Method of Producing Microparticles

Field of the Invention

This invention relates to microparticles produced by cells, their use and production thereof.

Background of the Invention

Stem cells have the ability to self-renew and to differentiate into functionally different cell types. They have the potential to be a powerful tool in the growing field of Regenerative Medicine, in particular regenerative therapy requiring tissue replacement, regeneration or repair (Banerjee et al. 2011). However, there are drawbacks to the use of stem cells in therapy: there is a need for a consistent and substantial supply of stem cells with functional and phenotypic stability and the associated high costs and time delay caused by cell generation, storage, transport and handling; there is a requirement for immunological compatibility to avoid rejection of the stem cells by the recipient; and there are complex regulatory issues related to potential safety risks of tumour or ectopic tissue formation. Further, despite the therapeutic efficacy of stem cell transplantation, there is no convincing evidence for a direct long-term effect of the transplanted stem cells, for example through engraftment and differentiation into reparative or replacement cells.

Neural stem cells (NSCs) are self-renewing, multipotent stem cells that generate neurons, astrocytes and oligodendrocytes (Kornblum, 2007). The medical potential of neural stem cells is well-documented. Damaged central nervous system (CNS) tissue has very limited regenerative capacity so that loss of neurological function is often chronic and progressive. Neural stem cells (NSCs) have shown promising results in stem cell-based therapy of neurological injury or disease (Einstein et al. 2008). Implanting neural stem cells (NSCs) into the brains of post-stroke animals has been shown to be followed by significant recovery in motor and cognitive tests (Stroemer et al. 2009). It is not completely understood how NSCs are able to restore function in damaged tissues but it is now becoming increasingly recognised that NSCs have multimodal repairing properties, including site-appropriate cell differentiation, pro-angiogenic and neurotrophic activity and immunomodulation promoting tissue repair by the native immune system and other host cells (Miljan & Sinden, 2009, Horie et al., 2011). It is likely that many of these effects are dependent on transient signalling from implanted neural stem cells to the host milieu, for example NSCs transiently express proinflammatory markers when implanted in ischaemic muscle tissue damage which directs and amplifies the natural pro-angiogenic and regulatory immune response to promote healing and repair (Hicks et al., unpublished data). In chronic stroke brain, NSCs also have a substantial neurotrophic effect. For example, they promote the repopulation of the stoke-damaged striatal brain tissue with host

brain derived doublecortin positive neroblasts (Hassani, O'Reilly, Pearse, Stroemer et al., PLoS One. 2012;7(11)).

Furthermore, on the basis of a large body of NSC restorative effects in animal models with chronic stroke, a clinical trial using neural stem cells is being carried out by ReNeuron Limited (Surrey, UK), to trial the treatment of disabled stroke patients using its "CTX0E03" conditionally-immortalised cortex-derived neural stem cells (Clinicaltrials.gov Identifier: NCT01151124).

Mesenchymal stem cells (MSCs) are lineage-restricted stem cells which have the potential to differentiate into mesenchymal cell types only, namely of the adipocytic, chondrocytic and osteocytic lineages (Pittenger et al 1999; Ding et al. 2011). MSCs (also referred to as Mesenchymal Stromal Cells and Mesenchymal Progenitor Cells) are derived from a variety of sources including bone marrow, blood, adipose and other somatic tissues. The therapeutic potential of MSCs, however, is more directed towards the application of their pro-angiogenic and immune modulating properties as undifferentiated cells. Production of human MSCs is limited by the inability of these cells to expand in numbers stably beyond approximately 15-20 population doublings.

Mesenchymal stem cell-conditioned medium (MSC-CM) has a therapeutic efficacy similar to that of MSCs themselves, suggesting a paracrine mechanism of MSC-based therapy (Timmers et al. 2007). WO-A-2009/105044 discloses that particles known as exosomes, secreted by MSCs, comprise at least one biological property of the MSCs and suggests the use of these MSC particles in therapy, while Théry et al. 2011 provides a general review of exosomes and other similar secreted vesicles. Whereas some of the drawbacks of using stem cells directly as therapeutic agents are overcome by using the mesenchymal stem cell-derived exosomes (e.g. storage, transport and handling), the problem remains of providing a consistent and substantial supply of functionally and phenotypically stable stem cells to produce the exosomes. For therapeutic use, the exosomes preferably need to be produced on a large scale. In the absence of a stem cell line, replenishment of the cells through repeated derivation from a source of stem cells is required, which incurs recurring costs for testing and validation of each new batch. Furthermore, the diseases and disorders that can be treated by MSCs may be limited.

There remains a need for improved stem cell-based therapies.

Summary of the Invention

The present invention is based on the surprising finding that microparticles can advantageously be produced by conditionally-immortalised cells. The conditionally-immortalised cells may be

stem cells. The Examples show the successful harvest of microparticles from conditionally immortalised neural stem cells and CD34+ cells. Conditional immortalisation provides a constant supply of clonal cells that produce microparticles such as exosomes. The conditionally immortalised cells are useful as "producer cells" for microparticles such as exosomes, which are typically harvested or isolated from the conditionally-immortalised cells.

A first aspect of the invention provides the use of a conditionally-immortalised cell to produce microparticles. The conditionally-immortalised cell is typically:

a mesenchymal stem cell, optionally selected from a bone marrow derived stem cell, an endometrial regenerative cell, a mesenchymal progenitor cell or a multipotent adult progenitor cell;

a neural stem cell selected from a neurosphere initiating stem cell, or an oligodendrocyte precursor cell;

a haematopoietic stem cell, optionally a CD34+ cell and/or isolated from umbilical cord blood, or optionally a CD34+/CXCR4+ cell; a non-haematopoietic umbilical cord blood stem cell;

a very small embryonic like stem cell (VSEL);

an induced pluripotent stem (iPS) cell;

a fibroblast; or

a dendritic cell.

The microparticle that is produced may be an exosome, microvesicle, membrane particle, membrane vesicle, exosome-like vesicle, ectosome-like vesicle, ectosome or exovesicle. Typically, the microparticle is an exosome. In one embodiment, the cell is a mesenchymal stem cell and the microparticle is an exosome.

Conditional immortalisation may be achieved by introducing an immortalisation factor which is inactive unless the cell is supplied with an activating agent. Such an immortalisation factor may be a gene such as c-mycER. The c-MycER gene product is a fusion protein comprising a c-Myc variant fused to the ligand-binding domain of a mutant estrogen receptor. The conditionally-immortalised cells are typically cultured in the presence of the activating agent. For c-MycER conditionally-immortalised cells, the activating agent is 4-hydroxytamoxifen (4-OHT). Accordingly, the microparticles are typically isolated from conditionally-immortalised cells that are in the immortalised state at the time of microparticle isolation.

It has also been found that it is possible to alter the production of microparticles by conditionally-immortalised 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 second aspect of the invention provides a method of producing a microparticle, comprising isolating a microparticle from a conditionally-immortalised cell-conditioned medium, wherein the cell is as defined above. In certain embodiments of this aspect:

the cell-conditioned medium may comprise one or more transforming growth factor-beta (TGF-β), interferon-gamma (IFN-γ) and/or tumour necrosis factor-alpha (TNF-α) which induce the release of microparticles by the stem cells into the medium;

the cells may be cultured under hypoxic conditions;

the cells may be co-cultured with a different cell type;

the cells may be cultured in a multi-compartment bioreactor; and/or

the cells may be stem cells that are partially-differentiated.

A further embodiment provides a method of producing a stem cell microparticle, typically a neural stem cell microparticle or a microparticle from another stem cell type (as detailed above). The method may comprise culturing the stem cells, typically conditionally-immortalised 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, 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 further aspect of the invention provides a microparticle obtainable by a method aspect of the invention.

Another aspect of the invention provides a method of screening for an agent that alters the production of a microparticle by a conditionally-immortalised cell, comprising contacting a conditionally-immortalised cell with a candidate agent and observing whether the rate of

production of microparticles by the contacted conditionally-immortalised cell increases or decreases compared to a control.

A further aspect of the invention provides a kit when used in a method for producing a microparticle, comprising: (a) a medium; (b) a conditionally-immortalised cell as defined herein; (c) optionally the one or more transforming growth factor-beta (TGF-β), interferon-gamma (IFN-γ) and/or tumour necrosis factor-alpha (TNF-α) 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 disclosed herein using the kit.

Further aspects and embodiments of the invention are defined below, and in the claims.
The invention also relates to the finding that neural stem cells contain microparticles that are therapeutically useful. The methods discussed herein with regard to the production of microparticles from neural stem cells may be applied to methods of producing microparticles from the other cell types described for the first aspect of the invention.

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 conditionally-immortalised 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, 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, 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, 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 further aspect of the invention 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, the microparticle is an exosome and therapy is of a disease or condition requiring tissue replacement, regeneration or repair. In another embodiment, 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 further 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.

Another aspect of the invention provides a composition comprising a neural stem cell microparticle and a pharmaceutically acceptable excipient, carrier or diluent.

Brief Description of the Drawings

Figure 1 depicts electron micrographs of CTX0E03 conditionally-immortalised neural stem cells producing microparticles. Panels A-E show intracellular multivesicular bodies (MVBs) containing exosomes between 30nm and 50nm in diameter and Panel F shows microvesicles >100nm in diameter released from neural stem cells through a process of budding at the cell membrane.

Figure 2 is an outline protocol for the identification, characterisation and production of microparticles from stem cells.

Figure 3 shows Human angiogenesis ELISA strip optical density read out performed on CTX0E03 conditioned and un-conditioned medium.

Figure 4A shows the amount of protein (measured by BCA assay) extracted from 15ml of media containing microparticles purified from the Integra system compared to normal culture conditions (3 days T175). Figure 4B shows the FACS detection (at 2ug/ml, 1:250) of (i) CD63 in Integra cultured CTX0E03 exosomes (top left panel) and microvesicles (top right panel) and (ii) CD81 in Integra cultured CTX0E03 exosomes (bottom left panel) and microvesicles (bottom right panel).

Figure 5 shows the amount of isolated total RNA measured at 260/280nm extracted from 15ml of media containing microparticles purified by filtration from the Integra system compared to normal culture conditions (3 days T175).

Figure 6A shows the results of a wound closure/scratch assay representing the migration activity of normal human dermal fibroblasts (NHDF) cultured in CTX0E03 conditioned media or upon the addition of purified CTX0E03 exosomes. Figure 6B shows the results of a scratch assay after 72 hours, comparing the effect of 10µg CTX0E03 exosomes to basal conditions (without exosomes). Figure 6C shows the % of healed areas for basal conditions, 2µg/ml exosomes, 6 µg/ml exosomes, 20 µg/ml exosomes and an LSGS (low serum growth supplement) positive control. The top panel of Figure 6C shows exosomes isolated from CTX0E03 cells cultured for 2 weeks in the Integra Celline system and the bottom panel of Figure 6C shows exosomes isolated from CTX0E03 cells cultured for 6 weeks in the Integra Celline system. Figure 6D compares CTX0E03 cells to a negative control (saline) in an *in vivo* injection wound healing assay.

Figure 7 shows the quantity of purified exosomes obtained per culture medium from standard CTX0E03 (T175) cultures vs the Integra CELLine system at the 3 week time point.

Figure 8A shows the concentration of exosomes harvested from two different flasks after 1 week, 2 weeks and 3 weeks of CTX0E03 Integra CELLine culture system. Figure 8B shows the concentration of exosomes harvested from a single Integra CELLine flask during a 6 week continuous culture of CTX0E03 cells.

