Claims

1. A composition for treating hemoglobinopathy, the composition comprising:

a second population of modified CD34-positive hematopoietic stem cells/progenitor cells ("CD34-positive HSPCs"),

wherein the second population of the modified CD34-positive HSPCs (“modified TR cells”) are derivedfrom an individual and are modified to reduce BCL11A function,

wherein the individual is selected for treatment based on afunctional evaluation from an evaluation step which comprises: evaluating the ability of a first population of modified CD34-positive HSPCs ("modified EV cells")to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiation, and

wherein the first populationof the modified CD34-positive HSPCs are derived from the individual and are modified to reduce BCL11A function.

2. The composition according to claim 1, wherein the evaluation step comprises:

a)isolating CD34-positive HSPCs from the bone marrow or peripheral blood sample of the individual to obtain an isolated CD34-positive HSPCs population ("isolated EV cells");

b)modifying the isolated EV cells to obtain a first population of the modified CD34-positive HSPCs cells with reduced BCL11A function ("modified EV cells");

c)evaluating the ability of the modified EV cells to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiation; and

wherein the second population of the modified CD34-positive HSPCs with reduced BCL11A function ("modified TR cells")are obtained by:

a’)mobilizing the CD34-positive HSPCs in the bone marrow of the individual to increase the amount of CD34-positive HSPCs in the peripheral blood;

b’)isolating CD34-positive HSPCs from the peripheral blood of the individual to obtain an isolated CD34-positive HSPCs population ("isolated TR cells"); and

c’)modifying the isolated TR cells to obtain the second population of the modified CD34-positive HSPCs with reduced BCL11A function ("modified TR cells").

3. The composition according to Claim 1, wherein the modified EV cells are modified by genetic modification, and/or the modified EV cells are obtained by genetically modifying the isolated EV cells, particularly, the isolated EV cells are genetically modifiedby a technology selected from the group consisting of: zinc finger nuclease (ZFN), transcription activator-like effector nuclease (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPRs), RNA editing, RNA interference.

4. The composition according to Claim 1, wherein the ability of the modified EV cells to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiation is evaluated in the evaluation step comprising:

1) culturing the modified EV cells under conditions allowing differentiation to obtain an erythrocyte population; and

2) determining the level of γ-globulin or fetal hemoglobin (HbF) produced by the erythrocytes.

5. The composition according to Claim 1, wherein the ability of the modified EV cells to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiation is evaluated in the evaluation step comprising: determining the mRNA level of γ-globulin, and/or

wherein the ability of the modified EV cells to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiationis evaluated in the evaluation step comprising: determining the protein level of fetal hemoglobin (HbF).

6. The composition according to Claim 1, wherein the individual has not undergone mobilization or pretreatment prior to the evaluation step, and/or

wherein the evaluation step is repeated at least once prior use in an individual.

7. The composition according to Claim 1, wherein the modified TRcells are modified by genetic modification.

8. The composition according to Claim 2, wherein the step of modifying the isolated TR cells comprises the step of genetically modifying the isolated TR cells by a technology selected from the group consisting of: zinc finger nuclease (ZFN), transcription activator-like effector nuclease (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPRs), RNA editing, RNA interference.

9. The composition according to Claim 2, wherein the step of mobilizing the CD34-positive HSPCs comprises the step of treating an individual with granulocyte colony stimulating factor (GCSF) and/or plerixafor.

10. The composition according to Claim 1, wherein the modified TR cells are for use in an individual who has been pretreated,

wherein, particularly,the pretreatment comprises chemotherapy, monoclonal antibody therapy, or systemic radiation,

wherein, more particularly,the pretreatment comprises chemotherapy,

wherein, further more particularly,the chemotherapy comprises use of one or more chemotherapeutic agents selected from the group consisting of: busulfan, cyclophosphamide, and fludarabine.

11. The composition according to Claim 2, wherein the isolated TR cells are cultured for one or more days prior to modification,

Wherein, particularly,the modified TR cells are cultured for one or more days prior to use in the individual.

12. The composition according to Claim 1, wherein the modified TR cells are stored under a freezing condition for at least 24 hours prior to use in the individual, and

Wherein, particularly,the modified TR cells are cultured for one or more days prior to being stored under a freezing condition.

13. The composition according to Claim 1, wherein the hemoglobinopathy is a disease selected from the group consisting of: sickle cell disease, sickle cell trait, hemoglobin C disease, hemoglobin C trait, hemoglobin S/C disease, hemoglobin D disease, hemoglobin E disease, thalassemia, hemoglobin-related disorder with increased oxygen affinity, hemoglobin-related disorder with decreased oxygen affinity, unstable hemoglobin disease and methemoglobinemia, and

particularly,the hemoglobinopathy is selected from the group consisting of: β-thalassemia and sickle cell anemia, more particularly, the hemoglobinopathy is β^0 or β^+ thalassemia.

14. The composition according to Claim 1, wherein the modified TR cells are for use immediately following the evaluation step.

