

What is claimed is:

1. A method of testing a human antibody comprising administering the antibody to a rodent comprising in its genome:

an immunoglobulin heavy chain locus that comprises:

- (i) an immunoglobulin heavy chain variable region comprising a V_H gene segment, a D_H gene segment and a J_H gene segment; and
- (ii) an immunoglobulin heavy chain constant region comprising:
 - (a) a C_H gene segment encoding an IgG constant domain comprising a human IgG1 C_{H1} domain, a human IgG1 hinge region, a human IgG1 C_{H2} domain, a human IgG1 C_{H3} domain, an IgG transmembrane domain and an IgG cytoplasmic domain, and/or
 - (b) a C_H gene segment encoding an IgG constant domain comprising a human IgG4 C_{H1} domain, a human IgG4 hinge region, a human IgG4 C_{H2} domain, a human IgG4 C_{H3} domain, an IgG transmembrane domain and an IgG cytoplasmic domain

wherein the immunoglobulin heavy chain variable region is operably linked to the immunoglobulin heavy chain constant region such that the rodent produces IgG antibodies comprising variable domains derived from the V_H gene segment, the D_H gene segment and the J_H gene segment and heavy chain constant domains derived from the C_H gene segment,

wherein the human antibody being tested comprises a human $CH1$, a human $CH2$, and a human $CH3$ domains of a human isotype that is present in the rodent immunoglobulin heavy chain constant region,

wherein the immunoglobulin heavy chain locus is positioned at an endogenous immunoglobulin heavy chain locus.

2. The method of claim 1, wherein the IgG transmembrane domain encoded by one or more of the C_H gene segments is a rodent or human IgG transmembrane domain.

3. The method of claim 1 or 2, wherein the IgG cytoplasmic domain encoded by one or more of the C_H gene segments is a rodent or human IgG cytoplasmic domain.

4. The method of claim 1, wherein:

- (a) the IgG1 domain is encoded by an allele selected from IGHG1*01, IGHG1*02, IGHG1*03, IGHG1*04 and IGHG1*05;
- (b) the IgG4 domain is encoded by an allele selected from IGHG4*01, IGHG4*02, IGHG4*03 and IGHG4*04;
- (c) the C_{γ2} gene segment is an allele selected from IGHG2*01, IGHG2*02, IGHG2*03, IGHG2*04, IGHG2*05 and IGHG2*06;
- (c) the C_{γ3} gene segment is an allele selected from IGHG3*01, IGHG3*02, IGHG3*03, IGHG3*04, IGHG3*05, IGHG3*06, IGHG3*07, IGHG3*08, IGHG3*09, IGHG3*10, IGHG3*11, IGHG3*12, IGHG3*13, IGHG3*14, IGHG3*15, IGHG3*16, IGHG3*17, IGHG3*18 and IGHG3*19,

and wherein the heavy chain constant domain of the human antibody is encoded by the same allele.

5. The method of claim 1, wherein:

- (a) one of the C_H gene segments is located at an endogenous C_{γ2a} or C_{γ2c} gene segment locus;
- (b) one of the C_H gene segments is located at an endogenous C_{γ1} gene segment locus;
- (c) one of the C_H gene segments is located at an endogenous C_{γ3} gene segment locus; and/or
- (d) one of the C_H gene segments is located at an endogenous C_{γ2b} gene segment locus.

6. The method of claim 1, wherein the immunoglobulin heavy chain constant region comprises a human C_μ gene segment, a human C_δ gene segment, a human C_{γ3} gene segment and a human C_{γ1} gene segment.

7. The method of claim 6, wherein the immunoglobulin heavy chain constant region further comprises a human C_{γ2} gene segment and a human C_{γ4} gene segment.

