

What is claimed is:

1. A non-human animal comprising in its germline genome an immunoglobulin heavy chain locus that comprises a rearranged human immunoglobulin heavy chain variable region nucleotide sequence.
2. The non-human animal of claim 1, wherein the non-human animal is a mammal.
3. The non-human animal of claim 2, wherein the mammal is a rodent.
4. The non-human animal of claim 3, wherein the rodent is selected from the group consisting of a mouse, a rat, and a hamster.
5. The non-human animal of claim 1, wherein the non-human animal is homozygous for the rearranged human immunoglobulin heavy chain variable region nucleotide sequence.
6. The non-human animal of claim 1, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is operably linked to a non-human heavy chain constant region gene sequence.
7. The non-human animal of claim 6, wherein the non-human heavy chain constant region gene sequence encodes an Fc.
8. The non-human animal of claim 7, wherein the non-human heavy chain constant region gene sequence is a mouse or a rat heavy chain constant region gene sequence.
9. The non-human animal of claim 1, wherein the non-human animal is a rodent, and the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is operably linked to a human heavy chain constant region gene sequence.
10. The non-human animal of any one of claims 6 to 9, 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.
11. The non-human animal of claim 1, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is derived from a human heavy chain V_H gene segment, a human heavy chain D gene segment, and a human heavy chain J_H gene segment.
12. The non-human animal of claim 11, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is derived from a human germline heavy chain V_H segment, a human germline heavy chain D segment, and a human germline heavy chain J_H segment.

13. The non-human animal 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.
14. The non-human animal 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 non-human animal or rendered non-functional.
15. The non-human animal of claim 1, wherein the non-human animal comprises a modification that deletes or renders non-functional endogenous functional V_H, D, and J_H gene segments; and the non-human animal comprises the rearranged human immunoglobulin heavy chain variable region nucleotide sequence, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is present ectopically.
16. The non-human animal 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.
17. The non-human animal of claim 1, wherein the non-human animal comprises an Adam6a gene, an Adam6b gene, or both.
18. The non-human animal of claim 1, 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).
19. The non-human animal of claim 18, wherein the nucleotide sequence encoding the unrearranged light chain V gene segment (V_L) and the unrearranged light chain (J_L) gene segment is operably linked to an immunoglobulin light chain constant region gene sequence.
20. The non-human animal of claim 19, wherein the light chain constant region gene sequence is selected from a rodent and a human constant region gene sequence.
21. The non-human animal of claim 20, wherein the rodent is selected from a mouse, a rat, and a hamster.
22. The non-human animal of claim 18, 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.
23. The non-human animal of claim 1, wherein the immunoglobulin heavy chain locus comprises a plurality of copies of the rearranged human immunoglobulin heavy chain variable

region nucleotide sequence.

24. A non-human immunoglobulin heavy chain locus in a genome of a non-human germ cell comprising a rearranged human immunoglobulin heavy chain variable region nucleotide sequence operably linked to a heavy chain constant region gene sequence, wherein the constant region gene sequence comprises a non-human sequence, a human sequence, or a combination thereof.

25. The immunoglobulin heavy chain locus of claim 24, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is operably linked to an endogenous non-human immunoglobulin constant region gene sequence.

26. The immunoglobulin heavy chain locus of claim 25, wherein the endogenous non-human immunoglobulin constant region gene sequence is a mouse or a rat heavy chain constant region gene sequence.

27. A method of making a non-human animal, the method comprising:

- (a) modifying a genome of a non-human animal to delete or render non-functional endogenous functional immunoglobulin heavy chain V_H, D, and J_H gene segments; and
- (b) placing in the genome a rearranged human immunoglobulin heavy chain variable region nucleotide sequence.

28. The method of claim 27, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is operably linked to a non-human immunoglobulin heavy chain constant region gene sequence.

29. The method of claim 28, wherein the non-human immunoglobulin heavy chain constant region gene sequence is a mouse or rat immunoglobulin heavy chain constant region gene sequence.

30. The method of claim 27, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is placed at an endogenous immunoglobulin heavy chain locus in the genome.

31. The method of claim 27, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is present in a germline genome of the non-human animal.

32. The method of claim 27, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is present at an ectopic locus in the genome.
33. The method of claim 27, wherein the non-human animal comprises a plurality of copies of the rearranged human immunoglobulin heavy chain variable region nucleotide sequence.
34. The method of claim 27, wherein the non-human animal comprises an Adam6a gene, an Adam6b gene or both.
35. The method of claim 27, wherein the non-human animal is a rodent selected from the group consisting of a mouse, a rat, or a hamster.
36. A non-human animal that is heterozygous for the immunoglobulin heavy chain locus of claim 24, wherein the non-human animal expresses the rearranged human immunoglobulin heavy chain variable region nucleotide sequence predominantly from the immunoglobulin heavy chain locus.
37. A non-human animal comprising a genetically modified immunoglobulin locus comprising:
- (a) a rearranged human immunoglobulin heavy chain variable region nucleotide sequence that is operably linked to a light chain constant region gene sequence; and
 - (b) an unrearranged human immunoglobulin light chain variable region nucleotide sequence that is operably linked to a heavy chain constant region gene sequence.
38. The non-human animal of claim 37, wherein the non-human animal is a mammal.
39. The non-human animal of claim 38, wherein the mammal is selected from the group consisting of a mouse, a rat, and a hamster.
40. The non-human animal of claim 37, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is operably linked to a κ light chain constant region gene sequence.
41. The non-human animal of claim 37, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is operably linked to a λ light chain constant region gene sequence.
42. The non-human animal of claim 37, wherein the light chain constant region gene sequence is a mouse or a rat light chain constant region gene sequence.
43. The non-human animal of claim 37, wherein the light chain constant region gene sequence is a human light chain constant region gene sequence.

