[0012] Disclosed is a modified T cell receptor, or antigen binding fragment thereof, comprising a Vα and a Vβ derived from a wild type T cell receptor, wherein the Vα, the Vβ, or both, comprise a mutation in one or more complementarity determining regions (CDRs) relative to the wild type T cell receptor, wherein the modified T cell receptor binds to the peptide/MHC antigen known as Survivin/HLA-A2 (the Survivin peptide LMLGEFLKL (SEQ ID NO:5), bound to the MHC product known as HLA-A2).

[0012a] In one aspect, the present invention provides a modified T-cell receptor, or antigen-binding fragment thereof, comprising a Vα and a Vβ derived from a wild type T-cell receptor, wherein the Vα or the Vβ or both, comprise a mutation in one or more complementarity determining regions (CDRs) relative to the wild type T-cell receptor, wherein the Vα comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2 and wherein the modified T-cell receptor binds to a complex of the peptide Survivin and the HLA-A2 molecule with a K_D value of 10^{-6}M to 10^{-12}M.

[0013] In one example, the modified T cell receptor comprises a modified Vα comprising an amino acid sequence having at least 80% identity to the Vα amino acid sequence set forth in SEQ ID NO:3, wherein the modified T cell receptor binds to Survivin/HLA-A2 with an affinity (K_A value) of 10^6 M higher.

[0014] In another example, the modified T cell receptor comprises a modified Vα comprising an amino acid sequence having at least 80% identity to the Vα amino acid sequence set forth in SEQ ID NO:4, wherein the modified T cell receptor binds to Survivin/HLA-A2 with an affinity (K_A value) of 10^6 M higher.

[0015] In another example, the T cell receptor is a single-chain T cell receptor comprising the amino acid sequence set forth in SEQ ID NO:6.

[0016] In another example, the T cell receptor is a single-chain T cell receptor comprising the amino acid sequence set forth in SEQ ID NO:7.

[0017] In another example, the T cell receptor contains at least one of the mutations in CDR3α selected from N92S, N100K, A101G, R102Y, and L103K of the amino acid sequence set forth in SEQ ID NO:3.

[0018] In another example, the T cell receptor contains at least one of the mutations in CDR3α selected from N92H, N100G, A101W, R102Y, and L103T of the amino acid sequence set forth in SEQ ID NO:4.

[0019] In one example, the modified T cell receptor is generated by in vitro selection of a yeast display library of mutant T cell receptors.

[0020] In another example, the modified T cell receptor is expressed as a soluble protein that binds to its target antigen.

[0021] In another example, the modified T cell receptor is expressed on the surface of T cells in order to mediate the activity of either $CD4^+$ or $CD8^+$ T cells.

[0022] Also disclosed is a therapeutic agent that targets cancer cells that express the survivin antigen, wherein the therapeutic agent

comprises a modified T cell receptor described herein. In one example, a therapeutic agent that targets cancer cells that express the survivin antigen, wherein the therapeutic agent comprises a human T cell that expresses a modified T cell receptor described herein.

[0022a] In another aspect, the present invention provides a therapeutic agent that targets cancer cells that express the survivin antigen, wherein the therapeutic agent comprises the modified T cell receptor disclosed herein.

[0022b] In yet another aspect, the present invention provides a therapeutic agent that targets cancer cells that express the survivin antigen, wherein the therapeutic agent comprises a human T cell that expresses the modified T cell receptor disclosed herein.

[0023] One example provides a method of treating a subject having a cancer that expresses the survivin antigen comprising administering a therapeutic agent described herein.

[0023a] In yet another aspect, the present invention provides use of the therapeutic agent disclosed herein in the manufacture of a medicament for treating a subject having a cancer that expresses the survivin antigen, wherein the therapeutic agent is to be administered to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Figure 1 is a diagram that shows a method for engineering single chain TCRs for improved affinity against a peptide:HLA.A2. The general process used to engineer high affinity TCRs is shown.

[0025] Figure 2A is a 3-dimensional diagram that shows a side view of the TCR:pepMHC complex (A6; PDB:1AO7). The variable (V) and constant (C) regions of the α-chain and β-chain are indicated. The structure shown does not include the Cα region of the TCR. HLA-A2 (α1, α2, α3, and β2m) is shown in gray, and the Tax peptide (LLFGYPVYV, SEQ ID NO:6) is shown in black. A6 and Survivin TCRs examined in the present invention all use the Vα2 segment (also referred to as TRAV12 based on IMGT nomenclature).

[0026] Figure 2B is a 3-dimensional diagram that shows the top down view of the TCR (CDR) footprint over the peptide-MHC (Tax/HLA-A2). Although no crystal

structures have been described for the Survivin TCR used in the present disclosure, this diagonal docking orientation, with the Vα region positioned over the α2 MHC helix and the N-terminal end of the peptide, and the Vβ region positioned over the α1 MHC helix and C-terminal end of the peptide, has been observed in virtually all complexes to date.

[0027] Figure 3 is a schematic of the yeast-display system for engineering single-chain T cell receptor fragments (Vα-linker Vβ or Vβ-linker-Vα).

[0028] Figures 4A and 4B show flow cytometry histograms of the Survivin error prone library after sorting with an antibody that recognizes a conformation epitope of Vβ20. The Survivin error prone library was sorted sequentially with a 1:10 dilution of BC hVβ20 FITC IgG, followed by AlexaFluor® 488 goat anti-mouse IgG (1:100) secondary antibody, for a total of 3 sorts. Aliquots of yeast cells after each sort were

What is claimed is:

1. A modified T-cell receptor, or antigen-binding fragment thereof, comprising a Vα and a Vβ derived from a wild type T-cell receptor, wherein the Vα or the Vβ or both, comprise a mutation in one or more complementarity determining regions (CDRs) relative to the wild type T-cell receptor, wherein the Vα comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2 and wherein the modified T-cell receptor binds to a complex of the peptide Survivin and the HLA-A2 molecule with a K_D value of 10^{-6}M to 10^{-12}M.

2. The modified T cell receptor of claim 1, wherein the modified T cell receptor comprises the single-chain T cell receptor with the amino acid sequence set forth in SEQ ID NO:3.

3. The modified T cell receptor of claim 1, wherein the modified T cell receptor comprises the single-chain T cell receptor with the amino acid sequence set forth in SEQ ID NO:4.

4. The modified T cell receptor of claim 1, wherein the modified T cell receptor comprises an amino acid substitution at one or more of CDR3α 92, CDR3α 100, CDR3α 101, CDR3α 102, and CDR3α 103.

5. The modified T cell receptor of claim 1, wherein the modified T cell receptor comprises one or more of the following amino acid mutations: TCR Vα chain mutations N92S, N100K, A101G, R102Y, and L103K.

6. The modified T cell receptor of claim 1, wherein the modified T cell receptor comprises one or more of the following amino acid mutations: TCR Vα chain mutations N92H, N100G, A101W, R102Y, and L103T.

7. The modified T cell receptor of claim 1 that is in soluble form.

8. A therapeutic agent that targets cancer cells that express the survivin antigen, wherein the therapeutic agent comprises the modified T cell receptor of claim 7.

9. A therapeutic agent that targets cancer cells that express the survivin antigen, wherein the therapeutic agent comprises a human T cell that expresses the modified T cell receptor of claim 1.

10. Use of the therapeutic agent of any one of claims 8 and 9 in the manufacture of a medicament for treating a subject having a cancer that expresses the survivin antigen, wherein the therapeutic agent is to be administered to the subject.