

CLAIMS

1. A non-human mammal or cell whose genome comprises an insertion of:
 - (a) a plurality of human IgH V regions, one or more human D regions and one or more human J regions upstream of a host non-human mammal constant region; and
 - (b) optionally a plurality of human Ig light chain kappa V regions and one or more human Ig light chain kappa J regions upstream of a host non-human mammal lambda or kappa constant region and/or a plurality of human Ig light chain lambda V regions and one or more human Ig light chain lambda J regions upstream of a host non-human mammal lambda or kappa constant region; and

wherein the non-human mammal is able to produce a repertoire of chimaeric antibodies, or chimaeric heavy chains, having a non-human mammal constant region and a human variable region,

the insertion being such that the non-human mammal is able to produce a repertoire of chimaeric antibodies or heavy antibody chains having a non-human mammal constant region and a human variable region, wherein insertion of (a) and (b) can be carried out in either order and each of steps (a) and (b) can be carried out in a stepwise manner or as a single step; and

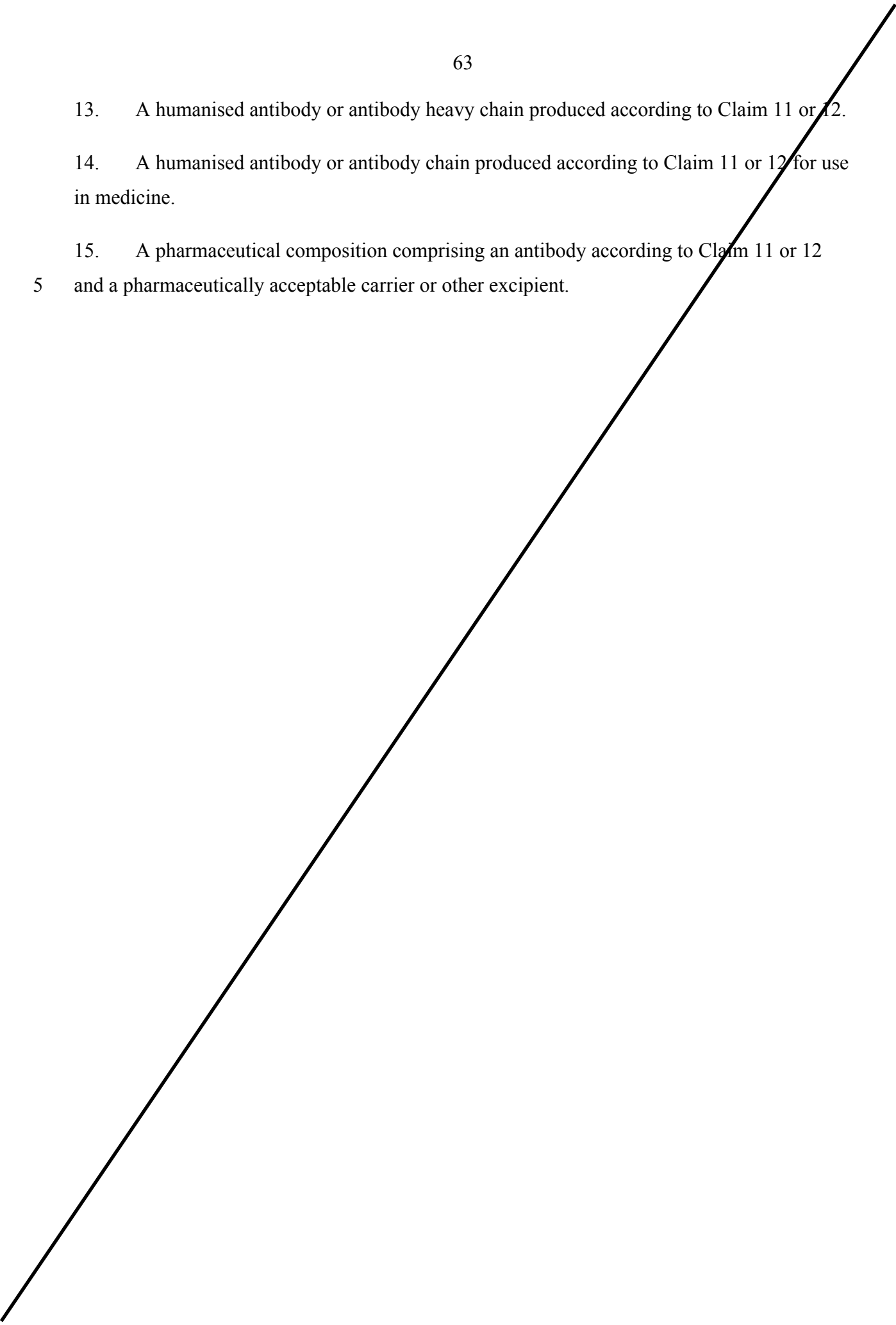
wherein the genome of the mammal comprises a non-human, non-host switch sequence.
2. A cell or mammal according to Claim 1 wherein the non-human, non-host switch sequence is S-mu.
3. A cell or mammal according to Claim 1 or 2 wherein the switch sequence is a rat switch.
4. A cell or mammal according to Claim 3 wherein the rat switch:

