

CLAIMS

1. A genetically modified ~~rodent~~mouse, whose germline genome comprises:
 - a first engineered endogenous immunoglobulin ~~κ~~κ light chain locus comprising:
 - (a) ~~(a)~~ one or more human ~~Vκ~~Vλ gene segments,
 - (b) ~~(b)~~ one or more human ~~Jκ~~Jλ gene segments, and
 - (c) ~~(c)~~ a ~~Cκ~~one mouse Cλ gene,
 wherein the one or more human ~~Vκ~~Vλ gene segments of (a) and the one or more human ~~Jκ~~ gene segments ~~Jλ~~ gene segments of (b) are in place of one or more endogenous mouse Vκ gene segments and one or more endogenous mouse Jκ gene segments;
 - wherein the one or more human Vλ gene segments of (a) and the one or more human Jλ gene segments of (b) are operably linked to the ~~Cκ~~one mouse Cλ gene; and of (c);
 - wherein the ~~rodent~~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 ~~rodent~~Cκmouse Cκ gene at the first engineered endogenous immunoglobulin ~~κ~~κ light chain locus.
2. The genetically modified ~~rodent~~mouse of claim 1, wherein the ~~rodent~~genetically modified mouse is homozygous for the first engineered endogenous immunoglobulin ~~κ~~κ light chain locus.
3. The genetically modified ~~rodent~~mouse of claim 1, wherein the ~~rodent~~genetically modified mouse is heterozygous for the first engineered endogenous immunoglobulin ~~κ~~κ light chain locus.
4. The genetically modified ~~rodent~~mouse of claim 3, wherein the germline genome of the ~~rodent~~genetically modified mouse comprises a second engineered endogenous immunoglobulin ~~κ~~κ light chain locus comprising:

(a) ~~(a)~~ one or more human ~~V_κ~~V_κ gene segments, and

(b) ~~(b)~~ one or more human ~~J_κ~~J_κ gene segments,

wherein the one or more human ~~V_κ~~V_κ gene segments and the one or more human ~~J_κ~~J_κ gene segments are operably linked to a ~~C_κ~~C_κ gene.

_____ 5. The genetically modified rodent of claim 4, wherein the C κ gene at the second engineered endogenous immunoglobulin κ light chain locus is an endogenous rodent C κ gene.

6. ~~_____ The genetically modified rodent~~mouse of any one of the preceding claims 1-5, wherein the rodent lacks a rodent C κ gene at the first engineered endogenous immunoglobulin κ light chain locus, wherein the

7. ~~_____ A genetically modified rodent, whose germline genome comprises:~~

(a) ~~a first engineered endogenous immunoglobulin κ light chain locus comprising:~~

~~(i) one or more human V λ gene segments,~~

~~(ii) one or more human J λ gene segments, and~~

~~(iii) a C λ gene,~~

~~wherein the one or more human V λ gene segments and the one or more human J λ gene segments are operably linked to the C λ gene, and~~

~~wherein the rodent lacks a rodent C κ gene at the first engineered endogenous immunoglobulin κ light chain locus; and~~

(b) ~~a second engineered endogenous immunoglobulin κ light chain locus comprising:~~

~~(i) one or more human V κ gene segments, and~~

~~(ii) one or more human J κ gene segments,~~

~~wherein the one or more human V κ gene segments and the one or more human J κ gene segments are operably linked to a C κ gene.~~

8. ~~_____ The genetically modified rodent of claim 7, wherein the C κ gene at the second engineered endogenous immunoglobulin κ light chain locus is an endogenous rodent C κ gene.~~

9. ~~_____ The genetically modified rodent of any one of claims 1-8, wherein the C λ gene at the first engineered endogenous immunoglobulin κ light chain locus comprises a rodent C λ gene.~~

10. ~~_____ The genetically modified rodent of any one of claims 1-9, wherein the first engineered endogenous immunoglobulin κ light chain locus~~of the mouse further comprises:

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

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

~~(iii) any combination thereof.~~

11. ~~The genetically modified rodent of any one of claims 1-10, wherein:~~

~~(i) the one or more human V λ gene segments comprise V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, V λ 3-1, or any combination thereof; and~~

~~(ii) the one or more human J λ gene segments comprise J λ 1, J λ 2, J λ 3, J λ 6, J λ 7, or any combination thereof.~~

12. ~~The genetically modified rodent of claim 11, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:~~

~~(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and~~

~~(ii) one or more human J λ non-coding sequences, wherein each of the one or more human J λ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J λ non-coding sequences naturally appears adjacent to a J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 of an endogenous human immunoglobulin λ light chain locus.~~

13. ~~The genetically modified rodent of claim 11, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:~~

~~(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and~~

~~(ii) one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous~~

immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus.

14. — The genetically modified rodent of any one of claims 1-13, wherein:

(i) the one or more human V λ gene segments comprise V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, V λ 3-1, or any combination thereof; and

(ii) the one or more human J λ gene segments comprise J λ 1, J λ 2, J λ 3, J λ 6, J λ 7, or any combination thereof.

15. — The genetically modified rodent of claim 14, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human J λ non-coding sequences, wherein each of the one or more human J λ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J λ non-coding sequences naturally appears adjacent to a J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 of an endogenous human immunoglobulin λ light chain locus.

16. — The genetically modified rodent of claim 14, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37,

V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus.

17. — A genetically modified rodent, whose germline genome comprises:

a first engineered endogenous immunoglobulin κ light chain locus comprising:

(i) one or more human V λ gene segments, wherein the one or more human V λ gene segments comprise V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, V λ 3-1, or any combination thereof;

(ii) one or more human J λ gene segments, wherein the one or more human J λ gene segments comprise J λ 1, J λ 2, J λ 3, J λ 6, J λ 7, or any combination thereof;

(iii) a rodent C λ gene;

(iv) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus;

(v) one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6, or J λ 7 in the engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus; and

(vi) a human κ light chain non-coding sequence between the one or more human V λ gene segments and the one or more human J λ gene segments that 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;

wherein the one or more human V λ gene segments, the one or more human J λ gene segments, and the rodent C λ gene are operably linked to each other, and

wherein the rodent $C\lambda$ gene is in place of a rodent $C\kappa$ gene of the endogenous immunoglobulin κ light chain locus.

18. — The genetically modified rodent of claim 17, wherein the germline genome of the rodent 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.

19. — The genetically modified rodent of claim 18, wherein the $C\kappa$ gene at the second engineered endogenous immunoglobulin κ light chain locus is an endogenous rodent $C\kappa$ gene.

20. — The genetically modified rodent of any one of claims 1-19, wherein the germline genome of the rodent further comprises:

an engineered endogenous immunoglobulin heavy chain locus, comprising:

- (a) ~~(a)~~ one or more human V_H gene segments,
- (b) ~~(b)~~ one or more human D_H gene segments, and
- (c) ~~(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 ~~rodent~~mouse immunoglobulin heavy chain constant region genes at the engineered endogenous immunoglobulin heavy chain locus.

21. — A 6. The genetically modified ~~rodent whose germline genome comprises:~~

(a) ~~an engineered endogenous immunoglobulin heavy chain locus comprising~~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 ~~operably linked to one or more~~
 endogenous immunoglobulin heavy chain constant region genes such that the rodent expresses
 immunoglobulin heavy chains that comprise a human heavy chain variable domain sequence and a rodent
 heavy chain constant domain sequence, wherein the germline genome is homozygous for the engineered
 endogenous immunoglobulin heavy chain locus;

(b) a first engineered endogenous immunoglobulin κ light chain locus comprising:

- (i) one or more human $V\lambda$ gene segments, wherein the one or more human $V\lambda$ gene segments comprise $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 2-18$, $V\lambda 3-16$,

V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, V λ 3-1, or any combination thereof;

(ii) one or more human J λ gene segments, wherein the one or more human J λ gene segments comprise J λ 1, J λ 2, J λ 3, J λ 6, J λ 7, or any combination thereof;

(iii) a rodent C λ gene;

(iv) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the second engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus;

(v) one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the second engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus; and

(vi) a human κ light chain non-coding sequence between the one or more human V λ gene segments and the one or more human J λ gene segments that 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;

wherein the one or more human V λ gene segments, the one or more human J λ gene segments, and the rodent C λ gene (c) are operably linked to each other;

wherein the rodent C λ gene is in place of a rodent C κ gene at the second endogenous immunoglobulin κ light chain locus; and

(e) a second engineered endogenous immunoglobulin κ light chain locus comprising one or more human V κ gene segments and one or more J κ gene segments operably linked to an endogenous rodent C κ region gene such that the rodent expresses immunoglobulin light chains that comprise a human κ light chain variable domain sequence and a rodent κ light chain constant domain sequence;

wherein the rodent expresses immunoglobulin light chains that comprise a human λ light chain variable domain sequence and a rodent λ light chain constant domain sequence.

