Claims

1. A nucleic acid molecule comprising

(a) a first nucleotide sequence encoding a recombinant T cell receptor (TCR) or an antigen binding portion thereof that specifically binds to an epitope of tyrosinase consisting of an amino acid sequence as set forth in SEQ ID NO: 51 (“anti-tyrosinase TCR”), wherein the epitope is complexed with an HLA class I molecule HLA-C*05 allele; wherein the anti-tyrosinase TCR comprises an alpha chain and a beta chain, wherein the alpha chain comprises a variable domain comprising an alpha chain CDR1, an alpha chain CDR2, and an alpha chain CDR3; and wherein the beta chain comprises a variable domain comprising a beta chain CDR1, a beta chain CDR2, and a beta chain CDR3; and wherein:

(i) the beta chain CDR3 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 10;

(ii) the beta chain CDR2 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 9;

(iii) the beta chain CDR1 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 8;

(iv) the alpha chain CDR3 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 7;

(v) the alpha chain CDR2 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 6; and

(vi) the alpha chain CDR1 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 51; and

(b) a second nucleotide sequence, wherein the second nucleotide sequence or the polypeptide encoded by the second nucleotide sequence inhibits the expression of an endogenous TCR.

2. The nucleic acid molecule of claim 1, wherein the HLA class I molecule is an HLA-C*05 allele, optionally selected from an HLA-C*05:01 allele, an HLA-C*05:03 allele, an HLA-C*05:04 allele, an HLA-C*05:05 allele, and an HLA-C*05:06 allele.

3. The nucleic acid molecule of claim 1 or 2, wherein:

(a) the alpha chain variable domain of the anti-tyrosinase TCR comprises the amino acid sequence of the variable domain present in the amino acid sequence set forth in SEQ ID NO: 1;

(b) the beta chain variable domain of the anti-tyrosinase TCR comprises the amino acid sequence of the variable domain present in the amino acid sequence set forth in SEQ ID NO: 2; or

(c) boh (a) and (b).

4. The nucleic acid molecule of any one of claims 1 to 3, wherein the alpha chain of the anti-tyrosinase TCR further comprises a constant region, wherein the constant region is different from endogenous constant region of the alpha chain, and wherein

(ii) the alpha chain constant region comprises an amino acid sequence having at least about 85% sequence identity to the constant region present in the amino acid sequence set forth in SEQ ID NO: 1; or

(ii) the alpha chain constant region comprises an amino acid sequence comprising at least 1 amino acid substitution relative to the constant region present in the amino acid sequence set forth in SEQ ID NO: 1.

5. The nucleic acid molecule of any one of claims 1 to 4, wherein the beta chain of the anti-tyrosinase TCR further comprises a constant region, wherein the constant region is different from endogenous constant regions of the beta chain, and wherein

(i) the beta chain constant region comprises an amino acid sequence having at least about 85% sequence identity to the constant region present in the amino acid sequence set forth in SEQ ID NO: 2; or

(ii) the beta chain constant region comprises an amino acid sequence comprising at least 1 amino acid substitution relative to the constant region present in the amino acid sequence set forth in SEQ ID NO: 2.

6. The nucleic acid molecule of any one of claims 1 to 5, wherein:

(i) the alpha chain comprises the amino acid sequence set forth in SEQ ID NO: 1,

(ii) the beta chain comprises the amino acid sequence set forth in SEQ ID NO: 2, or

(iii) both (i) and (ii).

7. The nucleic acid molecule of any one of claims 1 to 6, wherein the second nucleotide sequence

(i) is one or more siRNAs that reduce the expression of endogenous TCRs, wherein the one or more siRNAs are complementary to a target sequence within a nucleotide sequence encoding a constant region of the endogenous TCRs;

(ii) encodes Cas9; or

(iii) both (i) and (ii).

8. The nucleic acid molecule of claim 7, wherein the one or more siRNAs comprise one or more nucleotide sequences selected from the group consisting of SEQ ID NOs: 57-60.

9. The nucleic acid molecule of any one of claims 1 to 8, wherein the recombinant TCR or an antigen binding portion thereof comprises an alpha chain constant region, a beta chain constant region, or both; and wherein the alpha chain constant region, the beta chain constant region, or both comprises an amino acid sequence having at least 1 substitution within the target sequence relative to the corresponding amino acid sequence of an endogenous TCR.

10. A vector comprising the nucleic acid molecule of any one of claims 1 to 9.

11. A T cell receptor (TCR) or an antigen binding portion thereof comprising the alpha chain variable domain of the recombinant TCR or an antigen binding portion thereof of any one of claims 1 to 9 and the beta chain variable domain of the recombinant TCR or an antigen binding portion thereof of any one of claims 1 to 9.

12. A recombinant T cell receptor (TCR) or an antigen binding portion thereof ("recombinant TCR") that specifically binds human tyrosinase ("anti-tyrosinase TCR"), wherein the anti-tyrosinase TCR comprises an alpha chain and a beta chain, wherein the alpha chain comprises a variable domain comprising an alpha chain CDR1, an alpha chain CDR2, and an alpha chain CDR3; and wherein the beta chain comprises a variable domain comprising a beta chain CDR1, a beta chain CDR2, and a beta chain CDR3; and wherein:

(i) the beta chain CDR3 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 10;

(ii) the beta chain CDR2 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 9;

(iii) the beta chain CDRI of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 8;

(iv) the alpha chain CDR3 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 7;

(v) the alpha chain CDR2 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 6; and

(vi) the alpha chain CDR1 of the anti-tyrosinase TCR comprises an amino acid sequence as set forth in SEQ ID NO: 51.

13. The recombinant TCR of claim 12, wherein the alpha chain variable domain comprises the amino acid sequence of the variable domain present in the amino acid sequence set forth in SEQ ID NO: 1.

14. The recombinant TCR of claim 12 or 13 wherein the beta chain variable domain comprises the amino acid sequence of the variable domain present in the amino acid sequence set forth SEQ ID NO: 2.

15. The recombinant TCR of any one of claims 12 to 14, wherein the alpha chain further comprises a constant region, wherein the alpha chain constant region comprises an amino acid sequence having at least about 85% sequence identity to the constant region present in the amino acid sequence set forth in SEQ ID NO: 1.

16. The recombinant TCR of any one of claims 12 to 15, wherein the beta chain further comprises a constant region, and wherein the beta chain constant region comprises an amino acid sequence having at least about 85% sequence identity to the constant region present in the amino acid sequence set forth in SEQ ID NO: 2

17. The recombinant TCR of any one of claims 12 to 16, wherein:

    (a) the alpha chain comprises the amino acid sequence set forth in SEQ ID NO: 1;

    (b) the beta chain comprises the amino acid sequence set forth in SEQ ID NO: 2; or

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

18. A bispecific TCR comprising a first antigen-binding domain and a second antigen-binding domain, wherein the first antigen-binding domain comprises the TCR or an antigen-binding portion thereof of claim 11 or the recombinant TCR of any one of claims 12 to 17.

19. A cell comprising the nucleic acid molecule of any one of claims 1 to 9 or the vector of claim 10, wherein the cell is optionally selected from a T cell, a natural killer (NK) cell, a natural killer T (NKT) cell, and an ILC cell.

20. The cell of claim 19 for use in treating a cancer in a subject in need thereof.