

CLAIMS

1. A rodent whose genome comprises

~~a replacement of exons 2, 3 and 4 of a rodent SIRP α gene at an endogenous rodent SIRP α locus with exons 2, 3 and 4 of a human SIRP α gene to form a humanized SIRP α gene,~~

a humanized SIRP α gene,

wherein the humanized SIRP α gene is operably linked to a rodent SIRP α promoter at ~~the an~~ endogenous rodent SIRP α locus, and expresses ~~in the rodent~~ a humanized SIRP α protein in the rodent, and

wherein the humanized SIRP α protein comprises

(i) an extracellular portion that is at least 95% identical to amino acid residues 28-362 of the human SIRP α protein ~~encoded by~~ of SEQ ID NO: 4, and

(ii) the ~~human SIRP α gene and an~~ intracellular portion of ~~the~~ rodent SIRP α protein ~~encoded by the rodent SIRP α gene.~~

2. The rodent of claim 1, wherein the extracellular portion of the humanized SIRP α ~~gene~~protein comprises ~~exons 1, 5, 6, 7 and 8~~ amino acid residues 28-362 of the ~~rodent~~ human SIRP α ~~gene~~protein.

3. The rodent of claim 1 or 2, wherein the humanized SIRP α protein comprises the amino acid sequence as set forth in SEQ ID NO: 5.

4. The rodent according to any one of claims 1-3, wherein the rodent does not express a rodent SIRP α protein.

5. The rodent according to any one of claims 1-4, wherein the rodent is a mouse or a rat.

6. An isolated rodent cell or tissue whose genome comprises

~~a replacement of exons 2, 3 and 4 of a rodent SIRP α gene at an endogenous rodent SIRP α locus with exons 2, 3 and 4 of a human SIRP α gene to form~~ a humanized SIRP α gene,

wherein the humanized SIRP α gene is operably linked to a rodent SIRP α promoter at the endogenous rodent SIRP α locus, and encodes a humanized SIRP α protein, and

wherein the humanized SIRP α protein comprises ~~an extracellular portion of the human SIRP α protein encoded by the human SIRP α gene and an intracellular portion of the rodent SIRP α protein encoded by the rodent SIRP α gene.~~

~~_____ (i) an extracellular portion that is at least 95% identical to amino acid residues 28-_____ 362 of a human SIRP α protein of SEQ ID NO: 4, and~~

~~_____ (ii) the intracellular portion of a rodent SIRP α protein.~~

7. The isolated rodent cell or tissue of claim 6, wherein the ~~extracellular portion of the humanized SIRP α gene~~protein comprises ~~exons 1, 5, 6, 7 and 8~~amino acid residues 28-362 of the ~~rodent~~human SIRP α ~~gene~~protein.

8. The isolated rodent cell or tissue ~~according to any one of claim~~claims 6 ~~or 7~~, wherein the ~~isolated rodent cell or tissue is an isolated mouse cell or tissue~~ ~~does not express a rodent SIRP α protein, or an isolated rat cell or tissue.~~

9. The isolated rodent cell or tissue according to any one of claims 6-8, wherein the ~~isolated rodent cell or tissue~~ is ~~an isolated rat~~ a rodent embryonic stem cell ~~or tissue~~.

~~1010.~~ A rodent embryo, comprising the rodent embryonic stem cell of claim 9.

11. A method of making a rodent, comprising:

(a) ~~replacing exons 2, 3 and 4 of~~inserting a ~~rodent~~human SIRP α gene atnucleic acid sequence into an endogenous rodent SIRP α locus in a rodent embryonic stem (ES) cell ~~with exons 2, 3 and 4 of a human SIRP α gene~~ to form a humanized SIRP α gene,

wherein the humanized SIRP α gene is operably linked to a rodent SIRP α promoter at the endogenous rodent SIRP α locus and encodes a humanized SIRP α protein, and

wherein the humanized SIRP α protein comprises

(i) an extracellular portion that is at least 95% identical to amino acid residues 28-362 of the human SIRP α protein ~~encoded by~~of SEQ ID NO: 4, and

(ii) the ~~human SIRP α gene and an~~ intracellular portion of ~~the~~ rodent SIRP α protein ~~encoded by the rodent SIRP α gene~~,

thereby obtaining a modified rodent ES cell comprising the humanized SIRP α gene; and

(b) making a rodent using the modified ES cell obtained in (a).

~~1112.~~ The method of claim ~~1011~~, wherein the extracellular portion of the humanized SIRP α gene~~protein~~ comprises exons 1, 5, 6, 7 and 8amino acid residues 28-362 of the ~~rodent~~human SIRP α gene~~protein~~.

~~1213.~~ The method of ~~claim 10~~claim 11 or ~~1112~~, wherein the rodent is a mouse or a rat.

~~1314.~~ A method of assessing the therapeutic efficacy of a drug targeting human cells, comprising:

(a) providing a rodent according to any one of claims 1-5 into which one or more human cells have been transplanted;

(b) administering a drug candidate to the rodent; and

(c) monitoring the human cells in the rodent to determine the therapeutic efficacy of the drug candidate.

~~1415.~~ The method of claim ~~1314~~, wherein the rodent is a mouse or a rat.

16. A nucleic acid targeting vector, comprising:

a human genomic DNA fragment comprising exons 2, 3 and 4 of a human SIRP α gene,
flanked by

a 5' homology arm comprising a rodent genomic DNA fragment upstream of exon 2 of a
rodent SIRP α gene, and

a 3' homology arm comprising a rodent genomic DNA fragment downstream of exon 4 of
the rodent SIRP α gene;

wherein integration of the human genomic DNA fragment into the genome of a rodent
cell based on homologous recombination results in a replacement of exons 2, 3 and 4 of the
rodent SIRP α gene at an endogenous rodent SIRP α locus with exons 2, 3 and 4 of the human
SIRP α gene to form a humanized SIRP α gene,

wherein said humanized SIRP α gene is operably linked to the rodent SIRP α promoter at
said endogenous rodent SIRP α locus, and encodes a humanized SIRP α protein comprising an
extracellular portion of the human SIRP α protein encoded by said human SIRP α gene and an
intracellular portion of the rodent SIRP α protein encoded by said rodent SIRP α gene, and

wherein the rodent is selected from a mouse or a rat.

17. The nucleic acid targeting vector of claim 16, wherein said humanized SIRP α gene
comprises exons 1, 5, 6, 7 and 8 of said rodent SIRP α gene.