22. The genetically modified rodent of claim 20 or 21, wherein the one or more human one or more mouse V_H gene segments, one or more human mouse D_H gene segments, and one or more

~~human~~mouse J_H gene segments ~~are in place of one or more rodent V_H gene segments, one or more rodent D_H gene segments, one or more rodent J_H gene segments, or a combination thereof.~~

23. 7. The genetically modified ~~rodent~~mouse of ~~any one of claims 20-22, wherein the one~~claim 5 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 one or more rodent V_H gene segments, one or more rodent D_H gene segments, one or more rodent J_H gene segments, or any combination thereof.~~

24. ~~The genetically modified rodent of any one of claims 20-23~~6, wherein the engineered endogenous

immunoglobulin heavy chain locus further comprises:

(i) ~~(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) ~~(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) ~~(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) ~~(iv)~~ any combination thereof.

8. The genetically modified ~~rodent~~mouse of any one of claims ~~20-24~~5 to 7, wherein the one or more ~~rodent~~mouse immunoglobulin heavy chain constant region genes are one or more endogenous mouse immunoglobulin heavy chain constant region genes ~~are one or more endogenous rodent immunoglobulin heavy chain constant region genes.~~

~~26~~9. The genetically modified ~~rodent~~mouse of any one of claims ~~20-25~~5 to 8, wherein:

(i) ~~(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_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 ~~any~~a combination thereof,

(ii) ~~(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 ~~any~~a combination thereof, and

(iii) ~~(iii)~~ the one or more human J_H gene segments comprise J_H1, J_H2, J_H3, J_H4, J_H5, J_H6, or ~~any~~a combination thereof.

~~27~~10. The genetically modified ~~rodent~~mouse of any one of claims ~~20-26~~5 to 9, wherein the ~~engineered endogenous immunoglobulin heavy chain locus lacks a functional endogenous rodent Adam6 gene.~~

~~28.~~ The genetically modified rodent of any one of claims 20-27, wherein the germline genome further comprises one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof.

~~29.~~ The genetically modified rodent of claim 28, wherein the one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are expressed.

~~30.~~ The genetically modified rodent of claim 28 or 29, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included on the same chromosome as the engineered endogenous immunoglobulin heavy chain locus.

31. — ~~The genetically modified rodent of any one of claims 28-30, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included in the engineered endogenous immunoglobulin heavy chain locus.~~

32. — ~~The genetically modified rodent of any one of claims 28-31, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are in place of a human Adam6 pseudogene.~~

33. — ~~The genetically modified rodent of any one of claims 28-32, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof replace a human Adam6 pseudogene.~~

34. — ~~The genetically modified rodent of any one of claims 28-33, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are between a first human V_H-gene segment and a second human V_H-gene segment.~~

35. — ~~The genetically modified rodent of claim 34, wherein the first human V_H-gene segment is V_H1-2 and the second human V_H-gene segment is V_H6-1.~~

36. — ~~The genetically modified rodent of any one of claims 28-31, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are between a human V_H-gene segment and a human D_H-gene segment.~~

37. — ~~The genetically modified rodent of any one claims 20, and 22-36, wherein the rodent genetically modified mouse is homozygous for the engineered endogenous immunoglobulin heavy chain locus.~~

3811. The genetically modified rodent of any one of claims 9-37, wherein the rodent C λ -gene has a sequence that is at least 80% identical to a mouse C λ 1, mouse C λ 2 or a mouse C λ 3 gene.

39. — The genetically modified rodent of any one of the preceding claims 9-38, wherein the rodent C λ -gene comprises a mouse C λ 1-gene.

40. — The genetically modified rodent of any one of claims 9-39, wherein the rodent C λ -gene comprises a rat C λ -gene.

~~41. The genetically modified rodent of claim 40, wherein the rat C λ gene has a sequence that is at least 80% identical to a rat C λ 1, rat C λ 2, rat C λ 3 or a rat C λ 4 gene.~~

~~42. The genetically modified rodent of any one of claims 1-41, wherein the one or more human $V\lambda$ V λ gene segments of (a) and the one or more human $J\lambda$ J λ gene segments are in place of (b) replace one or more ~~rodent V κ mouse V κ~~ gene segments, one or more ~~rodent J κ mouse J κ~~ gene segments, or ~~any~~ a combination thereof.~~

~~4312. The genetically modified ~~rodent~~mouse of any one of the preceding claims 1-42, wherein the one or more human V λ gene segments and the one or more human J λ gene segments replace one or more rodent V κ gene segments, one or more rodent J κ gene segments, or any combination thereof.~~

~~44. The genetically modified rodent of any one of claims 1-43, wherein the first engineered endogenous immunoglobulin κ κ light chain locus further comprises a κ κ light chain non-coding sequence between the one or more human $V\lambda$ V λ gene segments and the one or more human $J\lambda$ J λ gene segments.~~

~~45~~

13. The genetically modified ~~rodent~~mouse of claim ~~44~~12, wherein the ~~κ light chain non-coding sequence is a human κ light chain non-coding sequence.~~

~~46. The genetically modified rodent of claim 45, wherein the human κ κ light chain non-coding sequence has a sequence that naturally appears between a human $V\kappa$ 4V κ 4-1 gene segment and a human $J\kappa$ 1J κ 1 gene segment in an endogenous human immunoglobulin κ κ light chain locus.~~

~~47.~~

14. The genetically modified ~~rodent~~mouse of any one of the preceding claims 1-46, further comprising an inactivated endogenous immunoglobulin λ light chain locus.

48. ~~— The genetically modified rodent of claim 47, wherein the rodent is heterozygous for the inactivated endogenous immunoglobulin λ light chain locus.~~

49. ~~— The genetically modified rodent of claim 47, wherein the rodent is homozygous for the inactivated endogenous immunoglobulin λ light chain locus.~~

50. ~~— The genetically modified rodent of any one of claims 1-49, wherein the endogenous $\forall\lambda$ endogenous $V\lambda$ gene segments, the endogenous $\exists\lambda J\lambda$ gene segments, and the endogenous $\epsilon\lambda C\lambda$ genes are deleted in whole or in part.~~

15. 51. ~~— The genetically modified rodent~~mouse of any one of the preceding claims ~~1-50~~, wherein ~~the rodent does not detectably express endogenous immunoglobulin λ light chain variable domains.~~

52. ~~— The genetically modified rodent of any one of claims 1-51, wherein the rodent does not detectably express endogenous immunoglobulin κ light chain variable domains.~~

53. ~~— The genetically modified rodent of any one of claims 1-52, wherein the rodent comprises a population of B cells that express antibodies, including immunoglobulin λ light chains that each include a human immunoglobulin λ light chain variable domain.~~

54. ~~— The genetically modified rodent of claim 53, wherein the 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 $\forall\lambda V\lambda$ gene segments of (a) or a somatically hypermutated variant thereof, and (ii) one of the one or more human $\exists\lambda J\lambda$ gene segments of (b) or a somatically hypermutated variant thereof.~~

16. 55. ~~— The genetically modified rodent~~mouse of any one of the preceding claims ~~1-54~~, wherein the germline genome ~~of the rodent~~ further comprises a nucleic acid sequence encoding an exogenous terminal deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element.

