

What is claimed is:

1. A method for making an antibody that binds an antigen of interest comprising:
 - (a) immunizing a mouse with an antigen of interest, wherein the mouse comprises in its germline genome:
 - (i) two unrearranged human V_k gene segments and five unrearranged human J_k gene segments operably linked to a light chain constant region sequence, wherein the two unrearranged human V_k gene segments are a human V_k1-39 gene segment and a human V_k3-20 gene segment, and wherein the five unrearranged human J_k gene segments are a human J_k1 gene segment, a human J_k2 gene segment, a human J_k3 gene segment, a human J_k4 gene segment, and a human J_k5 gene segment; and
 - (ii) one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments operably linked to a mouse heavy chain constant region sequence;
wherein the unrearranged human heavy chain gene segments and unrearranged human kappa light chain gene segments of the mouse are capable of rearranging to generate immunoglobulin heavy chain variable region sequences and immunoglobulin kappa light chain variable region sequences, respectively, and wherein the mouse does not comprise an endogenous V_k gene segment that is capable of rearranging to form a light chain variable region sequence, and
 - (b) obtaining an immunoglobulin heavy chain and/or kappa light chain variable region sequence that encodes an immunoglobulin heavy chain variable domain and/or an immunoglobulin light chain variable domain, respectively, of an antibody that specifically binds the antigen of interest,
 - (c) employing the immunoglobulin heavy chain and/or kappa light chain variable region sequence to produce an antibody that binds the antigen.
2. A method for making an antibody that binds an antigen of interest comprising the steps of:
 - (a) immunizing a mouse with an antigen of interest, wherein the mouse comprises in its germline genome:
 - (i) two unrearranged human V_k gene segments and five unrearranged human J_k gene segments operably linked to a light chain constant region sequence, wherein

the two unrearranged human V_k gene segments are a human V_k1-39 gene segment and a human V_k3-20 gene segment, and wherein the five unrearranged human J_k gene segments are a human J_k1 gene segment, a human J_k2 gene segment, a human J_k3 gene segment, a human J_k4 gene segment, and a human J_k5 gene segment; and

(ii) one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments operably linked to a mouse heavy chain constant region sequence;

wherein the unrearranged human heavy chain gene segments and unrearranged human kappa light chain gene segments of the mouse are capable of rearranging to generate immunoglobulin heavy chain variable domains and immunoglobulin kappa light chain variable domains, respectively;

wherein the mouse generates antibodies when immunized with the antigen, wherein the antibodies each comprise a human heavy chain variable domain operably linked to a mouse heavy chain constant domain and a human light chain variable domain operably linked to a light chain constant domain; and

wherein the mouse does not comprise an endogenous V_k gene segment that is capable of rearranging to form a light chain variable region sequence; and

(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 a human kappa light chain variable domain sequence of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse; and

(c) employing the immunoglobulin heavy chain and/or kappa light chain variable domain sequence to produce an antibody that binds the antigen.

3. The method of claim 1, wherein employing the human heavy and/or kappa light chain variable region sequence comprises employing the human heavy chain variable region sequence of (b) operably linked to a human heavy chain constant region sequence and/or employing the human kappa light chain variable region sequence of (b) operably linked to a human light chain constant region sequence.

4. The method of claim 3, wherein employing the human heavy chain variable region sequence of (b) operably linked to a human heavy chain constant region sequence comprises expressing the human heavy chain variable region sequence of (b) and the human heavy chain

constant region sequence.

5. The method of claim 3, wherein employing the human kappa light chain variable region sequence of (b) operably linked to a human light chain constant region sequence comprises expressing the human kappa light chain variable region sequence of (b) and the human light chain constant region sequence.

6. The method of claim 2, wherein employing the human heavy and/or kappa light chain variable domain sequence comprises employing the human heavy chain variable domain sequence of (b) operably linked to a human heavy chain constant domain sequence and/or employing the human kappa light chain variable domain sequence of (b) operably linked to a human light chain constant domain sequence.

7. The method of claim 2 or 6, 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.

8. The method of claim 2 or 6, wherein employing the human kappa 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 kappa light chain variable domain sequence of (b) and the human light chain constant domain sequence.