Figure 9 shows the fold change of expression levels of various mRNA markers measured in CTX0E03 cells cultured for 3 weeks in the Integra CELLine system compared to standard ("control") CTX0E03 (T175) cultures.

Figure 10 shows the fold up and down regulation of various miRNAs in exosomes obtained from CTX0E03 cells cultured for 3 weeks in Integra bioreactor culture and microparticles obtained from standard CTX0E03 (T175) cultures, assessed against a baseline expression level in CTX0E03 cells in standard (T175) culture.

Figure 11 depicts the miRNA profiles obtained from deep sequencing of miRNA from CTX0E03 cells ("CTX"), microvesicles ("MV") and exosomes ("EXO") cultured under standard (T175) conditions. Figure 11a and 11b show results from two cultures.

Figure 12 shows the effect of hNSC microvesicles on angiogenesis of HUVECs. Figure 12A is a photograph showing the clear increase in tube formation observed when microvesicles are added (right hand panels) compared to basal HUVECs. Figures 12B and 12C show the increase in total tube length provided by the hNSC microvesicles at various concentrations (0.05µg, 0.1 µg, 0.3µg – Figure 12B; and 0.6µg/ml – Figure 12C).

Figure 13 shows the effect of hNSC microvesicles on neurite outgrowth in PC-12 cells.

Figure 14 is an electropherogram showing the total RNA content profile in CTX0E03 cells, exosomes and microvesicles as determined by Agilent RNA bioanalyser.

Figure 15 is a schematic presentation of the percentage of coding genes fully overlapping exon, and non-coding transcripts located with intron or intergenic sequences (produced by running NGS BAM files against GENCODE sequence data set).

Figure 16 depicts the top ranking preferentially shuttled novel miRNAs in exosomes and MV compared to CTX0E03 producer cells.

Figure 17 shows the results of NanoSight analysis undertaken to determine the particle size and concentration of CTX0E03 exosomes (Figure 17A) and microvesicles (Figure 17B) cultured in the Integra Celline system for 1, 2, 3, 4, 5 and 6 weeks

Figure 18 shows Venn diagrams comparing the proteomic data from CTX0E03 exosomes and microvesicles (18A and 18B), and comparing neural stem cell exosomes with mesenchymal stem cell exosomes (18C and 18D). Figure 18A illustrates the number of unique proteins within CTX0E03 exosomes and microvesicles, isolated from week 2 Integra culture system. Figure 18B compares the biological processes associated with the identified proteins within the CTX0E03 exosomes and microvesicles. Figure 18C compares the CTX0E03 neural stem cell exosome proteome to a Mesenchymal Stem Cell exosome proteome, and Figure 18D compares the biological processes associated with the identified proteins in the MSC derived exosomes with the neural stem cell derived exosomes.

Figure 19 shows the 30 biological processes found to be associated with NSC derived exosomes and not mesenchymal stem cell exosomes.

Figure 20 shows the successful conditional immortalisation of CD34+ cells. (A) is a diagram of qRT-PCR cycles showing the presence of c-mycERTAM mRNA in lentivirus infected human CD34+ progenitor cells derived from cord blood. (B) is a control sample showing the detection of the exosome marker Alix in immunoprecipitate. (C) shows Alix expression in exosomes immunoprecipitated from both CD34+ and CD34+ cMycERTam cells.

Detailed Description of the Invention

The present invention is based on the surprising finding that microparticles can advantageously be produced by conditionally-immortalised cells. The conditionally-immortalised cells may be stem cells. The Examples show the successful production of microparticles by conditionally immortalised neural stem cells and CD34+ cells. Conditional immortalisation provides a constant supply of clonal cells that produce microparticles such as exosomes. The conditionally immortalised cells are useful as "producer cells" for microparticles such as exosomes, which are typically harvested or isolated from the conditionally-immortalised cells.

The present inventors have also surprisingly identified microparticles in neural stem cells. These microparticles retain some of the functions of the neural stem cells from which they are derived and are typically therapeutically useful for the same treatments as the neural stem cells. The microparticles are advantageous over the corresponding stem cells because they are smaller and less complex, thereby being easier to produce, maintain, store and transport, and have the potential to avoid some of the regulatory issues that surround stem cells. The microparticles can be produced continuously, by isolation from conditioned media, for example in a bioreactor such as a multi-compartment bioreactor, which allows for large scale production and the provision of an "off-the-shelf" therapy. The multi-compartment bioreactor is typically a two-compartment bioreactor.

It has further been found that, surprisingly, culturing stem cells (of any type, not limited to neural stem cells) in an environment that allows the stem cells to begin to differentiate, increases dramatically the yield of microparticles produced.

The inventors have surprisingly observed that culturing stem cells (of any type, not limited to neural stem cells) in a multi-compartment bioreactor, results in partial differentiation of the stem cells, into stem cells in a more differentiated form. This differentiation in culture does not require the addition of an agent to induce differentiation. This differentiation typically requires a culture period of at least one week, at least two weeks or at least three weeks. The changes to the stem cells that occur in culture in a multi-compartment bioreactor are reflected by the microparticles produced by the cultured stem cells. Therefore, by culturing stem cells in a multi-compartment bioreactor, it is possible to induce differentiation of the cells. Accordingly, microparticles from partially differentiated stem cells can be produced by harvesting microparticles from stem cells cultured in a multi-compartment bioreactor, typically for at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks or at least six weeks. Optionally, the cells, e.g. NSCs, have been cultured for no more than ten

weeks. In one embodiment, the invention provides a method of producing microparticles by isolating the microparticles from partially-differentiated neural stem cells.

The inventors have also found that it is possible to induce the secretion of microparticles from stem cells. This finding, which also is not limited to neural stem cells and can be used for the production of microparticles from any stem cell, allows for an improved yield of microparticles to be obtained from a stem cell culture. Several agents have been identified that enhance the secretion of microparticles to different degrees, which has the further advantage of being able to control the amount of microparticles that are secreted. Culturing stem cells under hypoxic conditions also improves microparticle production. Further, it has been found that co-culturing a stem cell with a different cell type, in particular an endothelial cell type can beneficially alter the microparticles that are produced by the stem cell.

In a further embodiment, the invention provides microparticles, typically exosomes, produced by serum-free stem cells. Serum is required for the successful culture of many cell lines, but contains many contaminants including its own exosomes. As described below, the inventors have produced microparticles from stem cells that do not require serum for successful culture.

Microparticles

The invention relates to the production of microparticles from conditionally-immortalised cells

The invention provides, in one aspect, microparticles obtainable from a conditionally-immortalised neural stem cell, mesenchymal stem cell or haematopoietic stem cell. A neural stem cell microparticle is a microparticle that is produced by a neural stem cell; a mesenchymal stem cell microparticle is a microparticle that is produced by a mesenchymal stem cell; a haematopoietic stem cell microparticle is a microparticle that is produced by a haematopoietic stem cell. Typically, the microparticle is secreted by the stem cell. More typically, the microparticle is an exosome or a microvesicle. Microparticles from some stem cells (that are not conditionally immortalised), such as mesenchymal stem cells, are known in the art.

A "microparticle" is an extracellular vesicle of 30 to 1000 nm diameter that is released from a cell. It is limited by a lipid bilayer that encloses biological molecules. The term "microparticle" is known in the art and encompasses a number of different species of microparticle, including a membrane particle, membrane vesicle, microvesicle, exosome-like vesicle, exosome, ectosome-like vesicle, ectosome or exovesicle. The different types of microparticle are distinguished based on diameter, subcellular origin, their density in sucrose, shape, sedimentation rate, lipid composition, protein markers and mode of secretion (i.e. following a

signal (inducible) or spontaneously (constitutive)). Four of the common microparticles and their distinguishing features are described in Table 1, below.

Table 1: Various Microparticles

Microparticle	Size	Shape	Markers	Lipids	Origin
Microvesicles	100-1000nm	Irregular	Integrins, selectins, CD40 ligand	Phosphatidylserine	Plasma membrane
Exosome-like vesicles	20-50nm	Irregular	TNFRI	No lipid rafts	MVB from other organelles
Exosomes	30-100nm; (<200nm)	Cup shaped	Tetraspanins (e.g. CD63, CD9), **Alix**, TSG101, ESCRT	Cholesterol, sphingomyelin, ceramide, lipid rafts, phosphatidylserine	Multivesicular endosomes
Membrane particles	50-80nm	Round	CD133, no CD63	Unknown	Plasma membrane

Microparticles are thought to play a role in intercellular communication by acting as vehicles between a donor and recipient cell through direct and indirect mechanisms. Direct mechanisms include the uptake of the microparticle and its donor cell-derived components (such as proteins, lipids or nucleic acids) by the recipient cell, the components having a biological activity in the recipient cell. Indirect mechanisms include microvesicle-recipient cell surface interaction, and causing modulation of intracellular signalling of the recipient cell. Hence, microparticles may mediate the acquisition of one or more donor cell-derived properties by the recipient cell. It has been observed that, despite the efficacy of stem cell therapies in animal models, the stem cells do not appear to engraft into the host. Accordingly, the mechanism by which stem cell therapies are effective is not clear. Without wishing to be bound by theory, the inventors believe that the microparticles secreted by neural stem cells play a role in the therapeutic utility of these cells and are therefore therapeutically useful themselves.

The microparticles and cells, e.g. stem cells, of the invention are isolated. The term "isolated" indicates that the microparticle, microparticle population, cell or cell population to which it refers is not within its natural environment. The microparticle, microparticle population, cell or cell population has been substantially separated from surrounding tissue. In some embodiments, the microparticle, microparticle population, cell or cell population is substantially separated from surrounding tissue if the sample contains at least about 75%, in some embodiments at least

about 85%, in some embodiments at least about 90%, and in some embodiments at least about 95% microparticles and/or stem cells. In other words, the sample is substantially separated from the surrounding tissue if the sample contains less than about 25%, in some embodiments less than about 15%, and in some embodiments less than about 5% of materials other than the microparticles and/or stem cells. Such percentage values refer to percentage by weight. The term encompasses cells or microparticles which have been removed from the organism from which they originated, and exist in culture. The term also encompasses cells or microparticles which have been removed from the organism from which they originated, and subsequently re-inserted into an organism. The organism which contains the re-inserted cells may be the same organism from which the cells were removed, or it may be a different organism.

Stem cells naturally produce microparticles by a variety of mechanisms, including budding of the plasma membrane (to form membrane vesicles and microvesicles) and as a result of the fusion of intracellular multivesicular bodies (which contain microparticles) with the cell membrane and the release of the microparticles into the extracellular compartment (to secrete exosomes and exosome-like vesicles).

In one embodiment, the neural stem cell that produces the microparticles of the invention can be a fetal, an embryonic, or an adult neural stem cell, such as has been described in US5851832, US6777233, US6468794, US5753506 and WO-A-2005121318. The fetal tissue may be human fetal cortex tissue. The cells can be selected as neural stem cells from the differentiation of induced pluripotent stem (iPS) cells, as has been described by Yuan et al. (2011) or a directly induced neural stem cell produced from somatic cells such as fibroblasts (for example by constitutively inducing Sox2, Klf4, and c-Myc while strictly limiting Oct4 activity to the initial phase of reprogramming as recently by Their *et al*, 2012). Human embryonic stem cells may be obtained by methods that preserve the viability of the donor embryo, as is known in the art (e.g. Klimanskaya *et al.*, 2006, and Chung *et al.* 2008). Such non-destructive methods of obtaining human embryonic stem cell may be used to provide embryonic stem cells from which microparticles of the invention can be obtained. Alternatively, microparticles of the invention can be obtained from adult stem cells, iPS cells or directly-induced neural stem cells. Accordingly, microparticles of the invention can be produced by multiple methods that do not require the destruction of a human embryo or the use of a human embryo as a base material.

