

We Claim:

1. A method for isolating a heavy chain variable domain and/or obtaining a nucleic acid sequence encoding the same, the method comprising isolating from a mouse (i) a heavy chain variable domain that specifically binds an antigen, (ii) a B cell that expresses an IgM- or an IgG-encoding nucleotide sequence comprising a heavy chain variable region nucleic acid that encodes the heavy chain variable domain, and/or (iii) the heavy chain variable region nucleic acid, wherein the mouse comprises a germline deletion of at least part of a nucleotide sequence encoding a CH1 domain of at least one endogenous IgG constant region, and wherein the mouse expresses an endogenous mouse IgM that comprises a functional CH1 domain and a secreted IgG antibody that lacks a functional CH1 domain.
2. The method of claim 1, further comprising culturing a host cell comprising a second nucleic acid sequence identical to or substantially identical to the heavy chain variable region nucleic acid to produce a binding protein comprising a heavy chain variable domain encoded by the second nucleic acid sequence.
3. The method of claim 2, wherein the binding protein further comprises a human heavy chain constant region selected from the group consisting of IgG1, IgG2a, IgG2b, and IgG3.
4. The method of claim 1, wherein the mouse further comprises a replacement of all or substantially all endogenous mouse V, D, and J gene segments with one or more human V, human D, and human J gene segments, wherein the one or more human V, D, and J gene segments are operably linked at the endogenous mouse locus to a mouse heavy chain constant region gene locus, and wherein the mouse heavy chain constant region gene locus comprises (i) an endogenous IgM constant region gene that encodes the endogenous mouse IgM comprising a functional CH1 domain, and (ii) an IgG gene comprising a deletion in at least part of a nucleotide sequence encoding a CH1 domain, wherein the IgG gene is selected from an IgG1, IgG2a, IgG2b, IgG3, and a combination thereof.
5. The method of claim 4, wherein the heavy chain variable domain is, or the nucleic acid sequence encodes, a human heavy chain variable domain.
6. The method of claim 4, further comprising culturing a host cell comprising a second nucleic acid sequence identical to or substantially identical to the heavy chain variable region nucleic acid to produce a binding protein comprising a heavy chain variable domain encoded by the second nucleic acid sequence.

7. The method of claim 6, wherein the binding protein further comprises a human heavy chain constant region selected from the group consisting of IgG1, IgG2a, IgG2b, and IgG3.
8. The method of claim 1, wherein the at least one IgG constant region is selected from the group consisting of an IgG1 constant region, an IgG2b constant region, an IgG2a constant region, and a combination thereof.
9. The method of claim 8, wherein the IgG constant region gene is an IgG1 constant region gene.
10. The method of claim 9, wherein the mouse further expresses (a) wild-type IgG3 protein; (b) wild-type IgG2a protein; and (c) IgG2b protein.
11. The method of claim 10, wherein the mouse further expresses (d) wild-type IgM protein; (e) wild-type IgD protein, (f) wild-type IgA protein; and (h) wild-type IgE protein.
12. The method of claim 1, wherein the IgG heavy chain antibody lacks the CH1 domain in whole.
13. The method of claim 12, wherein the IgG heavy chain antibody comprises an IgG1 hinge, a CH2 domain, and a CH3 domain.
14. The method of claim 1, wherein the mouse comprises a functional immunoglobulin light chain locus.
15. The method of claim 14, wherein the immunoglobulin light chain locus is a κ light chain gene locus.
16. The method of claim 14, wherein the immunoglobulin light chain locus is a λ light chain gene locus.
17. The method of claim 1, wherein the mouse is a strain selected from the group consisting of a 129 strain, a C57BL/6 strain, and a mixed 129xC57BL/6 strain.
18. The method of claim 17, wherein the mouse is 50% 129 and 50% C57BL/6.

19. The method of claim 1, further comprising the steps of culturing a hybridoma produced from the B cell to produce a heavy chain variable domain.
20. The method of claim 19, further comprising isolating nucleic acid sequence encoding a heavy chain variable domain from the hybridoma.
21. The method of claim 20, further comprising as last steps culturing a host cell with a second nucleic acid identical or substantially identical to the heavy chain variable region nucleic acid to produce a binding protein comprising a heavy chain variable domain encoded by the second nucleic acid sequence.
22. The method of claim 21, wherein the binding protein further comprises a human heavy chain constant region selected from the group consisting of IgG1, IgG2a, IgG2b, and IgG3.
23. A hybridoma produced from the B cell of claim 1.
24. A nucleic acid isolated according to the method of claim 1.
25. The method of claim 1, further comprising isolating the heavy chain variable region nucleic acid from the B cell.
26. A method for making a somatically mutated heavy chain variable domain and/or obtaining a nucleic acid sequence encoding same, the method comprising immunizing a mouse with an antigen such that the mouse comprises a heavy chain variable domain that specifically binds the antigen, a B cell that makes the heavy chain variable domain, and/or a nucleic acid sequence that encodes the heavy chain variable domain, wherein the mouse further comprises a germline deletion of at least part of a nucleotide sequence encoding a CH1 domain of at least one endogenous IgG constant region, and wherein the mouse expresses an endogenous mouse IgM that comprises a functional CH1 domain and a secreted IgG heavy chain antibody that lacks a functional CH1 domain.
27. The method of claim 1, wherein the mouse is immunized with the antigen prior to isolating (i) the heavy chain variable domain that specifically binds an antigen, (ii) the B cell that expresses an IgM- or an IgG-encoding nucleotide sequence comprising a heavy chain variable region nucleic acid that encodes the heavy chain variable domain, and/or (iii) the heavy chain variable region nucleic acid.

28. The method of claim 26, further comprising isolating from the mouse the heavy chain variable domain that specifically binds the antigen, the B cell that makes the heavy chain variable domain, and/or the nucleic acid sequence that encodes the heavy chain variable domain.