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.

~~A first~~One aspect of the invention provides a neural stem cell microparticle. 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 ~~embodiment~~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 ~~embodiments~~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 ~~embodiments~~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 ~~of the invention~~ is typically isolated or purified.

~~A second aspect of the invention~~In one example, disclosed herein is ~~provides~~ a 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,

neuropathy or any other disease or disorder that requires tissue regeneration, revascularisation or local anti-inflammatory action, including:

(i) Neurological disorder, disease or deficit, such as Parkinson's disease, Alzheimer's disease, Stroke, or ALS;

(ii) Lysosomal storage disorders;

(iii) Cardiovascular disorders, such as Myocardial Infarction, congestive heart failure, Peripheral Arterial Disease, diabetic ulcers, wound healing;

(iv) Diseases of the lung, including Idiopathic Pulmonary Fibrosis, Respiratory Distress Syndrome, Chronic Obstructive Pulmonary Disease, Idiopathic Pulmonary Hypertension, Cystic Fibrosis and Asthma;

(v) Metabolic or inflammatory disorders, such as Diabetes (I or II), rheumatoid arthritis, osteoarthritis, lupus, Crohn's disease, Inflammatory Bowel Disease, or Graft versus Host Disease;

(vi) Psychiatric disorders, such as Depression, Bipolar disorder, Schizophrenia or an Autistic syndrome disorder such as Autism, Asperger's syndrome or Rett Syndrome;

(vii) Blindness-causing diseases of the retina, such as Age-related macular degeneration, Stargardt disease, diabetic retinopathy, retinitis pigmentosa; and

(viii) Demyelinating diseases, such as multiple sclerosis, cerebral palsy, central pontine myelinolysis, tabes dorsalis, transverse myelitis, Devic's disease, progressive multifocal leukoencephalopathy, optic neuritis, leukodystrophies, Guillain-Barre syndrome, Anti-MAG peripheral neuropathy and Charcot-Marie-Tooth disease.

In one ~~embodiment~~example, the microparticle is an exosome and therapy is of a disease or condition requiring tissue replacement, regeneration or repair. In another ~~embodiment~~example, the microparticle is a microvesicle and the therapy is of a disease requiring angiogenesis or a neurological disease, disorder or deficit.

The therapy may also be a prophylactic therapy to induce tolerance, typically immunotolerance, in a host that is subsequently, concurrently or simultaneously to receive the stem cells from which the microparticle is derived. The administration of one or more doses of microparticles of the invention to a patient, prior to or concurrent with administration of a stem cell therapy, can be used to reduce the risk of an adverse immune response, i.e. "rejection", of the stem cell therapy.

~~A third~~Another aspect of the invention provides the use of a neural stem cell microparticle in the manufacture of a medicament for the treatment of a disease.

~~A fourth aspect of the invention provides~~ In one aspect, the invention refers to a method of producing a neural stem cell microparticle as defined herein, comprising isolating a microparticle from a neural stem cell-conditioned medium. In another aspect, the invention refers to 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; (ii) the stem cells were cultured under hypoxic conditions; (iii) the stem cells were co-cultured with a different cell type; (iv) the stem cells were cultured in a multi-compartment bioreactor; and/or (v) the stem cells were partially-differentiated. In one example, disclosed herein is a method of producing a stem cell microparticle, typically a neural stem cell microparticle. The method may comprise culturing the stem cells in an environment that allows stem cell differentiation and collecting the microparticles that are produced by the cells. The microparticles may be isolated from partially-differentiated neural stem cells. The stem cells may be cultured under conditions that allow the efficient removal of metabolic waste. In one ~~embodiment~~example, an environment that allows stem cell differentiation is culture in a multi-compartment bioreactor, typically for a prolonged period of time (for example more than seven days). The method may comprise isolating a microparticle from a stem cell-conditioned medium. The stem cell-conditioned medium may comprise one or more additive components or agents which stimulate the release of microparticles by the stem cells into the medium. The one or more components may be selected from transforming growth factor-beta (TGF-β), interferon-gamma (IFN-γ) and/or tumour necrosis factor-alpha (TNF-α). The microparticles may be isolated from stem cell-conditioned medium wherein the stem cells were cultured under hypoxic conditions. The microparticles may be isolated from stem cell-conditioned medium produced by stem cells co-cultured with a different cell type, typically endothelial cells, in order to create the NSC niche environment.

~~A fifth~~One aspect of the invention provides a microparticle obtainable by a method according to the ~~fourth~~ previous aspect of the invention.

In another aspect, the present invention refers to a composition comprising a microparticle according to any of claims 1-13 or 26 and a pharmaceutically acceptable excipient, carrier or diluent. ~~A sixth aspect of the invention provides~~In one example, there is disclosed herein a composition comprising a neural stem cell microparticle and a pharmaceutically acceptable excipient, carrier or diluent.

~~A seventh~~Yet another aspect of the invention provides a method of screening for an agent that alters the production of a microparticle by a stem cell, comprising contacting a stem cell with a

candidate agent and observing whether the rate of production of microparticles by the contacted stem cell increases or decreases compared to a control.

In another aspect, the invention refers to a kit for use in a method for producing the microparticle as defined herein comprising: (a) a medium; (b) a neural stem cell; (c) optionally the one or more components as defined herein; (d) optionally the microparticle as defined herein suitable for use as a control; (e) optionally a detection agent suitable for specific detection of the produced microparticles; and (f) instructions for producing the microparticle as defined herein using the kit.

~~An eighth aspect of the invention provides~~In one example, there is disclosed a kit for use in a method for producing a stem cell microparticle, comprising: (a) a medium suitable for culturing stem cells; (b) a stem cell; (c) optionally the one or more components of the fourth aspect of the invention; (d) optionally a stem cell microparticle suitable for use as a control; (e) optionally a detection agent suitable for specific detection of the produced microparticles; and (f) instructions for producing the stem cell microparticle using the kit.

~~A ninth~~One aspect of the invention provides a composition comprising two, three or all four of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532. This composition is optionally a