

What is claimed is:

1. A mouse that expresses a population of antigen-specific antibodies in response to challenge with an antigen, wherein all of the immunoglobulin light chains of the population of antigen-specific antibodies comprise a human light chain variable (V_L) region derived from the same single human V_L gene segment and the immunoglobulin heavy chains comprise a human heavy chain variable (V_H) region derived from a human V_H gene segment selected from V_H1-2 , V_H1-3 , V_H1-8 , V_H1-18 , V_H1-24 , 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_H3-20 , V_H3-21 , V_H3-23 , V_H3-30 , V_H3-33 , V_H3-43 , V_H3-48 , V_H3-53 , V_H3-64 , V_H3-72 , V_H3-73 , V_H4-31 , V_H4-34 , V_H4-39 , V_H4-59 , V_H5-51 , V_H6-1 .
2. The mouse of claim 1, wherein the same single human V_L gene segment is a human $V_{\kappa 1-39}$ gene segment.
3. The mouse of claim 1, wherein the same single human V_L gene segment is a human $V_{\kappa 3-20}$ gene segment.
4. The mouse of claim 1, wherein all of the immunoglobulin light chains comprise a human light chain J (J_L) gene segment.
5. The mouse of claim 4, wherein the human J_L gene segment is selected from a human $J_{\kappa 1}$ and a $J_{\kappa 5}$ gene segment.
6. The mouse of claim 1, wherein the mouse lacks a sequence selected from a mouse immunoglobulin V_L gene segment, a mouse immunoglobulin J_L gene segment, and a combination thereof.
7. The mouse of claim 1, wherein the human V_L region is operably linked to a human, mouse, or rat immunoglobulin light chain constant (C_L) region.
8. The mouse of claim 1, wherein the human V_L region is expressed from an endogenous immunoglobulin light chain locus.
9. The mouse of claim 1, wherein the human V_H region is operably linked to a human, mouse, or rat immunoglobulin heavy chain constant (C_H) region.

10. The mouse of claim 1, wherein the human V_H region is expressed from an endogenous immunoglobulin heavy chain locus.
11. A mouse that expresses a population of antigen-specific antibodies in response to challenge with an antigen, wherein all of the immunoglobulin light chains of the population of antigen-specific antibodies comprise a human V_L region derived from a human V_{K1-39} gene segment and the immunoglobulin heavy chains comprise a human heavy chain variable (V_H) region derived from a human V_H gene segment selected from V_{H1-18} , V_{H1-69} , V_{H2-5} , V_{H3-9} , V_{H3-13} , V_{H3-15} , V_{H3-20} , V_{H3-23} , V_{H3-30} , V_{H3-48} , V_{H3-53} , V_{H3-64} , V_{H4-31} , V_{H4-34} , V_{H4-39} , V_{H4-59} , V_{H5-51} and V_{H6-1} .
12. The mouse of claim 11, wherein the human V_L region comprises a J_{K5} sequence.
13. The mouse of claim 11, wherein the mouse lacks a mouse immunoglobulin V_L and/or J_L gene segment.
14. The mouse of claim 11, wherein the human V_L region is operably linked to a human, rat, or mouse immunoglobulin light chain constant (C_L) region.
15. The mouse of claim 11, wherein the human V_L region is expressed from an endogenous immunoglobulin light chain locus.
16. The mouse of claim 11, wherein the human V_H region comprises a sequence that encodes a human J_H region selected from a human J_{H1} , J_{H2} , J_{H3} , J_{H4} , J_{H5} , and J_{H6} gene segment.
17. The mouse of claim 11, wherein the human V_H region is operably linked to a human, rat, or mouse immunoglobulin heavy chain constant (C_H) region.
18. The mouse of claim 11, wherein the human V_H region is expressed from an endogenous immunoglobulin heavy chain locus.

