

CLAIMS

1. A method for targeted integration of an artificial Immunoglobulin (Ig) locus in a recipient non-human germ cell, fertilised oocyte or embryo comprising: introducing into a recipient non-human germ cell, fertilised oocyte or embryo a site-specific meganuclease targeting an endogenous Ig locus and a transgenic vector comprising an artificial Ig locus such that the artificial Ig locus integrates into the genome of the recipient non-human germ cell, fertilised oocyte or embryo by targeted integration and replaces the endogenous Ig locus, or parts thereof, by homologous recombination; wherein the meganuclease increases the frequency of homologous recombination through doublestrand DNA cleavage.
2. The method of claim 1 wherein the meganuclease is provided in a regulatable expression construct.
3. The method of claim 2 wherein the meganuclease is operably linked to an inducible promoter.
4. The method of any one of claims 1 to 3 further comprising selecting a cell in which the artificial Ig locus has integrated at the targeted site and in which a regulatable meganuclease expression construct has integrated into the genome.
5. The method of claim 4 further comprising fusing the selected cell with an enucleated nuclear transfer unit cell which is non-human, totipotent and capable of forming a functional neonate, to form a resulting cell.
6. The method of claim 4 or 5 wherein the enucleated nuclear transfer unit cell is an oocyte or an embryonic stem cell.
7. The method of any one of claims 4 to 6, further comprising:
 - i. injecting the selected cell into a developing non-human embryo; or
 - ii. cultivating the resulting cell in an appropriate medium and transferring into the resultant cell into a synchronised recipient for generating a transgenic non-human animal.
8. The method of any preceding claim, wherein the artificial Ig locus comprises fragments of human and non-human Ig-loci.
9. The method of any preceding claim, wherein the artificial Ig locus comprises at least one human V gene segment.
10. The method of any preceding claim, wherein the artificial Ig locus comprises multiple immunoglobulin gene segments, wherein the gene segments comprise at least one V region gene segment, one or more J gene segments, one or more D gene segments, and one or more constant region genes.
11. The method of any preceding claim, wherein the meganuclease target sequence is present in or proximal to gene segments selected from: a J gene segment; and a constant region gene segment.
12. The method of any preceding claim, further comprising the use of a second meganuclease, wherein the second meganuclease recognizes a second meganuclease target sequence present in or proximal to the endogenous Ig locus and selectively cleaves the endogenous Ig locus together with the first meganuclease but at a site distinct from that of the first meganuclease, thereby inactivating at least one endogenous Ig locus.
13. A transgenic non-human animal, obtainable by the method of claim 9, wherein the animal comprises:
 - i. at least one regulatable genomic meganuclease expression construct; and

ii. an artificial Ig locus replacing an endogenous Ig locus;

wherein the animal is capable of producing an antibody having a human idiotype.

14. The transgenic animal of claim 13, wherein the animal is selected from a bird, a rodent and a weasel.

15. The transgenic animal of claim 14 wherein the animal is a rat.

16. *In vitro* use of a transgenic vector for targeted integration,

wherein the transgenic vector comprises an inducible expression control region operably linked to a nucleic acid encoding a site specific meganuclease targeting an endogenous Ig locus, wherein the use comprises:

introducing the transgenic vector into a recipient non-human germ cell, fertilised oocyte or embryo such that the transgenic vector integrates into the genome of the germ cell, fertilised oocyte or embryo; and introducing a transgenic vector comprising an artificial Ig locus into the recipient non-human germ cell, fertilised oocyte or embryo such that the artificial locus integrates into the genome of the recipient nonhuman germ cell, fertilised oocyte or embryo by targeted integration.