56. ~~— The genetically modified rodent of claim 55, wherein the TdT is a short isoform of TdT (TdT_S).~~

57. — The genetically modified rodent of claim 55 or 56, wherein the transcriptional control element comprises 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, an immunoglobulin λ light chain transcriptional control element, or any combination thereof.

58. — The genetically modified rodent of any one of claims 55–57, wherein the nucleic acid sequence encoding an exogenous TdT is in the germline genome 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.

59. — A genetically modified rodent whose germline genome comprises

(a) a nucleic acid sequence encoding an exogenous terminal deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element;

(b) an engineered endogenous immunoglobulin heavy chain locus comprising 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 operably linked to one or more endogenous immunoglobulin heavy chain constant region genes such that the rodent expresses immunoglobulin heavy chains that each comprise a human heavy chain variable domain sequence and a rodent heavy chain constant domain sequence, wherein the germline genome is homozygous for the engineered endogenous immunoglobulin heavy chain locus; and

(c) an engineered endogenous immunoglobulin κ light chain locus comprising:

(i) one or more human $V\lambda$ gene segments, wherein the one or more human $V\lambda$ gene segments comprise $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 2-18$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, $V\lambda 3-1$ or any combination thereof;

(ii) one or more human $J\lambda$ gene segments, wherein the one or more human $J\lambda$ gene segments comprise $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$, $J\lambda 7$ or any combination thereof;

(iii) a rodent $C\lambda$ gene;

(iv) one or more human $V\lambda$ non-coding sequences, wherein each of the one or more human $V\lambda$ non-coding sequences is adjacent to the $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 2-18$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$ or $V\lambda 3-1$ in the engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $V\lambda$ non-coding sequences naturally appears adjacent to a $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 2-18$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$ or $V\lambda 3-1$ of an endogenous human immunoglobulin λ light chain locus;

(v) one or more human $J\kappa$ non-coding sequences, wherein each of the one or more human $J\kappa$ non-coding sequences is adjacent to the $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$ and $J\lambda 7$ in the engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $J\kappa$ non-coding

sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus, and

(vi) a human κ light chain non-coding sequence between the one or more human V λ gene segments and the one or more human J λ gene segments that comprises 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,

wherein the one or more human V λ gene segments, the one or more human J λ gene segments, and the rodent C λ gene are operably linked to each other,

wherein the rodent C λ gene is in place of a rodent C κ gene of the endogenous immunoglobulin κ light chain locus,

wherein the germline genome is homozygous for the engineered endogenous immunoglobulin κ light chain locus, and

wherein the rodent expresses immunoglobulin light chains that comprise a human λ light chain variable domain sequence fused to a rodent λ light chain constant domain sequence.

60. — The genetically modified rodent of any one of claims 1-59, wherein the rodent is a rat or a mouse.

61. — An isolated rodent cell obtained from a rodent of any one of claims 1-60.

62. — An immortalized cell generated from the isolated rodent cell of claim 61.

63. — The isolated rodent cell of 61, wherein the rodent cell is a rodent embryonic stem (ES) cell.

64. — A rodent embryo generated from the rodent ES cell of claim 63.

65. — Use of a rodent of any one of claims 1-60 for making an antibody.

66. — Use of a rodent of any one of claims 1-60 for making a light chain variable region sequence.

67. — Use of a rodent of any one of claims 1-60 for making a light chain variable domain sequence.

68. — An isolated B cell obtained from a rodent of any one claims 1-60, wherein the genome of the B cell comprises:

— (a) a rearranged human lambda light chain variable region sequence operably linked to a lambda light chain variable region sequence, wherein the rearranged human lambda light chain variable region sequence comprises:

(i) one of the one or more human V λ gene segments or a somatically hypermutated variant thereof, and

(ii) one of the one or more human J λ gene segments or a somatically hypermutated variant

thereof.

69. ~~The isolated B cell of claim 68, further comprising:~~

~~(b) a rearranged human heavy chain variable region sequence operably linked to a rodent heavy chain variable region sequence, wherein the rearranged human heavy chain variable region sequence comprises:~~

~~(i) one of the one or more human V_H gene segments or a somatically hypermuted variant thereof;~~

~~(ii) one of the one or more human D_H gene segments or a somatically hypermuted variant thereof; and~~

~~(iii) one of the one or more human J_H gene segments or a somatically hypermuted variant thereof.~~

70. ~~An antibody prepared by a method comprising the steps of:~~

~~(a) providing a rodent of any one of claims 1-60;~~

~~(b) immunizing the rodent with an antigen of interest;~~

~~(c) maintaining the rodent under conditions sufficient for the rodent to produce an immune response to the antigen of interest; and~~

~~(d) recovering from the rodent:~~

~~(i) an antibody that binds the antigen of interest;~~

~~(ii) a nucleotide that encodes a human light or heavy chain variable domain, a light chain, or a heavy chain of an antibody that binds the antigen of interest; or~~

~~(iii) a cell that expresses an antibody that binds the antigen of interest;~~

~~wherein an antibody of (d) includes human heavy chain variable and human λ light chain variable domains.~~

71. ~~An isolated rodent cell, whose genome comprises:~~

~~a first engineered endogenous immunoglobulin κ light chain locus comprising:~~

~~(a) one or more human V λ gene segments,~~

~~(b) one or more human J λ gene segments; and~~

~~(c) a C λ gene;~~

~~wherein the one or more human V λ gene segments and the one or more human J λ gene segments are operably linked to the C λ gene; and~~

~~wherein the isolated rodent cell lacks a rodent C κ gene at the first engineered endogenous immunoglobulin κ light chain locus.~~

72. ~~The isolated rodent cell of claim 71, wherein the isolated rodent cell is homozygous for the first engineered endogenous immunoglobulin κ light chain locus.~~

73. ~~The isolated rodent cell of claim 71, wherein the isolated rodent cell is heterozygous for the first~~

~~engineered endogenous immunoglobulin κ light chain locus.~~

~~74. The isolated rodent cell of claim 73, wherein the genome of the isolated rodent cell 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.~~

~~75. The isolated rodent cell of claim 74, wherein the $C\kappa$ gene at the second engineered endogenous immunoglobulin κ light chain locus is an endogenous rodent $C\kappa$ gene.~~

~~76. The isolated rodent cell of any one of claims 71-75, wherein the isolated rodent cell lacks a rodent $C\kappa$ gene at the first engineered endogenous immunoglobulin κ light chain locus.~~

~~77. The isolated rodent cell of any one of claims 71-76, wherein the $C\lambda$ gene at the first engineered endogenous immunoglobulin κ light chain locus comprises a rodent $C\lambda$ gene.~~

~~78. The isolated rodent cell of any one of claims 71-77, wherein the first engineered endogenous immunoglobulin κ light chain locus further comprises:~~

~~(i) one or more human $V\lambda$ non-coding sequences, each of which is adjacent to at least one of the one or more human $V\lambda$ gene segments, wherein the one or more human $V\lambda$ non-coding sequences naturally appears adjacent to a human $V\lambda$ gene segment in an endogenous human immunoglobulin λ light chain locus;~~

~~(ii) one or more human $J\lambda$ non-coding sequences, each of which is adjacent to at least one of the one or more human $J\lambda$ gene segments, wherein the one or more human $J\lambda$ non-coding sequences naturally appears adjacent to a human $J\lambda$ gene segment in an endogenous human immunoglobulin λ light chain locus; or~~

~~(iii) any combination thereof.~~

~~79. The isolated rodent cell of any one of claims 71-78, wherein:~~

~~(i) the one or more human $V\lambda$ gene segments comprise $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, $V\lambda 3-1$, or any combination thereof; and~~

~~(ii) the one or more human $J\lambda$ gene segments comprise $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$, $J\lambda 7$, or any combination thereof.~~

~~80. The isolated rodent cell of claim 79, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:~~

(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human J λ non-coding sequences, wherein each of the one or more human J λ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J λ non-coding sequences naturally appears adjacent to a J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 of an endogenous human immunoglobulin λ light chain locus.

81. — The isolated rodent cell of claim 79, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus;

(ii) one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus.

