CLAIMS

1. A composition comprising a population of culture expanded genetically unmodified mesenchymal lineage precursor or stem cells (MLPSCs) or conditioned media obtained therefrom for use in a method of treating progressive heart failure in a subject, in which the subject has persistent inflammation and, in which the MLPSCs have been culture expanded in a cell culture media comprising at least one pro-inflammatory cytokine.

2. A composition for use according to Claim 1, in which the MLPSCs have been culture expanded in media containing:

IFN-gamma and/or TNF-alpha; and/or,

one or more pro-inflammatory cytokines selected from the group consisting of IL-6; IL-8; IL-17A; MCP-1; MIP-1-alpha; MIP-1-beta; IP-10.

3. A composition for use according to Claim 1 or 2, in which the media contains three or more pro-inflammatory cytokines.

4. A composition for use according to Claim 2 or 3, in which:

(i) the level of IFN-gamma is < 1 ng/ml, preferably < 500 pg/ml, more preferably < 100 pg/ml; and/or

(ii) the level of TNF-alpha is < 1 ng/ml, preferably < 750 pg/ml, more preferably < 400 pg/ml.

5. A composition for use according to any preceding claim, in which the media contains serum which comprises the pro-inflammatory cytokine(s).

6. A composition for use according to Claim 5, in which the media comprises:

(i) a non-foetal serum;

(ii) a newborn mammalian serum; and/or

(iii) newborn calf serum (NBCS).

7. A composition for use according to Claim 5 or 6, in which:

(i) the serum is obtained no more than 21 days after birth;

(ii) the serum is obtained between the day of birth and 21 days after birth; between the day of birth and 14 days after birth; between the day of birth and 10 days after birth; or, between the day of birth and 7 days after birth; and/or

(iii) the serum is obtained between the day of birth and 10 days after birth.

8. A composition for use according to any preceding claim, in which the media is characterised by one or more or all of the following:

(i) a level of IFN-gamma greater than 1 pg/ml;

(ii) a level of TNF-alpha greater than 2 pg/ml;

(iii) a level of IL-6 greater than 3 pg/ml;

(iv) a level of IL-8 greater than 500 pg/ml;

(v) a level of IL-17A greater than 0.2 pg/ml;

(vi) a level of MCP-1 greater than 3 pg/ml;

(vii) a level of MIP-1-alpha greater than 0.5 pg/ml;

(viii) a level of MIP-1-beta greater than 3 pg/ml;

(ix) a level of IP-10 greater than 500 pg/ml.

9. A composition for use according to any of Claims 5 to 8, in which:

(i) the media comprises at least 5% (v/v) newborn calf serum;

(ii) the media comprises 5% non-fetal serum and 5% fetal serum; and/or

(iii) the media comprises human serum.

10. A composition for use according to any preceding claim, in which:

(i) the subject has myocardial ischemia and/or diabetes;

(ii) the subject has Class II heart failure according to the New York Heart Association (NYHA) classification scale; and/or

(iii) the subject has a micro-vascular disease and/or a macro-vascular disease.

11. A composition for use according to any preceding claim, in which:

(i) the subject's CRP level is ≥2 mg/L; and/or

(ii) the subject's C-reactive protein (CRP) level is between 2 and 5 mg/L, preferably between 2 and 4 mg/L, preferably between 2 and 3 mg/L.

12. A composition for use according to any preceding claim, in which:

(i) the subject has a LVEF of less than about 45%, preferably less than 40%, preferably between 30 and 35%;

(ii) the subject has a LVESV greater than 70 ml, preferably a LVESV between 70 ml and 160 ml;

(iii) the subject has had a heart failure hospitalisation event over the previous 9 months;

(iv) the subject has persistent left ventricular dysfunction; and/or

(v) the subject's heart failure results from an ischaemic event or from a non-ischaemic event.

13. A composition for use according to any preceding claim, in which

(i) the subject has a reduced risk of cardiac death after treatment, preferably in which the reduced risk is relative to risk of cardiac death in a subject that has not been administered MLPSCs;

(ii) treatment improves the subject's LVEF by at least 4 percentage points;

(iii) treatment improves the subject's LVEF by at least 5 percentage points or at least 6 percentage points;

(iv) treatment improves the subject's LVEF by between 4 and 7 percentage points; between 5 and 7 percentage points;

(v) the subject has a reduced risk of ischaemic MACE (MI or stroke) after treatment; and/or

(vi) treatment reduces the subject's risk of all-cause death, preferably in which treatment reduces the subject's risk of all-cause death by between 10% and 90%; greater than 50%; between 20 and 85%; preferably about 80%.

