CLAIMS:

1. A method of expanding hematopoietic stem cells, comprising

culturing a population of hematopoietic cells in the presence of mesenchymal lineage precursor or stem cells (MLPSCs) and at least one histone deacetylase inhibitor (HDACi) such that hematopoietic stem cells having the phenotype CD34+ are expanded.

2. The method of claim 1 wherein hematopoietic stem cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+ are expanded at least 5-fold, or at least 10-fold, or at least 20-fold, or at least 40-fold.

3. The method of claim 1 or claim 2 wherein the HDACi is selected from the group consisting of valproic acid (VPA), trichostatin (TSA), DLS3, MS275, SAHA, and HDAC6 inhibitorl61.

4. The method of claim 3 wherein the HDACi is VPA or TSA.

5. The method of any one of claims 1 to 4, wherein the hematopoietic cells are also cultured in the presence of one or more growth factors elected from the group consisting of: stem cell factor (SCF), flt3 ligand (FL), TPO, IL3 and IL6.

6. The method of any one of claims 1 to 5, wherein the hematopoietic cells are also cultured in the presence of one or more stem cell renewal agents selected from the group consisting of SR1 and UM171.

7. The method of any one of claims 1 to 6, wherein the MLPSCs are isolated by immunoselection and culture expanded.

8. The method of any one of claims 1 to 7, wherein the MLPSCs are culture expanded mesenchymal stem cells.

9. The method of any one of claims 1 to 8 wherein the population of hematopoietic cells is derived from bone marrow, umbilical cord, peripheral blood, liver, thymus, lymph or spleen.

10. The method of any one of claims 1 to 9 which further comprises isolating cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+ following culture expansion to provide an enriched population of cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+.

11. The method of any one of claims 1 to 9 which further comprises removing cells having the phenotype CD34+, CD45RA-, CD90+, CD49f+ following culture expansion to provide an enriched population of cells having the phenotype CD34+, CD49f-.

12. The method of claim 10 which further comprises introducing a heterologous nucleic acid into enriched cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+.

13. The method of claim 11 which further comprises introducing a heterologous nucleic acid into enriched cells having the phenotype CD34+, CD49f-.

14. The method according to any one of claims 1 to 9 wherein the MLPSCs comprise a heterologous nucleic acid molecule which is transferred to the hematopoietic stem cells having the phenotype CD34+, CD45RA-, CD90+, CD49f+ during culture expansion.

15. The method according to any one of claims 12 to 14 wherein the heterologous nucleic acid is present in the form of an expression vector.

16. The method according to claim 15 wherein the expression vector is selected from the group consisting of Lentivirus, Baculovirus, Retrovirus, Adenovirus (AdV), Adeno-associated virus (AAV) and a recombinant form thereof.

17. The method according to any one of claims 12 to 16 wherein the heterologous nucleic acid encodes a protein selected from the group consisting of a clotting factor, a hormone or a cytokine.

18. The method according to any one of claims 12 to 14 wherein the heterologous nucleic acid is a CRISPR system.

19. The method according to claim 18 wherein the CRISPR system comprises a Cas expression vector and a guide nucleic acid sequence specific for an endogenous gene in the hematopoietic stem cells.

20. The method of claim 18, wherein the CRISPR. system, comprises a Cas9 protein complexed with a guide nucleic acid sequence specific for an endogenous gene in the HSC.

21. The method of any one of claims 15 to 20, wherein the expression vector or the CRISPR system comprises an inducible promoter.

22. The method of claim 21, further comprising exposing the hematopoietic stem cell to an agent that activates the inducible promoter.

23. A composition comprising hematopoietic stem cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+ obtained by a method according to any one of claims 1 to 12 or 14 to 22.

24. A composition comprising hematopoietic stem cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD90+, CD45RA-, CD49f+ and MLPSCs at a ratio of at least 1:20, or at least 1:10, or at least 1:5, or at least 1:4.5, or at least 1:4 respectively.

25. The composition according to claim 23 or claim 24 further comprising a HDACi.

26. A composition comprising hematopoietic stem cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+, MLPSCs and an HDACI inhibitor.

27. The composition according to any one of claims 23 to 26 wherein the (i) CD34+, CD90+ or (ii) CD34+, CD90+, CD45RA-, CD49f+ cells comprises a heterologous nucleic acid molecule.

28. A composition according to claim 27 wherein the heterologous nucleic acid encodes a protein selected from the group consisting of a clotting factor, a hormone or a cytokine.

29. A composition according to claim 27 wherein the heterologous nucleic acid comprises a CRISPR system.

30. A composition according to any one of claims 23 to 29 wherein hematopoietic stem cells having the phenotype CD34+, CD90+, CD45RA-, CD49f+ constitute at least 2% of the total cells in the composition.

31. A composition according to any one of claims 23 to 30 wherein said composition contains a total amount of cells of at least 10^5 cells, 10^7 cells, 10^8 cells or 10^9 cells.