82. — The isolated rodent cell of any one of claims 71-81, wherein:

(a) the one or more human V λ gene segments comprise V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, V λ 3-1, or any combination thereof; and

(b) the one or more human J λ gene segments comprise J λ 1, J λ 2, J λ 3, J λ 6, J λ 7, or any combination

thereof:

83. ~~The isolated rodent cell of claim 82, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:~~

(i) ~~one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and~~

(ii) ~~one or more human J λ non-coding sequences, wherein each of the one or more human J λ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J λ non-coding sequences naturally appears adjacent to a J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 of an endogenous human immunoglobulin λ light chain locus.~~

84. ~~The isolated rodent cell of claim 82, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:~~

(i) ~~one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and~~

(ii) ~~one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus.~~

85. ~~The isolated rodent cell of any one of claims 71-84, wherein the genome of the rodent cell 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, the one or more human D_H-gene segments, and the one or more human J_H-gene segments are operably linked to one or more rodent immunoglobulin heavy chain constant region genes at the engineered endogenous immunoglobulin heavy chain locus.~~

86. — ~~The isolated rodent cell of claim 85, wherein the 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 are in place of one or more rodent V_H-gene segments, one or more rodent D_H-gene segments, one or more rodent J_H-gene segments, or a combination thereof.~~

87. — ~~The isolated rodent cell of claim 85 or 86, wherein the 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 one or more rodent V_H-gene segments, one or more rodent D_H-gene segments, one or more rodent J_H-gene segments, or any combination thereof.~~

88. — ~~The isolated rodent cell of any one of claims 85-87, 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.~~

89. — ~~The isolated rodent cell of any one of claims 85-88, wherein the one or more rodent immunoglobulin heavy chain constant region genes are one or more endogenous rodent immunoglobulin heavy chain constant region genes.~~

90. — ~~The isolated rodent cell of any one of claims 85-89, 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 any 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 any 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 any combination thereof.

91. — The isolated rodent cell of any one of claims 85-90, wherein the engineered endogenous immunoglobulin heavy chain locus lacks a functional endogenous rodent Adam6 gene.

92. — The isolated rodent cell of any one of claims 85-91, wherein the genome of the rodent cell further comprises one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof.

93. — The isolated rodent cell of claim 92, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included on the same chromosome as the engineered endogenous immunoglobulin heavy chain locus.

94. — The isolated rodent cell of claim 92 or 93, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included in the engineered endogenous immunoglobulin heavy chain locus.

95. — The isolated rodent cell of any one of claims 92-94, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are in place of a human Adam6 pseudogene.

96. — The isolated rodent cell of any one of claims 92-95, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof replace a human Adam6 pseudogene.

97. — The isolated rodent cell of any one of claims 92-96, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are between a first human V_H -gene segment and a second human V_H -gene segment.

98. — The isolated rodent cell of claim 97, wherein the first human V_H -gene segment is V_{H1-2} and the second human V_H -gene segment is V_{H6-1} .

99. — The isolated rodent cell of any one of claims 92-94, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are between a human V_H -gene segment and a human D_H -gene segment.

100. — The isolated rodent cell of any one of claims 85-99, wherein the isolated rodent cell is homozygous for the engineered endogenous immunoglobulin heavy chain locus.

101. — The isolated rodent cell of any one of claims 71-100, wherein the genome of the isolated rodent cell further comprises a nucleic acid sequence encoding an exogenous terminal deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element.

102. — The isolated rodent cell of claim 101, wherein the TdT is a short isoform of TdT (TdT_S).

103. — The isolated rodent cell of claim 101 or 102, wherein the transcriptional control element comprises 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, an immunoglobulin λ light chain transcriptional control element, or any combination thereof.

104. — The isolated rodent cell of any one of claims 101-103, wherein the nucleic acid sequence encoding an exogenous TdT is in the genome of the rodent cell 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.

105. — The isolated rodent cell of any one of claims 71-104, wherein the rodent cell is a rat cell or a mouse cell.

106. — An immortalized cell generated from the isolated rodent cell of any one of claims 71-105.

107. — The isolated rodent cell of any one of claims 71-105, wherein the rodent cell is a rodent embryonic stem (ES) cell.

108. — A rodent embryo generated from the rodent ES cell of claim 107.

109. — A method of making a genetically modified rodent comprising the steps of:

— (a) introducing one or more DNA fragments into the a first engineered immunoglobulin κ light chain locus in the genome of a rodent ES cell, wherein the one or more DNA fragments comprise:

- (i) one or more human V λ gene segments;
- (ii) one or more human J λ gene segments, and
- (iii) a C λ gene;

wherein the one or more human V λ gene segments, the one or more human J λ gene segments, and the C λ gene are introduced into the genome of the rodent ES cell at the endogenous immunoglobulin κ light chain locus, and wherein the one or more human V λ gene segments, the one or more human J λ gene segments, and the C λ gene are operably linked; and

——— (b) generating a rodent using the rodent ES cell generated in (a).

110. — The method of claim 109, wherein the genome of the rodent ES cell comprises a second engineered endogenous immunoglobulin κ light chain locus comprising:

(i) one or more human V κ gene segments, and

(ii) one or more human J κ gene segments,

wherein the one or more human V κ gene segments and the one or more human J κ gene segments are operably linked to a C κ gene.

111. — The method of claim 109 or 110, wherein the genome of the rodent ES cell comprises an engineered endogenous immunoglobulin heavy chain locus comprising:

(i) one or more human V H gene segments,

(ii) one or more human D H gene segments, and

(iii) one or more human J H gene segments,

wherein the one or more human V H gene segments, the one or more human D H gene segments, and the one or more human J H gene segments are operably linked to one or more rodent immunoglobulin heavy chain constant region genes at the engineered endogenous immunoglobulin heavy chain locus.

112. — The method of any one of claims 109–111, wherein the one or more DNA fragments further comprise at least one selection marker.

113. — The method of any one of claims 109–112, wherein the one or more DNA fragments further comprise at least one site-specific recombination site.

114. — The method of any one of claims 109–113, further comprising introducing one or more human V λ non-coding sequences and one or more human V λ non-coding sequences in the first engineered endogenous immunoglobulin κ light chain locus, wherein each of the one or more human V λ non-coding sequences is adjacent to a human V λ gene segment, and each of the one or more human J λ non-coding sequences is adjacent to a human J λ gene segment.

115. — The method of any one of claims 109–114, further comprising introducing a κ light chain non-coding sequence into the genome of the rodent ES cell so that the κ light chain non-coding sequence is between the one or more human V λ gene segments and the one or more human J λ gene segments in the first engineered endogenous immunoglobulin κ light chain locus.

116. — The method of any one claims 109–115, wherein the rodent ES cell is a rat ES cell or a mouse ES cell.

117. — A method of making a genetically modified rodent, comprising the step of:

(a) engineering a first endogenous immunoglobulin κ light chain locus in the germline genome of the

rodent to include:

- (i) ~~one or more human V λ gene segments,~~
- (ii) ~~one or more human J λ gene segments, and~~
- (iii) ~~a C λ gene,~~

~~wherein the one or more human V λ gene segments and the one or more human J λ gene segments are operably linked to the C λ gene, and~~

~~wherein the C λ gene is inserted at the first endogenous immunoglobulin κ light chain locus.~~

118. ~~The method of claim 117, wherein the method further comprises the step of:~~

~~(b) engineering a second endogenous immunoglobulin κ light chain locus in the germline genome of the rodent to include:~~

- ~~(i) one or more human V λ gene segments,~~
- ~~(ii) one or more human J λ gene segments, and~~
- ~~(iii) a C λ gene,~~

~~wherein the one or more human V λ gene segments and the one or more human J λ gene segments are operably linked to the C λ gene, and~~

~~wherein the C λ gene is inserted at the second endogenous immunoglobulin κ light chain locus.~~

119. ~~The method of claim 117, wherein the method further comprises the step of:~~

~~(b) engineering a second engineered endogenous immunoglobulin κ light chain locus in the germline genome of the rodent to include:~~