44. The non-human animal of claim 37, wherein the heavy chain constant region gene sequence is a mouse or a rat heavy chain constant region gene sequence.
45. The non-human animal of claim 37, wherein the heavy chain constant region gene sequence is a human heavy chain constant region gene sequence.
46. The non-human animal of any one of claims 44 or 45, wherein the heavy chain constant region gene sequence encodes a sequence selected from a CH1, a hinge, a CH2, a CH3, and a combination thereof.
47. The non-human animal of claim 37, wherein the unrearranged human immunoglobulin light chain variable region nucleotide sequence comprises a human κ light chain variable domain gene sequence.
48. The non-human animal of claim 37, wherein the unrearranged human immunoglobulin light chain variable region nucleotide sequence comprises a human λ light chain variable domain gene sequence.
49. The non-human animal of claim 37, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is derived from a human heavy chain V_H gene segment, a human heavy chain D gene segment, and a human heavy chain J_H gene segment.
50. The non-human animal of claim 49, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is derived from a human germline heavy chain V_H segment, a human germline heavy chain D segment, and a human germline heavy chain J_H segment.
51. The non-human animal of claim 49, wherein the human V_H gene segment is selected from the group consisting of V_H 1-2, V_H 1-3, V_H 1-8, V_H 1-18, V_H 1-24, V_H 1-45, V_H 1-46, V_H 1-58, V_H 1-69, V_H 2-5, V_H 2-26, V_H 2-70, V_H 3-7, V_H 3-9, V_H 3-11, V_H 3-13, V_H 3-15, V_H 3-16, V_H 3-20, V_H 3-21, V_H 3-23, V_H 3-30, V_H 3-30-3, V_H 3-30-5, V_H 3-33, V_H 3-35, V_H 3-38, V_H 3-43, V_H 3-48, V_H 3-49, V_H 3-53, V_H 3-64, V_H 3-66, V_H 3-72, V_H 3-73, V_H 3-74, V_H 4-4, V_H 4-28, V_H 4-30-1, V_H 4-30-2, V_H 4-30-4, V_H 4-31, V_H 4-34, V_H 4-39, V_H 4-59, V_H 4-61, V_H 5-51, V_H 6-1, V_H 7-4-1, V_H 7-81, and a polymorphic variant thereof.
52. The non-human animal of claim 49, wherein the human D gene segment is selected from the group consisting of D1-1, D1-7, D1-14, D1-20, D1-26, D2-2, D2-8, D2-15, D2-21, D3-3, D3-9, D3-10, D3-16, D3-22, D4-4, D4-11, D4-17, D4-23, D5-12, D5-5, D5-18, D5-24, D6-6,

D6-13, D6-19, D6-25, D7-27, and a polymorphic variant thereof.

53. The non-human animal of claim 49, 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.

54. The non-human animal of claim 37, 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).

55. The non-human animal of claim 37, wherein the genetically modified immunoglobulin locus is present in the germline of the non-human animal.

56. The non-human animal of claim 37, wherein substantially all endogenous functional V_H, D, and J_H gene segments are deleted from the immunoglobulin heavy chain locus of the non-human animal or rendered non-functional.

57. The non-human animal of claim 37, wherein the non-human animal comprises a modification that deletes or renders non-functional endogenous functional V_H, D, and J_H gene segments; and the non-human animal comprises the rearranged human immunoglobulin heavy chain variable region nucleotide sequence that is operably linked to the light chain constant region gene sequence, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is present at an ectopic locus in the genome.

58. The non-human animal of claim 37, wherein the non-human animal comprises an Adam6a gene, an Adam6b gene or both.

59. The non-human animal of claim 37, wherein a heavy chain variable domain encoded by the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is not immunogenic to the non-human animal.

60. The non-human animal of claim 37, wherein the genetically modified immunoglobulin locus comprises a plurality of copies of the rearranged human immunoglobulin heavy chain variable region nucleotide sequence that is operably linked to the light chain constant region gene sequence.

61. An immunoglobulin locus in a germline genome of a non-human animal comprising:

- (1) a rearranged human immunoglobulin heavy chain variable region nucleotide sequence that is operably linked to a light chain constant region gene sequence, and
- (2) an unrearranged human immunoglobulin light chain variable region nucleotide

sequence that is operably linked to a heavy chain constant region gene sequence.

62. The genetically modified immunoglobulin locus of claim 61, wherein the light chain constant region gene sequence is a κ light chain constant region gene sequence.

63. The genetically modified immunoglobulin locus of claim 61, wherein the light chain constant region gene sequence is a λ light chain constant region gene sequence.

64. The genetically modified immunoglobulin locus of claim 61, wherein the light chain constant region gene sequence is a mouse or rat light chain constant region gene sequence.

