

What is claimed is:

1. A mouse, comprising:
 - (a) a replacement at the endogenous mouse κ immunoglobulin light chain variable region locus of all or substantially all endogenous mouse κ immunoglobulin light chain variable region gene segments with a human $V_{\kappa}1-39/J$ gene segment, a human $V_{\kappa}3-20/J$ gene segment, or a combination thereof, wherein the human gene segment is operably linked to an endogenous mouse κ constant gene; and,
 - (b) a replacement of all or substantially all of the endogenous mouse heavy chain variable region gene locus with a plurality of human heavy chain variable region gene segments, wherein the human heavy chain variable region gene segments are operably linked to an endogenous mouse heavy chain constant gene, and the human heavy chain variable region gene segments are capable of rearranging and forming a rearranged human/mouse chimeric heavy chain gene.
2. The mouse of claim 1, wherein the mouse lacks an endogenous mouse κ immunoglobulin light chain variable region locus that is capable of rearranging and forming a gene that encodes a mouse κ variable region.
3. The mouse of claim 1, further comprising a mouse κ intronic enhancer 5' with respect to the mouse light chain constant region.
4. The mouse of claim 1, further comprising a mouse κ 3' enhancer.
5. The mouse of claim 1, wherein the plurality of human heavy chain variable region gene segments comprises a segment selected from a 1-2, 1-8, 1-24, 2-5, 3-7, 3-9, 3-11, 3-13, 3-15, 3-20, 3-23, 3-30, 3-33, 3-48, 4-31, 4-39, 4-59, 5-51, a 6-1 human immunoglobulin variable region gene segment.
6. The mouse of claim 1, wherein the plurality of human heavy chain variable region gene segments comprises a segment selected from a D1-7, D1-26, D3-3, D3-10, D3-16, D3-22, D5-5, D5-12, D6-6, D6-13, D7-27 gene segment, and a combination thereof.
7. The mouse of claim 1, wherein the mouse comprises a B cell that comprises a rearranged immunoglobulin heavy chain variable region gene sequence comprising a human heavy chain variable region gene derived from a V_H gene segment selected from a V_H2-5 , V_H3-23 , V_H3-30 , V_H4-39 , V_H4-59 , V_H5-51 , and derived from a D gene segment

selected from a D1-7, D1-26, D3-3, D3-16, D3-10, D3-22, D5-5, D5-12, D6-6, D6-13, and D7-27.

8. The mouse of claim 1, wherein the human V κ 1-39 gene segment is present in a rearrangement with a human J κ 5 gene segment.

9. The mouse of claim 1, wherein the human V κ 3-20 gene segment is present in a rearrangement with a human J κ 1 gene segment.

10. A method for selecting a human variable region for making a bispecific antibody, comprising:

(a) immunizing a genetically modified mouse with an antigen of interest, wherein the mouse comprises (i) a replacement at the endogenous mouse κ immunoglobulin light chain variable region locus of all or substantially all endogenous mouse κ immunoglobulin light chain variable region gene segments with a human V κ 1-39/J gene segment, a human V κ 3-20/J gene segment, or a combination thereof, wherein the human gene segment is operably linked to an endogenous mouse κ constant gene; and, (ii) a replacement of all or substantially all of the endogenous mouse heavy chain variable region gene locus with a plurality of human heavy chain variable region gene segments, wherein the human heavy chain variable region gene segments are operably linked to an endogenous mouse heavy chain constant gene, and the human heavy chain variable region gene segments are capable of rearranging and forming a rearranged human/mouse chimeric heavy chain gene;

(b) allowing the mouse to develop an immune response to the antigen of interest; and,

(c) identifying a clonally selected lymphocyte of the mouse that expresses an antibody that specifically binds the antigen of interest, and obtaining from the lymphocyte or the antibody a nucleotide sequence that encodes a human heavy chain variable region that specifically binds the antigen of interest; and,

(d) employing the nucleotide sequence of (c) in making a bispecific antibody.

11. The method of claim 10, wherein the mouse lacks an endogenous mouse κ immunoglobulin light chain variable region locus that is capable of rearranging and forming a gene that encodes a mouse κ variable region.

12. The method of claim 10, further comprising a mouse κ intronic enhancer 5' with respect to the mouse light chain constant region.

