

What is claimed is:

1. A genetically modified non-human animal, comprising in its genome:
an unrearranged T cell receptor (TCR) α variable gene locus comprising at least one human V α segment and at least one human J α segment, operably linked to a non-human TCR α constant gene sequence.
2. The animal of claim 1, wherein the unrearranged TCR α variable gene locus replaces an endogenous non-human TCR α variable gene locus.
3. The animal of claim 1, wherein endogenous non-human V α and J α segments are incapable of rearranging to form a rearranged V α /J α sequence.
4. The animal of claim 1, wherein the animal lacks a functional endogenous non-human TCR α variable locus.
5. The animal of claim 4, wherein the lack of the functional endogenous non-human TCR α variable locus comprises a deletion selected from the group consisting of (a) a deletion of all endogenous V α gene segments, (b) a deletion of all endogenous J α gene segments, and (c) a combination thereof.
6. The animal of claim 1, wherein the human V α and J α segments rearrange to form a rearranged human V α /J α sequence.
7. The animal of claim 6, wherein the animal expresses a T cell receptor comprising a human TCR α variable region on the surface of a T cell.
8. The animal of claim 1, wherein T cells of the animal undergo thymic T cell development to produce CD4 and CD8 single positive T cells.
9. The animal of claim 1, wherein the animal comprises a normal ratio of splenic CD3+ T cells to total splenocytes.
10. The animal of claim 1, wherein the animal generates a population of central and effector memory T cells to an antigen of interest.
11. The animal of claim 1, wherein the unrearranged TCR α variable gene locus comprises a complete repertoire of human J α segments and a complete repertoire of human V α segments.
12. The animal of claim 1, wherein the animal retains an endogenous non-human TCR α variable gene locus, and wherein the locus is a non-functional locus.
13. The animal of claim 1, wherein the animal is a rodent.

14. The animal of claim 13, wherein the rodent is a mouse.
15. A genetically modified non-human animal, comprising in its genome:
 - an unrearranged TCR β variable gene locus comprising at least one human V β segment, at least one human D β segment, and at least one human J β segment, operably linked to a non-human TCR β constant gene sequence.
16. The animal of claim 15, wherein the unrearranged TCR β variable gene locus replaces an endogenous non-human TCR β variable gene locus.
17. The animal of claim 15, wherein endogenous rodent V β , D β , and J β segments are incapable of rearranging to form a rearranged V β /D β /J β sequence.
18. The animal of claim 15, wherein the animal lacks a functional endogenous non-human TCR β variable locus.
19. The animal of claim 18, wherein the lack of the functional endogenous rodent TCR β variable locus comprises a deletion selected from the group consisting of (a) a deletion of all endogenous V β gene segments, (b) a deletion of all endogenous D β gene segments, (c) a deletion of all endogenous J β gene segments, and (d) a combination thereof.
20. The animal of claim 15, wherein the human V β , D β , and J β segments rearrange to form a rearranged human V β /D β /J β sequence.
21. The animal of claim 20, wherein the animal expresses a T cell receptor comprising a human TCR β variable region on the surface of a T cell.
22. The animal of claim 15, wherein T cells of the animal undergo thymic T cell development to produce CD4 and CD8 single positive T cells.
23. The animal of claim 15, wherein the animal comprises a normal ratio of splenic CD3+ T cells to total splenocytes.
24. The animal of claim 15, wherein the animal generates a population of central and effector memory T cells to an antigen of interest.
25. The animal of claim 15, wherein the unrearranged TCR β variable gene locus comprises a complete repertoire of human J β segments, a complete repertoire of human D β segments, and a complete repertoire of human V β segments.
26. The animal of claim 15, wherein the animal retains an endogenous non-human TCR β variable gene locus, and wherein the locus is a non-functional locus.
27. The animal of claim 15, wherein the animal is a rodent.

