

CLAIMS

1. A genetically modified mouse, whose germline genome comprises:
a first engineered endogenous immunoglobulin κ light chain locus comprising:
 - (a) one or more human $V\lambda$ gene segments,
 - (b) one or more human $J\lambda$ gene segments, and
 - (c) one mouse $C\lambda$ gene,wherein the one or more human $V\lambda$ gene segments of (a) and the one or more human $J\lambda$ gene segments of (b) are in place of one or more endogenous mouse $V\kappa$ gene segments and one or more endogenous mouse $J\kappa$ gene segments;
wherein the one or more human $V\lambda$ gene segments of (a) and the one or more human $J\lambda$ gene segments of (b) are operably linked to the one mouse $C\lambda$ gene of (c);
wherein the genetically modified mouse comprises a population of B cells that express antibodies,
wherein the antibodies include immunoglobulin λ , light chains that each include a human immunoglobulin λ , light chain variable domain; and
wherein the genetically modified mouse lacks a mouse $C\kappa$ gene at the first engineered endogenous immunoglobulin κ light chain locus.
2. The genetically modified mouse of claim 1, wherein the genetically modified mouse is homozygous for the first engineered endogenous immunoglobulin κ light chain locus.
3. The genetically modified mouse of claim 1, wherein the genetically modified mouse is heterozygous for the first engineered endogenous immunoglobulin κ light chain locus.
4. The genetically modified mouse of claim 3, wherein the germline genome of the genetically modified mouse comprises a second engineered endogenous immunoglobulin κ light chain locus comprising:
 - (a) one or more human $V\kappa$ gene segments, and
 - (b) one or more human $J\kappa$ gene segments,wherein the one or more human $V\kappa$ gene segments and the one or more human $J\kappa$ gene segments are operably linked to a $C\kappa$ gene.

5. The genetically modified mouse of any one of the preceding claims, wherein the germline genome of the mouse further comprises:

an engineered endogenous immunoglobulin heavy chain locus, comprising:

- (a) one or more human V_H gene segments,
- (b) one or more human D_H gene segments, and
- (c) one or more human J_H gene segments,

wherein the one or more human V_H gene segments of (a), the one or more human D_H gene segments of (b), and the one or more human J_H gene segments of (c) are operably linked to one or more mouse immunoglobulin heavy chain constant region genes at the engineered endogenous immunoglobulin heavy chain locus.

6. The genetically modified mouse of claim 5, wherein the one or more human V_H gene segments of (a), one or more human D_H gene segments of (b), and one or more human J_H gene segments of (c) are in place of one or more mouse V_H gene segments, one or more mouse D_H gene segments, one or more mouse J_H gene segments, or a combination thereof.

7. The genetically modified mouse of claim 5 or 6, wherein the engineered endogenous immunoglobulin heavy chain locus further comprises:

(i) one or more human V_H non-coding sequences, each of which is adjacent to at least one of the one or more human V_H gene segments, wherein each of the one or more V_H non-coding sequences naturally appears adjacent to a human V_H gene segment in an endogenous human immunoglobulin heavy chain locus;

(ii) one or more human D_H non-coding sequences, each of which is adjacent to at least one of the one or more human D_H gene segments, wherein each of the one or more D_H non-coding sequences naturally appears adjacent to a human D_H gene segment in an endogenous human immunoglobulin heavy chain locus;

(iii) one or more human J_H non-coding sequences, each of which is adjacent to at least one of the one or more human J_H gene segments, wherein each of the one or more J_H non-coding sequences naturally appears adjacent to a human J_H gene segment in an endogenous human immunoglobulin heavy chain locus; or

(iv) any combination thereof.

8. The genetically modified mouse of any one of claims 5 to 7, wherein the one or more mouse immunoglobulin heavy chain constant region genes are one or more endogenous mouse immunoglobulin heavy chain constant region genes.

9. The genetically modified mouse of any one of claims 5 to 8, wherein:

(i) the one or more human V_H gene segments comprise V_{H3-74} , V_{H3-73} , V_{H3-72} , V_{H2-70} , V_{H1-69} , V_{H3-66} , V_{H3-64} , V_{H4-61} , V_{H4-59} , V_{H1-58} , V_{H3-53} , V_{H5-51} , V_{H3-49} , V_{H3-48} , V_{H1-46} , V_{H1-45} , V_{H3-43} , V_{H4-39} , V_{H4-34} , V_{H3-33} , V_{H4-31} , V_{H3-30} , V_{H4-28} , V_{H2-26} , V_{H1-24} , V_{H3-23} , V_{H3-21} , V_{H3-20} , V_{H1-18} , V_{H3-15} , V_{H3-13} , V_{H3-11} , V_{H3-9} , V_{H1-8} , V_{H3-7} , V_{H2-5} , V_{H7-4-1} , V_{H4-4} , V_{H1-3} , V_{H1-2} , V_{H6-1} , or a combination thereof,

(ii) the one or more human D_H gene segments comprise D_{H1-1} , D_{H2-2} , D_{H3-3} , D_{H4-4} , D_{H5-5} , D_{H6-6} , D_{H1-7} , D_{H2-8} , D_{H3-9} , D_{H3-10} , D_{H5-12} , D_{H6-13} , D_{H2-15} , D_{H3-16} , D_{H4-17} , D_{H6-19} , D_{H1-20} , D_{H2-21} , D_{H3-22} , D_{H6-25} , D_{H1-26} , D_{H7-27} , or a combination thereof, and

(iii) the one or more human J_H gene segments comprise J_{H1} , J_{H2} , J_{H3} , J_{H4} , J_{H5} , J_{H6} , or a combination thereof.

10. The genetically modified mouse of any one of claims 5 to 9, wherein the genetically modified mouse is homozygous for the engineered endogenous immunoglobulin heavy chain locus.

11. The genetically modified mouse of any one of the preceding claims, wherein the one or more human $V\lambda$ gene segments of (a) and the one or more human $J\lambda$ gene segments of (b) replace one or more mouse $V\kappa$ gene segments, one or more mouse $J\kappa$ gene segments, or a combination thereof.

12. The genetically modified mouse of any one of the preceding claims, wherein the first engineered endogenous immunoglobulin κ light chain locus further comprises a κ light chain non-coding sequence between the one or more human $V\lambda$, gene segments and the one or more human $J\lambda$, gene segments.

13. The genetically modified mouse of claim 12, wherein the κ light chain non-coding sequence has a sequence that naturally appears between a human V κ 4-1 gene segment and a human J κ 1 gene segment in an endogenous human immunoglobulin κ light chain locus.

14. The genetically modified mouse of any one of the preceding claims, wherein the endogenous V λ gene segments, the endogenous J λ gene segments, and the endogenous C λ genes are deleted in whole or in part.

15. The genetically modified mouse of any one of the preceding claims, wherein each human immunoglobulin λ light chain variable domain is encoded by a rearranged human immunoglobulin λ light chain variable region sequence comprising (i) one of the one or more human V λ gene segments of (a) or a somatically hypermutated variant thereof, and (ii) one of the one or more human J λ gene segments of (b) or a somatically hypermutated variant thereof.

16. The genetically modified mouse of any one of the preceding claims, wherein the germline genome further comprises a nucleic acid sequence encoding an exogenous terminal deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element.