

T cells comprises contacting the population of T cells to an APC comprising the peptide-MHC complex. In some embodiments, identifying neoantigen-specific T cells further comprises isolating T cells of the T cell population specific to the peptide-MHC complex. In some embodiments, identifying neoantigen-specific T cells further comprises identifying or predicting T cells of the of the T cell population specific to the peptide-MHC complex based on TCR clonality. In some embodiments, identifying a variable sequence of a TCR from the neoantigen-specific T cells is performed before identifying neoantigen-specific T cells. In some embodiments, identifying a variable sequence of a TCR from the neoantigen-specific T cells comprises sequencing DNA, RNA, or amplified products thereof from one or more neoantigen-specific T cells that encode the variable sequence. In some embodiments, identifying a variable sequence of a TCR from the neoantigen-specific T cells comprises sequencing DNA, RNA, or amplified products thereof from a single neoantigen-specific T cell that encodes the variable sequence. In some embodiments, identifying a variable sequence of a TCR from the neoantigen-specific T cells comprises sequencing barcoded DNA or barcoded RNA, or amplified products thereof, from one or more neoantigen-specific T cells that encode the variable sequence. In some embodiments, identifying a variable sequence of a TCR from the neoantigen-specific T cells comprises pairing a TCR-alpha chain with a TCR-beta chain.

[0086] In some embodiments, expressing a recombinant TCR comprises expressing the variable sequence identified from a polynucleotide comprising a sequence encoding the variable sequence identified. In some embodiments, the polynucleotide is a vector. In some embodiments, the vector is a viral vector. In some embodiments, the viral vector is a lentiviral vector. In some embodiments, expressing a recombinant TCR comprises transducing or transfecting the polynucleotide into cells. In some embodiments, the cells are a T cell line or healthy donor PMBCs.

[0087] In some embodiments, identifying one or more peptides of a peptide-MHC complex that are presented by an APC comprises expressing the one or more peptides in cells. In some embodiments, identifying one or more peptides of a peptide-MHC complex that are presented by an APC comprises loading the one or more peptides onto MHCs of cells. In some embodiments, identifying one or more peptides of a peptide-MHC complex that are presented by an APC comprises eluting or isolating a peptide of the one or more peptides from a peptide MHC complex. In some embodiments, identifying one or more peptides of a peptide-MHC complex that are presented by an APC comprises performing mass spectrometry on a peptide of the one or more peptides that was isolated or eluted from a peptide-MHC complex. In some embodiments, performing a functional assay comprises determining expression of one or more cell markers. In some embodiments, the one or more cell markers comprise TNF- α , IFN- γ , LAMP-1, 4-1BB, IL-2, IL-17A, Granzyme B, PD-1, CD25, CD69, TIM3, LAG3, CTLA-4, CD62L, CD45RA, CD45RO, FoxP3, or any combination thereof.

[0087a] Provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating ~~an immune disease or cancer~~ colorectal cancer or endometrial adenocarcinoma.

[0087b] Provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject having a ~~disease or condition~~ colorectal cancer.

[0087c] Provided herein is a use of the pharmaceutical composition as described herein in the manufacture of a medicament for treating a subject with ~~endometrial adenocarcinoma~~ cancer.

[0087d] Provided herein is a method of identifying a subject with colorectal cancer or endometrial adenocarcinoma as a candidate for a therapeutic, the method comprising determining the subject as a subject that expresses a protein encoded by an HLA-A03:01 allele or an HLA-A11:01 allele, wherein the therapeutic is the pharmaceutical composition as described herein.

[0087e] Provided herein is a recombinant nucleic acid encoding a T cell receptor (TCR) identified from isolated neoantigen-specific human T cells, comprising a TCR beta chain construct comprising a complementarity determining region 3 (CDR3) having an amino acid sequence set forth in SEQ ID NO: 52, wherein the TCR specifically binds to a mutated RAS epitope in complex with a human MHC encoded by an HLA-A11:01 allele, wherein the mutated RAS epitope is VVGAVGVGK, VVVGAVGVGK, VVGACGVGK or VVVGACGVGK.

