

CLAIMS

1. A rodent comprising in its germline genome at an endogenous immunoglobulin heavy chain locus a rearranged human immunoglobulin heavy chain variable region nucleotide sequence operably linked to an endogenous heavy chain constant region gene sequence, wherein the rearranged heavy chain variable region nucleotide sequence encodes the sequence of V_H3-23/X₁X₂/J_H, wherein X₁ is any amino acid, and X₂ is any amino acid, and wherein the rodent is a rat or a mouse.
2. The rodent of claim 1, wherein X₁ is Gly and X₂ is Tyr.
3. The rodent of claim 1, wherein the human J_H gene segment is selected from the group consisting of J_H1, J_H2, J_H3, J_H4, J_H5, J_H6, and a polymorphic variant thereof.
4. The rodent of claim 1, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence encodes the sequence of human V_H3-23/GY/J_H4-4 (SEQ ID NO:137).
5. The rodent of claim 4, wherein the rodent is a mouse.
6. The rodent of claim 1, wherein the heavy chain constant region gene sequence is selected from a C_H1, a hinge, a C_H2, a C_H3, and a combination thereof.
7. The rodent of claim 1, wherein substantially all endogenous functional V_H, D, and J_H gene segments are deleted from the immunoglobulin heavy chain locus of the rodent or rendered non-functional.
8. The rodent of claim 1, wherein the rodent comprises a modification that deletes or renders non-functional endogenous functional V_H, D, and J_H gene segments.
9. The rodent of claim 1, wherein an immunoglobulin heavy chain variable domain encoded by the rearranged heavy chain variable region nucleotide sequence is not immunogenic to the

non-human animal.

10. The rodent of claim 1, wherein the rodent comprises an Adam6a gene, an Adam6b gene, or both.

11. The rodent of claim 1, wherein the rodent further comprises a nucleotide sequence encoding an unrearranged human immunoglobulin light chain V gene segment (V_L) and an unrearranged human immunoglobulin light chain J gene segment (J_L), wherein the nucleotide sequence is operably linked to an immunoglobulin light chain constant region gene sequence.

12. The rodent of claim 11, wherein the light chain constant region gene sequence is selected from a rodent and a human constant region gene sequence.

13. The rodent of claim 12, wherein the rodent constant region gene sequence is selected from a mouse constant region gene sequence, a rat constant region gene sequence, and a hamster constant region gene sequence.

14. The rodent of claim 11, wherein the unrearranged human immunoglobulin light chain (V_L) gene segment and the unrearranged human immunoglobulin (J_L) gene segment are operably linked, at an endogenous rodent locus, to a rodent immunoglobulin constant region gene sequence.

15. A method of making a rodent, the method comprising:

(a) modifying a genome of a rodent to delete or render non-functional substantially all endogenous functional immunoglobulin heavy chain V_H , D, and J_H gene segments of an endogenous immunoglobulin heavy chain locus, wherein the rodent is a rat or a mouse; and

(b) placing in the genome at the endogenous immunoglobulin heavy chain locus a rearranged human immunoglobulin heavy chain variable region nucleotide sequence, wherein the rearranged heavy chain variable region nucleotide sequence encodes the sequence of $V_H3-23/X_1X_2/J_H$ operably linked to an endogenous heavy chain constant region gene sequence,

wherein X_1 is any amino acid, and X_2 is any amino acid.

16. A modified rodent comprising in its genome:

(i) at an endogenous immunoglobulin heavy chain locus, a rearranged human heavy chain variable region nucleic acid sequence operably linked to an endogenous heavy chain constant region nucleic acid sequence, wherein the rearranged heavy chain variable region nucleic acid sequence encodes the sequence of $V_{H3-23}/X_1X_2/J_H$, wherein X_1 is any amino acid, and X_2 is any amino acid, wherein the rodent is a rat or a mouse; and

(ii) an immunoglobulin light chain locus comprising one or more but less than the wild type number of human immunoglobulin light chain V_L and J_L gene segments, operably linked to a light chain constant region nucleic acid sequence.

17. The modified rodent of claim 16, wherein X_1 is Gly and X_2 is Tyr.

18. The modified rodent of claim 16, wherein the human J_H gene segment is selected from the group consisting of J_{H1} , J_{H2} , J_{H3} , J_{H4} , J_{H5} , J_{H6} , and a polymorphic variant thereof.

