CLAIMS

1. A genetically modified mouse, comprising:

a nucleic acid sequence that encodes a human erythropoietin (hEPO) protein operably linked to an endogenous mouse *EPO* gene promoter at the mouse *EPO* locus, wherein the operable linkage results in a null mutation in the mouse *EPO* gene at the mouse *EPO* gene locus,

a nucleic acid sequence that encodes a human macrophage colony-stimulating factor (hM-CSF) protein operably linked to an endogenous mouse *M-csf* promoter at the mouse *M-csf* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *M-csf* gene,

a nucleic acid sequence that encodes a human interleukin 3 (hIL-3) protein operably linked to an endogenous mouse *IL-3* promoter at the mouse *IL-3* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *IL-3* gene,

a nucleic acid sequence that encodes a human granulocyte macrophage colony-stimulating factor (hGM-CSF) protein operably linked to an endogenous mouse *Gm-csf* promoter at the mouse *Gm-csf* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *Gm-csf* gene,

a nucleic acid sequence that encodes a human thrombopoietin (hTPO) protein operably linked to an endogenous mouse *TPO* promoter at the mouse *TPO* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *TPO* gene, and

a signal regulatory protein α (SIRPa) transgene that encodes a hSirpa protein, wherein the mouse expresses the hSirpa protein,

wherein the genetically modified mouse is immunodeficient.

2. The mouse according to claim 1, wherein the mouse is heterozygous for the allele comprising the nucleic acid sequence that encodes the hEPO.

3. The mouse according to claim 1, wherein the mouse is homozygous for the allele comprising the nucleic acid sequence that encodes the hEPO.

4. The mouse according to any one of claims 1-3, wherein the nucleic acid sequence that encodes the hEPO comprises human *EPO* genomic coding and non-coding sequence.

5. The mouse according to any one of claims 1-4, wherein the nucleic acid sequence that encodes the hEPO comprises human *EPO* cDNA sequence.

6. The mouse according to any one of claims 1-5, wherein the mouse is homozygous for: the nucleic acid encoding the hTPO, the nucleic acid encoding the hMcsf, the nucleic acid encoding the hIL-3, and the nucleic acid encoding the hGmcsf.

7. The mouse according to any one of claims 1-6, wherein the mouse further comprises an engraftment of human hematopoietic cells.

8. The mouse according to claim 7, wherein the human hematopoietic cells comprise one or more cells selected from the group consisting of a human CD34-positive cell, a human hematopoietic stem cell, a human myeloid precursor cell, a human erythroid precursor cell, a human myeloid cell, a human dendritic cell, a human monocyte, a human granulocyte, a human erythrocyte, a human neutrophil, a human mast cell, a human thymocyte, and a human B lymphocyte.

9. The mouse according to claim 8, wherein the mouse comprises clodronate.

10. The mouse according to claim 9, wherein the mouse further comprises an infection with a pathogen that targets human cells of the erythroid lineage.

11. The mouse according to claim 10, wherein the pathogen is selected from a *Plasmodium* sp., *Babesia* sp., and a *Theileri* sp.

12. The mouse according to any one of claims 1-11, wherein the immunodeficiency is caused by a deficiency of recombination activating gene 2 (Rag2).

13. The mouse according to any one of claims 1-12, wherein the immunodeficiency is caused by a deficiency of interleukin 2 receptor, gamma (IL2rg).

14. A method for identifying an agent that inhibits an infection by a pathogen that targets human cells of the erythroid lineage, wherein:

a. a candidate agent is to be administered to a genetically modified mouse, wherein the mouse comprises:

a nucleic acid sequence that encodes a human EPO protein (hEPO) operably linked to an endogenous mouse *EPO* gene promoter at the mouse *EPO* locus, wherein the operable linkage results in a null mutation in the mouse *EPO* gene at the mouse *EPO* gene locus,

a nucleic acid sequence that encodes a human macrophage colony-stimulating factor (hM-CSF) protein operably linked to an endogenous mouse *M-*

*csf* promoter at the mouse *M-csf* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *M-csf* gene,

a nucleic acid sequence that encodes a human interleukin 3 (hIL-3) protein operably linked to an endogenous mouse *IL-3* promoter at the mouse *IL-3* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *IL-3* gene,

a nucleic acid sequence that encodes a human granulocyte macrophage colony-stimulating factor (hGM-CSF) protein operably linked to an endogenous mouse *Gm-csf* promoter at the mouse *Gm-csf* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *Gm-csf* gene,

a nucleic acid sequence that encodes a human thrombopoietin (hTPO) protein operably linked to an endogenous mouse *TPO* promoter at the mouse *TPO* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *TPO* gene, and

a signal regulatory protein α (SIRPa) transgene that encodes a hSirpa protein, wherein the mouse expresses the hSirpa protein,

wherein the genetically modified mouse is immunodeficient,

an engraftment of human hematopoietic cells, and

an infection by a pathogen that targets human cells of the erythroid lineage,

b. whether the agent reduces the amount of the pathogen in the pathogen-infected mouse of step a is to be determined; and

c. the agent that reduces the amount of the pathogen in the pathogen-infected mouse is to be identified as the agent that inhibits an infection by a pathogen that targets human cells of the erythroid lineage.

15. The method according to claim 14, wherein the immunodeficiency is caused by a deficiency of recombination activating gene 2 (Rag2).

16. The method according to any one of claim 14 or claim 15, wherein the immunodeficiency is caused by a deficiency of interleukin 2 receptor, gamma (IL2rg).