65. A method of making a non-human animal that comprises a modified immunoglobulin locus, the method comprising:

(a) modifying a genome of a non-human animal to delete or render non-functional:

(i) endogenous functional immunoglobulin heavy chain V, D, and J gene segments, and

(ii) endogenous functional immunoglobulin light chain V and J gene segments;
and

(b) placing in the genome:

(i) a rearranged human immunoglobulin heavy chain variable region nucleotide sequence that is operably linked to a light chain constant region gene sequence,
and

(ii) an unrearranged human immunoglobulin light chain variable region nucleotide sequence that is operably linked to a heavy chain constant region gene sequence.

66. The method of claim 65, wherein the unrearranged human immunoglobulin light chain variable region nucleotide sequence encodes a κ light chain variable domain.

67. The method of claim 65, wherein the unrearranged human immunoglobulin light chain variable region nucleotide sequence encodes a λ light chain variable domain.

68. The method of claim 65, wherein the heavy chain constant region gene sequence is a non-human immunoglobulin heavy chain constant region gene sequence.

69. The method according to claim 68, wherein the non-human immunoglobulin heavy chain constant region gene sequence is a mouse or a rat heavy chain constant region gene

sequence.

70. The method of claim 68 or 69, wherein the heavy chain constant region gene sequence encodes a sequence selected from a CH1, a hinge, a CH2, a CH3, and a combination thereof.

71. The method of claim 65, wherein the non-human animal is a rodent selected from the group consisting of a mouse, a rat, or a hamster.

72. The method of claim 65, wherein the modified immunoglobulin locus is present in a germline genome of the non-human animal.

73. The method of claim 65, wherein the non-human animal comprises an Adam6a gene, an Adam6b gene or both.

74. A non-human animal comprising a modified immunoglobulin heavy chain locus that comprises a rearranged human immunoglobulin heavy chain variable region nucleotide sequence comprising a heavy chain V segment (V_H) sequence that is operably linked, via a spacer, to a heavy chain J segment (J_H) sequence, wherein the spacer comprises at least one amino acid residue.

75. The non-human animal of claim 74, wherein the non-human animal is a rodent.

76. The non-human animal of claim 75, wherein the rodent is selected from the group consisting of a mouse, a rat, and a hamster.

77. The non-human animal of claim 74, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is operably linked to a non-human heavy chain constant region gene sequence.

78. The non-human animal of claim 77, wherein the non-human heavy chain constant region gene sequence is a mouse or a rat constant region gene sequence.

79. The non-human animal of claim 74, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is operably linked to a human heavy chain constant region gene sequence.

80. The non-human animal of any one of claims 77 to 79, wherein the heavy chain constant region gene sequence encodes a sequence selected from a C_H1, a hinge, a C_H2, a C_H3, and a combination thereof.

81. The non-human animal of claim 74, wherein the V_H sequence and the J_H sequence are derived from a human V_H gene segment and a human J_H gene segment.

82. The non-human animal of claim 81, wherein the human V_H gene segment is selected from the group consisting of V_H1-2, V_H1-3, V_H1-8, V_H1-18, V_H1-24, V_H1-45, V_H1-46, V_H1-58, V_H1-69, V_H2-5, V_H2-26, V_H2-70, V_H3-7, V_H3-9, V_H3-11, V_H3-13, V_H3-15, V_H3-16, V_H3-20, V_H3-21, V_H3-23, V_H3-30, V_H3-30-3, V_H3-30-5, V_H3-33, V_H3-35, V_H3-38, V_H3-43, V_H3-48, V_H3-49, V_H3-53, V_H3-64, V_H3-66, V_H3-72, V_H3-73, V_H3-74, V_H4-4, V_H4-28, V_H4-30-1, V_H4-30-2, V_H4-30-4, V_H4-31, V_H4-34, V_H4-39, V_H4-59, V_H4-61, V_H5-51, V_H6-1, V_H7-4-1, V_H7-81, and a polymorphic variant thereof.

83. The non-human animal of claim 81, wherein the human V_H gene segment is V_H3-23 or a polymorphic variant thereof.

84. The non-human animal of claim 74, wherein the spacer encodes a sequence derived from a human D gene segment.

85. The non-human animal of claim 84, wherein the human D gene segment is selected from the group consisting of D1-1, D1-7, D1-14, D1-20, D1-26, D2-2, D2-8, D2-15, D2-21, D3-3, D3-9, D3-10, D3-16, D3-22, D4-4, D4-11, D4-17, D4-23, D5-12, D5-5, D5-18, D5-24, D6-6, D6-13, D6-19, D6-25, D7-27, and a polymorphic variant thereof.

86. The non-human animal according to claim 84, wherein the spacer encodes the sequence of D4-4 or a polymorphic variant thereof.

87. The non-human animal of claim 81, 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.

88. The non-human animal of claim 81, wherein the human J_H segment is J_H4-4 or a polymorphic variant thereof.

89. The non-human animal of claim 74, wherein the rearranged immunoglobulin heavy chain variable region nucleotide sequence encodes the sequence of human V_H3-23/GY/J_H4-4 (SEQ ID NO: 137).

90. The non-human animal of claim 74, wherein substantially all endogenous functional V_H, D, and J_H gene segments are deleted from the immunoglobulin heavy chain variable locus of the non-human animal or rendered non-functional.

91. The non-human animal of claim 74, wherein the non-human animal comprises a modification that deletes or renders non-functional endogenous functional V_H, D, and J_H gene segments; and the non-human animal comprises the rearranged human immunoglobulin heavy chain variable region nucleotide sequence at an ectopic locus of its genome.