28. The animal of claim 27, wherein the rodent is a mouse.
29. A genetically modified non-human animal, comprising in its genome:
- an unrearranged T cell receptor (TCR) α variable gene locus comprising at least one human $V\alpha$ segment and at least one human $J\alpha$ segment, operably linked to a non-human TCR α constant gene sequence; and,
- an unrearranged TCR β variable gene locus comprising at least one human $V\beta$ segment, at least one human $D\beta$ segment, and at least one human $J\beta$ segment, operably linked to a non-human TCR β constant gene sequence.
30. The animal of claim 29, wherein the unrearranged TCR α variable gene locus replaces an endogenous non-human TCR α variable gene locus, and wherein the unrearranged TCR β variable gene locus replaces an endogenous non-human TCR β variable gene locus.
31. The animal of claim 29, wherein endogenous non-human $V\alpha$ and $J\alpha$ segments are incapable of rearranging to form a rearranged $V\alpha/J\alpha$ sequence, and wherein endogenous non-human $V\beta$, $D\beta$, and $J\beta$ segments are incapable of rearranging to form a rearranged $V\beta/D\beta/J\beta$ sequence.
32. The animal of claim 29, wherein the animal lacks a functional endogenous non-human TCR α variable locus and lacks a functional endogenous non-human TCR β variable locus.
33. The animal of claim 32, wherein the lack of the functional endogenous non-human TCR α variable locus comprises a deletion selected from the group consisting of (a) a deletion of all endogenous $V\alpha$ gene segments, (b) a deletion of all endogenous $J\alpha$ gene segments, and (c) a combination thereof;
- and the lack of the functional endogenous non-human TCR β variable locus comprises a deletion selected from the group consisting of (a) a deletion of all endogenous $V\beta$ gene segments, (b) a deletion of all endogenous $D\beta$ gene segments, (c) a deletion of all endogenous $J\beta$ gene segments, and (d) a combination thereof.
34. The animal of claim 29, wherein the human $V\alpha$ and $J\alpha$ segments rearrange to form a rearranged human $V\alpha/J\alpha$ sequence, and the human $V\beta$, $D\beta$, and $J\beta$ segments rearrange to form a rearranged human $V\beta/D\beta/J\beta$ sequence.
35. The animal of claim 34, wherein the animal expresses a T cell receptor comprising a human variable region and a non-human constant region on a surface of a T cell.

36. The animal of claim 29, wherein T cells of the animal undergo thymic T cell development to produce CD4 and CD8 single positive T cells.
37. The animal of claim 29, wherein the animal comprises a normal ratio of splenic CD3+ T cells to total splenocytes.
38. The animal of claim 29, wherein the animal generates a population of central and effector memory T cells to an antigen of interest.
39. The animal of claim 29, wherein the unrearranged TCR α variable gene locus comprises 61 human J α segments and 8 human V α segments, and wherein the unrearranged TCR β variable gene locus comprises 14 human J β segments, 2 human D β segments, and 14 human V β segments.
40. The animal of claim 29, wherein the unrearranged TCR α variable gene locus comprises a complete repertoire of human J α segments and a complete repertoire of human V α segments, and wherein the unrearranged TCR β variable gene locus comprises a complete repertoire of human J β segments, a complete repertoire of human D β segments, and a complete repertoire of human V β segments.
41. The animal of claim 29, wherein the animal retains endogenous non-human TCR α and TCR β variable gene loci, and wherein the loci are non-functional loci.
42. The animal of claim 29, wherein the animal further comprises nucleotide sequences of human V δ segments at a humanized TCR α locus.
43. The animal of claim 42, wherein the animal further comprises a complete repertoire of human V δ segments, a complete repertoire of human D δ segments, and a complete repertoire of human J δ segments at the humanized TCR α locus.
44. The animal of claim 29, wherein the animal is a rodent.
45. The animal of claim 44, wherein the rodent is a mouse.
46. A method for making a genetically modified non-human animal that expresses a T cell receptor comprising a human variable region and a non-human constant region on a surface of a T cell comprising:

replacing in a first non-human animal an endogenous non-human TCR α variable gene locus with an unrearranged humanized TCR α variable gene locus comprising at least one human V α segment and at least one human J α segment to generate a humanized TCR α variable gene locus, wherein the humanized TCR α variable gene locus is operably linked to endogenous non-human TCR α constant region;

replacing in a second non-human animal an endogenous non-human TCR β variable gene locus with an unrearranged humanized TCR β variable gene locus comprising at least one human V β segment, at least one human D β segment, and at least one human J β segment to generate a humanized TCR β variable gene locus, wherein the humanized TCR β variable gene locus is operably linked to endogenous non-human TCR β constant region; and

breeding the first and the second animal to obtain a non-human animal that expresses a T cell receptor comprising a human variable region and a non-human constant region.

47. The method of claim 46, wherein endogenous non-human V α and J α segments are incapable of rearranging to form a rearranged V α /J α sequence, and wherein endogenous non-human V β , D β , and J β segments are incapable of rearranging to form a rearranged V β /D β /J β sequence.

48. The method of claim 46, wherein the genetically modified animal lacks a functional endogenous non-human TCR α variable locus and lacks a functional endogenous non-human TCR β variable locus.

49. The method of claim 48, wherein the lack of the functional endogenous non-human TCR α variable locus comprises a deletion selected from the group consisting of (a) a deletion of all endogenous V α gene segments, (b) a deletion of all endogenous J α gene segments, and (c) a combination thereof;

and the lack of the functional endogenous non-human TCR β variable locus comprises a deletion selected from the group consisting of (a) a deletion of all endogenous V β gene segments, (b) a deletion of all endogenous D β gene segments, (c) a deletion of all endogenous J β gene segments, and (d) a combination thereof.

