

CLAIMS

1. A genetically modified mouse comprising in its genome a recombination activating gene 2 (Rag-2) gene knock-out, an IL2 receptor gamma chain (IL2rg) gene knock-out, a replacement of a mouse M-CSF gene with a nucleic acid encoding a human M-CSF polypeptide at a mouse M-CSF gene locus, a replacement of a mouse IL-3 gene with a nucleic acid encoding a human IL-3 polypeptide at a mouse IL-3 gene locus, a replacement of a mouse GM-CSF gene with a nucleic acid encoding a human GM-CSF polypeptide at a mouse GM-CSF gene locus, an insertion of a nucleic acid encoding a human SIRPA polypeptide, and a replacement of a mouse TPO gene with a nucleic acid encoding a human TPO polypeptide at a mouse TPO gene locus, wherein each of the nucleic acids encoding the human M-CSF polypeptide, the human IL-3 polypeptide, the human GM-CSF polypeptide, the human SIRPA polypeptide, and the human TPO polypeptide is operably linked to a promoter, and wherein the mouse expresses the human M-CSF polypeptide, the human IL-3 polypeptide, the human GM-CSF polypeptide, the human SIRPA polypeptide, and the human TPO polypeptide.
2. The genetically modified mouse of claim 1, further comprising human hematopoietic cells.
3. The genetically modified mouse of claim 1, further comprising a human cancer cell.
4. The genetically modified mouse of claim 3, wherein the human cancer cell is a leukemia cell or a melanoma cell.
5. A method of hematopoietic stem and progenitor cell (HSPC) engraftment comprising a step of administering at least one HSPC to the genetically modified mouse of claim 1.
6. The method of claim 5, wherein the genetically modified mouse comprises a human cancer cell.
7. The method of claim 6, wherein the human cancer cell is a leukemia cell or a melanoma cell.
8. A genetically modified mouse comprising in its genome

a recombination activating gene 2 (Rag-2) gene knock-out,

an IL2 receptor gamma chain (IL2rg) gene knock-out,

a replacement of a mouse M-CSF gene with a nucleic acid encoding a human M-CSF polypeptide at a mouse M-CSF gene locus,

a replacement of a mouse IL-3 gene with a nucleic acid encoding a human IL-3 polypeptide at a mouse IL-3 gene locus,

a replacement of a mouse GM-CSF gene with a nucleic acid encoding a human GM-CSF polypeptide at a mouse GM-CSF gene locus,

an insertion of a nucleic acid encoding a human SIRPA polypeptide, and

a replacement of a mouse TPO gene with a nucleic acid encoding a human TPO polypeptide at a mouse TPO gene locus,

wherein each of the nucleic acids encoding the human M-CSF polypeptide, the human IL-3 polypeptide, the human GM-CSF polypeptide, the human SIRPA polypeptide, and the human TPO polypeptide is operably linked to a promoter,

wherein the mouse expresses the human M-CSF polypeptide, the human IL-3 polypeptide, the human GM-CSF polypeptide, the human SIRPA polypeptide, and the human TPO polypeptide,

and wherein, when engrafted with human CD34⁺ cells, the mouse exhibits a significantly higher proportion of human CD33⁺ myeloid cells in blood and bone marrow relative to a genetically modified mouse engrafted with human CD34⁺ cells which does not express the human M-CSF polypeptide, the human IL-3 polypeptide, the human GM-CSF polypeptide, the human SIRPA polypeptide, and the human TPO polypeptide.

9. The genetically modified mouse of claim 8, wherein the mouse is engrafted with human CD34⁺ cells.
10. The method of claim 5, wherein the administering step is not preceded by preconditioning irradiation of the genetically modified mouse.
11. A genetically modified mouse comprising in its genome

a recombination activating gene 2 (Rag-2) gene knock-out,

an IL2 receptor gamma chain (IL2rg) gene knock-out,

a replacement of a mouse M-CSF gene with a nucleic acid encoding a human M-CSF polypeptide at a mouse M-CSF gene locus,

a replacement of a mouse IL-3 gene with a nucleic acid encoding a human IL-3 polypeptide at a mouse IL-3 gene locus,

a replacement of a mouse GM-CSF gene with a nucleic acid encoding a human GM-CSF polypeptide at a mouse GM-CSF gene locus,

an insertion of a nucleic acid encoding a human SIRPA polypeptide, and

a replacement of a mouse TPO gene with a nucleic acid encoding a human TPO polypeptide at a mouse TPO gene locus,

wherein each of the nucleic acids encoding the human M-CSF polypeptide, the human IL-3 polypeptide, the human GM-CSF polypeptide, the human SIRPA polypeptide, and the human TPO polypeptide is operably linked to a promoter,

wherein the mouse expresses the human M-CSF polypeptide, the human IL-3 polypeptide, the human GM-CSF polypeptide, the human SIRPA polypeptide, and the human TPO polypeptide,

and wherein, when engrafted with human CD34+ cells and a human tumor, the mouse exhibits increased human myeloid cell infiltration of the engrafted tumor relative to a genetically modified mouse engrafted with human CD34+ cells and a human tumor, which does not express the human M-CSF polypeptide, the human IL-3 polypeptide, the human GM-CSF polypeptide, the human SIRPA polypeptide, and the human TPO polypeptide.

12. The genetically modified mouse of claim 11, wherein the mouse is engrafted with human CD34+ cells and a human tumor.

13. The genetically modified mouse of claim 1, wherein the human SIRPA polypeptide is a biologically active fragment of a full-length human SIRPA polypeptide.

14. The genetically modified mouse of claim 8, wherein the human SIRPA polypeptide is a biologically active fragment of a full-length human SIRPA polypeptide.
15. The genetically modified mouse of claim 11, wherein the human SIRPA polypeptide is a biologically active fragment of a full-length human SIRPA polypeptide.