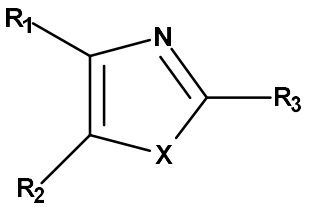
Claims:

1. A method for *ex vivo* expansion of ~~the~~ a total nucleated cells and/or ~~the~~ a subset of ~~the~~ a CD45+CD34+ hematopoietic stem cells and progenitor cells component of an umbilical cord blood, bone marrow ~~and/~~or mobilized peripheral blood ~~stem cell~~ sample comprising the steps of:

(i) culturing a total nucleated cells or a mononucleated cell fraction ~~and/~~or CD45+CD34+ hematopoietic stem cells and progenitor cells component of the sample in media; and

(ii) contacting the cell(s) of step (i) with a composition comprising at least one azole-based small molecule.

~~2. The method according to claim 1,~~ wherein the at least one azole based small molecule is represented by formula (I),



wherein:

X represents NR_4, or O ~~or S~~, where R_4 is H or methyl;

R_1 represents phenyl or pyridinyl ~~C_{6-10} aryl or a 6- to 10-membered heteroaromatic ring system~~ (which are unsubstituted or substituted with one or more substituents selected from Cl, Br, F and methyl ~~halo, C_{1-6} alkyl, C_{1-6} alkenyl or C_{1-6} alkynyl~~ (which latter ~~three~~ group~~s~~ ~~are~~ is unsubstituted or substituted with ~~one or more groups selected from halo~~F));

R_2 represents phenyl, pyridyl or dihydropyranyl ~~C_{6-10} aryl or a 6- to 10-membered heterocyclic ring system~~ (which are unsubstituted or substituted with one or more substituents selected from Cl, Br, F and methyl ~~halo, C_{1-6} alkyl, C_{1-6} alkenyl or C_{1-6} alkynyl~~ (which latter ~~three~~ group~~s~~ ~~are~~ is unsubstituted or substituted with ~~one or more groups selected from halo~~F));

R_3 represents ~~C_{6-16} aryl~~H, or naphthyl which~~that~~ is unsubstituted or substituted with one or more groups selected from Cl, F and ~~halo,~~ OR_5, ~~C_{1-6} alkyl, C_{1-6} alkenyl or C_{1-6} alkynyl (which latter three groups are unsubstituted or substituted with one or more groups selected from halo)~~ where R_5 is H or methyl, or;

~~R_4 and R_5 are independently selected from H or C_{1-4} alkyl (which latter group is unsubstituted or substituted with one or more groups selected from halo), or~~

salts and solvates thereof.

~~3. The method according to claim 2, wherein in formula I, X represents NR_4 or O.~~

~~4. The method according to claim 2 or 3, wherein in formula I, R_1 represents phenyl or a 6-membered heteroaromatic ring system (which are unsubstituted or substituted with one or more substituents selected from halo, C_{1-3} alkyl, (wherein the latter group is unsubstituted or substituted with one or more groups selected from halo)).~~

~~5. The method according to claim 4, wherein in formula I, R_1 represents phenyl or pyridinyl (which are unsubstituted or substituted with one or more substituents selected from Cl, Br, F and methyl (which latter group is unsubstituted or substituted with one or more groups selected from F)).~~

~~6. The method according to any one of claims 2 to 5, wherein in formula I, R_2 represents phenyl or a 6-membered heterocyclic ring system (which are unsubstituted or substituted with one or more substituents selected from halo or C_{1-3} alkyl (which latter group is unsubstituted or substituted with one or more groups selected from halo).~~

~~7. The method according to claim 6, wherein in formula I, R_2 represents phenyl, pyridyl or dihydropyranyl (which are unsubstituted or substituted with one or more substituents selected from Br, Cl, F or methyl (which latter group is unsubstituted or substituted with one or more groups selected from F).~~