50. The method of claim 46, wherein the human V α and J α segments rearrange to form a rearranged human V α /J α sequence, and the human V β , D β , and J β segments rearrange to form a rearranged human V β /D β /J β sequence.

51. The method of claim 46, wherein T cells of the rodent undergo thymic T cell development to produce CD4 and CD8 single positive T cells.

52. The method of claim 46, wherein the animal comprises a normal ratio of splenic CD3+ T cells to total splenocytes.

53. The method of claim 46, wherein the animal generates a population of central and effector memory T cells to an antigen of interest.
54. The method of claim 46, wherein the unrearranged humanized TCR α variable gene locus comprises 61 human J α segments and 8 human V α segments, and wherein the unrearranged humanized TCR β variable gene locus comprises 14 human J β segments, 2 human D β segments, and 14 human V β segments.
55. The method of claim 46, wherein the unrearranged humanized TCR α variable gene locus comprises a complete repertoire of human J α segments and a complete repertoire of human V α segments, and wherein the unrearranged humanized TCR β variable gene locus comprises a complete repertoire of human J β segments, a complete repertoire of human D β segments, and a complete repertoire of human V β segments.
56. The method of claim 46, wherein the non-human animal is a rodent.
57. The method of claim 56, wherein the rodent is a mouse.
58. A genetically modified mouse comprising in its genome:
- an unrearranged T cell receptor (TCR) α variable gene locus comprising a complete repertoire of human J α segments and a complete repertoire of human V α segments, operably linked to a mouse TCR α constant gene sequence, and
- an unrearranged TCR β variable gene locus comprising a complete repertoire of human J β segments, a complete repertoire of human D β segments, and a complete repertoire of human V β segments, operably linked to a mouse TCR β constant gene sequence.
59. The mouse of claim 58, wherein the unrearranged TCR α variable gene locus replaces endogenous mouse TCR α variable gene locus, and wherein the unrearranged TCR β variable gene locus replaces the endogenous mouse TCR β variable gene locus.
60. The mouse of claim 58, wherein the endogenous mouse V α and J α segments are incapable of rearranging to form a rearranged V α /J α sequence, and wherein the endogenous mouse V β , D β , and J β segments are incapable of rearranging to form a rearranged V β /D β /J β sequence.
61. The mouse of claim 58, wherein the human V α and J α segments rearrange to form a rearranged human V α /J α sequence, and the human V β , D β , and J β segments rearrange to form a rearranged human V β /D β /J β sequence.

62. The mouse of claim 61, wherein the mouse expresses a T cell receptor comprising a human variable region and a mouse constant region on a surface of a T cell.
63. The mouse of claim 58, wherein T cells of the mouse undergo thymic T cell development to produce CD4 and CD8 single positive T cells.
64. The mouse of claim 58, wherein the mouse comprises a normal ratio of splenic CD3+ T cells to total splenocytes.
65. The mouse of claim 58, wherein the mouse generates a population of central and effector memory T cells to an antigen of interest.
66. The mouse of claim 58, wherein the mouse further comprises a complete repertoire of V δ , a complete repertoire of D δ , and a complete repertoire of J δ segments at a humanized TCR α locus.
67. The mouse of claim 58, wherein the mouse retains endogenous mouse TCR α and TCR β variable gene loci, and wherein the loci are non-functional loci.
68. A method of producing a human T cell receptor to an antigen of interest comprising:
immunizing a non-human animal of claim 1 with the antigen of interest;
allowing the animal to mount an immune response;
isolating from the animal a T cell reactive to the antigen of interest;
determining a nucleic acid sequence of a human TCR variable region expressed by the T cell;
cloning the human TCR variable region into a nucleotide construct comprising a nucleic acid sequence of a human TCR constant region, wherein the human TCR variable region is operably linked to the human TCR constant region; and
expressing a human T cell receptor in a cell.

What is claimed is:

1. A genetically modified non-human animal, comprising in its genome:

an unrearranged T cell receptor (TCR) α variable gene locus comprising at least one human V α segment and at least one human J α segment, wherein the TCR α variable gene locus is operably linked to a non-human TCR α constant gene sequence, wherein the unrearranged TCR α variable gene locus replaces an endogenous non-human TCR α variable gene locus, and/or

an unrearranged TCR β variable gene locus comprising at least one human V β segment, at least one human D β segment, and at least one human J β segment, wherein the unrearranged TCR β variable gene locus is operably linked to a non-human TCR β constant gene sequence, wherein the unrearranged TCR β variable gene locus replaces an endogenous non-human TCR β variable gene locus.