Typically, the cell population from which the microparticles are produced, is substantially pure. The term "substantially pure" as used herein, refers to a population of cells that is at least about 75%, in some embodiments at least about 85%, in some embodiments at least about 90%, and in some embodiments at least about 95% pure, with respect to other cells that make up a total cell population. For example, with respect to stem cell, e.g. neural stem cell populations, this

term means that there are at least about 75%, in some embodiments at least about 85%, in some embodiments at least about 90%, and in some embodiments at least about 95% pure, stem cells compared to other cells that make up a total cell population. In other words, the term "substantially pure" refers to a population of stem cells of the present invention that contain fewer than about 25%, in some embodiments fewer than about 15%, and in some embodiments fewer than about 5%, of lineage committed cells in the original unamplified and isolated population prior to subsequent culturing and amplification.

A stem cell, e.g. neural stem cell, microparticle comprises at least one lipid bilayer which typically encloses a milieu comprising lipids, proteins and nucleic acids. The nucleic acids may be deoxyribonucleic acid (DNA) and/or ribonucleic acid (RNA). RNA may be messenger RNA (mRNA), micro RNA (miRNA) or any miRNA precursors, such as pri-miRNA, pre-miRNA, and/or small nuclear RNA (snRNA).

A stem cell, e.g. neural stem cell, microparticle retains at least one biological function of the stem cell from which it is derived. Biological functions that may be retained include the ability to promote angiogenesis and/or neurogenesis, the ability to effect cognitive improvement in the brain of a patient that has suffered a stroke, or the ability to accelerate blood flow recovery in peripheral arterial disease. For example, CTX0E03 cells are known to inhibit T cell activation in a PBMC assay and, in one embodiment, the microparticles of the invention retain this ability to inhibit T cell activation in a PBMC assay. PBMC assays are well-known to the skilled person and kits for performing the assay are commercially available.

Example 8, Table 2 and Figure 6 demonstrate that CTX0E03 stem cell exosomes retain the ability to close a wound in a "scratch" model of wound healing. The results in Figure 6A show that the migration activity of normal human dermal fibroblasts (NHDF) cultured in CTX0E03 conditioned media is almost the same as the migration activity observed on the addition of purified exosomes. Accordingly, one biological function that microparticles of the invention may retain is the ability to stimulate migration activity of normal human dermal fibroblasts (NHDF).

Example 8 also shows that microvesicles of the invention are able to stimulate angiogenesis of primary HUVECs and to stimulate neurite outgrowth of PC-12 cells. Accordingly, a biological function that microparticles of the invention may retain is the ability to stimulate angiogenesis of primary HUVECs and/or to stimulate neurite outgrowth of PC-12 cells.

The proteomic analysis in Example 13 indicates that neural stem cell exosomes comprise biological functions associated with the production, packaging, function and degradation of genetic material. Accordingly, in one embodiment, exosomes of the invention retain these

functions, typically one or more of RNA polymerase function, RNA degradation function, ribosome function and spliceosome function.

The microparticle has a diameter of 1000nm or less. Typically, the microparticle of the invention will have a diameter of 200nm or less, for example 100nm or less. As noted in Table 1 above, microvesicles have a diameter of 100nm to 1000nm. Exosomes are typically defined as having a diameter of 30-100nm, but more recent studies confirm that exosomes can also have a diameter between 100nm and 200nm, (e.g. Katsuda *et al*, Proteomics 2013 and Katsuda *et al*, Scientific Reports 2013). Accordingly, exosomes typically have a diameter between 30nm and 150nm. Membrane particles have a diameter of 50nm to 80nm and exosome-like particles have a diameter of 20nm-50nm. The diameter can be determined by any suitable technique, for example electron microscopy or dynamic light scattering. The term microparticle includes, but is not limited to: membrane particle, membrane vesicle, microvesicle, exosome-like vesicle, exosome, ectosome-like vesicle, ectosome or exovesicle.

Figure 1 panels A-E show the presence in neural stem cells of MVB's containing exosomes between 30-50nm in diameter, while panel F shows microvesicles >100nm in diameter. Table 20 and Figure 17 (below) show that typical neural stem cell exosomes were measured to have a diameter ranging from approximately 70nm to approximately 150nm, which is consistent with the size of exosomes (from mesenchymal stem cells) described in the art. Accordingly, exosomes of the invention typically have a diameter between 30nm and 200nm, more typically between 50nm and 150nm. As noted above, exosomes are typically positive for the Alix marker (UNIPROT Accession No. Q8WUM4).

Figure 1F and Table 20 shows the observed size of typical neural stem cell microvesicles, with a mode diameter of approximately 150nm – 200nm, or a median diameter of approximately 180nm – 350nm. Accordingly, microvesicles of the invention typically have a diameter between 100 and 1000nm, more typically between 150nm and 350nm.

Some microparticles of the invention express the CD133 surface marker. Other microparticles of the invention do not express the CD133 surface marker.

"Marker" refers to a biological molecule whose presence, concentration, activity, or phosphorylation state may be detected and used to identify the phenotype of a cell.

Exosomes are endosome-derived lipid microparticles of typically 30-100nm diameter and sometimes between 100nm and 200nm diameter, that are released from the cell by exocytosis. Exosome release occurs constitutively or upon induction, in a regulated and functionally

relevant manner. During their biogenesis, exosomes incorporate a wide range of cytosolic proteins (including chaperone proteins, integrins, cytoskeletal proteins and the tetraspanins) and genetic material. Consequently, exosomes are considered to be inter-cellular communication devices for the transfer of proteins, lipids and genetic material between cells, in the parent cell microenvironment and over considerable distance. Although the invention is not bound by this theory, it is possible that the exosomes are responsible for the efficacy of the neural stem cells. Therefore, exosomes from neural stem cells are themselves expected to be therapeutically efficacious.

Microparticles designed to have desired functions

Microparticles retain at least some of the functions of the stem cells that produce them. Therefore, it is possible to design microparticles by manipulating the stem cell (which can be any stem cell type and is not limited to neural stem cells, although the neural stem cell microparticles of the invention are expressly included as an embodiment) to possess one or more desired functions, typically protein or miRNA. The manipulation will typically be genetic engineering, to introduce one or more exogenous coding, non-coding or regulatory nucleic acid sequences into the stem cell. For example, if an exosome containing VEGF and/or bFGF is desired, then the exosome-producing stem cell can be transformed or transfected to express (high levels of) VEGF and/or bFGF, which would then be incorporated into the microparticles produced by that stem cell. Similarly, iPS cells can be used to produce microparticles, and these cells can be designed to produce the proteins and nucleic acids (e.g. miRNA) that are required in the microparticles produced by the iPS cells. The invention therefore provides *ad hoc* microparticles, from any stem cell type, that contain a function that is not naturally present in the stem cell from which is produced, i.e. the microparticles (e.g. exosomes) contain one or more exogenous protein or nucleic acid sequences, are not naturally-occurring and are engineered. The use of conditionally-immortalised cells advantageously provides for the continuous production of these designed microparticles.

In one embodiment, isolated or purified microparticles are loaded with one or more exogenous nucleic acids, lipids, proteins, drugs or prodrugs which are intended to perform a desired function in a target cell. This does not require manipulation of the stem cell and the exogenous material can optionally be directly added to the microparticles. For example, exogenous nucleic acids can be introduced into the microparticles by electroporation. The microparticles can then be used as vehicles or carriers for the exogenous material. In one embodiment, microparticles that have been isolated from the cells that produced them are loaded with exogenous siRNA, typically by electroporation, to produce microparticles that can be deployed to silence one or more pathological genes. In this way, microparticles can be used as vehicles to deliver one or more agents, typically therapeutic or diagnostic agents, to a target cell. An example of this is a

neural stem cell exosome comprising exogenous siRNA capable of silencing one or more pathological genes.

Microparticle Marker

The invention provides a population of isolated neural stem cell microparticles, wherein the population essentially comprises only microparticles of the invention, i.e. the microparticle population is pure. In many aspects, the microparticle population comprises at least about 80% (in other aspects at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9% or 100%) of the microparticles of the invention.

The isolated neural stem cell microparticle of the invention is characterised in that it has a distinctive expression profile for certain markers and is distinguished from microparticles from other cell types. When a marker is described herein, its presence or absence may be used to distinguish the microparticle. For example, the term "may comprise" or "may express" also discloses the contrary embodiment wherein that marker is not present, e.g. the phrase "the microparticle may comprise one or more tetraspanins, typically CD63, CD81, CD9, CD53, CD82 and/or CD37" also describes the contrary embodiment wherein the microparticle may not comprise one or more tetraspanins, typically CD63, CD81, CD9, CD53, CD82 and/or CD37.

The stem cell, e.g. neural stem cell, microparticle of the invention is typically considered to carry a marker if at least about 70% of the microparticles of the population, e.g. 70% of the membrane particles, membrane vesicles, microvesicles, exosome-like vesicles, exosomes, ectosome-like vesicles, ectosomes or exovesicles show a detectable level of the marker. In other aspects, at least about 80%, at least about 90% or at least about 95% or at least about 97% or at least about 98% or more of the population show a detectable level of the marker. In certain aspects, at least about 99% or 100% of the population show detectable level of the markers. Quantification of the marker may be detected through the use of a quantitative RT-PCR (qRT-PCR) or through fluorescence activated cell sorting (FACS). It should be appreciated that this list is provided by way of example only, and is not intended to be limiting. Typically, a neural stem cell microparticle of the invention is considered to carry a marker if at least about 90% of the microparticles of the population show a detectable level of the marker as detected by FACS.

The markers described herein are considered to be expressed by a cell of the population of the invention, if its expression level, measured by qRT-PCR has a crossing point (Cp) value below or equal to 35 (standard cut off on a qRT-PCR array). The Cp represents the point where the amplification curve crosses the detection threshold, and can also be reported as crossing threshold (ct).

In one embodiment, the invention relates to microparticles produced by a neural stem cell population characterised in that the cells of the population express one or more of the markers Nestin, Sox2, GFAP, βIII tubulin, DCX, GALC, TUBB3, GDNF and IDO. In another embodiment, the microparticle is an exosome and the population of exosomes expresses one or more of DCX (doublecortin – an early neuronal marker), GFAP (Glial fibrillary acidic protein - an astrocyte marker), GALC, TUBB3, GDNF and IDO.

The neural stem cell microparticles of the invention may express one or more protein markers at a level which is lower or higher than the level of expression of that marker in a mesenchymal stem cell microparticle of the same species. Protein markers that are expressed by the CTX0E03 cell microparticles are identified herein and below. In some embodiments, the microparticles may express a protein marker at a level relative to α tubulin or other such control protein(s). In some embodiments, the microparticles of the invention may express that protein at a level of at least +/-1.2 fold change relative to the control protein, typically at least +/-1.5 fold change relative to the control protein, at least +/-2 fold change relative to the control protein or at least +/-3 fold change relative to the control protein. In some embodiments, the microparticles may express a protein marker at a level of between 10^{-2} and 10^{-6} copies per cell relative to α tubulin or other control protein. In some embodiments, the microparticles of the invention may express that protein at a level of between 10^{-2} and 10^{-3} copies per cell relative to α tubulin or other control protein.