9. The method of claim 1 or claim 2, wherein the two unrearranged human V κ gene segments and five unrearranged human J κ gene segments in the germline genome of the mouse are operably linked to a mouse light chain constant region sequence.

10. The method of claim 9, wherein the mouse light chain constant region sequence is a mouse C κ region sequence.

11. The method of claim 9, wherein the two unrearranged human V κ gene segments and five unrearranged human J κ gene segments in the germline genome of the mouse are present at an endogenous immunoglobulin light chain locus.

12. The method of claim 11, wherein the germline genome of the mouse comprises in order: the human V κ 1-39 gene segment, the human V κ 3-20 gene segment, the human J κ 1 gene segment, the human J κ 2 gene segment, the human J κ 3 gene segment, the human J κ 4 gene segment, and the human J κ 5 gene segment.
13. The method of claim 1 or claim 2, wherein the one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments in the germline genome of the mouse are present at an endogenous immunoglobulin heavy chain locus.
14. The method of claim 13, wherein the mouse does not comprise an endogenous mouse immunoglobulin V_H gene segment that is capable of rearranging to form an immunoglobulin heavy chain variable region.
15. The method of claim 1 or claim 2, wherein the mouse comprises a nonfunctional immunoglobulin λ light chain locus.
16. A method for making an antibody comprising:
- (1) expressing in a single cell:
 - (a) a first nucleic acid sequence that encodes a first immunoglobulin heavy chain, the first nucleic acid sequence comprising a first human heavy chain variable region sequence operably linked to a human heavy chain constant region sequence, wherein the first human heavy chain variable region sequence was obtained from a B cell of a mouse, wherein the mouse has been immunized with an antigen of interest including an epitope and the mouse comprises in its germline genome:
 - (i) two unrearranged human V κ gene segments and five unrearranged human J κ gene segments operably linked to a light chain constant region sequence, wherein the two unrearranged human V κ gene segments are a human V κ 1-39 gene segment and a human V κ 3-20 gene segment, and wherein the five unrearranged human J κ gene segments are a human J κ 1 gene segment, a human J κ 2 gene segment, a human J κ 3 gene segment, a human J κ 4 gene segment, and a human J κ 5 gene segment; and

(ii) one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments operably linked to a mouse heavy chain constant region sequence;

wherein the unrearranged human heavy chain gene segments and unrearranged human kappa light chain gene segments of the mouse are capable of rearranging and encoding human heavy chain variable domains and human kappa light chain variable domains of an antibody, respectively;

wherein the mouse does not comprise an endogenous V_κ gene segment that is capable of rearranging to form a light chain variable region sequence; and

wherein the first human heavy chain variable region sequence encodes a first human heavy chain variable domain that, with a kappa light chain variable domain, recognizes the epitope; and

(b) a second nucleic acid sequence that encodes an immunoglobulin light chain, the second nucleic acid sequence comprising a human kappa light chain variable region sequence operably linked to a human light chain constant region sequence, wherein the human kappa light chain variable region sequence comprises: a human V_κ1-39 gene segment, a human V_κ3-20 gene segment, or a somatically hypermutated version thereof;

(2) maintaining the cell under conditions sufficient to express a fully human antibody; and

(3) isolating the antibody.

17. The method of claim 16, wherein the two unrearranged human V_κ gene segments and five unrearranged human J_κ gene segments in the germline genome of the mouse are operably linked to a mouse light chain constant region sequence.

18. The method of claim 17, wherein the mouse light chain constant region sequence of the mouse is a mouse C_κ region sequence.

19. The method of claim 17, wherein the two unrearranged human V_κ gene segments and five unrearranged human J_κ gene segments in the germline genome of the mouse are present at an endogenous immunoglobulin light chain locus.

20. The method of claim 19, wherein the germline genome of the mouse comprises in order: the human V κ 1-39 gene segment, the human V κ 3-20 gene segment, the human J κ 1 gene segment, the human J κ 2 gene segment, the human J κ 3 gene segment, the human J κ 4 gene segment, and the human J κ 5 gene segment.

21. The method of claim 16, wherein the one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments in the germline genome of the mouse are present at an endogenous immunoglobulin heavy chain locus.

22. The method of claim 21, wherein the mouse does not comprise an endogenous mouse V_H gene segment that is capable of rearranging to form a heavy chain variable region.