- ~~(i) one or more human V κ gene segments, and~~
- ~~(ii) one or more human J κ gene segments,~~

~~wherein the one or more human V κ gene segments and the one or more human J κ gene segments are operably linked to a C κ gene.~~

120. ~~The method of claim 119, wherein the C κ gene at the second engineered endogenous immunoglobulin κ light chain locus is an endogenous rodent C κ gene.~~

121. ~~The method of any one of claims 117-120, wherein the method further comprises the step of:~~

~~(c) engineering an engineered endogenous immunoglobulin heavy chain locus in the germline genome of the rodent to include:~~

- ~~(i) one or more human V H gene segments,~~
- ~~(ii) one or more human D H gene segments, and~~
- ~~(iii) one or more human J H gene segments,~~

~~wherein the one or more human V H gene segments, the one or more human D H gene segments, and the one or more human J H gene segments are operably linked to one or more rodent immunoglobulin heavy chain constant region genes.~~

122. — The method of any one of claims 117-121, wherein the step of engineering a first endogenous immunoglobulin κ light chain locus in the germline genome of the rodent is carried out in a rodent ES cell whose genome comprises a second engineered endogenous immunoglobulin κ light chain locus comprising one or more human V κ gene segments, and one or more human J κ gene segments, wherein the one or more human V κ gene segments and the one or more human J κ gene segments are operably linked to a C κ gene.

123. — The method of claim 122, wherein the C κ gene at the second engineered endogenous immunoglobulin κ light chain locus is an endogenous rodent C κ gene.

124. — The method of any one of claims 117-120, 122 and 123, wherein the step of engineering is carried out in a rodent ES cell whose genome comprises an engineered endogenous immunoglobulin heavy chain locus comprising 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 operably linked to one or more rodent immunoglobulin heavy chain constant region genes.

125. — The method of any one of claims 121-124, wherein the engineered endogenous immunoglobulin heavy chain locus comprises 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 human V H non-coding sequences naturally appears adjacent to a human V H gene segment in an endogenous human immunoglobulin heavy chain locus.

126. — The method of any one of claims 121-125, wherein the engineered endogenous immunoglobulin heavy chain locus comprises 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.

127. — The method of any one of claims 121-126, wherein the engineered endogenous immunoglobulin heavy chain locus comprises 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.

128. — The method of any one of claims 109-127, wherein the first engineered endogenous immunoglobulin κ light chain locus lacks a rodent C κ gene.

129. — The method of any one of claims 110-115 and 119-128, wherein the C κ gene at the second engineered endogenous immunoglobulin κ light chain locus is an endogenous rodent C κ gene.

130. — The method of any one of claims 109-129, wherein the $C\lambda$ gene at the first engineered endogenous immunoglobulin κ light chain locus comprises a rodent $C\lambda$ gene.

131. — The method of any one of claims 109-130, wherein the first engineered endogenous immunoglobulin κ light chain locus further comprises:

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

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

(iii) any combination thereof.

132. — The method of any one of claims 109-131, wherein:

(i) the one or more human $V\lambda$ gene segments comprise $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, $V\lambda 3-1$, or any combination thereof; and

(ii) the one or more human $J\lambda$ gene segments comprise $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$, $J\lambda 7$, or any combination thereof.

133. — The method of claim 132, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human $V\lambda$ non-coding sequences, wherein each of the one or more human $V\lambda$ non-coding sequences is adjacent to the $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, or $V\lambda 3-1$ in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $V\lambda$ non-coding sequences naturally appears adjacent to a $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, or $V\lambda 3-1$ of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human $J\lambda$ non-coding sequences, wherein each of the one or more human $J\lambda$ non-coding sequences is adjacent to the $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$ or $J\lambda 7$ in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $J\lambda$ non-coding sequences naturally appears adjacent to a $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$ or $J\lambda 7$ of an endogenous human immunoglobulin λ light chain locus.

134. — The method of claim 132, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human $V\lambda$ non-coding sequences, wherein each of the one or more human $V\lambda$ non-coding sequences is adjacent to the $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 2-18$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$ or $V\lambda 3-1$ in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $V\lambda$ non-coding sequences naturally appears adjacent to a $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 2-18$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$ or $V\lambda 3-1$ of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human $J\kappa$ non-coding sequences, wherein each of the one or more human $J\kappa$ non-coding sequences is adjacent to the $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$ or $J\lambda 7$ in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $J\kappa$ non-coding sequences naturally appears adjacent to a $J\kappa 1$, $J\kappa 2$, $J\kappa 3$, $J\kappa 4$, or $J\kappa 5$ of an endogenous human immunoglobulin κ light chain locus.

135. — The method of any one of claims 109-134, wherein:

(i) the one or more human $V\lambda$ gene segments comprise $V\lambda 4-69$, $V\lambda 8-61$, $V\lambda 4-60$, $V\lambda 6-57$, $V\lambda 10-54$, $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, $V\lambda 3-1$, or any combination thereof; and

(ii) the one or more human $J\lambda$ gene segments comprise $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$, $J\lambda 7$, or any combination thereof.

136. — The method of claim 135, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human $V\lambda$ non-coding sequences, wherein each of the one or more human $V\lambda$ non-coding sequences is adjacent to the $V\lambda 4-69$, $V\lambda 8-61$, $V\lambda 4-60$, $V\lambda 6-57$, $V\lambda 10-54$, $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, or $V\lambda 3-1$ in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $V\lambda$ non-coding sequences naturally appears adjacent to a $V\lambda 4-69$, $V\lambda 8-61$, $V\lambda 4-60$, $V\lambda 6-57$, $V\lambda 10-54$, $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, or $V\lambda 3-1$ of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human $J\lambda$ non-coding sequences, wherein each of the one or more human $J\lambda$ non-

coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J λ non-coding sequences naturally appears adjacent to a J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 of an endogenous human immunoglobulin λ light chain locus.

137. — The method of claim 135, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus.

138. — The method of any one of claims 111-116 and 121-137, wherein the 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 are in place of one or more rodent V_H-gene segments, one or more rodent D_H-gene segments, one or more rodent J_H-gene segments, or a combination thereof.

139. — The method of any one of claims 111-116 and 121-138, wherein the 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 one or more rodent V_H-gene segments, one or more rodent D_H-gene segments, one or more rodent J_H-gene segments, or any combination thereof.

140. — The method of any one of claims 111-116 and 121-139, 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.

141. — The method of any one of claims 111-116 and 121-140, wherein the one or more rodent immunoglobulin heavy chain constant region genes are one or more endogenous rodent immunoglobulin heavy chain constant region genes.

142. — The method of any one of claims 111-116 and 121-141, 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 any 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 any 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 any combination thereof.

143. — The method of any one of claims 111-116 and 121-142, wherein the engineered endogenous immunoglobulin heavy chain locus lacks a functional endogenous rodent Adam6 gene.

144. — The method of any one of claims 111-116 and 121-143, wherein the genome of the rodent ES cell or the germline genome of the rodent further comprises one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof.

145. — The method of claim 144, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included on the same chromosome as the engineered endogenous immunoglobulin heavy chain locus.

146. — The method of claim 144 or 145, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included in the engineered endogenous immunoglobulin heavy chain locus.

147. — The method of any one of claims 144-146, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are in place of a human Adam6 pseudogene.

