We claim:

1. A mouse having a genome comprising a modification of an immunoglobulin heavy chain locus, wherein the modification reduces or eliminates endogenous ADAM6 function, and the mouse further comprises a nucleic acid sequence encoding a mouse ADAM6 protein or an ortholog or homolog thereof or a functional fragment of the corresponding ADAM6 protein.

2. The mouse of claim 1, wherein said nucleic acid sequence is positioned at an ectopic position.

3. The mouse of claim 1 or 2, wherein the nucleic acid sequence is at an endogenous immunoglobulin locus.

4. The mouse of claim 1 or 2, wherein the nucleic acid sequence is integrated into the mouse genome at a position other than an endogenous immunoglobulin locus.

5. The mouse of any one of claims 1-4, wherein the modification of the immunoglobulin heavy chain locus comprises the placement of one or more human immunoglobulin gene sequences.

6. The mouse of any one of claims 1-4, wherein the modification of the immunoglobulin heavy chain locus comprises the replacement of one or more sequences in an mouse immunoglobulin heavy chain locus with one or more human immunoglobulin gene sequences.

7. The mouse of claim 6, wherein the modification of the immunoglobulin heavy chain locus comprises the replacement of one or more endogenous heavy chain V (V_H) gene segments with one or more human heavy chain V (V_H) gene segments.

8. The mouse of claim 1, wherein the modification of the immunoglobulin heavy chain locus comprises the replacement of an endogenous heavy chain variable gene sequence with a human heavy chain variable gene sequence.

9. The mouse of any one of claims 1-8, wherein the nucleic acid sequence encodes a mouse ADAM6a protein and/or ADAM6b protein, or an ortholog, a homolog or a functional fragment thereof.

10. A method for modifying an immunoglobulin heavy chain locus of a mouse, comprising:

(a) making a first modification of the mouse immunoglobulin heavy chain locus that results in a reduction or elimination of endogenous mouse ADAM6 activity in a male mouse; and,

(b) making a second modification of the mouse to add a nucleic acid sequence that confers upon the mouse ADAM6 activity that is functional in a male mouse.

11. The method according to claim 10, wherein the nucleic acid sequence in step (b) is added at an ectopic position.

12. The method according to claim 10 or 11, wherein the first modification comprises the placement of one or more human immunoglobulin gene sequences.

13. The method according to claim 10 or 11, wherein the first modification comprises the replacement of one or more sequences in the mouse immunoglobulin heavy chain locus with one or more human immunoglobulin gene sequences.

14. The method according to claim 13, wherein the first modification comprises the replacement of one or more endogenous V_H gene segments with one or more human V_H gene segments.

15. The method according to claim 10, wherein the first modification comprises the replacement of an endogenous heavy chain variable gene sequence with a human heavy chain variable gene sequence.

16. The method according to any one of claims 10-15, wherein the first and the second modification are made simultaneously.

17. A mouse obtainable by the method of any one of claims 10-16.

18. An isolated cell from a mouse of any one of claims 1-9 and 17.

19. An isolated tissue from a mouse of any one of claims 1-9 and 17.

20. Use of a mouse according to any one of claims 1-9 and 17 for the generation of a

human-mouse reverse chimeric antibody, a fully human antibody, a fully human Fab fragment, and/or a fully human $F(ab)_2$ fragment.

21. A method for generating a reverse-chimeric mouse-human antibody specific against an antigen comprising the steps of:

a) immunizing a mouse according to any one of claims 1-9 and 17 with the antigen;

b) isolating at least one cell from the mouse producing a reverse-chimeric mouse-human antibody specific against the antigen; and

c) culturing at least one cell producing an antibody of step b) and obtaining said antibody.

22. The method of claim 21, wherein the culturing in step c) is performed on at least one hybridoma cell generated from the at least one cell obtained in step b).

23. A method for generating a fully human antibody specific against an antigen comprising the steps of:

a) immunizing a mouse according to any one of claims 1-9 and 17 with the antigen;

b) isolating at least one cell from the mouse producing a reverse-chimeric mouse-human antibody specific against the antigen;

c) generating at least one cell producing a fully human antibody derived from the antibody of step b) and specific against the antigen; and

d) culturing at least one cell producing an antibody of step c) and obtaining said antibody.

24. The method of any one of claims 21 and 23, wherein the at least one cell obtained in step b) is a splenocyte or a B cell.

25. The method of any one of claims 21-24, wherein the antibody is a monoclonal antibody.

26. The method of any one of claims 21-25, wherein immunizing with the antigen of step a) is carried out with protein, DNA, a combination of DNA and protein, or cells expressing the antigen.

27. Use of a nucleic acid sequence encoding a mouse ADAM6 protein or an ortholog or homolog thereof or a functional fragment of the corresponding ADAM6 protein for restoring or enhancing the fertility of a mouse having a genome comprising a modification of an immunoglobulin heavy chain locus, wherein the modification reduces or eliminates endogenous ADAM6 function.