13. The method of claim 10, further comprising a mouse κ 3' enhancer.
14. The method of claim 10, wherein the plurality of human heavy chain variable region gene segments comprises a segment selected from a 1-2, 1-8, 1-24, 2-5, 3-7, 3-9, 3-11, 3-13, 3-15, 3-20, 3-23, 3-30, 3-33, 3-48, 4-31, 4-39, 4-59, 5-51, a 6-1 human immunoglobulin variable region gene segment.
15. The method of claim 10, wherein the plurality of human heavy chain variable region gene segments comprises a segment selected from a D1-7, D1-26, D3-3, D3-10, D3-16, D3-22, D5-5, D5-12, D6-6, D6-13, D7-27 gene segment, and a combination thereof.
16. The method of claim 10, wherein the mouse comprises a B cell that comprises a rearranged immunoglobulin heavy chain variable region gene sequence comprising a human heavy chain variable region gene derived from a VH gene segment selected from a VH2-5, VH3-23, VH3-30, VH4-39, VH4-59, VH5-51, and derived from a D gene segment selected from a D1-7, D1-26, D3-3, D3-16, D3-10, D3-22, D5-5, D5-12, D6-6, D6-13, and D7-27.
17. The method of claim 10, wherein the human V κ 1-39 gene segment is present in a rearrangement with a human J κ 5 gene segment.
18. The method of claim 10, wherein the human V κ 3-20 gene segment is present in a rearrangement with a human J κ 1 gene segment.
19. The method of claim 10, wherein steps (a) through (d) are performed a first time for a first antigen of interest to generate a first human heavy chain variable region sequence, and steps (a) through (d) are performed a second time for a second antigen of interest to generate a second human heavy chain variable region sequence, and wherein the first human heavy chain variable region sequence is expressed fused with a first human heavy chain constant region to form a first human heavy chain, the second human heavy chain variable region sequence is expressed fused with a second human heavy chain constant region to form a second human heavy chain, wherein the first and the second human heavy chains are expressed in the presence of a single human light chain derived from a V κ 1-39 or a V κ 3-20 gene segment.

20. The method of claim 19, wherein the first human heavy chain comprises a modification that eliminates or substantially reduces the affinity of the first human heavy chain to protein A, and the second human heavy chain retains the ability to bind protein A.

21. The method of claim 20, wherein the modification that eliminates or substantially reduces affinity of the first human heavy chain to protein A is selected from a 95R (EU 435R), a 96F (EU 436F), and a combination thereof.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A mouse, comprising:
 - (a) a single rearranged human immunoglobulin light chain variable region (V_L/J_L) that encodes a human V_L domain of an immunoglobulin light chain, wherein the single rearranged human V_L/J_L region is selected from a human $V_{\kappa}1-39/J$ gene segment or a human $V_{\kappa}3-20/J$ gene segment; and,
 - (b) a replacement of endogenous heavy chain variable (V_H) gene segments with one or more human V_H gene segments, wherein the human V_H gene segments are operably linked to an endogenous heavy chain constant (C_H) region gene, and the human V_H gene segments are capable of rearranging and forming a human/mouse chimeric heavy chain gene.
2. The mouse of claim 1, wherein the mouse comprises an immunoglobulin light chain variable region locus that does not comprise an endogenous V_L gene segment that is capable of rearranging and forming an immunoglobulin light chain gene.
3. The mouse of claim 1 or claim 2, further comprising a mouse κ intronic enhancer and/or a mouse κ 3' enhancer.
4. The mouse of any one of claims 1 to 3, wherein the single rearranged human immunoglobulin light chain variable region (V_L/J_L) is operably linked to a mouse C_L region.
5. The mouse of claim 4, wherein the C_L region is a C_{κ} region.
6. The mouse of any one of claims 1 to 5, wherein the one or more human V_H gene segments comprise at least 19, at least 39, at least 80, or 81 unrearranged human V_H gene segments.
7. The mouse of claims 1 to 5, wherein the one or more human V_H gene segments comprise at least 12, at least 25, or at least 43 functional human V_H gene segments.
8. The mouse of claim 1, 6 or 7, wherein the one or more human V_H gene segments are selected from 1-2, 1-8, 1-24, 2-5, 3-7, 3-9, 3-11, 3-13, 3-15, 3-20, 3-23, 3-30, 3-33, 3-48, 4-31, 4-39, 4-59, 5-51, 6-1 and a combination thereof.

9. The mouse of any one of claims 1 to 8, further comprising at least one unrearranged human D gene segment and at least one unrearranged human J gene segment.
10. The mouse of claim 9, wherein the at least one unrearranged human D gene
5 segments are selected from D1-7, D1-26, D3-3, D3-10, D3-16, D3-22, D5-5, D5-12, D6-6, D6-13, D7-27, and a combination thereof.
11. The mouse of claim 9, wherein the at least one unrearranged human J gene segment is selected from J1, J3, J4, J5, J6, and a combination thereof.
12. The mouse of claim 1, wherein the mouse comprises a B cell that comprises a rearranged immunoglobulin heavy chain variable region gene sequence comprising a human heavy chain variable region gene derived from a V_H gene segment selected from a V_H2-5, V_H3-23, V_H3-30, V_H4-39, V_H4-59, and V_H5-51, and derived from a D gene segment selected
5 from a D1-7, D1-26, D3-3, D3-16, D3-10, D3-22, D5-5, D5-12, D6-6, D6-13, and D7-27.
13. The mouse of claim 1, wherein the human V_κ1-39 gene segment is present in a rearrangement with a human J_κ5 gene segment.
- 10 14. The mouse of claim 1, wherein the human V_κ3-20 gene segment is present in a rearrangement with a human J_κ1 gene segment.
15. An isolated cell from the mouse of claim 1.
- 25 16. The cell of claim 15, wherein the cell is an embryonic stem (ES) cell.
17. The cell of claim 15, wherein the cell is a lymphocyte.
18. The cell of claim 17, wherein the lymphocyte is a B cell.
- 30 19. A hybridoma made with the B cell of claim 18.
20. A reverse chimeric antibody made by the mouse of any one of claims 1 to 14, wherein the reverse chimeric antibody comprises a light chain comprising a human V_L and a mouse
35 C_L, and a heavy chain comprising a human V_H and a mouse C_H.