CLAIMS

What is claimed is:

1. A mouse or an isolated mouse cell comprising:

(i) an unrearranged T cell receptor (TCR) α variable region sequence comprising at least one unrearranged human T cell variable region Vα segment and at least one unrearranged human T cell variable region Jα segment operably linked to a mouse TCR α constant gene sequence, optionally at an endogenous mouse TCR α variable gene locus, and

(ii) an unrearranged TCR β variable region sequence comprising at least one unrearranged human T cell variable region Vβ segment, at least one unrearranged human T cell variable region Dβ segment, and at least one unrearranged human T cell variable region Jβ segment operably linked to a mouse TCR β constant gene sequence, optionally at an endogenous mouse TCR β variable gene locus, wherein the unrearranged TCR β variable region sequence comprises a mouse TCRB non-coding sequence comprising:

a TCRBDJ1 non-coding sequence, e.g., a contiguous non-coding sequence comprising non-coding recombinant signal sequences (RSSs) and other non-coding intergenic sequences found between a unrearranged TRBD1 segment and a TRBJ1 segment and/or between any two consecutive unrearranged TRBJ1 segments, and/or

a TCRBDJ2 non-coding sequence, e.g., a contiguous non-coding sequence comprising non-coding recombinant signal sequences (RSSs) and other non-coding intergenic sequences found between a unrearranged TRBD2 segment and a TRBJ2 segment and/or between any two consecutive unrearranged TRBJ2 segments,

wherein the unrearranged human T cell variable region segments are capable of rearranging in a T cell to form genes that encode human T cell receptor variable domains that specifically bind an antigen of interest.

2. The mouse or isolated mouse cell of claim 1, wherein:

(i) the at least one unrearranged human T cell variable region Vα segment comprises a repertoire of unrearranged human T cell variable region Vα segments, the at least one unrearranged human T cell variable region Jα segment comprises a repertoire of unrearranged human T cell variable region Jα gene segments, and

(ii) the at least one unrearranged human T cell variable region Vβ segment comprises a repertoire of unrearranged human Vβ segments, the at least one unrearranged human T cell variable region Dβ segment comprises an unrearranged human T cell variable region Dβ1 segment and an unrearranged human T cell variable region Dβ2 segment, and the at least one unrearranged human T cell variable region Jβ segment comprises at least one unrearranged human T cell variable region Jβ1 segment and at least one unrearranged human T cell variable region Jβ2 segment,

wherein the mouse TCRB non-coding sequence comprises (i) a mouse TCRBD1-TCRBJ1 non-coding nucleic acid sequence between the at least one unrearranged human T cell variable region Dβ1 segment and the at least one unrearranged human T cell variable region Jβ1 segment and (ii) a mouse TCRBD2-TCRBJ2 non-coding nucleic acid sequence between the at least one unrearranged human T cell variable region Dβ2 segment and the at least one unrearranged human T cell variable region Jβ2 segment.

3. The mouse or isolated mouse cell of claim 1 or claim 2, wherein:

(I) the endogenous mouse TCR α variable gene locus comprises a deletion selected from the group consisting of

(a) a deletion of all endogenous TCR Vα gene segments,

(b) a deletion of all endogenous TCR Jα gene segments, and

(c) a combination thereof, or

(II) the endogenous mouse TCR β variable gene locus comprises a deletion selected from the group consisting of

(a) a deletion of all endogenous TCR Vβ gene segments,

(b) a deletion of all endogenous TCR Dβ gene segments,

(c) a deletion of all endogenous TCR Jβ gene segments, and

(d) a combination thereof, or

(III) the endogenous mouse TCR α variable gene locus comprises a deletion selected from the group consisting of

(a) a deletion of all endogenous TCR Vα gene segments,

(b) a deletion of all endogenous TCR Jα gene segments, and (c) a combination thereof, and

the endogenous mouse TCR β variable gene locus comprises a deletion selected from the group consisting of

(a) a deletion of all endogenous TCR Vβ gene segments,

(b) a deletion of all endogenous TCR Dβ gene segments,

(c) a deletion of all endogenous TCR Jβ gene segments, and

(d) a combination thereof.