19. The modified rodent of claim 16, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence encodes the sequence of human $V_{H3-23}/GY/J_{H4-4}$ (SEQ ID NO:137).

20. The modified rodent of claim 16, wherein the one or more but less than the wild type number of human immunoglobulin light chain V_L and J_L gene segments are operably linked to the light chain constant region nucleic acid sequence at an endogenous locus.

21. The modified rodent of claim 16, wherein the immunoglobulin light chain locus comprises two human V_L gene segments, $V_{\kappa 1-39}$ and $V_{\kappa 3-20}$.

22. The modified rodent of claim 16, wherein at least one of the human light chain V_L or J_L gene segments encode one or more histidine codons that are not encoded by a corresponding human germline light chain variable gene segment.

23. The modified rodent of claim 16, wherein at least one of the V_L gene segments comprises an addition or substitution of at least one non-histidine codon encoded by the corresponding human germline V_L segment sequence with a histidine codon.
24. The modified rodent of claim 23, wherein the added or substituted histidine codon is present in CDR3.
25. The mouse claim 5, wherein the mouse comprises an Adam6a gene, an Adam6b gene, or both.
26. The mouse of claim 5, wherein the non-human animal further comprises a nucleotide sequence encoding an unrearranged human immunoglobulin light chain V gene segment (V_L) and an unrearranged human immunoglobulin light chain J gene segment (J_L), wherein the nucleotide sequence is operably linked to an immunoglobulin light chain constant region gene sequence.
27. The rodent of claim 16, wherein the rodent is a mouse.

CLAIMS

1. A rodent comprising in its germline genome at an endogenous immunoglobulin heavy chain locus a rearranged human immunoglobulin heavy chain variable region nucleotide sequence operably linked to an endogenous heavy chain constant region gene sequence, wherein the rearranged heavy chain variable region nucleotide sequence encodes the sequence of V_H3-23/X₁X₂/J_H, wherein X₁ is any amino acid, and X₂ is any amino acid, and wherein the rodent is a rat or a mouse.
2. The rodent of claim 1, wherein X₁ is Gly and X₂ is Tyr.
3. The rodent of claim 1, wherein the human J_H gene segment is selected from the group consisting of J_H1, J_H2, J_H3, J_H4, J_H5, J_H6, and a polymorphic variant thereof.
4. The rodent of claim 1, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence encodes the sequence of human V_H3-23/GY/J_H4-4 (SEQ ID NO:137).
5. The rodent of claim 4, wherein the rodent is a mouse.
6. The rodent of claim 1, wherein the heavy chain constant region gene sequence is selected from a C_H1, a hinge, a C_H2, a C_H3, and a combination thereof.
7. The rodent of claim 1, wherein substantially all endogenous functional V_H, D, and J_H gene segments are deleted from the immunoglobulin heavy chain locus of the rodent or rendered non-functional.
8. The rodent of claim 1, wherein the rodent comprises a modification that deletes or renders non-functional endogenous functional V_H, D, and J_H gene segments.
9. The rodent of claim 1, wherein an immunoglobulin heavy chain variable domain encoded

by the rearranged heavy chain variable region nucleotide sequence is not immunogenic to the non-human animal.

10. The rodent of claim 1, wherein the rodent comprises an Adam6a gene, an Adam6b gene, or both.

11. The rodent of claim 1, wherein the rodent further comprises a nucleotide sequence encoding an unrearranged human immunoglobulin light chain V gene segment (V_L) and an unrearranged human immunoglobulin light chain J gene segment (J_L), wherein the nucleotide sequence is operably linked to an immunoglobulin light chain constant region gene sequence.

12. The rodent of claim 11, wherein the light chain constant region gene sequence is selected from a rodent and a human constant region gene sequence.

13. The rodent of claim 12, wherein the rodent is selected from a mouse, a rat, and a hamster.

14. The rodent of claim 11, wherein the unrearranged human immunoglobulin light chain (V_L) gene segment and the unrearranged human immunoglobulin (J_L) gene segment are operably linked, at an endogenous rodent locus, to a rodent immunoglobulin constant region gene sequence.