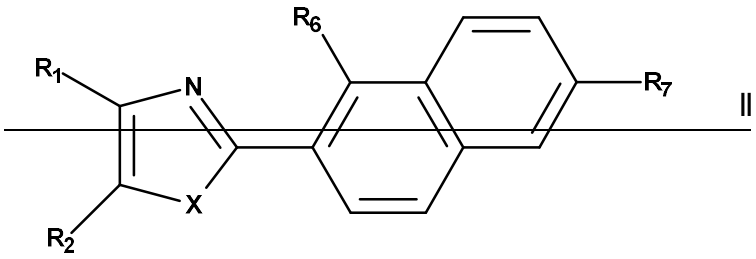
~~8. The method according to any one of claims 2 to 7, wherein in formula I, R_3 represents C_{10-16} aryl that is unsubstituted or substituted with one or more groups selected from halo, OR_5 and C_{1-3} alkyl (which latter group is unsubstituted or substituted with one or more groups selected from halo).~~

~~9. The method according to claim 8, wherein in formula I, R_3 represents naphthyl, phenanthracenyl or pyrenyl (which are unsubstituted or substituted with one or more groups selected from Br, Cl, F, OR_5 and methyl (which latter group is unsubstituted or substituted with one or more groups selected from F).~~

~~10. The method according to claim 9, wherein in formula I, R_3 represents naphthyl which group is unsubstituted or substituted with one or more groups selected from Cl, F, and OR_5.~~

~~11. The method according to any one of claims 2 to 10, wherein in formula I, R_4 and R_5 are independently selected from H or methyl (which latter group is unsubstituted or substituted with one or more groups selected from F).~~

~~12. The method according to any one of claims 2 to 11, wherein the compound of formula I is represented as a compound of formula II,~~



II

~~wherein:~~

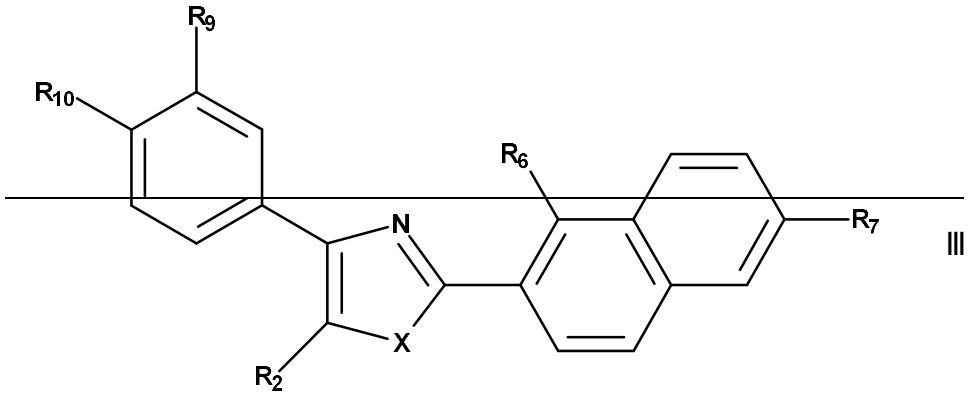
~~R_6 represents H, Cl, Br and F;~~

~~R_7 represents H, Cl, Br, F, OR_8;~~

~~R_8 represents C_{1-3} alkyl which is unsubstituted or substituted with one or more substituents selected from Cl and F; and~~

~~R_1 and R_2 are as defined in any of claims 2 to 11, or salts and solvates thereof.~~

~~13. The method according to any one of claims 2 to 11, wherein the compound of formula I is represented as a compound of formula III,~~



III

~~wherein:~~

~~R_9 represents H, Cl, Br, F or C_{1-3} alkyl (which is unsubstituted or substituted with one or more substituents selected from Cl and F);~~

~~R_{10} represents H, Cl, Br, or F;~~

~~R_2 is as defined in any of claims 2 to 12; and~~

~~R_6 and R_7 are as defined in claim 12, or salts and solvates thereof.~~

~~14~~2. The method according to ~~any one of claims 1 to 13~~claim 1, wherein the at least one azole-based small molecule is selected from:

(A) the list:

(i) 4-[2-(1-fluoronaphthalen-2-yl)-4(5)-(4-fluorophenyl)-1*H*-imidazol-5(4)-yl]pyridine;