17. A method for identifying an agent that prevents an infection by a pathogen that targets human cells of the erythroid lineage, wherein:

a. a genetically modified mouse is to be contacted with clodronate, wherein the mouse comprises:

a nucleic acid sequence that encodes a human EPO protein (hEPO) operably linked to an endogenous mouse *EPO* gene promoter at the mouse *EPO*

locus, wherein the operable linkage results in a null mutation in the mouse *EPO* gene at the mouse *EPO* gene locus,

a nucleic acid sequence that encodes a human macrophage colony-stimulating factor (hM-CSF) protein operably linked to an endogenous mouse *M-csf* promoter at the mouse *M-csf* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *M-csf* gene,

a nucleic acid sequence that encodes a human interleukin 3 (hIL-3) protein operably linked to an endogenous mouse *IL-3* promoter at the mouse *IL-3* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *IL-3* gene,

a nucleic acid sequence that encodes a human granulocyte macrophage colony-stimulating factor (hGM-CSF) protein operably linked to an endogenous mouse *Gm-csf* promoter at the mouse *Gm-csf* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *Gm-csf* gene,

a nucleic acid sequence that encodes a human thrombopoietin (hTPO) protein operably linked to an endogenous mouse *TPO* promoter at the mouse *TPO* gene locus and wherein the mouse is heterozygous null or homozygous null for the mouse *TPO* gene, and

a signal regulatory protein α (SIRPa) transgene that encodes a hSirpa protein, wherein the mouse expresses the hSirpa protein,

wherein the genetically modified mouse is immunodeficient,

an engraftment of human hematopoietic cells,

b. a candidate agent is to be administered to the genetically modified mouse of step a,

c. the genetically modified mouse of step a is to be injected with parasitized reticulocytes or erythrocytes, and

d. whether the agent prevents the infection of the human reticulocytes and/or erythrocytes of the mouse of step a is to be determined,

e. the agent that prevents the infection of the human reticulocytes and/or erythrocytes of the mouse of step a is to be identified as the agent prevents an infection by a pathogen that targets human cells of the erythroid lineage.

18. The method according to claim 17, wherein the immunodeficiency is caused by a deficiency of recombination activating gene 2 (Rag2).

19. The method according to any one of claim 17 or claim 18, wherein the immunodeficiency is caused by a deficiency of interleukin 2 receptor, gamma (IL2rg).

20. The method according to claim 14 or 17, wherein the mouse is heterozygous for the allele comprising the nucleic acid sequence that encodes hEPO.

21. The method according to claim 14 or 17, wherein the mouse is homozygous for the allele comprising the nucleic acid sequence that encodes hEPO.

22. The method according to any one of claims 14-21, wherein the nucleic acid sequence that encodes the hEPO comprises human *EPO* genomic coding and non-coding sequence.

23. The method according to any one of claims 14-21, wherein the nucleic acid sequence that encodes hEPO comprises human *EPO* cDNA sequence.

24. The method according to any one of claims 14-23, wherein the mouse is homozygous for: the nucleic acid encoding the hTPO, the nucleic acid encoding the hMcsf, the nucleic acid encoding the hIL-3, and the nucleic acid encoding the hGmcsf.

25. The method according to any one of claims 14-24, wherein the human hematopoietic cells comprise one or more cells selected from the group consisting of a human CD34-positive cell, a human hematopoietic stem cell, a human myeloid precursor cell, a human erythroid precursor cell, a human myeloid cell, a human dendritic cell, a human monocyte, a human granulocyte, a human erythrocyte, a human neutrophil, a human mast cell, a human thymocyte, and a human B lymphocyte.

26. The method according to any one of claims 14-25, wherein the pathogen is selected from a *Plasmodium* sp., *Babesia* sp., and a *Theileri* sp.

27. The method according to claim 26, wherein the pathogen is a *Plasmodium* sp. and the *Plasmodium* sp. is selected from *P. falciparum* and *P. vivax.*

28. A method for making a mouse comprising a human hematopoietic system, wherein:

a population of cells comprising human hematopoietic progenitor cells is to be transplanted into the genetically modified mouse according to any one of claims 1-6.

29. The method according to claim 28, wherein the population of cells comprising human hematopoietic progenitor cells is to be transplanted via tail-vein injection, fetal liver injection, or retro-orbital injection.

30. The method according to claim 28 or 29, wherein the genetically modified mouse is to be sublethally irradiated prior to transplantation.

31. The method according to any one of claims 28-30, wherein the human hematopoietic progenitor cells are CD34+ cells.

32. The method according to any one of claims 28-31, wherein the human hematopoietic progenitor cells are from fetal liver, adult bone marrow, or umbilical cord blood.

33. A method for making a mouse that is infected with a human parasite that targets human cells of the erythroid lineage, wherein:

a population of cells comprising human hematopoietic progenitor cells is to be transplanted into the genetically modified mouse according to any one of claims 1-6,

the mouse is to be injected with clodronate, and

the mouse is to be injected with parasitized human red blood cells (PRBCs).

34. The method according to claim 33, wherein the mouse is to be further injected with healthy human red blood cells.

35. The method according to claim 33, wherein the parasite is selected from a *Plasmodium* sp., *Babesia* sp., and a *Theileri* sp.

36. The method according to claim 35, wherein the parasite is a *Plasmodium* sp. and the *Plasmodium* sp. is selected from *P. falciparum* and *P. vivax.*