The neural stem cell microparticles of the invention may express one or more miRNAs (including miRNA precursors) at a level which is lower or higher than the level of expression of that miRNA (including miRNA precursors) in a mesenchymal stem cell microparticle of the same species. miRNA markers that are expressed by the CTX0E03 cell microparticles are identified below. In some embodiments, the microparticles of the invention may express the marker miRNA at a level of least +/- 1.5 fold change, typically at least +/- 2 fold change or at least +/- 3 fold change (calculated according to the ΔΔct method, which is well-known) relative to U6B or 15a, or any other miRNA reference gene, also referred to as an internal control gene.

The neural stem cell microparticles of the invention may express one or more mRNAs at a level which is lower or higher than the level of expression of that mRNA in a mesenchymal stem cell microparticle of the same species. In some embodiments, the microparticles of the invention may express the marker mRNA at a level of least +/- 1.5 fold change, typically at least +/- 2 fold change or at least +/- 3 fold change (calculated according to the ΔΔct method) relative to ATP5B or YWHAZ, or any other reference gene, also referred to as an internal control gene.

Exosomes of the invention typically express specific integrins, tetraspanins, MHC Class I and/or Class II antigens, CD antigens and cell-adhesion molecules on their surfaces, which may facilitate their uptake by specific cell types. Exosomes contain a variety of cytoskeletal proteins, GTPases, clathrin, chaperones, and metabolic enzymes (but mitochondrial, lysosomal and ER proteins are excluded, so the overall profile does not resemble the cytoplasm). They also contain mRNA splicing and translation factors. Finally, exosomes generally contain several proteins such as HSP70, HSP90, and annexins that are known to play signalling roles yet are not secreted by classical (ER-Golgi) mechanisms.

The lipid bilayer of an exosome is typically enriched with cholesterol, sphingomyelin and ceramide. Exosomes also express one or more tetraspanin marker proteins. Tetraspanins include CD81, CD63, CD9, CD53, CD82 and CD37. Exosomes can also include growth factors, cytokines and RNA, in particular miRNA. Exosomes typically express one or more of the markers TSG101, Alix, CD109, thy-1 and CD133. Alix (Uniprot accession No. Q8WUM4), TSG101 (Uniprot accession No. Q99816) and the tetraspanin proteins CD81 (Uniprot accession No. P60033) and CD9 (Uniprot accession No. P21926) are characteristic exosome markers.

Alix is an endosomal pathway marker. Exosomes are endosomal-derived and, accordingly, a microparticle positive for this marker is characterised as an exosome. Exosomes of the invention are typically positive for Alix. Microvesicles of the invention are typically negative for Alix.

Microparticle proteome

Tables 18 and 20 list all proteins detected by mass spectrometry in exosomes and microvesicles, respectively, isolated from CTX0E03 cells cultured for two weeks in an Integra Celline multicompartment bioreactor. In one embodiment, exosomes of the invention comprise at least 70%, at least 80%, at least 90%, at least 95%, at least 99% or at least 99.5% of the proteins listed in Table 18. Similarly, microvesicles of the invention typically comprise at least 70% at least 80%, at least 90%, at least 95%, at least 99% or at least 99.5% of the proteins listed in Table 20. In a further embodiment, the proteome of a microvesicle or exosome of the invention is least 70%, at least 80%, at least 90%, at least 95%, at least 99% or at least 99.5% identical to the proteome provided in Table 18 (exosome) or Table 20 (microvesicle). When determining the protein content of a microparticle or exosome, mass spectrometry is typically used, for example the LC/MS/MS method described in Example 13.

Tables 19 and 21 show the 100 most abundant proteins detected by mass spectrometry in exosomes and microvesicles, respectively, isolated from CTX0E03 cells cultured for two weeks in an Integra Celline multicompartment bioreactor. Typically, an exosome of the invention

comprises the first ten proteins listed in Table 19, more typically the first 20, the first 30, the first 40 or the first 50 proteins listed in Table 19. Similarly, a microparticle of the invention typically comprises the first ten proteins listed in Table 21, more typically the first 20, the first 30, the first 40 or the first 50 proteins listed in Table 21. In one embodiment, an exosome of the invention comprises all 100 proteins listed in Table 19. In one embodiment, a microvesicle of the invention comprises all 100 proteins listed in Table 21. Typically, the 100 most abundant proteins in an exosome or microvesicle of the invention contain at least 70 of the proteins identified in Table 19 (exosome) or Table 21 (microparticle). More typically, the 100 most abundant proteins in an exosome or microvesicle of the invention contain at least 80, at least 90, at least 95, 96, 97, 98 or 99, or all 100 of the proteins identified in Table 19 (exosome) or Table 21 (microparticle).

Microparticle miRNA content

Example 12 (and the related Figure 11) shows the results of deep sequencing of miRNA present in CTX0E03 cells, microvesicles and exosomes produced by these cells. This Example shows that, surprisingly, the number of different miRNA species present in the microparticles is greatly reduced compared to the number of different miRNA species present in the cells; the microparticles contain fewer than 120 different miRNAs whereas the cells contain between 450 and 700 miRNA species. The microparticles contain a majority of hsa-miR-1246.

The data in Example 12 also show that the microparticles are characterised by four main miRNA species, namely hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532. These four miRNAs are the only miRNAs present at a read count of greater than 1000 in the microparticles; these four miRNAs are present in massive excess compared to the other miRNAs in the microparticles. This is in contrast to the profile in the cells, which contain a much greater number of miRNAs present at high (read count greater than 1000) or very high (read count greater than 10,000) levels. Although not bound by theory, the inventors propose that hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532 are selectively trafficked (or otherwise incorporated) into the microparticles and are thought to play a role in the function of the microparticles.

Typically, in one embodiment microparticles, e.g. exosomes, of the invention contain one, two, three or all four of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532. Each of these miRNA markers is typically present at a read count (optionally determined using the deep sequence technique described in Example 12) of at least 1000 per microparticle. hsa-miR-1246 may optionally have a read count of at least 2000, 5000, 10,000, 20,000, or 25,000 per microparticle. Hsa-miR-4492 may optionally have a read count of at least 2000, 3000, 4000 or

5000 per microparticle. Hsa-miR-4532 may optionally have a read count of at least 2000 or 3000 per microparticle.

In one embodiment, each of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and/or hsa-miR-4532 is present in the microparticle, e.g. exosome, at a higher read count than is present in the cell that produced the microparticle. In particular, miR-1246 typically has a read count in the microparticle at least twice the read count in the cell, more typically at least 4, 5, 6, 7, or 8 times the read count in the cell, and optionally 10, 15 or 20 times the read count in the cell.

In one embodiment, microparticles of the invention contain hsa-let-7a-5p, has-miR-92b-3p, hsa-miR-21-5p, hsa-miR-92a-3p, hsa-miR-10a-5p, hsa-100-5p and/or hsa-99b-5p at a lower read count than is present in the cell that produced the microparticle. Typically, each of these miRNAs has a read count of less than 1000 in the microparticles of the invention, more typically less than 100, for example less than 50. Optionally, microparticles of the invention contain hsa-let-7a-5p at a read count of less than 50 or less than 25.

In one embodiment, microparticles of the invention contain fewer than 150 types of miRNA (i.e. different miRNA species) when analysed by deep sequencing, typically fewer than 120 types of miRNA.

In one embodiment, hsa-miR-1246 is the most abundant miRNA in the microparticles of the invention (optionally determined using the deep sequence technique described in Example 12). Typically, at least 40% of the total count of miRNA in microparticles (e.g. microvesicles and exosomes) of the invention is hsa-miR-1246. Typically, at least 50% of the total count of miRNA in exosomes of the invention is hsa-miR-1246.

hsa-miR-4492 is typically the second-most abundant miRNA in the microparticles of the invention. Typically, at least 3% of the total count of miRNA in microparticles (e.g. microvesicles and exosomes) of the invention is hsa-miR-4492. More typically, at least 4% of the total count of miRNA in microparticles (e.g. microvesicles and exosomes) of the invention is hsa-miR-4492.

Typically, at least 2% of the total count of miRNA in microparticles (e.g. microvesicles and exosomes) of the invention is hsa-miR-4532.

Typically, at least 1% of the total count of miRNA in microparticles (e.g. microvesicles and exosomes) of the invention is hsa-miR-4488.

In one embodiment microparticles of the invention contain one or both of hsa-miR-4508, hsa-miR-4516 at a level at least 0.1% of the total miRNA content of the particle.

One or more of hsa-miR-3676-5p, hsa-miR-4485, hsa-miR-4497, hsa-miR-21-5p, hsa-miR-3195, hsa-miR-3648, hsa-miR-663b, hsa-miR-3656, hsa-miR-3687, hsa-miR-4466, hsa-miR-4792, hsa-miR-99b-5p and hsa-miR-1973 may be present in the microparticles of the invention.

Typically, each of hsa-let-7a-5p and hsa-100-5p is present at less than 1%, more typically less than 0.1% or less than 0.05% of the total miRNA count in microparticles of the invention.

In a typical exosome of the invention, at least 50% of the total count of miRNA is hsa-miR-1246, and less than 0.1% of the total miRNA count is hsa-let-7a-5p.

In one embodiment, at least 90% of the total count of miRNA in microparticles of the invention comprises hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532. Typically, at least 95% or 96% of the total count of miRNA in microparticles of the invention comprises hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532. Less than 10% of the total miRNA content of these microparticles is an miRNA that is not hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532.

Combinations of the miRNA embodiments discussed above are provided. For example, a microparticle of the invention typically contains each of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532 at a read count of at least 1000 and contains each of hsa-let-7a-5p, hsa-miR-92b-3p, hsa-miR-21-5p, hsa-miR-92a-3p, hsa-miR-10a-5p, hsa-100-5p and hsa-99b-5p at a read count of less than 100. Typically, at least 90% or at least 95% of the total miRNA in these microparticles is hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532.

A microparticle (e.g. microvesicle or exosome) of the invention typically has hsa-miR-1246 as the most abundant miRNA and hsa-miR-4492 is the second-most abundant miRNA. In this embodiment, at least 40% of the total count of miRNA in microparticles (e.g. microvesicles and exosomes) of the invention is hsa-miR-1246 and at least 3% of the total count of miRNA in the microparticle is hsa-miR-4492. At least 2% of the total count of miRNA in these microparticles is hsa-miR-4532 and at least 1% of the total count of miRNA in these microparticles is hsa-miR-4488. Each of hsa-let-7a-5p and hsa-100-5p is present at less than 0.1% of the total miRNA count in these microparticles.

Plotting the deep sequencing results in the exosomes and microvesicles as relative fold change compared to the cells confirms that hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-

4532 are significantly upregulated in the exosomes and microvesicles compared to the cells. This comparison also shows that miRNA hsa-miR-3195 is the miRNA that is most upregulated, in both exosomes and microvesicles. Although the absolute reads of hsa-miR-3195 are in the range of ~40 for exosomes and microvesicles, there is no hsa-miR-3195 detected in the cells. Accordingly, hsa-miR-3195 is uniquely found in the exosomes and microvesicles of the invention and, in one embodiment, an exosome or microvesicle of the invention comprises hsa-miR-3195.