(ii) 4-[2-(1-fluoronaphthalen-2-yl)-4-(*m*-tolyl)-1*H*-imidazol-5-yl]pyridine;

(iii) 4-[2-(naphthalen-2-yl)-4(5)-(*m*-tolyl)-1H-imidazol-5(4)-yl]pyridine;

(iv) 4-[2-(naphthalen-2-yl)-4(5)-(4-fluorophenyl)-1*H*-imidazol-5(4)-yl]pyridine;

(v) 4-[2-(1-bromonaphthalen-2-yl)-4(5)-(4-fluorophenyl)-1*H*-imidazol-5(4)-yl]pyridine;

(vi) 4-[2-(1-fluoronaphthalen-2-yl)-4-[3-(trifluoromethyl)phenyl]-1*H*-imidazol-5-yl]pyridine;

(vii) 2-(1-fluoronaphthalen-2-yl)-4-(pyridin-4-yl)-5-(*m*-tolyl)oxazole;

(viii) 5(4)-(3,6-dihydro-2*H*-pyran-4-yl)-2-(1-fluoronaphthalen-2-yl)-4(5)-(*m*-tolyl)-1*H*-imidazole;

(ix) 5(4)-(3,6-dihydro-2*H*-pyran-4-yl)-2-(6-methoxynaphthalen-2-yl)-4(5)-(*m*-tolyl)-1*H*-imidazole; and

(x) 5(4)-(3,6-dihydro-2*H*-pyran-4-yl)-2-(1-fluoronaphthalen-2-yl)-4(5)-(4-fluorophenyl)-1*H*-imidazole;

(xi) 4-(4(5)-(4-fluorophenyl)-2-(7-methoxynaphthalen-2-yl)-1*H*-imidazol-5(4)-yl)pyridine;

(xii) 4-[4(5)-(*m*-tolyl)-1*H*-imidazol-5(4)-yl]pyridine; and

(xiii) 4-[4(5)-(4-fluorophenyl)-1H-imidazol-5(4)-yl]pyridine~~.~~; or

(B)

~~15. The method according to claim 14, wherein the at least one azole-based small molecule is selected from~~ the list:

(i) 4-[2-(1-fluoronaphthalen-2-yl)-4(5)-(4-fluorophenyl)-1*H*-imidazol-5(4)-yl]pyridine;

(ii) 4-[2-(1-fluoronaphthalen-2-yl)-4-(*m*-tolyl)-1*H*-imidazol-5-yl]pyridine;

(iii) 4-[2-(naphthalen-2-yl)-4(5)-(*m*-tolyl)-1H-imidazol-5(4)-yl]pyridine;

(iv) 4-[2-(naphthalen-2-yl)-4(5)-(4-fluorophenyl)-1*H*-imidazol-5(4)-yl]pyridine;

(v) 4-[2-(1-bromonaphthalen-2-yl)-4(5)-(4-fluorophenyl)-1*H*-imidazol-5(4)-yl]pyridine;

(vi) 4-[2-(1-fluoronaphthalen-2-yl)-4-[3-(trifluoromethyl)phenyl]-1*H*-imidazol-5-yl]pyridine; and

(vii) 2-(1-fluoronaphthalen-2-yl)-4-(pyridin-4-yl)-5-(*m*-tolyl)oxazole.

~~16~~3. The method according to ~~any one of the preceding claims~~claim 1 or 2, wherein the hematopoietic stem cells and progenitor cells are expanded in the presence of:

(a) at least one cytokine selected from the group comprising stem cell factor (SCF), thrombopoietin (TPO), Fms-related tyrosine kinase 3 ligand (FLT-3L), interleukin 3 (IL-3), interleukin 6 (IL-6), granulocyte-colony stimulating factor (GCSF) and insulin-like growth factor binding protein 2 (IGFBP-2~~).~~); or

(b)

~~17. The method according to claim 16, wherein the hematopoietic stem cells and progenitor cells are expanded in the presence of~~ SCF, TPO, FLT-3L and IGFBP-2.