8. The method of any one of claims 1 to 7, wherein the immunoglobulin heavy chain locus further comprises a rodent or human intronic enhancer (E_i), and/or a rodent or human 3' regulatory region (3' RR).
9. The method of any one of claims 1 to 8, wherein the immunoglobulin heavy chain locus further comprises a rodent or human S_μ switch site, a rodent or human $S_{\gamma 3}$ switch site, a rodent or human $S_{\gamma 1}$ switch site, a rodent $S_{\gamma 2b}$ switch site, a rodent $S_{\gamma 2a}$, a rodent $S_{\gamma 2c}$ switch site, a human $S_{\gamma 2}$ switch site, a human $S_{\gamma 4}$ switch site, a rodent or human S_ϵ switch site, and/or a rodent or human S_α switch site.
10. The method of any one of claims 1 to 9, wherein the V_H gene segment is a rodent V_H gene segment, the D_H gene segment is a rodent D_H gene segment and the J_H gene segment is a rodent J_H gene segment.
11. The method of any one of claims 1 to 9, wherein the V_H gene segment is a human V_H gene segment, the D_H gene segment is a human D_H gene segment and the J_H gene segment is a human J_H gene segment.
12. The method of any one *claims* 1 to 11, wherein the immunoglobulin heavy chain locus replaces all or part of the endogenous immunoglobulin heavy chain locus.
13. The method of claim 1, wherein the rodent comprises in its genome an endogenous immunoglobulin heavy chain locus that comprises:
- (i) an immunoglobulin heavy chain variable region comprising a human V_H gene segment, a human D_H gene segment and a human J_H gene segment;
 - (ii) a rodent intronic enhancer (E_i);
 - (iii) an immunoglobulin heavy chain constant region comprising:
 - (a) a rodent C_μ gene segment;
 - (b) a rodent C_δ gene segment;
 - (c) a rodent $C_{\gamma 3}$ gene segment;
 - (d) a rodent $C_{\gamma 1}$ gene segment;
 - (e) a rodent $C_{\gamma 2b}$ gene segment;
 - (f) a modified C_H gene segment encoding a human IgG1 C_{H1} domain, a human IgG1 hinge region, a human IgG1 C_{H2} domain, a

human IgG1 C_H3 domain, a rodent IgG2a transmembrane domain,
and a rodent IgG2a cytoplasmic domain;

(g) a rodent C_ε gene segment; and

(h) a rodent C_α gene segment; and

(iv) a rodent 3' regulatory region (3' RR),

wherein the immunoglobulin heavy chain variable region is operably linked to the immunoglobulin heavy chain constant region such that the rodent produces IgG antibodies comprising variable domains derived from the human V_H gene segment, the human D_H gene segment and the human J_H gene segment and heavy chain constant domains derived from the modified C_H gene segment.

14. The method of claim 1, wherein the rodent comprises in its genome:
an endogenous immunoglobulin heavy chain locus that comprises:

(i) an immunoglobulin heavy chain variable region comprising a human V_H gene segment, a human D_H gene segment and a human J_H gene segment;

(ii) a rodent intronic enhancer (E_i);

(iii) an immunoglobulin heavy chain constant region comprising:

(a) a rodent C_μ gene segment;

(b) a rodent C_δ gene segment;

(c) a rodent C_γ3 gene segment;

(d) a rodent C_γ1 gene segment;

(e) a rodent C_γ2b gene segment;

(f) a modified C_H gene segment encoding a human IgG1 C_H1 domain, a human IgG1 hinge region, a human IgG1 C_H2 domain, a human IgG1 C_H3 domain, a human IgG1 transmembrane domain, and a human IgG1 cytoplasmic domain;

(g) a rodent C_ε gene segment; and

(h) a rodent C_α gene segment; and

(iv) a rodent 3' regulatory region (3' RR),

wherein the immunoglobulin heavy chain variable region is operably linked to the immunoglobulin heavy chain constant region such that the rodent produces

IgG antibodies comprising variable domains derived from the human V_H gene segment, the human D_H gene segment and the human J_H gene segment and heavy chain constant domains derived from the modified C_H gene segment.

15. The method of claim 1, wherein the rodent comprises in its genome: an endogenous immunoglobulin heavy chain locus that comprises:
- (i) an immunoglobulin heavy chain variable region comprising a human V_H gene segment, a human D_H gene segment and a human J_H gene segment;
 - (ii) a rodent intronic enhancer (E_i);
 - (iii) an immunoglobulin heavy chain constant region comprising:
 - (a) a rodent C_μ gene segment;
 - (b) a rodent C_δ gene segment;
 - (c) a rodent $C_{\gamma 3}$ gene segment;
 - (d) a modified C_H gene segment encoding a human IgG4 C_{H1} domain, a human IgG4 hinge region, a human IgG4 C_{H2} domain, a human IgG4 C_{H3} domain, a rodent IgG1 transmembrane domain, and a rodent IgG1 cytoplasmic domain;
 - (e) a rodent $C_{\gamma 2b}$ gene segment;
 - (f) a rodent $C_{\gamma 2a}$ and/or $C_{\gamma 2c}$ gene segment;
 - (g) a rodent C_ϵ gene segment; and
 - (h) a rodent C_α gene segment; and
 - (iv) a rodent 3' regulatory region (3' RR),

wherein the immunoglobulin heavy chain variable region is operably linked to the immunoglobulin heavy chain constant region such that the rodent produces IgG antibodies comprising variable domains derived from the human V_H gene segment, the human D_H gene segment and the human J_H gene segment and heavy chain constant domains derived from the modified C_H gene segment.