In one embodiment, microparticles of the invention comprise one or more of the following miRNA precursors:

AC079949.1 (SEQ ID NO:738)
GGCCGCGCCCCGTTTCCCAGGACAAAGGGCACTCCGCACCGGACCCTGGTCCCAGCG;

AP000318.1 (SEQ ID NO: 739)
CCCACTCCCTGGCGCCGCTTGTGGAGGGCCCAAGTCCTTCTGATTGAGGCCCAACCCGTGGAAG;

AL161626.1 (SEQ ID NO:740)
CGCCGGGACCGGGGTCCGGGGCGGAGTGCCCTTCCTCCTGGGAAACGGGGTGCGGC;

AC004943.1 (SEQ ID NO:741)
GCTTCACGTCCCCACCGGCGGCGGCGGCGGTGGCAGTGGCGGCGGCGGCGGCGGTGGCGGCGGCGGCGGCGGCGGCG
GCTC; and

AL121897.1 (SEQ ID NO:742)
GCCGCCCCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCCGCTTTCGGCTCGGGCCTCAGGTGAGTCGGAG
GGGCCGGGCGCC

In one embodiment, microparticles of the invention comprise one, two or three of the following mature miRNAs derived from the precursors listed above (as detailed in part D of Example 12):

ggcggagugcccuucuuccugg (derived from AL161626.1-201) (SEQ ID NO:743)
ggagggcccaaguccuucugau (derived from AP000318.1-201) (SEQ ID NO:744)
gaccaggguccggugcggagug (derived from AC079949.1-201) (SEQ ID NO:745)

These 5 miRNA precursors and 3 mature miRNAs have not previously been isolated and each sequence is therefore also provided as a new sequence *per se*. Accordingly, in one aspect, the invention provides a composition comprising one or more of the miRNA precursors AC079949.1, AP000318.1, AL161626.1, AC004943.1 and AL121897.1. In another embodiment, the invention provides a composition comprising one or more of the mature miRNAs ggcggagugcccuucuuccugg (derived from AL161626.1-201), ggagggcccaaguccuucugau (derived from AP000318.1-201) and gaccaggguccggugcggagug (derived from AC079949.1-201). Optionally, the composition is a pharmaceutical composition comprising one or more of

the miRNA precursors and/or one or more of the mature miRNAs and a pharmaceutically-acceptable carrier or diluent. As noted in Example 12, these miRNAs and precursors appear to be selectively shuttled into the exosomes and microvesicles and so may be at least partially responsible for the function of the microparticles.

Example 12 also shows that neural stem cell microparticles comprise a variety of non-coding RNA species. In one embodiment, microparticles of the invention comprise one or more of ribosomal RNA, small nucleolar RNA, small nuclear RNA, microRNA, large intergenic non-coding RNA and miscellaneous other RNA (e.g. RMRP, vault RNA, metazoan SRP and/or RNY).

Example 4 shows miRNAs present in microparticles produced by the CTX0E03 cells and having a Cp below 35 as determined by a qRT-PCR array. Typically, in one embodiment microparticles of the invention contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60 or more, or all, of the following miRNAs (identified according by name according to Ambros *et al* and accessible at www.mirbase.org):

hsa-let-7a
hsa-let-7b
hsa-let-7c
hsa-let-7d
hsa-let-7e
hsa-let-7f
hsa-let-7g
hsa-let-7i
hsa-miR-100
hsa-miR-101
hsa-miR-103a
hsa-miR-106b
hsa-miR-10a
hsa-miR-10b
hsa-miR-124
hsa-miR-125a-5p
hsa-miR-125b
hsa-miR-126
hsa-miR-127-5p
hsa-miR-128
hsa-miR-129-5p
hsa-miR-130a

hsa-miR-132
hsa-miR-134
hsa-miR-137
hsa-miR-141
hsa-miR-146b-5p
hsa-miR-150
hsa-miR-155
hsa-miR-15a
hsa-miR-15b
hsa-miR-16
hsa-miR-17
hsa-miR-181a
hsa-miR-182
hsa-miR-183
hsa-miR-185
hsa-miR-18a
hsa-miR-18b
hsa-miR-192
hsa-miR-194
hsa-miR-195
hsa-miR-196a
hsa-miR-205
hsa-miR-20a
hsa-miR-20b
hsa-miR-21
hsa-miR-210
hsa-miR-214
hsa-miR-218
hsa-miR-219-5p
hsa-miR-22
hsa-miR-222
hsa-miR-23b
hsa-miR-24
hsa-miR-26a
hsa-miR-301a
hsa-miR-302a
hsa-miR-302c
hsa-miR-33a
hsa-miR-345
hsa-miR-375

hsa-miR-378
hsa-miR-424
hsa-miR-7
hsa-miR-9
hsa-miR-92a
hsa-miR-93
hsa-miR-96
hsa-miR-99a

In one embodiment, the CTX0E03 microparticles contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30 or more of the following miRNAs (which are selected from the list above):

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
hsa-miR-99a

Proteins detected by a dot-blot

Example 5 shows proteins present in microparticles produced by the CTX0E03 cells, as detected by a dot-blot. Typically, microparticles of the invention contain 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or all of the following proteins:

EDA-A2
Galectin-3
IGFBP-2
IGFBP-rp1/IGFBP-7
IL-1a
LECT2
MCP-1
SPARC
TIMP-1
Thrombospondin-1
VEGF

Galectin-3 and Thrombospondin-1 are also identified as present in exosomes and microvesicles in Example 13. TIMP-1 is identified in Example 13 as being present in exosomes.

Example 5 also shows that the microparticles produced by the CTX0E03 cells may also express 1, 2, 3, 4 or 5 of the following proteins:

EGF-R/ErbB1
MDC
Endostatin
Follistatin
Csk

EGF-R and Csk are also identified as present in exosomes and microvesicles in Example 13.

Galectin-3, SPARC, TIMP-1, Thrombospondin-1, VEGF, MDC and Endostatin are known to be modulate angiogenesis. Accordingly, microparticles containing one or more of these proteins are useful in treating diseases or disorders requiring modulation of angiogenesis.

IL-1a, LECT2, MCP-1 and Csk are known to modulate inflammation. Accordingly, microparticles containing one or more of these proteins are useful in treating diseases or disorders requiring modulation of inflammation.

Microparticles containing one or more of (i) Galectin-3, SPARC, TIMP-1, Thrombospondin-1, VEGF, MDC and Endostatin, and one or more of (ii) IL-1a, LECT2, MCP-1 and Csk, may be useful for treating diseases or disorders requiring modulation of angiogenesis and inflammation.

Neural Stem cells in multi-compartment bioreactor culture

As shown in Example 10 and Figure 9 below, after multi-compartment bioreactor culture for three weeks, neural stem cells express a number of markers at significantly higher levels than neural stem cells cultured according to standard procedure in a standard single-compartment T175 flask. In one embodiment, microparticles of the invention are isolated from NSCs that have been cultured, typically in a multi-compartment bioreactor, for at least two weeks, typically at least three weeks, at least four weeks, at least five weeks or at least six weeks. Optionally, the NSCs have been cultured for no more than ten weeks, e.g. between 2 and 10 weeks, between 3 and 10 weeks, between 4 and 10 weeks, between 5 and 10 weeks or between 6 and 10 weeks. Microparticles may also be isolated from the other cell types described herein, including mesenchymal stem cells and haematopoietic stem cells, that have been cultured for these periods in a bioreactor.

CTX0E03 neural stem cells cultured for three weeks in a multi-compartment bioreactor express DCX, GALC, GFAP, TUBB3, GDNF and IDO at a higher level than neural stem cells cultured in a standard single-compartment T175 cell culture. Accordingly neural stem cells that have been cultured in a multi-compartment bioreactor, typically for a week or more, ten days or more, two weeks or more, or at least three weeks, four weeks, five weeks or more, may express one or more of DCX, GALC, GFAP, TUBB3, GDNF and IDO. Cells cultured in a two-compartment bioreactor typically show increased expression of one or more of DCX, GALC, GFAP, TUBB3, GDNF and IDO compared to the stem cells cultured under standard conditions. The expression level of these markers in the multi-compartment bioreactor-cultured cells is typically significantly higher than in the cells cultured in a standard single-compartment T175 culture flask. Typically, a stem cell cultured in a multi-compartment bioreactor expresses one or more of DCX1, GALC, GFAP, TUBB3, GDNF or IDO at a level least 2 fold higher than in CTX0E03 cells cultured in a T-175 flask according to standard culture procedure. In one embodiment, microparticles, typically exosomes, are obtained from neural stem cells that show increased expression of one or more of DCX, GALC, GFAP, TUBB3, GDNF and IDO compared to the stem cells cultured under standard conditions. For example, microparticles can be obtained from freshly filtered conditioned medium collected from Integra CeLLine bioreactor cultured neural stem cells.

The upregulated markers include DCX (doublecortin – an early neuronal marker), GFAP (Glial fibrillary acidic protein - an astrocyte marker), GALC, TUBB3, GDNF and IDO. CTX0E03 cells

are able to differentiate into 3 different cell types: neurons, astrocytes and oligodendrocytes. The high levels of DCX and GFAP after three weeks in a multi-compartment bioreactor indicates that the cultured stem cells have partially differentiated and have entered the neuronal (DCX+ cells) and/or astrocytic (GFAP+ cells) lineage. Accordingly, in one embodiment the invention provides a microparticle produced by a neural stem cell population that expresses (i) one or more markers associated with a neuronal lineage, typically DCX and/or (ii) one or more markers associated with an astrocytic lineage, typically GFAP. In another embodiment, the invention provides neural stem cell microparticles, typically exosomes, that express (i) one or more markers associated with a neuronal lineage, typically DCX and/or (ii) one or more markers associated with an astrocytic lineage, typically GFAP. These cells, or the microparticles (typically exosomes) derived from these cells, express DCX and/or GFAP at a higher level than the corresponding stem cells in standard (T-175) culture. Typically, these cells or microparticles express DCX and/or GFAP at a level at least 2 fold more than the stem cells, more typically at least 2.5 fold more than the corresponding stem cells in standard culture, at least 5 fold more than the corresponding stem cells in standard culture, at least 7.5 fold more than the corresponding stem cells in standard culture or at least 10 fold more than the corresponding stem cells in standard culture. For expression of DCX, the fold change in the cells or microparticles compared to the corresponding stem cells in standard (T-175) culture can optionally be at least 20 fold, at least 50 fold, at least 100 fold, at least 500 fold or at least 1000 fold more than the standard stem cells.

The term "bioreactor" is to be given its usual meaning in the art, i.e. an apparatus used to carry out a bioprocess. The bioreactors described herein are suitable for use in cell culture, e.g. stem cell culture. Simple bioreactors for cell culture are single compartment flasks, such as the commonly-used T-175 flask (e.g. the BD Falcon™ 175 cm² Cell Culture Flask, 750 ml, tissue-culture treated polystyrene, straight neck, blue plug-seal screw cap, BD product code 353028). Bioreactors can have multiple compartments, as is known in the art. These multi-compartment bioreactors typically contain at least two compartments separated by one or more membranes or barriers that separate the compartment containing the cells from one or more compartments containing gas and/or culture medium. Multi-compartment bioreactors are well-known in the art. An example of a multi-compartment bioreactor is the Integra CeLLine bioreactor, which contains a medium compartment and a cell compartment separated by means of a 10 kDa semi-permeable membrane; this membrane allows a continuous diffusion of nutrients into the cell compartment with a concurrent removal of any inhibitory waste product. The individual accessibility of the compartments allows to supply cells with fresh medium without mechanically interfering with the culture. A silicone membrane forms the cell compartment base and provides an optimal oxygen supply and control of carbon dioxide levels by providing a short diffusion

pathway to the cell compartment. Any multi-compartment bioreactor may be used according to the invention.

