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 Vκ gene segments and one or more human Jκ gene segments.

16. The mouse of claim 15, wherein the one or more human Vκ gene segments and one or more human Jκ 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.

CLAIMS

We claim:

1. A genetically modified mouse 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 V_H gene segments, one or more human D_H gene segments, and one or more human J_H gene segments into the endogenous mouse heavy chain locus, wherein the human V_H, D_H and J_H gene segments are operably linked to a heavy chain constant region gene;

so that the mouse is characterized in that:

(i) it is fertile; and

(ii) when it is immunized with an antigen, it generates antibodies comprising heavy chain variable domains encoded by the one or more human V_H, one or more human D_H, and one or more human J_H gene segments, linked to heavy chain constant domains encoded by the heavy chain constant region gene, wherein the antibodies show specific binding to the antigen.

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 human heavy chain variable region locus.

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

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

6. The mouse of claim 1, wherein the one or more human V_H gene segments includes at least 18, at least 39, or at least 80 human V_H gene segments.

7. The mouse of claim 1, wherein the human immunoglobulin heavy chain variable region locus comprises at least 18 human V_H gene segments, at least one and up to 27 human DH gene segments, and at least one and up to six human J_H gene segments.

8. The mouse of claim 1, wherein the human immunoglobulin heavy chain variable region locus comprises at least 39 human V_H gene segments, at least one and up to 27 human DH gene segments and at least one and up to six human J_H gene segments.

9. The mouse of claim 1, wherein the human immunoglobulin heavy chain variable region locus comprises 80 human V_H gene segments, at least one and up to 27 human DH gene segments, and at least one and up to six human J_H gene segments.

10. The mouse of claim 1, wherein the constant region gene is a mouse constant region gene.

11. The mouse of claim 10, 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.

12. The mouse of claim 1, further comprising an insertion of one or more human Vκ gene segments and one or more human Jκ gene segments into the endogenous κ light chain locus.

13. The mouse of claim 12, wherein the one or more human Vκ gene segments and one or more human Jκ gene segments are operably linked to a rodent light chain constant region gene.

14. 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 V_H gene segments, one or more human D_H gene segments, and one or more human J_H gene segments into the endogenous heavy chain locus, wherein the human V_H, D_H and J_H gene segments are operably linked to a heavy chain constant region gene.

15. The isolated cell of claim 14, wherein the cell is an embryonic stem cell.

16. A mouse embryo generated from the embryonic stem cell of claim 15.

17. The isolated cell of claim 14, wherein the cell is a B cell.

18. A hybridoma made from the B cell of claim 17.

19. An immortalized cell made from the isolated cell of claim 14.

20. A method of providing an 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, which mouse has a genome comprising (a) and (b) of claim 1;

(b) isolating at least one B cell from the mouse producing an antibody specific against the antigen; and

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

21. The method of claim 20, wherein step (c) further comprises making a hybridoma employing the cell of step (b) and culturing the hybridoma.

22. The method of claim 20, 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).

23. The method of claim 20, 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.