~~148. The method of any one of claims 144-147, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof replace a human Adam6 pseudogene.~~

~~149. The method of any one of claims 144-148, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are between a first human V_H-gene segment and a second human V_H-gene segment.~~

~~150. The method of claim 149, wherein the first human V_H-gene segment is V_H1-2 and the second human V_H-gene segment is V_H6-1.~~

~~151. The method of any one of claims 144-146, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are between a human V_H-gene segment and a human D_H-gene segment.~~

~~152. The method of any one claims 111-116 and 121-151, wherein the rodent is homozygous for the engineered endogenous immunoglobulin heavy chain locus.~~

~~153. The method of any one of claims 109-152, wherein the genome of the rodent ES cell or the germline genome of the rodent further comprises a nucleic acid sequence encoding an exogenous terminal deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element.~~

~~154. The method of claim 153, wherein the TdT is a short isoform of TdT (TdTS).~~

~~155. The method of claim 153 or 154, wherein the transcriptional control element comprises 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, an immunoglobulin λ light chain transcriptional control element, or any combination thereof.~~

~~156. The method of any one of claims 153-155, wherein the nucleic acid sequence encoding an exogenous TdT is 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.~~

~~157. The method of any one claims 109-156, wherein the rodent is a rat or a mouse.~~

~~158. A method of producing an antibody in a genetically modified rodent, the method comprising the steps of:~~

~~— (a) immunizing a rodent with an antigen of interest,~~

wherein the rodent has a germline genome comprising:

a first engineered endogenous immunoglobulin κ light chain locus, comprising:

- (i) one or more human V λ gene segments,
- (ii) one or more human J λ gene segments, and
- (iii) a C λ gene,

wherein the one or more human V λ gene segments and the one or more human J λ gene segments are operably linked to the C λ gene, and

wherein the C λ gene (c) is in the place of a rodent C κ gene at the first engineered endogenous immunoglobulin κ light chain locus;

—— (b) maintaining the rodent under conditions sufficient for the rodent to produce an immune response to the antigen of interest; and

—— (c) recovering from the rodent:

- (i) an antibody that binds the antigen of interest,
- (ii) a nucleotide that encodes a human light or heavy chain variable domain, a light chain, or a heavy chain of an antibody that binds the antigen of interest, or
- (iii) a cell that expresses an antibody that binds the antigen of interest.

159. — The method of claim 158, wherein the cell of the rodent is a B cell.

160. — The method of claim 159, further comprising producing a hybridoma from the B cell.

161. — A method of making an antibody, comprising:

—— (a) expressing a first nucleotide sequence that encodes an immunoglobulin heavy chain in a host cell, wherein the first nucleotide sequence includes a human heavy chain variable region sequence;

—— (b) expressing a second nucleotide sequence that encodes an immunoglobulin λ light chain in a host cell, wherein the second nucleotide sequence includes a human λ light chain variable region sequence that was identified from a genetically modified rodent whose germline genome comprises:

a first engineered endogenous immunoglobulin κ light chain locus comprising:

- (i) one or more human V λ gene segment,
- (ii) one or more human J λ gene segment, and
- (iii) a C λ gene,

wherein the one or more human V λ gene segment and the one or more human J λ gene segment are operably linked to the C λ gene, and

wherein the rodent lacks a rodent C κ gene at the engineered endogenous immunoglobulin κ light chain locus;

—— (c) culturing the host cell so that immunoglobulin light chains and immunoglobulin heavy chains are expressed and form an antibody; and

(d) obtaining the antibody from the host cell or host cell culture.

~~162. The method of claim 161, wherein the first nucleotide further includes a human heavy chain constant region gene.~~

~~163. The method of claim 161 or 162, wherein the second nucleotide further includes a human λ light chain constant region gene.~~

~~164. The method of any one of claims 158-163, wherein the rodent is homozygous for the first engineered endogenous immunoglobulin κ light chain locus.~~

~~165. The method of any one of claims 158-163, wherein the rodent is heterozygous for the first engineered endogenous immunoglobulin κ light chain locus.~~

~~166. The method of claim 165, wherein the germline genome of the rodent comprises a second engineered endogenous immunoglobulin κ light chain locus comprising:~~

~~(a) one or more human V κ gene segments, and~~

~~(b) one or more human J κ gene segments;~~

~~wherein the one or more human V κ gene segments and the one or more human J κ gene segments are operably linked to a C κ gene.~~

~~167. The method of claim 166, wherein the C κ gene at the second engineered endogenous immunoglobulin κ light chain locus is an endogenous rodent C κ gene.~~

~~168. The method of any one of claims 158-167, wherein the rodent lacks a rodent C κ gene at the first engineered endogenous immunoglobulin κ light chain locus.~~

~~169. The method of any one of claims 158-168, wherein the C λ gene at the first engineered endogenous immunoglobulin κ light chain locus comprises a rodent C λ gene.~~

~~170. The method of any one of claims 158-169, wherein the first engineered endogenous immunoglobulin κ light chain locus further comprises:~~

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

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

~~(iii) any combination thereof.~~

~~171. The method of any one of claims 158-170, wherein:~~

(i) the one or more human $V\lambda$ gene segments comprise $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, $V\lambda 3-1$, or any combination thereof; and

(ii) the one or more human $J\lambda$ gene segments comprise $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$, $J\lambda 7$, or any combination thereof.

172. — The method of claim 171, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human $V\lambda$ non-coding sequences, wherein each of the one or more human $V\lambda$ non-coding sequences is adjacent to the $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, or $V\lambda 3-1$ in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $V\lambda$ non-coding sequences naturally appears adjacent to a $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$, or $V\lambda 3-1$ of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human $J\lambda$ non-coding sequences, wherein each of the one or more human $J\lambda$ non-coding sequences is adjacent to the $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$ or $J\lambda 7$ in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $J\lambda$ non-coding sequences naturally appears adjacent to a $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$ or $J\lambda 7$ of an endogenous human immunoglobulin λ light chain locus.

173. — The method of claim 171, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human $V\lambda$ non-coding sequences, wherein each of the one or more human $V\lambda$ non-coding sequences is adjacent to the $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 2-18$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$ or $V\lambda 3-1$ in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $V\lambda$ non-coding sequences naturally appears adjacent to a $V\lambda 5-52$, $V\lambda 1-51$, $V\lambda 9-49$, $V\lambda 1-47$, $V\lambda 7-46$, $V\lambda 5-45$, $V\lambda 1-44$, $V\lambda 7-43$, $V\lambda 1-40$, $V\lambda 5-39$, $V\lambda 5-37$, $V\lambda 1-36$, $V\lambda 3-27$, $V\lambda 3-25$, $V\lambda 2-23$, $V\lambda 3-22$, $V\lambda 3-21$, $V\lambda 3-19$, $V\lambda 2-18$, $V\lambda 3-16$, $V\lambda 2-14$, $V\lambda 3-12$, $V\lambda 2-11$, $V\lambda 3-10$, $V\lambda 3-9$, $V\lambda 2-8$, $V\lambda 4-3$ or $V\lambda 3-1$ of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human $J\kappa$ non-coding sequences, wherein each of the one or more human $J\kappa$ non-coding sequences is adjacent to the $J\lambda 1$, $J\lambda 2$, $J\lambda 3$, $J\lambda 6$ or $J\lambda 7$ in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human $J\kappa$ non-coding sequences

naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus.

174. — The method of any one of claims 158-173, wherein:

(i) the one or more human V λ gene segments comprise V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, V λ 3-1, or any combination thereof; and

(ii) the one or more human J λ gene segments comprise J λ 1, J λ 2, J λ 3, J λ 6, J λ 7, or any combination thereof.

175. — The method of claim 174, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and

(ii) one or more human J λ non-coding sequences, wherein each of the one or more human J λ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J λ non-coding sequences naturally appears adjacent to a J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 of an endogenous human immunoglobulin λ light chain locus.

176. — The method of claim 174, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11,

~~V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus;~~

~~(ii) one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus.~~

~~177. The method of any one of claims 158-176, wherein the germline genome of the rodent 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, the one or more human D_H-gene segments, and the one or more human J_H-gene segments are operably linked to one or more rodent immunoglobulin heavy chain constant region genes at the engineered endogenous immunoglobulin heavy chain locus.~~

~~178. The method of claim 177, wherein the 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 are in place of one or more rodent V_H-gene segments, one or more rodent D_H-gene segments, one or more rodent J_H-gene segments, or a combination thereof.~~

~~179. The method of claim 177 or 178, wherein the 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 one or more rodent V_H-gene segments, one or more rodent D_H-gene segments, one or more rodent J_H-gene segments, or any combination thereof.~~

~~180. The method of any one of claims 177-179, 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.~~

181. — The method of any one of claims 177-180, wherein the one or more rodent immunoglobulin heavy chain constant region genes are one or more endogenous rodent immunoglobulin heavy chain constant region genes.