23. The method of claim 16, wherein the mouse comprises a nonfunctional immunoglobulin λ light chain locus.

24. The method of claim 16, wherein the second nucleic acid sequence comprises a hV κ /hJ κ /mC κ junction sequence selected from SEQ ID NOs: 38-49.

25. The method of claim 16, wherein the antibody made by the method is a bispecific antibody.

26. A method for generating a human heavy and/or kappa light chain variable region sequence comprising:

(a) immunizing a genetically modified mouse with an antigen, wherein the mouse generates antibodies when immunized with the antigen, and wherein the mouse has a germline genome that comprises:

(i) two unrearranged human V κ gene segments and five unrearranged human J κ gene segments operably linked to a light chain constant region sequence, wherein the two unrearranged human V κ gene segments are a human V κ 1-39 gene segment and a human V κ 3-20 gene segment, and wherein the five unrearranged human J κ gene segments are a human J κ 1 gene segment, a human J κ 2 gene segment, a human J κ 3 gene segment, a human J κ 4 gene segment, and a human J κ 5 gene segment; and

(ii) one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments operably linked to a mouse heavy chain constant region sequence;

wherein the unrearranged human heavy chain gene segments and unrearranged human kappa light chain gene segments of the mouse are capable of rearranging and encoding human heavy chain variable domains and human kappa light chain variable domains of an antibody, respectively, and wherein the mouse does not comprise an endogenous V_k gene segment that is capable of rearranging to form a light chain variable region sequence, and

(b) determining a human heavy and/or kappa light chain variable region sequence that encodes a human heavy and/or kappa light chain variable domain of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse.

27. A method for generating a human heavy and/or kappa light chain variable domain sequence comprising:

(a) immunizing a genetically modified mouse with an antigen, wherein the mouse generates antibodies when immunized with the antigen, and wherein the mouse has a germline genome that comprises:

(i) two unrearranged human V_k gene segments and five unrearranged human J_k gene segments operably linked to a light chain constant region sequence, wherein the two unrearranged human V_k gene segments are a human V_k1-39 gene segment and a human V_k3-20 gene segment, and wherein the five unrearranged human J_k gene segments are a human J_k1 gene segment, a human J_k2 gene segment, a human J_k3 gene segment, a human J_k4 gene segment, and a human J_k5 gene segment; and

(ii) one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments operably linked to a mouse heavy chain constant region sequence;

wherein the unrearranged human heavy chain gene segments and unrearranged human kappa light chain gene segments of the mouse are capable of rearranging and encoding human heavy chain variable domains and human kappa light chain variable domains of an antibody, respectively, and wherein the mouse does not comprise an endogenous V_k gene segment that is capable of rearranging to form a light chain variable region sequence, and

(b) determining a human heavy and/or kappa light chain variable domain sequence of an antibody that specifically binds the antigen and that was generated by the genetically modified mouse.

28. The method of claim 27, wherein determining a human heavy and/or kappa light chain variable domain sequence comprises determining a nucleotide sequence that encodes the human heavy and/or kappa light chain variable domain sequence.

29. The method of claim 26 or 27, wherein the two unrearranged human V κ gene segments and five unrearranged human J κ gene segments in the germline genome of the mouse are operably linked to a mouse light chain constant region sequence.

30. The method of claim 29, wherein the mouse light chain constant region sequence is a mouse C κ region sequence.

31. The method of claim 29, wherein the two unrearranged human V κ gene segments and five unrearranged human J κ gene segments in the germline genome of the mouse are present at an endogenous immunoglobulin light chain locus.

32. The method of claim 31, wherein the germline genome of the mouse comprises in order: the human V κ 1-39 gene segment, the human V κ 3-20 gene segment, the human J κ 1 gene segment, the human J κ 2 gene segment, the human J κ 3 gene segment, the human J κ 4 gene segment, and the human J κ 5 gene segment.

33. The method of claim 26 or 27, wherein the one or more unrearranged human V $_H$ gene segments, one or more unrearranged human D $_H$ gene segments, and one or more unrearranged human J $_H$ gene segments in the germline genome of the mouse are present at an endogenous immunoglobulin heavy chain locus.

34. The method of claim 33, wherein the mouse does not comprise an endogenous mouse immunoglobulin V $_H$ gene segment that is capable of rearranging to form an immunoglobulin heavy chain variable region.

