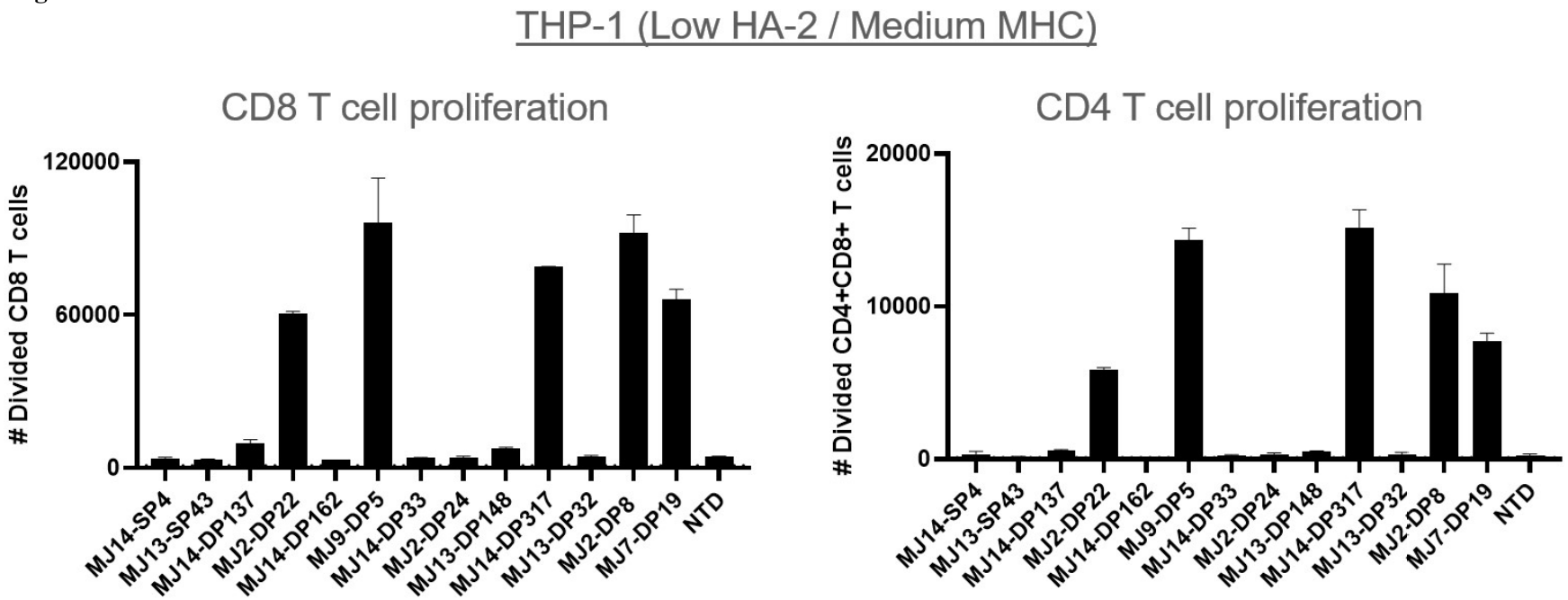
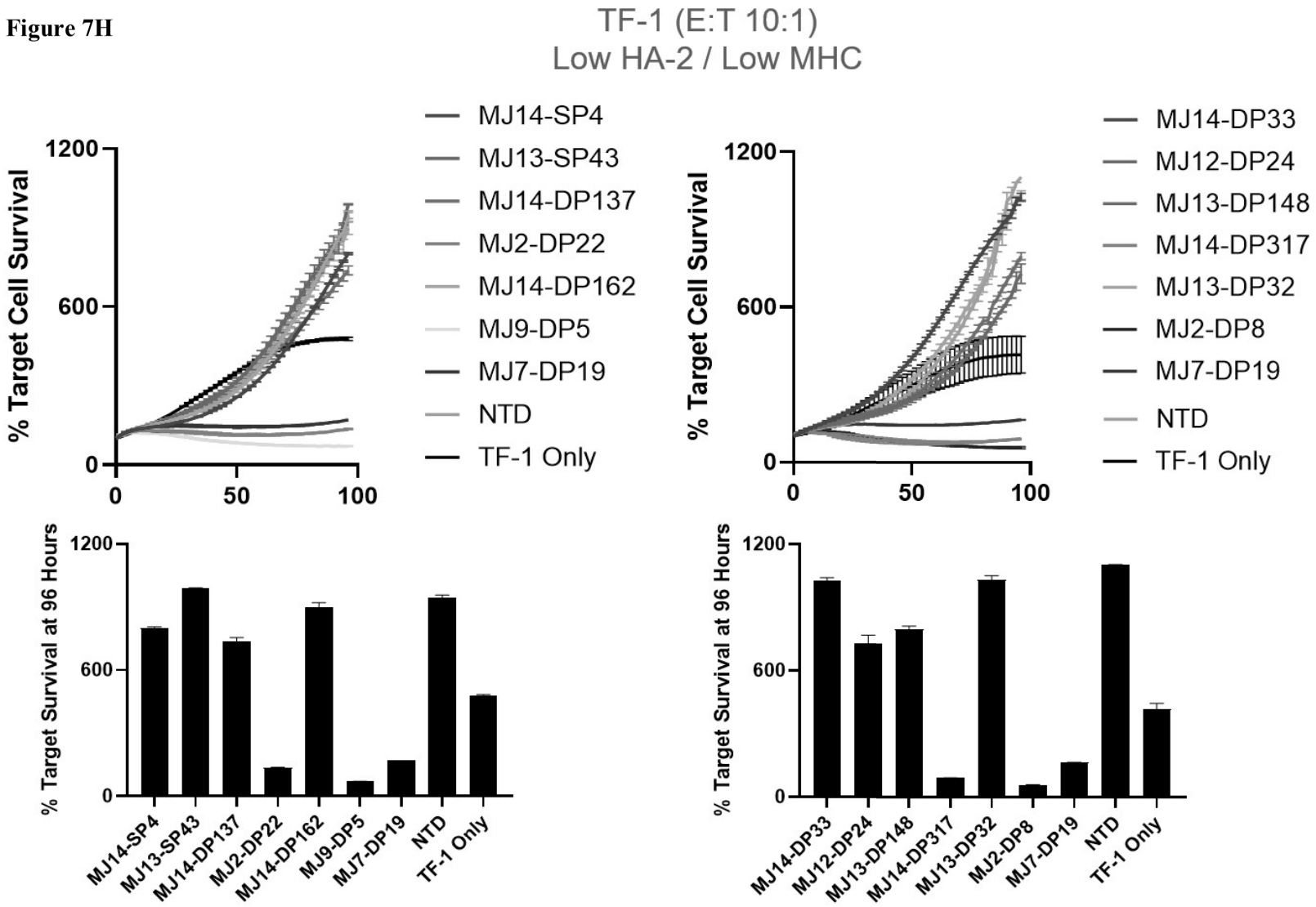

THP-1 (Low HA-2 / Medium MHC)
CD8 T cell proliferation
Divided CD8 T cells
120000
60000
0
CD4 T cell proliferation
Divided CD4+CD8+ T cells
20000
10000
0
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ14-DP33
MJ2-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD

Figure 7H


TF-1 (E:T 10:1)
Low HA-2 / Low MHC
% Target Cell Survival
1200
600
0
0
50
100
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ7-DP19
NTD
TF-1 Only
% Target Survival at 96 Hours
MJ14-DP33
MJ12-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19

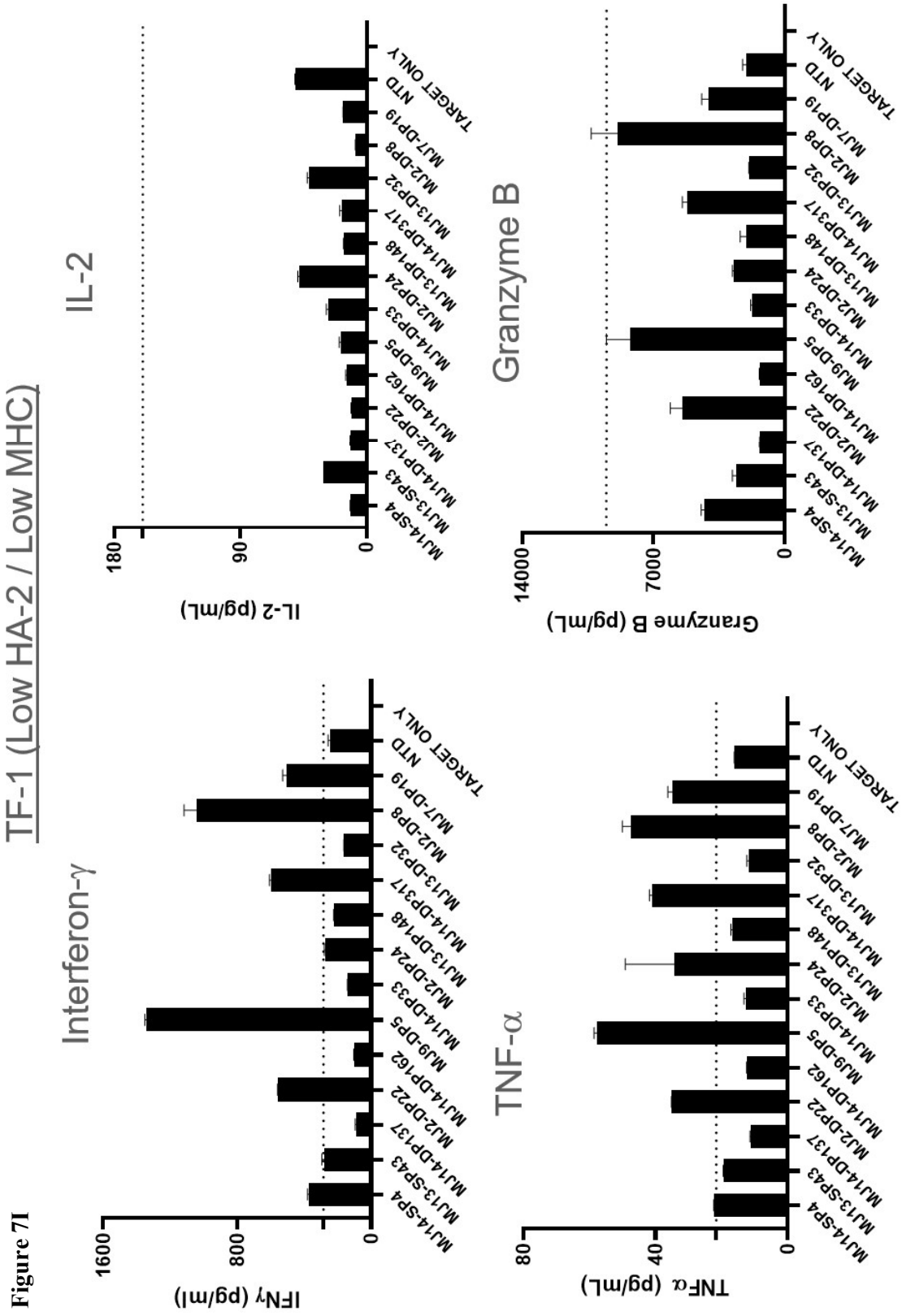

TF-1 (Low HA-2 / Low MHC)
Interferon-γ
IFNγ (pg/ml)
1600
800
0
IL-2
IL-2 (pg/mL)
180
90
0
TNF-α
TNFα (pg/mL)
80
40
0
Granzyme B
Granzyme B (pg/mL)
14000
7000
0
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ14-DP33
MJ2-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD
TARGET ONLY

Figure 7I

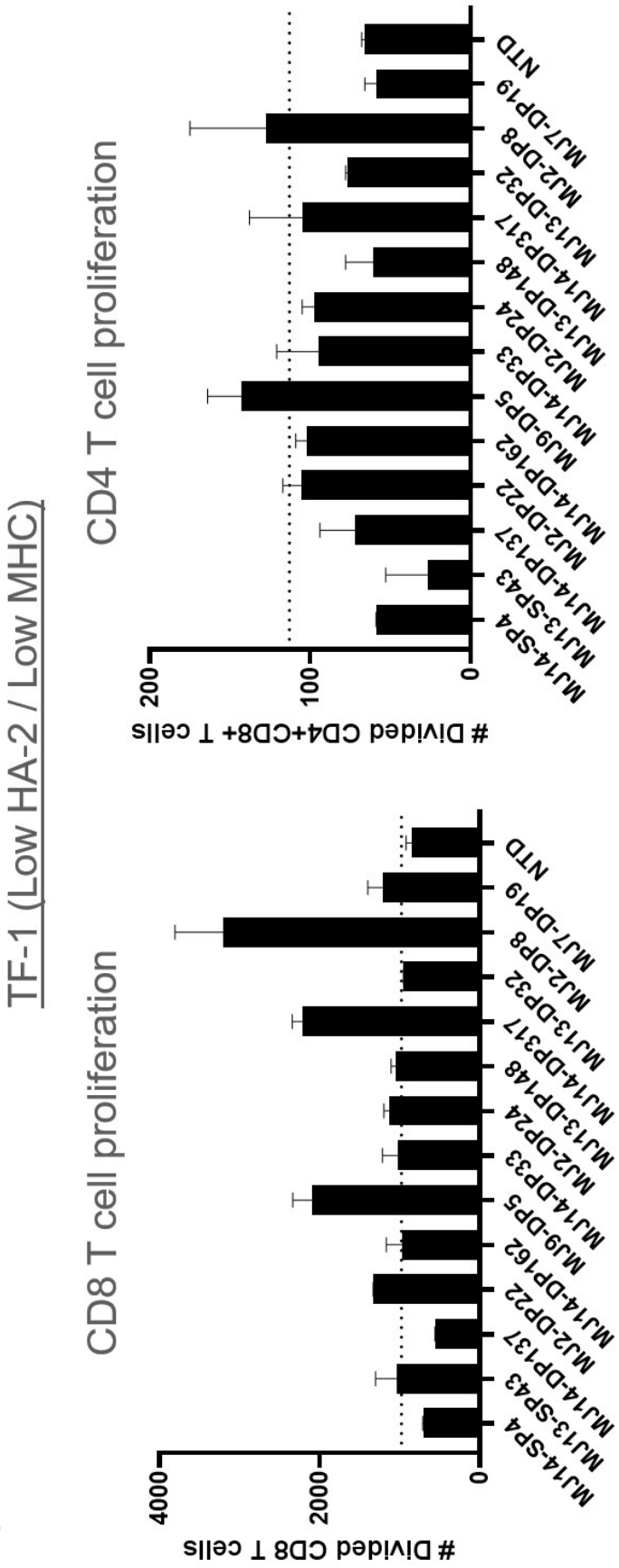
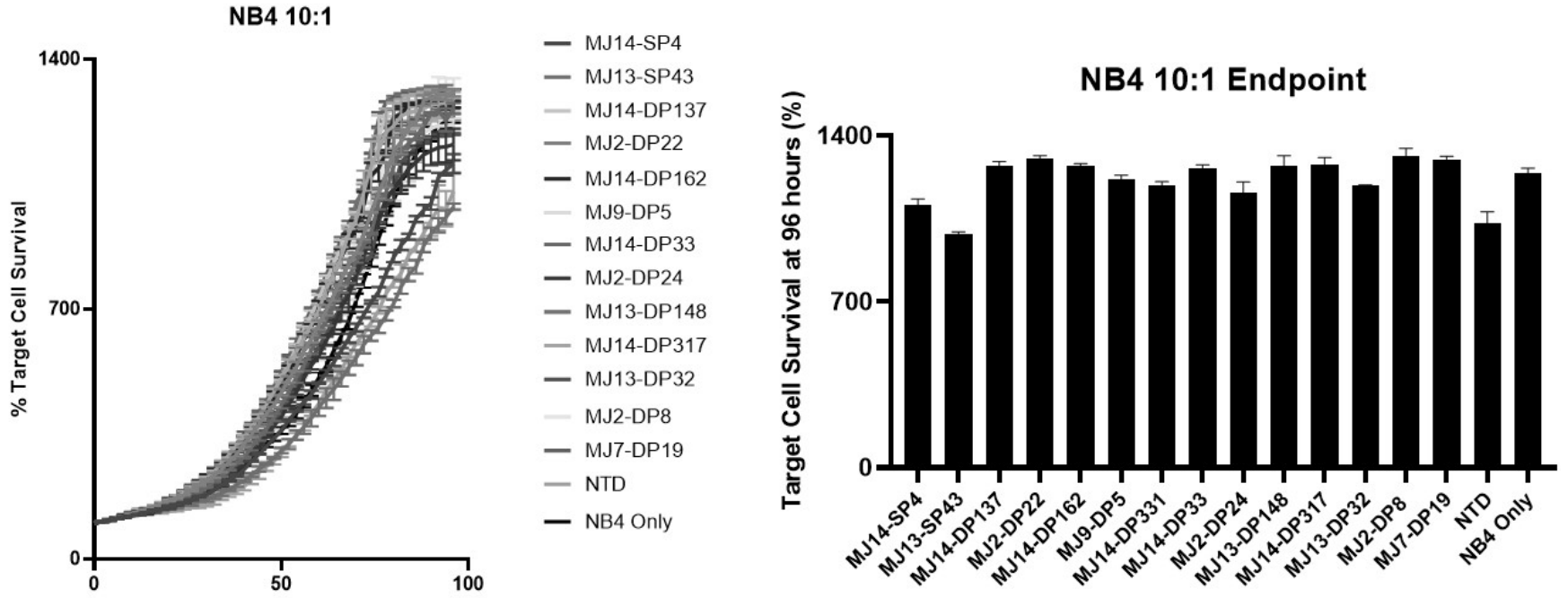

TF-1 (Low HA-2 / Low MHC)
CD8 T cell proliferation
Divided CD8 T cells
4000
2000
0
CD4 T cell proliferation
Divided CD4+CD8+ T cells
200
100
0
MJ14-SP4
MJ13-SP4
MJ14-DP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ14-DP33
MJ2-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD

Figure 7J

Figure 7K


NB4 (E:T 10:1)
Irrelevant MHC
NB4 10:1
% Target Cell Survival
1400
700
0
0
50
100
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ14-DP33
MJ2-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD
NB4 Only
NB4 10:1 Endpoint
Target Cell Survival at 96 hours (%)
1400
700
0
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ14-DP331
MJ14-DP33
MJ2-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD
NB4 Only

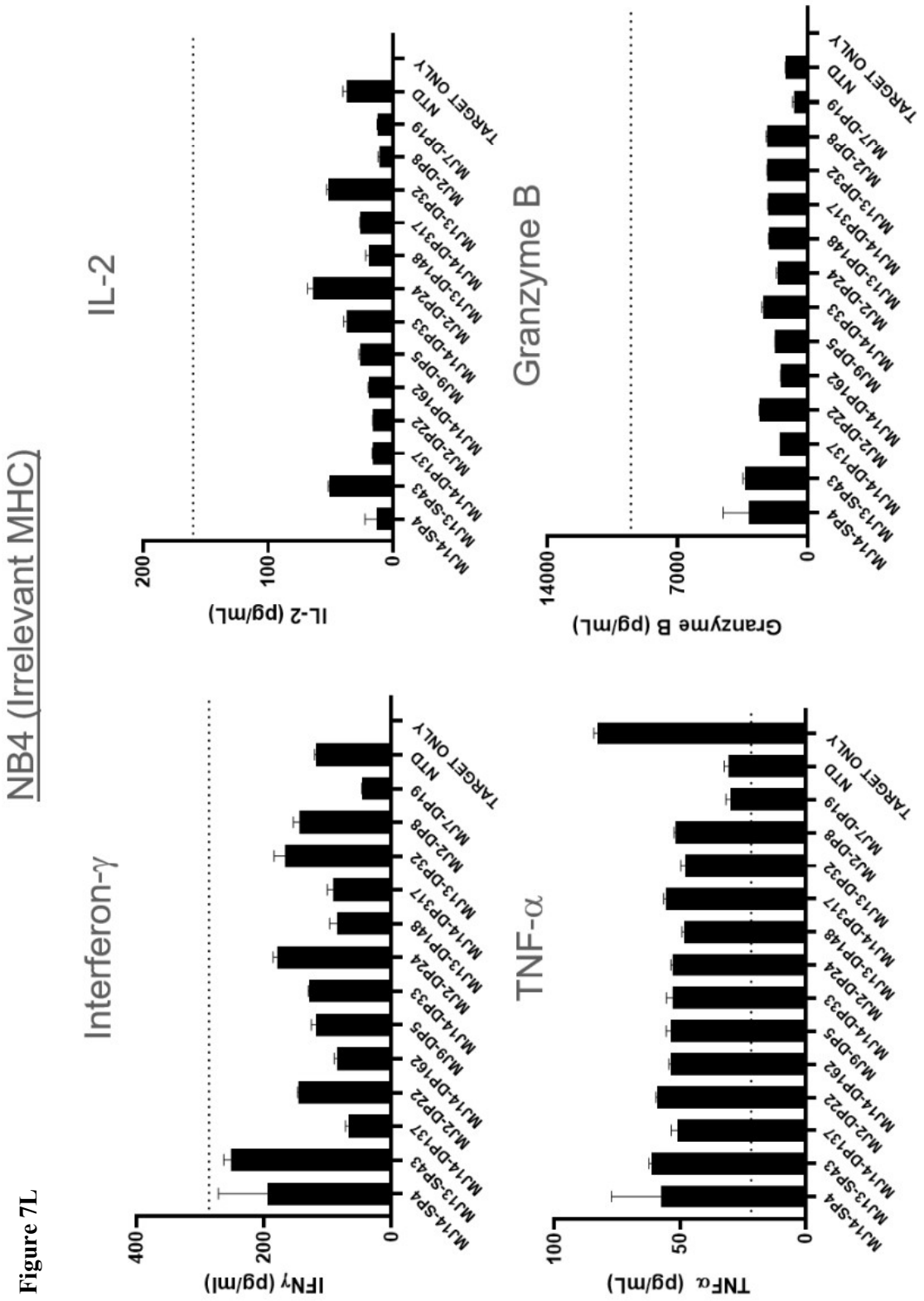

NB4 (Irrelevant MHC)
Interferon-γ
IFNγ (pg/ml)
400
200
0
IL-2
IL-2 (pg/mL)
200
100
0
TNF-α
TNFα (pg/mL)
100
50
0
Granzyme B
Granzyme B (pg/mL)
14000
7000
0
MJ14-SP4
MJ13-SP43
MJ14-DP137
MJ2-DP22
MJ14-DP162
MJ9-DP5
MJ14-DP33
MJ2-DP24
MJ13-DP148
MJ14-DP317
MJ13-DP32
MJ2-DP8
MJ7-DP19
NTD
TARGET ONLY

Figure 7L

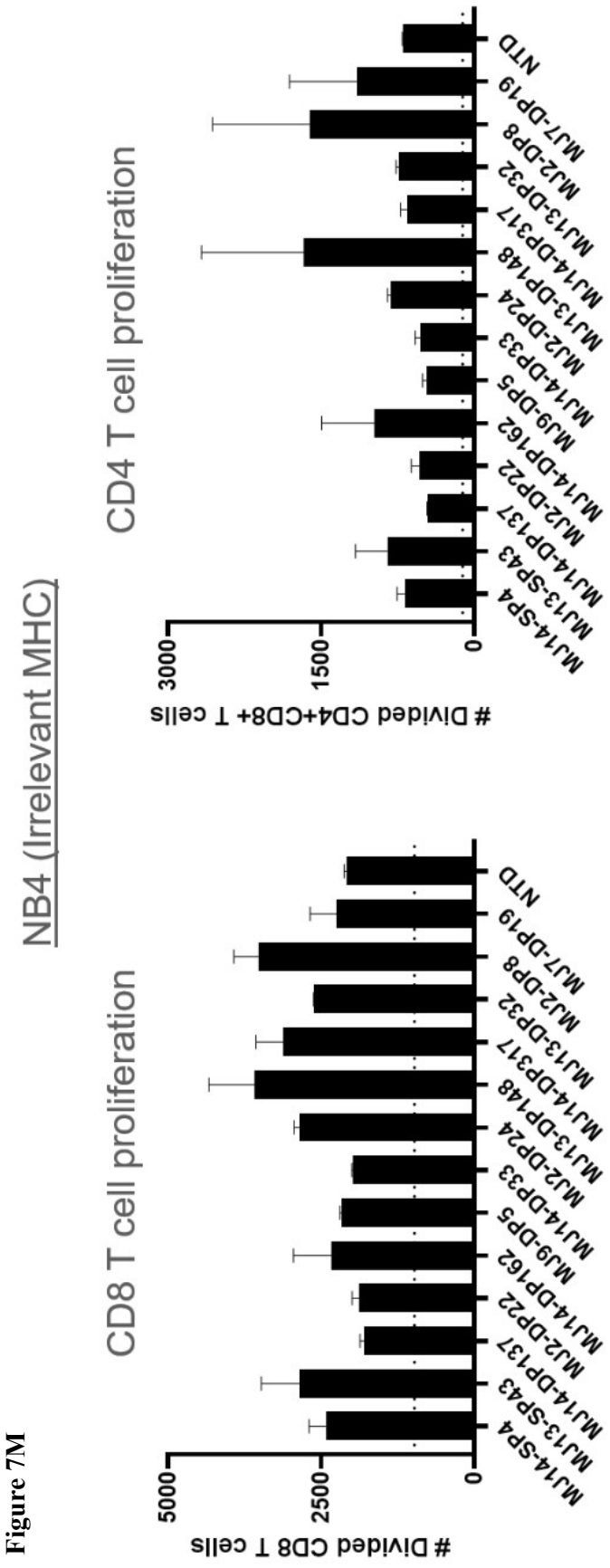

NB4 (Irrelevant MHC)
CD8 T cell proliferation
Divided CD8 T cells
5000
2500
0
CD4 T cell proliferation
Divided CD4+CD8+ T cells
3000
1500
0
M14-SP4
M13-SP43
M14-DP137
M12-DP22
M14-DP162
M9-DP5
M14-DP33
M12-DP24
M13-DP148
M14-DP317
M13-DP32
M12-DP8
M17-DP19
NTD