92. The non-human animal of claim 74, wherein a heavy chain variable domain encoded by the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is not immunogenic to the non-human animal.

93. The non-human animal of claim 74, wherein the non-human animal comprises an Adam6a gene, an Adam6b gene, or both.

94. An immunoglobulin heavy chain locus in a germline genome of a non-human animal, comprising a rearranged human immunoglobulin heavy chain variable region nucleotide sequence comprising a heavy chain variable gene segment (V_H) that is operably linked, via a spacer, to a heavy chain J gene segment (J_H), wherein the spacer encodes at least one amino acid residue.

95. The immunoglobulin heavy chain locus of claim 94, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is operably linked to a non-human heavy chain constant region gene sequence.

96. The immunoglobulin heavy chain locus of claim 95, wherein the non-human heavy chain constant region gene sequence is a mouse or a rat heavy chain constant region gene sequence.

97. The immunoglobulin heavy chain locus of claim 94, wherein the immunoglobulin locus comprises a plurality of copies of the rearranged heavy chain variable region nucleotide sequence.

98. A method of making a non-human animal comprising a modified immunoglobulin heavy chain locus, the method comprising:

- (a) modifying a genome of a non-human animal to delete or render non-functional endogenous functional immunoglobulin heavy chain V_H , D, and J_H gene segments; and
- (b) placing in the genome a rearranged human immunoglobulin heavy chain variable region nucleotide sequence comprising a heavy chain variable gene segment (V_H) that is operably linked, via a spacer, to a heavy chain J gene segment (J_H), wherein the spacer comprises at least one amino acid residue.

99. The method of claim 98, wherein the rearranged human immunoglobulin heavy chain nucleotide sequence is operably linked to a non-human immunoglobulin heavy chain constant region gene sequence.

100. The method of claim 99, wherein the non-human immunoglobulin heavy chain constant region gene sequence is a mouse or a rat heavy chain constant region gene sequence.

101. The method of claim 98, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is placed at an endogenous immunoglobulin heavy chain locus in the genome.

102. The method of claim 98, wherein the rearranged human immunoglobulin heavy chain variable region nucleotide sequence is present at an ectopic locus in the genome.

103. The method of claim 98, wherein the modified heavy chain locus comprises a plurality of copies of the rearranged human immunoglobulin heavy chain variable region nucleotide sequence.

104. The method of claim 98, wherein the non-human animal is a rodent selected from the group consisting of a mouse, a rat, or a hamster.

105. The method of claim 98, wherein the non-human animal comprises an Adam6a gene, an Adam6b gene or both.

106. The method of claim 98, wherein the modified immunoglobulin heavy chain locus is present in a germline genome of the non-human animal.

107. A modified non-human animal comprising in its genome:

- (i) an immunoglobulin heavy chain locus that comprises a rearranged human heavy chain variable region nucleic acid sequence operably linked to a heavy chain constant region nucleic acid sequence; 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.

108. The modified non-human animal of claim 107, wherein the non-human animal is a mammal.

109. The modified non-human animal of claim 108, wherein the mammal is a rodent.

110. The modified non-human animal of claim 109, wherein the rodent is selected from the group consisting of a mouse, a rat, and a hamster.

111. The modified non-human animal of claim 107, wherein the heavy chain constant region

nucleic acid sequence is a rodent constant region sequence that encodes an immunoglobulin isotype selected from IgM, IgD, IgG, IgE, IgA, and a combination thereof.

112. The modified non-human animal of claim 107, wherein the light chain constant region nucleic acid sequence is a rodent κ or λ constant region nucleic acid sequence.

113. The modified non-human animal of claim 107, wherein the rearranged human heavy chain variable region nucleic acid sequence is selected from a human germline V_H segment, a human germline D segment, and a human germline J_H segment.

114. The modified non-human animal of claim 107, wherein the rearranged human heavy chain variable region nucleic acid sequence is operably linked to the constant region nucleic acid sequence at an endogenous locus.

115. The modified non-human animal of claim 107, 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.

116. The modified non-human animal of claim 107, wherein the non-human animal comprises no more than two human immunoglobulin unrearranged V_L gene segments, and one, two, or three or more human unrearranged J_L gene segments.

117. The modified non-human animal of claim 113, wherein the human germline V_H gene segment selected from the group consisting of V_{H1-2} , V_{H1-3} , V_{H1-8} , V_{H1-18} , V_{H1-24} , V_{H1-45} , V_{H1-46} , V_{H1-58} , V_{H1-69} , V_{H2-5} , V_{H2-26} , V_{H2-70} , V_{H3-7} , V_{H3-9} , V_{H3-11} , V_{H3-13} , V_{H3-15} , V_{H3-16} , V_{H3-20} , V_{H3-21} , V_{H3-23} , V_{H3-30} , $V_{H3-30-3}$, $V_{H3-30-5}$, V_{H3-33} , V_{H3-35} , V_{H3-38} , V_{H3-43} , V_{H3-48} , V_{H3-49} , V_{H3-53} , V_{H3-64} , V_{H3-66} , V_{H3-72} , V_{H3-73} , V_{H3-74} , V_{H4-4} , V_{H4-28} , $V_{H4-30-1}$, $V_{H4-30-2}$, $V_{H4-30-4}$, V_{H4-31} , V_{H4-34} , V_{H4-39} , V_{H4-59} , V_{H4-61} , V_{H5-51} , V_{H6-1} , V_{H7-4-1} , V_{H7-81} , and a polymorphic variant thereof.