35. The method of claim 26 or 27, wherein the mouse comprises a nonfunctional immunoglobulin λ light chain locus.
36. A method of making a nucleotide sequence encoding fully human heavy chain and/or a fully human kappa light chain comprising the steps of:
- (a) immunizing a genetically modified mouse with an antigen, wherein the mouse has a germline genome that comprises:
 - (i) two unrearranged human Vk gene segments and five unrearranged human Jk gene segments operably linked to a light chain constant region sequence, wherein the two unrearranged human Vk gene segments are a human Vk1-39 gene segment and a human Vk3-20 gene segment, and wherein the five unrearranged human Jk gene segments are a human Jk1 gene segment, a human Jk2 gene segment, a human Jk3 gene segment, a human Jk4 gene segment, and a human Jk5 gene segment; and
 - (ii) one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments operably linked to a mouse heavy chain constant region sequence;wherein the unrearranged human heavy chain gene segments and unrearranged human kappa light chain gene segments of the mouse are capable of rearranging and encoding human heavy chain variable domains and human kappa light chain variable domains of an antibody, respectively, and wherein the mouse does not comprise an endogenous Vk gene segment that is capable of rearranging to form a light chain variable region sequence, and
 - (b) determining a human heavy and/or kappa light chain variable region sequence that encodes a human heavy and/or kappa light chain variable domain of an antibody, respectively, that specifically binds the antigen and that was generated by the genetically modified mouse; and
 - (c) operably linking the human heavy chain variable region sequence to a human heavy chain constant region sequence to form a nucleotide sequence encoding a fully human heavy chain and/or operably linking the human kappa light chain variable region sequence to a human kappa light chain constant region sequence to form a nucleotide sequence encoding a fully human kappa light chain.
37. A method of making a fully human heavy chain and/or a fully human kappa light chain

comprising the steps of:

(a) immunizing a genetically modified mouse with an antigen, wherein the mouse has a germline genome that comprises:

(i) two unrearranged human Vk gene segments and five unrearranged human Jk gene segments operably linked to a light chain constant region sequence, wherein the two unrearranged human Vk gene segments are a human Vk1-39 gene segment and a human Vk3-20 gene segment, and wherein the five unrearranged human Jk gene segments are a human Jk1 gene segment, a human Jk2 gene segment, a human Jk3 gene segment, a human Jk4 gene segment, and a human Jk5 gene segment; and

(ii) one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments operably linked to a mouse heavy chain constant region sequence;

wherein the unrearranged human heavy chain gene segments and unrearranged human kappa light chain gene segments of the mouse are capable of rearranging and encoding human heavy chain variable domains and human kappa light variable domains of an antibody, respectively, and wherein the mouse does not comprise an endogenous Vk gene segment that is capable of rearranging to form a light chain variable region sequence, and

(b) determining a human heavy and/or kappa 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 chain variable domain sequence to a human heavy chain constant domain sequence to form a fully human heavy chain and/or operably linking the human kappa light chain variable domain sequence to a human kappa light chain constant domain sequence to form a fully human kappa light chain.

38. The method of claim 37, wherein determining a human heavy or kappa light chain variable domain sequence comprises determining a nucleotide sequence that encodes the human heavy and/or light chain variable domain sequence, respectively.

39. The method of claim 37, wherein operably linking the human heavy and/or 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

and/or light chain variable domain sequence to a nucleotide sequence encoding the human heavy and/or light chain constant domain sequence, respectively.

40. The method of claims 36 or 37, wherein the two unrearranged human V_{κ} gene segments and five unrearranged human J_{κ} gene segments in the germline genome of the mouse are operably linked to a mouse light chain constant region sequence.

41. The method of claim 40, wherein the mouse light chain constant region sequence is a mouse C_{κ} region sequence.

42. The method of claims 36 or 37, wherein the two unrearranged human V_{κ} gene segments and five unrearranged human J_{κ} gene segments in the germline genome of the mouse are present at an endogenous immunoglobulin light chain locus.