4. The mouse or isolated mouse cell of any one of claims 1-3, wherein

(I) the endogenous mouse TCR α variable gene locus comprises a replacement selected from the group consisting of

(a) a replacement at least one endogenous T cell variable region Vα gene segment with the at least one unrearranged human T cell variable region Vα gene segment,

(b) a replacement of at least one endogenous T cell variable region Jα gene segment with the at least unrearranged human T cell variable region Jα segment, and

(c) a combination thereof, or

(II) the endogenous mouse TCR β variable gene locus comprises a replacement selected from the group consisting of

(a) a replacement of at least one endogenous T cell variable region Vβ gene segment with the at least one unrearranged human T cell variable region Vβ segment,

(b) a replacement of at least one endogenous T cell variable region Dβ gene segment with the at least one unrearranged human T cell variable region Dβ segment,

(c) a replacement of at least one endogenous T cell variable region Jβ gene segment with the at least one unrearranged human T cell variable region Jβ segment, and

(d) a combination thereof, or

(III) the endogenous mouse TCR α variable gene locus comprises a replacement selected from the group consisting of

(a) a replacement at least one endogenous T cell variable region Vα gene segment with the at least one unrearranged human T cell variable region Vα gene segment,

(b) a replacement of at least one endogenous T cell variable region Jα gene segment with the at least unrearranged human T cell variable region Jα segment, and

(c) a combination thereof, and

the endogenous mouse TCR β variable gene locus comprises a replacement selected from the group consisting of

(a) a replacement of at least one endogenous T cell variable region Vβ gene segment with the at least one unrearranged human T cell variable region Vβ segment,

(b) a replacement of at least one endogenous T cell variable region Dβ gene segment with the at least one unrearranged human T cell variable region Dβ segment,

(c) a replacement of at least one endogenous T cell variable region Jβ gene segment with the at least one unrearranged human T cell variable region Jβ segment, and

(d) a combination thereof.

5. The mouse or isolated mouse cell of any one of claims 1-4, wherein

(I) the endogenous mouse TCR α variable gene locus comprises:

(a) a replacement of all endogenous T cell variable region Vα gene segments with the at least one unrearranged human T cell variable region Vα gene segment, optionally wherein the at least one unrearranged human T cell variable

region Vα gene segment comprises a plurality or all unrearranged human T cell variable region Vα gene segments from TRAV1-1 to TRAV41,

(b) a replacement of all endogenous T cell variable region Jα gene segments with the at least one unrearranged human T cell variable region Jα segment, optionally wherein the at least one unrearranged human T cell variable region Jα segment comprises a plurality or all unrearranged human T cell variable region Jα gene segments from TRAJ1 to TRAJ61, or

(c) a combination thereof,

(II) the endogenous mouse TCR β variable gene locus comprises

(a) a replacement of all contiguous endogenous T cell variable region Vβ gene segments with the at least one unrearranged human T cell variable region Vβ segment, optionally wherein the at least one unrearranged human T cell variable region Vβ gene segment comprises a plurality or all unrearranged human T cell variable region Vβ gene segments from TRBV1 to TRBV29-1,

(b) a replacement of all endogenous T cell variable region Dβ gene segments with the at least one unrearranged human T cell variable region Dβ gene segment, optionally wherein the at least one unrearranged human T cell variable region Dβ gene segment comprises an unrearranged human T cell variable region Dβ1 gene segment and/or an unrearranged human T cell variable region Dβ2 gene segment,

(c) a replacement of all endogenous T cell variable region Jβ gene segments with the at least one unrearranged human T cell variable region Jβ segment, optionally wherein the at least one unrearranged human T cell variable region Jβ segment comprises a plurality or all unrearranged human Jβ segments from TRBJ1-1 to TRBJ1-6 and/or a plurality or all unrearranged human Jβ segments from TRBJ2-1 to TRBJ2-7, or

(d) a combination thereof, or

(III) the endogenous mouse TCR α variable gene locus comprises

(a) a replacement of all endogenous T cell variable region Vα gene segments with the at least one unrearranged human T cell variable region Vα gene segment, optionally wherein the at least one unrearranged human T cell variable region Vα gene segment comprises a plurality or all unrearranged human T cell variable region gene segments from TRAV1-1 to TRAV41,

(b) a replacement of all endogenous T cell variable region Jα gene segments with the at least one unrearranged human T cell variable region Jα segment, optionally wherein the at least one unrearranged human T cell variable region Jα segment comprises a plurality or all unrearranged human T cell variable region gene segments from TRAJ1 to TRAJ61, or