15. A method to provide an information for determining whether an individual suffering from hemoglobinopathy is suitable or unsuitable for treating with a second population of the modified CD34-positive HSPCs ("modified TR cells") derived from the individual and modified to reduce BCL11A function;

wherein the method comprises an evaluation step comprising: evaluating the ability of a first population of the modified CD34-positive HSPCs to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiation;

wherein the first population of the modified CD34-positive HSPCs are derived from the individual and are modified to reduce BCL11A function ("modified EV cells");

wherein if the first population of the modified CD34-positive HSPCs produce a desired level of γ-globin or fetal hemoglobin (HbF), the individual is determined to be suitable for treatment; and

wherein if the first population of the modified CD34-positive HSPCs do not produce a desired level of γ-globin or fetal hemoglobin (HbF), the individual is determined not to be suitable for treating with the modified TR cells.

16. The method according to Claim 15, wherein the evaluation step comprises:

a)isolating CD34-positive HSPCs from the bone marrow or peripheral blood sample of the individual to obtain an isolated CD34-positive HSPCs population ("isolated EV cells");

b)modifying the isolated EV cells to obtain a first population of the modified CD34-positive HSPCs cells with reduced BCL11A function ("modified EV cells");

c)evaluating the ability of the modified EV cells to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiation; and

wherein the second population of the modified CD34-positive HSPCs with reduced BCL11A function ("modified TR cells")are obtained by:

a')mobilizing the CD34-positive HSPCs in the bone marrow of the individual to increase the amount of CD34-positive HSPCs in the peripheral blood;

b')isolating CD34-positive HSPCs from the peripheral blood of the individual to obtain an isolated CD34-positive HSPCs population ("isolated TR cells");

c')modifying the isolated TR cells to obtain the second population of the modified CD34-positive HSPCs with reduced BCL11A function ("modified TR cells"); and

wherein the modified TR cells are for use in treating an individual suffering from hemoglobinopathy

17. The method according to Claim 15, wherein the modified EV cells are modified by genetic modification, and/or the modified EV cells are obtained by genetically modifying the isolated EV cells, particularly, the isolated EV cells aregenetically modifiedby a technology selected from the group consisting of: zinc finger nuclease (ZFN), transcription activator-like effector nuclease (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPRs), RNA editing, RNA interference.

18. The method according to Claim 15, wherein the ability of the modified EV cells to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiation is evaluated in the evaluation step comprising:

1) culturing the modified EV cells under conditions allowing differentiation to obtain an erythrocyte population; and

2) determining the level of γ-globulin or fetal hemoglobin (HbF) produced by the erythrocytes.

19. The method according to Claim 15, wherein the ability of the modified EV cells to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiation is evaluated in the evaluation step comprising: determining the mRNA level of γ-globulin, and/or

whereinthe ability of the modified EV cells to produce a desired level of γ-globin or fetal hemoglobin (HbF) after differentiationis evaluated in the evaluation step comprising: determining the protein level of fetal hemoglobin (HbF).

20. The method according to Claim 15, wherein the individual has not undergone mobilization or pretreatment prior to the evaluation step, and/or

whereinthe evaluation step is repeated at least once prior use in an individual.

21. The method according to Claim 15, wherein the modified TRcells are modified by genetic modification.

22.The method according to Claim 16, wherein the step of modifying the isolated TR cells comprises: the step of genetically modifying the isolated TR cells by a technology selected from the group consisting of: zinc finger nuclease (ZFN), transcription activator-like effector nuclease (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPRs), RNA editing, RNA interference.

23. The method according to Claim 16, wherein the step of mobilizing the CD34-positive HSPCs comprises: the step of treating an individual with granulocyte colony stimulating factor (GCSF) and/or plerixafor.

24. The method according to Claim 15, wherein the modified TR cells are for use in an individual who has been pretreated,

wherein, particularly, the pretreatment comprises chemotherapy, monoclonal antibody therapy, or systemic radiation,

wherein, more particularly,the pretreatment comprises chemotherapy, and

wherein, further more particularly,the chemotherapy comprises use of one or more chemotherapeutic agents selected from the group consisting of: busulfan, cyclophosphamide, and fludarabine.

25. The method according to Claim 16, wherein the isolated TR cells are cultured for one or more days prior to modification, and

wherein, particularly, the modified TR cells are cultured for one or more days prior to use in the individual.

26. The method according to Claim 15, wherein the modified TR cells are stored under a freezing condition for at least 24 hours prior to use in the individual, and

wherein, particularly,the modified TR cells are cultured for one or more days prior to being stored under a freezing condition.

27. The method according to Claim 15, wherein the hemoglobinopathy is a disease selected from the group consisting of: sickle cell disease, sickle cell trait, hemoglobin C disease, hemoglobin C trait, hemoglobin S/C disease, hemoglobin D disease, hemoglobin E disease, thalassemia, hemoglobin-related disorder with increased oxygen affinity, hemoglobin-related disorder with decreased oxygen affinity, unstable hemoglobin disease and methemoglobinemia, and

particularly, the hemoglobinopathy is selected from the group consisting of: β-thalassemia and sickle cell anemia, more particularly, the hemoglobinopathy is β^0 or β^+ thalassemia.

28. The method according to Claim 15, wherein the modified TR cells are for use immediately following the evaluation step.