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 *ex vivo*, ~~and~~

increasing activity or expression of DNA (cytosine-5-)-methyltransferase 3 beta (Dnmt3b) ~~and/or GTPase IMAP Family Member 6 (Gimap6)~~ in the cells, by contacting the cells with an effective amount of a Piezo1 agonist or introducing an Dnmt3b-encoding episome or Dnmt3b-encoding transcript into the cells,

under conditions sufficient for stimulating formation of HSCs, and

recovering the 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.~~

2~~6~~. The method of claim ~~5~~1, wherein the Piezo1 agonist is Yoda1.

3~~7~~. The method of claim ~~6~~2, 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.

4~~8~~. The method of ~~any one of claims 1 to 7~~claim 1, wherein the increasing activity or expression of Dnmt3b comprises introducing an Dnmt3b-encoding episome or Dnmt3b-encoding transcript in the cells~~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~~.

5~~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~~-~~.

610. The method of any one of claims 1 to ~~9~~5, wherein source cells are obtained or derived from a subject, wherein the subject is optionally a universally compatible donor.

711. The method of claim ~~10~~6, wherein the source cells are obtained or derived from a subject who has a blood, bone marrow, metabolic, or immune disease.

812. The method of claim ~~11~~7, 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.~~

914. The method of claim ~~13~~6, wherein the source cells were derived from ~~the~~a recipient for which administration of the HSCs is intended.

1015. The method of any one of claims 1 to ~~14~~9, 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.~~

1119. 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.~~

1223. The method of any one of claims 1 to 2211, wherein administration of the HSCs result in engraftengraftment in a hematopoietic niche and reconstitutionreconstitute to functional, multi-lineage adult blood.

1324. The method of any one of claims 1 to 2312, wherein HE cells are obtained from Embryoid Bodies differentiated 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.~~