Figure 7M

Figure 8A

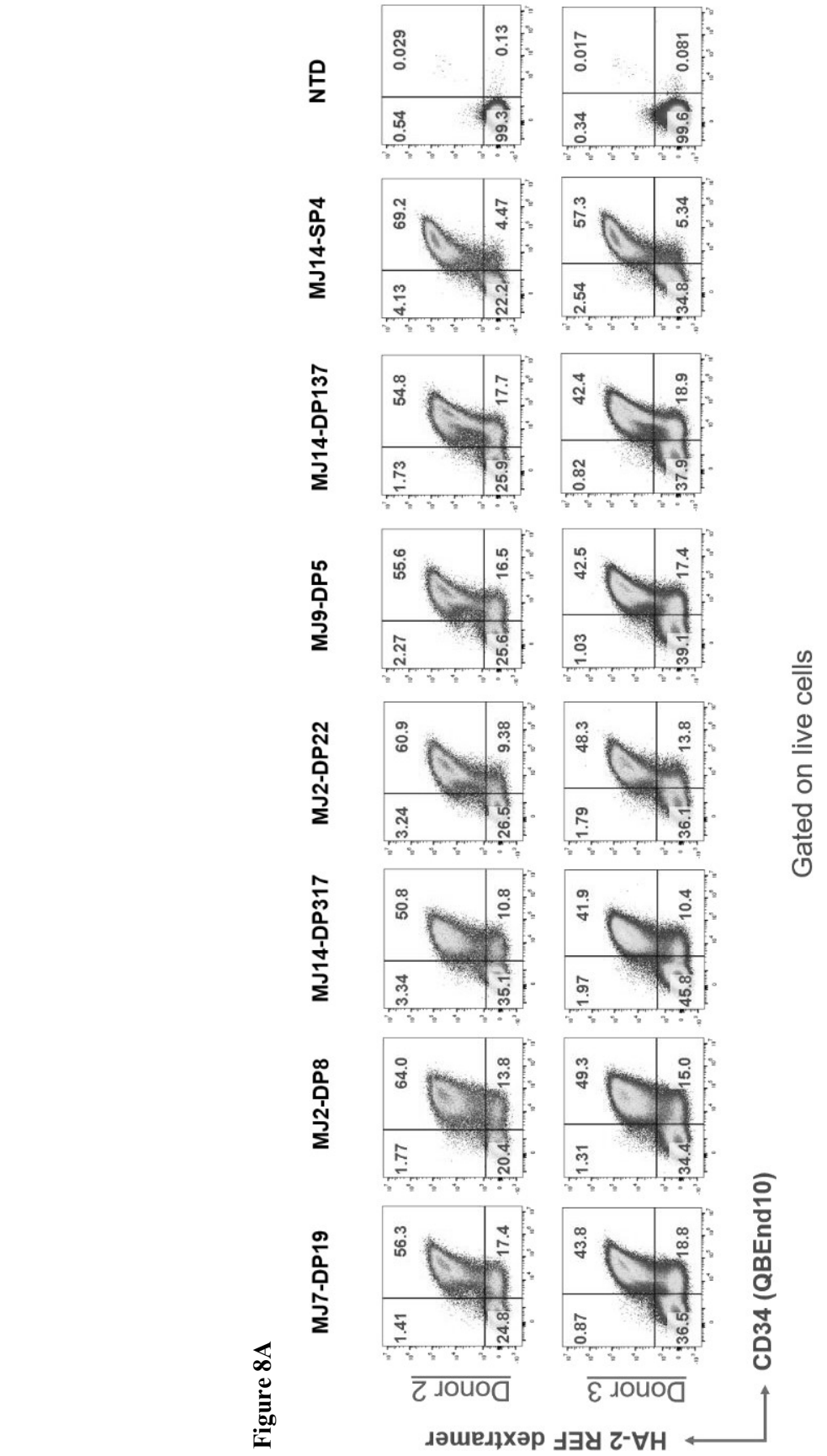

MJ7-DP19
MJ2-DP8
MJ14-DP317
MJ2-DP22
MJ9-DP5
MJ14-DP137
MJ14-SP4
NTD
Donor 2
Donor 3
HA-2 REF dextramer
CD34 (QBEnd10)
Gated on live cells

Figure 8B

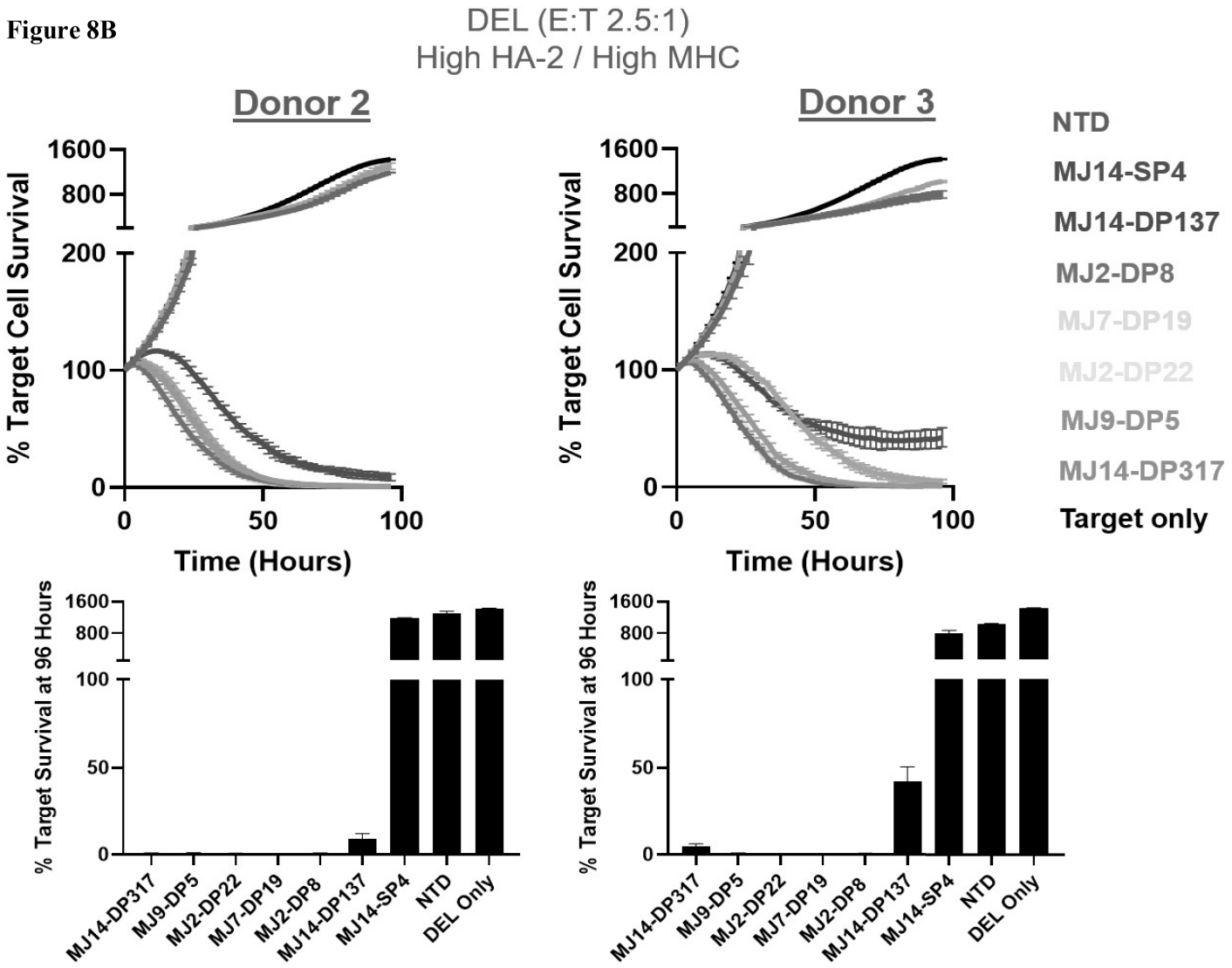

DEL (E:T 2.5:1)
High HA-2 / High MHC
Donor 2
Donor 3
% Target Cell Survival
Time (Hours)
NTD
MJ14-SP4
MJ14-DP137
MJ2-DP8
MJ7-DP19
MJ2-DP22
MJ9-DP5
MJ14-DP317
Target only
% Target Survival at 96 Hours
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD
DEL Only

Figure 8C

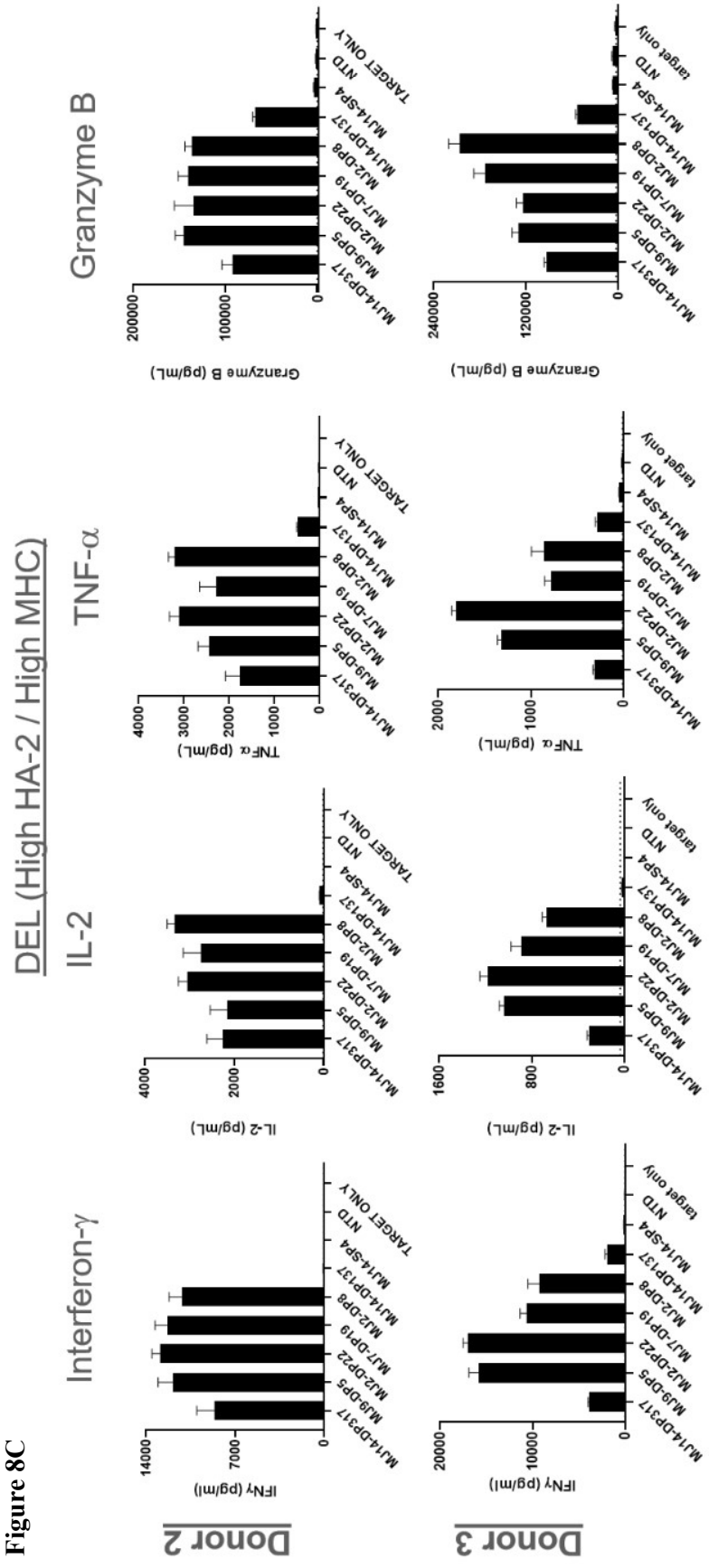

DEL (High HA-2 / High MHC)
Interferon-γ
IL-2
TNF-α
Granzyme B
Donor 2
Donor 3
IFNγ (pg/ml)
IL-2 (pg/mL)
TNFα (pg/mL)
Granzyme B (pg/mL)
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD
TARGET ONLY
target only

Figure 8D

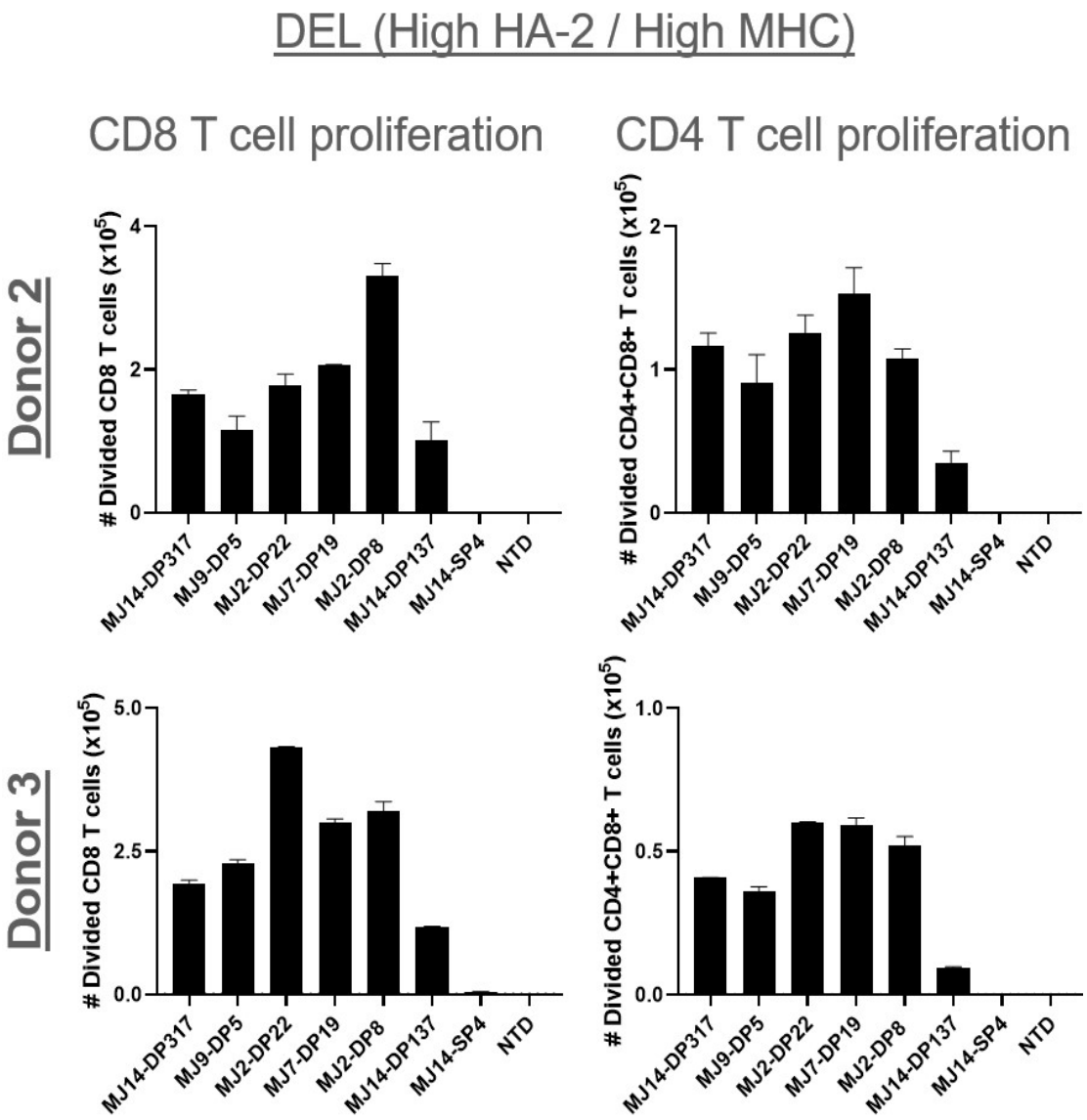
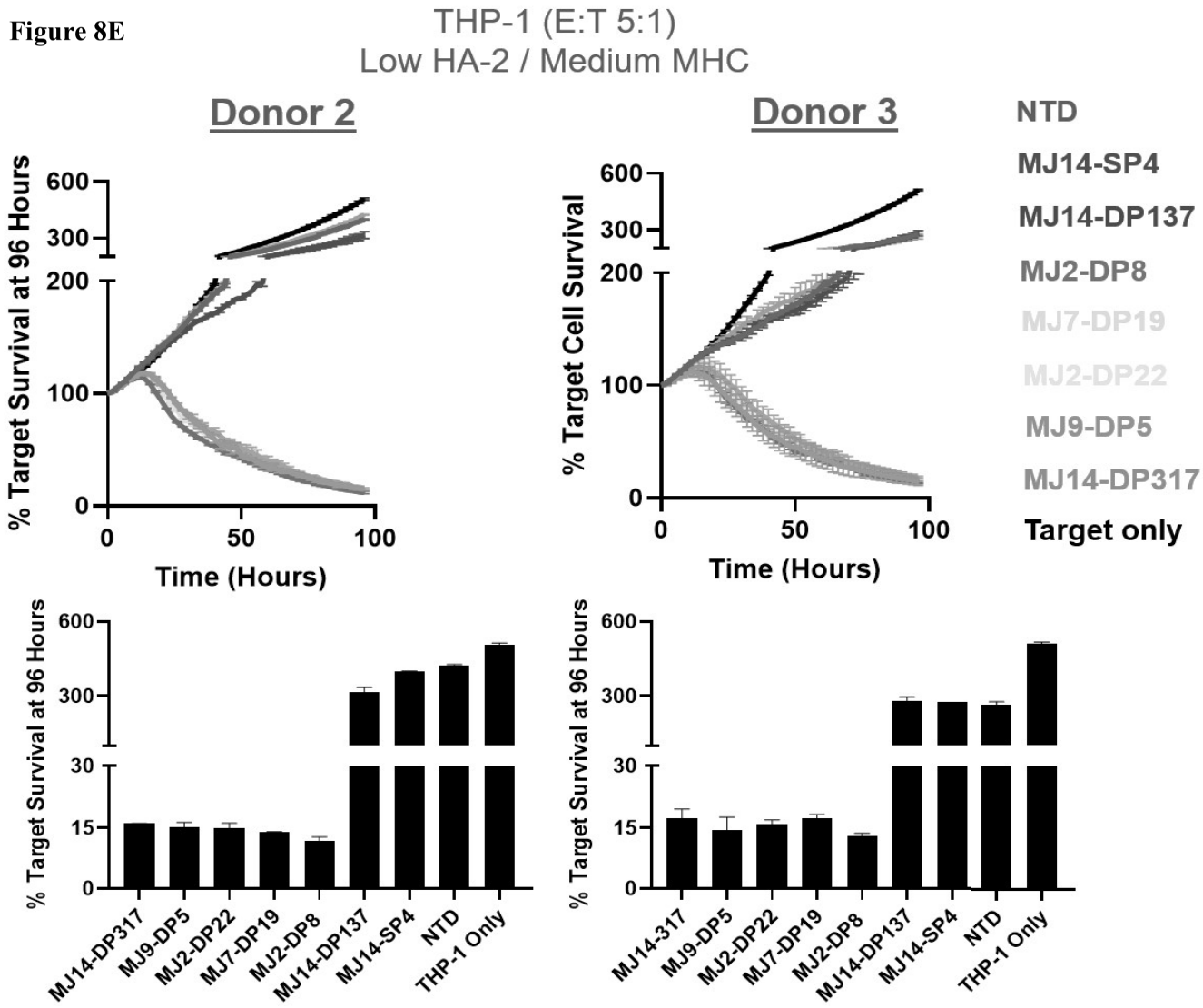

DEL (High HA-2 / High MHC)
CD8 T cell proliferation
CD4 T cell proliferation
Donor 2
Donor 3
Divided CD8 T cells (x10^5)
Divided CD4+CD8+ T cells (x10^5)
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD

Figure 8E


THP-1 (E:T 5:1)
Low HA-2 / Medium MHC
Donor 2
Donor 3
% Target Survival at 96 Hours
% Target Cell Survival
Time (Hours)
NTD
MJ14-SP4
MJ14-DP137
MJ2-DP8
MJ7-DP19
MJ2-DP22
MJ9-DP5
MJ14-DP317
Target only
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD
THP-1 Only
MJ14-317

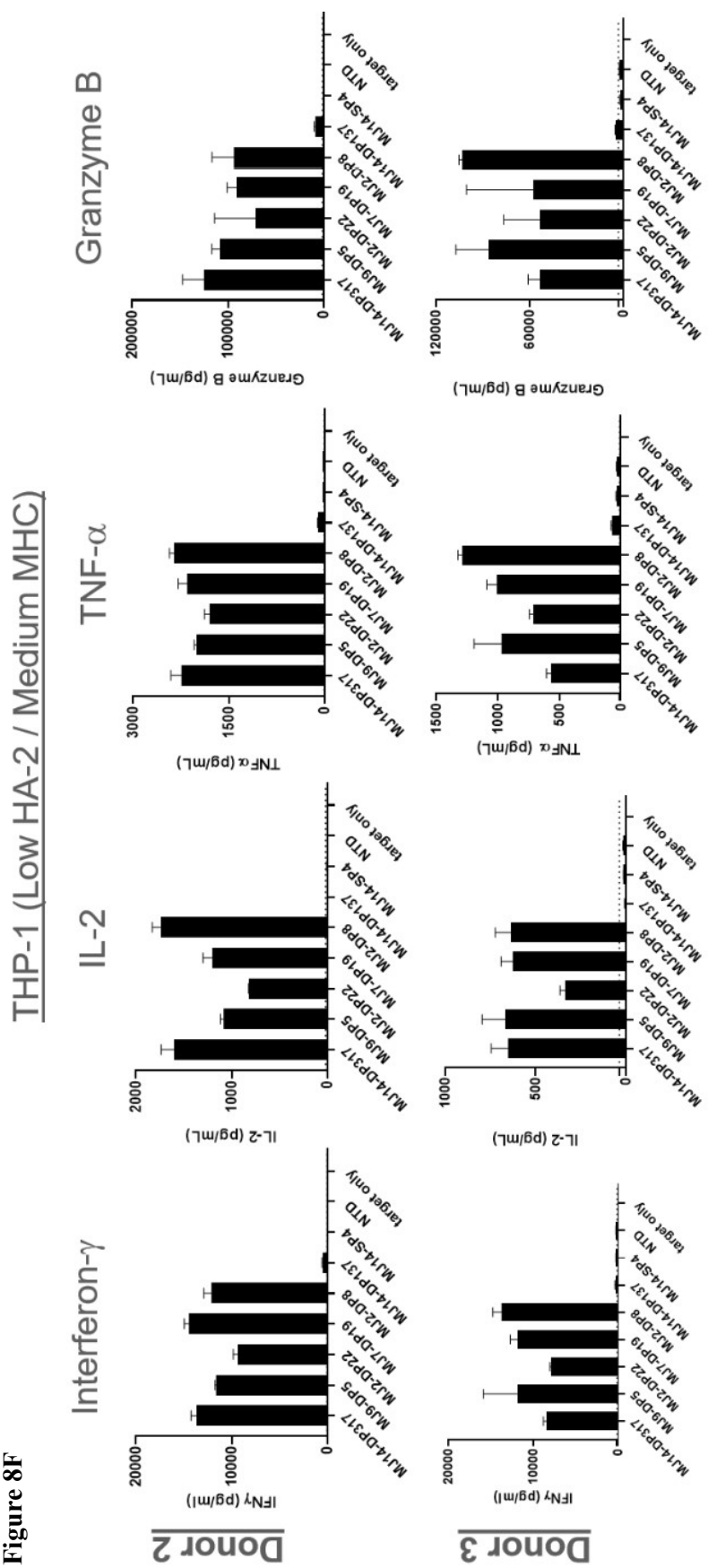

THP-1 (Low HA-2 / Medium MHC)
Interferon-γ
IL-2
TNF-α
Granzyme B
Donor 2
Donor 3
IFNγ (pg/ml)
IL-2 (pg/mL)
TNFα (pg/mL)
Granzyme B (pg/mL)
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD
target only

Figure 8F

Figure 8G

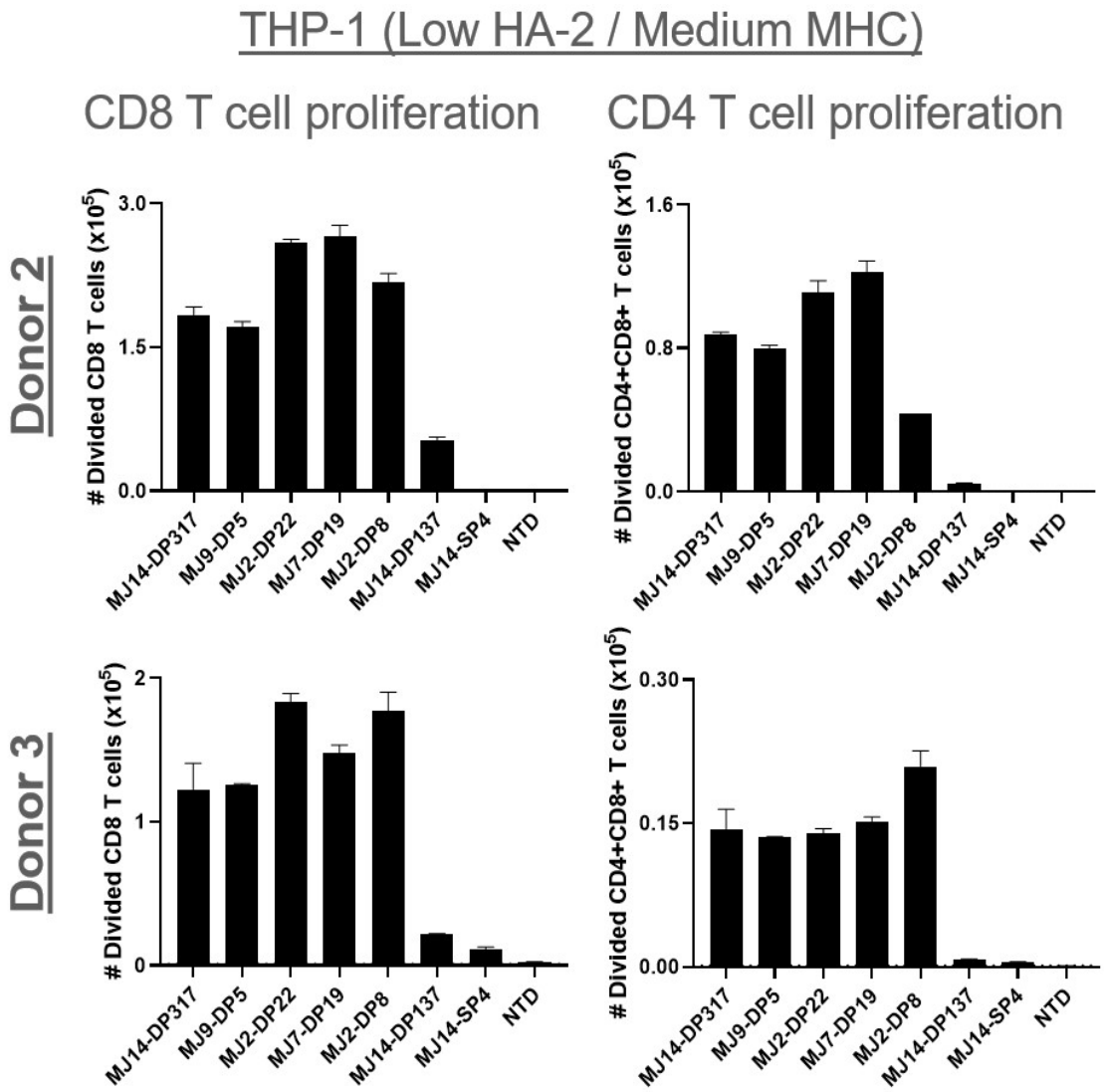
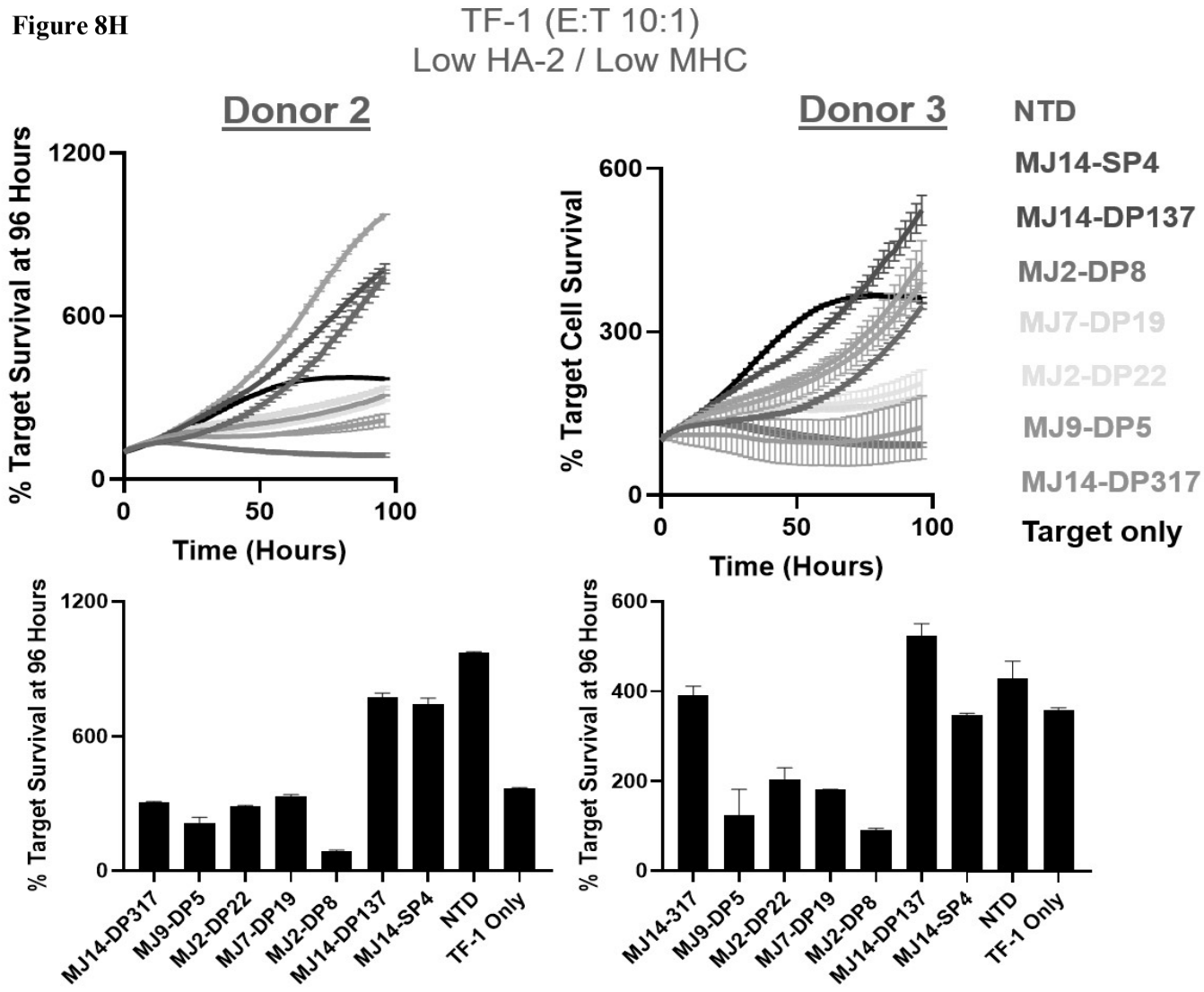