14. A composition for use according to any preceding claim, in which the subject has a left ventricular assist device (LVAD), optionally in which the subject's IL-6 level is increased relative to baseline at least 60 days after LVAD implantation.

15. A composition for use according to any preceding claim, in which:

(i) the composition is formulated for administration transendocardially and/or intravenously;

(ii) the cells are allogeneic;

(iii) the cells have been cryopreserved prior to administration; and/or

(iv) the composition comprises between 1 x 10^7 and 2 x 10^8 cells.

16. A composition for use according to any preceding claim, in which the MLPSCs are mesenchymal precursor cells (MPCs).

17. A composition for use according to any preceding claim, in which the MLPSCs are mesenchymal stem cells (MSCs).

18. A method for selecting a population of culture expanded mesenchymal lineage precursor or stem cells (MLPSCs) for use in treatment of progressive heart failure in a subject in which the MLPSCs have been culture expanded in a cell culture media comprising at least one pro-inflammatory cytokine, the method comprising:

(i) obtaining a population of MLPSCs,

(ii) determining the level of one or more angiogenic markers in the population of MLPSCs, in which the one or more angiogenic markers is selected from the group consisting of:

the level of VEGF, angiogenin, SDF-1α expressed by the MLPSCs under culture conditions; and/or,

the level of endothelial network formation, endothelial network length, endothelial branch length measured after treating a population of endothelial cells with conditioned media obtained from the MLPSCs;

(iii) selecting for use in treatment the MLPSCs that have increased level(s) of the one or more angiogenic markers.

19. A culture expanded population of mesenchymal lineage precursor or stem cells (MLPSCs), in which the population of MLPSCs are selected based on high angiogenic potential as determined by the level of one or more of the following measured after treating a population of endothelial cells with conditioned media obtained from the MLPSCs:

endothelial network formation;

endothelial network length; or

endothelial branch length.

20. A culture expanded population according to Claim 19, in which:

(i) MLPSCs that express an increased level of angiogenin relative to a control population are selected;

(ii) MLPSCs that induce increased levels of one or more of endothelial network formation, endothelial length, or endothelial branch length, relative to a control population are selected;

in which the control population is a population of MLPSCs that have been culture expanded in a cell culture media comprising 10% foetal calf serum.

21. A method of manufacturing drug product which comprises a population of mesenchymal lineage precursor or stem cells (MLPSCs), the method comprising: acquiring a determination of whether a test population of MLPSCs have a predetermined level of angiogenic potential under culture conditions, and processing at least a portion of the test population of MLPSCs as a drug product if the test population of MLPSCs have at least the predetermined level of angiogenic potential under culture conditions, thereby manufacturing the drug product; or discarding at least a portion of the test population of MLPSCs if the population of MLPSCs has less than the predetermined level of angiogenic potential under culture conditions, in which angiogenic potential is measured by:

a predetermined level of one or more of the following as measured after treating a population of endothelial cells with conditioned media obtained from the MLPSCs:

endothelial network formation;

endothelial network length; and/or,

endothelial branch length measured in an in-vitro angiogenesis assay.

22. A method for determining the potency of a population of culture expanded mesenchymal lineage precursor or stem cells (MLPSCs) in which the MLPSCs have been culture expanded in a cell culture media comprising at least one pro-inflammatory cytokine, the method comprising determining the level of one or more angiogenic markers in the

population of MLPSCs, in which the one or more angiogenic markers is selected from the group consisting of:

the level of VEGF, angiogenin, SDF-1α expressed by the MLPSCs under culture conditions; and/or,

the level of endothelial network formation, endothelial network length, endothelial branch length measured after treating a population of endothelial cells with conditioned media obtained from the MLPSCs,

in which an increased level of one or more angiogenic markers is indicative of biological activity or therapeutic efficacy.

23. A method according to any of Claims 18, 21 or 22, or a culture expanded population according to Claim 19 or 20, in which the MLPSCs have been culture expanded in cell culture media containing:

IFN-gamma and/or TNF-alpha; and/or,

one or more pro-inflammatory cytokines selected from the group consisting of IL-6; IL-8; IL-17A; MCP-1; MIP-1-alpha; MIP-1-beta; IP-10; and/or

newborn calf serum (NBCS).