

CLAIMS

1. A mouse whose germline genome comprises an endogenous immunoglobulin λ 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 or more human $C\lambda$ gene segments,

wherein (a) and (b) are operably linked to (c) and a mouse $C\lambda$ gene segment, and wherein the endogenous immunoglobulin λ light chain locus further comprises: one or more mouse immunoglobulin λ light chain enhancers ($E\lambda$), and one or more human immunoglobulin λ light chain enhancers ($E\lambda$), and wherein the mouse expresses an immunoglobulin λ light chain comprising a human λ variable domain and either a human λ constant domain or a mouse λ constant domain.

2. The mouse of claim 1, wherein the endogenous immunoglobulin λ light chain locus comprises two mouse $E\lambda$ s.
3. The mouse of claim 2, wherein the two mouse $E\lambda$ s are a mouse $E\lambda$ and a mouse $E\lambda 3-1$.
4. The mouse of claim 1, wherein the endogenous immunoglobulin λ light chain locus comprises three human $E\lambda$ s.
5. The mouse of claim 1, wherein the germline genome further comprises

(i) an endogenous immunoglobulin heavy chain locus comprising insertion of one or more human V_H gene segments, one or more human D_H gene segments and one or more human J_H gene segments, which human V_H , D_H and J_H gene segments are operably linked to a mouse immunoglobulin heavy chain constant region; or

(ii) an endogenous immunoglobulin heavy chain locus comprising insertion of one or more human V_H gene segments, one or more human D_H gene segments and one or more human J_H gene segments, which human V_H , D_H and J_H gene segments are operably linked to a mouse immunoglobulin heavy chain constant region, and an endogenous immunoglobulin κ light

chain locus comprising insertion of one or more human V_k gene segments and one or more human J_k gene segments, which human V_k and J_k gene segments are operably linked to a mouse immunoglobulin C_k region.

6. The mouse of claim 5, wherein the insertion of one or more human V_H gene segments, one or more human D_H gene segments and one or more human J_H gene segments replace mouse V_H, D_H gene segments.
7. The mouse of claim 6, wherein the insertion includes human non-coding DNA that naturally appears between human V_H, D_H, and J_H gene segments, and combinations thereof.
8. The mouse of claim 5, wherein the insertion of one or more human V_k gene segments and one or more human J_k gene segments replace mouse V_k and J_k gene segments.
9. The mouse of claim 8, wherein the insertion includes human non-coding DNA that naturally appears between human V_k and J_k gene segments, and combinations thereof.
10. The mouse of claim 5, wherein the mouse immunoglobulin heavy chain constant region is an endogenous mouse immunoglobulin heavy chain constant region.
11. The mouse of claim 5, wherein the mouse C_k region is an endogenous mouse C_k region.
12. The mouse of claim 1, wherein the endogenous immunoglobulin λ light chain locus comprises a deletion of endogenous V_λ and J_λ gene segments, in whole or in part.
13. The mouse of claim 1, wherein the mouse C_λ gene segment is a mouse C_λ1 gene segment.
14. The mouse of claim 5, wherein the immunoglobulin κ light chain locus comprises insertion of the proximal V_k duplication, in whole or in part, of a human immunoglobulin κ light chain locus.
15. The mouse of claim 5, wherein the immunoglobulin heavy chain locus lacks an endogenous mouse Adam6 gene.
16. The mouse of claim 15, wherein the immunoglobulin heavy chain locus further comprises insertion of one or more nucleotide sequences encoding one or more mouse Adam6 polypeptides.

17. The mouse of claim 5, wherein the mouse is homozygous for the endogenous immunoglobulin heavy chain locus.
18. The mouse of claim 5, wherein the mouse is homozygous for the endogenous immunoglobulin κ light chain locus.
19. The mouse of claim 1, wherein the mouse is homozygous for the endogenous immunoglobulin λ light chain locus.
20. A method of making a mouse whose germline genome comprises an engineered endogenous immunoglobulin λ light chain locus, the method comprising
- (a) introducing a DNA fragment into a mouse embryonic stem cell, said DNA fragment comprising a nucleotide sequence that includes
- (i) one or more human $V\lambda$ gene segments,
 - (ii) one or more human $J\lambda$ gene segments, and
 - (iii) one or more human $C\lambda$ gene segments,
- wherein (i)-(iii) are operably linked to a mouse $C\lambda$ gene segment, and
- wherein the nucleotide sequence further comprises one or more human immunoglobulin λ light chain enhancers ($E\lambda$);
- (b) obtaining the mouse embryonic stem cell generated in (a); and
- (c) creating a mouse using the mouse embryonic stem cell of (b).
21. A method of making a mouse whose germline genome comprises an engineered endogenous immunoglobulin λ light chain locus, which engineered endogenous immunoglobulin λ light chain locus comprises insertion of one or more human $V\lambda$ gene segments, one or more human $J\lambda$ gene segments and one or more human $C\lambda$ gene segments, which human $V\lambda$ and $J\lambda$ gene segments are operably linked to a mouse or a human $C\lambda$ gene segment, and which endogenous immunoglobulin λ light chain locus further comprises one or more mouse

immunoglobulin λ light chain enhancers ($E\lambda$), and one or more human immunoglobulin λ light chain enhancers ($E\lambda$), the method comprising

modifying the germline genome of a mouse so that it comprises an engineered immunoglobulin λ light chain locus that includes insertion of one or more human $V\lambda$ gene segments, one or more human $J\lambda$ gene segments and one or more human $C\lambda$ gene segments, which human $V\lambda$ and $J\lambda$ gene segments are operably linked to a mouse or a human $C\lambda$ gene segment, and which endogenous immunoglobulin λ light chain locus further comprises one or more mouse immunoglobulin λ light chain enhancers ($E\lambda$), and one or more human immunoglobulin λ light chain enhancers ($E\lambda$), thereby making said mouse.