CLAIMS

1. A method for determining a tolerant fraction (TF) score indicative of a risk of developing an immune-related adverse event (irAE) from immune checkpoint inhibitor (ICI) therapy, the method comprising:

a) classifying T cell receptor β (TCRβ) genes of one or more isolated T-cells as productive TCRβ gene or repaired TCRβ gene;

b) classifying TCRβ genes of one or more isolated T-cells from a donor pool as a productive TCRβ gene or repaired TCRβ gene; and

c) calculating a tolerant fraction (*TF*) score, wherein the *TF* score is a ratio of a productive fraction (F_{PROD}) and a total fraction (F_{TOTAL}), wherein F_{PROD} is the number of TCRβ genes identified as productive TCRβ genes from the subject that overlap with TCRβ genes identified as productive TCRβ genes from the pool of donors, and F_{TOTAL} is sum of the number of TCRβ genes identified as productive TCRβ genes that overlap with TCRβ genes identified as productive TCRβ genes from the donor pool and the number of TCRβ genes identified as productive TCRβ genes that overlap with TCRβ genes identified as repaired TCRβ genes from the donor pool , thereby predicting a risk of developing irAE from ICI therapy in a subject from whom the one or more isolated T-cells in (a) were obtained;

and wherein the method is performed in vitro.

2. The method of claim 1, wherein productive TCRβ genes can produce a T cell receptor (TCR) that is tolerant to self-antigens, and wherein the repaired TCRβ genes can produce a TCR that is not tolerant to self-antigens, optionally wherein TCRs that are not tolerant to self-antigens can induce auto-immune toxicity.

3. The method of any one of claims 1-2, further comparing the *TF* score to a *TF* threshold, wherein a *TF* score greater than the *TF* threshold indicates a lower risk of developing irAE from ICI therapy and a *TF* score lower than the *TF* threshold indicates a higher risk of developing irAE from ICI therapy.

4. The method of claim 3, wherein the *TF* threshold is about 82.5%.

5. The method of any one of claims 1-4, wherein the risk is predicted prior to a treatment with an ICI therapy.

6. The method of any one of claims 1-5, further comprising the method to be

administered to the subject having a lower risk of developing irAE an ICI therapy.

7. The method of any one of claims 1-6, wherein classifying TCRβ genes comprise:

obtaining TCRβ genes sequences comprising multiple gene segments and somatic alterations;

translating at least one of the multiple gene segments or somatic alterations into an amino acid sequence;

identifying a TCRβ gene encoding an amino acid sequence capable of antigen recognition as a productive TCRβ gene;

identifying a TCRβ gene without an amino acid sequence capable of antigen recognition as a non-productive TCRβ gene;

repairing the amino acid sequence of a TCRβ gene identified as non-productive to generate a repaired TCRβ gene capable of antigen recognition: and

classifying the TCRβ gene as a productive TCRβ genes or as a repaired TCRβ genes.

8. The method of claim 7, wherein the gene segments are selected from the group consisting of variable (V) gene segments, diversity (D) gene segments, joining (J) gene segments, and any combination thereof.

9. The method of any one of claims 7-8, wherein the non-productive TCRβ gene is a TCRβ gene with out-of-frame gene segments or a TCRβ gene with a stop codon in a somatic junction between gene segments.

10. The method of any one of claims 7-9, wherein repairing non-productive TCRβ gene comprises adding or removing one or more nucleotides at a somatic junction between gene segments to bring the gene segments in a same reading frame and/or mutating a nucleotide in a somatic region between gene segments to convert a stop codon into an amino acid.

11. The method of any one of claims 7-10, wherein the TCRβ gene sequence comprises a complimentary determining region 1 (CDR1) sequence of the TCRβ gene, a CDR2 sequence of the TCRβ gene, a CDR3 sequence of the TCRβ gene, a combination thereof, or a sequence of a complete TCRβ gene, optionally wherein the TCRβ gene sequence comprises a CDR3 sequence of the TCRβ gene, optionally wherein the method comprises removing the first three amino acids and the last three amino acids of the CDR3 sequences from the TCRβ gene sequence.

12. The method of any one of claims 7-11, wherein obtaining a TCRβ gene sequence comprises sequencing TCRβ genes from a peripheral blood mononucleated cell sample from the subject; optionally wherein obtaining a TCRβ gene sequence further comprises isolating T cells from the sample, optionally wherein isolating T cells is by cell sorting and/or RNA expression, optionally wherein the T cells are non-regulatory T cells.

13. The method of any one of claims 1-12, wherein the cell is a peripheral blood mononucleated cell from a subject having cancer.

14. The method of claim 13, wherein the cancer is selected from the group consisting of melanoma, prostate cancer, non-small cell lung cancer, mesothelioma, bladder cancer and renal cancer.

15. The method of any one of claims 1-14, wherein the ICI therapy is selected from the group consisting of ipilimumab, tremelimumab, atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab, ipilimumab plus nivolumab, and combinations thereof.