CLAIMS

1. A genetically modified mouse, comprising:

   a nucleic acid sequence incorporated into the genome of the genetically modified mouse, which sequence encodes a human SIRPα protein and is operably linked to a SIRPα gene promoter; and

   a nucleic acid sequence incorporated into the genome of the genetically modified mouse, which sequence encodes a human IL-15 protein and is operably linked to an IL-15 gene promoter, wherein the genetically modified mouse expresses the human SIRPα protein and the human IL-15 protein.

2. The genetically modified mouse according to claim 1, wherein the SIRPα gene promoter is an endogenous mouse SIRPα gene promoter at the mouse SIRPα gene locus.

3. The genetically modified mouse according to claim 1, wherein the genetically modified mouse is heterozygous for the allele comprising the nucleic acid sequence that encodes the human SIRPα protein.

4. The genetically modified mouse according to claim 1, wherein the genetically modified mouse is homozygous for the allele comprising the nucleic acid sequence that encodes the human SIRPα protein.

5. The genetically modified mouse according to claim 1, wherein the IL-15 gene promoter is an endogenous mouse IL-15 gene promoter at the mouse IL-15 gene locus.

6. The genetically modified mouse according to claim 5, wherein the genetically modified mouse is heterozygous for the allele comprising the nucleic acid sequence that encodes the human IL-15 protein.

7. The genetically modified mouse according to claim 5, wherein the genetically modified mouse is homozygous for the allele comprising the nucleic acid sequence that encodes the human IL-15 protein.

8. The genetically modified mouse according to claim 1, wherein the nucleic acid sequence that encodes the human IL-15 protein comprises human IL-15 genomic coding and non-coding sequence.

9. The genetically modified mouse according to claim 1, wherein the human IL-15 protein is a functional fragment of a full length human IL-15 protein.

10. The genetically modified mouse according to claim 1, wherein the genetically modified mouse is immunodeficient.

11. The genetically modified mouse according to claim 10, wherein the genetically modified mouse comprises a Rag2 gene knock-out.

12. The genetically modified mouse according to claim 10, wherein the genetically modified mouse comprises an IL2rg gene knock-out.

13. The genetically modified mouse according to claim 1, wherein the genetically modified mouse comprises an engraftment of human hematopoietic cells.

14. The genetically modified mouse according to claim 13, wherein the genetically modified mouse comprises an infection with a human pathogen.

15. The genetically modified mouse according to claim 14, wherein the human pathogen activates, induces and/or targets T cells and/or natural killer (NK) cells.

16. The genetically modified-mouse according to claim 14, wherein the human pathogen is a pathogen that infects human intestine.

17. The genetically modified mouse according to claim 14, wherein the pathogen infects human lung.

18. A method of making a mouse expressing a human IL-15 protein and a human SIRPα protein, comprising:

introducing into a genome of a first mouse a nucleic acid sequence encoding a human SIRPα protein, wherein the sequence encoding the human SIRPα protein is operably linked to an SIRPα gene promoter sequence;

introducing into a genome of a second mouse a nucleic acid sequence encoding a human IL-15 protein, wherein the sequence encoding the human IL-15 protein is operably linked to a IL-15 promoter sequence; and

breeding the first mouse and the second mouse to produce a third mouse that comprises the nucleic acid sequence encoding the human IL-15 protein and the nucleic acid sequence encoding the human SIRPα protein, wherein the third mouse expresses the human IL-15 protein and the human SIRPα protein.

19. The method of claim 18, wherein the steps of introducing comprise generating a mouse from a pluripotent stem cell comprising the nucleic acid encoding human IL-15 or human SIRPα.

20. An animal engraftment model, comprising a genetically modified mouse comprising:

a nucleic acid sequence incorporated into the genome of the genetically modified mouse, which sequence encodes a human SIRPα protein and is operably linked to a SIRPα gene promoter;

a nucleic acid sequence incorporated into the genome of the genetically modified mouse, which sequence encodes a human IL-15 protein and is operably linked to an IL-15 gene promoter; and

an engraftment of human hematopoietic cells, wherein the genetically modified mouse (i) expresses the human SIRPα protein and the human IL-15 protein, and (ii) comprises human intraepithelial lymphocytes (IELs) in the small intestine and Peyer's patches of the genetically modified mouse.

21. A method of identifying an agent that inhibits an infection by a pathogen that activates, induces and/or targets human T cells and/or natural killer (NK) cells, the method comprising:

administering an agent to an genetically modified mouse, wherein the genetically modified mouse is deficient for an endogenous immune system and comprises:

(i) a nucleic acid sequence incorporated into the genome of the genetically modified mouse, which sequence encodes a human SIRPα protein and is operably linked to a SIRPα gene promoter,

(ii) a nucleic acid sequence incorporated into the genome of the genetically modified mouse, which sequence encodes a human IL-15 protein and is operably linked to an IL-15 gene promoter,

(iii) an engraftment of human hematopoietic cells, and

(iv) an infection by a pathogen that activates, induces and/or targets human T cells and/or natural killer cells, wherein the genetically modified mouse expresses the human SIRPα protein and the human IL-15 protein; and

determining whether the agent reduces the amount of the pathogen in the pathogen-infected mouse.

22. A method of determining the efficacy a candidate therapeutic antibody or antigen-binding protein in NK-cell mediated killing of a target cell, comprising:

administering the candidate therapeutic antibody or antigen-binding protein to a genetically modified mouse, wherein the genetically modified mouse is deficient for an endogenous immune system and comprises:

(i) a nucleic acid sequence incorporated into the genome of the genetically modified-mouse, which sequence encodes a human SIRPα protein and is operably linked to a SIRPα gene promoter,

(ii) a nucleic acid sequence incorporated into the genome of the genetically modified mouse, which sequence encodes a human IL-15 protein and is operably linked to an IL-15 gene promoter, and

(iii) an engraftment of human hematopoietic cells, wherein the genetically modified mouse expresses the human SIRPα protein and the human IL-15 protein; and

determining whether the candidate therapeutic antibody or antigen-binding protein activates NK cell antibody-dependent cellular cytotoxicity against the target cell in the genetically modified mouse.

23. The genetically modified mouse according to claim 2, comprising a null mutation in the mouse SIRPα gene at the mouse SIRPα gene locus.

24. The genetically modified mouse according to claim 23, wherein the null mutation is a deletion of at least mouse SIRPα exons 2-4.

25. The genetically modified mouse according to claim 1, wherein the human SIRPα protein is a functional fragment of a full length human SIRPα protein.

26. The genetically modified mouse according to claim 25, wherein the functional fragment comprises an extracellular domain of human SIRPα.

27. The genetically modified non-human animal according to claim 5, comprising a null mutation in the non-human IL-15 gene at the non-human animal IL-15 gene locus.

28. The genetically modified mouse according to claim 27, wherein the null mutation is a deletion of at least mouse IL-15 exons 5-8.