16. The method of claim 1, wherein the rodent comprises in its genome: an endogenous immunoglobulin heavy chain locus that comprises:

- (i) an immunoglobulin heavy chain variable region comprising a human V_H gene segment, a human D_H gene segment and a human J_H gene segment;
- (ii) a rodent intronic enhancer (E_i);
- (iii) an immunoglobulin heavy chain constant region comprising:
 - (a) a rodent C_μ gene segment;
 - (b) a rodent C_δ gene segment;
 - (c) a rodent $C_{\gamma 3}$ gene segment;
 - (d) a modified C_H gene segment encoding a human IgG4 C_{H1} domain, a human IgG4 hinge region, a human IgG4 C_{H2} domain, a human IgG4 C_{H3} domain, a human IgG4 transmembrane domain, and a human IgG4 cytoplasmic domain;
 - (e) a rodent $C_{\gamma 2b}$ gene segment;
 - (f) a rodent $C_{\gamma 2a}$ and/or $C_{\gamma 2c}$ gene segment;
 - (g) a rodent C_ϵ gene segment; and
 - (h) a rodent C_α gene segment; and
- (iv) a rodent 3' regulatory region (3' RR),

wherein the immunoglobulin heavy chain variable region is operably linked to the immunoglobulin heavy chain constant region such that the rodent produces IgG antibodies comprising variable domains derived from the human V_H gene segment, the human D_H gene segment and the human J_H gene segment and heavy chain constant domains derived from the modified C_H gene segment.

17. The method of claim 1, wherein the rodent comprises in its genome: an endogenous immunoglobulin heavy chain locus that comprises:

- (i) an immunoglobulin heavy chain variable region comprising a human V_H gene segment, a human D_H gene segment and a human J_H gene segment;
- (ii) a human intronic enhancer (E_i);
- (iii) an immunoglobulin heavy chain constant region comprising:
 - (a) a human C_μ gene segment;
 - (b) a human C_δ gene segment;

- (c) a human $C_{\gamma 3}$ gene segment;
- (d) a human $C_{\gamma 1}$ gene segment; and
- (iv) a rodent 3' regulatory region (3' RR),

wherein the immunoglobulin heavy chain variable region is operably linked to the immunoglobulin heavy chain constant region such that the rodent produces IgG antibodies comprising a fully human heavy chain.

18. The method of claim 1, wherein the rodent comprises in its genome: an endogenous immunoglobulin heavy chain locus that comprises:

- (i) an immunoglobulin heavy chain variable region comprising a human V_H gene segment, a human D_H gene segment and a human J_H gene segment;
- (ii) a human intronic enhancer (E_i);
- (iii) an immunoglobulin heavy chain constant region comprising:
 - (a) a human C_{μ} gene segment;
 - (b) a human C_{δ} gene segment;
 - (c) a human $C_{\gamma 3}$ gene segment;
 - (d) a human $C_{\gamma 1}$ gene segment;
 - (c) a human $C_{\gamma 2}$ gene segment;
 - (d) a human $C_{\gamma 4}$ gene segment; and
- (iv) a rodent 3' regulatory region (3' RR),

wherein the immunoglobulin heavy chain variable region is operably linked to the immunoglobulin heavy chain constant region such that the rodent produces IgG antibodies comprising a fully human heavy chain.

19. The method of claim 1, wherein the rodent comprises in its genome: an endogenous immunoglobulin heavy chain locus that comprises:

- (i) an immunoglobulin heavy chain variable region comprising a rodent V_H gene segment, a rodent D_H gene segment and a rodent J_H gene segment;
- (ii) a rodent intronic enhancer (E_i);
- (iii) an immunoglobulin heavy chain constant region comprising:
 - (a) a human C_{μ} gene segment;

- (b) a human C_δ gene segment;
- (c) a human C_{γ3} gene segment;
- (d) a human C_{γ1} gene segment; and
- (iv) a rodent 3' regulatory region (3' RR),

wherein the immunoglobulin heavy chain variable region is operably linked to the immunoglobulin heavy chain constant region such that the rodent produces IgG antibodies comprising a heavy chain comprising a rodent variable domain and a human constant domain.