118. The modified non-human animal of claim 113, wherein the human germline V_H gene segment is V_{H3-23} gene segment.

119. The modified non-human animal of claim 107, wherein the rearranged heavy chain variable region nucleic acid sequence encodes the sequence of human V_{H3-23}/J_{H4-4} (SEQ ID NO: 137).

120. The modified non-human animal of claim 107, wherein the rearranged heavy chain

variable region nucleic acid sequence encodes the sequence of $V_H3-23/X_1X_2/J$, wherein X_1 is any amino acid, and X_2 is any amino acid.

121. The modified non-human animal of claim 120, wherein X_1 is Gly and X_2 is Tyr.

122. The modified non-human animal of claim 107, wherein the immunoglobulin heavy chain locus comprises a functional Adam6a gene, Adam6b gene, or both.

123. The modified non-human animal of claim 122, wherein the Adam6a gene, Adam6b gene, or both are endogenous Adam6 genes.

124. The modified non-human animal of claim 107, wherein the modified non-human animal comprises an Adam6a gene, Adam6b gene, or both at an ectopic locus of the genome.

125. The modified non-human animal of claim 107, wherein the human variable region V_L and J_L gene segments are capable of rearranging and encoding a human immunoglobulin light chain variable domain.

126. The modified non-human animal of claim 107, wherein the immunoglobulin light chain locus comprises two human V_L gene segments, $V_{\kappa 1-39}$ and $V_{\kappa 3-20}$.

127. The modified non-human animal of claim 126, wherein the gene segments are germline gene segments.

128. The modified non-human animal of claim 126, wherein the non-human animal comprises $J_{\kappa 1}$, $J_{\kappa 2}$, $J_{\kappa 3}$, $J_{\kappa 4}$, and $J_{\kappa 5}$ gene segments.

129. The modified non-human animal of claim 107, wherein two or more, three or more, four or more, or five or more human V_L gene segments and two or more human J_L gene segments are present at an endogenous light chain locus.

130. The modified non-human animal of claim 107, 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.

131. The modified non-human animal of claim 107, 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.

132. The modified non-human animal of claim 131, wherein the added or substituted histidine codon is present in CDR3.

133. The modified non-human animal of claim 107, wherein the human V_L gene segments are human V_κ1-39 and V_κ3-20 gene segments, and each of the human V_κ1-39 and V_κ3-20 gene segments comprises a substitution of at least one non-histidine codon encoded by a corresponding human germline V_L gene segment with the histidine codon.

134. The modified non-human animal of claim 133, wherein the substitution is of three non-histidine codons of the human V_κ1-39 gene segment, wherein the substitution is designed to express histidines at positions 106, 108, and 111.

135. The modified non-human animal of claim 133, wherein the substitution is of four non-histidine codons of the human V_κ1-39 gene segment, and the substitution is designed to express histidines at positions 105, 106, 108, and 111.

136. The modified non-human animal of claim 133, wherein the substitution is of three non-histidine codons of the human V_κ3-20 gene segment, and the substitution is designed to express histidines at positions 105, 106, and 109.

137. The modified non-human animal of claim 133, wherein the substitution is of four non-histidine codons of the human V_κ3-20 gene segment, and the substitution is designed to express histidines at positions 105, 106, 107, and 109.

138. The modified non-human animal of claim 107, wherein the non-human animal, upon stimulation by an antigen of interest, expresses an antigen-binding protein that specifically binds the antigen, wherein the antigen-binding protein comprises an amino acid sequence derived from the human V_L and J_L gene segments, and wherein the antigen-binding protein comprises at least one histidine residue at an amino acid position encoded by the human V_L gene segment.

139. The modified non-human animal of claim 107, wherein the non-human animal expresses a population of antigen-binding proteins in response to an antigen, wherein all antigen-binding proteins in the population comprise: (a) immunoglobulin heavy chains comprising human heavy chain variable domains derived from the rearranged human variable region nucleic acid sequence; and (b) immunoglobulin light chains comprising immunoglobulin light chain variable

domains derived from a rearrangement of the human V_L gene segments and the J_L gene segments in the genome of the non-human animal, and wherein at least one of the human V_L gene segments encodes one or more histidine codons that are not encoded by the corresponding human germline V_L gene segment.

140. A method for making a non-human animal comprising a modified immunoglobulin locus, comprising:

(a) modifying a genome of a non-human animal to delete or render non-functional:

(i) endogenous functional immunoglobulin heavy chain V_H , D, and/or J_H gene segments, and

(ii) endogenous functional immunoglobulin light chain V_L and J_L gene segments; and

(b) placing in the modified genome of the non-human animal:

(i) a rearranged human immunoglobulin heavy chain variable region nucleic acid sequence in operable linkage to an immunoglobulin heavy chain constant region nucleic acid sequence; and

(ii) one or more but less than the wild type number of human immunoglobulin light chain V_L and J_L gene segments in operable linkage to an immunoglobulin light chain constant region nucleic acid sequence.

141. The method of claim 140, wherein the non-human animal is a rodent.

142. The method of claim 141, wherein the rodent is a mouse, a rat, or a hamster.

143. The method of claim 140, wherein the rearranged human immunoglobulin heavy chain variable region nucleic acid sequence is operably linked to a mouse or rat heavy chain constant region gene sequence selected from a CH1, a hinge, a CH2, a CH3, and a combination thereof.