THP-1 (Low HA-2 / Medium MHC)
CD8 T cell proliferation
CD4 T cell proliferation
Donor 2
Donor 3
Divided CD8 T cells (x10^5)
Divided CD4+CD8+ T cells (x10^5)
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD

Figure 8H


TF-1 (E:T 10:1)
Low HA-2 / Low MHC
Donor 2
Donor 3
% Target Survival at 96 Hours
% Target Cell Survival
Time (Hours)
NTD
MJ14-SP4
MJ14-DP137
MJ2-DP8
MJ7-DP19
MJ2-DP22
MJ9-DP5
MJ14-DP317
Target only
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD
TF-1 Only
MJ14-317

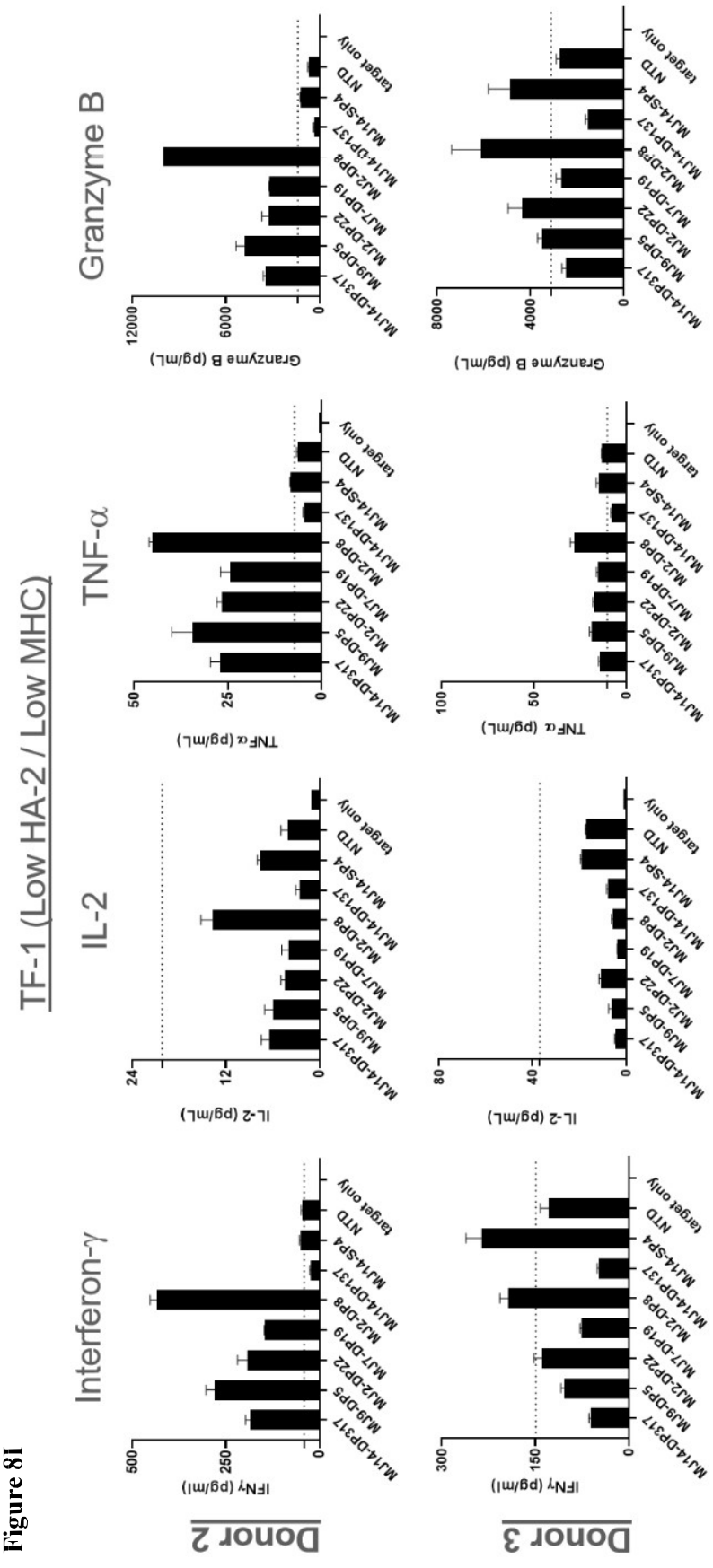

TF-1 (Low HA-2 / Low MHC)
Interferon-γ
IL-2
TNF-α
Granzyme B
Donor 2
Donor 3
IFNγ (pg/ml)
IL-2 (pg/mL)
TNFα (pg/mL)
Granzyme B (pg/mL)
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD
target only

Figure 8I

Figure 8J

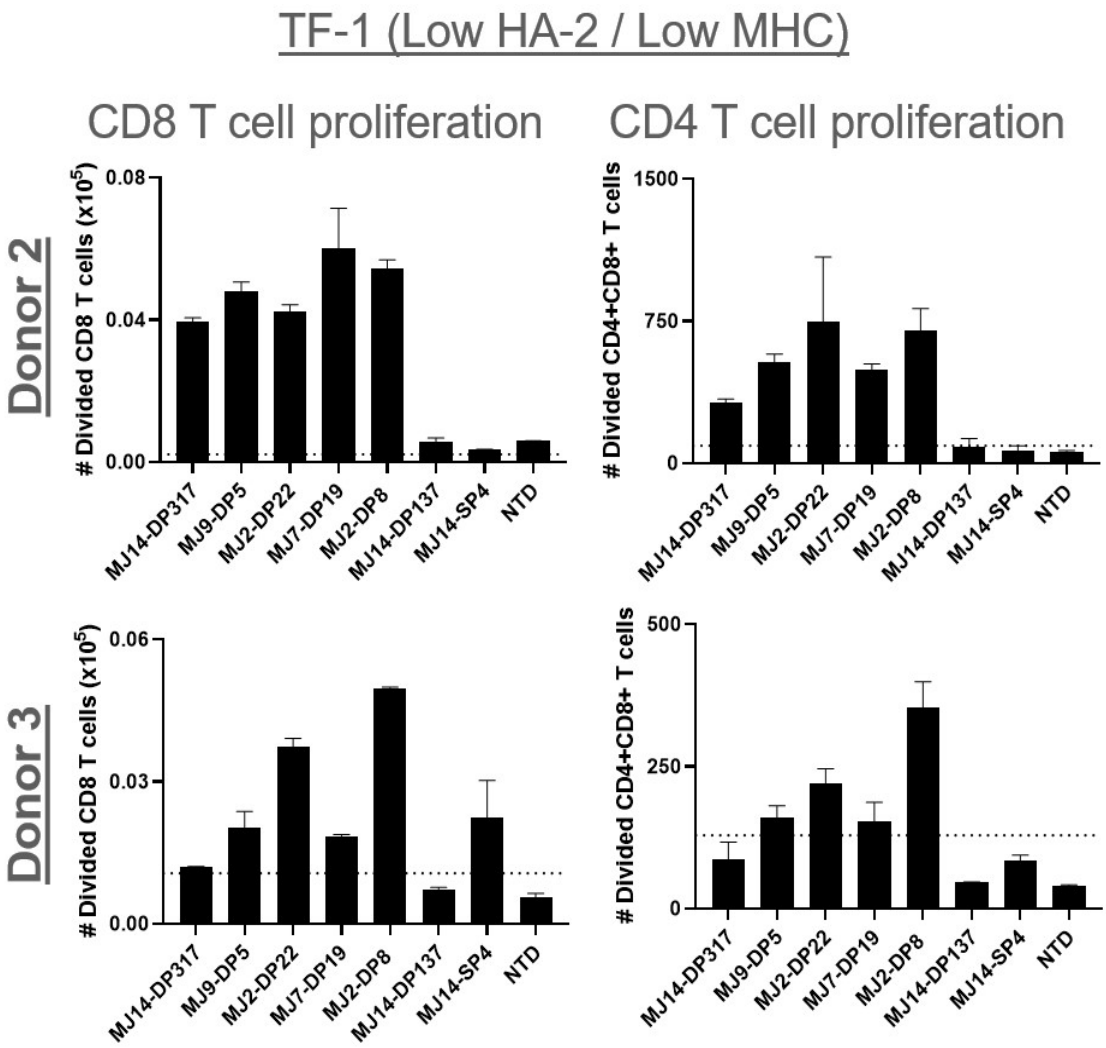
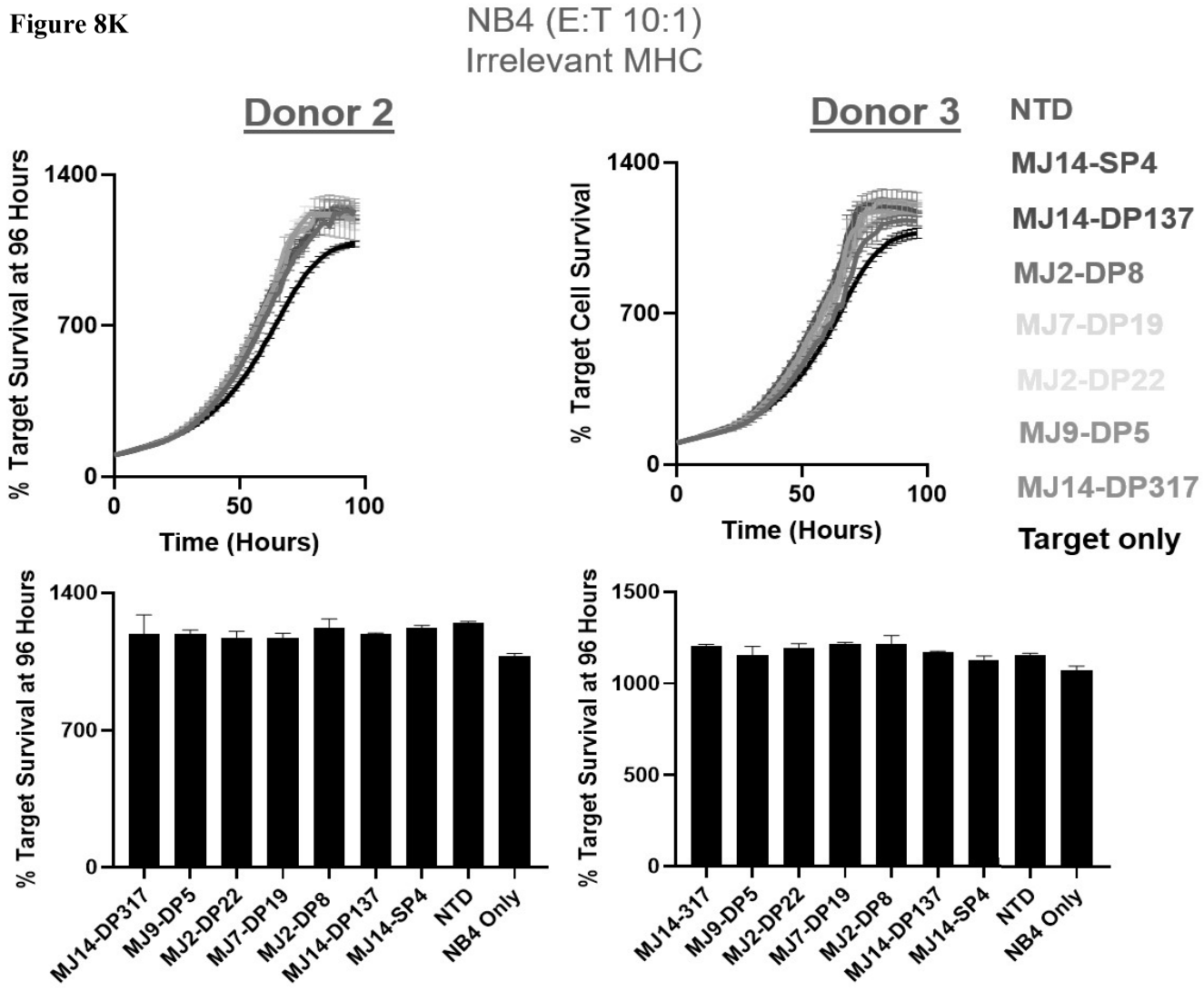

TF-1 (Low HA-2 / Low MHC)
CD8 T cell proliferation
CD4 T cell proliferation
Donor 2
Donor 3
Divided CD8 T cells (x10^5)
Divided CD4+CD8+ T cells
0.08
0.04
0.00
1500
750
0
0.06
0.03
500
250
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD

Figure 8K


NB4 (E:T 10:1)
Irrelevant MHC
Donor 2
Donor 3
% Target Survival at 96 Hours
% Target Cell Survival
Time (Hours)
NTD
MJ14-SP4
MJ14-DP137
MJ2-DP8
MJ7-DP19
MJ2-DP22
MJ9-DP5
MJ14-DP317
Target only
MJ14-DP317
MJ14-317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD
NB4 Only

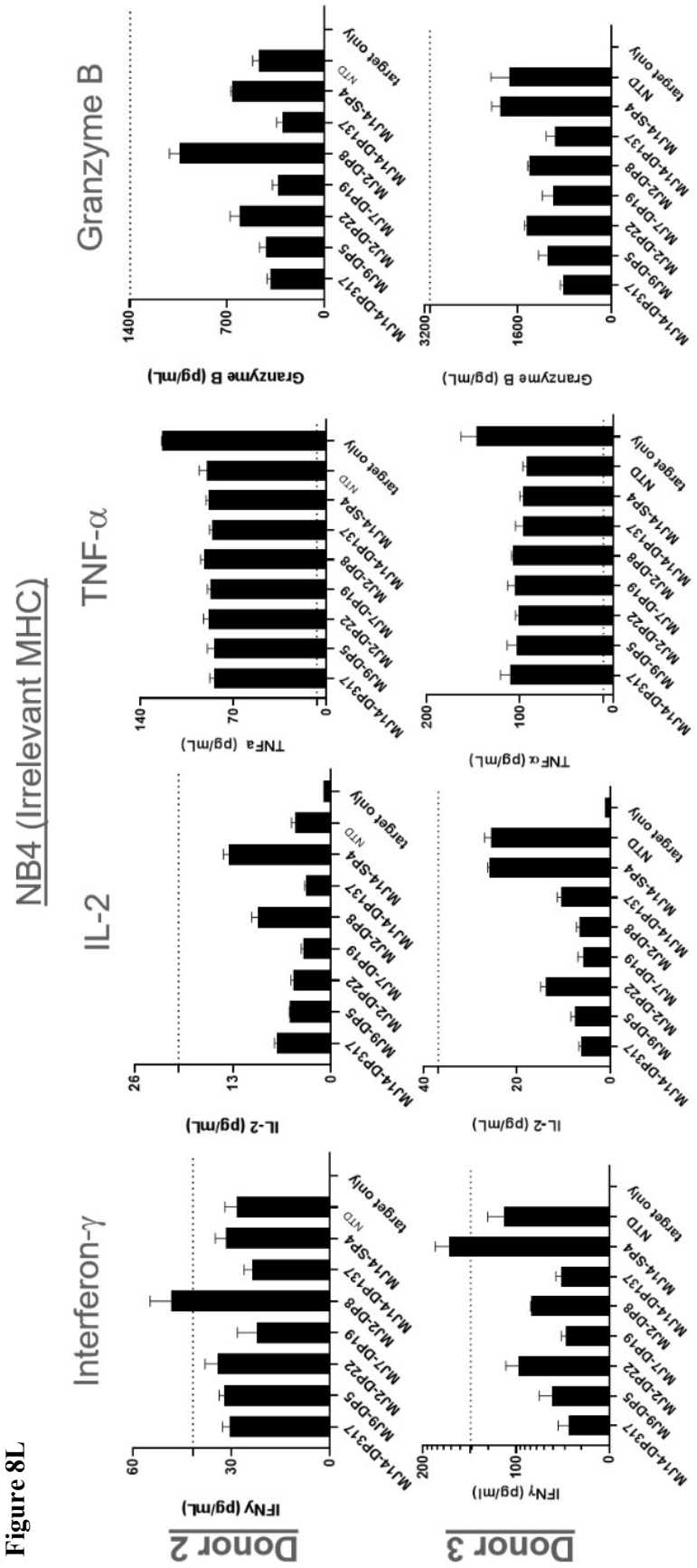

NB4 (Irrelevant MHC)
Interferon-γ
IL-2
TNF-α
Granzyme B
Donor 2
Donor 3
IFNγ (pg/mL)
IL-2 (pg/mL)
TNFa (pg/mL)
Granzyme B (pg/mL)
IFNγ (pg/ml)
TNFα (pg/mL)
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD
target only

Figure 8L

Figure 8M

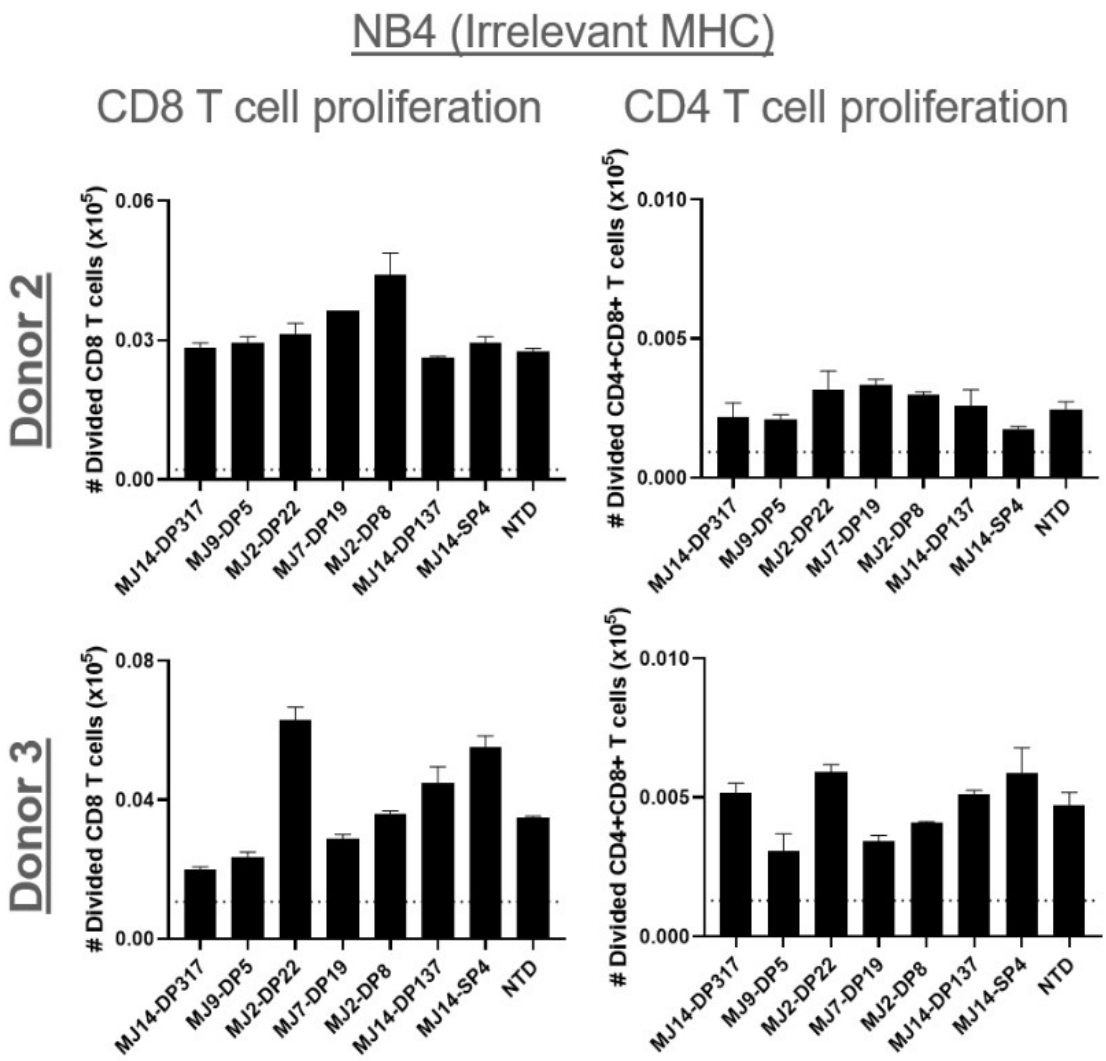

NB4 (Irrelevant MHC)
CD8 T cell proliferation
CD4 T cell proliferation
Donor 2
Donor 3
Divided CD8 T cells (x10^5)
Divided CD4+CD8+ T cells (x10^5)
0.06
0.03
0.00
0.010
0.005
0.000
0.08
0.04
MJ14-DP317
MJ9-DP5
MJ2-DP22
MJ7-DP19
MJ2-DP8
MJ14-DP137
MJ14-SP4
NTD

Figure 9

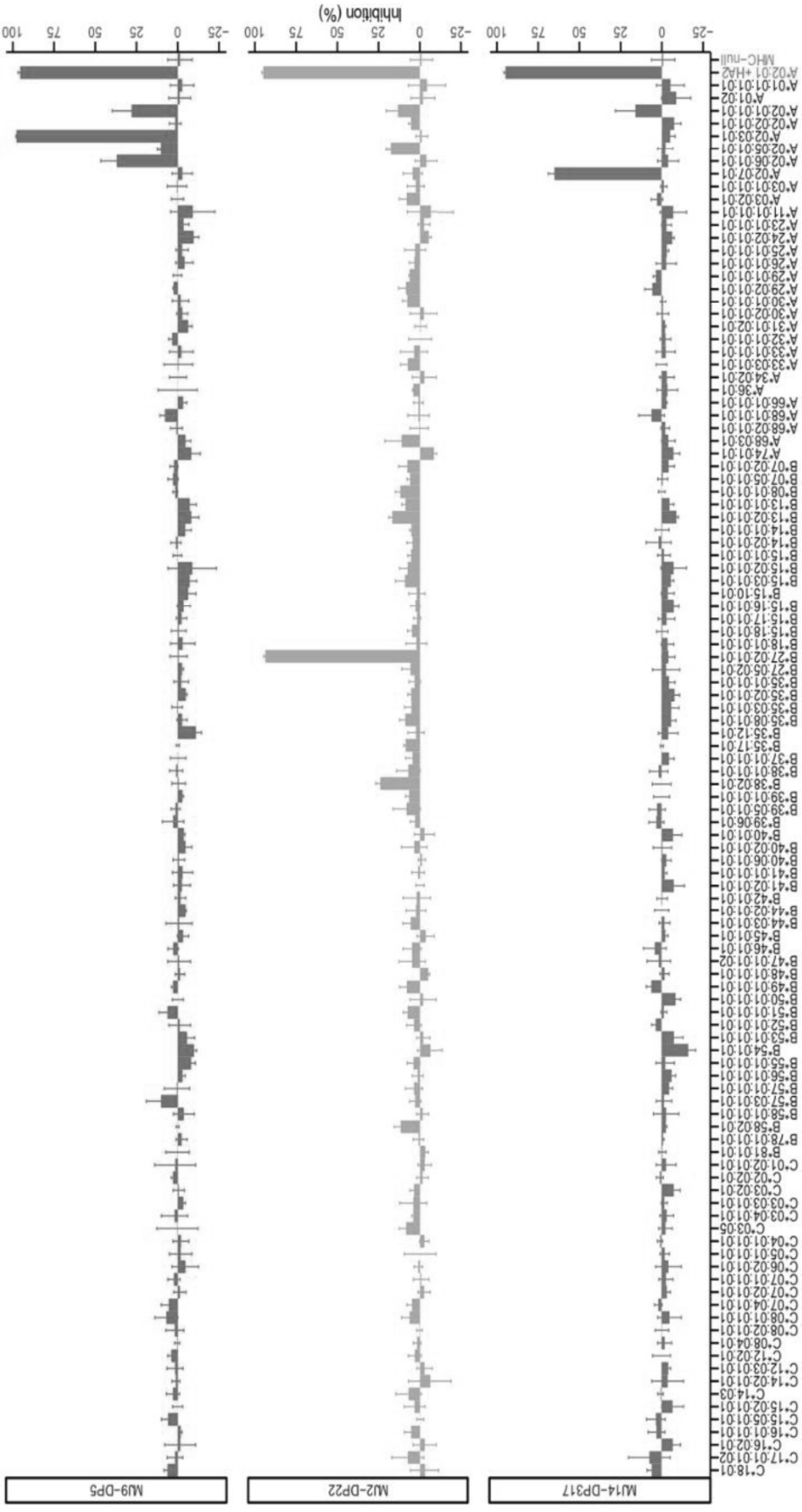

Inhibition (%)
-25
0
25
50
75
100
MJ14-DP317
MJ2-DP22
MJ9-DP5
MHC-null
A*02:01 +HA2
A*01:01:01:01
A*01:02
A*02:01:01:01
A*02:01:01:02
A*02:03:01
A*02:05:01:01
A*02:06:01:01
A*02:07:01
A*03:01:01:01
A*03:02:01
A*11:01:01:01
A*23:01:01:01
A*24:02:01:01
A*25:01:01:01
A*26:01:01:01
A*29:01:01:01
A*29:02:01:01
A*30:01:01:01
A*30:02:01:01
A*31:01:02:01
A*32:01:01:01
A*33:01:01:01
A*33:03:01:01
A*34:02:01
A*36:01
A*66:01:01:01
A*68:01:01:01
A*68:02:01:01
A*68:03:01
A*74:01:01
B*07:02:01:01
B*07:05:01:01
B*08:01:01:01
B*13:01:01:01
B*13:02:01:01
B*14:01:01:01
B*14:02:01:01
B*15:01:01:01
B*15:02:01:01
B*15:03:01:01
B*15:10:01
B*15:16:01:01
B*15:17:01:01
B*15:18:01:01
B*18:01:01:01
B*27:02:01:01
B*27:05:02:01
B*35:01:01:01
B*35:02:01:01
B*35:03:01:01
B*35:08:01:01
B*35:12:01
B*35:17:01
B*37:01:01:01
B*38:01:01:01
B*38:02:01
B*39:01:01:01
B*39:05:01:01
B*39:06:01
B*40:01:01
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B*58:02:01
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C*01:02:01:01
C*02:02:01
C*03:02:01
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C*14:03
C*15:02:01:01
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C*16:02:01
C*17:01:01:02
C*18:01