182. — The method of any one of claims 177-181, 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 any 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 any 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 any combination thereof.

183. — The method of any one of claims 177-182, wherein the engineered endogenous immunoglobulin heavy chain locus lacks a functional endogenous rodent Adam6 gene.

184. — The method of any one of claims 177-183, wherein the germline genome of the rodent further comprises one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof.

185. — The method of claim 184, wherein the one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are expressed.

186. — The method of claim 184 or 185, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included on the same chromosome as the engineered endogenous immunoglobulin heavy chain locus.

187. — The method of any one of claims 184-186, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included in the engineered endogenous immunoglobulin heavy chain locus.

188. — The method of any one of claims 184-187, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are in place of a human Adam6 pseudogene.

189. — The method of any one of claims 184-188, wherein the one or more nucleotide sequences encoding

~~one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof replace a human Adam6 pseudogene.~~

190. — The method of any one of claims 184–189, wherein the one or more nucleotide sequences encoding ~~one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof~~ are between a first human V_H-gene segment and a second human V_H-gene segment.

191. — The method of claim 190, wherein the first human V_H-gene segment is V_H1–2 and the second human V_H-gene segment is V_H6–1.

192. — The method of any one of claims 184–187, wherein the one or more nucleotide sequences encoding ~~one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof~~ are between a human V_H-gene segment and a human D_H-gene segment.

193. — The method of any one claims 177–192, wherein the rodent is homozygous for the engineered endogenous immunoglobulin heavy chain locus.

194. — The method of any one of claims 158–193, wherein the rodent comprises a population of B cells that express antibodies, including immunoglobulin λ light chains that each include a human immunoglobulin λ light chain variable domain.

195. — The method of claim 194, wherein the 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 or a somatically hypermutated variant thereof, and (ii) one of the one or more human J_λ-gene segments or a somatically hypermutated variant thereof.

196. — The method of any one of claims 158–195, wherein the germline genome of the rodent further comprises a nucleic acid sequence encoding an exogenous terminal deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element.

197. — The method of claim 196, wherein the TdT is a short isoform of TdT (TdTS).

198. — The method of claim 196 or 197, wherein the transcriptional control element comprises 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, an immunoglobulin λ light chain transcriptional control element, or any combination thereof.

199. — The method of any one of claims 196–198, wherein the nucleic acid sequence encoding an exogenous TdT is in the germline genome 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.

200. — The method any one of claims 158–199, wherein the rodent is a rat or a mouse.

201. — A rodent embryonic stem (ES) cell, whose genome comprises:

a first engineered endogenous immunoglobulin κ light chain locus comprising:

- (a) one or more human V λ gene segments,
- (b) one or more human J λ gene segments, and
- (c) a C λ gene,

wherein the one or more human V λ gene segments and the one or more human J λ gene segments are operably linked to the C λ gene, and

wherein the rodent ES cell lacks a rodent C κ gene at the first engineered endogenous immunoglobulin κ light chain locus.

202. — The rodent ES cell of claim 201, wherein the rodent ES cell is homozygous for the first engineered endogenous immunoglobulin κ light chain locus.

203. — The rodent ES cell of claim 201, wherein the rodent ES cell is heterozygous for the first engineered endogenous immunoglobulin κ light chain locus.

204. — The rodent ES cell of claim 203, wherein the genome of the rodent ES cell comprises a second engineered endogenous immunoglobulin κ light chain locus comprising:

- (i) one or more human V κ gene segments, and
- (ii) one or more human J κ gene segments,

wherein the one or more human V κ gene segments and the one or more human J κ gene segments are operably linked to a C κ gene.

205. — The rodent ES cell of claim 204, wherein the C κ gene at the second engineered endogenous immunoglobulin κ light chain locus is an endogenous rodent C κ gene.

206. — The rodent ES cell of any one of claims 201–205, wherein the genome of the rodent ES cell comprises an engineered endogenous immunoglobulin heavy chain locus comprising:

- (i) one or more human V H gene segments,
- (ii) one or more human D H gene segments, and
- (iii) one or more human J H gene segments,

wherein the one or more human V H gene segments, the one or more human D H gene segments, and the one or more human J H gene segments are operably linked to one or more rodent immunoglobulin heavy chain constant region genes at the engineered endogenous immunoglobulin heavy chain locus.

207. ~~The rodent ES cell of claims 201-206, wherein the rodent lacks a rodent C κ gene at the first engineered endogenous immunoglobulin κ light chain locus.~~

208. ~~The rodent ES cell of any one of claims 201-207, wherein the C λ gene at the first engineered endogenous immunoglobulin κ light chain locus comprises a rodent C λ gene.~~

209. ~~The rodent ES cell of any one of claims 201-208, wherein the first engineered endogenous immunoglobulin κ light chain locus further comprises:~~

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

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

~~(iii) any combination thereof.~~

210. ~~The rodent ES cell of any one of claims 201-209, wherein:~~

~~(i) the one or more human V λ gene segments comprise V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, V λ 3-1, or any combination thereof; and~~

~~(ii) the one or more human J λ gene segments comprise J λ 1, J λ 2, J λ 3, J λ 6, J λ 7, or any combination thereof.~~

211. ~~The rodent ES cell of claim 210, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:~~

~~(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and~~

~~(ii) one or more human J λ non-coding sequences, wherein each of the one or more human J λ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous~~

immunoglobulin κ light chain locus, and wherein each of the one or more human J λ non-coding sequences naturally appears adjacent to a J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 of an endogenous human immunoglobulin λ light chain locus.

212. — The rodent ES cell of claim 210, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus;

(ii) one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus.

213. — The rodent ES cell of any one of claims 201-212, wherein:

(i) the one or more human V λ gene segments comprise V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, V λ 3-1, or any combination thereof; and

(ii) the one or more human J λ gene segments comprise J λ 1, J λ 2, J λ 3, J λ 6, J λ 7, or any combination thereof.

214. — The rodent ES cell of claim 213, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:

(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27,

~~V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3, or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and~~

~~(ii) one or more human J λ non-coding sequences, wherein each of the one or more human J λ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J λ non-coding sequences naturally appears adjacent to a J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 of an endogenous human immunoglobulin λ light chain locus.~~

~~215. The rodent ES cell of claim 213, wherein the first engineered endogenous immunoglobulin κ light chain locus comprises:~~

~~(i) one or more human V λ non-coding sequences, wherein each of the one or more human V λ non-coding sequences is adjacent to the V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human V λ non-coding sequences naturally appears adjacent to a V λ 4-69, V λ 8-61, V λ 4-60, V λ 6-57, V λ 10-54, V λ 5-52, V λ 1-51, V λ 9-49, V λ 1-47, V λ 7-46, V λ 5-45, V λ 1-44, V λ 7-43, V λ 1-40, V λ 5-39, V λ 5-37, V λ 1-36, V λ 3-27, V λ 3-25, V λ 2-23, V λ 3-22, V λ 3-21, V λ 3-19, V λ 2-18, V λ 3-16, V λ 2-14, V λ 3-12, V λ 2-11, V λ 3-10, V λ 3-9, V λ 2-8, V λ 4-3 or V λ 3-1 of an endogenous human immunoglobulin λ light chain locus; and~~

~~(ii) one or more human J κ non-coding sequences, wherein each of the one or more human J κ non-coding sequences is adjacent to the J λ 1, J λ 2, J λ 3, J λ 6 or J λ 7 in the first engineered endogenous immunoglobulin κ light chain locus, and wherein each of the one or more human J κ non-coding sequences naturally appears adjacent to a J κ 1, J κ 2, J κ 3, J κ 4, or J κ 5 of an endogenous human immunoglobulin κ light chain locus.~~

~~216. The rodent ES cell of any one of claims 201-215, wherein the genome of the rodent ES cell 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, the one or more human D_H-gene segments, and the one or more human J_H-gene segments are operably linked to one or more rodent immunoglobulin heavy chain constant region genes at the engineered endogenous immunoglobulin heavy chain locus.~~

~~217. The rodent ES cell of claim 216, wherein the 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 are in place of one or more rodent V_H-gene segments, one or more rodent D_H-gene segments, one or more rodent J_H-gene segments, or a combination~~

thereof.