Example 11, Table 3 and Figure 10 show that the miRNA content of exosomes produced by neural stem cells that have been cultured in a multi-compartment bioreactor, for three weeks, is different from the miRNA content of stem cells cultured in standard T-175 flasks and from microparticles produced by the neural stem cells cultured in a single-compartment T175 culture flask for three weeks. In one embodiment, the invention provides a microparticle, typically an exosome, wherein at least two, three, four, five, six or seven miRNAs are up or down regulated compared to in the corresponding stem cells cultured in standard T-175 flasks, as calculated by Fold Regulation (see Example 11). The Fold Regulation of each miRNA is optionally at least two-fold up or down.

It can be seen from Figure 6C and Example 8 that exosomes isolated from NSCs show particularly surprising efficacy when the NSCs have been cultured for several weeks. Accordingly, in one embodiment, exosomes of the invention are isolated from NSCs that have been cultured, typically in a multi-compartment bioreactor, for at least two weeks, typically at least three weeks, at least four weeks, at least five weeks or at least six weeks. Optionally, the NSCs have been cultured for no more than ten weeks, e.g. between 2 and 10 weeks, between 3 and 10 weeks, between 4 and 10 weeks, between 5 and 10 weeks or between 6 and 10 weeks.

In one embodiment, neural stem cell exosomes of the invention express one, two, three, four, five, six or seven of the following miRNAs at a higher level than is expressed in the corresponding stem cells cultured in standard T-175 flasks, as calculated by Fold Regulation (where an asterisk indicates an miRNA where at least a two-fold regulation increase is preferred):

hsa-miR-146b-5p*
hsa-let-7c*
hsa-miR-99a*
hsa-miR-132*
hsa-miR-378*
hsa-miR-181a*
hsa-let-7b*

In one embodiment, neural stem cell exosomes of the invention express one, two, three, four, five, six, seven, eight, nine, ten or more of the following miRNAs at a lower level than is expressed in the corresponding stem cells cultured in standard T-175 flasks, as calculated by

Fold Regulation (where an asterisk indicates an miRNA where at least a two-fold regulation decrease is preferred):

hsa-miR-7*
hsa-miR-106b*
hsa-miR-101*
hsa-miR-302a*
hsa-miR-301a*
hsa-miR-183*
hsa-miR-219-5p*
hsa-miR-18a*
hsa-miR-15a*
hsa-miR-182*
hsa-miR-33a*
hsa-miR-96*
hsa-miR-18b*

In a further embodiment, NSC exosomes of the invention comprise (i) an increased level of at least one, two, three, four, five, six or seven of the miRNAs indicated above as being increased in exosomes compared to the corresponding cells in standard culture and (ii) a decreased level of at least one, two, three, four, five, six, seven, eight, nine, ten or more or more of the miRNAs indicated above as being decreased in exosomes compared to the corresponding cells in standard culture. For example, a neural stem cell exosome may contain a fold-regulation increase in three or more or more of the miRNAs indicated above as being increased in exosomes compared to the corresponding cells in standard culture and a fold-regulation decrease in three or more of the miRNAs indicated above as being decreased in exosomes compared to the corresponding cells in standard culture. In another exemplary embodiment, a neural stem cell exosome may contain a fold-regulation increase in five or more of the miRNAs indicated above as being increased in exosomes compared to the corresponding cells in standard culture and a fold-regulation decrease in five or more of the miRNAs indicated above as being decreased in exosomes compared to the corresponding cells in standard culture.

The term “expressed” is used to describe the presence of a marker within a cell or microparticle. In order to be considered as being expressed, a marker must be present at a detectable level. By “detectable level” is meant that the marker can be detected using one of the standard laboratory methodologies such as qRT-PCR, or qPCR, blotting, Mass Spectrometry or FACS analysis. A gene is considered to be expressed by a cell or microparticle of the population of the invention if expression can be reasonably detected at a crossing point (cp) values below or equal 35. The terms “express” and “expression” have corresponding meanings. At an expression level below this cp value, a marker is considered not to be expressed. The comparison between the expression level of a marker in a stem cell or microparticle of the invention, and the expression level of the same marker in another cell or microparticle, such as for example an mesenchymal stem cell, may preferably be conducted by comparing the two

cell/microparticle types that have been isolated from the same species. Preferably this species is a mammal, and more preferably this species is human. Such comparison may conveniently be conducted using a reverse transcriptase polymerase chain reaction (RT-PCR) experiment.

As used herein, the term "significant expression" or its equivalent terms "positive" and "+" when used in regard to a marker shall be taken to mean that, in a cell or microparticle population, more than 20%, preferably more than, 30%, 40%, 50%, 60%, 70%, 80%, 90% 95%, 98%, 99% or even all of the cells of the cells/microparticles express said marker.

As used herein, "negative" or "-" as used with respect to markers shall be taken to mean that, in a cell or microparticle population, less than 20%, 10%, preferably less than 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1 % or none of the cells/microparticles express said marker.

Expression of microparticle surface markers may be determined, for example, by means of flow cytometry and/or FACS for a specific cell surface marker using conventional methods and apparatus (for example a Beckman Coulter Epics XL FACS system used with commercially available antibodies and standard protocols known in the art) to determine whether the signal for a specific microparticle surface marker is greater than a background signal. The background signal is defined as the signal intensity generated by a non-specific antibody of the same isotype as the specific antibody used to detect each surface marker. For a marker to be considered positive the specific signal observed is typically more than 20%, preferably stronger than 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, 500%, 1000%, 5000%, 10000% or above, greater relative to the background signal intensity. Alternative methods for analysing expression of microparticle surface markers of interest include visual analysis by electron microscopy using antibodies against cell-surface markers of interest.

"Fluorescence activated cell sorting (FACS)" is a method of cell purification based on the use of fluorescent labelled antibodies. The antibodies are directed to a marker on the cell surface, and therefore bind to the cells of interest. The cells are then separated based upon the fluorescent emission peak of the cells.

Microparticle markers (including surface and intracellular proteins) can also be analysed by various methods known to one skilled in the art to assay protein expression, including but not limited to gel electrophoresis followed by western blotting with suitable antibodies, immunoprecipitation followed by electrophoretic analysis, and/or electron microscopy as described above, with microparticle permeabilisation for intraparticle markers. For example, expression of one or more tetraspanins may be assayed using one or more of the above

methods or any other method known to one skilled in the art. RNA levels may also be analysed to assess marker expression, for example qRT-PCR.

Microparticle Function

As noted above, a stem cell microparticle retains at least one biological function of the stem cell from which it is derived. Biological functions that may be retained include the ability to promote angiogenesis, tissue regeneration, tissue repair, and/or neurogenesis, the ability to effect cognitive improvement in the brain of a patient that has suffered a stroke, or the ability to accelerate blood flow recovery in peripheral arterial disease.

For example, CTX0E03 cells are known to inhibit T cell activation in a PBMC assay and, in one embodiment, the microparticles of the invention retain this ability to inhibit T cell activation in a PBMC assay. PBMC assays are well-known to the skilled person and kits for performing the assay are commercially available.

Example 8, Table 2 and Figure 6 demonstrate that CTX0E03 stem cell exosomes retain the ability to close a wound in a "scratch" model of wound healing. The results show that the migration activity of normal human dermal fibroblasts (NHDF) cultured in CTX0E03 conditioned media is almost the same as the migration activity observed on the addition of purified exosomes. Accordingly, one biological function that microparticles of the invention may retain is the ability to stimulate migration activity of normal human dermal fibroblasts (NHDF). NHDF migration assays are known in the art. Stimulation of NHDF migration may be determined using an *in vitro* scratch (wound closure) assay, for example the assay of Example 8(A). Wound closure is calculated as the area covered by NHDF cells in relation to the initial wound area as determined at 0 hours. Stimulation of NHDF migration in this assay is typically defined as an increase in wound closure, typically a wound closure at least 1.2x greater, more typically at least 1.5x greater, than the wound closure under basal conditions (without the microparticles) after 24 hours. After 48 hours, the wound closure is typically at least 1.2x greater or 1.5x greater, more typically at least 2x greater, than the wound closure under basal conditions (without the microparticles). Stimulation of NHDF migration may also be defined as causing a wound closure of 100%, as determined by the scratch assay, at least 24 hours before 100% wound closure is observed under basal conditions.

Example 8 also shows that microvesicles of the invention are able to stimulate angiogenesis of primary HUVECs and to stimulate neurite outgrowth of PC-12 cells. Accordingly, a biological function that microparticles of the invention may retain is the ability to stimulate angiogenesis of primary HUVECs and/or to stimulate neurite outgrowth of PC-12 cells. Angiogenesis and neurite outgrowth assays are known in the art. Stimulation of angiogenesis of primary HUVECs

may be determined using a 24 hour angiogenesis assay using an ibidi μ-slide and Wimtube detection and analysis of tube length and bifurcation points, for example the assay of Example 8(B). Stimulation of angiogenesis in this assay is typically defined as an increase compared to basal angiogenesis, e.g. >100% basal angiogenesis, typically at least 110%, at least 120% or at least 140% basal angiogenesis (i.e. at least 1.1x, at least 1.2x or at least 1.4x the basal level of angiogenesis). Stimulation of neurite outgrowth may be determined by detecting outgrowth of PC-12 cells through a 1μm insert, for example the assay of Example 8(C). Stimulation of neurite outgrowth in this assay is typically defined as an increase in neurite outgrowth compared to basal conditions (without microparticles), or an increase in neurite outgrowth when the microparticle is combined with NGF compared to the addition of NGF alone, as quantified by a spectrophotometer.

The proteomic analysis in Example 13 indicates that neural stem cell exosomes comprise biological functions associated with the production, packaging, function and degradation of genetic material. Accordingly, in one embodiment, exosomes of the invention retain these functions, typically one or more of RNA polymerase function, RNA degradation function, ribosome function and spliceosome function.

Immunogenicity

The (allogeneic) neural stem cell microparticles of the invention typically either do not trigger an immune response *in vitro* or *in vivo* or trigger an immune response which is substantially weaker than that which would be expected to be triggered upon injection of an allogeneic stem cell population into a patient. In certain aspects of the invention, the neural stem cell microparticles are considered not to trigger an immune response if at least about 70% of the microparticles do not trigger an immune response. In some embodiments, at least about 80%, at least about 90% or at least about 95%, 99% or more of the microparticles do not trigger an immune response. Preferably the microparticles of the invention do not trigger an antibody mediated immune response or do not trigger a humoral immune response. More preferably the microparticles of the invention do not trigger either an antibody mediated response or a humoral immune response *in vitro*. More preferably still, the microparticles of the invention do not trigger a mixed lymphocyte immune response. It will be understood by one skilled in the art that the ability of the cells of the invention to trigger an immune response can be tested in a variety of ways.

CTX0E03 cells transplanted in a rodent model of limb ischemia have been previously demonstrated a faster and transient up-regulation of host genes involved in angiogenesis, such as CCL11, CCL2, CXCL1, CXCL5, IGF1, IL1β, IL6, HGF, HIF1α, bFGF, VEGFA, and VEGFC, compared to vehicle treated controls. hNSC treatment transiently elevates host innate immune and angiogenic responses and accelerates tissue regeneration.