[0087f] Provided herein is a pharmaceutical composition comprising: (a) the recombinant nucleic acid as described herein; or, the vector as described herein; or, the cell as described herein; and, (b) a pharmaceutically acceptable excipient or diluent.

CLAIMS

What is claimed is:

1. A recombinant nucleic acid encoding a T cell receptor (TCR) identified from isolated neoantigen-specific human T cells, comprising a TCR beta chain construct comprising a complementarity determining region 3 (CDR3) having an amino acid sequence set forth in SEQ ID NO: 52, wherein the TCR specifically binds to a mutated RAS epitope in complex with a human MHC encoded by an HLA-A11:01 allele, wherein the mutated RAS epitope is VVGAVGVGK, VVVGAVGVGK, VVGACGVGK or VVVGACGVGK.
2. The recombinant nucleic acid encoding a T cell receptor (TCR) of claim 1, wherein the TCR beta chain construct further comprises a complementarity determining region 1 (CDR1) and a complementarity determining region 2 (CDR2), wherein the CDR1 has an amino acid sequence set forth in SEQ ID NO: 50; and the CDR2 has an amino acid sequence set forth in SEQ ID NO: 51.
3. The recombinant nucleic acid encoding a T cell receptor (TCR) of claim 1 or claim 2, wherein the TCR beta chain construct comprises a variable region having at least 80% sequence identity to an amino acid sequence set forth in SEQ ID NO: 58.
4. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the preceding claims, wherein, the TCR beta chain construct comprises a variable region having at least 90% sequence identity to an amino acid sequence set forth in SEQ ID NO: 58.
5. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the preceding claims, wherein, the TCR beta chain construct comprises a variable region having at least 95%, 96%, 97%, 98% or 99% sequence identity to an amino acid sequence set forth in SEQ ID NO: 58.
6. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the preceding claims, wherein, the TCR beta chain construct comprises a variable region having an amino acid sequence set forth in SEQ ID NO: 58.
7. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the preceding claims, further comprising a TCR alpha chain construct having a CDR1, a CDR2, and a CDR3,
wherein, the CDR1 has an amino acid sequence set forth in SEQ ID NO: 47;
the CDR2 has an amino acid sequence set forth in SEQ ID NO: 48; and,
the ~~CDR~~CDR3 has an amino acid sequence set forth in SEQ ID NO: 49.
8. The recombinant nucleic acid of any one of the preceding claims, comprising:
 - (a) a sequence having at least 80% sequence identity with SEQ ID NOs: 56 or 57, wherein the sequence comprises a sequence encoding at least SEQ ID NO: 52; and
 - (b) a sequence having at least 80% sequence identity with SEQ ID NOs: 53 or 54, wherein the sequence comprises a sequence encoding at least SEQ ID NO: 49.

9. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the preceding claims, wherein the TCR alpha chain construct comprises a variable region having at least 80% sequence identity to an amino acid sequence set forth in SEQ ID NO: 55.
10. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the preceding claims, wherein, the TCR alpha chain construct comprises a variable region having at least 90% sequence identity to an amino acid sequence set forth in SEQ ID NO: 55.
11. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the preceding claims, wherein, the TCR alpha chain construct comprises a variable region having at least 95%, 96%, 97%, 98% or 99% sequence identity to an amino acid sequence set forth in SEQ ID NO: 55.
12. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the preceding claims, wherein, the TCR alpha chain construct comprises a variable region having an amino acid sequence set forth in SEQ ID NO: 55.
13. The recombinant nucleic acid encoding a TCR of claim 1, wherein the TCR comprises:
 - (a) a beta chain having an amino acid sequence set forth in SEQ ID NO: 60, or an amino acid sequence that is at least 80% identical to SEQ ID NO: 60.
 - (b) an alpha chain having an amino acid sequence set forth in SEQ ID NO: 59, or an amino acid sequence that is at least 80% identical to SEQ ID NO: 59.
14. The recombinant nucleic acid encoding a TCR of any one of the preceding claims, wherein the TCR binds to an epitope from human RAS comprising a mutation G12V.
- ~~15. A recombinant nucleic acid encoding a TCR comprising a TCR beta chain construct and a TCR alpha chain construct, the TCR beta chain construct comprising a complementarity determining region 3 (CDR3) having an amino acid sequence selected from SEQ ID NO: 537 and 563.~~
- ~~16. The recombinant nucleic acid of claim 15, wherein the TCR beta chain construct comprising a CDR3 having an amino acid sequence of SEQ ID NO: 537, comprises a variable region having at least 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to an amino acid sequence set forth in SEQ ID NO: 541.~~
- ~~17. The recombinant nucleic acid of claim 16, wherein the TCR alpha chain construct comprises a variable region having at least 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to an amino acid sequence set forth in SEQ ID NO: 539 or SEQ ID NO: 552.~~
- ~~18. The recombinant nucleic acid of claim 15, wherein the TCR beta chain construct comprising a CDR3 having an amino acid sequence of SEQ ID NO: 563, comprises a variable region having at least 80%, 90%, 95%, 96%, 97%, 98% or 99% sequence identity to an amino acid sequence set forth in SEQ ID NO: 567.~~