comprises or consists of GAGCT (296 repeats), GGGGT (50 repeats), and GGGCT (83 repeats), and/or

comprises 3, 4, 5, 6 or more contiguous repeats of the sequence GGGCT

optionally wherein the rat switch has the sequence of SEQ ID NO 1.

5. A cell or mammal according to any preceding claim wherein the switch is from mouse 129 strain, optionally having SEQ ID no 4, or wherein the switch is from mouse C57 strain, optionally having SEQ ID no 5.
6. A cell or mammal according to any one of Claim 1-5 wherein the cell or mammal genome is modified to prevent or reduce expression of fully host-species specific antibodies.
7. A cell or mammal according to any one of Claim 1- 6 wherein the insertion of the human DNA is made between the non-human mammal constant region and the last, 3' non-human mammal J region.
8. A cell or mammal according to any one of Claim 1-7 wherein the mammal is a mouse and the insertion of the human heavy chain DNA is made in a mouse genome between co-ordinates 114,667,090 and 114,665,190 of mouse chromosome 12 (co-ordinates refer to NCBIM37 for the mouse genome, relating to mouse strain C57BL/6J) or at equivalent position in another non-human mammal genome.
9. A cell or mammal according to any one of Claim 1-8 wherein the human IgH VDJ region comprises nucleotides 105,400,051 to 106,368,585 from human chromosome 14 (co-ordinates refer to NCBI36 for the human genome, ENSEMBL Release 54), or an equivalent human region from another human.
10. A cell or mammal according to any one of Claim 1- 9 wherein the cell or mammal is homozygous at one, two or all three immunoglobulin loci for DNA encoding a chimaeric antibody chain.
11. A method for producing an antibody or antibody heavy chain specific to a desired antigen, the method comprising immunizing a non-human mammal as claimed in any preceding claim with the desired antigen and recovering the antibody or antibody chain or recovering a cell producing the antibody or heavy chain.
12. A method for producing a fully humanised antibody or antibody heavy chain comprising immunizing a non-human mammal according to any preceding claim and then replacing the non-human mammal constant region of an antibody or heavy chain specifically reactive with the antigen with a human constant region, suitably by engineering of the nucleic acid encoding the antibody or chain.

13. A humanised antibody or antibody heavy chain produced according to Claim 11 or 12.
 14. A humanised antibody or antibody chain produced according to Claim 11 or 12 for use in medicine.
 15. A pharmaceutical composition comprising an antibody according to Claim 11 or 12
- 5 and a pharmaceutically acceptable carrier or other excipient.
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CLAIMS

1. A mouse whose genome comprises:

(a) a plurality of human IgH V regions, one or more human D regions and one or more human J regions upstream of a host non-human mammal constant region;

5 (b) one or more human Ig light chain kappa V regions and one or more human Ig light chain kappa J regions upstream of a mouse kappa constant region and optionally one or more human Ig light chain lambda V regions and one or more human Ig light chain lambda J regions upstream of a mouse lambda constant region;

10 wherein the mouse is able to produce a repertoire of chimaeric antibodies, or chimaeric heavy chains and chimaeric light chains, having a mouse constant region and a human variable region;

wherein the mouse genome comprises a chimaeric antibody chain locus, the locus encoding a chimaeric heavy chain; and

15 in which the locus comprises a mouse constant region nucleotide sequence and a rearranged VDJ nucleotide sequence produced by in vivo rearrangement of a human V region, a human D region and a human J region;

the V region being a V1-3 segment; and

the mouse expressing more V1-3 JH4 or V1-3 JH6 antibodies than any of, individually, V1-3 JH1, V1-3 JH2, V1-3 JH3 or V1-3 JH5 antibodies.

