CLAIMS

1. A method of screening a candidate agent for the ability to modulate hematopoietic cell development and/or activity, the method comprising,

contacting a genetically modified, immunodeficient, rodent with a candidate agent, wherein the genetically modified, immunodeficient rodent is engrafted with human hematopoietic cells and comprises a nucleic acid encoding human IL-6 operably linked to an IL-6 promoter, wherein the rodent expresses a human IL-6 polypeptide and does not express a functional native IL-6 polypeptide, and at least one additional nucleic acid selected from the group consisting of:

i) a nucleic acid encoding human SIRPa operably linked to a SIRPa promoter, wherein the rodent expresses a human SIRPa polypeptide;

ii) a nucleic acid encoding human M-CSF operably linked to a M-CSF promoter, wherein the rodent expresses a human M-CSF polypeptide;

iii) a nucleic acid encoding human IL-3 operably linked to an IL-3 promoter, wherein the rodent expresses a human IL-3 polypeptide;

iv) a nucleic acid encoding human GM-CSF operably linked to a GM-CSF promoter, wherein the rodent expresses a human GM-CSF polypeptide; and

v) a nucleic acid encoding human TPO operably linked to a TPO promoter, wherein the rodent expresses a human TPO polypeptide; and

monitoring one or more output parameters indicative of hematopoietic cell development and/or activity in the genetically modified rodent to determine whether the candidate agent modulates hematopoietic cell development and/or activity.

2. The method of claim 1, wherein the IL-6 promoter is the rodent IL-6 promoter, and the nucleic acid encoding human IL-6 is operably linked to the rodent IL-6 promoter at the rodent IL-6 locus.

3. The method of claim 1 or 2, wherein the SIRPa promoter is the rodent SIRPa promoter, the M-CSF promoter is the rodent M-CSF promoter, the IL-3 promoter is the rodent IL-3 promoter, the GM-CSF promoter is the rodent GM-CSF promoter, and the TPO promoter is the rodent TPO promoter.

4. The method of any one of claims 1-3, wherein the rodent does not express a recombination activating gene (RAG), IL2 receptor gamma chain (IL2rg), or both a RAG and IL2rg.

5. The method of claim 4, wherein the rodent does not express either a recombination activating gene 2 (RAG2) or an IL2rg.

6. The method of any one of claims 1-5, wherein the one or more output parameters are reflective of the viability of the human hematopoietic cells.

7. The method of any one of claims 1-5, wherein the one or more output parameters are reflective of the total number of the human hematopoietic cells.

8. The method of any one of claims 1-5, wherein the one or more output parameters are reflective of the number of human hematopoietic cells of a particular cell type.

9. The method of any one of claims 1-5, wherein the one or more output parameters are reflective of the apoptotic state of the human hematopoietic cells.

10. The method of any one of claims 1-5, wherein the one or more output parameters are selected from the amount of DNA fragmentation, the amount of cell blebbing, and the amount of phosphatidylserine on the cell surface of the human hematopoietic cells.

11. The method of any one of claims 1-5, wherein the one or more output parameters are reflective of the differentiation capacity of the human hematopoietic cells.

12. The method of any one of claims 1-5, wherein the one or more output parameters are reflective of the function of the human hematopoietic cells.

13. The method of any one of claims 1-12, wherein the human hematopoietic cells are CD34+ cells.

14. The method of any one of claims 1-13, further comprising transplanting a population of human hematopoietic cells into the genetically modified, immunodeficient rodent to provide the genetically modified, immunodeficient rodent engrafted with human hematopoietic cells.

15. The method of any one of claims 1-5, wherein the one or more output parameters provide a quantitative readout.