- ~~19. The recombinant nucleic acid of claim 18, wherein the TCR comprising the TCR alpha chain construct comprises a variable region having at least 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to an amino acid sequence set forth in SEQ ID NO: 565.~~
20. A vector comprising the recombinant nucleic acid of any one of the claims 1-~~19~~14.
- ~~21~~16. A cell comprising the recombinant nucleic acid of any one of the claims 1-~~19~~14 or the vector of claim ~~20~~15.
- ~~22. A recombinant nucleic acid encoding a TCR construct comprising:~~
- ~~— (a) a TCR beta chain construct, and~~
- ~~— (b) a TCR alpha chain construct;~~
- ~~— wherein the TCR recognizes and binds to an epitope from human RAS comprising a point mutation G12V or G12C, the epitope being in a human MHC protein complex, wherein the human MHC protein is an HLA antigen encoded by the HLA A*03:01 allele.~~
- ~~23. The recombinant nucleic acid of claim 22, wherein the TCR beta chain construct comprises a CDR3 having an amino acid sequence set forth in SEQ ID NO: 68.~~
- ~~24. The recombinant nucleic acid encoding a T cell receptor (TCR) of claim 22, wherein the TCR beta chain construct further comprises a complementarity determining region 1 (CDR1) and a complementarity determining region 2 (CDR2), wherein the CDR1 has an amino acid sequence set forth in SEQ ID NO: 66; and the CDR2 has an amino acid sequence set forth in SEQ ID NO: 67.~~
- ~~25. The recombinant nucleic acid encoding a T cell receptor (TCR) of claim 23 or claim 24, further comprising a TCR alpha chain construct having a CDR1, a CDR2, and a CDR3,~~
- ~~— wherein, the CDR1 has an amino acid sequence set forth in SEQ ID NO: 63;~~
- ~~— the CDR2 has an amino acid sequence set forth in SEQ ID NO: 64; and,~~
- ~~— the CDR has an amino acid sequence set forth in SEQ ID NO: 65.~~
- ~~26. The recombinant nucleic acid encoding a T cell receptor (TCR) of 17. The recombinant nucleic acid of any one of the claims 23-25, wherein the TCR beta chain construct comprises a variable region having at least 80%, or at least 90%, 95%, 96%, 97%, 98% or 99% sequence identity to an amino acid sequence set forth in SEQ ID NO: 74.~~
- ~~27. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 23-26, wherein, the TCR beta chain construct comprises a variable region having an amino acid sequence set forth in SEQ ID NO: 74.~~
- ~~28. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 23-27, wherein the TCR alpha chain construct comprises a variable region having at least 80%, or at least 90%, 95%, 96%, 97%, 98% or 99% sequence identity to an amino acid sequence set forth in SEQ ID NO: 71.~~