19. A mouse that expresses a population of antigen-specific antibodies in response to challenge with an antigen, wherein all of the immunoglobulin light chains of the population of antigen-specific antibodies comprise a human V_L region derived from a human V_κ3-20 gene segment and the immunoglobulin heavy chains comprise a human heavy chain variable (V_H) region derived from a human V_H gene segment selected from V_H1-18, V_H1-69, V_H2-70, V_H3-11, V_H3-30, V_H3-33, V_H3-53, V_H4-39, V_H4-59, V_H5-51 and V_H6-1.
20. The mouse of claim 19, wherein the human V_L region comprises a J_κ5 sequence.
21. The mouse of claim 19, wherein the mouse lacks a mouse immunoglobulin V_L and/or J_L gene segment.
22. The mouse of claim 19, wherein the human V_L region is operably linked to a human, rat, or mouse immunoglobulin light chain constant (C_L) region.
23. The mouse of claim 19, wherein the human V_L region is expressed from an endogenous immunoglobulin light chain locus.
24. The mouse of claim 19, wherein the human V_H region comprises a sequence that encodes a human J_H region selected from a human J_H2, J_H3, J_H4, J_H5, and J_H6 gene segment.
25. The mouse of claim 19, wherein the human V_H region is operably linked to a human, rat, or mouse immunoglobulin heavy chain constant (C_H) region.
26. The mouse of claim 19, wherein the human V_H region is expressed from an endogenous immunoglobulin heavy chain locus.
27. A method for making a genetically modified mouse is provided, comprising replacing all or substantially all mouse V_H gene segments at the endogenous mouse heavy chain locus with human V_H gene segments; wherein the mouse is genetically modified to comprise no more than one or two rearranged human light chain V_L/J_L sequences replacing all mouse light chain gene segments; wherein the human heavy chain variable gene segments are linked to a mouse constant gene, and the rearranged human light chain sequences are

linked to a human or mouse constant gene; wherein the human V_H gene segments are selected from V_{H1-2} , V_{H1-3} , V_{H1-8} , V_{H1-18} , V_{H1-24} , 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_{H3-20} , V_{H3-21} , V_{H3-23} , V_{H3-30} , V_{H3-33} , V_{H3-43} , V_{H3-48} , V_{H3-53} , V_{H3-64} , V_{H3-72} , V_{H3-73} , V_{H4-31} , V_{H4-34} , V_{H4-39} , V_{H4-59} , V_{H5-51} , V_{H6-1} , and a combination thereof.

28. The method of claim 27, wherein the two rearranged human light chain V_L/J_L gene segments comprise a rearranged $V_{K1-39/J}$, a rearranged $V_{K3-20/J}$, and a combination thereof.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A genetically modified mouse comprising a population of B cells that each express a human immunoglobulin light chain variable domain derived from a single rearranged human Vk1-39/Jk sequence which is present in the germline of the mouse, wherein the single rearranged human Vk1-39/Jk sequence comprises a human germline Vk1-39 gene segment and a human germline Jk gene segment, which single rearranged human Vk1-39/Jk sequence is operably linked to an immunoglobulin light chain constant region sequence, and wherein the human immunoglobulin light chain variable domain is expressed from a sequence that is identical to or is a somatically hypermutated variant of the rearranged human Vk1-39/Jk sequence; and

wherein the B cells of the population include at least one B cell that expresses a human immunoglobulin heavy chain variable domain derived from a human V_H gene segment selected from the group consisting of V_H1-46, V_H2-26, V_H3-21, and V_H3-64.

2. The mouse of claim 1, wherein the B cells of the population together express human immunoglobulin heavy chain variable domains derived from each human V_H gene segment of the group consisting of V_H1-46, V_H2-26, V_H3-21, and V_H3-64.

3. The mouse of claim 1 or claim 2, wherein the single rearranged human Vk1-39/Jk sequence is:

- (a) a rearranged human Vk1-39/Jk5 sequence comprising a human germline Vk1-39 gene segment and a human germline Jk5 gene segment;
- (b) operably linked to a mouse Ck region;
- (c) positioned so that it replaces an endogenous unrearranged immunoglobulin Vk gene segment and an endogenous unrearranged immunoglobulin Jk gene segment;
- (d) positioned so that it replaces all functional endogenous unrearranged immunoglobulin Vk gene segments and endogenous unrearranged immunoglobulin Jk gene segments; and/or
- (e) operably linked to an immunoglobulin light chain constant region sequence selected from a mouse or rat immunoglobulin light chain constant region sequence.