20 2. A mouse cell whose genome comprises:

(a) a plurality of human IgH V regions, one or more human D regions and one or more human J regions upstream of a mouse constant region;

25 (b) one or more human Ig light chain kappa V regions and one or more human Ig light chain kappa J regions upstream of a mouse kappa constant region and optionally one or more human Ig light chain lambda V regions and one or more human Ig light chain lambda J regions upstream of a mouse lambda constant region;

in which the mouse genome comprises a chimaeric antibody chain locus, the locus encoding a chimaeric heavy chain; and

in which the locus comprises a mouse constant region nucleotide sequence and a rearranged VDJ nucleotide sequence produced by in vivo rearrangement of a human V region, a human D region and a human J region, the V region being a V1-3 segment; the mouse expressing more V1-3 JH4 or V1-3 JH6 antibodies than any of, individually, V1-3 JH1, V1-3 JH2, V1-3 JH3 or V1-3 JH5 antibodies; and in which the cell is a B cell or hybridoma.

3. A rat whose genome comprises:

(a) a plurality of human IgH V regions, one or more human D regions and one or more human J regions upstream of a rat constant region;

(b) one or more human Ig light chain kappa V regions and one or more human Ig light chain kappa J regions upstream of a rat kappa constant region and optionally one or more human Ig light chain lambda V regions and one or more human Ig light chain lambda J regions upstream of a rat lambda constant region;

in which the rat is able to produce a repertoire of chimaeric antibodies, or chimaeric heavy chains and chimaeric light chains, having a rat constant region and a human variable region;

in which the rat genome comprises a chimaeric antibody chain locus, the locus encoding a chimaeric heavy chain; and

in which the locus comprises a rat constant region nucleotide sequence and a rearranged VDJ nucleotide sequence produced by the in vivo rearrangement of a human V region, a human D region and a human J region, the V region being a V1-3 segment; and

the rat expressing more V1-3 JH4 or V1-3 JH6 antibodies than any of, individually, V1-3 JH1, V1-3 JH2, V1-3 JH3 or V1-3 JH5 antibodies.

4. A rat cell whose genome comprises:

(a) a plurality of human IgH V regions, one or more human D regions and one or more human J regions upstream of a rat constant region;

(b) one or more human Ig light chain kappa V regions and one or more human Ig light chain kappa J regions upstream of a rat kappa constant region and optionally one or

more human Ig light chain lambda V regions and one or more human Ig light chain lambda J regions upstream of a rat lambda constant region;

in which the rat genome comprises a chimaeric antibody chain locus, the locus encoding a chimaeric heavy chain; and

5 in which the locus comprises a rat constant region nucleotide sequence and a rearranged VDJ nucleotide sequence produced by the in vivo rearrangement of a human V region, a human D region and a human J region, the V region being a V1-3 segment;

the rat expressing more V1-3 JH4 or V1-3 JH6 antibodies than any of, individually, V1-3 JH1, V1-3 JH2, V1-3 JH3 or V1-3 JH5 antibodies; and

10 in which the cell is a B cell or hybridoma.

5. A mouse according to Claim 1, a rat according to Claim 3, or a cell according to Claim 2 or Claim 4 comprising a switch comprising SEQ ID NO 1.

6. A mouse, rat or cell according to any preceding claim, in which the human VDJ regions are operably linked in the genome with a sequence from a rat mu constant region.

15 7. A mouse, rat or cell according to any preceding claim, in which the genome comprises endogenous VDJ regions which have not been deleted.

8. A mouse, rat or cell according to any any preceding claim, in which the genome does not comprise constant region DNA from another non-human organism.