Figure 10A

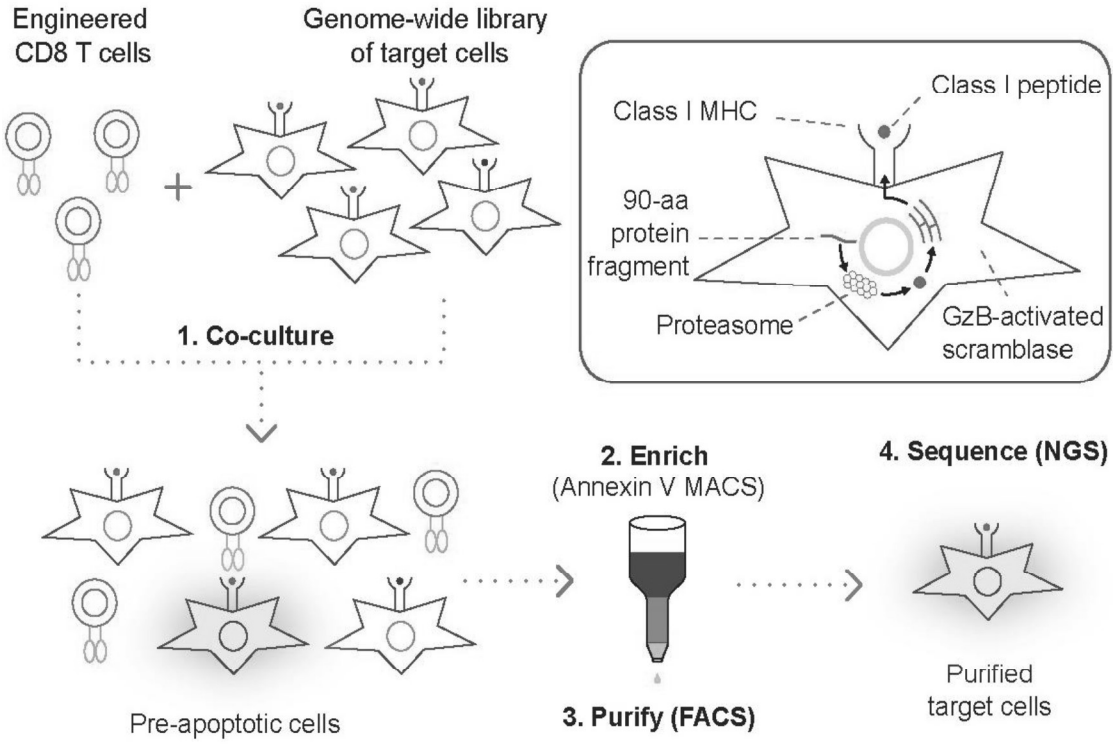


Figure 10B

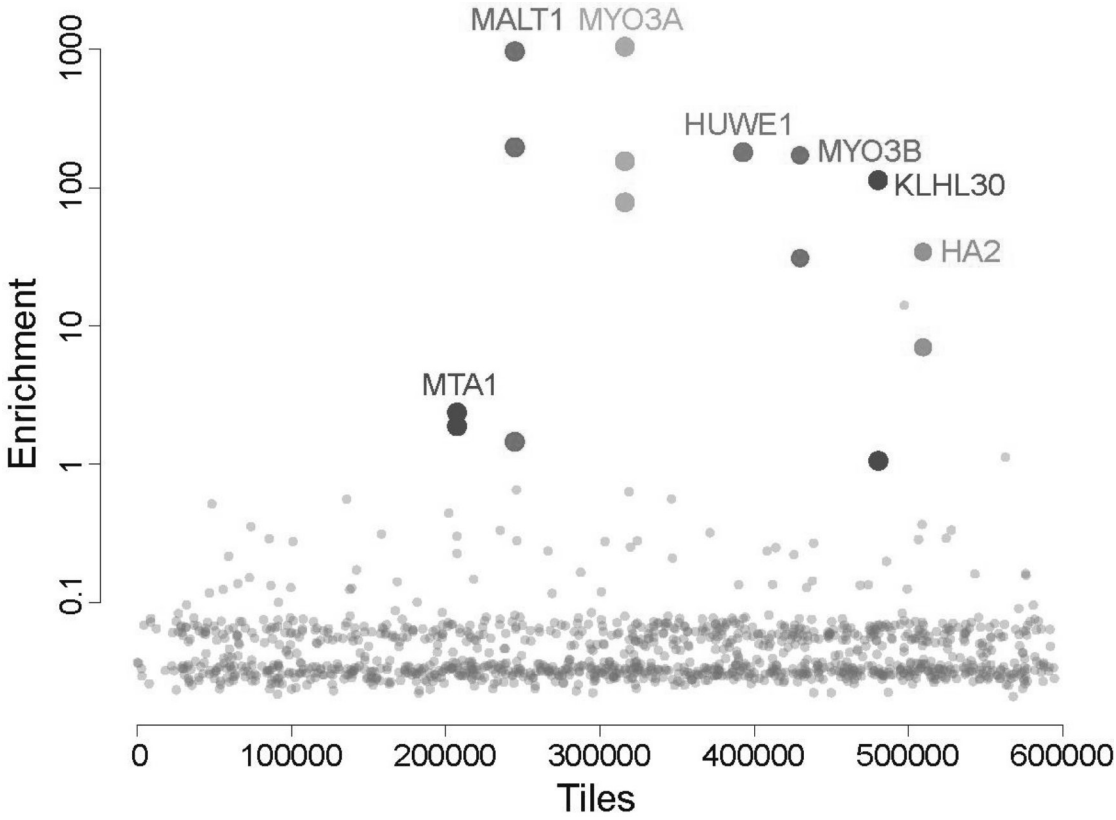


Figure 11A

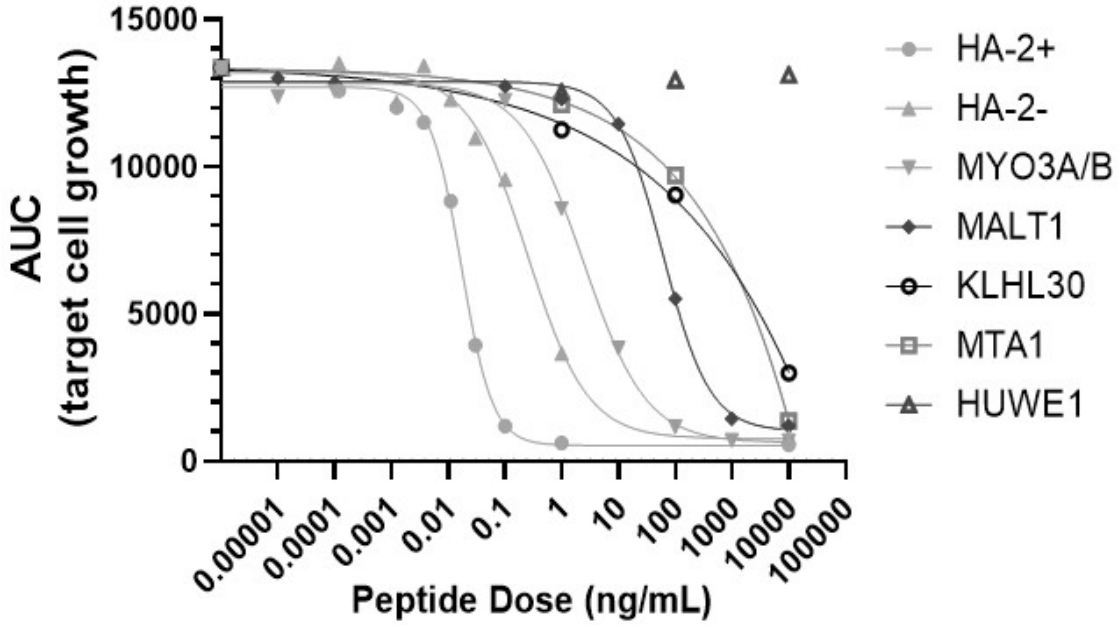


Figure 11B

Peptide	EC_{50} (pg/mL)	R^2
HA-2$^+$	17.06	0.997
HA-2$^-$	251.50	0.991
MYO3A/B	2,450	0.997
MALT1	62,160	0.998
KLHL30	n/a	n/a
MTA1	n/a	n/a
HUWE1	n/a	n/a

Figure 12A

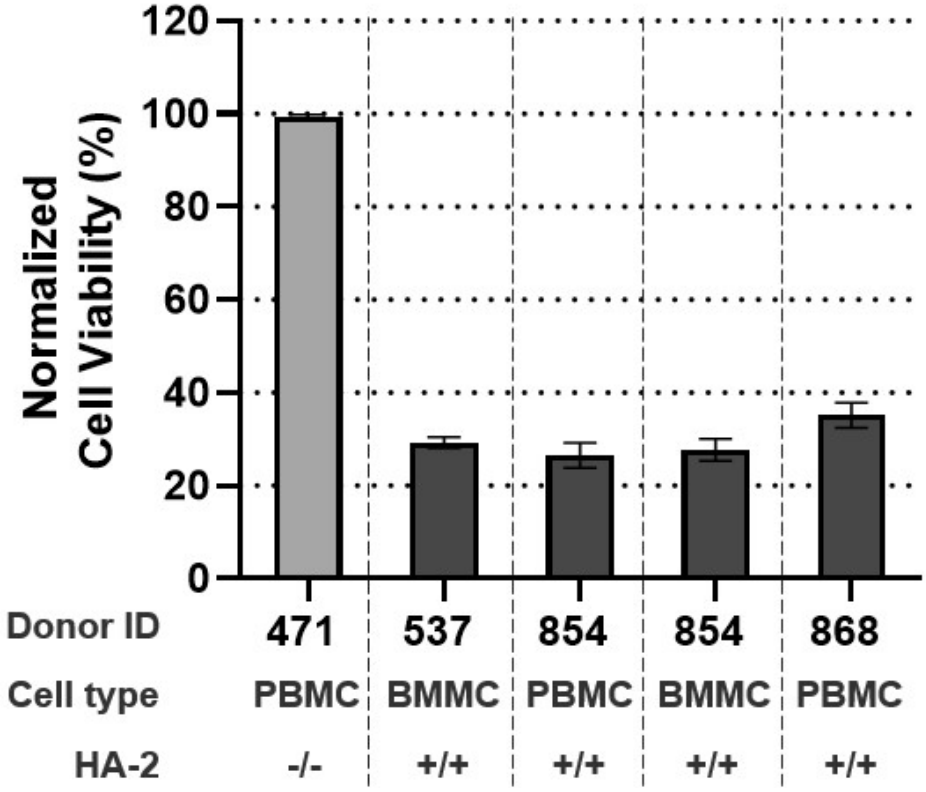


Figure 12B

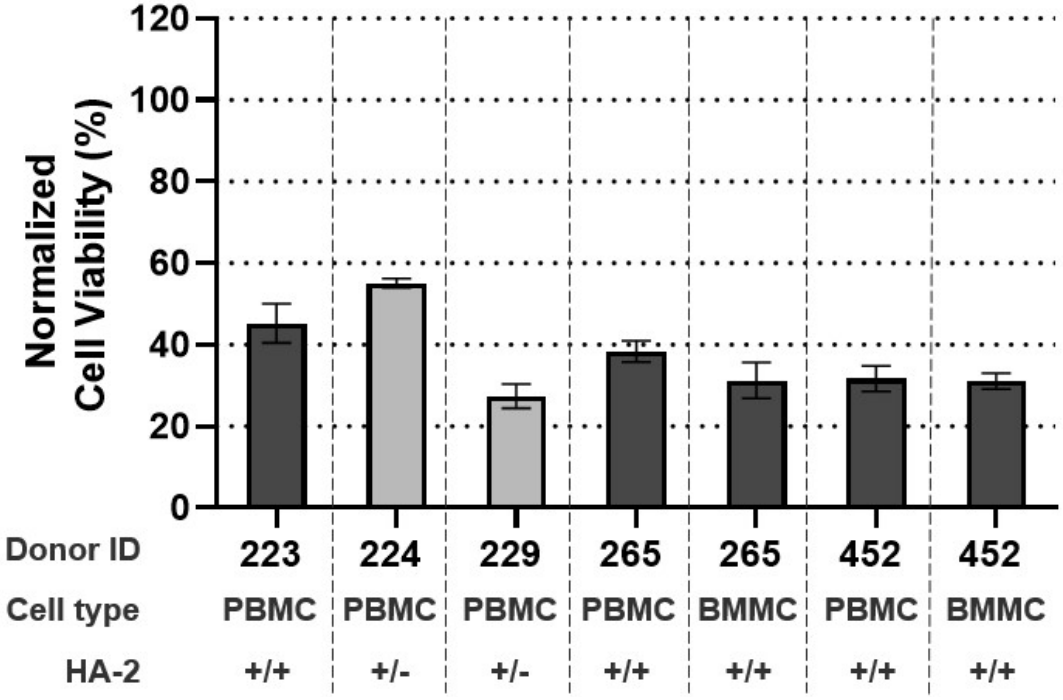


Figure 13

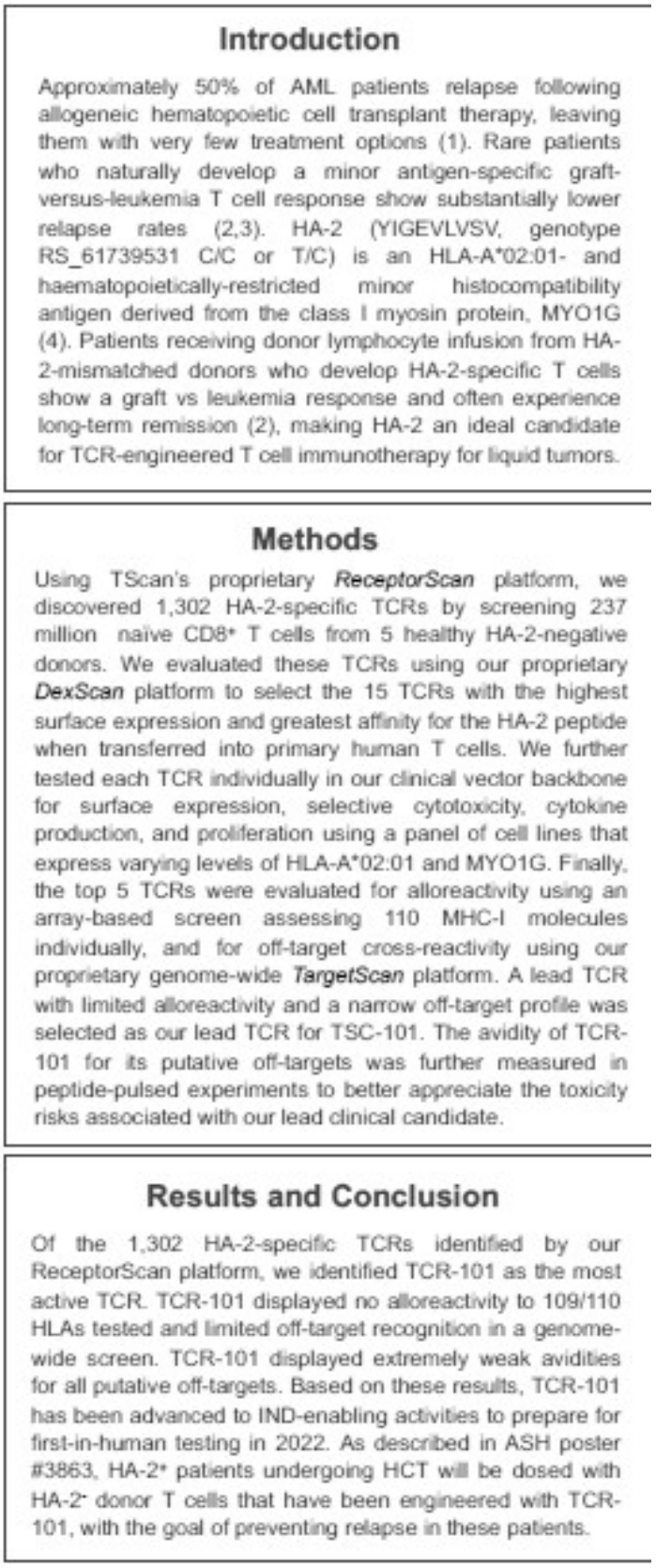
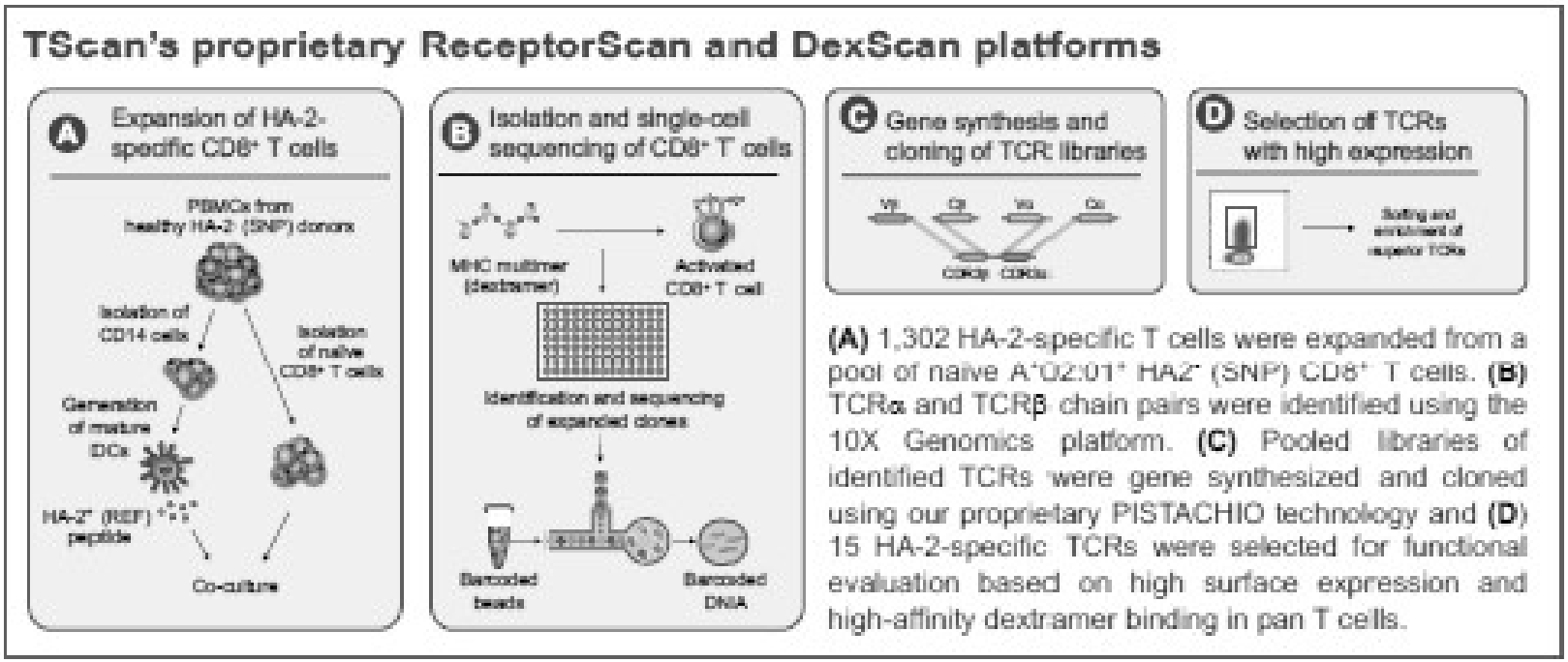

Introduction
Approximately 50% of AML patients relapse following allogeneic hematopoietic cell transplant therapy, leaving them with very few treatment options (1). Rare patients who naturally develop a minor antigen-specific graft-versus-leukemia T cell response show substantially lower relapse rates (2,3). HA-2 (YIGEVLVSV, genotype RS_61739531 C/C or T/C) is an HLA-A*02:01- and haematopoietically-restricted minor histocompatibility antigen derived from the class I myosin protein, MYO1G (4). Patients receiving donor lymphocyte infusion from HA-2-mismatched donors who develop HA-2-specific T cells show a graft vs leukemia response and often experience long-term remission (2), making HA-2 an ideal candidate for TCR-engineered T cell immunotherapy for liquid tumors.
Methods
Using TScan's proprietary ReceptorScan platform, we discovered 1,302 HA-2-specific TCRs by screening 237 million naïve CD8+ T cells from 5 healthy HA-2-negative donors. We evaluated these TCRs using our proprietary DexScan platform to select the 15 TCRs with the highest surface expression and greatest affinity for the HA-2 peptide when transferred into primary human T cells. We further tested each TCR individually in our clinical vector backbone for surface expression, selective cytotoxicity, cytokine production, and proliferation using a panel of cell lines that express varying levels of HLA-A*02:01 and MYO1G. Finally, the top 5 TCRs were evaluated for alloreactivity using an array-based screen assessing 110 MHC-I molecules individually, and for off-target cross-reactivity using our proprietary genome-wide TargetScan platform. A lead TCR with limited alloreactivity and a narrow off-target profile was selected as our lead TCR for TSC-101. The avidity of TCR-101 for its putative off-targets was further measured in peptide-pulsed experiments to better appreciate the toxicity risks associated with our lead clinical candidate.
Results and Conclusion
Of the 1,302 HA-2-specific TCRs identified by our ReceptorScan platform, we identified TCR-101 as the most active TCR. TCR-101 displayed no alloreactivity to 109/110 HLAs tested and limited off-target recognition in a genome-wide screen. TCR-101 displayed extremely weak avidities for all putative off-targets. Based on these results, TCR-101 has been advanced to IND-enabling activities to prepare for first-in-human testing in 2022. As described in ASH poster #3863, HA-2+ patients undergoing HCT will be dosed with HA-2- donor T cells that have been engineered with TCR-101, with the goal of preventing relapse in these patients.

Figure 13 (cont.)



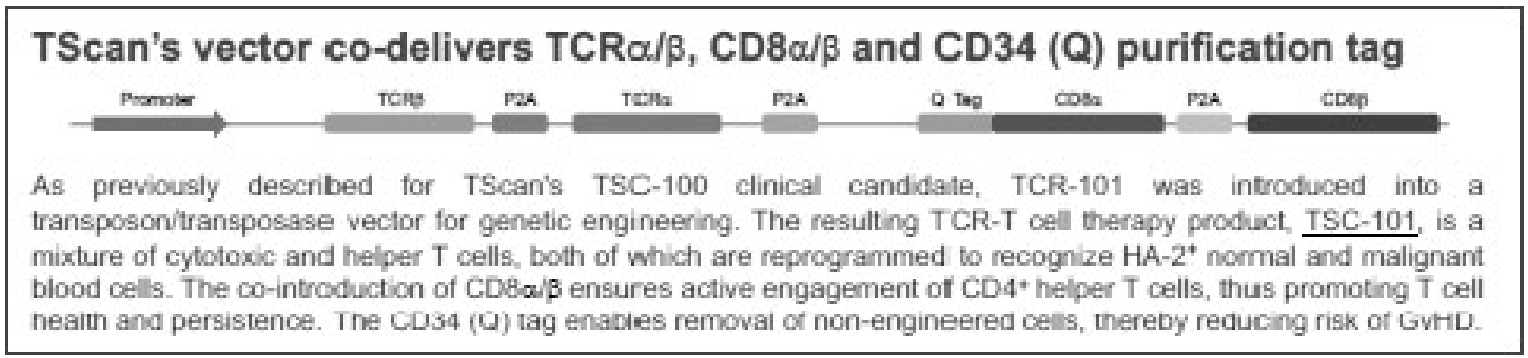
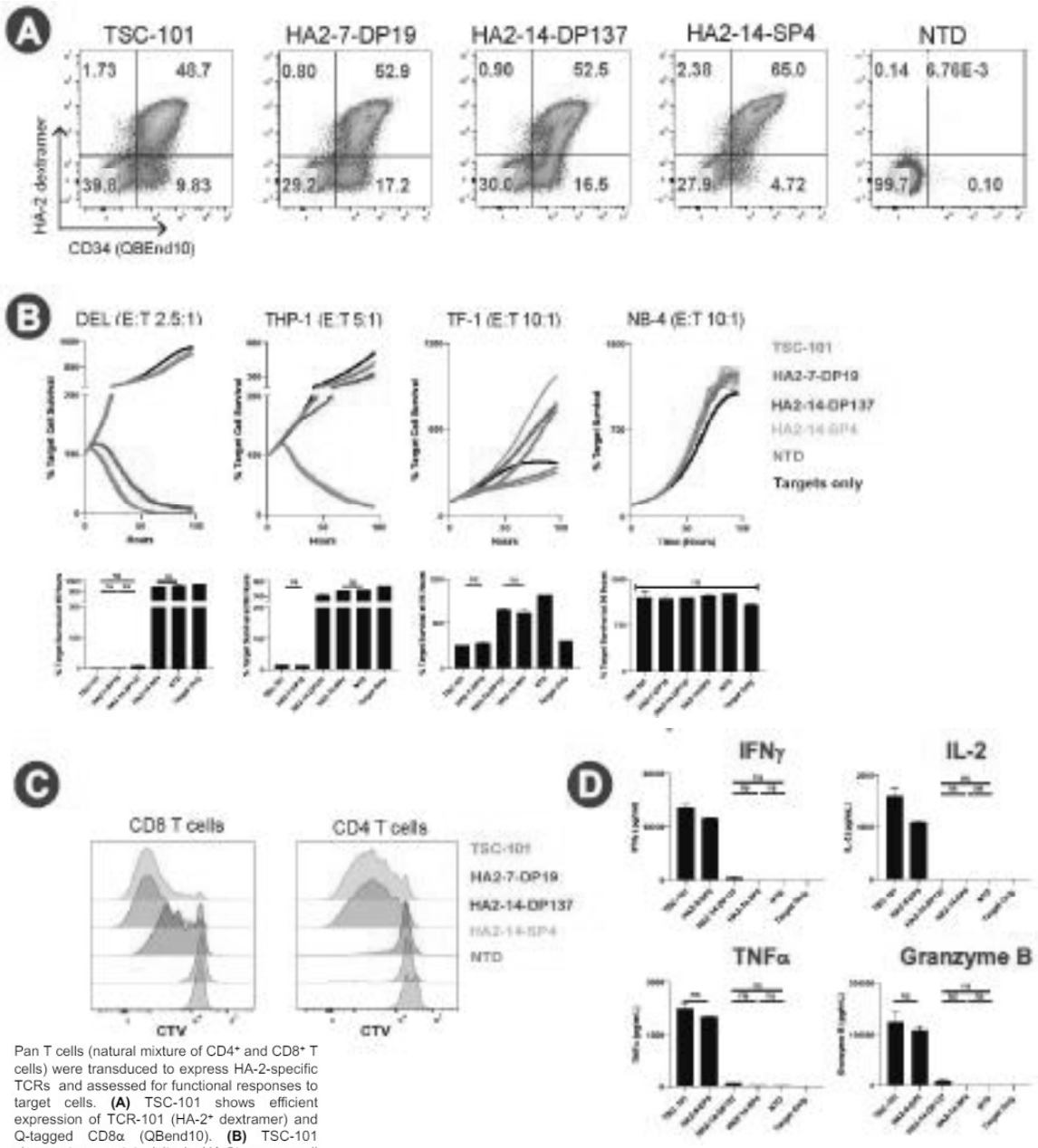


Figure 13 (cont.)