43. The method of claim 42, wherein the germline genome of the mouse comprises in order: the human $V_{\kappa}1$ -39 gene segment, the human $V_{\kappa}3$ -20 gene segment, the human $J_{\kappa}1$ gene segment, the human $J_{\kappa}2$ gene segment, the human $J_{\kappa}3$ gene segment, the human $J_{\kappa}4$ gene segment, and the human $J_{\kappa}5$ gene segment.

44. The method of claims 36 or 37, wherein the one or more unrearranged human V_H gene segments, one or more unrearranged human D_H gene segments, and one or more unrearranged human J_H gene segments in the germline genome of the mouse are present at an endogenous immunoglobulin heavy chain locus.

45. The method of claim 44, wherein the mouse does not comprise an endogenous mouse immunoglobulin V_H gene segment that is capable of rearranging to form an immunoglobulin heavy chain variable region.

46. The method of claims 36 or 37, wherein the mouse comprises a nonfunctional immunoglobulin λ light chain locus.

47. A method of making a mouse comprising genetically modifying the germline genome of the mouse so that it includes:

(a) two unrearranged human immunoglobulin V κ gene segments and five unrearranged human immunoglobulin J κ gene segments operably linked to an immunoglobulin light chain constant region, wherein the two unrearranged human immunoglobulin V κ gene segments are a human V κ 1-39 gene segment and a human V κ 3-20 gene segment, and the five unrearranged human immunoglobulin J κ gene segments are human J κ 1, human J κ 2, human J κ 3, human J κ 4, and human J κ 5; and

(b) one or more human immunoglobulin V $_H$ gene segments, one or more human immunoglobulin D $_H$ gene segments, and one or more human immunoglobulin J $_H$ gene segments operably linked to a mouse immunoglobulin constant region sequence;

wherein the human immunoglobulin kappa light chain gene segments are capable of rearranging and encoding human immunoglobulin light chain variable domains, and further wherein the mouse does not comprise an endogenous immunoglobulin V κ gene segment that is capable of rearranging to form an immunoglobulin light chain variable region sequence.

48. The method of claim 47, wherein the two unrearranged human immunoglobulin V κ gene segments and the five unrearranged human immunoglobulin J κ gene segments are operably linked to a mouse or rat immunoglobulin light chain constant region sequence, wherein the immunoglobulin light chain constant region sequence is a rat C κ region or a mouse C κ region.

49. The method of any one of claims 47 to 48, wherein the two unrearranged human immunoglobulin V κ gene segments and five unrearranged human immunoglobulin J κ gene segments are present at an endogenous kappa immunoglobulin light chain locus.

50. The method of any one of claims 47 to 49, wherein the one or more human immunoglobulin V $_H$ gene segments, one or more human immunoglobulin D $_H$ gene segments, and one or more human immunoglobulin J $_H$ gene segments are operably linked to a mouse constant region sequence.

51. The method of any one of claims 47 to 50, wherein the human immunoglobulin heavy chain gene segments are capable of rearranging and encoding human immunoglobulin heavy chain variable domains.

52. The method of any one of claims 47 to 51, wherein the mouse comprises a functional λ immunoglobulin light chain locus.
53. The method of any one of claims 47 to 52, wherein the mouse comprises a nonfunctional λ immunoglobulin light chain locus.
54. The method of any one of claims 48 to 53, wherein the two unrearranged human immunoglobulin V κ gene segments and five unrearranged human immunoglobulin J κ gene segments operably linked to a mouse or rat light chain constant region sequence are present at an endogenous mouse κ immunoglobulin light chain variable region locus.
55. The method of claim 54, wherein the germline genome of the mouse comprises in order: two human V κ segments which are the human V κ 1-39 gene segment and the human V κ 3-20 gene segment, a human J κ 1, a human J κ 2, a human J κ 3, a human J κ 4 and a human J κ 5.
56. The method of any one of claims 47 to 55, wherein the mouse comprises a DLC-5J locus, wherein the DLC-5J locus comprises a hV κ /hJ κ /mC κ junction sequence selected from SEQ ID NOs: 38-49.
57. An isolated cell from a mouse made by the method of any one of claims 47 to 56.
58. The cell of claim 57, wherein the cell is an embryonic stem (ES) cell.
59. The cell of claim 57, wherein the cell is a B cell.
60. A hybridoma made with the B cell of claim 59.
61. A method for making an antibody that binds an antigen of interest comprising
immunizing a genetically modified mouse made according to any one of claims 47 to 56
with an antigen of interest,
obtaining an immunoglobulin variable region sequence from the mouse, and
employing the immunoglobulin variable region sequence to produce an antibody that
binds the antigen.