144. The method of claim 140, wherein the rearranged human immunoglobulin heavy chain variable region nucleic acid sequence and the human immunoglobulin light chain V_L and J_L gene segments are placed at or near a corresponding nucleotide sequence of the wild type non-human animal.

145. The method of claim 140, wherein the rearranged immunoglobulin human heavy chain variable region nucleic acid sequence and the human immunoglobulin light chain V_L and J_L gene segments are placed at an ectopic locus in the genome.

146. The method of claim 140, wherein the non-human animal comprises an immunoglobulin heavy chain locus comprising an endogenous Adam6a gene, Adam6b gene, or both.

147. The method of claim 140, wherein the non-human animal comprises an Adam6a gene, Adam6b gene, or both at an ectopic locus of the genome.

148. The method of claim 140, wherein the rearranged human immunoglobulin heavy chain variable region nucleic acid sequence encodes the sequence of human V_H3-23/GY/J_H4-4 (SEQ ID NO: 137).

149. The method of claim 140, wherein the immunoglobulin light chain constant region nucleic acid sequence is a rat or a mouse C_κ constant region nucleic acid sequence.

150. The method of claim 140, wherein the human immunoglobulin light chain V_L and J_L gene segments are capable of rearranging and encoding a human immunoglobulin light chain variable domain.

151. The method of claim 140, wherein the non-human animal comprises an immunoglobulin light chain locus comprising two human V_L gene segments, V_κ1-39 and V_κ3-20.

152. The method of claim 151, wherein the non-human animal comprises J_κ1, J_κ2, J_κ3, J_κ4, and J_κ5 gene segments.

153. The method of claim 140, wherein two or more, three or more, four or more, or five or more human V_L gene segments and two or more human J_L gene segments are present at an endogenous light chain locus.

154. The method of claim 140, wherein at least one of the human immunoglobulin 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.

155. The method of claim 140, wherein at least one of the V_L gene segments comprises an addition or a substitution of at least one non-histidine codon encoded by the corresponding

human germline V_L segment sequence with a histidine codon.

156. The method of claim 155, wherein the added or substituted histidine codon is present in CDR3.

157. The method of claim 155, wherein the human V_L gene segments are human V_κ1-39 and V_κ3-20 gene segments, and each of the human V_κ1-39 and V_κ3-20 gene segments comprises the substitution of at least one non-histidine codon encoded by a corresponding human germline V_L gene segment with the histidine codon.

158. The method of claim 157, wherein the substitution is of three non-histidine codons of the human V_κ1-39 gene segment, and wherein the substitution is designed to express histidines at positions 106, 108, and 111.

159. The method of claim 157, wherein the substitution is of four non-histidine codons of the human V_κ1-39 gene segment, and wherein the substitution is designed to express histidines at positions 105, 106, 108, and 111.

160. The method of claim 157, wherein the substitution is of three non-histidine codons of the human V_κ3-20 gene segment, and wherein the substitution is designed to express histidines at positions 105, 106, and 109.

161. The method of claim 157, wherein the substitution is of four non-histidine codons of the human V_κ3-20 gene segment, and the substitution is designed to express histidines at positions 105, 106, 107, and 109.

162. A method for obtaining a nucleic acid sequence that encodes an immunoglobulin light chain variable domain (V_L) capable of binding an antigen independently from a heavy chain variable domain, comprising:

- (a) immunizing a non-human animal with an antigen of interest or an immunogen thereof, wherein the non-human animal comprises in its genome (i) a rearranged human immunoglobulin heavy chain variable region nucleic acid sequence operably linked to a heavy chain constant region nucleic acid sequence; and (ii) two or more but less than the wild type number of human immunoglobulin light chain variable region gene segments (V_L and J_L) operably linked to a light chain constant region nucleic acid

sequence;

(b) allowing the non-human animal to mount an immune response;

(c) isolating from the immunized non-human animal a cell comprising a nucleic acid sequence that encodes a light chain variable domain that can bind the antigen; and

(d) obtaining from the cell a nucleic acid sequence that encodes the light chain variable domain (V_L domain) that can bind the antigen.

163. The method of claim 162, wherein isolating step (c) is carried out via fluorescence-activated cell sorting (FACS) or flow cytometry.

164. The method of claim 162, wherein the cell comprising the nucleic acid sequence that encodes the light chain variable domain that binds the antigen is a lymphocyte.

165. The method of claim 164, wherein the lymphocyte comprises natural killer cells, T cells, or B cells.

166. The method of claim 162, wherein the method further comprises: (c)' fusing the lymphocyte with a cancer cell.

167. The method of claim 166, wherein the cancer cell is a myeloma cell.

168. The method of claim 162, wherein the nucleic acid sequence of (d) is fused with a nucleic acid sequence encoding an immunoglobulin constant region nucleic acid sequence.

169. The method of claim 162, wherein the light chain constant region nucleic acid sequence is a human kappa sequence or a human lambda sequence.

170. The method of claim 162, wherein the heavy chain constant region nucleic acid sequence is a human sequence selected from a CH1, a hinge, a CH2, a CH3, and a combination thereof.

171. The method of claim 162, wherein the nucleic acid sequence of (d) comprises one or more histidine codon substitutions or insertions that are derived from the unrearranged V_L gene segment in the genome of the animal.

