transplantation procedures are desired. Such novel agents would increase the chance for hematopoietic recovery, while reducing the chance for the serious complications following hematopoietic cellular transplantation.

SUMMARY OF THE INVENTION

[0009] Accordingly, there is a need for novel methods and compositions useful for hematopoietic recovery following hematopoietic stem cell transplantation (HSCT).

[0009a] One aspect relates to the use of a pharmaceutical composition in the manufacture of a medicament for restoring hematopoiesis and reducing infection complications, wherein: (a) the pharmaceutical composition comprises Interleukin-12 (IL-12) in an effective dose of about 10 to about 300 ng/kg of IL-12, and (b) the pharmaceutical composition is to be administered in one or more effective dose(s) within 72 hours or less following myeloablative therapy, within 72 hours or less prior to myeloablative therapy, or within 72 hours or less prior to and within 72 hours or less following myeloablative therapy, wherein the myeloablative therapy is to be administered prior to a hematopoietic stem cell transplant.

[0009b] Another aspect relates to the use of a pharmaceutical composition in the manufacture of a medicament for restoring hematopoiesis and reducing infectious complications in a human subject wherein: (a) the pharmaceutical composition comprises Interleukin-12 (IL-12) in an effective dose of about 10 to about 300 ng/kg of IL-12, and (b) the pharmaceutical composition is to be administered in one or more effective dose(s) within 72 hours or less following myeloablative therapy, within 72 hours or less prior to myeloablative therapy, or within 72 hours or less prior to and within 72 hours or less following myeloablative therapy, wherein the myeloablative therapy is to be administered prior to a hematopoietic stem cell transplant, and wherein hematopoiesis is restored via activation of the IL-12 receptor on hematopoietic cells in the bone marrow.

[0010] The present disclosure provides methods and therapeutic agents that target multiple pathways of hematopoiesis and innate immunity and can be used therapeutically for a broad range of clinical disorders including hematopoietic recovery following hematopoietic stem cell transplantation (HSCT). In some aspects the present disclosure provides methods and therapeutic agents that can improve hernatopoietic recovery following HSCT.

[0011] In one aspect, the invention relates to composition comprising a recombinant human interleukin-12 (rHuIL-12) and/or its mouse homologue, IL-12 (rMuIL-12), and methods of using those compositions to reconstitute bone marrow using a single, low dose administered either before or after total body irradiation (TBI). It has been surprisingly shown, for example, that recombinant human interleukin-12 (rHuIL-12) and its mouse homologue, IL-12 (rMuIL-12) have the remarkable ability to reconstitute bone marrow using a single, low dose administered either before or after total body irradiation (TBI).

[0012] In other aspects the invention relates to methods of administering rHuIL-12 to stimulate hematopoiesis, which can act, for example, through interaction of rHuIL-12 with IL-12 receptors expressed on HSC and niche cells. In other aspects, the invention relates to methods of treating with rHuIL-12 as an adjunct to hematopoietic cellular transplants or other methods for enhancing HSC engraftment and bone marrow recovery following transplantation.

[0013] In one aspect, a method of protecting a subject from system, organ, tissue, or cellular damage, following exposure of the subject to ionizing radiation comprising: administering a dose of therapeutically effective amount of a pharmaceutical composition comprising substantially isolated IL-12 to the subject following myoablation and non-myoablation. Exemplary myeloablative methods can include for example, radiation,

WHAT IS CLAIMED IS:

1. Use of a pharmaceutical composition in the manufacture of a medicament for restoring hematopoiesis and reducing infection complications in a human subject, wherein:

(a) the pharmaceutical composition comprises Interleukin-12 (IL-12) in an effective dose of about 10 to about 300 ng/kg of IL-12, and

(b) the pharmaceutical composition is to be administered in one or more effective dose(s) within 72 hours or less following myeloablative therapy, within 72 hours or less prior to myeloablative therapy, or within 72 hours or less prior to and within 72 hours or less following myeloablative therapy, wherein the myeloablative therapy is to be administered prior to a hematopoietic stem cell transplant.

2. Use of a pharmaceutical composition in the manufacture of a medicament for restoring hematopoiesis and reducing infectious complications in a human subject wherein:

(a) the pharmaceutical composition comprises Interleukin-12 (IL-12) in an effective dose of about 10 to about 300 ng/kg of IL-12, and

(b) the pharmaceutical composition is to be administered in one or more effective dose(s) within 72 hours or less following myeloablative therapy, within 72 hours or less prior to myeloablative therapy, or within 72 hours or less prior to and within 72 hours or less following myeloablative therapy, wherein the myeloablative therapy is to be administered prior to a hematopoietic stem cell transplant, and wherein hematopoiesis is restored via activation of the IL-12 receptor on hematopoietic cells in the bone marrow.

3. The use of claim 1 or 2, where radiation therapy is used in the myeloablative therapy.

4. The use of claim 1 or 2, where chemotherapy is used in the myeloablative therapy.

5. The use of claim 1 or 2, wherein the myeloablative therapy is a combination of radiation therapy and chemotherapy.

6. The use of any one of claims 1-5, wherein hematopoiesis is restored via an increased number of progenitor cells in the bone marrow.

7. The use of any one of claims 1-6, wherein hematopoiesis is restored in the peripheral blood.

8. The use of claim 7, wherein peripheral blood counts are increased.

9. The use of claim 7 or 8, wherein platelets are increased.

10. The use of any one of claims 7-9, wherein white blood cells are increased.

11. The use of any one of claims 7-10, wherein reticulocytes are increased.

12. The use of any one of claims 7-11, wherein red blood cells are increased.

13. The use of any one of claims 2-12, wherein the hematopoietic cells comprise niche cells and stem cells.

14. The use of claim 13, wherein the niche cells comprise osteoblasts.

15. The use of any one of claims 2-12, where hematopoiesis is restored following activation of the IL-12 receptor on megakaryocytes.

16. The use of claim 15, wherein the megakaryocytes are immature.

17. The use of any one of claims 2-14, wherein hematopoiesis is restored following activation of the IL-12 receptor on osteoblastic cells, megakaryocyte cells, and hematopoietic stem cells in the bone marrow.

18. The use of any one of claims 1-17, wherein the hematopoietic stem cell transplant is an autologous transplant.

19. The use of any one of claims 1-17, wherein the hematopoietic stem cell transplant is an allogenic transplant.

20. The use of any one of claims 1-19, wherein mobilization and collection of hematopoietic stem cells is to be done prior to myeloablative therapy.

21. The use of claim 20, wherein mobilization and collection of hematopoietic stem cells yields a low count of CD34+ cells.

22. The use of any one of claims 1-21, wherein the myeloablative therapy is given to treat a hematopoietic malignancy selected from the group consisting of chronic myeloid leukemia, chronic lymphocytic leukemia, mantle cell lymphoma, low-grade non-Hodgkin's lymphoma, acute myeloid leukemia, intermediate grade lymphoma, multiple myeloma, myelodysplastic syndrome and Hodgkin's disease.

23. The use of any one of claims 1-22, wherein the IL-12 is a recombinant human IL-12.