Pan T cells (natural mixture of CD4⁺ and CD8⁺ T cells) were transduced to express HA-2-specific TCRs and assessed for functional responses to target cells. **(A)** TSC-101 shows efficient expression of TCR-101 (HA-2⁺ dextramer) and Q-tagged CD8α (QBend10). **(B)** TSC-101 shows strong cytotoxicity in HA-2⁺ cancer cell lines. DEL (HLA-A*02:01^{high}/HA-2^{high}), THP-1 (HLA-A*02:01^{high}/HA-2^{low}), TF-1 (HLA-A*02:01^{low}/HA-2^{low}), NB4 (HLA-A*02:01^{negative}). **(C)** TSC-101 exhibits HA-2-specific CD8⁺ and CD4⁺ T cell proliferation when co-cultured with HA-2⁺ THP-1 cells. Histograms show dilution of Cell Trace Violet dye used to label T cells. **(D)** TSC-101 efficiently secretes cytokines when co-cultured with THP-1 cells. Different HA-2-specific TCRs were compared by one-way ANOVA followed by Tukey's multiple comparisons test, in which each TCR was compared to every other TCR. Differences that were non-significant (ns) are shown; all other differences were significant with $P<0.05$. Data are representative of 2-3 unique donors.

Figure 13 (cont.)

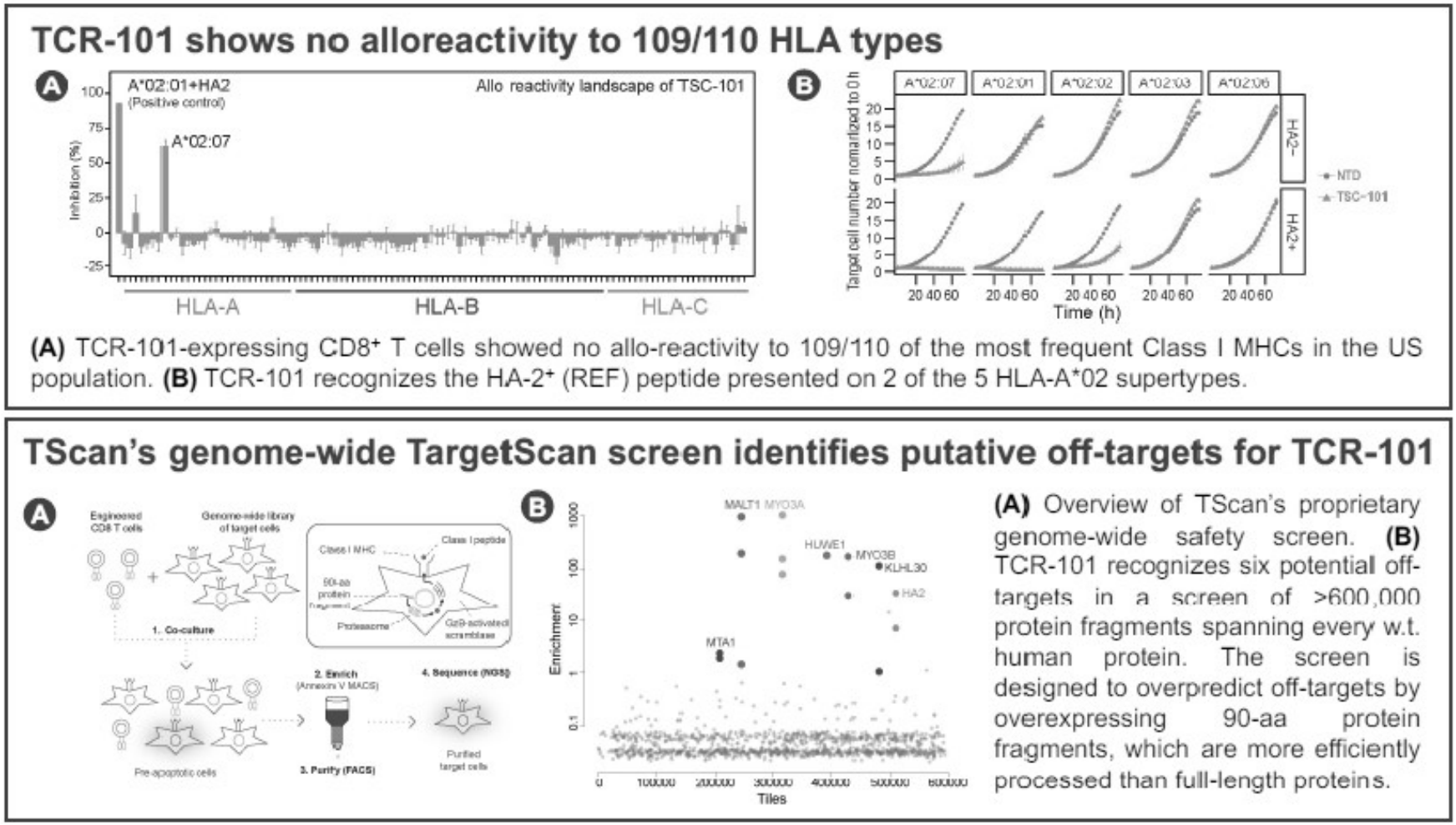
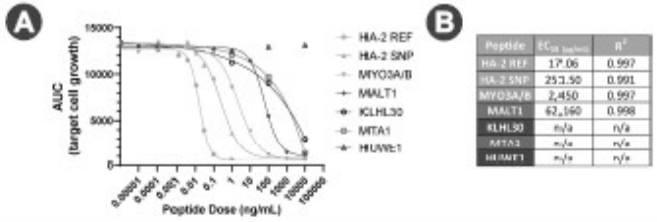


Figure 13 (cont.)

TSC-101 displays >100-3,000-fold lower affinity for putative off-target peptides

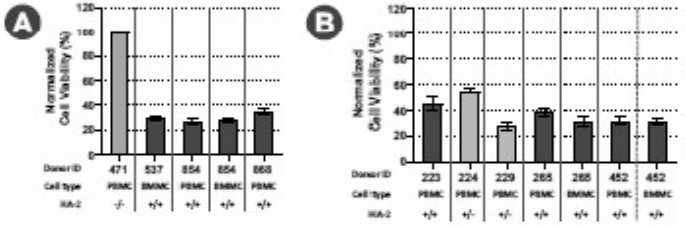


B

Peptide	EC_{50} (pg/mL)	R^2
HA-2 REF	17.06	0.997
HA-2 SNP	253.50	0.991
MYO3A/B	2,450	0.997
MALT1	62,160	0.998
KLHL30	n/a	n/a
MTA1	n/a	n/a
HUWE1	n/a	n/a

(A) The affinity of TCR-101 for on- and off-target peptides was measured by calculating Area under the curve (AUC) for T2 cell growth as a function of peptide dose. **(B)** Individual EC_{50} values for HA-2$^+$ REF peptide, HA-2$^-$ SNP peptide, putative off-target MYO3A/B and MALT1 peptides are shown. 3-point titration did not enable the calculation of the EC_{50} values for MTA1, KLHL30 and HUWE1.

TSC-101 exhibits robust cytotoxicity against primary AML and ALL tumor samples



TSC-101 and nonengineered control (NC) T cells were co-cultured for 20 h with HLA-A*02:01-positive PBMCs or BMMCs from **(A)** AML or **(B)** ALL patients at an E:T of 10:1. The viability of targets upon coculture with TSC-101 T cells was then assessed by flow cytometry and normalized to the viability of targets upon coculture with NC. Data are representative of 3 donors.

Summary and Next Steps

Therapeutic TCRs for TCR-T must exhibit high affinity for their targets but low recognition of off-targets. By screening 237 million naïve T cells from five HA-2-negative donors, we isolated an ultrahigh affinity TCR (EC_{50} = 17 pg/mL) that does not recognize off-targets with appreciable affinity. Using a nonviral vector, we developed an enhanced T cell product comprising both cytotoxic and helper T cells derived from HLA-A*02:01-negative donors. TSC-101 is being advanced to clinical development to prevent relapse in patients with AML, MDS, and ALL undergoing HCT (see ASH 2021 poster #3863).

References

1. Rautenberg C., Germing U., Haas R. *et al. Int. J. Mol. Sci.,* 2019, **20**, 228.
2. Marijt W. A. E., Heemskerk M. H. M, Kloosterboer F. M. *et al. Proc Natl Acad Sci USA,* 2003, **100,** 2742-2747.
3. Spierings E., Kim Y., Hendriks M. *et al. Biol Blood Marrow Transplant,* 2013, **19,** 1244-1253.
4. Pierce R.A., Field E.D., Mutis T. *et al. J. Immunol.* 2001, **167**, 3223-3230.

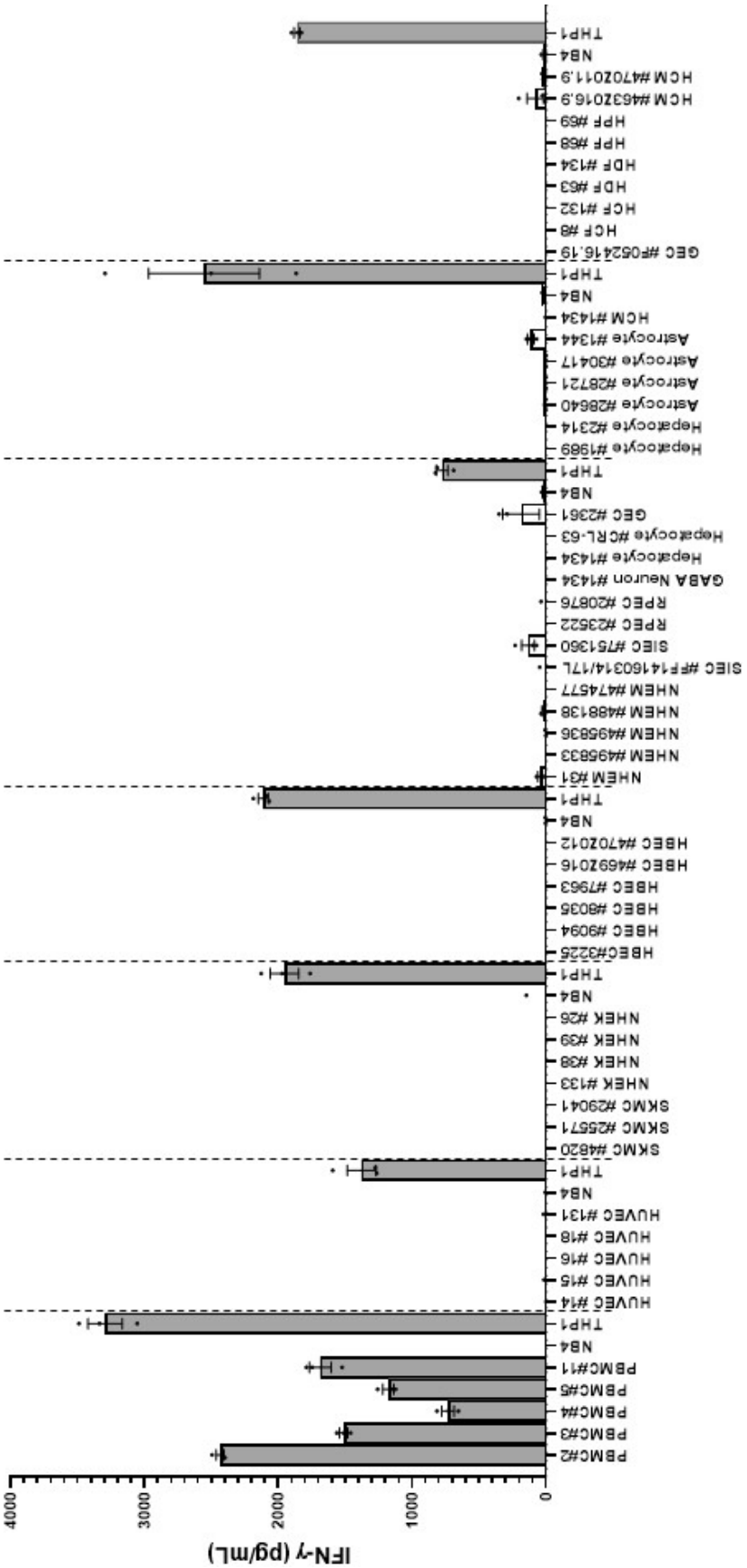

IFN-γ (pg/mL)
4000
3000
2000
1000
0
PBMC#2
PBMC#3
PBMC#4
PBMC#5
PBMC#11
NB4
THP1
HUVEC #14
HUVEC #15
HUVEC #16
HUVEC #18
HUVEC #131
NB4
THP1
SKMC #4820
SKMC #25571
SKMC #29041
NHEK #133
NHEK #38
NHEK #39
NHEK #25
NB4
THP1
HBEC#3225
HBEC #9094
HBEC #8035
HBEC #7963
HBEC #6920l6
HBEC #4702012
NB4
THP1
NHEM #31
NHEM #495833
NHEM #495836
NHEM #488138
NHEM #474577
SIEC #FF14160314/17L
SIEC #751360
RPEC #23522
RPEC #20876
GABA Neuron #1434
Hepatocyte #1434
Hepatocyte #CRL-63
GEC #2361
NB4
THP1
Hepatocyte #1989
Hepatocyte #2314
Astrocyte #28640
Astrocyte #28721
Astrocyte #30417
Astrocyte #1344
HCM #1434
NB4
THP1
GEC #F052416.19
HCF #8
HCF #132
HDF #63
HDF #134
HPF #68
HPF #69
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HCM #4702011.9
NB4
THP1

Figure 14A

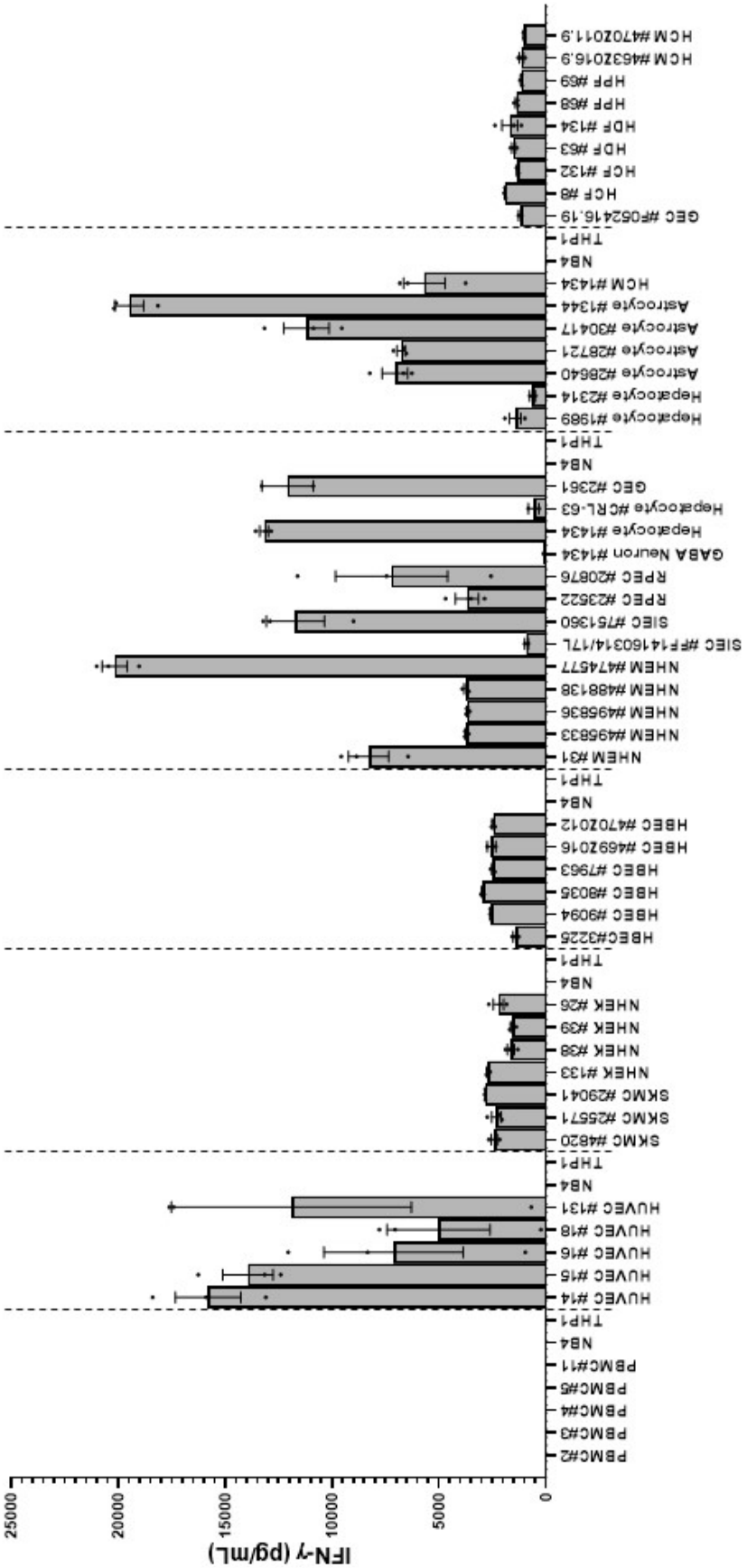

IFN-γ (pg/mL)
25000
20000
15000
10000
5000
0
PBMC#2
PBMC#3
PBMC#4
PBMC#5
PBMC#11
NB4
THP1
HUVEC #14
HUVEC #15
HUVEC #16
HUVEC #18
HUVEC #131
NB4
THP1
SKMC #4820
SKMC #25571
SKMC #29041
NHEK #133
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NB4
THP1
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NB4
THP1
NHEM #31
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NHEM #495836
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NHEM #474577
SIEC #FF14160314/17L
SIEC #751360
RPEC #23522
RPEC #20876
GABA Neuron #1434
Hepatocyte #1434
Hepatocyte #CRL-63
GEC #2361
NB4
THP1
Hepatocyte #1989
Hepatocyte #2314
Astrocyte #28640
Astrocyte #28721
Astrocyte #30417
Astrocyte #1344
HCM #1434
NB4
THP1
GEC #F052416.19
HCF #8
HCF #132
HDF #63
HDF #134
HPF #68
HPF #69
HCM #463Z016.9
HCM #470Z011.9

Figure 14B

SEQUENCE LISTING

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<120> BINDING PROTEINS RECOGNIZING HA-2 ANTIGEN AND USES THEREOF

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<140> PCT/US2022/024725
<141> 2022-04-14

<150> 63/329,560
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<150> 63/288,078
<151> 2021-12-10

<150> 63/215,760
<151> 2021-06-28

<150> 63/174,818
<151> 2021-04-14

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1 5 10 15

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20 25 30

Val Gln Glu Gly Lys Asn Leu Thr Ile Asn Cys Thr Ser Ser Lys Thr
35 40 45

```
Leu Tyr Gly Leu Tyr Trp Tyr Lys Gln Lys Tyr Gly Glu Gly Leu Ile
    50                  55                  60

Phe Leu Met Met Leu Gln Lys Gly Gly Glu Glu Lys Ser His Glu Lys
65                  70                  75                  80

Ile Thr Ala Lys Leu Asp Glu Lys Lys Gln Gln Ser Ser Leu His Ile
                85                  90                  95

Thr Ala Ser Gln Pro Arg His Ala Gly Ile Tyr Leu Cys Gly Ala Arg
            100                 105                 110

Lys Lys Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
        115                 120                 125

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
    130                 135                 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145                 150                 155                 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
                165                 170                 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
```

180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg
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polypeptide

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            20                  25                  30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
        35                  40                  45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
    50                  55                  60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
                85                  90                  95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
            100                 105                 110

Ser Ser Ser Gly Pro Thr Ser Pro Gln His Phe Gly Asp Gly Thr Arg
        115                 120                 125
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Leu Ser Ile Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala
130 135 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
145 150 155 160

Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser
165 170 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro
180 185 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
195 200 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
210 215 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225 230 235 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
245 250 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln

260 265 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
275 280 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
290 295 300

Lys Arg Lys Asp Phe
305

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1 5 10 15

Ala Trp Val Ser Ser Gln Glu Leu Glu Gln Ser Pro Gln Ser Leu Ile
20 25 30

Val Gln Glu Gly Lys Asn Leu Thr Ile Asn Cys Thr Ser Ser Lys Thr

35 40 45

Leu Tyr Gly Leu Tyr Trp Tyr Lys Gln Lys Tyr Gly Glu Gly Leu Ile
50 55 60

Phe Leu Met Met Leu Gln Lys Gly Gly Glu Glu Lys Ser His Glu Lys
65 70 75 80

Ile Thr Ala Lys Leu Asp Glu Lys Lys Gln Gln Ser Ser Leu His Ile
85 90 95

Thr Ala Ser Gln Pro Arg His Ala Gly Ile Tyr Leu Cys Gly Ala Arg
100 105 110

Lys Lys Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
115 120 125

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
130 135 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145 150 155 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 6
<211> 309
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 6

Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Ser Gly Pro Thr Ser Pro Gln His Phe Gly Asp Gly Thr Arg

115 120 125

Leu Ser Ile Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala
130 135 140

Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr
145 150 155 160

Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser
165 170 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro
180 185 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
195 200 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
210 215 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225 230 235 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
245 250 255

Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln
260 265 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
275 280 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
290 295 300

Lys Arg Lys Asp Phe
305

<210> 7
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 7
Met Lys Ser Leu Arg Val Leu Leu Val Ile Leu Trp Leu Gln Leu Ser
1 5 10 15

Trp Val Trp Ser Gln Gln Lys Glu Val Glu Gln Asn Ser Gly Pro Leu
20 25 30

```
Ser Val Pro Glu Gly Ala Ile Ala Ser Leu Asn Cys Thr Tyr Ser Asp
        35                  40                  45

Arg Gly Ser Gln Ser Phe Phe Trp Tyr Arg Gln Tyr Ser Gly Lys Ser
    50                  55                  60

Pro Glu Leu Ile Met Phe Ile Tyr Ser Asn Gly Asp Lys Glu Asp Gly
65                  70                  75                  80

Arg Phe Thr Ala Gln Leu Asn Lys Ala Ser Gln Tyr Val Ser Leu Leu
                85                  90                  95

Ile Arg Asp Ser Gln Pro Ser Asp Ser Ala Thr Tyr Leu Cys Ala Val
            100                 105                 110

Asn Lys Gly Gly Gly Thr Ser Tyr Gly Lys Leu Thr Phe Gly Gln Gly
        115                 120                 125

Thr Ile Leu Thr Val His Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
    130                 135                 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145                 150                 155                 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
```

165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 8
<211> 308
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 8

Met Gly Pro Gln Leu Leu Gly Tyr Val Val Leu Cys Leu Leu Gly Ala
1 5 10 15

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

Val Thr Gly Lys Lys Leu Thr Val Thr Cys Ser Gln Asn Met Asn His
35 40 45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Gln
50 55 60

Ile Tyr Tyr Ser Met Asn Val Glu Val Thr Asp Lys Gly Asp Val Pro
65 70 75 80

Glu Gly Tyr Lys Val Ser Arg Lys Glu Lys Arg Asn Phe Pro Leu Ile
85 90 95

Leu Glu Ser Pro Ser Pro Asn Gln Thr Ser Leu Tyr Phe Cys Ala Ser
100 105 110

```
Ser Trp Thr Leu Asn Thr Glu Ala Phe Phe Gly Gln Gly Thr Arg Leu
        115                 120                 125

Thr Val Val Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val
    130                 135                 140

Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu
145                 150                 155                 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
                165                 170                 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
            180                 185                 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
        195                 200                 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
    210                 215                 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225                 230                 235                 240

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
```

245 250 255

Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Phe
305

<210> 9
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 9
Met Lys Ser Leu Arg Val Leu Leu Val Ile Leu Trp Leu Gln Leu Ser
1 5 10 15

Trp Val Trp Ser Gln Gln Lys Glu Val Glu Gln Asn Ser Gly Pro Leu

```
            20                  25                  30

Ser Val Pro Glu Gly Ala Ile Ala Ser Leu Asn Cys Thr Tyr Ser Asp
        35                  40                  45

Arg Gly Ser Gln Ser Phe Phe Trp Tyr Arg Gln Tyr Ser Gly Lys Ser
    50                  55                  60

Pro Glu Leu Ile Met Phe Ile Tyr Ser Asn Gly Asp Lys Glu Asp Gly
65                  70                  75                  80

Arg Phe Thr Ala Gln Leu Asn Lys Ala Ser Gln Tyr Val Ser Leu Leu
                85                  90                  95

Ile Arg Asp Ser Gln Pro Ser Asp Ser Ala Thr Tyr Leu Cys Ala Val
            100                 105                 110

Asn Lys Gly Gly Gly Thr Ser Tyr Gly Lys Leu Thr Phe Gly Gln Gly
        115                 120                 125

Thr Ile Leu Thr Val His Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
    130                 135                 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145                 150                 155                 160
```