32. A method of treating a hematologic disorder in a subject in need thereof which comprises administering to the subject composition according to any one of claims 23 to 31.

CLAIMS

1. A method of expanding hematopoietic stem cells, comprising

culturing a population of hematopoietic stem cells in the presence of mesenchymal lineage precursor or stem cells (MLPSCs) and at least one histone deacetylase inhibitor (HDACi) such that hematopoietic stem cells having the phenotype CD34+ are expanded.

2. A method according to Claim 1, in which hematopoietic stem cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+ are expanded at least 5-fold, or at least 10-fold, or at least 20-fold, or at least 40-fold.

3. A method according to Claim 1 or 2, in which the HDACi is selected from the group consisting of valproic acid (VPA), trichostatin (TSA), DLS3, MS275, SAHA, and HDAC6 inhibitorl61.

4. A method according to Claim 3, in which the HDACi is VPA or TSA.

5. A method according to any preceding claim, in which the hematopoietic cells are also cultured in the presence of one or more growth factors elected from the group consisting of: stem cell factor (SCF), flt3 ligand (FL), TPO, IL3 and IL6.

6. A method according to any preceding claim, in which the hematopoietic cells are also cultured in the presence of one or more stem cell renewal agents selected from the group consisting of SR1 and UM171.

7. A method according to any preceding claim, in which the MLPSCs are isolated by immunoselection and culture expanded.

8. A method according to any preceding claim, in which the MLPSCs are culture expanded mesenchymal stem cells.

9. A method according to any preceding claim, in which the population of hematopoietic cells is derived from bone marrow, umbilical cord, peripheral blood, liver, thymus, lymph or spleen.

10. A method according to any preceding claim, which further comprises isolating cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+

following culture expansion to provide an enriched population of cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+.

11. A method according to any of Claims 1 to 9, which further comprises removing cells having the phenotype CD34+, CD45RA-, CD90+, CD49f+ following culture expansion to provide an enriched population of cells having the phenotype CD34+, CD49f-.

12. A method according Claim 10, which further comprises introducing a heterologous nucleic acid into enriched cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+.

13. A method according to Claim 11, which further comprises introducing a heterologous nucleic acid into enriched cells having the phenotype CD34+, CD49f-.

14. A method according to any of Claims 1 to 9, in which the MLPSCs comprise a heterologous nucleic acid molecule which is transferred to the hematopoietic stem cells having the phenotype CD34+, CD45RA-, CD90+, CD49f+ during culture expansion.

15. A method according to Claim 12, 13 or 14, in which the heterologous nucleic acid is present in the form of an expression vector.

16. A method according to Claim 15, in which the expression vector is selected from the group consisting of Lentivirus, Baculovirus, Retrovirus, Adenovirus (AdV), Adeno-associated virus (AAV) and a recombinant form thereof.

17. A method according to any of Claims 12 to 16, in which the heterologous nucleic acid encodes a protein selected from the group consisting of a clotting factor, a hormone or a cytokine.

18. A method according to any of Claims 12 to 14, in which the heterologous nucleic acid is a CRISPR system.

19. A method according to Claim 18, in which the CRISPR system comprises a Cas expression vector and a guide nucleic acid sequence specific for an endogenous gene in the hematopoietic stem cells.

20. A method according to Claim 18, in which the CRISPR. system, comprises a Cas9 protein complexed with a guide nucleic acid sequence specific for an endogenous gene in the HSC.

21. A method according to any of Claims 15 to 20, in which the expression vector or the CRISPR system comprises an inducible promoter.

22. A method according to Claim 21, further comprising exposing the hematopoietic stem cell to an agent that activates the inducible promoter.

23. A composition comprising hematopoietic stem cells having the phenotype (i) CD34+, CD90+ or (ii) CD34+, CD45RA-, CD90+, CD49f+, MLPSCs and an HDAC inhibitor.

24. A composition according to Claim 23, in which the (i) CD34+, CD90+ or (ii) CD34+, CD90+, CD45RA-, CD49f+ cells comprises a heterologous nucleic acid molecule.

25. A composition according to Claim 24, in which the heterologous nucleic acid encodes a protein selected from the group consisting of a clotting factor, a hormone or a cytokine.

26. A composition according to Claim 24, in which the heterologous nucleic acid comprises a CRISPR system.

27. A composition according to any of Claims 23 to 26, in which hematopoietic stem cells having the phenotype CD34+, CD90+, CD45RA-, CD49f+ constitute at least 2% of the total cells in the composition.

28. A composition according to any of Claims 23 to 27, in which the composition contains a total amount of cells of at least 10^5 cells, 10^7 cells, 10^8 cells or 10^9 cells.

29. Use of a composition according to any of Claims 23 to 28 in the manufacture of a medicament for the treatment of a hematologic disorder.