

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.

[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.

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

CLAIMS

What is claimed is:

1. A recombinant nucleic acid encoding a T cell receptor (TCR) 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.
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 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.
21. A cell comprising the recombinant nucleic acid of any one of the claims 1-19 or the vector of claim 20.
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 A03:01 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 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 epitope binds to the human MHC with a greater affinity than a corresponding wild-type epitope.
53. The nucleic acid of any one of claims 1-52, wherein the 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. The nucleic acid of any one of claims 1-53, wherein the mutation is not present in non-cancer cells of a subject.
55. The nucleic acid of any one of claims 1-54, 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. The nucleic acid of any one of claims 1-55, wherein the nucleic acid is operably linked to a promoter.
57. The cell of any one of the claims 21, 31, 40, and 49, wherein the cell is a CD4+ T cell.
58. The cell of any one of the claims 21, 31, 40, and 49, wherein the cell is a CD8+ T cell.
59. The cell of any one of the claims 21, 31, 40, and 49, wherein the cell is isolated from a subject having a RAS mutation.
60. A pharmaceutical composition comprising:
 - (a) the nucleic acid of any one of claims 1-56; or,

the vector of any one of claims 15, 25, 34, 43; or,

the cell of any one of claims 16, 26, 35, 44;

and, (b) a pharmaceutically acceptable excipient or diluent.

61. The pharmaceutical composition of claim 55, further comprising an immunomodulatory agent or an adjuvant.
62. The pharmaceutical composition of claim 56, wherein the adjuvant is poly I:C.
63. The pharmaceutical composition of any one of claims 60-62, for use in treating an immune disease or cancer.
64. Use of the pharmaceutical composition of any one of claims 60-62 in the manufacture of a medicament for treating an immune disease or cancer.
65. 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 in the manufacture of a medicament for treating a subject with cancer.
67. A method of identifying a subject with cancer 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.