(c) a combination thereof, and

the endogenous mouse TCR β variable gene locus comprises

(a) a replacement of all contiguous endogenous T cell variable region Vβ gene segments with the at least one unrearranged human T cell variable region Vβ segment, optionally wherein the at least one unrearranged human T cell variable region Vβ gene segment comprises a plurality or all unrearranged human T cell variable region gene segments from TRBV1 to TRBV29-1,

(b) a replacement of all endogenous T cell variable region Dβ gene segments with the at least one unrearranged human T cell variable region Dβ gene segment, optionally wherein the at least one unrearranged human T cell variable region Dβ gene segment comprises an unrearranged human T cell variable region Dβ1 gene segment and/or an unrearranged human T cell variable region Dβ2 gene segment,

(c) a replacement of all endogenous T cell variable region Jβ gene segments with the at least one unrearranged human T cell variable region Jβ segment, optionally wherein the at least one unrearranged human T cell variable region Jβ segment comprises a plurality or all unrearranged human Jβ segments from TRBJ1-1 to TRBJ1-6 and/or a plurality or all unrearranged human Jβ segments from TRBJ2-1 toTRBJ2-7, or

(d) a combination thereof.

6. The mouse or isolated mouse cell of any one of claims 1-5, wherein

(I) the endogenous mouse TCR α variable gene locus comprises:

(a) a replacement of all endogenous T cell variable region Vα gene segments with all unrearranged human T cell variable region Vα gene segments from TRAV1-1 to TRAV41,

(b) a replacement of all endogenous T cell variable region Jα gene segments with all unrearranged human T cell variable region Jα gene segments from TRAJ1 to TRAJ61, or

(c) a combination thereof,

(II) the endogenous mouse TCR β variable gene locus comprises

(a) a replacement of all contiguous endogenous T cell variable region Vβ gene segments with all unrearranged human T cell variable region Vβ gene segments from TRBV1 to TRBV29-1,

(b) a replacement of an endogenous T cell variable region Dβ1 gene segment with an unrearranged human T cell variable region Dβ1 gene segment and a replacement of an endogenous T cell variable region Dβ2 gene segment with an unrearranged human T cell variable region Dβ2 gene segment,

(c) a replacement of

an endogenous TRBJ1-1 gene segment with an unrearranged human TRBJ1-1 gene segment,

an endogenous TRBJ1-2 gene segment with an unrearranged human TRBJ1-2 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-1 segment and a mouse TRBJ1-2 segment,

an endogenous TRBJ1-3 gene segment with an unrearranged human TRBJ1-3 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-2 segment and a mouse TRBJ1-3 segment,

an endogenous TRBJ1-4 gene segment with an unrearranged human TRBJ1-4 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-3 segment and a mouse TRBJ1-4 segment,

an endogenous TRBJ1-5 gene segment with an unrearranged human TRBJ1-5 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-4 segment and a mouse TRBJ1-5 segment,

an endogenous TRBJ1-6 gene segment with an unrearranged human TRBJ1-6 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-5 segment and a mouse TRBJ1-6 segment,

an endogenous TRBJ2-1 gene segment with an unrearranged human TRBJ2-1 gene segment,

an endogenous TRBJ2-2 gene segment with an unrearranged human TRBJ2-2 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-1 segment and a mouse TRBJ2-2 segment,

an endogenous TRBJ2-3 gene segment with an unrearranged human TRBJ2-3 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-2 segment and a mouse TRBJ2-3 segment,

an endogenous TRBJ2-4 gene segment with an unrearranged human TRBJ2-4 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-3 segment and a mouse TRBJ2-4 segment,

an endogenous TRBJ2-5 gene segment with an unrearranged human TRBJ2-5 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-4 segment and a mouse TRBJ2-5 segment,

an endogenous TRBJ2-6 gene segment with an unrearranged human TRBJ2-6 gene segment, optionally wherein the mouse TCRB non-coding

sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-5 segment and a mouse TRBJ2-6 segment, and

an endogenous TRBJ2-7 gene segment with an unrearranged human TRBJ2-7 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-6 segment and a mouse TRBJ2-7 segment or

