Claims

1. A genetically modified rodent comprising in its genome:

a humanized signal-regulatory protein alpha (SIRPα) gene comprising a nucleic acid sequence that encodes a humanized signal-regulatory protein alpha (hSirpa) protein operably linked to an endogenous rodent *SIRPα* gene promoter at the rodent *SIRPα* gene locus in the genome of the genetically modified rodent, wherein the humanized SIRPα gene comprises a replacement of a portion of an endogenous rodent SIRPα coding sequence, wherein the genetically modified rodent expresses the hSIRPα protein, and wherein the hSIRPα protein possesses wild-type human SIRPα receptor function and comprises a signaling domain of an endogenous mouse SIRPα protein; and

a humanized interleukin-15 (IL-15) gene comprising a nucleic acid sequence that encodes a human IL-15 (hIL-15) protein operably linked to an endogenous rodent *IL-15* gene promoter at the rodent *IL-15* gene locus in the genome of the genetically modified rodent, wherein the humanized IL-15 gene comprises a replacement of some or all of an endogenous rodent IL-15 coding sequence, wherein the genetically modified rodent expresses the hIL-15 protein, and wherein the hIL-15 protein possesses wild-type human IL-15 signaling function;

wherein the genetically modified rodent is a mouse or a rat.

2. The genetically modified rodent of claim 1, wherein the humanized SIRPα gene comprises exon 1 of a rodent SIRPα gene, exons 2, 3 and 4 of a human SIRPα gene, and exons 5, 6, 7 and 8 of the rodent SIRPα gene.

3. The genetically modified rodent of claim 1 or 2, wherein the genetically modified rodent is homozygous for the humanized SIRPα gene.

4. The genetically modified rodent of any one of claims 1 to 3, wherein the humanized IL-15 gene comprises exons 3 and 4 of a rodent IL-15 gene and exons 5, 6, 7 and 8 of a human IL-15 gene.

5. The genetically modified rodent of any one of claims 1 to 4, wherein the genetically modified rodent is homozygous for the humanized IL-15 gene.

6. The genetically modified rodent of any one of claims 1 to 5, wherein:

the humanized SIRPα gene comprises a replacement of exons 2, 3 and 4 of the rodent SIRPα gene at the endogenous rodent SIRPα locus with exons 2, 3 and 4 of the human SIRPα gene;

the humanized IL-15 gene comprises a replacement of exons 5, 6, 7 and 8 of the rodent IL-15 gene at the endogenous rodent IL-15 locus with exons 5, 6, 7 and 8 of the human IL-15 gene.

7. The genetically modified rodent of any one of claims 1 to 6, wherein the genetically modified rodent is immunodeficient.

8. The genetically modified rodent of claim 7, wherein the genetically modified rodent comprises a Rag2 gene knock-out.

9. The genetically modified rodent of claim 7, wherein the genetically modified rodent comprises an IL2rg gene knock-out.

10. The genetically modified rodent of claim 7, wherein the genetically modified rodent comprises a Rag2 gene knock-out and an IL2rg gene knock-out.

11. The genetically modified rodent of any one of claims 7-10, wherein the genetically modified rodent comprises an engraftment of human hematopoietic cells.

12. The genetically modified rodent of claim 11, wherein the genetically modified rodent comprises an infection with a human pathogen.

13. The genetically modified rodent of claim 12, wherein the human pathogen is selected from the group consisting of: a human pathogen that activates, induces and/or targets T cells; a human pathogen that activates, induces and/or targets natural killer (NK) cells; a human pathogen that infects human intestine; a human rotavirus; a human pathogen that infects human lung; and an influenza virus.

14. The genetically modified rodent of any one of claims 7 to 11, wherein the genetically modified rodent comprises a transplanted human tumor.

15. The genetically modified rodent of any one of claims 1 to 14, wherein the genetically modified rodent is a mouse.