The CTX0E03 cell line has been previously demonstrated, using a human PBMC assay, not to be immunogenic. Accordingly, microparticles produced by CTX0E03 cells are also expected to be non-immunogenic. The lack of immunogenicity allows the microparticles to avoid clearance by the host/patient immune system and thereby exert their therapeutic effect without a deleterious immune and inflammatory response.

Stem Cells

The stem cell that produces the microparticle may be a stem cell line, i.e. a culture of stably dividing stem cells. A stem cell line can to be grown in large quantities using a single, defined source. Immortalisation may arise from a spontaneous event or may be achieved by introducing exogenous genetic information into the stem cell which encodes immortalisation factors, resulting in unlimited cell growth of the stem cell under suitable culture conditions. Such exogenous genetic factors may include the gene "myc", which encodes the transcription factor Myc. The exogenous genetic information may be introduced into the stem cell through a variety of suitable means, such as transfection or transduction. For transduction, a genetically engineered viral vehicle may be used, such as one derived from retroviruses, for example lentivirus.

Additional advantages are provided by using a conditionally immortalised stem cell line, in which the expression of the immortalisation factor can be regulated without adversely affecting the production of therapeutically effective microparticles. This may be achieved by introducing an immortalisation factor which is inactive unless the cell is supplied with an activating agent. Such an immortalisation factor may be a gene such as c-mycER. The c-MycER gene product is a fusion protein comprising a c-Myc variant fused to the ligand-binding domain of a mutant estrogen receptor. C-MycER only drives cell proliferation in the presence of the synthetic steroid 4-hydroxytamoxifen (4-OHT) (Littlewood et al.1995). This approach allows for controlled expansion of e.g. neural stem cells *in vitro*, while avoiding undesired *in vivo* effects on host cell proliferation (e.g. tumour formation) due to the presence of c-Myc or the gene encoding it in microparticles derived from the neural stem cell line. A suitable c-mycER conditionally immortalized neural stem cell is described in United States Patent 7416888. The use of a conditionally immortalised neural stem cell line therefore provides an improvement over existing stem cell microparticle isolation and production. Other methods of conditional immortalisation are known in the art.

Preferred conditionally-immortalised cell lines include the CTX0E03, STR0C05 and HPC0A07 neural stem cell lines, which have been deposited at the European Collection of Animal Cultures (ECACC), Vaccine Research and Production laboratories, Public Health Laboratory

Services, Porton Down, Salisbury, Wiltshire, SP4 0JG, with Accession No. 04091601 (CTX0E03); Accession No.04110301 (STR0C05); and Accession No.04092302 (HPC0A07). The derivation and provenance of these cells is described in EP1645626 B1. The advantages of these cells are retained by microparticles produced by these cells.

The cells of the CTX0E03 cell line may be cultured in the following culture conditions:

- Human Serum Albumin 0.03%
- Transferrin, Human 5µg/ml
- Putrescine Dihydrochloride 16.2 µg/ml
- Insulin Human recombinant 5 µ/ml
- Progesterone 60 ng/ml
- L-Glutamine 2 mM
- Sodium Selenite (selenium) 40 ng/ml

Plus basic Fibroblast Growth Factor (10 ng/ml), epidermal growth factor (20 ng/ml) and 4-hydroxytamoxifen 100nM for cell expansion. The cells can be differentiated by removal of the 4-hydroxytamoxifen. Typically, the cells can either be cultured at 5% CO_2/37°C or under hypoxic conditions of 5%, 4%, 3%, 2% or 1% O_2. These cell lines do not require serum to be cultured successfully. Serum is required for the successful culture of many cell lines, but contains many contaminants including its own exosomes. A further advantage of the CTX0E03, STR0C05 or HPC0A07 neural stem cell lines, or any other cell line that does not require serum, is that the contamination by serum is avoided.

The cells of the CTX0E03 cell line (and microparticles derived from these cells) are multipotent cells originally derived from 12 week human fetal cortex. The isolation, manufacture and protocols for the CTX0E03 cell line is described in detail by Sinden, et al. (U.S. Pat. 7,416,888 and EP1645626 B1). The CTX0E03 cells are not "embryonic stem cells", i.e. they are not pluripotent cells derived from the inner cell mass of a blastocyst; isolation of the original cells did not result in the destruction of an embryo.

The CTX0E03 cells (and microparticles derived from these cells) are angiogenic and so are useful in treating diseases requiring angiogenesis, such as Peripheral Arterial Disease. The cells (and microparticles derived from these cells) are also neurogenic and are therefore useful in treating diseases requiring neurogenesis, such as the ischaemia (stroke) damaged brain. CTX0E03 is a clonal cell line that contains a single copy of the c-mycER transgene that was delivered by retroviral infection and is conditionally regulated by 4-OHT (4-hydroxytamoxifen). The C-mycER transgene expresses a fusion protein that stimulates cell proliferation in the

presence of 4-OHT and therefore allows controlled expansion when cultured in the presence of 4-OHT. This cell line is clonal, expands rapidly in culture (doubling time 50-60 hours) and has a normal human karyotype (46 XY). It is genetically stable and can be grown in large numbers. The cells are safe and non-tumorigenic. In the absence of growth factors and 4-OHT, the cells undergo growth arrest and differentiate into neurons and astrocytes. Once implanted into an ischemia-damaged brain, these cells migrate only to areas of tissue damage.

The development of the CTX0E03 cell line has allowed the scale-up of a consistent product for clinical use. Production of cells from banked materials allows for the generation of cells in quantities for commercial application (Hodges et al, 2007).

Pollock *et al* 2006 describes that transplantation of CTX0E03 in a rat model of stroke (MCAo) caused statistically significant improvements in both sensorimotor function and gross motor asymmetry at 6–12 weeks post-grafting. These data indicate that CTX0E03has the appropriate biological and manufacturing characteristics necessary for development as a therapeutic cell line.

Stevanato et al 2009 confirms that CTX0E03 cells downregulated c-mycERTAM transgene expression both *in vitro* following EGF, bFGF and 4-OHT withdrawal and *in vivo* following implantation in MCAo rat brain. The silencing of the c-mycERTAM transgene in vivo provides an additional safety feature of CTX0E03 cells for potential clinical application.

Smith *et al* 2012 describe preclinical efficacy testing of CTX0E03 in a rat model of stroke (transient middle cerebral artery occlusion). The results indicate that CTX0E03 implants robustly recover behavioral dysfunction over a 3 month time frame and that this effect is specific to their site of implantation. Lesion topology is potentially an important factor in the recovery, with a stroke confined to the striatum showing a better outcome compared to a larger area of damage.

Neural retinal stem cell lines (for example as described in US 7514259) may also be used according to the invention.

The term “culture medium” or “medium” is recognized in the art, and refers generally to any substance or preparation used for the cultivation of living cells. The term “medium”, as used in reference to a cell culture, includes the components of the environment surrounding the cells. Media may be solid, liquid, gaseous or a mixture of phases and materials. Media include liquid growth media as well as liquid media that do not sustain cell growth. Media also include gelatinous media such as agar, agarose, gelatin and collagen matrices. Exemplary gaseous

media include the gaseous phase to which cells growing on a petri dish or other solid or semisolid support are exposed. The term "medium" also refers to material that is intended for use in a cell culture, even if it has not yet been contacted with cells. In other words, a nutrient rich liquid prepared for bacterial culture is a medium. Similarly, a powder mixture that when mixed with water or other liquid becomes suitable for cell culture may be termed a "powdered medium". "Defined medium" refers to media that are made of chemically defined (usually purified) components. "Defined media" do not contain poorly characterized biological extracts such as yeast extract and beef broth. "Rich medium" includes media that are designed to support growth of most or all viable forms of a particular species. Rich media often include complex biological extracts. A "medium suitable for growth of a high density culture" is any medium that allows a cell culture to reach an OD600 of 3 or greater when other conditions (such as temperature and oxygen transfer rate) permit such growth. The term "basal medium" refers to a medium which promotes the growth of many types of microorganisms which do not require any special nutrient supplements. Most basal media generally comprise of four basic chemical groups: amino acids, carbohydrates, inorganic salts, and vitamins. A basal medium generally serves as the basis for a more complex medium, to which supplements such as serum, buffers, growth factors, lipids, and the like are added. In one aspect, the growth medium may be a complex medium with the necessary growth factors to support the growth and expansion of the cells of the invention while maintaining their self-renewal capability. Examples of basal media include, but are not limited to, Eagles Basal Medium, Minimum Essential Medium, Dulbecco's Modified Eagle's Medium, Medium 199, Nutrient Mixtures Ham's F-10 and Ham's F-12, McCoy's 5A, Dulbecco's MEM/F-I 2, RPMI 1640, and Iscove's Modified Dulbecco's Medium (IMDM).

Pharmaceutical Compositions

The stem cell microparticle of the invention is useful in therapy and can therefore be formulated as a pharmaceutical composition. A pharmaceutically acceptable composition typically includes at least one pharmaceutically acceptable carrier, diluent, vehicle and/or excipient in addition to the microparticles of the invention. An example of a suitable carrier is Ringer's Lactate solution. A thorough discussion of such components is provided in Gennaro (2000) Remington: The Science and Practice of Pharmacy. 20th edition, ISBN: 0683306472.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The composition, if desired, can also contain minor amounts of pH buffering agents. The carrier may comprise storage media such as Hypothermosol®, commercially available from BioLife Solutions Inc., USA. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E W Martin. Such compositions will contain a prophylactically or therapeutically effective amount of a prophylactic or therapeutic microparticle preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the subject. The formulation should suit the mode of administration. In a preferred embodiment, the pharmaceutical compositions are sterile and in suitable form for administration to a subject, preferably an animal subject, more preferably a mammalian subject, and most preferably a human subject.

The pharmaceutical composition of the invention may be in a variety of forms. These include, for example, semi-solid, and liquid dosage forms, such as lyophilized preparations, liquid solutions or suspensions, injectable and infusible solutions. The pharmaceutical composition is preferably injectable. A particular advantage of the microparticles of the invention is their improved robustness compared to the stem cells from which they are obtained; the microparticles can therefore be subjected to formulation, such as lyophilisation, that would not be suitable for stem cells.

It is preferred that the methods, medicaments and compositions of the invention are used for treating or repairing damaged tissue, and/or for the treatment, modulation, prophylaxis, and/or amelioration of one or more symptoms associated with tissue disorders. Particularly preferred is the use of the methods, medicaments, compositions and microparticles of the invention in regenerative therapy, typically the treatment of stroke, peripheral arterial disease or blindness-causing diseases of the retina.

Pharmaceutical compositions will generally be in aqueous form. Compositions may include a preservative and/or an antioxidant.

To control tonicity, the pharmaceutical composition can comprise a physiological salt, such as a sodium salt. Sodium chloride (NaCl) is preferred, which may be present at between 1 and 20 mg/ml. Other salts that may be present include potassium chloride, potassium dihydrogen phosphate, disodium phosphate dehydrate, magnesium chloride and calcium chloride.

Compositions may include one or more buffers. Typical buffers include: a phosphate buffer; a Tris buffer; a borate buffer; a succinate buffer; a histidine buffer; or a citrate buffer. Buffers will typically be included at a concentration in the 5-20mM range. The pH of a composition will

generally be between 5 and 8, and more typically between 6 and 8 *e.g.* between 6.5 and 7.5, or between 7.0 and 7.8.