(d) a combination thereof, or

(III) the endogenous mouse TCR α variable gene locus comprises

(a) a replacement of all endogenous T cell variable region Vα gene segments with all unrearranged human T cell variable region Vα gene segments from TRAV1-1 to TRAV41,

(b) a replacement of all endogenous T cell variable region Jα gene segments with all unrearranged human T cell variable region Jα gene segments from TRAJ1 to TRAJ61, or

(c) a combination thereof, and

(IV) the endogenous mouse TCR β variable gene locus comprises

(a) a replacement of all contiguous endogenous T cell variable region Vβ gene segments with all unrearranged human T cell variable region Vβ gene segments from TRBV1 to TRBV29-1,

(b) a replacement of an endogenous T cell variable region Dβ1 gene segment with an unrearranged human T cell variable region Dβ1 gene segment and a replacement of an endogenous T cell variable region Dβ2 gene segment with an unrearranged human T cell variable region Dβ2 gene segment,

(c) a replacement of

an endogenous TRBJ1-1 gene segment with an unrearranged human TRBJ1-1 gene segment,

an endogenous TRBJ1-2 gene segment with an unrearranged human TRBJ1-2 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-1 segment and a mouse TRBJ1-2 segment,

an endogenous TRBJ1-3 gene segment with an unrearranged human TRBJ1-3 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-2 segment and a mouse TRBJ1-3 segment,

an endogenous TRBJ1-4 gene segment with an unrearranged human TRBJ1-4 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-3 segment and a mouse TRBJ1-4 segment,

an endogenous TRBJ1-5 gene segment with an unrearranged human TRBJ1-5 gene segment, optionally wherein the mouse TCRB non-coding

sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-4 segment and a mouse TRBJ1-5 segment,

an endogenous TRBJ1-6 gene segment with an unrearranged human TRBJ1-6 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ1-5 segment and a mouse TRBJ1-6 segment,

an endogenous TRBJ2-1 gene segment with an unrearranged human TRBJ2-1 gene segment,

an endogenous TRBJ2-2 gene segment with an unrearranged human TRBJ2-2 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-1 segment and a mouse TRBJ2-2 segment,

an endogenous TRBJ2-3 gene segment with an unrearranged human TRBJ2-3 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-2 segment and a mouse TRBJ2-3 segment,

an endogenous TRBJ2-4 gene segment with an unrearranged human TRBJ2-4 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-3 segment and a mouse TRBJ2-4 segment,

an endogenous TRBJ2-5 gene segment with an unrearranged human TRBJ2-5 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-4 segment and a mouse TRBJ2-5 segment,

an endogenous TRBJ2-6 gene segment with an unrearranged human TRBJ2-6 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-5 segment and a mouse TRBJ2-6 segment, and

an endogenous TRBJ2-7 gene segment with an unrearranged human TRBJ2-7 gene segment, optionally wherein the mouse TCRB non-coding sequence comprises a mouse non-coding sequence found between a mouse TRBJ2-6 segment and a mouse TRBJ2-7 segment, or

(d) a combination thereof.

7. The mouse or isolated mouse cell of any one of the preceding claims, wherein

(I) the endogenous mouse TCR α variable gene locus comprises:

(a) a replacement of all endogenous T cell variable region Vα gene segments with all unrearranged human T cell variable region Vα gene segments from TRAV1-1 to TRAV41, and

(b) a replacement of all endogenous T cell variable region Jα gene segments with all unrearranged human T cell variable region Jα gene segments from TRAJ1 to TRAJ61; and

(II) the endogenous mouse TCR β variable gene locus comprises

(a) a replacement of all contiguous endogenous T cell variable region Vβ gene segments with all unrearranged human T cell variable region Vβ gene segments from TRBV1 to TRBV29-1,

(b)(i) a replacement of an endogenous tcrbdj1 cluster with a humanized TCRBDJ1 cluster comprising an unrearranged human TCRBD1 segment and (ii) each of an unrearranged human TCRBJ1-1 segment, an unrearranged human TCRBJ1-2 segment, an unrearranged human TCCRBJ1-3 segment, an unrearranged human TCRBJ1-4 segment, an unrearranged human TCRBJ1-5 segment, and an unrearranged human TCRBJ1-6 segment,

wherein the humanized TCRBDJ1 cluster comprises a mouse TCRBDJ1 non-coding sequence between the unrearranged human TCRBD1 segment and the unrearranged human TCRBJ1-1 segment and a mouse TCRBDJ1 non-coding sequence between any two consecutive unrearranged human TCRBJ1 gene segments, optionally wherein the unrearranged human TCRBD1 and TCRBJ1 gene segments flank the same mouse TCRBDJ1 non-coding sequences as are normally flanked by the corresponding mouse tcrbdj1 gene segments, and