218. — The rodent ES cell of claim 216 or 217, wherein the 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 one or more rodent V_H -gene segments, one or more rodent D_H -gene segments, one or more rodent J_H -gene segments, or any combination thereof.

219. — The rodent ES cell of any one of claims 216-218, 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.

220. — The rodent ES cell of any one of claims 216-219, wherein the one or more rodent immunoglobulin heavy chain constant region genes are one or more endogenous rodent immunoglobulin heavy chain constant region genes.

221. — The rodent ES cell of any one of claims 216-220, 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 any 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 any 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 any combination thereof.

222. — The rodent ES cell of any one of claims 216-221, wherein the engineered endogenous immunoglobulin heavy chain locus lacks a functional endogenous rodent $\text{A} \mu 6$ gene.

223. — The rodent ES cell of any one of claims 216-222, wherein the genome of the rodent further comprises

~~one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof.~~

224. ~~— The rodent ES cell of claim 223, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included on the same chromosome as the engineered endogenous immunoglobulin heavy chain locus.~~

225. ~~— The rodent ES cell of claim 223 or 224, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are included in the engineered endogenous immunoglobulin heavy chain locus.~~

226. ~~— The rodent ES cell of any one of claims 223–225, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are in place of a human Adam6 pseudogene.~~

227. ~~— The rodent ES cell of any one of claims 223–226, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof replace a human Adam6 pseudogene.~~

228. ~~— The rodent ES cell of any one of claims 223–227, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are between a first human V_H-gene segment and a second human V_H-gene segment.~~

229. ~~— The rodent ES cell of claim 228, wherein the first human V_H-gene segment is V_H1-2 and the second human V_H-gene segment is V_H6-1.~~

230. ~~— The rodent ES cell of any one of claims 223–225, wherein the one or more nucleotide sequences encoding one or more rodent ADAM6 polypeptides, functional orthologs, functional homologs, or functional fragments thereof are between a human V_H-gene segment and a human D_H-gene segment.~~

231. ~~— The rodent ES cell of any one claims 216–230, wherein the rodent cell is homozygous for the engineered endogenous immunoglobulin heavy chain locus.~~

232. ~~— The rodent ES cell of any one of claims 201–231, wherein the genome of the rodent ES cell further comprises a nucleic acid sequence encoding an exogenous terminal deoxynucleotidyltransferase (TdT) operably linked to a transcriptional control element.~~

233. ~~— The rodent ES cell of claim 232, wherein the TdT is a short isoform of TdT (TdTS).~~

234. ~~— The rodent ES cell of claim 232 or 233, wherein the transcriptional control element comprises 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, an immunoglobulin λ light chain transcriptional control element, or any combination thereof.~~

~~235. The rodent ES cell of any one of claims 232-234, wherein the nucleic acid sequence encoding an exogenous TdT is 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.~~

~~236. The rodent ES cell of any one of claims 201-235, wherein the rodent ES cell is a rat ES cell or a mouse ES cell.~~

~~237. A method of making a fully human antibody specific against an antigen comprising the steps of:~~

- ~~(a) immunizing a rodent according to any one of claims 1-60 with the antigen;~~
- ~~(b) determining a nucleotide sequence that encodes a human heavy chain variable domain of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse and/or determining a nucleotide sequence that encodes a human λ light chain variable domain of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse; and~~
- ~~(c) expressing a fully human antibody by employing:~~
 - ~~(i) the nucleotide sequence encoding a human heavy chain variable domain of (b) operably linked to a human heavy chain constant region gene, and/or~~
 - ~~(ii) the nucleotide sequence encoding a human λ light chain variable domain of (b) operably linked to a human light chain constant region gene.~~

~~238. A method of making a fully human antibody specific against an antigen comprising the steps of:~~

- ~~(a) expressing in a mammalian cell a fully human antibody comprising two human λ light chains and two human heavy chains, wherein each human λ light chain includes a human λ light chain variable domain encoded by a human λ light chain variable region and each human heavy chain includes a human heavy chain variable domain encoded by a human heavy chain variable region, wherein the nucleotide sequence of at least one human heavy or λ light chain variable region was obtained from a rodent according to any one of claims 1-60; and~~
- ~~(b) obtaining the fully human antibody.~~

~~239. A method of making a fully human antibody specific against an antigen comprising the steps of:~~

- ~~(a) immunizing a rodent according to any one of claims 1-60;~~
- ~~(b) determining a human heavy chain variable domain sequence of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse and/or determining of a human λ light chain variable domain sequence of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse; and~~

- (e) ~~expressing a fully human antibody by employing:~~
- (i) ~~the human heavy chain variable domain sequence of (b) operably linked to a human heavy chain constant domain sequence, and/or~~
 - (ii) ~~the human λ light chain variable domain sequence of (b) operably linked to a human light chain constant domain sequence.~~

240. ~~The method of claim 239, wherein employing the human heavy chain variable domain sequence of (b) operably linked to a human heavy chain constant domain sequence comprises expressing a nucleotide sequence that encodes the human heavy chain variable domain sequence of (b) and the human heavy chain constant domain sequence.~~

241. ~~The method of claim 239 or 240, wherein employing the human λ light chain variable domain sequence of (b) operably linked to a human light chain constant domain sequence comprises expressing a nucleotide sequence that encodes the human λ light chain variable domain sequence of (b) and the human light chain constant domain sequence.~~

242. ~~A method of making a fully human antibody specific against an antigen comprising the steps of:~~

- (a) ~~expressing in a mammalian cell said fully human antibody comprising two human λ light chains and two human heavy chains, wherein each human λ light chain includes a human light chain variable domain and each human heavy chain includes a human heavy chain variable domain, wherein the amino acid sequence of at least one human heavy or λ light chain variable domain was obtained from a rodent of any one of claims 1-60; and~~
- ~~(b) obtaining the fully human antibody.~~

243. ~~A method for generating a human heavy or λ light chain variable domain sequence comprising the steps of:~~

- (a) ~~immunizing a rodent of any one of claims 1-60; and~~
- (b) ~~determining a human heavy or λ light chain variable domain sequence of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse.~~

244. ~~The method of claim 243, wherein determining a human heavy or λ light chain variable domain sequence comprises determining a nucleotide sequence that encodes the human heavy or λ light chain variable domain sequence.~~

245. ~~A method of making a fully human heavy chain or a fully human light chain comprising the steps of:~~

- (a) ~~immunizing a rodent of any one of claims 1-60;~~
- (b) ~~determining a human heavy or λ light chain variable domain sequence of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse; and~~
- (c) ~~operably linking the human heavy or λ light chain variable domain sequence to a human~~

~~heavy or light chain constant domain sequence, respectively, to form a fully human heavy chain or a fully human light chain.~~

246. ~~The method of claim 245, wherein operably linking the human heavy or λ light chain variable domain sequence to a human heavy or light chain constant domain sequence, respectively, comprises operably linking a nucleotide sequence encoding the human heavy or λ light chain variable domain sequence to a nucleotide sequence encoding the human heavy or light chain constant domain sequence.~~

247. ~~A method for generating a human heavy or λ light chain variable region sequence comprising the steps of:~~

- ~~(a) immunizing a rodent of any one of claims 1-60; and~~
- ~~(b) determining a human heavy or λ light chain variable region sequence that encodes a human heavy or λ light chain variable domain, respectively, of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse.~~

248. ~~A method of making a nucleotide sequence encoding a fully human heavy chain or a fully human light chain comprising the steps of:~~

- ~~(a) immunizing a rodent of any one of claims 1-60;~~
- ~~(b) determining a human heavy or λ light chain variable region sequence that encodes a human heavy or λ light chain variable domain, respectively, of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse; and~~
- ~~(c) operably linking the human heavy or λ light chain variable region sequence to a human heavy or light chain constant region gene, respectively, to form a nucleotide sequence encoding a fully human heavy chain or a fully human light chain.~~