15. A method of making a rodent, the method comprising:

(a) modifying a genome of a rodent to delete or render non-functional substantially all endogenous functional immunoglobulin heavy chain V_H , D, and J_H gene segments of an endogenous immunoglobulin heavy chain locus, wherein the rodent is a rat or a mouse; and

(b) placing in the genome at the endogenous immunoglobulin heavy chain locus a rearranged human immunoglobulin heavy chain variable region nucleotide sequence, wherein the rearranged heavy chain variable region nucleotide sequence encodes the sequence of $V_{H3-23}/X_1X_2/J_H$ operably linked to an endogenous heavy chain constant region gene sequence,

wherein X_1 is any amino acid, and X_2 is any amino acid.

16. A modified rodent comprising in its genome:

(i) at an endogenous immunoglobulin heavy chain locus, a rearranged human heavy chain variable region nucleic acid sequence operably linked to an endogenous heavy chain constant region nucleic acid sequence, wherein the rearranged heavy chain variable region nucleic acid sequence encodes the sequence of $V_H3-23/X_1X_2/J_H$, wherein X_1 is any amino acid, and X_2 is any amino acid, wherein the rodent is a rat or a mouse; and

(ii) an immunoglobulin light chain locus comprising one or more but less than the wild type number of human immunoglobulin light chain V_L and J_L gene segments, operably linked to a light chain constant region nucleic acid sequence.

17. The modified rodent of claim 16, wherein X_1 is Gly and X_2 is Tyr.

18. The modified rodent of claim 16, wherein the human J_H gene segment is selected from the group consisting of J_H1 , J_H2 , J_H3 , J_H4 , J_H5 , J_H6 , and a polymorphic variant thereof.

19. The modified rodent of claim 16, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence encodes the sequence of human $V_H3-23/GY/J_H4-4$ (SEQ ID NO:137).

20. The modified rodent of claim 16, wherein the one or more but less than the wild type number of human immunoglobulin light chain V_L and J_L gene segments are operably linked to the light chain constant region nucleic acid sequence at an endogenous locus.

21. The modified rodent of claim 16, wherein the immunoglobulin light chain locus comprises two human V_L gene segments, $V_{\kappa1}-39$ and $V_{\kappa3}-20$.

22. The modified rodent of claim 16, wherein at least one of the human light chain V_L or J_L gene segments encode one or more histidine codons that are not encoded by a corresponding human germline light chain variable gene segment.

23. The modified rodent of claim 16, wherein at least one of the V_L gene segments comprises an addition or substitution of at least one non-histidine codon encoded by the corresponding human germline V_L segment sequence with a histidine codon.

24. The modified rodent of claim 23, wherein the added or substituted histidine codon is present in CDR3.

25. The mouse claim 5, wherein the mouse comprises an Adam6a gene, an Adam6b gene, or both.

26. The mouse of claim 5, wherein the non-human animal further comprises a nucleotide sequence encoding an unrearranged human immunoglobulin light chain V gene segment (V_L) and an unrearranged human immunoglobulin light chain J gene segment (J_L), wherein the nucleotide sequence is operably linked to an immunoglobulin light chain constant region gene sequence.

27. The rodent of claim 16, wherein the rodent is a mouse.

CLAIMS

1. A rodent comprising in its germline genome at an endogenous immunoglobulin heavy chain locus a rearranged human immunoglobulin heavy chain variable region nucleotide sequence operably linked to an endogenous heavy chain constant region gene sequence, wherein the rearranged heavy chain variable region nucleotide sequence encodes the sequence of V_H3-23/X₁X₂/J_H, wherein X₁ is any amino acid, and X₂ is any amino acid, and wherein the rodent is a rat or a mouse.
2. The rodent of claim 1, wherein X₁ is Gly and X₂ is Tyr.
3. The rodent of claim 1, wherein the human J_H gene segment is selected from the group consisting of J_H1, J_H2, J_H3, J_H4, J_H5, J_H6, and a polymorphic variant thereof.
4. The rodent of claim 1, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence encodes the sequence of human V_H3-23/GY/J_H4-4 (SEQ ID NO:137).
5. The rodent of claim 4, wherein the rodent is a mouse.
6. The rodent of claim 1, wherein the heavy chain constant region gene sequence is selected from a C_H1, a hinge, a C_H2, a C_H3, and a combination thereof.
7. The rodent of claim 1, wherein substantially all endogenous functional V_H, D, and J_H gene segments are deleted from the immunoglobulin heavy chain locus of the rodent or rendered non-functional.
8. The rodent of claim 1, wherein the rodent comprises a modification that deletes or renders non-functional endogenous functional V_H, D, and J_H gene segments.
9. The rodent of claim 1, wherein an immunoglobulin heavy chain variable domain encoded by the rearranged heavy chain variable region nucleotide sequence is not immunogenic to the

non-human animal.

