

What is claimed is:

1. A genetically modified mouse comprising in its germline genome:
 - a nucleic acid sequence encoding a human Terminal Deoxynucleotidyltransferase (TdT) operably linked to a human or mouse transcriptional control element, wherein the transcriptional control element is active in pre-B cells;
 - a human immunoglobulin heavy chain variable region comprising unrearranged human immunoglobulin heavy chain V, D, and J gene segments operably linked to a human or mouse immunoglobulin heavy chain constant region; and
 - a human immunoglobulin light chain variable region comprising unrearranged human immunoglobulin light chain V and J gene segments operably linked to a human or mouse immunoglobulin light chain constant region,wherein productive antibodies of the genetically modified mouse have at least 10% greater frequency of unique immunoglobulin light chain CDR3 sequences than productive antibodies of a corresponding mouse that lacks human TdT.
2. The genetically modified mouse of claim 1, wherein the nucleic acid sequence encoding the human TdT is located at an immunoglobulin κ light chain locus, an immunoglobulin λ light chain locus, an immunoglobulin heavy chain locus, a RAG1 locus, or a RAG2 locus.
3. The genetically modified mouse of claim 1, wherein at least 20% of V-J immunoglobulin light chain junctions in the mouse comprise non-template additions.
4. The genetically modified mouse of claim 1, wherein the immunoglobulin light chain constant region is a mouse immunoglobulin light chain constant region.
5. The genetically modified mouse of claim 4, wherein the immunoglobulin variable region and the mouse immunoglobulin light chain constant region are located at an endogenous immunoglobulin light chain locus.

6. The genetically modified mouse of claim 7, wherein human immunoglobulin heavy chain variable region and the immunoglobulin heavy chain constant region are located at an endogenous immunoglobulin heavy chain locus.
7. The genetically modified mouse of claim 1, wherein the immunoglobulin heavy chain constant region is mouse immunoglobulin heavy chain constant region.
8. The genetically modified mouse of claim 1, wherein the human immunoglobulin light chain V and J gene segments are human V κ and J κ gene segments.
9. The genetically modified mouse of claim 1, wherein the human immunoglobulin light chain V and J gene segments are human V λ and J λ gene segments.
10. The genetically modified mouse of claim 8, wherein the immunoglobulin light chain constant region is a κ constant region.
11. The genetically modified mouse of claim 9, wherein the immunoglobulin light chain constant region is a λ constant region.
12. The genetically modified mouse of claim 6, wherein the κ constant region is a mouse κ constant region.
13. The genetically modified mouse of claim 11, wherein the λ constant region is a mouse λ constant region.
14. The genetically modified mouse of claim 12, wherein the immunoglobulin variable region and the mouse κ constant region are located at an endogenous immunoglobulin κ locus.

15. The genetically modified mouse of claim 13, wherein the immunoglobulin variable region and the mouse λ constant region are located at an endogenous immunoglobulin λ locus.
16. The genetically modified mouse of claim 1, wherein the TdT is a short isoform of human TdT (TdT_S).
17. The genetically modified mouse of claim 1, wherein the human or mouse transcriptional control element is 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 or an immunoglobulin λ light chain transcriptional control element.
18. A genetically modified mouse comprising in its germline genome:
a nucleic acid sequence encoding a human Terminal Deoxynucleotidyltransferase (TdT) operably linked to a human or mouse transcriptional control element, wherein the transcriptional control element is active in pre-B cells;
a human immunoglobulin heavy chain variable region comprising unrearranged human immunoglobulin heavy chain V, D, and J gene segments operably linked to a human or mouse immunoglobulin heavy chain constant region; and
a human immunoglobulin light chain variable region comprising unrearranged human immunoglobulin light chain V and J gene segments operably linked to a human or mouse immunoglobulin light chain constant region,
wherein the nucleic acid sequence encoding the human TdT is located at an immunoglobulin κ light chain locus, and wherein the human or mouse transcriptional control element is a mouse RAG1 transcriptional control element, a mouse RAG2 transcriptional control element, a mouse immunoglobulin heavy chain transcriptional control element, a mouse immunoglobulin κ light chain transcriptional control element, or a mouse immunoglobulin λ light chain transcriptional control element.

19. The genetically modified mouse of claim 1, wherein the nucleic acid sequence encoding the human TdT was randomly inserted into the genome, and wherein the human or rodent transcriptional control element is a mouse RAG1 transcriptional control element, a mouse RAG2 transcriptional control element, a mouse immunoglobulin heavy chain transcriptional control element, a mouse immunoglobulin κ light chain transcriptional control element, or a mouse immunoglobulin λ light chain transcriptional control element.

20. A genetically modified mouse comprising in its germline genome:
a nucleic acid sequence encoding a human Terminal Deoxynucleotidyltransferase (TdT) operably linked to a human or mouse transcriptional control element, wherein the transcriptional control element is active in pre-B cells;

a human immunoglobulin heavy chain variable region comprising unrearranged human immunoglobulin heavy chain V, D, and J gene segments operably linked to a human or mouse immunoglobulin heavy chain constant region; and

a human immunoglobulin light chain variable region comprising unrearranged human immunoglobulin light chain V and J gene segments operably linked to a human or mouse immunoglobulin light chain constant region, wherein:

- (a) the human or mouse transcriptional control element is a mouse RAG2 transcriptional control element, and the nucleic acid sequence was randomly integrated into the germline genome without disrupting any endogenous coding regions;
- (b) the human or mouse transcriptional control element is a mouse RAG2 transcriptional control element, and the nucleic acid sequence is located at an immunoglobulin κ light chain locus; or
- (c) the human or mouse transcriptional control element is a mouse transcriptional control element comprising a mouse IgVH1-72 promoter and a mouse E μ enhancer, and the nucleic acid sequence was randomly integrated into the germline genome without disrupting any endogenous coding regions; or

(d) the human or mouse transcriptional control element is a mouse transcriptional control element comprising a mouse IgVH1-72 promoter and a mouse E μ enhancer, and the nucleic acid sequence is located at an immunoglobulin κ light chain locus.

21. The genetically modified mouse of claim 8, wherein at least 20% of V-J immunoglobulin κ light chain junctions in the mouse comprise non-template additions.