

CLAIMS

1. A method for generating a fully human antibody specific against an antigen comprising the steps of:
- 5 (a) immunizing a mouse with the antigen, wherein the mouse has undergone immunoglobulin gene sequence rearrangement so that it comprises a B cell that comprises:
- (i) a rearranged human heavy chain variable region sequence operably linked to a mouse heavy chain constant region sequence, the rearranged human heavy chain variable region sequence comprising a human V_H gene segment, a human D_H gene segment, and a human J_H
- 10 gene segment; and
- (ii) a rearranged human light chain variable region sequence operably linked to a light chain constant region sequence, the rearranged human light chain variable region sequence comprising a human V_L gene segment and a human J_L gene segment; wherein, the B cell further comprises in its genome an inserted nucleic acid sequence encoding a
- 15 mouse ADAM6 protein that is functional in a male mouse;
- (b) isolating at least one splenocyte or B cell from the mouse producing an antibody specific against the antigen;
- (c) generating at least one cell producing a fully human antibody, which includes a human variable domain encoded by a human variable region sequence found in the at least one
- 20 splenocyte or B cell of step (b), wherein the fully human antibody is specific against the antigen;
- (d) culturing the at least one cell producing the fully human antibody of step (c); and
- (e) obtaining the fully human antibody of step (d).
- 25 2. A method for generating a fully human antibody specific against an antigen comprising the steps of:
- (a) expressing in a mammalian cell said fully human antibody comprising two human light chains and two human heavy chains, wherein each human light chain includes a human light chain domain encoded by a human light chain variable region sequence and each human
- 30 heavy chain includes a human heavy chain variable domain encoded by a human heavy chain variable region sequence, wherein one or more human variable region sequences were derived by:
- (i) immunizing a mouse with the antigen, wherein the mouse has undergone immunoglobulin gene sequence rearrangement so that it comprises a B cell that comprises:

- (A) a rearranged human heavy chain variable region sequence operably linked to a mouse heavy chain constant region sequence, the rearranged human heavy chain variable region sequence comprising a human V_H gene segment, a human D_H gene segment, and a human J_H gene segment; and
- 5 (B) a rearranged human light chain variable region sequence operably linked to a light chain constant region sequence, the rearranged human light chain variable region sequence comprising a V_L gene segment and a human J_L gene segment;
- wherein the B cell further comprises in its genome an inserted nucleic acid sequence encoding a mouse ADAM6 protein that is functional in a male mouse;
- 10 (ii) isolating at least one splenocyte or B cell producing an antibody specific against the antigen from the mouse; and
- (iii) determining one or more human variable region sequences of the antibody produced from the at least one splenocyte or B cell;
- (b) culturing the mammalian cell so that the fully human antibody is produced; and
- 15 (c) obtaining said fully human antibody.
3. The method of claim 1, wherein the fully human antibody is a monoclonal antibody.
4. The method of claim 1, wherein immunizing with the antigen of step (a) is carried out with
- 20 protein, DNA, a combination of DNA and protein, or cells expressing the antigen.
5. The method of claim 1, wherein the inserted nucleic acid sequence encoding a mouse ADAM6 protein is on a transgene driven by a heterologous promoter.
- 25 6. The method of claim 5, wherein the heterologous promoter is a non-immunoglobulin promoter.
7. The method of claim 1, wherein the mouse heavy chain constant region sequence comprises a mouse heavy chain sequence selected from the group consisting of a C_H1 , a
- 30 hinge, a C_H2 , a C_H3 , and a combination thereof.
8. The method of claim 1, wherein a majority of the B cells of the mouse comprise the inserted nucleic acid sequence encoding a mouse ADAM6 protein.