4. The mouse of any one of claims 1-3, wherein the sequence encoding the human immunoglobulin heavy chain variable domain is:
 - (a) operably linked to a mouse immunoglobulin heavy chain constant (CH) region sequence encoding a CH1, a hinge, a CH2, a CH3, or a combination thereof; and/or
 - (b) present in an endogenous immunoglobulin heavy chain locus.
5. The mouse of any one of claims 1-4, wherein the germline of the genetically modified mouse lacks any endogenous unrearranged immunoglobulin V_k gene segment functional for expression in an immunoglobulin light chain and the germline of the genetically modified mouse lacks any endogenous unrearranged immunoglobulin J_k gene segment functional for expression in an immunoglobulin light chain.
6. Use of a genetically modified mouse of any one of claims 1-5 in making an antigen-binding protein, which antigen-binding protein comprises a first immunoglobulin heavy chain and/or a second immunoglobulin heavy chain.
7. The use of claim 6, wherein the B cells of the mouse together express human immunoglobulin heavy chain variable domains derived from human V_H gene segments including each of V_H1-46, V_H2-26, V_H3-21, and V_H3-64.
8. The use of claim 6 or claim 7, wherein the first immunoglobulin heavy chain comprises a first human heavy chain variable domain expressed from an immunoglobulin heavy chain variable region obtained from a B cell of the mouse, and/or the second immunoglobulin heavy chain of the antigen-binding protein comprises a second human heavy chain variable domain expressed from an immunoglobulin heavy chain variable region obtained from a B cell of the mouse.
9. The use of claim 8, wherein the first and/or second human immunoglobulin heavy chain variable domain of the antigen-binding protein is derived from a human V_H gene segment selected from the group consisting of V_H1-46, V_H2-26, V_H3-21, and V_H3-64.
10. The use of any one of claims 6-9, wherein the mouse is immunized with a first antigen of interest and wherein the B cells of the population include at least one B cell that expresses a first antibody to said first antigen of interest; and/or wherein the mouse is

immunized with a second antigen of interest and wherein the B cells of the population include at least one B cell that expresses a second antibody to said second antigen of interest.

11. The use of claim 10, wherein the first and second antibodies bind different antigens.

12. The use of claim 10, wherein the first and the second antigens are the same antigen, and the first and the second antibodies bind different epitopes of the same antigen.

13. The use of any one of claims 10-12, wherein the making of the antigen-binding protein comprises selecting a first immunoglobulin heavy chain, comprising a first human immunoglobulin heavy chain variable domain, from a first antibody to said first antigen of interest expressed by the at least one B cell, and/or selecting a second immunoglobulin heavy chain, comprising a second human immunoglobulin heavy chain variable domain, from a second antibody to said second antigen of interest expressed by at least one B cell.

14. A use of a first mouse of any one of claims 1-5, and a second mouse of any one of claim 1-5, in making an antigen-binding protein, wherein the use comprises:

- (a) providing the first mouse, wherein the first mouse is immunized with a first antigen of interest wherein the B cells of the population of the first mouse include at least one B cell that expresses a first antibody, comprising a first immunoglobulin heavy chain comprising a first immunoglobulin heavy chain variable domain, to said first antigen of interest, and providing the second mouse, wherein the second mouse is immunized with a second antigen of interest, wherein the B cells of the population of the second mouse include at least one B cell that expresses a second antibody, comprising a second immunoglobulin heavy chain comprising a second immunoglobulin heavy chain variable domain, to said second antigen of interest;
- (b) selecting a first immunoglobulin heavy chain, comprising a first human immunoglobulin heavy chain variable domain from said first antibody to said first antigen of interest, and selecting a second immunoglobulin heavy chain, comprising a second human immunoglobulin heavy chain variable domain from said second antibody to said second antigen of interest, wherein the first and second human immunoglobulin heavy chain variable domains are different;
- (c) determining the sequences of the first and second human immunoglobulin heavy chain variable domains; and

- (d) employing the sequences of the first and second human immunoglobulin heavy chain variable domains to make a bispecific antigen-binding protein.

- 15. The use of claim 14, wherein said first mouse and said second mouse are the same mouse or different mice.
- 16. The use of claim 14 or claim 15, wherein the first and second antigens are the same antigen, and the first and the second antibodies bind different epitopes of the same antigen.
- 17. The use of any one of claims 14-16, wherein the making of the antigen-binding protein comprises expressing a first immunoglobulin heavy chain comprising the first human immunoglobulin heavy chain variable domain selected from the first mouse and/or a second immunoglobulin heavy chain comprising the second human immunoglobulin heavy chain variable domain selected from the second mouse together in a cell that also expresses an immunoglobulin light chain derived from a rearranged human V κ 1-39/J κ sequence.
- 18. The use of any one of claims 6 to 17, wherein the antigen-binding protein is a fully human antigen-binding protein.
- 19. The use of any one of claims 6 to 18, wherein the antigen-binding protein is a bispecific antigen-binding protein.
- 20. A bispecific antigen-binding protein produced according the use of any one of claims 6 to 19.