CLAIMS

1. A method of identifying an MHC class II-specific T cell receptor (TCR) comprising contacting a T cell with a complex comprising an MHC class II molecule and a peptide;

wherein the T cell expresses CD4 and one or more TCRs;

wherein the MHC class II molecule comprises an alpha chain and a beta chain, wherein the MHC class II molecule has a higher affinity for CD4 than a naturally occurring MHC class II molecule has for the CD4; and

wherein the MHC class II-specific TCR specifically binds the complex comprising the MHC class II molecule and the peptide.

2. The method of claim 1, wherein

(i) the beta chain of the MHC class II molecule comprises an amino acid sequence having one or more mutations relative to a wild-type beta chain of a MHC class II molecule;

(ii) the alpha chain of the MHC class II molecule comprises an amino acid sequence having one or more mutations relative to a wild-type alpha chain of a MHC class II molecule; or

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

3. The method of claim 1 or 2, wherein

(a) (i) the beta chain of the HLA class II molecule is an HLA-DP allele, (ii) the alpha chain of the HLA class II molecule is an HLA-DP allele, or (iii) both (i) and (ii);

(b) (i) the beta chain of the HLA class II molecule is an HLA-DQ allele, (ii) the alpha chain of the HLA class II molecule is an HLA-DQ allele, or (iii) both (i) and (ii); or

(c) (i) the beta chain of the HLA class II molecule is an HLA-DR allele, (ii) the alpha chain of the HLA class II molecule is an HLA-DR allele, of (iii) both (i) and (ii).

4. The method of any one of claims 1 to 3, wherein

(a) (i) the beta chain of the HLA class II molecule comprises a DP1, DP2, DP3, DP4, DP5, DP6, DP8, or DP9 allele;

(ii) the alpha chain of the MHC class II molecule comprises an HLA-DPA1*01, HLA-DPA1*02, HLA-DPA1*03, or HLA-DPA1*04 allele; or

(iii) both (i) and (ii);

(b) (i) the beta chain of the HLA class II molecule comprises a DQ2, DQ3, DQ4, DQ5, or DQ6 allele;

(ii) the alpha chain of the MHC class II molecule comprises an HLA-DQA1*01, HLA-DQA1*02, HLA-DQA1*03, HLA-DQA1*04, HLA-DQA1*05, or HLA-DQA1*06 allele; or

(iii) both (i) and (ii); or

(c) (i) the beta chain of the HLA class II molecule comprises a DR2, DR3, DR4, DR5, DR6, DR7, DR8, DR9, DR10, DR11, DR12, DR13, DR14, DR15, or DR16 allele;

(ii) the alpha chain of the MHC class II molecule comprises an HLA-DRA1*01 allele; or

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

5. The method of claim 3 or 4, wherein

(i) the beta chain of the MHC class II molecule comprises an amino acid other than leucine at a position corresponding to amino acid residue 112 of SEQ ID NO: 1;

(ii) the beta chain of the MHC class II molecule comprises an amino acid other than valine at a position corresponding to amino acid residue 141 of SEQ ID NO: 1; or

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

6. The method of claim 5, wherein

(i) the amino acid other than leucine at a position corresponding to amino acid residue 112 of SEQ ID NO: 1 comprises a hydrophobic side chain;

(ii) the amino acid other than valine at a position corresponding to amino acid residue 141 of SEQ ID NO: 1 comprises a hydrophobic side chain; or

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

7. The method of claim 5 or 6, wherein

(i) the amino acid other than leucine at a position corresponding to amino acid residue 112 of SEQ ID NO: 1 is selected from the group consisting of an alanine, a valine, an isoleucine, a methionine, a phenylalanine, a tyrosine, and a tryptophan; ;

(ii) wherein the amino acid other than valine at a position corresponding to amino acid residue 141 of SEQ ID NO: 1 is selected from an alanine, an isoleucine, a leucine, a methionine, a phenylalanine, a tyrosine, and a tryptophan; or

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

8. The method of any one of claims 5 to 7, wherein

(i) the amino acid other than leucine at a position corresponding to amino acid residue 112 of SEQ ID NO: 1 is a tryptophan;

(ii) the amino acid other than valine at a position corresponding to amino acid residue 141 of SEQ ID NO: 1 is a methionine; or