(c)(i) a replacement of an endogenous tcrbdj2 cluster with a humanized TCRBDJ2 cluster comprising an unrearranged human TCRBD2 segment and (ii) each of an unrearranged human TRBJ2-1 segment, an unrearranged human TRBJ2-2 segment, an unrearranged human TCRBJ2-3 segment, an unrearranged human TCRBJ2-4 segment, an unrearranged human TCRBJ2-5 segment, an unrearranged human TCRBJ2-6 segment, and an unrearranged human TCRBJ2-7 segment,

wherein the humanized TCRBDJ2 cluster comprises a mouse TCRBDJ2 non-coding sequence between the unrearranged human TCRBD2 segment and any unrearranged human TCRBJ2 segment and a mouse TCRBDJ2 non-coding sequence between any two consecutive unrearranged human TCRBJ2 gene segments, optionally wherein the unrearranged human TCRBD2 and TCRBJ2 gene segments flank the same mouse TCRBDJ2 non-coding sequences as are normally flanked by the corresponding mouse tcrbdj2 gene segments.

8. The mouse of any one of the preceding claims, wherein the unrearranged TCR α variable region sequence is in the germline genome and/or the unrearranged TCR β variable region sequence is in the germline genome.

9. The mouse of any one of the preceding claims or the isolated mouse cell of any one of claims 1-7, wherein the TCR α variable region sequence is operably linked to endogenous TCRα regulatory elements and/or the TCR β variable region sequence is operably linked to endogenous TCRβ regulatory elements.

10. The mouse of any one of the preceding claims, wherein the mouse expresses a T cell receptor on the surface of a T cell, the T cell receptor comprising a humanized TCRα chain and a humanized TCRβ chain,

wherein the humanized TCRα chain is encoded by a rearranged human Vα/Jα sequence operably linked to the mouse TCRα constant region sequence, wherein the rearranged human Vα/Jα sequence is formed by rearrangement of the at least one human T cell variable region Vα segment and at least one human T cell variable region Jα segment,

wherein the humanized TCRβ chain is encoded by a rearranged human Vβ/Dβ/Jβ sequence operably linked to the mouse TCRβ constant region sequence, wherein the rearranged human Vβ/Dβ/Jβ sequence is formed by rearrangement of the at least one human T cell variable region Vβ segment, at least one T cell variable region Dβ segment, and at least one human T cell variable region Jβ segment, optionally wherein the TCRβ chain is encoded by a rearranged Vβ/Dβ2/Jβ2 sequence.

11. The mouse of any one of the preceding claims, wherein at least 10% of the TCR expressed by the mouse is derived from gene segments from the TCRBDJ1 cluster and at least 10% of the TCR expressed by the mouse is derived from gene segments from the TCRBDJ2 cluster.

12. A method of making the mouse of any one of claim 1-11 or the isolated mouse cell of any one of claims 1-7, and 9, comprising modifying the genome of the mouse or the isolated mouse cell to comprise

both the unrearranged TCR α variable region sequence and the unrearranged TCR β variable region sequence.

13. The method of claim 12, wherein the method comprises replacing a contiguous mouse TCRB sequence comprising a mouse TCRBD gene segment and a mouse TCRBJ gene segment with a nucleic acid sequence comprising the at least one unrearranged human T cell variable region Dβ segment, a mouse TCRBD-TCRBJ non-coding nucleic acid sequence, and the at least one unrearranged human T cell variable region Jβ segment, such that the at least one unrearranged human T cell variable region Dβ segment, the mouse TCRBD-TCRBJ non-coding nucleic acid sequence, and the at least one unrearranged human T cell variable region Jβ segment are operably linked to the mouse TCRβ constant gene sequence.

