

CLAIMS

1. A method of making a genetically modified mouse comprising in its germline at least one unrearranged human immunoglobulin light chain variable region (V_L) gene segment and at least one unrearranged human immunoglobulin light chain joining (J_L) gene segment operably linked with a heavy chain constant region nucleic acid sequence, the method comprising:

(a) modifying a totipotent mouse cell to include a hybrid immunoglobulin locus comprising at least one unrearranged human V_L gene segments and at least one unrearranged human J_L gene segment operably linked to an immunoglobulin heavy chain constant region nucleic acid sequence that encodes an immunoglobulin heavy chain constant region capable of associating with a light chain constant region;

(b) maintaining the totipotent mouse cell under suitable conditions to develop into a genetically modified mouse comprising in its germline the hybrid immunoglobulin locus comprising at least one unrearranged human light chain V_L gene segment and at least one unrearranged human J segment operably linked with a heavy chain constant region nucleic acid sequence,

wherein each of the at least one unrearranged human V_L and unrearranged J_L gene segments comprise recombination signal sequences that allow the unrearranged human V_L and J_L gene segments to recombine and form a rearranged human immunoglobulin light chain variable region (V_L/J_L) nucleotide sequence linked to the immunoglobulin heavy chain constant region nucleic acid sequence derived from the hybrid immunoglobulin locus.

2. The method of claim 1, wherein the one or more unrearranged human V_L gene segments comprise one or more unrearranged human V_{κ} gene segments, one or more unrearranged human V_{λ} gene segments, or a combination thereof, and wherein the at least one unrearranged human J_L gene segment is an unrearranged human J_{κ} gene segment, a n unrearranged human J_{λ} gene segment, or a combination thereof.

3. The method of claim 1 or claim 2, wherein the immunoglobulin heavy chain constant region nucleic acid sequence is selected from the group consisting of a C_{H1} sequence, a hinge sequence, a C_{H2} sequence, a C_{H3} sequence, and a combination thereof.

4. The method of any one of claims 1-3, wherein the hybrid immunoglobulin locus is an endogenous mouse immunoglobulin heavy chain locus, and wherein the one or more

unrearranged light chain human V_L gene segments and the at least one unrearranged human J_L gene segment replace one or more endogenous mouse heavy chain variable region (V_H) gene segments and one or more endogenous mouse heavy chain joining (J_H) gene segments, respectively, of the endogenous mouse heavy chain locus.

5. The method of any one of claims 1-4, wherein the one or more unrearranged human V_L gene segments replace all functional mouse V_H gene segments of the endogenous mouse immunoglobulin heavy chain locus.

6. The method of any one of claims 1-5, wherein the at least one unrearranged J_L gene replaces all functional mouse J_H gene segments of the endogenous mouse heavy chain locus.

7. The method of any one of claims 1-6, wherein the one or more unrearranged V_L gene segment and the at least one unrearranged J_L gene segment are operably linked and the mouse lacks a functional D segment between the one or more unrearranged V_L gene segments and the at least one unrearranged J_L gene segment.

8. The method any one of claims 1-7, wherein the one or more unrearranged V_L gene segments are human V_κ gene segments and the at least one unrearranged J_L gene segment is a human J_κ segment.

9. The method of any one of claims 1-8, wherein the totipotent mouse cell comprises an unrearranged human light chain V_L gene segment and an unrearranged human light chain joining J_L gene segment operably linked to a light chain constant gene.

10. The method of claim 9, wherein the light chain constant gene is a mouse light chain constant gene.

11. The method of claim 9 or claim 10, wherein the unrearranged human light chain V_L gene segment and an unrearranged human light chain joining J_L gene segment operably linked to a light chain constant gene are respectively an unrearranged human V_κ gene segment and an unrearranged human J_κ gene segment.

12. The method any one of claims 9-12, wherein the light chain constant gene is a mouse light chain κ constant gene.

13. A totipotent mouse cell comprising an immunoglobulin locus comprising at least one unrearranged human V_L gene segments and at least one unrearranged human J_L gene segment operably linked to an immunoglobulin heavy chain constant region nucleic acid sequence that encodes an immunoglobulin heavy chain constant region capable of associating with a light chain constant region;

wherein each of the at least one unrearranged human V_L and unrearranged J_L gene segments comprise recombination signal sequences that allow the unrearranged human V_L and J_L gene segments to recombine and form a rearranged human immunoglobulin light chain variable region (V_L/J_L) nucleotide sequence linked to the immunoglobulin heavy chain constant region nucleic acid sequence derived from the hybrid immunoglobulin locus.

14. The totipotent mouse cell of claim 13, wherein the one or more unrearranged human V_L gene segments comprise one or more unrearranged human V_κ gene segments, one or more unrearranged human V_λ gene segments, or a combination thereof, and wherein the at least one unrearranged human J_L gene segment is an unrearranged human J_κ gene segment, an unrearranged human J_λ gene segment, or a combination thereof.

15. The totipotent mouse cell of claim 13 or claim 14, wherein the immunoglobulin heavy chain constant region nucleic acid sequence is selected from the group consisting of a C_H1 sequence, a hinge sequence, a C_H2 sequence, a C_H3 sequence, and a combination thereof.

16. The totipotent mouse cell of any one of claims 13-15, wherein the hybrid immunoglobulin locus is an endogenous mouse immunoglobulin heavy chain locus, and wherein the one or more unrearranged light chain human V_L gene segments and the at least one unrearranged human J_L gene segment replace one or more endogenous mouse heavy chain variable region (V_H) gene segments and one or more endogenous mouse heavy chain joining (J_H) gene segments, respectively, of the endogenous mouse heavy chain locus.

17. The totipotent mouse cell of any one of claims 13-16, wherein the one or more unrearranged human V_L gene segments replace all functional mouse V_H gene segments of the endogenous mouse immunoglobulin heavy chain locus.

18. The totipotent mouse cell of any one of claims 13-17, wherein the at least one unrearranged J_L gene replaces all functional mouse J_H gene segments of the endogenous mouse heavy chain locus.
19. The totipotent mouse cell of any one of claims 13-18, wherein the one or more unrearranged V_L gene segment and the at least one unrearranged J_L gene segment are operably linked and the mouse lacks a functional D segment between the one or more unrearranged V_L gene segments and the at least one unrearranged J_L gene segment.
20. The totipotent mouse cell of any one of claims 13-19, wherein the one or more unrearranged V_L gene segments are human V_κ gene segments and the at least one unrearranged J_L gene segment is a human J_κ segment.
21. The totipotent mouse cell of any one of claims 13-20, wherein the totipotent mouse cell comprises an unrearranged human light chain V_L gene segment and an unrearranged human light chain joining J_L gene segment operably linked to a light chain constant gene.
22. The totipotent mouse cell of claim 21, wherein the light chain constant gene is a mouse light chain constant gene.
23. The totipotent mouse cell of claim 21 or claim 22, wherein the unrearranged human light chain V_L gene segment and an unrearranged human light chain joining J_L gene segment operably linked to a light chain constant gene are respectively an unrearranged human V_κ gene segment and an unrearranged human J_κ gene segment.
24. The totipotent mouse cell of any one of claims 21-23, wherein the light chain constant gene is a mouse light chain κ constant gene.
25. The totipotent mouse cell of any one of claims 13-24, wherein the totipotent mouse cell is a mouse embryonic stem cell.