172. A method for making an antigen-binding protein that comprises an immunoglobulin light chain variable domain that can bind an antigen independently from a heavy chain variable

domain, comprising:

(a) immunizing a genetically modified non-human animal with a first antigen that comprises a first epitope or immunogenic portion thereof, wherein the non-human animal comprises in its genome:

(i) a rearranged human heavy chain variable region nucleic acid sequence operably linked to a heavy chain constant region nucleic acid sequence; and

(ii) two or more but less than the wild type number of human immunoglobulin light chain variable region gene segments (V_L and J_L) operably linked to an immunoglobulin light chain constant region nucleic acid sequence;

(b) allowing the non-human animal to mount an immune response to the first epitope or immunogenic portion thereof;

(c) isolating from the non-human animal a cell comprising a nucleic acid sequence that encodes a light chain variable domain that specifically binds the first epitope or immunogenic portion thereof;

(d) obtaining from the cell of (c) the nucleic acid sequence that encodes the light chain variable domain that specifically binds the first epitope or immunogenic portion thereof;

(e) employing the nucleic acid sequence of (d) in an expression construct, fused to a human immunoglobulin constant region nucleic acid sequence; and

(f) expressing the nucleic acid sequence of (d) in a production cell line that expresses a human immunoglobulin heavy chain that specifically binds a second antigen or epitope to form an antigen-binding protein whose light chain is encoded by the nucleic acid of (d) and that binds the first epitope or immunogenic portion thereof independently from the heavy chain, and whose heavy chain specifically binds the second antigen or epitope.

173. The method of claim 172, 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.

174. The method of claim 172, wherein the first epitope is derived from a cell surface receptor.

175. The method of claim 174, wherein the cell surface receptor is an Fc receptor.

176. The method of claim 175, wherein the Fc receptor is FcRn.

177. The method of claim 172, wherein the second antigen or epitope is derived from a soluble antigen.

178. The method of claim 172, wherein the second antigen or epitope is derived from a cell surface receptor.

179. The method of claim 172, wherein the first antigen is an Fc receptor, the second antigen is a soluble protein, and the antigen-binding protein comprises one or more histidine substitutions and insertions derived from the V_L gene segment in the genome of the non-human animal.

180. A method for obtaining a nucleic acid sequence that encodes an immunoglobulin light chain variable domain (V_L) capable of binding an antigen independently from a heavy chain variable domain, comprising:

(a) immunizing a non-human animal with a first antigen that comprises a first epitope or immunogenic portion thereof, wherein the non-human animal comprises in its genome:
(i) a rearranged human immunoglobulin heavy chain variable region nucleic acid sequence operably linked to a heavy chain constant region nucleic acid sequence, and
(ii) an unrearranged human immunoglobulin light chain variable region nucleic acid sequence operably linked to a light chain constant region nucleic acid sequence;

(b) allowing the non-human animal to mount an immune response;

(c) isolating from the immunized non-human animal a cell comprising a nucleic acid sequence that encodes a light chain variable domain that can bind the antigen; and

(d) obtaining from the cell a nucleic acid sequence that encodes the light chain variable domain (V_L domain) that can bind the antigen.

181. The method of claim 180, wherein isolating step (c) is carried out via fluorescence-activated cell sorting (FACS) or flow cytometry.

182. The method of claim 180, wherein the cell comprising the nucleic acid sequence that

encodes the light chain variable domain that binds the antigen is a lymphocyte.

183. The method of claim 182, wherein the lymphocyte comprises natural killer cells, T cells, or B cells.

184. The method of claim 180, wherein the method further comprises: (c)' fusing the lymphocyte with a cancer cell.

185. The method of claim 184, wherein the cancer cell is a myeloma cell.

186. The method of claim 180, wherein the nucleic acid sequence of (d) is fused with a nucleic acid sequence encoding an immunoglobulin constant region nucleic acid sequence.

187. The method of claim 180, wherein the light chain constant region nucleic acid sequence is a human kappa sequence or a human lambda sequence.

188. The method of claim 180, wherein the heavy chain constant region nucleic acid sequence is a human sequence selected from a CH1, a hinge, a CH2, a CH3, and a combination thereof.

189. The method of claim 180, wherein the nucleic acid sequence of (d) comprises one or more histidine codon substitutions or insertions that are derived from the unrearranged V_L gene segment in the genome of the animal.

190. A method for obtaining a nucleic acid sequence that encodes an immunoglobulin light chain variable domain (V_L) capable of binding an antigen independently from a heavy chain variable domain, comprising:

(a) immunizing a non-human animal with a first antigen that comprises a first epitope or immunogenic portion thereof, wherein the non-human animal comprises in its genome: (i) a rearranged human immunoglobulin heavy chain variable region nucleic acid sequence operably linked to a light chain constant region nucleic acid sequence, and (ii) human immunoglobulin light chain variable region gene segments (V_L and J_L) operably linked to a heavy chain constant region nucleic acid sequence;

(b) allowing the non-human animal to mount an immune response;

(c) isolating from the immunized non-human animal a cell comprising a nucleic acid sequence that encodes a light chain variable domain that can bind the antigen; and

(d) obtaining from the cell a nucleic acid sequence that encodes the light chain variable domain (V_L domain) that can bind the antigen.

191. The method of claim 190, wherein isolating step (c) is carried out via fluorescence-activated cell sorting (FACS) or flow cytometry.