62. The method of claim 61, wherein the method further comprises:
expressing in a single cell:
(a) a first human immunoglobulin heavy chain variable region sequence of the genetically modified mouse made according to any one of claims 57 to 66 which has been immunized, wherein the human immunoglobulin heavy chain variable region sequence is fused with a human C_H gene sequence; and
(b) a human immunoglobulin light chain variable region sequence, wherein the human immunoglobulin light chain variable region sequence is fused with a human immunoglobulin light chain constant region sequence;
maintaining the cell under conditions sufficient to express a fully human antibody; and
isolating the antibody from the cell.

63. The method according to claim 62, wherein the cell comprises a second human immunoglobulin heavy chain variable region sequence of a genetically modified mouse made according to any one of claims 47 to 56 which has been immunized,

wherein the second human immunoglobulin heavy chain variable region sequence is fused with a human immunoglobulin heavy chain constant region sequence, wherein the first human immunoglobulin heavy chain variable region sequence encodes a first human immunoglobulin heavy chain variable domain that recognizes a first epitope, and the second human immunoglobulin heavy chain variable region sequence encodes a second human immunoglobulin heavy chain variable domain that recognizes a second epitope,

wherein the first epitope and the second epitope are not identical, and wherein the first and the second human immunoglobulin heavy chain variable domains interact with the human immunoglobulin light chain variable domain encoded by the human immunoglobulin light chain variable region sequence.

64. A method of producing an antibody comprising immunizing a genetically modified mouse made according to any one of claims 47 to 56 with an antigen and obtaining a human immunoglobulin heavy chain variable domain amino acid sequence, or encoding nucleotide sequence, from a resulting antibody produced by the genetically modified mouse against the antigen, and utilizing said human immunoglobulin heavy chain variable domain amino acid sequence or encoding nucleic acid sequence in making an antibody.

65. The method of claim 64, wherein the method further comprises:

(a) identifying the human immunoglobulin heavy chain variable domain amino acid sequence, or encoding nucleotide sequence, from two different antibodies against different epitopes of the antigen that the genetically modified mouse has been immunized with; or

(b) immunizing the same genetically modified mouse, or a further mouse made according to any one of claims 47 to 56, with a different antigen, then identifying a human immunoglobulin heavy chain variable domain amino acid sequence, or encoding nucleotide sequence, from an antibody produced by the genetically modified mouse that is specific for said different antigen, and generating a bispecific antibody

by employing the two different human immunoglobulin heavy chain variable domain amino acid sequences, or encoding nucleotide sequences.

66. A mouse embryonic stem (ES) cell that has been genetically modified so that it comprises in its genome:

exactly two unrearranged human immunoglobulin V κ gene segments and five unrearranged human immunoglobulin J κ gene segments operably linked to a mouse immunoglobulin light chain constant region sequence, wherein the two unrearranged human immunoglobulin V κ gene segments are a human V κ 1-39 gene segment and a human V κ 3-20 gene segment, and wherein the five unrearranged human immunoglobulin J κ gene segments are a human J κ 1 gene segment, a human J κ 2 gene segment, a human J κ 3 gene segment, a human J κ 4 gene segment, and a human J κ 5 gene segment.

67. The genetically modified mouse ES cell of claim 66, further comprising in its genome:

one or more unrearranged human immunoglobulin V H gene segments, one or more unrearranged human immunoglobulin D H gene segments, and one or more unrearranged human immunoglobulin J H gene segments operably linked to a mouse immunoglobulin heavy chain constant region sequence at the endogenous heavy chain loci.

68. The genetically modified ES cell of claim 67, wherein the genome of the ES cell does not comprise an endogenous mouse immunoglobulin V H gene segment that is capable of rearranging to form an immunoglobulin heavy chain variable region.

