It has also been found that it is possible to alter the production of microparticles by stem cells by the addition of components to the culture medium, by culturing the stem cells under hypoxic conditions, or by co-culture with other cell types, thereby providing an improved method of producing stem cell microparticles.

One aspect of the invention provides an isolated neural stem cell microparticle, which comprises one, two, three or four of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532, wherein the microparticle is derived from a neural stem cell line, wherein the neural stem cell line is CTX0E03 having ECACC Accession No. 04091601. The microparticle may be an exosome, microvesicle, membrane particle, membrane vesicle, exosome-like vesicle, ectosome-like vesicle, ectosome or exovesicle. Typically, the microparticle is an exosome. The microparticle may be derived from a neural stem cell that has been cultured in an environment that allows stem cell differentiation. The microparticle may be isolated from partially-differentiated neural stem cells. In one example, an environment that allows stem cell differentiation is a multi-compartment bioreactor, typically where the cells are cultured for more than seven days. The microparticle may be derived from a neural stem cell line. In some examples, the neural stem cell line may be the "CTX0E03" cell line, the "STR0C05" cell line, the "HPC0A07" cell line or the neural stem cell line disclosed in Miljan et al Stem Cells Dev. 2009. In some examples, the microparticle is derived from a stem cell line that does not require serum to be maintained in culture. The microparticle may have a size of between 30 nm and 1000 nm, or between 30 and 200 nm, or between 30 and 100 nm, as determined by electron microscopy; and/or a density in sucrose of 1.1-1.2 g/ml. The microparticle may comprise RNA. The RNA may be mRNA, miRNA, and/or any other small RNA. The microparticle may comprise one, two, three or four of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532. The microparticle may comprise one or more lipids, typically selected from ceramide, cholesterol, sphingomyelin, phosphatidylserine, phosphatidylinositol, phosphatidylcholine. The microparticle may comprise one or more tetraspanins, typically CD63, CD81, CD9, CD53, CD82 and/or CD37. The microparticle may comprise one or more of TSG101, Alix, CD109, thy-1 and CD133. The microparticle may comprise at least 10 of the proteins present in Table 19 or Table 21. The microparticle may comprise at least one biological activity of a neural stem cell or a neural stem cell-conditioned medium. At least one biological activity may be a tissue regenerative activity. The microparticle is typically isolated or purified.

In one example, disclosed herein is an isolated neural stem cell microparticle for use in therapy. The therapy may be regenerative therapy requiring tissue replacement, regeneration or repair, for example where the therapy requires angiogenesis, neurogenesis and/or neuroprotection. The therapy may be for a neurological disease, disorder or deficit. The therapy may improve functional and/or cognitive recovery. The therapy may be of stroke, peripheral arterial disease,

CLAIMS

1. An isolated neural stem cell microparticle, which comprises one, two, three or four of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532, wherein the microparticle is derived from a neural stem cell line, wherein the neural stem cell line is CTX0E03 having ECACC Accession No. 04091601.

2. The isolated neural stem cell microparticle of claim 1, wherein the microparticle is an exosome, microvesicle, membrane particle, membrane vesicle, exosome-like vesicle, ectosome-like vesicle, ectosome or exovesicle.

3. The isolated neural stem cell microparticle of any preceding claim, wherein the microparticle has:

   (a) a size of between 30 nm and 1000 nm, or between 30 and 200 nm, or between 30 and 100 nm, as determined by electron microscopy; or
   (b) a density in sucrose of 1.1-1.2 g/ml.

4. The isolated neural stem cell microparticle of any preceding claim, comprising mRNA.

5. The isolated neural stem cell microparticle of any preceding claim, comprising one or more of:

   (a) a lipid selected from ceramide, cholesterol, sphingomyelin, phosphatidylserine, phosphatidylinositol, and/or phosphatidylcholine;
   (b) miRNA selected from hsa-let-7g, hsa-miR-101, hsa-miR-10a, hsa-miR-10b, hsa-miR-126, hsa-miR-128, hsa-miR-129-5p, hsa-miR-130a, hsa-miR-134, hsa-miR-137, hsa-miR-155, hsa-miR-15a, hsa-miR-15b, hsa-miR-16, hsa-miR-17, hsa-miR-182, hsa-miR-183, hsa-miR-185, hsa-miR-18b, hsa-miR-192, hsa-miR-194, hsa-miR-195, hsa-miR-20a, hsa-miR-20b, hsa-miR-210, hsa-miR-218, hsa-miR-301a, hsa-miR-302a, hsa-miR-302c, hsa-miR-345, hsa-miR-375, hsa-miR-378, hsa-miR-7, hsa-miR-9, hsa-miR-93, hsa-miR-96, and hsa-miR-99a;
   (c) a tetraspanin, optionally selected from CD63, CD81,CD9, CD53, CD82 and/or CD37;
   (d) TSG101, Alix, CD109 and/or thy-1; and/or
   (e) CD133.

6. The isolated neural stem cell microparticle of any preceding claim, comprising:
   (a) at least 10 of the proteins present in Table 19 or Table 21; and/or

(b) at least one biological activity of a neural stem cell or a neural stem cell-conditioned medium, optionally regenerative activity.

7. The isolated neural stem cell microparticle of any preceding claim, for use in therapy.

8. The isolated neural stem cell microparticle for use according to claim 7, wherein:
   (i) the microparticle is an exosome and therapy is of a disease or condition requiring tissue replacement, regeneration or repair; or
   (ii) the microparticle is a microvesicle and the therapy is of a disease requiring angiogenesis or a neurological disease, disorder or deficit.

9. A method of producing an isolated neural stem cell microparticle as defined in any of claims 1-6, comprising isolating the microparticle from a neural stem cell-conditioned medium.

10. A method of producing a stem cell microparticle, comprising isolating a microparticle from a stem cell-conditioned medium wherein:

   (i) the stem cell-conditioned medium comprises one or more components which induce the release of microparticles by the stem cells into the medium, wherein the one or more components are selected from: transforming growth factor-beta (TGF-β), interferon-gamma (INF-γ) and tumour necrosis factor-alpha (TNF-α);
   (ii) the stem cells were co-cultured with a different cell type, optionally wherein the different cell type is an endothelial cell; and/or
   (iii) the stem cells were cultured in a multi-compartment bioreactor;

   optionally wherein the stem cell is a neural stem cell, optionally as defined in claim 1.

11. A composition comprising an isolated microparticle according to any of claims 1-6 and a pharmaceutically acceptable excipient, carrier or diluent.