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

9. The method of any one of claims 3 to 8, wherein the beta chain of the MHC class II molecule comprises

(a) an amino acid other than leucine at a position corresponding to amino acid residue 114 of SEQ ID NO: 11;

(b) an amino acid other than valine at a position corresponding to amino acid residue 143 of SEQ ID NO: 11; and

(c) at least three of:

(i) an amino acid other than asparagine at a position corresponding to amino acid residue 110 of SEQ ID NO: 11,

(ii) an amino acid other than isoleucine at a position corresponding to amino acid residue 116 of SEQ ID NO: 11,

(iii) an amino acid other than serine at a position corresponding to amino acid residue 118 of SEQ ID NO: 11, and

(iv) an amino acid other than proline at a position corresponding to amino acid residue 146 of SEQ ID NO: 11.

10. The method of claim 9, wherein

(i) the amino acid other than leucine at a position corresponding to amino acid residue 114 of SEQ ID NO: 11 is selected from the group consisting of an alanine, a valine, an isoleucine, a methionine, a phenylalanine, a tyrosine, and a tryptophan;

(ii) the amino acid other than valine at a position corresponding to amino acid residue 143 of SEQ ID NO: 11 is selected from an alanine, an isoleucine, a leucine, a methionine, a phenylalanine, a tyrosine, and a tryptophan;

(iii) the amino acid other than asparagine at a position corresponding to amino acid residue 110 of SEQ ID NO: 11 is selected from a serine, a threonine, and a glutamine;

(iv) the amino acid other than isoleucine at a position corresponding to amino acid residue 116 of SEQ ID NO: 11 is selected from an alanine, a valine, a leucine, a methionine, a phenylalanine, a tyrosine, and a tryptophan;

(v) the amino acid other than serine at a position corresponding to amino acid residue 118 of SEQ ID NO: 11 is selected from an arginine, a histidine, and a lysine;

(vi) the amino acid other than proline at a position corresponding to amino acid residue 146 of SEQ ID NO: 11 is selected from a serine, a threonine, an asparagine, and a glutamine; or

(vii) any combination of (i)-(vi).

11. The method of claim 9 or 10, wherein

(i) the amino acid other than leucine at a position corresponding to amino acid residue 114 of SEQ ID NO: 11 is a tryptophan;

(ii) the amino acid other than valine at a position corresponding to amino acid residue 143 of SEQ ID NO: 11 is a methionine;

(iii) the amino acid other than asparagine at a position corresponding to amino acid residue 110 of SEQ ID NO: 11 is a glutamine;

(iv) the amino acid other than isoleucine at a position corresponding to amino acid residue 116 of SEQ ID NO: 11 is valine;

(v) the amino acid other than serine at a position corresponding to amino acid residue 118 of SEQ ID NO: 11 is a histidine;

(vi) the amino acid other than proline at a position corresponding to amino acid residue 146 of SEQ ID NO: 11 is a glutamine; or

(vii) any combination of (i)-(vi).

12. The method of any one of claims 3 to 11, wherein the beta chain comprises:

(a) an amino acid other than leucine at a position corresponding to amino acid residue 114 of SEQ ID NO: 19;

(b) an amino acid other than valine at a position corresponding to amino acid residue 143 of SEQ ID NO: 19; and

(c) at least two of:

(i) an amino acid other than serine at a position corresponding to amino acid residue 118 of SEQ ID NO: 19,

(ii) an amino acid other than lysine at a position corresponding to amino acid residue 139 of SEQ ID NO: 19,

(iii) an amino acid other than glycine at a position corresponding to amino acid residue 146 of SEQ ID NO: 19,

(iv) an amino acid other than threonine at a position corresponding to amino acid residue 157 of SEQ ID NO: 19,

(v) an amino acid other than threonine at a position corresponding to amino acid residue 163 of SEQ ID NO: 19, and

(vi) an amino acid other than valine at a position corresponding to amino acid residue 164 of SEQ ID NO: 19.

