

We claim:

1. A method for making an antibody that binds to an antigen of interest, wherein the method comprises:

culturing a host cell comprising a first nucleotide sequence including a human light chain variable region sequence operably linked to a human light chain constant region sequence and a second nucleotide sequence including a human heavy chain variable region sequence operably linked to a human heavy chain constant region sequence, so that an antibody that binds to the antigen of interest including a light chain encoded by the first nucleotide sequence and a heavy chain encoded by the second nucleotide sequence is expressed, wherein the human light chain variable region sequence and the human heavy chain variable region sequence were identified from a B cell of a genetically modified mouse exposed to the antigen of interest that includes in its genome:

(i) an insertion of one or more human V λ gene segments and one or more human J λ gene segments upstream of a mouse immunoglobulin light chain constant region gene, wherein the one or more human V λ gene segments and one or more human J λ gene segments are operably linked to the mouse immunoglobulin light chain constant region gene,

(ii) 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 upstream of a mouse immunoglobulin heavy chain constant region gene, wherein the 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 are operably linked to the mouse immunoglobulin heavy chain constant region gene, and

(iii) an inserted nucleotide sequence that encodes an ADAM6 protein or a functional fragment thereof, wherein the ADAM6 protein is expressed from the inserted nucleic acid sequence.

2. The method of claim 1, wherein the mouse immunoglobulin light chain constant region gene is a mouse C κ .

3. The method of claim 1, wherein the mouse immunoglobulin light chain constant region gene is a mouse C λ .

4. The method of claim 3, wherein the mouse C λ is a mouse C λ 2.

5. The method of claim 3, wherein the mouse C λ is at least 90% identical to mouse

CA2.

6. The method of claim 1, wherein the insertion of the one or more human V λ gene segments and one or more human J λ gene segments upstream of the mouse immunoglobulin light chain constant region gene comprises an insertion of at least 12 human V λ gene segments and at least one human J λ gene segment.

7. The method of claim 1, wherein the insertion of the one or more human V λ gene segments and one or more human J λ gene segments upstream of the mouse immunoglobulin light chain constant region gene comprises an insertion of at least 28 human V λ gene segments and at least one human J λ gene segment.

8. The method of claim 1, wherein the insertion of the one or more human V λ gene segments and one or more human J λ gene segments upstream of the mouse immunoglobulin light chain constant region gene comprises an insertion of at least 40 human V λ gene segments and at least one human J λ gene segment.

9. The method of claim 1, wherein the inserted nucleotide sequence that encodes an ADAM6 protein or a functional fragment thereof is present at the immunoglobulin heavy chain locus of the mouse.

10. The method of claim 9, wherein the inserted nucleotide sequence that encodes an ADAM6 protein or a functional fragment thereof is positioned between two human gene segments included in the 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.

11. The method of claim 10, wherein the inserted nucleotide sequence that encodes an ADAM6 protein or a functional fragment thereof is positioned between two human V_H gene segments.

12. The method of claim 10, wherein the inserted nucleotide sequence that encodes an ADAM6 protein or a functional fragment thereof is positioned between a V_H gene segment and a D_H gene segment.

13. The method of claim 1, wherein the inserted nucleotide sequence that encodes an ADAM6 protein or a functional fragment thereof is on the same chromosome as the insertion of the 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.

14. The method of claim 1, wherein the inserted nucleotide sequence that encodes an ADAM6 protein or a functional fragment thereof is present at a position other than the immunoglobulin heavy chain locus of the mouse.

15. The method of claim 1, wherein the mouse further comprises a human V_κ-J_κ intergenic region from a human κ light chain locus, wherein the human V_κ-J_κ intergenic region is contiguous with the one or more human V_λ gene segments and one or more human J_λ gene segments.

16. The method of claim 15, wherein the human V_κ-J_κ intergenic region is placed between a human V_λ gene segment and a human J_λ gene segment.

17. The method of claim 15, wherein the human V_κ-J_κ intergenic region comprises SEQ ID NO: 158.

18. The method of claim 1, wherein the method further comprises:

- exposing the genetically modified mouse to the antigen of interest;
- isolating at least one B lymphocyte of the genetically modified mouse, wherein the at least one B lymphocyte expresses an antibody that binds the antigen of interest, wherein the expressed antibody includes an immunoglobulin light chain that is encoded by a nucleic acid comprising the human light chain variable region sequence operably linked to a mouse immunoglobulin light chain constant region gene;
- identifying the human light chain variable region sequence;
- ligating the human light chain variable region sequence to a nucleic acid sequence that encodes a human immunoglobulin light chain constant region sequence, thereby generating the first nucleotide sequence including a human light chain variable region sequence operably linked to a human light chain constant region sequence;
- identifying the human heavy chain variable region sequence;
- ligating the human heavy chain variable region sequence to a nucleic acid sequence that encodes a human immunoglobulin heavy chain constant region sequence, thereby generating the second nucleotide sequence including a human heavy chain variable region sequence operably linked to a human heavy chain constant region sequence; and
- introducing the first and second nucleotide sequences into the host cell, wherein the host cell expresses an antibody that binds to the antigen of interest.

19. The method of claim 1, where the method further comprises:
recovering the antibody expressed in the host cell.