28. The use of claim 27, wherein said nucleic acid sequence is integrated into the genome of the mouse at an ectopic position.

29. The use of claim 27 or 28, wherein said nucleic acid sequence is integrated into the genome of the mouse at an endogenous immunoglobulin locus.

30. The use of claim 27 or 28, wherein the nucleic acid sequence is integrated into the genome of the mouse at a position other than an endogenous immunoglobulin locus.

We claim:

1. A genetically modified mouse whose genome comprises:

a) ectopic placement of an ADAM6 gene that is functional in a male mouse; and

b) a modified immunoglobulin heavy chain variable region locus comprising an insertion of one or more human VH gene segments, one or more human DH gene segments, and one or more human JH gene segments into the endogenous heavy chain locus, wherein the human VH, DH and JH gene segments are operably linked to a heavy chain constant region gene.

2. The mouse of claim 1, wherein the insertion reduces or eliminates Adam6 activity of a cell or tissue of a male mouse.

3. The mouse of claim 1, wherein the ADAM6 gene is present at the modified heavy chain variable region locus.

4. The mouse of claim 1, wherein the ADAM6 gene is present at a position other than the modified heavy chain variable gene locus.

5. The mouse of claim 1, wherein the ADAM6 gene includes mouse ADAM6a and/or mouse ADAM6b.

6. The mouse of claim 1, wherein the modified immunoglobulin heavy chain variable region locus comprises an insertion of a plurality of human V_H gene segments, a plurality of human D_H gene segments, and a plurality of human J_H gene segments.

7. The mouse of claim 6, wherein the plurality of human V_H gene segments includes at least 18, at least 39, or at least 80 human V_H gene segments.

8. The mouse of claim 6, wherein the modified immunoglobulin heavy chain variable region locus comprises at least 18 human V_H gene segments, 27 human D_H gene segments, and six human J_H gene segments.

9. The mouse of claim 6, wherein the modified immunoglobulin heavy chain variable region locus comprises at least 39 human V_H gene segments, 27 human D_H gene segments and six human J_H gene segments.

10. The mouse of claim 6, wherein the modified immunoglobulin heavy chain variable region locus comprises 80 human V_H gene segments, 27 human D_H gene segments, and six human J_H gene segments.

11. The mouse of claim 6, wherein the plurality of human V_H gene segments, plurality of human D_H gene segments, and plurality of human J_H gene segments are operably linked to a rodent heavy chain constant region gene.

12. The mouse of claim 11, wherein the constant region gene is a mouse constant region gene.

13. The mouse of claim 12, wherein the mouse constant region gene comprises a constant region selected from a CH_1, a hinge, a CH_2, a CH_3 and/or a CH_4 or a combination thereof.

14. The mouse of claim 12, wherein the mouse constant region comprises CH_2 and CH_3 regions.

15. The mouse of claim 6, further comprising one or more human $V\kappa$ gene segments and one or more human $J\kappa$ gene segments.

16. The mouse of claim 15, wherein the one or more human $V\kappa$ gene segments and one or more human $J\kappa$ gene segments are present at an endogenous immunoglobulin κ light chain locus.

17. An isolated mouse cell whose genome comprises:

(a) ectopic placement of an ADAM6 gene; and

(b) a human immunoglobulin heavy chain variable region locus comprising an insertion of one or more human VH gene segments, one or more human DH gene segments, and one or more human JH gene segments into the endogenous heavy chain locus, wherein the human VH, DH and JH gene segments are operably linked to a heavy chain constant region gene.

18. The isolated mouse cell of claim 17, wherein the heavy chain constant region comprises mouse CH_2 and CH_3 regions.

19. The isolated cell of claim 17, wherein the cell is an embryonic stem cell.

20. A mouse embryo generated from the embryonic stem cell of claim 19.

20. The isolated cell of claim 17, wherein the cell is a B cell.

21. A hybridoma made from the B cell of claim 20.

22. An immortalized cell made from the isolated cell of claim 17.

23. A method of providing a chimeric antibody specific for an antigen of interest, the method comprising the steps of:

(a) immunizing a mouse of claim 1 with the antigen of interest;

(b) isolating at least one B cell from the mouse producing a chimeric antibody specific against the antigen, which chimeric antibody comprises human variable regions and mouse constant regions; and

(c) culturing at least one B cell producing the chimeric antibody of step b) and obtaining said chimeric antibody.

24. The method of claim 23, wherein the culturing in step (c) is performed on at least one hybridoma cell generated from the at least one B cell obtained in step (b).

25. The method of claim 23, wherein the at least one B cell obtained in step (b) is derived from the spleen, a lymph node or bone marrow of the mouse from step (a).

26. The method of claim 23, wherein immunizing with the antigen of interest in step (a) is carried out with protein, DNA, a combination of DNA and protein, or cells expressing the antigen.

27. The method of claim 23, wherein the mouse constant regions comprise mouse CH_2 and CH_3 regions.