~~18~~4. The method according to any one of the preceding claims, comprising culturing the umbilical cord blood, bone marrow and/or mobilized peripheral blood mononuclear cell(s) with the at least one azole-based small molecule for:

i) a period of at least 9 days~~.~~; or

ii) a period of about 11 days.

~~19. The method according to any one of the preceding claims, comprising culturing the umbilical cord blood, bone marrow and/or mobilized peripheral blood mononuclear cell(s) with the at least one azole-based small molecule for a period of about 11 days.~~

~~20~~5. The method according to ~~any one of the preceding claims~~claim 3 or 4, wherein the cytokines are added to the culture at day 0 and/or at day 7, and/or the at least one azole-based small molecule is added to the culture at day 0 and/or at day 7.

~~21. The method according to any one of the preceding claims, wherein the at least one azole-based small molecule is added to the culture at day 0 and/or at day 7.~~

6~~22~~. The method according to any one of the preceding claims, further comprising the step of harvesting the cells after about 10 to 11 days in culture.

~~23. The method according to any one of the preceding statements, wherein~~
~~a) CD45+CD34+CD38−CD45RA− hematopoietic progenitor cells are expanded; and/or~~
~~b) CD45+CD34+CD38−CD45RA−CD90+ hematopoietic stem cells are expanded; and/or~~
~~c) CD45+CD34+CD38−CD45RA−CD90+CD49f+ hematopoietic stem cells are expanded.~~

~~24~~7. The method according to any one of the preceding claims, further comprising the step of separately retaining a CD34- cell fraction (comprising lymphoid cells) for later co-transplantation with the *ex vivo* expanded cells.

~~25~~8. A ~~combination and/or kit~~composition comprising at least one azole-based small molecule defined in ~~any one of claims 1 to 15~~claim 1 or 2; and at least one cytokine selected from the group comprising SCF, TPO, FLT-3L and IGFBP-2 for use in *ex vivo* expansion of the hematopoietic stem cells and progenitor cells component of umbilical cord blood, bone marrow and/or mobilized peripheral blood.

~~26. The combination and/or kit of claim 25, wherein the at least one cytokine is selected from the group comprising SCF, TPO, FLT-3L and IGFBP-2 for use in *ex vivo* expansion of the hematopoietic stem cells and progenitor cells component of umbilical cord blood, bone marrow and/or mobilized peripheral blood.~~

~~27. The combination and/or kit of claim 25 or 26, wherein the at least one azole-based small molecule expands CD45+CD34+CD38−CD45RA−CD90+ hematopoietic stem cells and/or CD45+CD34+CD38−CD45RA−CD90+CD49f+ hematopoietic stem cells and/or CD45+CD34+CD38−CD45RA− hematopoietic progenitor cells.~~

~~28. A composition comprising at least one azole-based small molecule defined in any one of claims 1 to 15 for use in *ex vivo* expansion of the hematopoietic stem cells and progenitor cells component of umbilical cord blood, bone marrow and/or mobilized peripheral blood.~~

~~29. Use of cells obtained by a method according to any one of claims 1 to 15 or 24 in the manufacture of a medicament for the treatment of a disease requiring hematopoietic stem cell transplantation.~~

~~30. Use according to claim 29, wherein the medicament comprises the *ex vivo* expanded cells and the retained CD34- lymphoid cells.~~

9~~31~~. Use of a composition comprising at least one azole-based small molecule defined in ~~any one of claims 1 to 15~~claim 1 or 2 in *ex vivo* expansion of the hematopoietic stem cells and progenitor cells component of umbilical cord blood, bone marrow and/or mobilized peripheral blood.

~~32. Use according to claim 31, wherein the at least one azole-based small molecule expands CD45+CD34+CD38-CD45RA-CD90+ hematopoietic stem cells and/or CD45+CD34+CD38-CD45RA-CD90+CD49f+ hematopoietic stem cells and/or CD45+CD34+CD38-CD45RA- hematopoietic progenitor cells.~~

~~33. A method of treatment comprising administering to a subject in need of such treatment an efficacious amount of hematopoietic stem cells and progenitor cells, with optionally retained CD34- lymphoid cells, obtained by a method according to any one of claims 1 to 15 or 24.~~