WHAT IS CLAIMED IS:

1. A method of preparing a population of hematopoietic stem cells (HSCs), the method comprising:
providing a population comprising endothelial and/or hemogenic endothelial (HE) cells, and increasing activity or expression of DNA (cytosine-5-)-methyltransferase 3 beta (Dnmt3b) and/or GTPase IMAP Family Member 6 (Gimap6) in the cells,
under conditions sufficient for stimulating formation of HSCs.

2. The method of claim 1, further comprising, recovering the HSCs.

3. The method of claim 2, comprising contacting the endothelial and/or HE cells with an effective amount of an agonist that increases the activity or expression of Dnmt3b.

4. The method of claim 3, wherein the agonist is of a mechanosensitive receptor or a mechanosensitive channel.

5. The method of claim 4, wherein the mechanosensitive receptor is Piezo1.

6. The method of claim 5, wherein the Piezo1 agonist is Yoda1.

7. The method of claim 6, wherein the effective amount of the Yoda1 agonist is in the range of 5 to 500 uM, or in the range of 5 to 100 μM.

8. The method of any one of claims 1 to 7, wherein the increasing activity or expression of Dnmt3b comprises increasing the mRNA expression of Dnmt3b, introducing a Dnmt3b transgene and/or an episome, and/or introducing a genetic modification of Dnmt3b expression elements in the endothelial and/or HE cells.

9. The method of claim 1, wherein the endothelial and/or HE cells are derived from HLA-modified or HLA-null cells, and/or transgene-free cells, and are optionally derived by genetic or chemical induction of iPS cells or somatic cells .

10. The method of any one of claims 1 to 9, wherein source cells are obtained or derived from a subject, wherein the subject is optionally a universally compatible donor.

11. The method of claim 10, wherein the source cells are obtained or derived from a subject who has a blood, bone marrow, metabolic, or immune disease.

12. The method of claim 11, wherein the subject does not have a hematological malignancy.

13. The method of claim 10, wherein the population of HSCs are to be administered to a recipient.

14. The method of claim 13, wherein the source cells were derived from the recipient.

15. The method of any one of claims 1 to 14, wherein the hematopoietic stem cells comprise long term hematopoietic stem cells (LT-HSCs).

16. The method of claim 15, further comprising providing biomechanical stimuli to increase the activity or expression of Dnmt3b.

17. The method of any one of claims 1 to 16, further comprising increasing the activity or expression of *Gimap6* in the endothelial cells.

18. The method of claim 17, wherein the increasing activity or expression of *Gimap6* comprises increasing the mRNA expression of *Gimap6*, introducing a *Gimap6* transgene, and/or introducing an episome, and/or introducing a genetic modification of *Gimap6* expression elements in the HE cells.

19. The method of claim 1, wherein the method comprises providing a population comprising hemogenic endothelial (HE) cells to a bioreactor.

20. The method of claim 19, wherein the bioreactor provides a cyclic-strain biomechanical stretching.

21. The method of claim 20, wherein the cyclic-strain biomechanical stretching increases the activity or expression of Dnmt3b.

22. The method of claim 20, wherein the cyclic-strain biomechanical stretching increases the activity or expression of Gimap6.

23. The method of any one of claims 1 to 22, wherein the HSCs engraft in a hematopoietic niche and reconstitute to functional, multi-lineage adult blood.

24. The method of any one of claims 1 to 23, wherein HE cells are obtained from induced pluripotent stem cells (iPSCs), non-hematopoietic stem cells, somatic cells, or endothelial cells.

25. A pharmaceutical composition comprising a population of HSCs prepared by the method of any one of claims 1 to 24, and a pharmaceutically acceptable vehicle.

26. The pharmaceutical composition of claim 25, comprising at least $10^2$ cells.

27. Use of a therapeutically effective amount of hematopoietic stem cells (HSCs) prepared by the method of any one of claims 1 to 24 or the pharmaceutical composition of claims 25 or 26 in the manufacture of a medicament for treating a subject in need of hematopoietic stem cell therapy or transplantation, wherein the medicament is to be administered to the subject.

28. The use of claim 27, wherein the subject has malignant or non-malignant form of blood, bone marrow, metabolic, or immune disease.

29. The use of claim 27 or 28, wherein the subject has multiple myeloma; non-Hodgkin lymphoma; Hodgkin disease; acute myeloid leukemia; neuroblastoma; a germ cell tumor; an autoimmune disorder (systemic lupus erythematosus (SLE) or systemic sclerosis); myelodysplastic syndrome, or amyloidosis.

30. The hematopoietic stem cells (HSCs) prepared by the method of any one of claims 1 to 24, or the pharmaceutical composition of claims 25 or 26, for use in treating a subject in need of hematopoietic stem cell therapy or transplantation.

31. The HSCs or pharmaceutical composition for the use of claim 30, wherein the subject has malignant or non-malignant form of blood, bone marrow, metabolic, or immune disease.

32. The HSCs or pharmaceutical composition for the use of claim 30 or 31, wherein the subject has multiple myeloma; non-Hodgkin lymphoma; Hodgkin disease; acute myeloid leukemia; neuroblastoma; a germ cell tumor; an autoimmune disorder (systemic lupus erythematosus (SLE) or systemic sclerosis); myelodysplastic syndrome, or amyloidosis.