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 10

<211> 308

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 10

Met Gly Pro Gln Leu Leu Gly Tyr Val Val Leu Cys Leu Leu Gly Ala
1 5 10 15

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

Val Thr Gly Lys Lys Leu Thr Val Thr Cys Ser Gln Asn Met Asn His
35 40 45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Leu Gly Leu Arg Gln
50 55 60

Ile Tyr Tyr Ser Met Asn Val Glu Val Thr Asp Lys Gly Asp Val Pro
65 70 75 80

Glu Gly Tyr Lys Val Ser Arg Lys Glu Lys Arg Asn Phe Pro Leu Ile
85 90 95

Leu Glu Ser Pro Ser Pro Asn Gln Thr Ser Leu Tyr Phe Cys Ala Ser

100 105 110

Ser Trp Thr Leu Asn Thr Glu Ala Phe Phe Gly Gln Gly Thr Arg Leu
115 120 125

Thr Val Val Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val
130 135 140

Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr Leu
145 150 155 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
165 170 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
180 185 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
195 200 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
210 215 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225 230 235 240

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
245 250 255

Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Phe
305

<210> 11
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 11
Met Ala Ser Ala Pro Ile Ser Met Leu Ala Met Leu Phe Thr Leu Ser
1 5 10 15

Gly Leu Arg Ala Gln Ser Val Ala Gln Pro Glu Asp Gln Val Asn Val
20 25 30

Ala Glu Gly Asn Pro Leu Thr Val Lys Cys Thr Tyr Ser Val Ser Gly
35 40 45

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

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

Gly Phe Glu Ala Glu Phe Asn Lys Ser Gln Thr Ser Phe His Leu Lys
85 90 95

Lys Pro Ser Ala Leu Val Ser Asp Ser Ala Leu Tyr Phe Cys Ala Val
100 105 110

Arg Asp Pro Gly Asn Tyr Gly Gln Asn Phe Val Phe Gly Pro Gly Thr
115 120 125

Arg Leu Ser Val Leu Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr
130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr

145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 12

<211> 311

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 12

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Thr Gly Val Ser Gln Asp Pro Arg His Lys Ile Thr
20 25 30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
85 90 95

```
Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
            100                 105                 110

Ser Ser Leu Leu Gly His Thr Gln Glu Thr Gln Tyr Phe Gly Pro Gly
        115                 120                 125

Thr Arg Leu Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
    130                 135                 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
145                 150                 155                 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
                165                 170                 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
            180                 185                 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
        195                 200                 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
    210                 215                 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
```

225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 13
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 13
Met Ala Ser Ala Pro Ile Ser Met Leu Ala Met Leu Phe Thr Leu Ser

1 5 10 15

Gly Leu Arg Ala Gln Ser Val Ala Gln Pro Glu Asp Gln Val Asn Val
20 25 30

Ala Glu Gly Asn Pro Leu Thr Val Lys Cys Thr Tyr Ser Val Ser Gly
35 40 45

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

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

Gly Phe Glu Ala Glu Phe Asn Lys Ser Gln Thr Ser Phe His Leu Lys
85 90 95

Lys Pro Ser Ala Leu Val Ser Asp Ser Ala Leu Tyr Phe Cys Ala Val
100 105 110

Arg Asp Pro Gly Asn Tyr Gly Gln Asn Phe Val Phe Gly Pro Gly Thr
115 120 125

Arg Leu Ser Val Leu Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr
130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 14

<211> 311

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 14

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Thr Gly Val Ser Gln Asp Pro Arg His Lys Ile Thr
20 25 30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu

85 90 95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100 105 110

Ser Ser Leu Leu Gly His Thr Gln Glu Thr Gln Tyr Phe Gly Pro Gly
115 120 125

Thr Arg Leu Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr
260 265 270

His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 15
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 15

Met Met Lys Cys Pro Gln Ala Leu Leu Ala Ile Phe Trp Leu Leu Leu
1 5 10 15

Ser Trp Val Ser Ser Glu Asp Lys Val Val Gln Ser Pro Leu Ser Leu
20 25 30

Val Val His Glu Gly Asp Thr Val Thr Leu Asn Cys Ser Tyr Glu Val
35 40 45

Thr Asn Phe Arg Ser Leu Leu Trp Tyr Lys Gln Glu Lys Lys Ala Pro
50 55 60

Thr Phe Leu Phe Met Leu Thr Ser Ser Gly Ile Glu Lys Lys Ser Gly
65 70 75 80

Arg Leu Ser Ser Ile Leu Asp Lys Lys Glu Leu Phe Ser Ile Leu Asn
85 90 95

Ile Thr Ala Thr Gln Thr Gly Asp Ser Ala Ile Tyr Leu Cys Ala Val
100 105 110

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

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val

130 135 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145 150 155 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 16
<211> 312
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 16
Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1 5 10 15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
20 25 30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
35 40 45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
50 55 60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro
65 70 75 80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
85 90 95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
100 105 110

Ser Ser Pro Arg Thr Gly Gly Ile Gly Asn Thr Ile Tyr Phe Gly Glu
115 120 125

Gly Ser Trp Leu Thr Val Val Glu Asp Leu Asn Lys Val Phe Pro Pro
130 135 140

Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln
145 150 155 160

Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
165 170 175

Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser
180 185 190

Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
195 200 205

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn

210 215 220

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
225 230 235 240

Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val
245 250 255

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser
260 265 270

Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
275 280 285

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
290 295 300

Ala Met Val Lys Arg Lys Asp Phe
305 310

<210> 17
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 17

```
Met Met Lys Cys Pro Gln Ala Leu Leu Ala Ile Phe Trp Leu Leu Leu
1               5                  10                  15

Ser Trp Val Ser Ser Glu Asp Lys Val Val Gln Ser Pro Leu Ser Leu
            20                  25                  30

Val Val His Glu Gly Asp Thr Val Thr Leu Asn Cys Ser Tyr Glu Val
        35                  40                  45

Thr Asn Phe Arg Ser Leu Leu Trp Tyr Lys Gln Glu Lys Lys Ala Pro
    50                  55                  60

Thr Phe Leu Phe Met Leu Thr Ser Ser Gly Ile Glu Lys Lys Ser Gly
65                  70                  75                  80

Arg Leu Ser Ser Ile Leu Asp Lys Lys Glu Leu Phe Ser Ile Leu Asn
                85                  90                  95

Ile Thr Ala Thr Gln Thr Gly Asp Ser Ala Ile Tyr Leu Cys Ala Val
            100                 105                 110

Glu Ala Gly Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
        115                 120                 125
```

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
130 135 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145 150 155 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg

260 265 270

Leu Trp Ser
275

<210> 18
<211> 312
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 18
Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1 5 10 15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
20 25 30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
35 40 45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
50 55 60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro

65 70 75 80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
85 90 95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
100 105 110

Ser Ser Pro Arg Thr Gly Gly Ile Gly Asn Thr Ile Tyr Phe Gly Glu
115 120 125

Gly Ser Trp Leu Thr Val Val Glu Asp Leu Asn Lys Val Phe Pro Pro
130 135 140

Glu Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln
145 150 155 160

Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
165 170 175

Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser
180 185 190

Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
195 200 205

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn
210 215 220

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
225 230 235 240

Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val
245 250 255

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser
260 265 270

Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
275 280 285

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
290 295 300

Ala Met Val Lys Arg Lys Asp Phe
305 310

<210> 19
<211> 279
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 19

Met Leu Thr Ala Ser Leu Leu Arg Ala Val Ile Ala Ser Ile Cys Val
1 5 10 15

Val Ser Ser Met Ala Gln Lys Val Thr Gln Ala Gln Thr Glu Ile Ser
20 25 30

Val Val Glu Lys Glu Asp Val Thr Leu Asp Cys Val Tyr Glu Thr Arg
35 40 45

Asp Thr Thr Tyr Tyr Leu Phe Trp Tyr Lys Gln Pro Pro Ser Gly Glu
50 55 60

Leu Val Phe Leu Ile Arg Arg Asn Ser Phe Asp Glu Gln Asn Glu Ile
65 70 75 80

Ser Gly Arg Tyr Ser Trp Asn Phe Gln Lys Ser Thr Ser Ser Phe Asn
85 90 95

Phe Thr Ile Thr Ala Ser Gln Val Val Asp Ser Ala Val Tyr Phe Cys
100 105 110

Ala Leu Ser Glu Leu Ala Tyr Ser Gly Ala Gly Ser Tyr Gln Leu Thr

115 120 125

Phe Gly Lys Gly Thr Lys Leu Ser Val Ile Pro Asn Ile Gln Asn Pro
130 135 140

Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser
145 150 155 160

Val Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser
165 170 175

Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg
180 185 190

Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser
195 200 205

Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp
210 215 220

Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu
225 230 235 240

Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val
245 250 255

Ile Gly Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu
260 265 270

Met Thr Leu Arg Leu Trp Ser
275

<210> 20
<211> 312
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 20
Met Gly Thr Arg Leu Leu Cys Trp Ala Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

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

Glu Lys Arg Gln Ser Val Ala Phe Trp Cys Asn Pro Ile Ser Gly His
35 40 45

Ala Thr Leu Tyr Trp Tyr Gln Gln Ile Leu Gly Gln Gly Pro Lys Leu
50 55 60

```
Leu Ile Gln Phe Gln Asn Asn Gly Val Val Asp Asp Ser Gln Leu Pro
65                  70                  75                  80

Lys Asp Arg Phe Ser Ala Glu Arg Leu Lys Gly Val Asp Ser Thr Leu
                85                  90                  95

Lys Ile Gln Pro Ala Lys Leu Glu Asp Ser Ala Val Tyr Leu Cys Ala
            100                 105                 110

Ser Ser Leu Gln Gly Leu Pro Asp Thr Asp Thr Gln Tyr Phe Gly Pro
        115                 120                 125

Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro
    130                 135                 140

Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln
145                 150                 155                 160

Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
                165                 170                 175

Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser
            180                 185                 190

Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
```

195 200 205

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn
210 215 220

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
225 230 235 240

Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val
245 250 255

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser
260 265 270

Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
275 280 285

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
290 295 300

Ala Met Val Lys Arg Lys Asp Phe
305 310

<210> 21
<211> 279
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 21

```
Met Leu Thr Ala Ser Leu Leu Arg Ala Val Ile Ala Ser Ile Cys Val
1               5                  10                  15

Val Ser Ser Met Ala Gln Lys Val Thr Gln Ala Gln Thr Glu Ile Ser
            20                  25                  30

Val Val Glu Lys Glu Asp Val Thr Leu Asp Cys Val Tyr Glu Thr Arg
        35                  40                  45

Asp Thr Thr Tyr Tyr Leu Phe Trp Tyr Lys Gln Pro Pro Ser Gly Glu
    50                  55                  60

Leu Val Phe Leu Ile Arg Arg Asn Ser Phe Asp Glu Gln Asn Glu Ile
65                  70                  75                  80

Ser Gly Arg Tyr Ser Trp Asn Phe Gln Lys Ser Thr Ser Ser Phe Asn
                85                  90                  95

Phe Thr Ile Thr Ala Ser Gln Val Val Asp Ser Ala Val Tyr Phe Cys
            100                 105                 110
```

```
Ala Leu Ser Glu Leu Ala Tyr Ser Gly Ala Gly Ser Tyr Gln Leu Thr
        115                 120                 125

Phe Gly Lys Gly Thr Lys Leu Ser Val Ile Pro Asn Ile Gln Asn Pro
    130                 135                 140

Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser
145                 150                 155                 160

Val Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser
                165                 170                 175

Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg
            180                 185                 190

Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser
        195                 200                 205

Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp
    210                 215                 220

Thr Phe Phe Pro Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu
225                 230                 235                 240

Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val
```

245 250 255

Ile Val Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu
260 265 270

Met Thr Leu Arg Leu Trp Ser
275

<210> 22
<211> 312
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 22
Met Gly Thr Arg Leu Leu Cys Trp Ala Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

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

Glu Lys Arg Gln Ser Val Ala Phe Trp Cys Asn Pro Ile Ser Gly His
35 40 45

Ala Thr Leu Tyr Trp Tyr Gln Gln Ile Leu Gly Gln Gly Pro Lys Leu

```
    50                  55                  60

Leu Ile Gln Phe Gln Asn Asn Gly Val Val Asp Asp Ser Gln Leu Pro
65                  70                  75                  80

Lys Asp Arg Phe Ser Ala Glu Arg Leu Lys Gly Val Asp Ser Thr Leu
                85                  90                  95

Lys Ile Gln Pro Ala Lys Leu Glu Asp Ser Ala Val Tyr Leu Cys Ala
            100                 105                 110

Ser Ser Leu Gln Gly Leu Pro Asp Thr Asp Thr Gln Tyr Phe Gly Pro
        115                 120                 125

Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro
    130                 135                 140

Glu Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln
145                 150                 155                 160

Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
                165                 170                 175

Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser
            180                 185                 190
```

Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
195 200 205

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn
210 215 220

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
225 230 235 240

Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val
245 250 255

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser
260 265 270

Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
275 280 285

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
290 295 300

Ala Met Val Lys Arg Lys Asp Phe
305 310

<210> 23

<211> 274

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 23

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
50 55 60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg

100 105 110

Ser Gly Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr
115 120 125

Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr
130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 24
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

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

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

```
Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
    50                  55                  60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
                85                  90                  95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
            100                 105                 110

Ser Ser Phe Ser Gly Ser Thr Gln Glu Thr Gln Tyr Phe Gly Pro Gly
        115                 120                 125

Thr Arg Leu Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
    130                 135                 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
145                 150                 155                 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
                165                 170                 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
```

180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 25

<211> 274

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 25

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
50 55 60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg
100 105 110

Ser Gly Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr
115 120 125

Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr
130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr

225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 26
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 26
Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His

35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Phe Ser Gly Ser Thr Gln Glu Thr Gln Tyr Phe Gly Pro Gly
115 120 125

Thr Arg Leu Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr
260 265 270

His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe

305 310

<210> 27
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 27
Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
50 55 60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile

85 90 95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg
100 105 110

Trp Gly Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr
115 120 125

Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr
130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 28
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 28
Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Ser Ser Ala Gly Phe Thr Asp Thr Gln Tyr Phe Gly Pro Gly
115 120 125

Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu

165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 29
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 29
Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
50 55 60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

```
Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
                85                  90                  95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg
            100                 105                 110

Trp Gly Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr
        115                 120                 125

Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr
    130                 135                 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145                 150                 155                 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
                165                 170                 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
            180                 185                 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
        195                 200                 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
```

210 215 220

Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 30
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 30
Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala

```
            20                  25                  30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
        35                  40                  45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
    50                  55                  60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
                85                  90                  95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
            100                 105                 110

Ser Ser Ser Ser Ala Gly Phe Thr Asp Thr Gln Tyr Phe Gly Pro Gly
        115                 120                 125

Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
    130                 135                 140

Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys
145                 150                 155                 160
```

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr
260 265 270

His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala

290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 31
<211> 273
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 31
Met Leu Leu Glu His Leu Leu Ile Ile Leu Trp Met Gln Leu Thr Trp
1 5 10 15

Val Ser Gly Gln Gln Leu Asn Gln Ser Pro Gln Ser Met Phe Ile Gln
20 25 30

Glu Gly Glu Asp Val Ser Met Asn Cys Thr Ser Ser Ser Ile Phe Asn
35 40 45

Thr Trp Leu Trp Tyr Lys Gln Glu Pro Gly Glu Gly Pro Val Leu Leu
50 55 60

Ile Ala Leu Tyr Lys Ala Gly Glu Leu Thr Ser Asn Gly Arg Leu Thr

65 70 75 80

Ala Gln Phe Gly Ile Thr Arg Lys Asp Ser Phe Leu Asn Ile Ser Ala
85 90 95

Ser Ile Pro Ser Asp Val Gly Ile Tyr Phe Cys Ala Gly Pro Pro Met
100 105 110

Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys
115 120 125

Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln
130 135 140

Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp
145 150 155 160

Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr
165 170 175

Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser
180 185 190

Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn
195 200 205

Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro
210 215 220

Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp
225 230 235 240

Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu
245 250 255

Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp
260 265 270

Ser

<210> 32
<211> 309
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 32
Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

```
Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
            20                  25                  30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
        35                  40                  45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
    50                  55                  60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
                85                  90                  95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
            100                 105                 110

Ser Ser Leu Phe Ser Arg His Glu Gln Phe Phe Gly Pro Gly Thr Arg
        115                 120                 125

Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala
    130                 135                 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
```

145 150 155 160

Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser
165 170 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro
180 185 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
195 200 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
210 215 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225 230 235 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
245 250 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln
260 265 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
275 280 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
290 295 300

Lys Arg Lys Asp Phe
305

<210> 33
<211> 273
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 33
Met Leu Leu Glu His Leu Leu Ile Ile Leu Trp Met Gln Leu Thr Trp
1 5 10 15

Val Ser Gly Gln Gln Leu Asn Gln Ser Pro Gln Ser Met Phe Ile Gln
20 25 30

Glu Gly Glu Asp Val Ser Met Asn Cys Thr Ser Ser Ser Ile Phe Asn
35 40 45

Thr Trp Leu Trp Tyr Lys Gln Glu Pro Gly Glu Gly Pro Val Leu Leu
50 55 60

```
Ile Ala Leu Tyr Lys Ala Gly Glu Leu Thr Ser Asn Gly Arg Leu Thr
65                  70                  75                  80

Ala Gln Phe Gly Ile Thr Arg Lys Asp Ser Phe Leu Asn Ile Ser Ala
                85                  90                  95

Ser Ile Pro Ser Asp Val Gly Ile Tyr Phe Cys Ala Gly Pro Pro Met
            100                 105                 110

Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys
        115                 120                 125

Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln
    130                 135                 140

Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp
145                 150                 155                 160

Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr
                165                 170                 175

Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser
            180                 185                 190

Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn
```

195 200 205

Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser
210 215 220

Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp
225 230 235 240

Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu
245 250 255

Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp
260 265 270

Ser

<210> 34
<211> 309
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 34
Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr

1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Leu Phe Ser Arg His Glu Gln Phe Phe Gly Pro Gly Thr Arg
115 120 125

Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala
130 135 140

```
Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr
145                 150                 155                 160

Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser
                165                 170                 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro
            180                 185                 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
        195                 200                 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
    210                 215                 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225                 230                 235                 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
                245                 250                 255

Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln
            260                 265                 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
```

275 280 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
290 295 300

Lys Arg Lys Asp Phe
305

<210> 35
<211> 273
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 35
Met Val Leu Lys Phe Ser Val Ser Ile Leu Trp Ile Gln Leu Ala Trp
1 5 10 15

Val Ser Thr Gln Leu Leu Glu Gln Ser Pro Gln Phe Leu Ser Ile Gln
20 25 30

Glu Gly Glu Asn Leu Thr Val Tyr Cys Asn Ser Ser Ser Val Phe Ser
35 40 45

Ser Leu Gln Trp Tyr Arg Gln Glu Pro Gly Glu Gly Pro Val Leu Leu

```
    50                  55                  60

Val Thr Val Val Thr Gly Gly Glu Val Lys Lys Leu Lys Arg Leu Thr
65                  70                  75                  80

Phe Gln Phe Gly Asp Ala Arg Lys Asp Ser Ser Leu His Ile Thr Ala
                85                  90                  95

Ala Gln Thr Gly Asp Thr Gly Leu Tyr Leu Cys Ala Gly Ala Gly Met
            100                 105                 110

Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys
        115                 120                 125

Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln
    130                 135                 140

Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp
145                 150                 155                 160

Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr
                165                 170                 175

Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser
            180                 185                 190
```

Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn
195 200 205

Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro
210 215 220

Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp
225 230 235 240

Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu
245 250 255

Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp
260 265 270

Ser

<210> 36
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 36

```
Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1               5                  10                  15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
            20                  25                  30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
        35                  40                  45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
    50                  55                  60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro
65                  70                  75                  80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
                85                  90                  95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
            100                 105                 110

Ser Ser Leu Thr Ser Gly Arg Leu Asn Glu Gln Phe Phe Gly Pro Gly
        115                 120                 125

Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
```

130 135 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 37
<211> 273
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 37
Met Val Leu Lys Phe Ser Val Ser Ile Leu Trp Ile Gln Leu Ala Trp
1 5 10 15

Val Ser Thr Gln Leu Leu Glu Gln Ser Pro Gln Phe Leu Ser Ile Gln
20 25 30

Glu Gly Glu Asn Leu Thr Val Tyr Cys Asn Ser Ser Ser Val Phe Ser
35 40 45

```
Ser Leu Gln Trp Tyr Arg Gln Glu Pro Gly Glu Gly Pro Val Leu Leu
    50                  55                  60

Val Thr Val Val Thr Gly Gly Glu Val Lys Lys Leu Lys Arg Leu Thr
65                  70                  75                  80

Phe Gln Phe Gly Asp Ala Arg Lys Asp Ser Ser Leu His Ile Thr Ala
                85                  90                  95

Ala Gln Thr Gly Asp Thr Gly Leu Tyr Leu Cys Ala Gly Ala Gly Met
            100                 105                 110

Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys
        115                 120                 125

Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln
    130                 135                 140

Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp
145                 150                 155                 160

Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr
                165                 170                 175

Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser
```

180 185 190

Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn
195 200 205

Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser
210 215 220

Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp
225 230 235 240

Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu
245 250 255

Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp
260 265 270

Ser

<210> 38
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 38

Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1 5 10 15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
20 25 30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
35 40 45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
50 55 60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro
65 70 75 80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
85 90 95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
100 105 110

Ser Ser Leu Thr Ser Gly Arg Leu Asn Glu Gln Phe Phe Gly Pro Gly
115 120 125

```
Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
    130                 135                 140

Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys
145                 150                 155                 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
                165                 170                 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
            180                 185                 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
        195                 200                 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
    210                 215                 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225                 230                 235                 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
                245                 250                 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr
```

260 265 270

His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 39
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 39
Met Lys Lys Leu Leu Ala Met Ile Leu Trp Leu Gln Leu Asp Arg Leu
1 5 10 15

Ser Gly Glu Leu Lys Val Glu Gln Asn Pro Leu Phe Leu Ser Met Gln
20 25 30

Glu Gly Lys Asn Tyr Thr Ile Tyr Cys Asn Tyr Ser Thr Thr Ser Asp

35 40 45

Arg Leu Tyr Trp Tyr Arg Gln Asp Pro Gly Lys Ser Leu Glu Ser Leu
50 55 60

Phe Val Leu Leu Ser Asn Gly Ala Val Lys Gln Glu Gly Arg Leu Met
65 70 75 80

Ala Ser Leu Asp Thr Lys Ala Arg Leu Ser Thr Leu His Ile Thr Ala
85 90 95

Ala Val His Asp Leu Ser Ala Thr Tyr Phe Cys Ala Val Pro Met Gly
100 105 110

Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu
115 120 125

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu
210 215 220

Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 40
<211> 308
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 40

Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Arg Gly Pro Gly Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu
115 120 125

Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val

130 135 140

Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu
145 150 155 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
165 170 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
180 185 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
195 200 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
210 215 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225 230 235 240

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
245 250 255

Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Phe
305

<210> 41
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 41
Met Lys Lys Leu Leu Ala Met Ile Leu Trp Leu Gln Leu Asp Arg Leu
1 5 10 15

Ser Gly Glu Leu Lys Val Glu Gln Asn Pro Leu Phe Leu Ser Met Gln
20 25 30

Glu Gly Lys Asn Tyr Thr Ile Tyr Cys Asn Tyr Ser Thr Thr Ser Asp
35 40 45

```
Arg Leu Tyr Trp Tyr Arg Gln Asp Pro Gly Lys Ser Leu Glu Ser Leu
    50                  55                  60

Phe Val Leu Leu Ser Asn Gly Ala Val Lys Gln Glu Gly Arg Leu Met
65                  70                  75                  80

Ala Ser Leu Asp Thr Lys Ala Arg Leu Ser Thr Leu His Ile Thr Ala
                85                  90                  95

Ala Val His Asp Leu Ser Ala Thr Tyr Phe Cys Ala Val Pro Met Gly
            100                 105                 110

Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu
        115                 120                 125

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
    130                 135                 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145                 150                 155                 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
                165                 170                 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
```

180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp
210 215 220

Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 42
<211> 308
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 42
Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr

1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Arg Gly Pro Gly Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu
115 120 125

Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val
130 135 140

```
Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr Leu
145                 150                 155                 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
                165                 170                 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
            180                 185                 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
        195                 200                 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
    210                 215                 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225                 230                 235                 240

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
                245                 250                 255

Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln Gly
            260                 265                 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
```

275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Phe
305

<210> 43
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 43
Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr

50 55 60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg
100 105 110

Pro Gly Asp Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
115 120 125

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
130 135 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145 150 155 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 44
<211> 309
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 44

Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Phe Phe Gln Gly Glu Thr Gln Tyr Phe Gly Pro Gly Thr Arg
115 120 125

Leu Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala

130 135 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
145 150 155 160

Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser
165 170 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro
180 185 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
195 200 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
210 215 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225 230 235 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
245 250 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln
260 265 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
275 280 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
290 295 300

Lys Arg Lys Asp Phe
305

<210> 45
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 45
Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

```
Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
    50                  55                  60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65                  70                  75                  80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
                85                  90                  95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg
            100                 105                 110

Pro Gly Asp Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
        115                 120                 125

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
    130                 135                 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145                 150                 155                 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
                165                 170                 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
```

180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 46
<211> 309
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 46

Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Phe Phe Gln Gly Glu Thr Gln Tyr Phe Gly Pro Gly Thr Arg
115 120 125

```
Leu Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala
    130                 135                 140

Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr
145                 150                 155                 160

Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser
                165                 170                 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro
            180                 185                 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
        195                 200                 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
    210                 215                 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225                 230                 235                 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
                245                 250                 255

Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln
```

260 265 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
275 280 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
290 295 300

Lys Arg Lys Asp Phe
305

<210> 47
<211> 291
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 47
Met Ala Phe Trp Leu Arg Ser Leu Gly Leu His Phe Arg Pro His Leu
1 5 10 15