- ~~29. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 23-28, wherein the TCR alpha chain construct comprises a variable region having an amino acid sequence set forth in SEQ ID NO: 71.~~
- ~~30. A vector comprising a recombinant nucleic acid of any one of the claims 23-29.~~
- ~~31. A cell comprising any one of the recombinant nucleic acid of any one of the claims 23-29 or the vector of claim 30.~~
- ~~32. The recombinant nucleic acid of claim 22, wherein the TCR beta chain construct comprises a CDR3 having an amino acid sequence set forth in SEQ ID NO: 84.~~
- ~~33. The recombinant nucleic acid encoding a T cell receptor (TCR) of claim 32, wherein the TCR beta chain construct further comprises a complementarity determining region 1 (CDR1) and a complementarity determining region 2 (CDR2), wherein the CDR1 has an amino acid sequence set forth in SEQ ID NO: 82; and the CDR2 has an amino acid sequence set forth in SEQ ID NO: 83.~~
- ~~34. The recombinant nucleic acid encoding a T cell receptor (TCR) of claim 32 or claim 33, further comprising a TCR alpha chain construct having a CDR1, a CDR2, and a CDR3, wherein, the CDR1 has an amino acid sequence set forth in SEQ ID NO: 79;~~
- ~~the CDR2 has an amino acid sequence set forth in SEQ ID NO: 80; and,~~
- ~~the CDR3 has an amino acid sequence set forth in SEQ ID NO: 81.~~
- ~~35. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 32-34, wherein the TCR beta chain construct comprises a variable region having at least 80%, or at least 90%, 95%, 96%, 97%, 98% or 99% sequence identity to an amino acid sequence set forth in SEQ ID NO: 90.~~
- ~~36. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 32-35, wherein, the TCR beta chain construct comprises a variable region having an amino acid sequence set forth in SEQ ID NO: 90.~~
- ~~37. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 32-36, wherein the TCR alpha chain construct comprises a variable region having at least 80%, or at least 90%, 95%, 96%, 97%, 98% or 99% sequence identity to an amino acid sequence set forth in SEQ ID NO: 87.~~
- ~~38. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 32-37, wherein the TCR alpha chain construct comprises a variable region having an amino acid sequence set forth in SEQ ID NO: 87.~~
- ~~39. A vector comprising the recombinant nucleic acid of any one of the claims 32-38.~~
- ~~40. A cell comprising any one of the recombinant nucleic acid of any one of the claims 32-38 or the vector of claim 39.~~

- ~~41. The recombinant nucleic acid of claim 22, wherein the TCR beta chain construct comprises a CDR3 having an amino acid sequence set forth in SEQ ID NO: 388.~~
- ~~42. The recombinant nucleic acid encoding a T cell receptor (TCR) of claim 41, wherein the TCR beta chain construct further comprises a complementarity determining region 1 (CDR1) and a complementarity determining region 2 (CDR2), wherein the CDR1 has an amino acid sequence set forth in SEQ ID NO: 386; and the CDR2 has an amino acid sequence set forth in SEQ ID NO: 387.~~
- ~~43. The recombinant nucleic acid encoding a T cell receptor (TCR) of claim 41 or claim 42, further comprising a TCR alpha chain construct having a CDR1, a CDR2, and a CDR3, wherein, the CDR1 has an amino acid sequence set forth in SEQ ID NO: 383; the CDR2 has an amino acid sequence set forth in SEQ ID NO: 384; and, the CDR has an amino acid sequence set forth in SEQ ID NO: 385.~~
- ~~44. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 41-43, wherein the TCR beta chain construct comprises a variable region having at least 80%, or at least 90%, 95%, 96%, 97%, 98% or 99% sequence identity to an amino acid sequence set forth in SEQ ID NO: 394.~~
- ~~45. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 41-44, wherein, the TCR beta chain construct comprises a variable region having an amino acid sequence set forth in SEQ ID NO: 394.~~
- ~~46. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 32-36, wherein the TCR alpha chain construct comprises a variable region having at least 80%, or at least 90%, 95%, 96%, 97%, 98% or 99% sequence identity to an amino acid sequence set forth in SEQ ID NO: 391.~~
- ~~47. The recombinant nucleic acid encoding a T cell receptor (TCR) of any one of the claims 32-37, wherein the TCR alpha chain construct comprises a variable region having an amino acid sequence set forth in SEQ ID NO: 391.~~
- ~~48. A recombinant vector comprising the recombinant nucleic acid of any one of the claims 41-47.~~
- ~~49. A cell comprising any one of the recombinant nucleic acid of any one of the claims 41-47 or the vector of claim 48.~~
- ~~50. The nucleic acid of any one of claims 1-49, wherein the epitope has a length of from 8-25 amino acids.~~
- ~~51. The nucleic acid of any one of claims 1-50, wherein the epitope comprises a mutation that differs from the wild type epitope by at least one amino acid.~~

