

What is claimed is:

1. A genetically modified non-human animal comprising in its genome:
a nucleic acid sequence encoding an exogenous Terminal
Deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element; and
an immunoglobulin variable region comprising unrearranged human
immunoglobulin variable region gene segments operably linked to an immunoglobulin
constant region gene.
2. The genetically modified non-human animal of claim 1, wherein the transcriptional
control element drives expression of the nucleic acid sequence encoding the exogenous TdT
in pro-B cells and/or pre-B cells.
3. The genetically modified non-human animal of claim 2, wherein the transcriptional
control element is selected from the group consisting of a RAG1 transcriptional control
element, a RAG2 transcriptional control element, an immunoglobulin heavy chain
transcriptional control element, an immunoglobulin κ light chain transcriptional control
element and/or an immunoglobulin λ light chain transcriptional control element.
4. The genetically modified non-human animal of any one of claims 1 to 3, wherein
the nucleic acid sequence encoding the exogenous TdT is located at an immunoglobulin κ
light chain locus, an immunoglobulin λ light chain locus, an immunoglobulin heavy chain
locus, a RAG1 locus, a RAG2 locus.
5. The genetically modified non-human animal of any one of claims 1 to 4, wherein at
least 10% of the V-J immunoglobulin light chain junctions in the animal comprise non-
template additions.
6. The genetically modified non-human animal of any one of claims 1 to 5, wherein
the human immunoglobulin variable region gene segments are human heavy chain variable
region gene segments.
7. The genetically modified non-human animal of claim 6, wherein the constant region
gene is a heavy chain constant region gene.
8. The genetically modified non-human animal of claim 7, wherein the heavy chain
constant region gene is of endogenous species origin.

9. The genetically modified non-human animal of any one of claims 6 to 8, wherein the immunoglobulin variable region and the immunoglobulin constant region gene are located at an endogenous immunoglobulin heavy chain locus.
10. The genetically modified non-human animal of any one of claims 6 to 9, further comprising in its genome an immunoglobulin variable region comprising unrearranged human light chain variable region gene segments operably linked to a second immunoglobulin constant region gene.
11. The genetically modified non-human animal of claim 10, wherein the immunoglobulin variable region operably linked to the second immunoglobulin constant region gene is located at an endogenous immunoglobulin light chain locus.
12. The genetically modified non-human animal of claim 11, wherein the human immunoglobulin variable region gene segments operably linked to the second immunoglobulin constant region gene are human κ chain variable region gene segments.
13. The genetically modified non-human animal of claim 11, wherein the human immunoglobulin variable region gene segments operably linked to the second immunoglobulin constant region gene are human λ chain variable region gene segments.
14. The genetically modified non-human animal of any one of claims 11 to 13, wherein the second constant region gene is a κ constant region gene.
15. The genetically modified non-human animal of any one of claims 11 to 13, wherein the second constant region gene is a λ constant region gene.
16. The genetically modified non-human animal of claim 14, wherein the κ constant region gene is of endogenous species origin.
17. The genetically modified non-human animal of claim 15, wherein the λ constant region gene is of endogenous species origin.
18. The genetically modified non-human animal of claim 16, wherein the endogenous immunoglobulin light chain locus is an immunoglobulin κ locus.
19. The genetically modified non-human animal of claim 17, wherein the endogenous immunoglobulin light chain locus is an immunoglobulin λ locus.

20. The genetically modified non-human animal of any one of claims 1 to 19, wherein the unrearranged human immunoglobulin variable region gene segments undergo rearrangement during B cell development to generate rearranged variable region genes in the B cells of the non-human animal.
21. The genetically modified non-human animal of claim 20, wherein at least 10% of the rearranged variable region genes comprise non-template additions.
22. A genetically modified non-human animal comprising in its genome:
a nucleic acid sequence encoding an exogenous Terminal Deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element; and
a T cell receptor (TCR) variable region comprising unrearranged human TCR variable region gene segments operably linked to a TCR constant region gene.
23. The genetically modified non-human animal of claim 22, wherein the human TCR variable region gene segments are human TCR α variable region gene segments.
24. The genetically modified non-human animal of claim 22, wherein the human TCR variable region gene segments are human TCR β variable region gene segments.
25. The genetically modified non-human animal of any one of claims 22 to 24, wherein the unrearranged human TCR variable region gene segments undergo rearrangement during T cell development to generate rearranged TCR variable region genes in the T cells of the non-human animal.
26. The genetically modified non-human animal of claim 25, wherein at least 10% of the rearranged variable region genes comprise non-template additions.
27. A genetically modified non-human animal comprising in its genome:
a nucleic acid sequence encoding an exogenous Terminal Deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element; and
an immunoglobulin variable region comprising unrearranged human immunoglobulin variable region gene segments operably linked to a TCR constant region gene.
28. The genetically modified non-human animal of claim 27, wherein the human immunoglobulin variable region gene segments are heavy chain gene segments.