69. The genetically modified ES cell of any one of claims 66 to 68, wherein the two unrearranged human immunoglobulin V κ gene segments and five unrearranged human immunoglobulin J κ gene segments are present at the endogenous immunoglobulin κ light chain locus.
70. The genetically modified ES cell of claim 66 or 67, wherein the genome of the genetically modified mouse ES cell does not comprise a functional λ light chain locus.
71. The genetically modified mouse ES cell of claim 66 or 67, wherein the mouse light chain constant region is a mouse C κ constant region.
72. The genetically modified mouse ES cell of claim 71, wherein the mouse C κ constant region is an endogenous mouse C κ constant region.
73. The genetically modified mouse ES cell of claim 66 or 67, wherein the human V κ 1-39 gene segment in genome of the genetically modified mouse ES cell is a human germline V κ 1-39 gene segment and the human V κ 3-20 gene segment in the genome of the genetically modified mouse ES cell is a human germline V κ 3-20 gene segment.
74. The genetically modified mouse ES cell of claim 66 or 67, wherein the genome of the genetically modified mouse ES cell comprises in order: the human V κ 1-39 gene segment, the human V κ 3-20 gene segment, the human J κ 1 gene segment, the human J κ 2 gene segment, the human J κ 3 gene segment, the human J κ 4 gene segment, and the human J κ 5 gene segment.
75. The genetically modified mouse ES cell of any one of claims 66 to 74, wherein the genome of the genetically modified mouse ES cell comprises a DLC-5J locus, wherein the DLC-5J locus comprises a hV κ /hJ κ /mC κ junction sequence selected from SEQ ID NOs: 38-49.
76. A method of making a mouse comprising gestating a mouse embryo derived from the genetically modified ES cell of claim 66 or 67 in a surrogate mother and allowing the surrogate mother to give birth to progeny derived in whole or in part from the genetically modified ES cell.

77. A method of making a genetically modified mouse ES cell, the method comprising genetically modifying an ES cell so that it comprises in its genome exactly two unrearranged human immunoglobulin V κ gene segments and five unrearranged human immunoglobulin J κ gene segments operably linked to a mouse immunoglobulin light chain constant region sequence, wherein the two unrearranged human immunoglobulin V κ gene segments are a human V κ 1-39 gene segment and a human V κ 3-20 gene segment, and wherein the five unrearranged human immunoglobulin J κ gene segments are a human J κ 1 gene segment, a human J κ 2 gene segment, a human J κ 3 gene segment, a human J κ 4 gene segment, and a human J κ 5 gene segment.

78. The method of claim 77, wherein the genetically modified mouse ES cell further comprises in its genome one or more unrearranged human immunoglobulin V H gene segments, one or more unrearranged human immunoglobulin D H gene segments, and one or more unrearranged human immunoglobulin J H gene segments operably linked to a mouse immunoglobulin heavy chain constant region sequence at the endogenous heavy chain loci.

79. The method of claim 77 or 78, wherein the mouse light chain constant region is a mouse C κ constant region.

80. The method of claim 79, wherein the mouse light chain constant region is an endogenous mouse C κ constant region.

81. The method of claim 78, wherein the genome of the genetically modified ES cell does not comprise an endogenous mouse immunoglobulin V H gene segment that is capable of rearranging to form an immunoglobulin heavy chain variable region.

82. The method of any one of claims 77 to 81, wherein the two unrearranged human immunoglobulin V κ gene segments and five unrearranged human immunoglobulin J κ gene segments are present at the endogenous immunoglobulin κ light chain locus.

83. The method of claim 77 or 78, wherein the genome of the genetically modified mouse ES cell does not comprise a functional λ light chain locus.

84. The method of claim 77 or 78, wherein the human V κ 1-39 gene segment in the genome of the genetically modified mouse ES cell is a human germline V κ 1-39 gene segment and the human V κ 3-20 gene segment in the genome of the genetically modified mouse ES cell is a human germline V κ 3-20 gene segment.

85. The method of claim 77 or 78, wherein the genome of the genetically modified mouse ES cell comprises in order: the human V κ 1-39 gene segment, the human V κ 3-20 gene segment, the human J κ 1 gene segment, the human J κ 2 gene segment, the human J κ 3 gene segment, the human J κ 4 gene segment, and the human J κ 5 gene segment.

86. The method of any one of claims 77 to 85, wherein the genetically modified mouse ES cell comprises a DLC-5J locus, wherein the DLC-5J locus comprises a hV κ /hJ κ /mC κ junction sequence selected from SEQ ID NOs: 38-49.