20 9. Use of a mouse for producing a repertoire of chimaeric antibodies, or chimaeric heavy chains and chimaeric light chains, having a mouse constant region and a human variable region, the mouse genome comprising:

(a) a plurality of human IgH V regions, one or more human D regions and one or more human J regions upstream of a mouse constant region;

25 (b) one or more human Ig light chain kappa V regions and one or more human Ig light chain kappa J regions upstream of a mouse kappa constant region and optionally one or more human Ig light chain lambda V regions and one or more human Ig light chain lambda J regions upstream of a mouse lambda constant region;

in which the mouse is able to produce a repertoire of chimaeric antibodies, or chimaeric heavy chains and chimaeric light chains, having a mouse constant region and a human variable region;

in which the mouse genome comprises a chimaeric antibody chain locus, the locus encoding a chimaeric heavy chain; and

in which the locus comprises a mouse constant region nucleotide sequence and a rearranged VDJ nucleotide sequence produced by the in vivo rearrangement of a human V region, a human D region and a human J region, the V region being a V1-3 segment; and

the mouse expressing more V1-3 JH4 or V1-3 JH6 antibodies than any of, individually, V1-3 JH1, V1-3 JH2, V1-3 JH3 or V1-3 JH5 antibodies.

10. Use of a rat for producing a repertoire of chimaeric antibodies, or chimaeric heavy chains and chimaeric light chains, having a rat constant region and a human variable region, the rat genome comprising:

(a) a plurality of human IgH V regions, one or more human D regions and one or more human J regions upstream of a rat constant region;

(b) one or more human Ig light chain kappa V regions and one or more human Ig light chain kappa J regions upstream of a rat kappa constant region and optionally one or more human Ig light chain lambda V regions and one or more human Ig light chain lambda J regions upstream of a rat lambda constant region;

in which the rat is able to produce a repertoire of chimaeric antibodies, or chimaeric heavy chains and chimaeric light chains, having a rat constant region and a human variable region;

in which the rat genome comprises a chimaeric antibody chain locus, the locus encoding a chimaeric heavy chain; and

in which the locus comprises a rat constant region nucleotide sequence and a rearranged VDJ nucleotide sequence produced by the in vivo rearrangement of a human V region, a human D region and a human J region, the V region being a V1-3 segment; and

the rat expressing more V1-3 JH4 or V1-3 JH6 antibodies than any of, individually, V1-3 JH1, V1-3 JH2, V1-3 JH3 or V1-3 JH5 antibodies.

11. A method for producing an antibody or antibody heavy chain or antibody light chain specific to a desired antigen, the method comprising immunizing a mouse according to any of Claims 1 or 5 to 8 or a rat according to any of Claims 3 or 5 to 8 with the desired antigen and recovering the antibody or antibody chain or recovering a cell producing the antibody or antibody chain.
12. A method according to Claim 11, further comprising replacing the mouse or rat constant region of an antibody or chimaeric antibody chain to produce a fully humanised antibody or antibody chain.
13. A method according to Claim 11 or Claim 12 further comprising generating an antibody derivative of the antibody or antibody chain, in which the derivative is specifically reactive with the antigen.
14. A mouse, rat, cell, use or method according to any of Claims 1 to 13, in which the rearranged VDJ nucleotide sequence is produced by the in vivo rearrangement of human V1-3 and JH4 with D3-9, D3-10, D6-13 or D-19; or V1 -3 and JH6 with D3-9, D3- 10, D6-13 or D-19.
5. A method according to any of Claims 11 to 14 further comprising combining the antibody, antibody chain or antibody derivative with a pharmaceutically acceptable carrier or other excipient to produce a pharmaceutical composition.
16. A method according to any of Claims 11 to 15 further comprising making a kit comprising the antibody, antibody chain or derivative.
17. An antibody, antibody chain or antibody derivative, or a recovered cell producing the antibody or antibody chain, produced by a method according to any of Claims 11 to 14.
18. A pharmaceutical composition comprising an antibody, antibody chain or antibody derivative produced by a method according to any of Claims 11 to 14 and a pharmaceutically acceptable carrier or other excipient.
19. A kit comprising an antibody, antibody chain or antibody derivative produced by a method according to any of Claims 11 to 14 or a pharmaceutical composition according to Claim 18.

20. A mouse according to Claim 1, a cell according to Claim 2 or Claim 4, a rat according to Claim 3, use according to Claim 9 or Claim 10, a method according to Claim 11, an antibody, antibody chain or antibody derivative, or a recovered cell producing the antibody or antibody chain, according to Claim 17, a pharmaceutical composition according to Claim 18, or a kit
- 5 according to Claim 19, substantially as hereinbefore described, with reference to the examples and figures.