29. The genetically modified non-human animal of claim 27, wherein the human immunoglobulin variable region gene segments are κ chain gene segments.
30. The genetically modified non-human animal of claim 27, wherein the human immunoglobulin variable region gene segments are λ chain gene segments.
31. The genetically modified non-human animal of any one of claims 28 or 29, wherein the TCR constant region gene is a TCR α constant region gene.
32. The genetically modified non-human animal of claim 28, wherein the TCR constant region gene is a TCR β constant region gene.
33. The genetically modified non-human animal of any one of claims 22 to 32, wherein the transcriptional control element drives expression of the nucleic acid sequence encoding the exogenous TdT in CD4/CD8 double-negative (DN) thymocytes and/or CD4/CD8 double-positive (DP) thymocytes.
34. The genetically modified non-human animal of claim 33, wherein the transcriptional control element is a RAG1 transcriptional control element, a RAG2 transcriptional control element, a TCR α transcriptional control element, a TCR β transcriptional control element, a TCR γ transcriptional control element and/or a TCR δ transcriptional control element.
35. The genetically modified non-human animal of any one of claims 22 to 34, wherein the nucleic acid sequence encoding the exogenous TdT is located at a RAG1 locus, a RAG2 locus, a TCR α chain locus, a TCR β chain locus, a TCR γ chain locus and/or a TCR δ chain locus.
36. The genetically modified non-human animal of any one of claims 1 to 35, wherein the non-human animal is a mammal.
37. The genetically modified non-human animal of claim 36, wherein the mammal is a rodent.
38. The genetically modified non-human animal of claim 37, wherein the rodent is a rat or a mouse.
39. A method inducing expression of an antibody comprising a human variable domain, the method comprising exposing a genetically modified non-human animal of any one of

claims 1 to 21 to an antigen such that the genetically modified non-human animal produces an antibody comprising a human variable domain specific for the antigen.

40. A method of making a T cell expressing a T cell receptor (TCR) comprising a human variable domain specific to a peptide presented on a MHC, the method comprising:

- (a) exposing a genetically modified non-human animal of any one of claims 22 to 26 to an antigen comprising a peptide or a nucleic acid encoding an antigen comprising a peptide such that the peptide is presented on a MHC in the non-human animal; and
- (b) obtaining a T cell expressing a TCR specific for the peptide presented on the MHC from the genetically modified non-human animal of (a).

41. A method of making T cell expressing a chimeric antigen receptor (CAR) comprising a human immunoglobulin variable domain and an immunoglobulin constant specific to a peptide presented on a MHC, the method comprising:

- (a) exposing a genetically modified non-human animal of any one of claims 27 to 32 to an antigen comprising a peptide or a nucleic acid encoding an antigen comprising a peptide such that the peptide is presented on a MHC in the non-human animal; and
- (b) obtaining a T cell expressing a CAR specific for the peptide presented on the MHC from the genetically modified non-human animal of (a).

42. A genetically modified non-human animal ES cell comprising in its genome:

- a nucleic acid sequence encoding an exogenous Terminal Deoxynucleotidyltransferase (TdT); and
- an immunoglobulin variable region comprising unrearranged human immunoglobulin variable region gene segments operably linked to an immunoglobulin constant region gene.

43. A genetically modified non-human animal ES cell comprising in its genome:

- a nucleic acid sequence encoding an exogenous Terminal Deoxynucleotidyltransferase (TdT); and
- an T cell receptor (TCR) variable region comprising unrearranged human TCR variable region gene segments operably linked to a TCR constant region gene.

44. A genetically modified non-human animal ES cell comprising in its genome:

- a nucleic acid sequence encoding an exogenous Terminal Deoxynucleotidyltransferase (TdT); and

an immunoglobulin variable region comprising unrearranged human immunoglobulin variable region gene segments operably linked to a TCR constant region gene.

45. A method of making a genetically modified non-human animal comprising using the genetically modified non-human animal ES cell of any one of claims 42 to 44.

46. A method of making a non-human animal comprising a genetic modification comprising engineering the non-human animal to comprise in its germline:

a nucleic acid sequence encoding an exogenous Terminal Deoxynucleotidyltransferase (TdT); and

an immunoglobulin variable region comprising unrearranged human immunoglobulin variable region gene segments operably linked to an immunoglobulin constant region gene.

47. A method of making a non-human animal comprising a genetic modification comprising engineering the non-human animal to comprise in its germline:

a nucleic acid sequence encoding an exogenous Terminal Deoxynucleotidyltransferase (TdT); and

a T cell receptor (TCR) variable region comprising unrearranged human TCR variable region gene segments operably linked to a TCR constant region gene.

48. A method of making a non-human animal comprising a genetic modification comprising engineering the non-human animal to comprise in its germline:

a nucleic acid sequence encoding an exogenous Terminal Deoxynucleotidyltransferase (TdT); and

an immunoglobulin variable region comprising unrearranged human immunoglobulin variable region gene segments operably linked to a TCR constant region gene.

49. The genetically modified non-human animal, non-human animal ES cell or the method of any one of the preceding claims, wherein the Terminal Deoxynucleotidyltransferase (TdT) is a human TdT.

50. The genetically modified non-human animal, non-human animal ES cell or the method of any one of the preceding claims, wherein the Terminal Deoxynucleotidyltransferase (TdT) is the short isoform of TdT (TdTS).