Gly Arg Arg Met Glu Ser Phe Leu Gly Gly Val Leu Leu Ile Leu Trp
20 25 30

Leu Gln Val Asp Trp Val Lys Ser Gln Lys Ile Glu Gln Asn Ser Glu

35 40 45

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

Thr Asn Tyr Ser Pro Ala Tyr Leu Gln Trp Tyr Arg Gln Asp Pro Gly
65 70 75 80

Arg Gly Pro Val Phe Leu Leu Leu Ile Arg Glu Asn Glu Lys Glu Lys
85 90 95

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

Leu Phe His Ile Thr Ala Ser Gln Pro Ala Asp Ser Ala Thr Tyr Leu
115 120 125

Cys Ala Leu Val Gly Gly Gly Tyr Gln Lys Val Thr Phe Gly Thr Gly
130 135 140

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

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
165 170 175

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
180 185 190

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
195 200 205

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
210 215 220

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
225 230 235 240

Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
245 250 255

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg
260 265 270

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
275 280 285

Leu Trp Ser
290

<210> 48

<211> 310

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 48

Met Ser Leu Gly Leu Leu Cys Cys Gly Ala Phe Ser Leu Leu Trp Ala
1 5 10 15

Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Arg Val Leu
20 25 30

Lys Thr Gly Gln Ser Met Thr Leu Leu Cys Ala Gln Asp Met Asn His
35 40 45

Glu Tyr Met Tyr Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
50 55 60

Ile His Tyr Ser Val Gly Glu Gly Thr Thr Ala Lys Gly Glu Val Pro
65 70 75 80

Asp Gly Tyr Asn Val Ser Arg Leu Lys Lys Gln Asn Phe Leu Leu Gly
85 90 95

Leu Glu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Thr

100 105 110

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

Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val
130 135 140

Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala
145 150 155 160

Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu
165 170 175

Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp
180 185 190

Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys
195 200 205

Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg
210 215 220

Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp
225 230 235 240

Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala
245 250 255

Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln
260 265 270

Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys
275 280 285

Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met
290 295 300

Val Lys Arg Lys Asp Phe
305 310

<210> 49
<211> 291
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 49
Met Ala Phe Trp Leu Arg Ser Leu Gly Leu His Phe Arg Pro His Leu
1 5 10 15

```
Gly Arg Arg Met Glu Ser Phe Leu Gly Gly Val Leu Leu Ile Leu Trp
            20                  25                  30

Leu Gln Val Asp Trp Val Lys Ser Gln Lys Ile Glu Gln Asn Ser Glu
        35                  40                  45

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

Thr Asn Tyr Ser Pro Ala Tyr Leu Gln Trp Tyr Arg Gln Asp Pro Gly
65                  70                  75                  80

Arg Gly Pro Val Phe Leu Leu Leu Ile Arg Glu Asn Glu Lys Glu Lys
                85                  90                  95

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

Leu Phe His Ile Thr Ala Ser Gln Pro Ala Asp Ser Ala Thr Tyr Leu
        115                 120                 125

Cys Ala Leu Val Gly Gly Gly Tyr Gln Lys Val Thr Phe Gly Thr Gly
    130                 135                 140

Thr Lys Leu Gln Val Ile Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
```

145 150 155 160

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
165 170 175

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
180 185 190

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
195 200 205

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
210 215 220

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
225 230 235 240

Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
245 250 255

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg
260 265 270

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
275 280 285

Leu Trp Ser
290

<210> 50
<211> 310
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 50
Met Ser Leu Gly Leu Leu Cys Cys Gly Ala Phe Ser Leu Leu Trp Ala
1 5 10 15

Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Arg Val Leu
20 25 30

Lys Thr Gly Gln Ser Met Thr Leu Leu Cys Ala Gln Asp Met Asn His
35 40 45

Glu Tyr Met Tyr Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
50 55 60

Ile His Tyr Ser Val Gly Glu Gly Thr Thr Ala Lys Gly Glu Val Pro
65 70 75 80

Asp Gly Tyr Asn Val Ser Arg Leu Lys Lys Gln Asn Phe Leu Leu Gly
85 90 95

Leu Glu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Thr
100 105 110

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

Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val
130 135 140

Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala
145 150 155 160

Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu
165 170 175

Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp
180 185 190

Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys
195 200 205

Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg

210 215 220

Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp
225 230 235 240

Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala
245 250 255

Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His
260 265 270

Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys
275 280 285

Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met
290 295 300

Val Lys Arg Lys Asp Phe
305 310

<210> 51
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 51

Met Arg Leu Val Ala Arg Val Thr Val Phe Leu Thr Phe Gly Thr Ile
1 5 10 15

Ile Asp Ala Lys Thr Thr Gln Pro Thr Ser Met Asp Cys Ala Glu Gly
20 25 30

Arg Ala Ala Asn Leu Pro Cys Asn His Ser Thr Ile Ser Gly Asn Glu
35 40 45

Tyr Val Tyr Trp Tyr Arg Gln Ile His Ser Gln Gly Pro Gln Tyr Ile
50 55 60

Ile His Gly Leu Lys Asn Asn Glu Thr Asn Glu Met Ala Ser Leu Ile
65 70 75 80

Ile Thr Glu Asp Arg Lys Ser Ser Thr Leu Ile Leu Pro His Ala Thr
85 90 95

Leu Arg Asp Thr Ala Val Tyr Tyr Cys Ile Val Arg Pro Arg Asn Tyr
100 105 110

Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu Ser
115 120 125

```
Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg
    130                 135                 140

Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp
145                 150                 155                 160

Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr
                165                 170                 175

Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser
            180                 185                 190

Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe
        195                 200                 205

Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser
    210                 215                 220

Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn
225                 230                 235                 240

Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu
                245                 250                 255

Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
```

260 265 270

<210> 52
<211> 317
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 52
Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Thr Gly Val Ser Gln Asp Pro Arg His Lys Ile Thr
20 25 30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu

85 90 95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100 105 110

Ser Ser Leu Asp Phe Asp Leu Gly Gln Thr Arg Arg Ala Asn Glu Lys
115 120 125

Leu Phe Phe Gly Ser Gly Thr Gln Leu Ser Val Leu Glu Asp Leu Asn
130 135 140

Lys Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu
145 150 155 160

Ile Ser His Thr Gln Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe
165 170 175

Phe Pro Asp His Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val
180 185 190

His Ser Gly Val Ser Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala
195 200 205

Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala
210 215 220

Thr Phe Trp Gln Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe
225 230 235 240

Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro
245 250 255

Val Thr Gln Ile Val Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly
260 265 270

Phe Thr Ser Val Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu
275 280 285

Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser
290 295 300

Ala Leu Val Leu Met Ala Met Val Lys Arg Lys Asp Phe
305 310 315

<210> 53
<211> 271
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 53

Met Arg Leu Val Ala Arg Val Thr Val Phe Leu Thr Phe Gly Thr Ile
1 5 10 15

Ile Asp Ala Lys Thr Thr Gln Pro Thr Ser Met Asp Cys Ala Glu Gly
20 25 30

Arg Ala Ala Asn Leu Pro Cys Asn His Ser Thr Ile Ser Gly Asn Glu
35 40 45

Tyr Val Tyr Trp Tyr Arg Gln Ile His Ser Gln Gly Pro Gln Tyr Ile
50 55 60

Ile His Gly Leu Lys Asn Asn Glu Thr Asn Glu Met Ala Ser Leu Ile
65 70 75 80

Ile Thr Glu Asp Arg Lys Ser Ser Thr Leu Ile Leu Pro His Ala Thr
85 90 95

Leu Arg Asp Thr Ala Val Tyr Tyr Cys Ile Val Arg Pro Arg Asn Tyr
100 105 110

Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu Ser
115 120 125

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

130 135 140

Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp
145 150 155 160

Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr
165 170 175

Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser
180 185 190

Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe
195 200 205

Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp Val
210 215 220

Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn
225 230 235 240

Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu Leu
245 250 255

Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 54

<211> 317

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 54

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Thr Gly Val Ser Gln Asp Pro Arg His Lys Ile Thr
20 25 30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
85 90 95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100 105 110

Ser Ser Leu Asp Phe Asp Leu Gly Gln Thr Arg Arg Ala Asn Glu Lys
115 120 125

Leu Phe Phe Gly Ser Gly Thr Gln Leu Ser Val Leu Glu Asp Leu Asn
130 135 140

Lys Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Lys Ala Glu
145 150 155 160

Ile Ala His Thr Gln Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe
165 170 175

Phe Pro Asp His Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val
180 185 190

His Ser Gly Val Ser Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala
195 200 205

Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala
210 215 220

Thr Phe Trp Gln Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe

225 230 235 240

Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro
245 250 255

Val Thr Gln Ile Val Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly
260 265 270

Ile Thr Ser Ala Ser Tyr His Gln Gly Val Leu Ser Ala Thr Ile Leu
275 280 285

Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser
290 295 300

Ala Leu Val Leu Met Ala Met Val Lys Arg Lys Asp Phe
305 310 315

<210> 55
<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 55
Met Val Lys Ile Arg Gln Phe Leu Leu Ala Ile Leu Trp Leu Gln Leu

1 5 10 15

Ser Cys Val Ser Ala Ala Lys Asn Glu Val Glu Gln Ser Pro Gln Asn
20 25 30

Leu Thr Ala Gln Glu Gly Glu Phe Ile Thr Ile Asn Cys Ser Tyr Ser
35 40 45

Val Gly Ile Ser Ala Leu His Trp Leu Gln Gln His Pro Gly Gly Gly
50 55 60

Ile Val Ser Leu Phe Met Leu Ser Ser Gly Lys Lys Lys His Gly Arg
65 70 75 80

Leu Ile Ala Thr Ile Asn Ile Gln Glu Lys His Ser Ser Leu His Ile
85 90 95

Thr Ala Ser His Pro Arg Asp Ser Ala Val Tyr Ile Cys Ala Val Asp
100 105 110

Gly Thr Gly Gly Thr Lys Lys Thr Ser Tyr Asp Lys Val Ile Phe Gly
115 120 125

Pro Gly Thr Ser Leu Ser Val Ile Pro Asn Ile Gln Asn Pro Asp Pro
130 135 140

Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys
145 150 155 160

Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp
165 170 175

Ser Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met
180 185 190

Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe
195 200 205

Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe
210 215 220

Phe Pro Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser
225 230 235 240

Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly
245 250 255

Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr
260 265 270

Leu Arg Leu Trp Ser

275

<210> 56
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 56

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

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

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

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

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

Gly Arg Phe Ser Gly Arg Gln Phe Ser Asn Ser Arg Ser Glu Met Asn

85 90 95

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

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

Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 57
<211> 277
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 57

Met Val Lys Ile Arg Gln Phe Leu Leu Ala Ile Leu Trp Leu Gln Leu
1 5 10 15

Ser Cys Val Ser Ala Ala Lys Asn Glu Val Glu Gln Ser Pro Gln Asn
20 25 30

Leu Thr Ala Gln Glu Gly Glu Phe Ile Thr Ile Asn Cys Ser Tyr Ser
35 40 45

Val Gly Ile Ser Ala Leu His Trp Leu Gln Gln His Pro Gly Gly Gly
50 55 60

Ile Val Ser Leu Phe Met Leu Ser Ser Gly Lys Lys Lys His Gly Arg
65 70 75 80

Leu Ile Ala Thr Ile Asn Ile Gln Glu Lys His Ser Ser Leu His Ile
85 90 95

Thr Ala Ser His Pro Arg Asp Ser Ala Val Tyr Ile Cys Ala Val Asp
100 105 110

Gly Thr Gly Gly Thr Lys Lys Thr Ser Tyr Asp Lys Val Ile Phe Gly
115 120 125

Pro Gly Thr Ser Leu Ser Val Ile Pro Asn Ile Gln Asn Pro Asp Pro

130 135 140

Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys
145 150 155 160

Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp
165 170 175

Ser Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met
180 185 190

Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe
195 200 205

Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe
210 215 220

Phe Pro Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser
225 230 235 240

Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val
245 250 255

Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr
260 265 270

Leu Arg Leu Trp Ser
275

<210> 58
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 58
Met Gly Ser Arg Leu Leu Cys Trp Val Leu Leu Cys Leu Leu Gly Ala
1 5 10 15

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

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

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

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

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

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

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

Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro

210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr
260 265 270

His Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 59
<211> 265
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 59

Met Lys Lys Leu Leu Ala Met Ile Leu Trp Leu Gln Leu Asp Arg Leu
1 5 10 15

Ser Gly Glu Leu Lys Val Glu Gln Asn Pro Leu Phe Leu Ser Met Gln
20 25 30

Glu Gly Lys Asn Tyr Thr Ile Tyr Cys Asn Tyr Ser Thr Thr Ser Asp
35 40 45

Arg Leu Tyr Trp Tyr Arg Gln Asp Pro Gly Lys Ser Leu Glu Ser Leu
50 55 60

Phe Val Leu Leu Ser Asn Gly Ala Val Lys Gln Glu Gly Arg Leu Met
65 70 75 80

Ala Ser Leu Asp Thr Lys Ala Arg Leu Ser Thr Leu His Ile Thr Ala
85 90 95

Ala Val His Asp Leu Ser Ala Thr Tyr Phe Cys Ala Val Asp Thr Asn
100 105 110

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

```
Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp
    130                 135                 140

Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser
145                 150                 155                 160

Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp
                165                 170                 175

Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn
            180                 185                 190

Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro
        195                 200                 205

Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys Asp Val Lys Leu
    210                 215                 220

Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu
225                 230                 235                 240

Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
                245                 250                 255

Leu Leu Met Thr Leu Arg Leu Trp Ser
```

260 265

<210> 60
<211> 308
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 60
Met Ser Ile Gly Leu Leu Cys Cys Val Ala Phe Ser Leu Leu Trp Ala
1 5 10 15

Ser Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu
20 25 30

Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
35 40 45

Asn Ser Met Tyr Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
50 55 60

Ile Tyr Tyr Ser Ala Ser Glu Gly Thr Thr Asp Lys Gly Glu Val Pro
65 70 75 80

Asn Gly Tyr Asn Val Ser Arg Leu Asn Lys Arg Glu Phe Ser Leu Arg

85 90 95

Leu Glu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
100 105 110

Ser Glu Ile Gln Gly Glu Lys Leu Phe Phe Gly Ser Gly Thr Gln Leu
115 120 125

Ser Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val
130 135 140

Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu
145 150 155 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
165 170 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
180 185 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
195 200 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
210 215 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225 230 235 240

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
245 250 255

Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Phe
305

<210> 61
<211> 265
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 61

Met Lys Lys Leu Leu Ala Met Ile Leu Trp Leu Gln Leu Asp Arg Leu
1 5 10 15

Ser Gly Glu Leu Lys Val Glu Gln Asn Pro Leu Phe Leu Ser Met Gln
20 25 30

Glu Gly Lys Asn Tyr Thr Ile Tyr Cys Asn Tyr Ser Thr Thr Ser Asp
35 40 45

Arg Leu Tyr Trp Tyr Arg Gln Asp Pro Gly Lys Ser Leu Glu Ser Leu
50 55 60

Phe Val Leu Leu Ser Asn Gly Ala Val Lys Gln Glu Gly Arg Leu Met
65 70 75 80

Ala Ser Leu Asp Thr Lys Ala Arg Leu Ser Thr Leu His Ile Thr Ala
85 90 95

Ala Val His Asp Leu Ser Ala Thr Tyr Phe Cys Ala Val Asp Thr Asn
100 105 110

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

Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp

130 135 140

Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln Thr Asn Val Ser
145 150 155 160

Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys Thr Val Leu Asp
165 170 175

Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val Ala Trp Ser Asn
180 185 190

Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro
195 200 205

Glu Asp Thr Phe Phe Pro Ser Ser Asp Val Pro Cys Asp Val Lys Leu
210 215 220

Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu
225 230 235 240

Leu Val Ile Val Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn
245 250 255

Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265

<210> 62

<211> 308

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 62

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

Ser Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu
20 25 30

Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
35 40 45

Asn Ser Met Tyr Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
50 55 60

Ile Tyr Tyr Ser Ala Ser Glu Gly Thr Thr Asp Lys Gly Glu Val Pro
65 70 75 80

Asn Gly Tyr Asn Val Ser Arg Leu Asn Lys Arg Glu Phe Ser Leu Arg
85 90 95

```
Leu Glu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
            100                 105                 110

Ser Glu Ile Gln Gly Glu Lys Leu Phe Phe Gly Ser Gly Thr Gln Leu
        115                 120                 125

Ser Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val
    130                 135                 140

Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr Leu
145                 150                 155                 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
                165                 170                 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
            180                 185                 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
        195                 200                 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
    210                 215                 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
```

225 230 235 240

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
245 250 255

Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Phe
305

<210> 63
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 63
Met Lys Lys Leu Leu Ala Met Ile Leu Trp Leu Gln Leu Asp Arg Leu

1 5 10 15

Ser Gly Glu Leu Lys Val Glu Gln Asn Pro Leu Phe Leu Ser Met Gln
20 25 30

Glu Gly Lys Asn Tyr Thr Ile Tyr Cys Asn Tyr Ser Thr Thr Ser Asp
35 40 45

Arg Leu Tyr Trp Tyr Arg Gln Asp Pro Gly Lys Ser Leu Glu Ser Leu
50 55 60

Phe Val Leu Leu Ser Asn Gly Ala Val Lys Gln Glu Gly Arg Leu Met
65 70 75 80

Ala Ser Leu Asp Thr Lys Ala Arg Leu Ser Thr Leu His Ile Thr Ala
85 90 95

Ala Val His Asp Leu Ser Ala Thr Tyr Phe Cys Ala Val Arg Met Gly
100 105 110

Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu
115 120 125

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu
210 215 220

Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 64

<211> 308

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 64

Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala

100 105 110

Ser Ser Phe Ala Ser Gln Pro Gln His Phe Gly Asp Gly Thr Arg Leu
115 120 125

Ser Ile Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val
130 135 140

Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu
145 150 155 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
165 170 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
180 185 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
195 200 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
210 215 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225 230 235 240

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
245 250 255

Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Phe
305

<210> 65
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 65
Met Lys Lys Leu Leu Ala Met Ile Leu Trp Leu Gln Leu Asp Arg Leu
1 5 10 15

Ser Gly Glu Leu Lys Val Glu Gln Asn Pro Leu Phe Leu Ser Met Gln
20 25 30

Glu Gly Lys Asn Tyr Thr Ile Tyr Cys Asn Tyr Ser Thr Thr Ser Asp
35 40 45

Arg Leu Tyr Trp Tyr Arg Gln Asp Pro Gly Lys Ser Leu Glu Ser Leu
50 55 60

Phe Val Leu Leu Ser Asn Gly Ala Val Lys Gln Glu Gly Arg Leu Met
65 70 75 80

Ala Ser Leu Asp Thr Lys Ala Arg Leu Ser Thr Leu His Ile Thr Ala
85 90 95

Ala Val His Asp Leu Ser Ala Thr Tyr Phe Cys Ala Val Arg Met Gly
100 105 110

Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu
115 120 125

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe

145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp
210 215 220

Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 66
<211> 308
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 66

Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

```
Ser Ser Phe Ala Ser Gln Pro Gln His Phe Gly Asp Gly Thr Arg Leu
        115                 120                 125

Ser Ile Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val
    130                 135                 140

Phe Glu Pro Ser Lys Ala Glu Ile Ala His Thr Gln Lys Ala Thr Leu
145                 150                 155                 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
                165                 170                 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
            180                 185                 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
        195                 200                 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
    210                 215                 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225                 230                 235                 240

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
```

245 250 255

Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr His Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Phe
305

<210> 67
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 67
Met Lys Arg Ile Leu Gly Ala Leu Leu Gly Leu Leu Ser Ala Gln Val
1 5 10 15

Cys Cys Val Arg Gly Ile Gln Val Glu Gln Ser Pro Pro Asp Leu Ile

20 25 30

Leu Gln Glu Gly Ala Asn Ser Thr Leu Arg Cys Asn Phe Ser Asp Ser
35 40 45

Val Asn Asn Leu Gln Trp Phe His Gln Asn Pro Trp Gly Gln Leu Ile
50 55 60

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

Ala Thr Thr Val Ala Thr Glu Arg Tyr Ser Leu Leu Tyr Ile Ser Ser
85 90 95

Ser Gln Thr Thr Asp Ser Gly Val Tyr Phe Cys Ala Val Glu Gly Gly
100 105 110

Ser Tyr Asn Tyr Gly Gln Asn Phe Val Phe Gly Pro Gly Thr Arg Leu
115 120 125

Ser Val Leu Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu
210 215 220

Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 68
<211> 313
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 68

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Thr Gly Val Ser Gln Asp Pro Arg His Lys Ile Thr
20 25 30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
85 90 95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100 105 110

Ser Ser Leu Val Arg Glu Arg Glu Arg Gly Asn Glu Gln Phe Phe Gly

115 120 125

Pro Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro
130 135 140

Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr
145 150 155 160

Gln Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His
165 170 175

Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val
180 185 190

Ser Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser
195 200 205

Arg Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln
210 215 220

Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser
225 230 235 240

Glu Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile
245 250 255

Val Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val
260 265 270

Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu
275 280 285

Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu
290 295 300

Met Ala Met Val Lys Arg Lys Asp Phe
305 310

<210> 69
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 69
Met Lys Arg Ile Leu Gly Ala Leu Leu Gly Leu Leu Ser Ala Gln Val
1 5 10 15

Cys Cys Val Arg Gly Ile Gln Val Glu Gln Ser Pro Pro Asp Leu Ile
20 25 30

```
Leu Gln Glu Gly Ala Asn Ser Thr Leu Arg Cys Asn Phe Ser Asp Ser
        35                  40                  45

Val Asn Asn Leu Gln Trp Phe His Gln Asn Pro Trp Gly Gln Leu Ile
    50                  55                  60

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

Ala Thr Thr Val Ala Thr Glu Arg Tyr Ser Leu Leu Tyr Ile Ser Ser
                85                  90                  95

Ser Gln Thr Thr Asp Ser Gly Val Tyr Phe Cys Ala Val Glu Gly Gly
            100                 105                 110

Ser Tyr Asn Tyr Gly Gln Asn Phe Val Phe Gly Pro Gly Thr Arg Leu
        115                 120                 125

Ser Val Leu Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
    130                 135                 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145                 150                 155                 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
```

165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp
210 215 220

Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 70
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 70

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
50 55 60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg
100 105 110

Val Arg Asp Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
115 120 125

```
Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
    130                 135                 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145                 150                 155                 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
                165                 170                 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
            180                 185                 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
        195                 200                 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
    210                 215                 220

Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225                 230                 235                 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg
                245                 250                 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
```

260 265 270

Leu Trp Ser
275

<210> 71
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 71
Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1 5 10 15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
20 25 30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
35 40 45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
50 55 60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro

65 70 75 80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
85 90 95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
100 105 110

Ser Ser Pro Pro Gly Gly Gln Gly Glu Lys Leu Phe Phe Gly Ser Gly
115 120 125

Thr Gln Leu Ser Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 72
<211> 275
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 72

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
50 55 60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg
100 105 110

Val Arg Asp Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly

```
        115                 120                 125

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
    130                 135                 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145                 150                 155                 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
                165                 170                 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
            180                 185                 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
        195                 200                 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
    210                 215                 220

Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225                 230                 235                 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg
                245                 250                 255
```

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 73
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 73
Met Lys Ser Leu Arg Val Leu Leu Val Ile Leu Trp Leu Gln Leu Ser
1 5 10 15

Trp Val Trp Ser Gln Gln Lys Glu Val Glu Gln Asn Ser Gly Pro Leu
20 25 30

Ser Val Pro Glu Gly Ala Ile Ala Ser Leu Asn Cys Thr Tyr Ser Asp
35 40 45

Arg Gly Ser Gln Ser Phe Phe Trp Tyr Arg Gln Tyr Ser Gly Lys Ser
50 55 60

Pro Glu Leu Ile Met Phe Ile Tyr Ser Asn Gly Asp Lys Glu Asp Gly
65 70 75 80

Arg Phe Thr Ala Gln Leu Asn Lys Ala Ser Gln Tyr Val Ser Leu Leu
85 90 95

Ile Arg Asp Ser Gln Pro Ser Asp Ser Ala Thr Tyr Leu Cys Ala Val
100 105 110

Lys Gly Ala Gly Tyr Ser Thr Leu Thr Phe Gly Lys Gly Thr Met Leu
115 120 125

Leu Val Ser Pro Asp Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala

195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu
210 215 220

Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 74
<211> 307
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 74
Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala
1 5 10 15

Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu

20 25 30

Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
35 40 45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
50 55 60

Ile His Tyr Ser Val Gly Ala Gly Ile Thr Asp Gln Gly Glu Val Pro
65 70 75 80

Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg
85 90 95

Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
100 105 110

Ser Asp Gly Gly Ala Leu Ala Tyr Phe Gly Pro Gly Thr Arg Leu Thr
115 120 125

Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val Phe
130 135 140

Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu Val
145 150 155 160

Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp
165 170 175

Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Pro
180 185 190

Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser
195 200 205

Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe
210 215 220

Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr
225 230 235 240

Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp
245 250 255

Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly Val
260 265 270

Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
275 280 285

Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys Arg

290 295 300

Lys Asp Phe
305

<210> 75
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 75
Met Lys Ser Leu Arg Val Leu Leu Val Ile Leu Trp Leu Gln Leu Ser
1 5 10 15

Trp Val Trp Ser Gln Gln Lys Glu Val Glu Gln Asn Ser Gly Pro Leu
20 25 30

Ser Val Pro Glu Gly Ala Ile Ala Ser Leu Asn Cys Thr Tyr Ser Asp
35 40 45

Arg Gly Ser Gln Ser Phe Phe Trp Tyr Arg Gln Tyr Ser Gly Lys Ser
50 55 60

Pro Glu Leu Ile Met Phe Ile Tyr Ser Asn Gly Asp Lys Glu Asp Gly

65 70 75 80

Arg Phe Thr Ala Gln Leu Asn Lys Ala Ser Gln Tyr Val Ser Leu Leu
85 90 95

Ile Arg Asp Ser Gln Pro Ser Asp Ser Ala Thr Tyr Leu Cys Ala Val
100 105 110

Lys Gly Ala Gly Tyr Ser Thr Leu Thr Phe Gly Lys Gly Thr Met Leu
115 120 125

Leu Val Ser Pro Asp Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp
210 215 220

Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 76
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 76
Met Met Lys Cys Pro Gln Ala Leu Leu Ala Ile Phe Trp Leu Leu Leu
1 5 10 15

Ser Trp Val Ser Ser Glu Asp Lys Val Val Gln Ser Pro Leu Ser Leu
20 25 30

Val Val His Glu Gly Asp Thr Val Thr Leu Asn Cys Ser Tyr Glu Val
35 40 45

Thr Asn Phe Arg Ser Leu Leu Trp Tyr Lys Gln Glu Lys Lys Ala Pro
50 55 60

Thr Phe Leu Phe Met Leu Thr Ser Ser Gly Ile Glu Lys Lys Ser Gly
65 70 75 80

Arg Leu Ser Ser Ile Leu Asp Lys Lys Glu Leu Phe Ser Ile Leu Asn
85 90 95

Ile Thr Ala Thr Gln Thr Gly Asp Ser Ala Ile Tyr Leu Cys Ala Val
100 105 110

Glu Ser Gly Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
115 120 125

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
130 135 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145 150 155 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp

165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 77
<211> 312
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 77

Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1 5 10 15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
20 25 30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
35 40 45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
50 55 60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro
65 70 75 80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
85 90 95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
100 105 110

Ser Ser Pro Arg Thr Gly Gly Asp Gly Asn Thr Ile Tyr Phe Gly Glu
115 120 125

Gly Ser Trp Leu Thr Val Val Glu Asp Leu Asn Lys Val Phe Pro Pro
130 135 140

Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln
145 150 155 160

Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
165 170 175

Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser
180 185 190

Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
195 200 205

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn
210 215 220

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
225 230 235 240

Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val

245 250 255

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser
260 265 270

Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
275 280 285

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
290 295 300

Ala Met Val Lys Arg Lys Asp Phe
305 310

<210> 78
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 78
Met Met Lys Cys Pro Gln Ala Leu Leu Ala Ile Phe Trp Leu Leu Leu
1 5 10 15

Ser Trp Val Ser Ser Glu Asp Lys Val Val Gln Ser Pro Leu Ser Leu

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            20                  25                  30

Val Val His Glu Gly Asp Thr Val Thr Leu Asn Cys Ser Tyr Glu Val
        35                  40                  45

Thr Asn Phe Arg Ser Leu Leu Trp Tyr Lys Gln Glu Lys Lys Ala Pro
    50                  55                  60

Thr Phe Leu Phe Met Leu Thr Ser Ser Gly Ile Glu Lys Lys Ser Gly
65                  70                  75                  80

Arg Leu Ser Ser Ile Leu Asp Lys Lys Glu Leu Phe Ser Ile Leu Asn
                85                  90                  95