10. The rodent of claim 1, wherein the rodent comprises an Adam6a gene, an Adam6b gene, or both.

11. The rodent of claim 1, wherein the rodent further comprises a nucleotide sequence encoding an unrearranged human immunoglobulin light chain V gene segment (V_L) and an unrearranged human immunoglobulin light chain J gene segment (J_L), wherein the nucleotide sequence is operably linked to an immunoglobulin light chain constant region gene sequence.

12. The rodent of claim 11, wherein the light chain constant region gene sequence is selected from a rodent and a human constant region gene sequence.

13. The rodent of claim 12, wherein the rodent constant region gene sequence is selected from a mouse constant region gene sequence, a rat constant region gene sequence, and a hamster constant region gene sequence.

14. The rodent of claim 11, wherein the unrearranged human immunoglobulin light chain (V_L) gene segment and the unrearranged human immunoglobulin (J_L) gene segment are operably linked, at an endogenous rodent locus, to a rodent immunoglobulin constant region gene sequence.

15. A method of making a rodent, the method comprising:

(a) modifying a genome of a rodent to delete or render non-functional substantially all endogenous functional immunoglobulin heavy chain V_H , D, and J_H gene segments of an endogenous immunoglobulin heavy chain locus, wherein the rodent is a rat or a mouse; and

(b) placing in the genome at the endogenous immunoglobulin heavy chain locus a rearranged human immunoglobulin heavy chain variable region nucleotide sequence, wherein the rearranged heavy chain variable region nucleotide sequence encodes the sequence of $V_H3-23/X_1X_2/J_H$ operably linked to an endogenous heavy chain constant region gene sequence,

wherein X_1 is any amino acid, and X_2 is any amino acid.

16. A modified rodent comprising in its genome:

(i) at an endogenous immunoglobulin heavy chain locus, a rearranged human heavy chain variable region nucleic acid sequence operably linked to an endogenous heavy chain constant region nucleic acid sequence, wherein the rearranged heavy chain variable region nucleic acid sequence encodes the sequence of $V_{H3-23}/X_1X_2/J_H$, wherein X_1 is any amino acid, and X_2 is any amino acid, wherein the rodent is a rat or a mouse; and

(ii) an immunoglobulin light chain locus comprising one or more but less than the wild type number of human immunoglobulin light chain V_L and J_L gene segments, operably linked to a light chain constant region nucleic acid sequence.

17. The modified rodent of claim 16, wherein X_1 is Gly and X_2 is Tyr.

18. The modified rodent of claim 16, wherein the human J_H gene segment is selected from the group consisting of J_{H1} , J_{H2} , J_{H3} , J_{H4} , J_{H5} , J_{H6} , and a polymorphic variant thereof.

19. The modified rodent of claim 16, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence encodes the sequence of human $V_{H3-23}/GY/J_{H4-4}$ (SEQ ID NO:137).

20. The modified rodent of claim 16, wherein the one or more but less than the wild type number of human immunoglobulin light chain V_L and J_L gene segments are operably linked to the light chain constant region nucleic acid sequence at an endogenous locus.

21. The modified rodent of claim 16, wherein the immunoglobulin light chain locus comprises two human V_L gene segments, $V_{\kappa 1-39}$ and $V_{\kappa 3-20}$.

22. The modified rodent of claim 16, wherein at least one of the human light chain V_L or J_L gene segments encode one or more histidine codons that are not encoded by a corresponding human germline light chain variable gene segment.

23. The modified rodent of claim 16, wherein at least one of the V_L gene segments comprises an addition or substitution of at least one non-histidine codon encoded by the corresponding human germline V_L segment sequence with a histidine codon.
24. The modified rodent of claim 23, wherein the added or substituted histidine codon is present in CDR3.
25. The mouse claim 5, wherein the mouse comprises an Adam6a gene, an Adam6b gene, or both.
26. The mouse of claim 5, wherein the non-human animal further comprises a nucleotide sequence encoding an unrearranged human immunoglobulin light chain V gene segment (V_L) and an unrearranged human immunoglobulin light chain J gene segment (J_L), wherein the nucleotide sequence is operably linked to an immunoglobulin light chain constant region gene sequence.
27. The rodent of claim 16, wherein the rodent is a mouse.