- ~~52.~~ The nucleic acid of any one of claims ~~1-51~~, wherein the ~~1-14~~, wherein the mutated RAS epitope binds to the human MHC with ~~a greater~~an affinity that is 100 times more than that of a corresponding wild-type epitope.
- ~~53~~18. The recombinant nucleic acid of any one of claims 1-~~52~~14 and 17, wherein the mutated RAS epitope binds to the human MHC with a KD or an IC50 less than 500 nM, 250 nM, 150 nM, 100 nM, 50 nM, 25 nM or 10 nM.
- ~~54~~19. The nucleic acid of any one of claims 1-~~53~~14, 17 and 18, wherein the ~~mutation~~mutated RAS epitope is not present in non-cancer cells of a subject.
- ~~55~~20. The recombinant nucleic acid of any one of claims 1-~~54~~14, 17-19, wherein the TCR binds to a MHC-peptide complex with a KD or an IC50 of less than 500 nM, 250 nM, 150 nM, 100 nM, 50 nM, 25 nM or 10 nM.
- ~~56~~21. The recombinant nucleic acid of any one of claims 1-~~55~~14, 17-20, wherein the nucleic acid is operably linked to a promoter.
- ~~57~~22. The cell of any one of the claims ~~21, 31, 40, and 49~~, 16, wherein the cell is a CD4+ T cell.
- ~~58~~23. The cell of any one of the claims ~~21, 31, 40, and 49~~16, wherein the cell is a CD8+ T cell.
- ~~59~~24. The cell of any one of the claims ~~21, 31, 40, and 49~~16, wherein the cell is isolated from a subject having a RAS mutation.
- ~~60~~25. A pharmaceutical composition comprising:
 (a) the recombinant nucleic acid of any one of claims 1-~~56~~14, 17-21; or,
 the vector of ~~any one of claims~~ claim ~~15, 25, 34, 43~~; or,
 the cell of ~~any one of claims 16, 26, 35, 44~~claim 16; and,
~~and~~, (b) a pharmaceutically acceptable excipient or diluent.
- ~~61~~26. The pharmaceutical composition of claim ~~55~~25, further comprising an immunomodulatory agent or an adjuvant.
- ~~62~~27. The pharmaceutical composition of claim ~~56~~26, wherein the adjuvant is poly I:C.
- ~~63.~~ ~~The~~28. Use of the pharmaceutical composition of any one of claims ~~60-62~~25-27 in the manufacture of a medicament for ~~use in~~-treating ~~an immune disease or a colorectal cancer or~~ endometrial adenocarcinoma.
- ~~64~~29. Use of the pharmaceutical composition of any one of claims ~~60-62~~25-27 in the manufacture of a medicament for treating ~~an immune disease or a~~ subject having a colorectal cancer.
- ~~65~~30. Use of the pharmaceutical composition of any one of claims ~~60-63 in the manufacture of a~~ medicament for treating a subject having a disease or condition.
- ~~66.~~ ~~Use of the pharmaceutical composition of any one of claims 60-63~~25-27 in the manufacture of a medicament for treating a subject with ~~cancer~~endometrial adenocarcinoma.

~~67~~31. A method of identifying a subject with ~~cancer~~colorectal cancer or endometrial adenocarcinoma as a candidate for a therapeutic, the method comprising determining the subject as a subject that expresses a protein encoded by an HLA-A03:01 allele or an HLA-A11:01 allele, wherein the therapeutic is the pharmaceutical composition selected from any one of claims ~~60-63~~25-27.