14. The method of claim 13, wherein the contiguous mouse TCRB sequence comprises (a) a mouse TCRBD1 gene segment and a mouse TCRBJ1-6 gene segment and/or (b) a mouse TCRBD2 gene segment and a mouse TCRBJ2-7 gene segment, and

wherein the nucleic acid comprises:

(A) a humanized TCRBDJ1 cluster comprising an unrearranged human TCRBD1 gene segment, an unrearranged human TCRBJ1 gene segment, and a mouse TCRBDJ1 non-coding sequence, wherein the humanized TCRBDJ1 cluster comprises:

an unrearranged human TRBJ1-1 gene segment, an unrearranged human TRBJ1-2 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ1-1 gene segment and the unrearranged human TRBJ1-2 gene segment,

an unrearranged human TRBJ1-2 gene segment, an unrearranged human TRBJ1-3 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ1-2 gene segment and the unrearranged human TRBJ1-3 gene segment,

an unrearranged human TRBJ1-3 gene segment, an unrearranged human TRBJ1-4 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ1-3 gene segment and the unrearranged human TRBJ1-4 gene segment,

an unrearranged human TRBJ1-4 gene segment, an unrearranged human TRBJ1-5 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ1-4 gene segment and the unrearranged human TRBJ1-5 gene segment,

an unrearranged human TRBJ1-5 gene segment, an unrearranged human TRBJ1-6 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ1-5 gene segment and the unrearranged human TRBJ1-6 gene segment, or

any combination of an unrearranged human TRBJ1-1 gene segment, an unrearranged human TRBJ1-2 gene segment, an unrearranged human TRBJ1-3 gene segment, an unrearranged human TRBJ1-4 gene segment, an unrearranged human TRBJ1-5 gene segment, and an unrearranged human TRBJ1-6 gene segment, wherein the humanized TCRBDJ1 cluster comprises a mouse TCRBDJ1 non-coding sequence between the unrearranged human TCRBD1 gene segment and any unrearranged human TCRBJ1 gene segment and mouse TCRBDJ1 non-coding sequence between any two consecutive unrearranged human TCRBJ1 gene segments, optionally wherein the unrearranged human TCRBD1 and TCRBJ1 gene segments flank the same

mouse TCRBDJ1 non-coding sequences as are normally flanked by the corresponding mouse tcrbdj1 gene segments; and/or

(B) a humanized TCRBDJ2 cluster comprising an unrearranged human TCRBD2 gene segment, an unrearranged human TCRBJ2 gene segment, and a mouse TCRBDJ2 non-coding sequence, wherein the humanized TCRBDJ2 cluster comprises:

an unrearranged human TRBJ2-1 gene segment, an unrearranged human TRBJ2-2 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ2-1 gene segment and the an unrearranged human TRBJ2-2 gene segment,

unrearranged human TRBJ2-2 gene segment, an unrearranged human TRBJ2-3 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ2-2 gene segment and the unrearranged human TRBJ2-3 gene segment,

an unrearranged human TRBJ2-3 gene segment, an unrearranged human TRBJ2-4 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ2-3 gene segment and the unrearranged human TRBJ2-4 gene segment,

an unrearranged human TRBJ2-4 gene segment, an unrearranged human TRBJ2-5 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ2-4 gene segment and the unrearranged human TRBJ2-5 gene segment,

an unrearranged human TRBJ2-5 gene segment, an unrearranged human TRBJ2-6 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ2-5 gene segment and the unrearranged human TRBJ2-6 gene segment,

an unrearranged human TRBJ2-6 gene segment, an unrearranged human TRBJ2-7 gene segment, and a mouse TCRB non-coding sequence between the unrearranged human TRBJ2-6 gene segment and the unrearranged human TRBJ27 gene segment, or

any combination of an unrearranged human TRBJ2-1 gene segment, an unrearranged human TRBJ2-2 gene segment, an unrearranged human TRBJ2-3 gene segment, an unrearranged human TRBJ2-4 gene segment, an unrearranged human TRBJ2-5 gene segment, an unrearranged human TRBJ2-6 gene segment, and an unrearranged human TRBJ2-7 gene segment, wherein the humanized TCRBDJ2 cluster comprises a mouse TCRBDJ2 non-coding sequence between the unrearranged human TCRBD2 gene segment and any unrearranged human TCRBJ2 gene segment and mouse TCRBDJ2 non-coding sequence between any two consecutive unrearranged human TCRBJ2 gene segments, optionally wherein the unrearranged human TCRBD2 and TCRBJ2

gene segments flank the same mouse TCRBDJ2 non-coding sequences as are normally flanked by the corresponding mouse tcrbdj1 gene segments.