9. The method of claim 1, wherein at least 90% of the B cells of the mouse comprise in their genome the inserted nucleic acid sequence encoding a mouse ADAM6 protein.
10. The method of claim 1, wherein the culturing in step (c) is performed on at least one
5 hybridoma cell generated from the at least one cell obtained in step (b).
11. The method of claim 1, wherein an inserted nucleic acid sequence encoding a mouse ADAM6 protein
(A) is present on the same chromosome as the rearranged immunoglobulin sequence; and/or
10 (B) is present at an ectopic position.
12. The method of claim 2, wherein the fully human antibody is a monoclonal antibody.
13. The method of claim 2, wherein immunizing with the antigen of step (i) is carried out
15 with protein, DNA, a combination of DNA and protein, or cells expressing the antigen.
14. The method of claim 2, wherein the inserted nucleic acid sequence encoding a mouse ADAM6 protein is on a transgene driven by a heterologous promoter.
- 20 15. The method of claim 14, wherein the heterologous promoter is a non-immunoglobulin promoter.
16. The method of claim 2, wherein the mouse heavy chain constant region sequence comprises a mouse heavy chain sequence selected from the group consisting of a C_H1, a
25 hinge, a C_H2, a C_H3, and a combination thereof.
17. The method of claim 2, wherein a majority of the B cells of the mouse comprise the inserted nucleic acid sequence encoding a mouse ADAM6 protein.
- 30 18. The method of claim 2, wherein at least 90% of the B cells of the mouse comprise in their genome the inserted nucleic acid sequence encoding a mouse ADAM6 protein.
19. The method of claim 2, wherein an inserted nucleic acid sequence encoding a mouse ADAM6 protein

(a) is present on the same chromosome as the rearranged immunoglobulin sequence; and/or
(b) is present at an ectopic position.

20. The method of claim 1, wherein the V_L gene segment is V_κ1-5, V_κ1-6, V_κ1-8, V_κ1-9,
5 V_κ1-12, V_κ1-16, V_κ1-17, V_κ1-27, V_κ1-33, V_κ1-37, V_κ1-39, V_κ2-24, V_κ2-28, V_κ2-29,
V_κ2-30, V_κ2-40, V_κ3-11, V_κ3-15, V_κ3-20, V_κ4-1, or V_κ6-21.

21. The method of claim 2, wherein the V_L gene segment is V_κ1-5, V_κ1-6, V_κ1-8, V_κ1-9,
V_κ1-12, V_κ1-16, V_κ1-17, V_κ1-27, V_κ1-33, V_κ1-37, V_κ1-39, V_κ2-24, V_κ2-28, V_κ2-29,
10 V_κ2-30, V_κ2-40, V_κ3-11, V_κ3-15, V_κ3-20, V_κ4-1, or V_κ6-21.

22. The method of claim 1, wherein the V_H gene segment is V_H6-1, V_H1-2, V_H1-3, V_H2-5,
V_H3-7, V_H1-8, V_H3-9, V_H3-11, V_H3-13, V_H3-15, V_H3-16, V_H1-18, V_H3-20, V_H3-21, V_H3-23,
V_H1-24, V_H2-26, V_H4-28, V_H3-30, V_H4-31, V_H3-33, V_H4-34, V_H3-35, V_H3-38, V_H4-39, V_H3-
15 43, V_H1-45, V_H1-46, V_H3-48, V_H3-49, V_H5-51, V_H3-53, V_H1-58, V_H4-59, V_H4-61, V_H3-64,
V_H3-66, V_H1-69, V_H2-70, V_H3-72, V_H3-73 or V_H3-74.

23. The method of claim 2, wherein the V_H gene segment is V_H6-1, V_H1-2, V_H1-3, V_H2-5,
V_H3-7, V_H1-8, V_H3-9, V_H3-11, V_H3-13, V_H3-15, V_H3-16, V_H1-18, V_H3-20, V_H3-21, V_H3-23,
20 V_H1-24, V_H2-26, V_H4-28, V_H3-30, V_H4-31, V_H3-33, V_H4-34, V_H3-35, V_H3-38, V_H4-39, V_H3-
43, V_H1-45, V_H1-46, V_H3-48, V_H3-49, V_H5-51, V_H3-53, V_H1-58, V_H4-59, V_H4-61, V_H3-64,
V_H3-66, V_H1-69, V_H2-70, V_H3-72, V_H3-73 or V_H3-74.