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*,
increasing activity or expression of DNA (cytosine-5-)-methyltransferase 3 beta (Dnmt3b) 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, wherein the Piezo1 agonist is Yoda1.

3. The method of claim 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. The method of claim 1, wherein the increasing activity or expression of Dnmt3b comprises introducing an Dnmt3b-encoding episome or Dnmt3b-encoding transcript in the cells.

5. 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.

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

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

8. The method of claim 7, wherein the subject does not have a hematological malignancy.

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

10. The method of any one of claims 1 to 9, wherein the hematopoietic stem cells comprise long term hematopoietic stem cells (LT-HSCs).

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

12. The method of any one of claims 1 to 11, wherein administration of the HSCs result in engraftment in a hematopoietic niche and reconstitution to functional, multi-lineage adult blood.

13. The method of any one of claims 1 to 12, wherein HE cells are obtained from Embryoid Bodies differentiated from induced pluripotent stem cells (iPSCs).