192. The method of claim 190, wherein the cell comprising the nucleic acid sequence that encodes the light chain variable domain that binds the antigen is a lymphocyte.

193. The method of claim 192, wherein the lymphocyte comprises natural killer cells, T cells, or B cells.

194. The method of claim 190, wherein the method further comprises: (c)' fusing the lymphocyte with a cancer cell.

195. The method of claim 194, wherein the cancer cell is a myeloma cell.

196. The method of claim 190, wherein the nucleic acid sequence of (d) is fused with a nucleic acid sequence encoding an immunoglobulin constant region nucleic acid sequence.

197. The method of claim 190, wherein the light chain constant region nucleic acid sequence is a human kappa sequence or a human lambda sequence.

198. The method of claim 190, wherein the heavy chain constant region nucleic acid sequence is a human sequence selected from a CH1, a hinge, a CH2, a CH3, and a combination thereof.

199. The method of claim 190, wherein the nucleic acid sequence of (d) comprises one or more histidine codon substitutions or insertions that are derived from the unrearranged V_L gene segment in the genome of the animal.

200. A method for making an antigen-binding protein that comprises an immunoglobulin light chain variable domain that can bind an antigen independently from a heavy chain variable domain, comprising:

(a) immunizing a genetically modified non-human animal with a first antigen that comprises a first epitope or immunogenic portion thereof, wherein the non-human animal comprises in its genome:

(i) a rearranged human heavy chain variable region nucleic acid sequence operably linked to a heavy chain constant region nucleic acid sequence; and

(ii) unrearranged human immunoglobulin light chain variable region gene segments (V_L and J_L) operably linked to a light chain constant region nucleic acid sequence;

(b) allowing the non-human animal to mount an immune response to the first epitope or immunogenic portion thereof;

(c) isolating from the non-human animal a cell comprising a nucleic acid sequence that encodes a light chain variable domain that specifically binds the first epitope or immunogenic portion thereof;

(d) obtaining from the cell of (c) the nucleic acid sequence that encodes the light chain variable domain that specifically binds the first epitope or immunogenic portion thereof;

(e) employing the nucleic acid sequence of (d) in an expression construct, fused to a human immunoglobulin constant region nucleic acid sequence; and

(f) expressing the nucleic acid sequence of (d) in a production cell line that expresses a human immunoglobulin heavy chain that specifically binds a second antigen or epitope to form an antigen-binding protein whose light chain is encoded by the nucleic acid of (d) and that binds the first epitope or immunogenic portion thereof independently from the heavy chain, and whose heavy chain specifically binds the second antigen or epitope.

201. The method of claim 200, 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.

202. The method of claim 200, wherein the first epitope is derived from a cell surface receptor.

203. The method of claim 202, wherein the cell surface receptor is an Fc receptor.

204. The method of claim 203, wherein the Fc receptor is FcRn.

205. The method of claim 200, wherein the second antigen or epitope is derived from a soluble antigen.

206. The method of claim 200, wherein the second antigen or epitope is derived from a cell surface receptor.

207. The method of claim 200, wherein the first antigen is an Fc receptor, the second antigen is a soluble protein, and the antigen-binding protein comprises one or more histidine substitutions and insertions derived from the V_L gene segment in the genome of the non-human animal.

208. A method for making an antigen-binding protein that comprises an immunoglobulin light chain variable domain that can bind an antigen independently from a heavy chain variable domain, comprising:

(a) immunizing a genetically modified non-human animal with a first antigen that comprises a first epitope or immunogenic portion thereof, wherein the non-human animal comprises in its genome:

(i) a rearranged human heavy chain variable region nucleic acid sequence operably linked to a light chain constant region nucleic acid sequence; and

(ii) unrearranged human immunoglobulin light chain variable region gene segments (V_L and J_L) operably linked to a heavy chain constant region nucleic acid sequence;

(b) allowing the non-human animal to mount an immune response to the first epitope or immunogenic portion thereof;

(c) isolating from the non-human animal a cell comprising a nucleic acid sequence that encodes a light chain variable domain that specifically binds the first epitope or immunogenic portion thereof;

(d) obtaining from the cell of (c) the nucleic acid sequence that encodes the light chain variable domain that specifically binds the first epitope or immunogenic portion thereof;

(e) employing the nucleic acid sequence of (d) in an expression construct, fused to a human immunoglobulin constant region nucleic acid sequence; and

(f) expressing the nucleic acid sequence of (d) in a production cell line that expresses a human immunoglobulin heavy chain that specifically binds a second antigen or epitope

to form an antigen-binding protein whose light chain is encoded by the nucleic acid of (d) and that binds the first epitope or immunogenic portion thereof independently from the heavy chain, and whose heavy chain specifically binds the second antigen or epitope.

209. The method of claim 208, 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.

210. The method of claim 208, wherein the first epitope is derived from a cell surface receptor.

211. The method of claim 210, wherein the cell surface receptor is an Fc receptor.

212. The method of claim 211, wherein the Fc receptor is FcRn.

213. The method of claim 208, wherein the second antigen or epitope is derived from a soluble antigen.

214. The method of claim 208, wherein the second antigen or epitope is derived from a cell surface receptor.

215. The method of claim 208, wherein the first antigen is an Fc receptor, the second antigen is a soluble protein, and the antigen-binding protein comprises one or more histidine substitutions and insertions derived from the V_L gene segment in the genome of the non-human animal.

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, $V_{\kappa 1-39}$ 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.