2. The animal of claim 1, wherein endogenous non-human V α and J α segments are incapable of rearranging to form a rearranged V α /J α sequence and/or endogenous rodent V β , D β , and J β segments are incapable of rearranging to form a rearranged V β /D β /J β sequence.

3. The animal of claim 1, wherein the animal lacks a functional endogenous non-human TCR α and/or TCR β variable locus.

4. The animal of claim 3, wherein the lack of the functional endogenous non-human TCR α variable gene locus comprises a deletion selected from the group consisting of (a) a deletion of all endogenous V α gene segments, (b) a deletion of all endogenous J α gene segments, and (c) a combination thereof and/or the lack of the functional endogenous rodent TCR β variable gene locus comprises a deletion selected from the group consisting of (a) a deletion of all endogenous V β gene segments, (b) a deletion of all endogenous D β gene segments, (c) a deletion of all endogenous J β gene segments, and (d) a combination thereof.

5. The animal of claim 1, wherein the human V α and J α segments rearrange to form a rearranged human V α /J α sequence and/or the human V β , D β , and J β segments rearrange to form a rearranged human V β /D β /J β sequence.

6. The animal of any one of claims 1 to 5, wherein the animal expresses a T cell receptor comprising a human TCR α and/or TCR β variable region on the surface of a T cell.
7. The animal of any one of claims 1 to 6, wherein T cells of the animal undergo thymic T cell development to produce CD4 and CD8 single positive T cells.
8. The animal of any one of claims 1 to 7, wherein the animal comprises a normal ratio of splenic CD3⁺ T cells to total splenocytes.
9. The animal of any one of claims 1 to 8, wherein the animal generates a population of central and effector memory T cells to an antigen of interest.
10. The animal of any one of claims 1 to 9, wherein the unrearranged TCR α variable gene locus comprises a complete repertoire of human J α segments and a complete repertoire of human V α segments and/or the unrearranged TCR β variable gene locus comprises a complete repertoire of human J β segments, a complete repertoire of human D β segments, and a complete repertoire of human V β segments.
11. The animal of claim 1, wherein the animal retains an endogenous non-human TCR α variable gene locus and/or an endogenous non-human TCR β variable gene locus, and wherein the endogenous non-human TCR α variable gene locus and/or the endogenous non-human TCR β variable gene locus is a non-functional locus.
12. The animal of any one of claims 1 to 11, wherein the animal is a rodent.
13. The animal of claim 12, wherein the rodent is a mouse.
14. A genetically modified non-human animal according to any one of claims 1 to 13, comprising in its genome:

an unrearranged T cell receptor (TCR) α variable gene locus comprising at least one human V α segment and at least one human J α segment, operably linked to a non-human TCR α constant gene sequence; and,

an unrearranged TCR β variable gene locus comprising at least one human V β segment, at least one human D β segment, and at least one human J β segment, operably linked to a non-human TCR β constant gene sequence.

15. The animal of claim 14, wherein the animal expresses a T cell receptor comprising a human variable region and a non-human constant region on a surface of a T cell.

16. The animal of claim 14, wherein the unrearranged TCR α variable gene locus comprises 61 human J α segments and 8 human V α segments, and wherein the unrearranged TCR β variable gene locus comprises 14 human J β segments, 2 human D β segments, and 14 human V β segments.

17. The animal of claim 14, wherein the animal further comprises an unrearranged TCR δ variable region locus comprising human V δ segments.

18. The animal of claim 17, wherein the animal further comprises a complete repertoire of human V δ segments, a complete repertoire of human D δ segments, and a complete repertoire of human J δ segments at the humanized TCR α locus.

19. A genetically modified non-human animal according to any one of claims 1 to 18, wherein the non-human animal is a mouse comprising in its genome:

an unrearranged T cell receptor (TCR) α variable gene locus comprising a complete repertoire of human J α segments and a complete repertoire of human V α segments, operably linked to a mouse TCR α constant gene sequence, and

an unrearranged TCR β variable gene locus comprising a complete repertoire of human J β segments, a complete repertoire of human D β segments, and a complete repertoire of human V β segments, operably linked to a mouse TCR β constant gene sequence.

20. A method of producing a human T cell receptor to an antigen of interest comprising:

- immunizing a non-human animal of any one of claims 1 to 19 with the antigen of interest;
- allowing the animal to mount an immune response;
- isolating from the animal a T cell reactive to the antigen of interest;
- determining a nucleic acid sequence of a human TCR variable region expressed by the T cell;
- cloning the nucleic acid sequence of the human TCR variable region into a nucleotide construct comprising a nucleic acid sequence of a human TCR constant region, wherein the nucleic acid sequence of the human TCR variable region is operably linked to the nucleic acid sequence of the human TCR constant region; and
- expressing a human T cell receptor in a cell.