Ile Thr Ala Thr Gln Thr Gly Asp Ser Ala Ile Tyr Leu Cys Ala Val
            100                 105                 110

Glu Ser Gly Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
        115                 120                 125

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
    130                 135                 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145                 150                 155                 160
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Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 79

<211> 274

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 79

Met Glu Lys Met Leu Glu Cys Ala Phe Ile Val Leu Trp Leu Gln Leu
1 5 10 15

Gly Trp Leu Ser Gly Glu Asp Gln Val Thr Gln Ser Pro Glu Ala Leu
20 25 30

Arg Leu Gln Glu Gly Glu Ser Ser Ser Leu Asn Cys Ser Tyr Thr Val
35 40 45

Ser Gly Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly
50 55 60

Pro Glu Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys
65 70 75 80

Glu Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile
85 90 95

Thr Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Gln

100 105 110

Ala Ser Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr
115 120 125

Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr
130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 80
<211> 315
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 80
Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1 5 10 15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
20 25 30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
35 40 45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
50 55 60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro
65 70 75 80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
85 90 95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
100 105 110

Ser Ser Pro Val Pro Val Pro Leu Pro Thr Thr Gln Glu Thr Gln Tyr
115 120 125

Phe Gly Pro Gly Thr Arg Leu Leu Val Leu Glu Asp Leu Asn Lys Val
130 135 140

Phe Pro Pro Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser
145 150 155 160

His Thr Gln Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro
165 170 175

Asp His Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser

180 185 190

Gly Val Ser Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn
195 200 205

Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe
210 215 220

Trp Gln Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly
225 230 235 240

Leu Ser Glu Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr
245 250 255

Gln Ile Val Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr
260 265 270

Ser Val Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu
275 280 285

Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu
290 295 300

Val Leu Met Ala Met Val Lys Arg Lys Asp Phe
305 310 315

<210> 81

<211> 274

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 81

Met Glu Lys Met Leu Glu Cys Ala Phe Ile Val Leu Trp Leu Gln Leu
1 5 10 15

Gly Trp Leu Ser Gly Glu Asp Gln Val Thr Gln Ser Pro Glu Ala Leu
20 25 30

Arg Leu Gln Glu Gly Glu Ser Ser Ser Leu Asn Cys Ser Tyr Thr Val
35 40 45

Ser Gly Leu Arg Gly Leu Phe Trp Tyr Arg Gln Asp Pro Gly Lys Gly
50 55 60

Pro Glu Phe Leu Phe Thr Leu Tyr Ser Ala Gly Glu Glu Lys Glu Lys
65 70 75 80

Glu Arg Leu Lys Ala Thr Leu Thr Lys Lys Glu Ser Phe Leu His Ile
85 90 95

Thr Ala Pro Lys Pro Glu Asp Ser Ala Thr Tyr Leu Cys Ala Val Gln
100 105 110

Ala Ser Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr
115 120 125

Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr
130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr

225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 82
<211> 273
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 82
Met Val Leu Lys Phe Ser Val Ser Ile Leu Trp Ile Gln Leu Ala Trp
1 5 10 15

Val Ser Thr Gln Leu Leu Glu Gln Ser Pro Gln Phe Leu Ser Ile Gln
20 25 30

Glu Gly Glu Asn Leu Thr Val Tyr Cys Asn Ser Ser Ser Val Phe Ser

35 40 45

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

Val Thr Val Val Thr Gly Gly Glu Val Lys Lys Leu Lys Arg Leu Thr
65 70 75 80

Phe Gln Phe Gly Asp Ala Arg Lys Asp Ser Ser Leu His Ile Thr Ala
85 90 95

Ala Gln Thr Gly Asp Thr Gly Leu Tyr Leu Cys Ala Gly Ala Pro Ser
100 105 110

Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys
115 120 125

Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln
130 135 140

Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp
145 150 155 160

Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr
165 170 175

Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser
180 185 190

Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn
195 200 205

Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro
210 215 220

Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp
225 230 235 240

Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu
245 250 255

Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp
260 265 270

Ser

<210> 83
<211> 310
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 83

Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1 5 10 15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
20 25 30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
35 40 45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
50 55 60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro
65 70 75 80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
85 90 95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
100 105 110

Ser Ser Pro Pro Gly Gln Asn Asn Glu Gln Phe Phe Gly Pro Gly Thr

115 120 125

Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val
130 135 140

Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala
145 150 155 160

Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu
165 170 175

Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp
180 185 190

Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys
195 200 205

Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg
210 215 220

Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp
225 230 235 240

Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala
245 250 255

Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln
260 265 270

Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys
275 280 285

Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met
290 295 300

Val Lys Arg Lys Asp Phe
305 310

<210> 84
<211> 273
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 84
Met Val Leu Lys Phe Ser Val Ser Ile Leu Trp Ile Gln Leu Ala Trp
1 5 10 15

Val Ser Thr Gln Leu Leu Glu Gln Ser Pro Gln Phe Leu Ser Ile Gln
20 25 30

Glu Gly Glu Asn Leu Thr Val Tyr Cys Asn Ser Ser Ser Val Phe Ser
35 40 45

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

Val Thr Val Val Thr Gly Gly Glu Val Lys Lys Leu Lys Arg Leu Thr
65 70 75 80

Phe Gln Phe Gly Asp Ala Arg Lys Asp Ser Ser Leu His Ile Thr Ala
85 90 95

Ala Gln Thr Gly Asp Thr Gly Leu Tyr Leu Cys Ala Gly Ala Pro Ser
100 105 110

Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys
115 120 125

Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln
130 135 140

Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp
145 150 155 160

Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr

165 170 175

Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser
180 185 190

Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn
195 200 205

Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser
210 215 220

Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp
225 230 235 240

Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu
245 250 255

Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp
260 265 270

Ser

<210> 85
<211> 272
<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 85

Met Lys Ser Leu Arg Val Leu Leu Val Ile Leu Trp Leu Gln Leu Ser
1 5 10 15

Trp Val Trp Ser Gln Gln Lys Glu Val Glu Gln Asn Ser Gly Pro Leu
20 25 30

Ser Val Pro Glu Gly Ala Ile Ala Ser Leu Asn Cys Thr Tyr Ser Asp
35 40 45

Arg Gly Ser Gln Ser Phe Phe Trp Tyr Arg Gln Tyr Ser Gly Lys Ser
50 55 60

Pro Glu Leu Ile Met Phe Ile Tyr Ser Asn Gly Asp Lys Glu Asp Gly
65 70 75 80

Arg Phe Thr Ala Gln Leu Asn Lys Ala Ser Gln Tyr Val Ser Leu Leu
85 90 95

Ile Arg Asp Ser Gln Pro Ser Asp Ser Ala Thr Tyr Leu Cys Ala Val
100 105 110

Arg Arg Ser Gly Tyr Ser Thr Leu Thr Phe Gly Lys Gly Thr Met Leu
115 120 125

Leu Val Ser Pro Asp Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu
210 215 220

Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu

245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 86
<211> 306
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 86
Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala
1 5 10 15

Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu
20 25 30

Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
35 40 45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
50 55 60

Ile His Tyr Ser Val Gly Ala Gly Ile Thr Asp Gln Gly Glu Val Pro

65 70 75 80

Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg
85 90 95

Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
100 105 110

Ser Leu Gly Ala Glu Ala Phe Phe Gly Gln Gly Thr Arg Leu Thr Val
115 120 125

Val Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val Phe Glu
130 135 140

Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu Val Cys
145 150 155 160

Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val
165 170 175

Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Pro Leu
180 185 190

Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser Arg
195 200 205

Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe Arg
210 215 220

Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr Gln
225 230 235 240

Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp Gly
245 250 255

Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly Val Leu
260 265 270

Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr
275 280 285

Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys Arg Lys
290 295 300

Asp Phe
305

<210> 87
<211> 272
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 87

Met Lys Ser Leu Arg Val Leu Leu Val Ile Leu Trp Leu Gln Leu Ser
1 5 10 15

Trp Val Trp Ser Gln Gln Lys Glu Val Glu Gln Asn Ser Gly Pro Leu
20 25 30

Ser Val Pro Glu Gly Ala Ile Ala Ser Leu Asn Cys Thr Tyr Ser Asp
35 40 45

Arg Gly Ser Gln Ser Phe Phe Trp Tyr Arg Gln Tyr Ser Gly Lys Ser
50 55 60

Pro Glu Leu Ile Met Phe Ile Tyr Ser Asn Gly Asp Lys Glu Asp Gly
65 70 75 80

Arg Phe Thr Ala Gln Leu Asn Lys Ala Ser Gln Tyr Val Ser Leu Leu
85 90 95

Ile Arg Asp Ser Gln Pro Ser Asp Ser Ala Thr Tyr Leu Cys Ala Val
100 105 110

Arg Arg Ser Gly Tyr Ser Thr Leu Thr Phe Gly Lys Gly Thr Met Leu

115 120 125

Leu Val Ser Pro Asp Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp
210 215 220

Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 88
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 88
Met Leu Leu Leu Leu Val Pro Val Leu Glu Val Ile Phe Thr Leu Gly
1 5 10 15

Gly Thr Arg Ala Gln Ser Val Thr Gln Leu Asp Ser His Val Ser Val
20 25 30

Ser Glu Gly Thr Pro Val Leu Leu Arg Cys Asn Tyr Ser Ser Ser Tyr
35 40 45

Ser Pro Ser Leu Phe Trp Tyr Val Gln His Pro Asn Lys Gly Leu Gln
50 55 60

Leu Leu Leu Lys Tyr Thr Ser Ala Ala Thr Leu Val Lys Gly Ile Asn
65 70 75 80

Gly Phe Glu Ala Glu Phe Lys Lys Ser Glu Thr Ser Phe His Leu Thr
85 90 95

Lys Pro Ser Ala His Met Ser Asp Ala Ala Glu Tyr Phe Cys Val Val
100 105 110

Met Arg Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu
115 120 125

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu

210 215 220

Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 89
<211> 308
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 89
Met Leu Leu Leu Leu Leu Leu Leu Gly Pro Gly Ser Gly Leu Gly Ala
1 5 10 15

Val Val Ser Gln His Pro Ser Trp Val Ile Cys Lys Ser Gly Thr Ser
20 25 30

Val Lys Ile Glu Cys Arg Ser Leu Asp Phe Gln Ala Thr Thr Met Phe

35 40 45

Trp Tyr Arg Gln Phe Pro Lys Gln Ser Leu Met Leu Met Ala Thr Ser
50 55 60

Asn Glu Gly Ser Lys Ala Thr Tyr Glu Gln Gly Val Glu Lys Asp Lys
65 70 75 80

Phe Leu Ile Asn His Ala Ser Leu Thr Leu Ser Thr Leu Thr Val Thr
85 90 95

Ser Ala His Pro Glu Asp Ser Ser Phe Tyr Ile Cys Ser Ala Lys Arg
100 105 110

Gly Asp Ala Phe Gly Glu Thr Gln Tyr Phe Gly Pro Gly Thr Arg Leu
115 120 125

Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val
130 135 140

Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu
145 150 155 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
165 170 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
180 185 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
195 200 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
210 215 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225 230 235 240

Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala
245 250 255

Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Phe

305

<210> 90
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 90

```
Met Leu Leu Leu Leu Val Pro Val Leu Glu Val Ile Phe Thr Leu Gly
1               5                  10                  15

Gly Thr Arg Ala Gln Ser Val Thr Gln Leu Asp Ser His Val Ser Val
            20                  25                  30

Ser Glu Gly Thr Pro Val Leu Leu Arg Cys Asn Tyr Ser Ser Ser Tyr
        35                  40                  45

Ser Pro Ser Leu Phe Trp Tyr Val Gln His Pro Asn Lys Gly Leu Gln
    50                  55                  60

Leu Leu Leu Lys Tyr Thr Ser Ala Ala Thr Leu Val Lys Gly Ile Asn
65                  70                  75                  80

Gly Phe Glu Ala Glu Phe Lys Lys Ser Glu Thr Ser Phe His Leu Thr
```

85 90 95

Lys Pro Ser Ala His Met Ser Asp Ala Ala Glu Tyr Phe Cys Val Val
100 105 110

Met Arg Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu
115 120 125

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp
210 215 220

Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 91
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 91
Met Ala Cys Pro Gly Phe Leu Trp Ala Leu Val Ile Ser Thr Cys Leu
1 5 10 15

Glu Phe Ser Met Ala Gln Thr Val Thr Gln Ser Gln Pro Glu Met Ser
20 25 30

Val Gln Glu Ala Glu Thr Val Thr Leu Ser Cys Thr Tyr Asp Thr Ser
35 40 45

```
Glu Ser Asp Tyr Tyr Leu Phe Trp Tyr Lys Gln Pro Pro Ser Arg Gln
    50                  55                  60

Met Ile Leu Val Ile Arg Gln Glu Ala Tyr Lys Gln Gln Asn Ala Thr
65                  70                  75                  80

Glu Asn Arg Phe Ser Val Asn Phe Gln Lys Ala Ala Lys Ser Phe Ser
                85                  90                  95

Leu Lys Ile Ser Asp Ser Gln Leu Gly Asp Ala Ala Met Tyr Phe Cys
            100                 105                 110

Ala Tyr Arg Ser Glu Arg Tyr Ser Thr Leu Thr Phe Gly Lys Gly Thr
        115                 120                 125

Met Leu Leu Val Ser Pro Asp Ile Gln Asn Pro Asp Pro Ala Val Tyr
    130                 135                 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145                 150                 155                 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
                165                 170                 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
```

180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 92
<211> 312
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 92

Met Leu Cys Ser Leu Leu Ala Leu Leu Leu Gly Thr Phe Phe Gly Val
1 5 10 15

Arg Ser Gln Thr Ile His Gln Trp Pro Ala Thr Leu Val Gln Pro Val
20 25 30

Gly Ser Pro Leu Ser Leu Glu Cys Thr Val Glu Gly Thr Ser Asn Pro
35 40 45

Asn Leu Tyr Trp Tyr Arg Gln Ala Ala Gly Arg Gly Leu Gln Leu Leu
50 55 60

Phe Tyr Ser Val Gly Ile Gly Gln Ile Ser Ser Glu Val Pro Gln Asn
65 70 75 80

Leu Ser Ala Ser Arg Pro Gln Asp Arg Gln Phe Ile Leu Ser Ser Lys
85 90 95

Lys Leu Leu Leu Ser Asp Ser Gly Phe Tyr Leu Cys Ala Trp Ser Val
100 105 110

Pro Tyr Leu Ala Gly Gly Lys Arg Pro Asp Thr Gln Tyr Phe Gly Pro
115 120 125

```
Gly Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro
    130                 135                 140

Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln
145                 150                 155                 160

Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
                165                 170                 175

Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser
            180                 185                 190

Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
        195                 200                 205

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn
    210                 215                 220

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
225                 230                 235                 240

Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val
                245                 250                 255

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser
```

260 265 270

Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
275 280 285

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
290 295 300

Ala Met Val Lys Arg Lys Asp Phe
305 310

<210> 93
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 93
Met Ala Cys Pro Gly Phe Leu Trp Ala Leu Val Ile Ser Thr Cys Leu
1 5 10 15

Glu Phe Ser Met Ala Gln Thr Val Thr Gln Ser Gln Pro Glu Met Ser
20 25 30

Val Gln Glu Ala Glu Thr Val Thr Leu Ser Cys Thr Tyr Asp Thr Ser

35 40 45

Glu Ser Asp Tyr Tyr Leu Phe Trp Tyr Lys Gln Pro Pro Ser Arg Gln
50 55 60

Met Ile Leu Val Ile Arg Gln Glu Ala Tyr Lys Gln Gln Asn Ala Thr
65 70 75 80

Glu Asn Arg Phe Ser Val Asn Phe Gln Lys Ala Ala Lys Ser Phe Ser
85 90 95

Leu Lys Ile Ser Asp Ser Gln Leu Gly Asp Ala Ala Met Tyr Phe Cys
100 105 110

Ala Tyr Arg Ser Glu Arg Tyr Ser Thr Leu Thr Phe Gly Lys Gly Thr
115 120 125

Met Leu Leu Val Ser Pro Asp Ile Gln Asn Pro Asp Pro Ala Val Tyr
130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 94
<211> 312
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 94

Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1 5 10 15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
20 25 30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
35 40 45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
50 55 60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro
65 70 75 80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
85 90 95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
100 105 110

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

115 120 125

Gly Ser Trp Leu Thr Val Val Glu Asp Leu Asn Lys Val Phe Pro Pro
130 135 140

Glu Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln
145 150 155 160

Lys Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val
165 170 175

Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser
180 185 190

Thr Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg
195 200 205

Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn
210 215 220

Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu
225 230 235 240

Asn Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val
245 250 255

Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser
260 265 270

Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu
275 280 285

Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met
290 295 300

Ala Met Val Lys Arg Lys Asp Phe
305 310

<210> 95
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 95
Met Leu Leu Glu His Leu Leu Ile Ile Leu Trp Met Gln Leu Thr Trp
1 5 10 15

Val Ser Gly Gln Gln Leu Asn Gln Ser Pro Gln Ser Met Phe Ile Gln
20 25 30

Glu Gly Glu Asp Val Ser Met Asn Cys Thr Ser Ser Ser Ile Phe Asn
35 40 45

Thr Trp Leu Trp Tyr Lys Gln Glu Pro Gly Glu Gly Pro Val Leu Leu
50 55 60

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

Ala Gln Phe Gly Ile Thr Arg Lys Asp Ser Phe Leu Asn Ile Ser Ala
85 90 95

Ser Ile Pro Ser Asp Val Gly Ile Tyr Phe Cys Ala Gly Pro Phe Gly
100 105 110

Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu
115 120 125

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile

165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu
210 215 220

Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 96
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 96

Met Gly Thr Arg Leu Leu Cys Trp Val Val Leu Gly Phe Leu Gly Thr
1 5 10 15

Asp His Thr Gly Ala Gly Val Ser Gln Ser Pro Arg Tyr Lys Val Ala
20 25 30

Lys Arg Gly Gln Asp Val Ala Leu Arg Cys Asp Pro Ile Ser Gly His
35 40 45

Val Ser Leu Phe Trp Tyr Gln Gln Ala Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Phe Ala Glu Arg Pro Glu Gly Ser Val Ser Thr Leu
85 90 95

Lys Ile Gln Arg Thr Gln Gln Glu Asp Ser Ala Val Tyr Leu Cys Ala
100 105 110

Ser Ser Leu Ile Gly Arg Gly Trp Asp Gly Tyr Thr Phe Gly Ser Gly
115 120 125

```
Thr Arg Leu Thr Val Val Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
    130                 135                 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
145                 150                 155                 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
                165                 170                 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
            180                 185                 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
        195                 200                 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
    210                 215                 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225                 230                 235                 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
                245                 250                 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr
```

260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 97
<211> 272
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 97
Met Leu Leu Glu His Leu Leu Ile Ile Leu Trp Met Gln Leu Thr Trp
1 5 10 15

Val Ser Gly Gln Gln Leu Asn Gln Ser Pro Gln Ser Met Phe Ile Gln
20 25 30

Glu Gly Glu Asp Val Ser Met Asn Cys Thr Ser Ser Ser Ile Phe Asn

35 40 45

Thr Trp Leu Trp Tyr Lys Gln Glu Pro Gly Glu Gly Pro Val Leu Leu
50 55 60

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

Ala Gln Phe Gly Ile Thr Arg Lys Asp Ser Phe Leu Asn Ile Ser Ala
85 90 95

Ser Ile Pro Ser Asp Val Gly Ile Tyr Phe Cys Ala Gly Pro Phe Gly
100 105 110

Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly Thr Lys Leu
115 120 125

Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu
130 135 140

Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe
145 150 155 160

Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile
165 170 175

Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn
180 185 190

Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala
195 200 205

Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Ser Asp
210 215 220

Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr
225 230 235 240

Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu
245 250 255

Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser
260 265 270

<210> 98
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 98

Met Leu Leu Leu Leu Val Pro Val Leu Glu Val Ile Phe Thr Leu Gly
1 5 10 15

Gly Thr Arg Ala Gln Ser Val Thr Gln Leu Asp Ser His Val Ser Val
20 25 30

Ser Glu Gly Thr Pro Val Leu Leu Arg Cys Asn Tyr Ser Ser Ser Tyr
35 40 45

Ser Pro Ser Leu Phe Trp Tyr Val Gln His Pro Asn Lys Gly Leu Gln
50 55 60

Leu Leu Leu Lys Tyr Thr Ser Ala Ala Thr Leu Val Lys Gly Ile Asn
65 70 75 80

Gly Phe Glu Ala Glu Phe Lys Lys Ser Glu Thr Ser Phe His Leu Thr
85 90 95

Lys Pro Ser Ala His Met Ser Asp Ala Ala Glu Tyr Phe Cys Val Val
100 105 110

Thr Gly Gly Ser Gly Gly Tyr Gln Lys Val Thr Phe Gly Thr Gly Thr
115 120 125

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

130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu
260 265 270

Trp Ser

<210> 99

<211> 311

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 99

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Thr Gly Val Ser Gln Asp Pro Arg His Lys Ile Thr
20 25 30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

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

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
85 90 95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100 105 110

Ser Ser Pro Leu Gly Thr Asp Gln Glu Thr Gln Tyr Phe Gly Pro Gly
115 120 125

Thr Arg Leu Leu Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys
145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro

210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 100
<211> 274
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic

polypeptide

<400> 100

Met Leu Leu Leu Leu Val Pro Val Leu Glu Val Ile Phe Thr Leu Gly
1 5 10 15

Gly Thr Arg Ala Gln Ser Val Thr Gln Leu Asp Ser His Val Ser Val
20 25 30

Ser Glu Gly Thr Pro Val Leu Leu Arg Cys Asn Tyr Ser Ser Ser Tyr
35 40 45

Ser Pro Ser Leu Phe Trp Tyr Val Gln His Pro Asn Lys Gly Leu Gln
50 55 60

Leu Leu Leu Lys Tyr Thr Ser Ala Ala Thr Leu Val Lys Gly Ile Asn
65 70 75 80

Gly Phe Glu Ala Glu Phe Lys Lys Ser Glu Thr Ser Phe His Leu Thr
85 90 95

Lys Pro Ser Ala His Met Ser Asp Ala Ala Glu Tyr Phe Cys Val Val
100 105 110

Thr Gly Gly Ser Gly Gly Tyr Gln Lys Val Thr Phe Gly Thr Gly Thr
115 120 125

Lys Leu Gln Val Ile Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr
130 135 140

Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr
145 150 155 160

Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val
165 170 175

Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys
180 185 190

Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala
195 200 205

Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser
210 215 220

Ser Asp Val Pro Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr
225 230 235 240

Asp Thr Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile
245 250 255

Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu

260 265 270

Trp Ser

<210> 101
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 101
Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
50 55 60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg

65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg
100 105 110

Pro Lys Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
115 120 125

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
130 135 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145 150 155 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys
195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
210 215 220

Ser Pro Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu
225 230 235 240

Thr Asp Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg
245 250 255

Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg
260 265 270

Leu Trp Ser
275

<210> 102
<211> 311
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic
polypeptide

<400> 102
Met Asp Thr Arg Leu Leu Cys Cys Ala Val Ile Cys Leu Leu Gly Ala
1 5 10 15

Gly Leu Ser Asn Ala Gly Val Met Gln Asn Pro Arg His Leu Val Arg
20 25 30

Arg Arg Gly Gln Glu Ala Arg Leu Arg Cys Ser Pro Met Lys Gly His
35 40 45

Ser His Val Tyr Trp Tyr Arg Gln Leu Pro Glu Glu Gly Leu Lys Phe
50 55 60

Met Val Tyr Leu Gln Lys Glu Asn Ile Ile Asp Glu Ser Gly Met Pro
65 70 75 80

Lys Glu Arg Phe Ser Ala Glu Phe Pro Lys Glu Gly Pro Ser Ile Leu
85 90 95

Arg Ile Gln Gln Val Val Arg Gly Asp Ser Ala Ala Tyr Phe Cys Ala
100 105 110

Ser Ser Leu Thr Ser Gly Ser Ser Asn Glu Gln Phe Phe Gly Pro Gly
115 120 125

Thr Arg Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu
130 135 140

Val Ala Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys

145 150 155 160

Ala Thr Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu
165 170 175

Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr
180 185 190

Asp Pro Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr
195 200 205

Cys Leu Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro
210 215 220

Arg Asn His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn
225 230 235 240

Asp Glu Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser
245 250 255

Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr
260 265 270

Gln Gln Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly
275 280 285

Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala
290 295 300

Met Val Lys Arg Lys Asp Phe
305 310

<210> 103
<211> 275
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 103
Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
35 40 45

Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
50 55 60

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg
100 105 110

Pro Lys Asn Tyr Gly Gly Ser Gln Gly Asn Leu Ile Phe Gly Lys Gly
115 120 125

Thr Lys Leu Ser Val Lys Pro Asn Ile Gln Asn Pro Asp Pro Ala Val
130 135 140

Tyr Gln Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe
145 150 155 160

Thr Asp Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp
165 170 175

Val Tyr Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe
180 185 190

Lys Ser Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys

195 200 205

Ala Asn Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro
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<220>
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polynucleotide

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peptide

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<223> This region may encompass 0-10 residues

<220>

<221> SITE

<222> (11)..(20)

<223> This region may encompass 0-10 residues

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<223> See specification as filed for detailed description of substitutions and preferred embodiments

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1 5 10 15

Ser Ser Ser Ser
20

<210> 108

<211> 10

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 108

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

<210> 109

<211> 8

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 109

Gly Gly Gly Ser Gly Gly Gly Ser

1 5

<210> 110

<211> 11

<212> PRT

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic peptide

<400> 110

Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Ser

1 5 10

<210> 111

<211> 9

<212> PRT

<213> Unknown

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<223> Description of Unknown:

"LAGLIDADG" family peptide motif sequence

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Leu Ala Gly Leu Ile Asp Ala Asp Gly

1 5

<210> 112

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<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic primer

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<210> 113

<211> 30

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic primer

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<210> 114

<211> 55

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic primer

<400> 114

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<210> 115

<211> 56

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic primer

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<210> 116

<211> 20

<212> DNA

<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic oligonucleotide

<400> 116
cggctactac aaccagagcg 20

<210> 117
<211> 20
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 117
agatcacact gacctggcag 20

<210> 118
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<220>
<223> Description of Artificial Sequence: Synthetic
oligonucleotide

<400> 118
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<210> 119
<211> 9
<212> PRT
<213> Homo sapiens

<400> 119

Tyr Val Gly Asp Ile Leu Ile Ala Leu

1 5

<210> 120

<211> 9

<212> PRT

<213> Homo sapiens

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Ala Val Asp Glu Phe Leu Leu Leu Leu

1 5

<210> 121

<211> 9

<212> PRT

<213> Homo sapiens

<400> 121

Lys Gln Ile Asp Gln Phe Leu Val Val

1 5

<210> 122

<211> 9

<212> PRT

<213> Homo sapiens

<400> 122

Lys Leu Glu Glu Val Leu Val Val Val

1 5

<210> 123

<211> 9

<212> PRT

<213> Homo sapiens

<400> 123

Gly Leu Thr Glu Asp Met Val Thr Val

1 5

<210> 124

<211> 10

<212> PRT

<213> Homo sapiens

<400> 124

Glu Leu Ala Gly Ile Gly Ile Leu Thr Val

1 5 10