13. The method of claim 12, wherein

(i) the amino acid other than leucine at a position corresponding to amino acid residue 114 of SEQ ID NO: 19 comprises a hydrophobic side chain;

(ii) the amino acid other than valine at a position corresponding to amino acid residue 143 of SEQ ID NO: 19 comprises a hydrophobic side chain;

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

14. The method of claim 12 or 13, wherein

(i) the amino acid other than leucine at a position corresponding to amino acid residue 114 of SEQ ID NO: 19 is selected from the group consisting of an

alanine, a valine, an isoleucine, a methionine, a phenylalanine, a tyrosine, and a tryptophan;

(ii) the amino acid other than valine at a position corresponding to amino acid residue 143 of SEQ ID NO: 19 is selected from an alanine, an isoleucine, a leucine, a methionine, a phenylalanine, a tyrosine, and a tryptophan;

(iii) the amino acid other than serine at a position corresponding to amino acid residue 118 of SEQ ID NO: 19 is selected from an arginine, a histidine, and a lysine;

(iv) the amino acid other than lysine at a position corresponding to amino acid residue 139 of SEQ ID NO: 19 is selected from a serine, a threonine, and a glutamine;

(v) the amino acid other than glycine at a position corresponding to amino acid residue 146 of SEQ ID NO: 19 is selected from a serine, an asparagine, a threonine, and a glutamine;

(vi) the amino acid other than threonine at a position corresponding to amino acid residue 157 of SEQ ID NO: 19 is selected from an alanine, a valine, an isoleucine, a leucine, a methionine, a phenylalanine, a tyrosine, and a tryptophan;

(vii) the amino acid other than threonine at a position corresponding to amino acid residue 163 of SEQ ID NO: 19 is selected from an alanine, a valine, an isoleucine, a leucine, a methionine, a phenylalanine, a tyrosine, and a tryptophan;

(viii) the amino acid other than valine at a position corresponding to amino acid residue 164 of SEQ ID NO: 19 is selected from a serine, an asparagine, a threonine, and a glutamine; or

(ix) any combination of (i)-(viii).

15. The method of any one of claims 12 to 14, wherein

(i) the amino acid other than leucine at a position corresponding to amino acid residue 114 of SEQ ID NO: 19 is a tryptophan;

(ii) the amino acid other than valine at a position corresponding to amino acid residue 143 of SEQ ID NO: 19 is a methionine;

(iii) wherein the amino acid other than serine at a position corresponding to amino acid residue 118 of SEQ ID NO: 19 is a histidine;

(iv) wherein the amino acid other than lysine at a position corresponding to amino acid residue 139 of SEQ ID NO: 19 is a threonine;

(v) the amino acid other than glycine at a position corresponding to amino acid residue 146 of SEQ ID NO: 19 is a glutamine;

(vi) the amino acid other than threonine at a position corresponding to amino acid residue 157 of SEQ ID NO: 19 is an isoleucine;

(vii) the amino acid other than threonine at a position corresponding to amino acid residue 163 of SEQ ID NO: 19 is a methionine;

(viii) the amino acid other than valine at a position corresponding to amino acid residue 164 of SEQ ID NO: 19 is a threonine; or

(ix) any combination of (i)-(viii).

16. The method of any one of claims 1 to 15, wherein the MHC class II molecule is a dimer, a trimer, or a tetramer.

17. The method of any one of claims 1 to 16, wherein the peptide comprises a fragment of a protein, comprising at least about 10 amino acids.

18. The method of any one of claims 1 to 17, wherein

(i) the MHC class II molecule is expressed on the surface of an antigen presenting cell;

(ii) the T cell is obtained from a human subject;

(iii) the T cell is a tumor infiltrating lymphocyte (TIL);

(iv) the MHC class II molecule has an affinity for CD4 that is at least about 2-fold higher than the binding affinity of a naturally occurring MHC class II molecule to CD4; or

(v) any combination of (i)-(iv).

19. The method of any one of claims 1 to 18, further comprising

(i) selecting the T cell that is bound by the MHC class II molecule;

(ii) isolating the TCR that is bound to the MHC class II molecule;

(iii) sequencing the TCR;

(iv) cloning the TCR;

(v) recombinantly expressing the TCR in a host cell;

(vi) both (i) and (ii);

(vii) a combination of (i), (ii), and (iii);

(viii) a combination of (i), (ii), and (iv);

(ix) a combination of (i), (ii), (iii), and (iv);

(x) a combination of (i), (ii), (iii), and (v);

(xi) a combination of (i), (ii), (iv), and (v); or

(xii) a combination of (i), (ii), (iii), (iv), and (v).

20. The method of any one of claims 1 to 19, wherein the MHC class II molecule binds CD4 with a K_D of less than about 100 μM.