15. A method of obtaining any one of: (1) a TCR protein that is specific for an antigen and comprises a human TCR variable domain, (2) the human TCR variable domain and (3) a nucleic acid sequence encoding the human TCR variable domain,

the method comprising

isolating from a mouse according to any one of claims 1-11 any one of:

(1) a T cell expressing a TCR protein that is specific for an antigen and comprises both a human TCR α variable domain and a human TCR β variable domain,

(2) either or both (i) the human TCR α variable domain and (ii) the human TCR β variable domain, and

(3) either or both (i) a nucleic acid sequence encoding the human TCR α variable domain and (ii) a nucleic acid sequence encoding the human TCR β variable domain.

16. The method of claim 15, wherein the method comprises isolating from the mouse a nucleic acid sequence encoding the human TCR α variable domain and a nucleic acid sequence encoding the human TCR β variable domain, the method further comprising

culturing a host cell in sufficient conditions for expressing (i) the nucleic acid sequence encoding the human TCR α variable domain in operable linkage with a human TCR α constant region (ii) the nucleic acid sequence encoding the human TCR β variable domain in operable linkage with a human TCR β constant region,

wherein the nucleic acid sequences encoding the human TCR α variable domain and the human TCR β variable domain are on the same or different expression vectors.

17. The method of claim 15 or claim 16, wherein the antigen is a tumor antigen, a viral antigen, or a bacterial antigen.

18. A T cell expressing a TCR protein comprising a human TCR variable domain specific for an antigen obtained according to the method of any one of claims 15-17.

19. A hybridoma produced from the T cell expressing a TCR protein comprising a human TCR variable domain specific for an antigen obtained according to the method of any one of claims 15-17.

20. A human T cell receptor variable domain obtained according to the method of any one of claims 15-17.

21. A nucleic acid comprising either or both (i) the nucleic acid sequence encoding the human TCR α variable domain and (ii) the nucleic acid sequence encoding the human TCR β variable domain isolated according to the method of any one of claims 15-17.

22. A host cell comprising the nucleic acid of claim 21.

23. An expression vector comprising the nucleic acid of claim 21.

24. The expression vector of claim 23, wherein the expression vector comprises at least one of (a) the nucleic acid sequence encoding a human TCRα variable domain operably linked to a sequence encoding a human TCRα constant region and (b) the nucleic acid sequence encoding the human TCRβ variable domain operably linked to a sequence encoding a human TCRβ constant region.

25. The isolated mouse cell of any one of claims 1-7, and 9, wherein the isolated mouse cell is an embryonic stem cell.

26. A mouse embryonic stem (ES) cell made by the method of any one of claims 12-14.

27. A targeting vector comprising 5' and 3' homology arms for targeting a mouse TCRBDJ region, an unrearranged human TCRBD segment, an unrearranged human TCRBJ segment, and a mouse TRCBDJ non-coding sequence,

wherein targeting vector comprises the mouse TCRBDJ non-coding sequence between the unrearranged human TCRBD segment and an unrearranged human TCRBJ gene segment and between any two consecutive unrearranged human TCRBJ gene segments, optionally wherein the unrearranged human TCRBD and TCRBJ gene segments flank the same mouse TCRBDJ non-coding sequences as are normally flanked by the corresponding mouse tcrbdj gene segments.

28. The targeting vector of claim 27, wherein

(A) the unrearranged human TCRBD segment comprises a sequence set forth at the following human genomic coordinates on chromosome 7 (GRCh38 assembly):

142,786,213-142,786,224, and/or

142,796,365-142,796,414;

(B) the unrearranged human TCRBJ segment comprises a sequence set forth at the following human genomic coordinates on chromosome 7 (GRCh38 assembly):

142,786,880-142,786,927,
142,787,017-142,787,064,
142,787,630-142,787,679,
142,788,225-142,788,275,
142,788,498-142,788,547,
142,788,988-142,789,040,
142,795,686-142,795,740,
142,796,560-142,796,610,
142,796,847-142,796,895,
142,796,998-142,797,047,
142,797,119-142,797,166,
142,797,239-142,797,291, and/or
142,797,456-142,797,502.

29. A mouse genome or mouse cell comprising the targeting vector of claim 27 or claim 28.