20. The method of claim 1, wherein the rodent comprises in its genome: an endogenous immunoglobulin heavy chain locus that comprises:

- (i) an immunoglobulin heavy chain variable region comprising a rodent V_H gene segment, a rodent D_H gene segment and a rodent J_H gene segment;
- (ii) a rodent intronic enhancer (E_i);
- (iii) an immunoglobulin heavy chain constant region comprising:
 - (a) a human C_μ gene segment;
 - (b) a human C_δ gene segment;
 - (c) a human C_{γ3} gene segment;
 - (d) a human C_{γ1} gene segment;
 - (e) a human C_{γ2} gene segment;
 - (f) a human C_{γ4} gene segment; and
- (iv) a rodent 3' regulatory region (3' RR),

wherein the immunoglobulin heavy chain variable region is operably linked to the immunoglobulin heavy chain constant region such that the rodent produces IgG antibodies comprising a heavy chain comprising a rodent variable domain and a human constant domain.

21. The method of any one of claims 1 to 20, wherein the rodent further comprises in its genome:

an immunoglobulin kappa (κ) chain locus that comprises:

- (1) an immunoglobulin κ chain variable region comprising a human V_κ gene segment and a human J_κ gene segment; and

- (2) an immunoglobulin κ chain constant region comprising a human C_κ gene segment,

wherein the immunoglobulin κ chain variable region is operably linked to the immunoglobulin κ chain constant region such that the rodent produces antibodies comprising light chain variable domains derived from the human V_κ gene segment and the human J_κ gene segment and light chain constant domains derived from the human C_κ gene segment

wherein the human antibody being tested comprises a κ light chain.

22. The method of claim 21, wherein the immunoglobulin κ chain locus is positioned at an endogenous immunoglobulin κ chain locus.

23. The method of any one of claims 1 to 20, wherein the rodent further comprises in its genome:

an immunoglobulin lambda (λ) chain locus that comprises:

a human V_λ gene segment, a human J_λ gene segment and a human C_λ gene segment,

wherein the human V_λ gene segment and the human J_λ gene segment are operably linked to the human C_λ gene segment such that the rodent produces antibodies comprising light chain variable domains derived from the human V_λ gene segment and the human J_λ gene segment and light chain constant domains derived from the human C_λ gene segment,

wherein the human antibody being tested comprises an λ light chain.

24. The method of claim 23, wherein the immunoglobulin λ chain locus is positioned at an endogenous immunoglobulin λ chain locus.

25. The method of any one of claims 1 to 24, wherein the rodent further comprises in its genome:

- (a) a neonatal Fc receptor (FcRn) locus comprising a nucleic acid sequence encoding a FcRn polypeptide comprising a human extracellular domain, a human or rodent transmembrane domain and a human or rodent cytoplasmic domain;
- (b) a β -2-microglobulin (β 2M) locus comprising a nucleic acid sequence encoding a human or humanized β -2-microglobulin (β 2M) polypeptide;

- (c) an Fc epsilon receptor 1 alpha (FcεR1α) locus comprising a nucleic acid sequence encoding FcεR1α polypeptide comprising a human extracellular domain, a human or rodent transmembrane domain and a human or rodent cytoplasmic domain;
 - (d) a Fc gamma receptor 1a (FcγR1a) locus comprising a nucleic acid sequence encoding FcγR1a polypeptide comprising a human extracellular domain, a human or rodent transmembrane domain and a human or rodent cytoplasmic domain;
 - (e) a Fc gamma receptor 2a (FcγR2a) locus comprising a nucleic acid sequence encoding a human FcγR2a polypeptide;
 - (f) a Fc gamma receptor 3a (FcγR3a) locus comprising a nucleic acid sequence encoding a human FcγR3a polypeptide;
 - (g) a Fc gamma receptor 3b (FcγR3b) locus comprising a nucleic acid sequence encoding a human FcγR3b polypeptide; and/or
 - (h) a Fc gamma receptor 2c (FcγR2c) locus comprising a nucleic acid sequence encoding a human FcγR2c polypeptide.
26. The method of any one claims of claims 1 to 25, wherein the rodent is a mouse.
27. The method of any one of claims 1 to 26, further comprising measuring the therapeutic efficacy of the administered human antibody.
28. The method of any one of claims 1 to 26, further comprising administering a plurality of doses of the human antibody and determining a therapeutic efficacy, safety, and/or tolerability of each dose of the human antibody.
29. The method of any one of claims 1 to 26, further comprising measuring the immune response generated by the rodent against the human antibody.