The composition is preferably sterile. The composition is preferably gluten free. The composition is preferably non-pyrogenic.

In a typical embodiment, the microparticles are suspended in a composition comprising 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox®), Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, $H_2P0_4^-$, HEPES, lactobionate, sucrose, mannitol, glucose, dextron-40, adenosine and glutathione. Typically, the composition will not include a dipolar aprotic solvent, e.g. DMSO. Suitable compositions are available commercially, e.g. HypoThermasol®-FRS. Such compositions are advantageous as they allow the microparticles to be stored at 4°C to 25°C for extended periods (hours to days) or preserved at cryothermic temperatures, i.e. temperatures below -20°C. The microparticles may then be administered in this composition after thawing.

The pharmaceutical composition can be administered by any appropriate route, which will be apparent to the skilled person depending on the disease or condition to be treated. Typical routes of administration include intravenous, intra-arterial, intramuscular, subcutaneous, intracranial, intranasal or intraperitoneal. For treatment of a disorder of the brain, one option is to administer the microparticles intra-cerebrally, typically to the site of damage or disease.

The microparticles will be administered at a therapeutically or prophylactically-effective dose, which will be apparent to the skilled person. Due to the low or non-existent immunogenicity of the microparticles, it is possible to administer repeat doses without inducing a deleterious immune response.

Therapeutic uses

The microparticles of the invention are useful in the treatment or prophylaxis of disease. Accordingly, the invention includes a method of treating or preventing a disease or disorder in a patient using a microparticle of the invention. The term "patient" includes human and other mammalian subjects that receive either prophylactic or therapeutic treatment.

As noted above, the compositions comprising miRNAs of the invention are also useful in these therapies, and references to therapeutic uses of microparticles herein therefore applies equally to the compositions comprising miRNAs.

Therapeutically useful microparticles of the invention have regenerative activity. A microparticle having regenerative activity is a microparticle that is capable of activating or enhancing

regenerative processes, or inhibiting or reducing degenerative processes. Regenerative processes lead to renewal, restoration, repair and/or growth of cells and tissues. Degenerative processes lead to a loss of cell or tissue integrity and/or function. This may be particularly useful in treating damaged or disturbed cells or tissues, such as those resulting from Stroke, psychiatric disorders, myocardial infarction, Amyotrophic lateral sclerosis and Peripheral arterial disease.

The microparticles of the invention are useful in tissue regeneration. "Tissue regeneration" is the process of increasing the number of cells in a tissue following a trauma. The trauma can be anything which causes the cell number to diminish. For example, an accident, an autoimmune disorder or a disease state could constitute trauma. Tissue regeneration increases the cell number within the tissue and enables connections between cells of the tissue to be re-established, and the functionality of the tissue to be regained.

The therapy may be regenerative therapy requiring tissue replacement, regeneration or repair. 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, the microparticle and compositions containing them are not used for immune modulation. In one embodiment, the therapy is not related to immunomodulation.

The invention also provides a method for treating or preventing a disease or condition comprising administering an effective amount of the microparticle of the invention, thereby treating or preventing the disease. Typically, the disease or condition is as identified above.

The microparticles of the invention can be used to treat the same diseases as the stem cells from which they are obtained. Neural stem cells are known to be useful in the treatment of diseases including: Stroke, brain damage such as motor, sensory and/or cognitive deficit, psychiatric disorders, myocardial infarction, Amyotrophic lateral sclerosis, limb ischaemia, peripheral arterial disease. Accordingly, the microparticles of the invention are also useful in the treatment of Stroke, brain damage such as motor, sensory and/or cognitive deficit, psychiatric disorders, myocardial infarction, Amyotrophic lateral sclerosis, limb ischaemia, peripheral arterial disease.

Figure 6 and Example 8 demonstrate that exosomes obtained from neural stem cells stimulate wound healing. Accordingly, in one embodiment, exosomes of the invention are used to treat a disease or condition requiring tissue replacement, regeneration or repair. Such conditions include diabetic ulcers and wound healing. Figure 6C shows that exosomes isolated from NSCs cultured for 6 weeks are more efficacious than exosomes isolated from NSCs cultured for 2 weeks. Accordingly, in one embodiment, exosomes isolated from NSCs (typically CTX0E03 cells) that have been cultured (typically in a multi-compartment bioreactor) for at least 2 weeks, more typically at least 4 weeks or at least 6 weeks, are used to treat a disease or condition requiring tissue replacement, regeneration or repair. Optionally, the NSCs have been cultured for no more than ten weeks, e.g. between 2 and 10 weeks, between 3 and 10 weeks, between 4 and 10 weeks, between 5 and 10 weeks or between 6 and 10 weeks.

The observed increased efficacy of exosomes isolated from NSCs (CTX0E03 cells) that have been cultured (in a multi-compartment bioreactor) for 6 weeks correlates with the observed reduction in size of the exosomes to around 70nm diameter, which also occurred after culturing the cells for 6 weeks. Accordingly, in one embodiment, exosomes isolated from NSCs (typically CTX0E03 cells) that have been cultured (typically in a multi-compartment bioreactor) for at least 6 weeks are used to treat a disease or condition requiring tissue replacement, regeneration or repair. As noted above, optionally the NSCs have been cultured for no more than ten weeks,

e.g. between 6 and 10 weeks. In another embodiment, exosomes isolated from NSCs (typically CTX0E03 cells) having a diameter less than 100nm, typically less than 80nm, for example around 70nm diameter, are used to treat a disease or condition requiring tissue replacement, regeneration or repair.

As shown in Figure 12 and discussed in Example 8, microvesicles obtained from neural stem cells stimulate angiogenesis. Accordingly, in one embodiment, microvesicles of the invention are used to treat a disease or condition requiring angiogenesis, typically a disease or disorder that is treated by tissue regeneration and/or revascularisation. Microvesicles of the invention can be used in the treatment of cardiovascular disorders, such as Myocardial Infarction, congestive heart failure, Peripheral Arterial Disease, diabetic ulcers and wound healing. The stimulation of angiogenesis is also therapeutically useful in the treatment of ischaemia, in particular cardiac ischaemia and limb ischaemia. Figure 12 shows that microvesicles harvested from NSCs cultured for at least 3 weeks are more efficacious than microvesicles isolated from NSCs cultured for 1 or 2 weeks. Accordingly, in one embodiment, microvesicles isolated from NSCs (typically CTX0E03 cells) that have been cultured (typically in a multi-compartment bioreactor) for at least 3 weeks, more typically at least 4 weeks or at least 6 weeks, are used to treat a disease or condition requiring angiogenesis. Optionally, the NSCs have been cultured for no more than ten weeks, e.g. between 3 and 10 weeks, between 4 and 10 weeks, between 5 and 10 weeks or between 6 and 10 weeks.

As shown in Figure 13 and discussed in Example 8, microvesicles obtained from neural stem cells stimulate neurite outgrowth. Accordingly, in one embodiment, microvesicles of the invention are used to treat a neurological disease, disorder or deficit, such as Parkinson's disease, Alzheimer's disease, Stroke, neuropathy or ALS.

In prophylactic applications, pharmaceutical compositions or medicaments are administered to a patient susceptible to, or otherwise at risk of, a particular disease in an amount sufficient to eliminate or reduce the risk or delay the outset of the disease. In therapeutic applications, compositions or medicaments are administered to a patient suspected of, or already suffering from such a disease in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a therapeutically-or pharmaceutically-effective dose. In both prophylactic and therapeutic regimes, agents are typically administered in several dosages until a sufficient response has been achieved. Typically, the response is monitored and repeated dosages are given if the response starts to fade.

The microparticles of the invention may optionally be combined with a stem cell to provide a combination therapy. The stem cell is optionally the stem cell from which the microparticle is derived, e.g. if the microparticle is an exosome from a CTX0E03 cell, then the stem cell for use in combination therapy may be a CTX0E03 cell. A stem cell and microparticle can optionally be (i) administered together in a single pharmaceutical composition, (ii) administered contemporaneously or simultaneously but separately, or (iii) administered separately and sequentially, e.g. stem cell followed by microparticle, or microparticle followed by stem cell. When the stem cell and microparticle are administered separately and sequentially, the duration between the administration of the cell and microparticle may be one hour, one day, one week, two weeks or more.

In one embodiment, a prophylactic therapy induces tolerance, typically immunotolerance, in a host that is to receive the stem cells from which the microparticle is derived. In one embodiment, the administration of one or more doses of microparticles of the invention to a patient, prior to 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. In another embodiment, tolerance to the stem cells can be increased by administering stem cells together with microparticles of the invention, as discussed above.

Effective doses of the compositions of the present invention, for the treatment of the above described conditions vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Usually, the patient is a human.

The CTX0E03 cell line has been shown to be effective in treating stroke, peripheral arterial disease, brain damage such as motor, sensory and/or cognitive deficit, and psychiatric disorders. The cells are currently being tested in a clinical trial for treatment of disabled stroke patients (Clinicaltrials.gov Identifier: NCT01151124). WO-A-2012/004611 describes the use of the CTX0E03 cells in treating psychiatric disorders including unipolar and bipolar depression, schizophrenia, obsessive compulsive disorder, autism and autistic syndrome disorders. Accordingly, microparticles produced by CTX0E03 cells are also able to treat stroke, peripheral arterial disease, blindness-causing diseases of the retina (such as retinitis pigmentosa), brain damage such as motor, sensory and/or cognitive deficit, and psychiatric disorders.

As used herein, the terms "treat", "treatment", "treating" and "therapy" when used directly in reference to a patient or subject shall be taken to mean the amelioration of one or more symptoms associated with a disorder, or the prevention or prophylaxis of a disorder or one or

more symptoms associated with a disorder. The disorders to be treated include, but are not limited to, a degenerative disorder, a disorder involving tissue destruction, a neoplastic disorder, an inflammatory disorder, an autoimmune disease or an immunologically mediated disease including rejection of transplanted organs and tissues. Amelioration or prevention of symptoms results from the administration of the microparticles of the invention, or of a pharmaceutical composition comprising these microparticles, to a subject in need of said treatment.

Tracing administered cells and microparticles *in vivo*

The present invention provides a distinct marker profile for microparticles produced by neural stem cells. It is therefore possible to detect the presence of these microparticles *in vivo*, by testing a sample obtained from a patient and determining whether the marker profile in the sample matches that of the microparticles. If the sample profile matches the profile of the microparticles described herein, then this confirms the presence of the microparticles. This can be used to detect not only the presence and/or biodistribution of the microparticles themselves, but also the presence of stem cells producing the microparticles. This is particularly useful when detecting whether a stem cell administered *in vivo* has engrafted into the host tissue, and/or has migrated, for example in ADME(T) studies.

Detection of the microparticles *in vivo* can be used to monitor the course of a treatment wherein microparticles or stem cells are administered to a patient. Determining the presence, absence or amount of microparticles or cells producing microparticles of the invention in a patient allows the dosage regime to be altered accordingly, e.g. to increase or decrease the dose as required to provide an effective amount of microparticles or stem cells *in vivo*.

Methods of producing microparticles

Microparticles are isolated from cell conditioned media, typically stem cell conditioned media. The "conditioned medium" (CM) may be a growth medium for stem cells, which has been used to culture a mass culture of stem cells for at least about 12 hours, at least about 24 hours, at least about 48 hours or least about 72 hours, typically up to 168 hours (7 days), removed and sterilized by any suitable means, preferably by filtration, prior to use, if required.

Alternatively, microparticles may be harvested from a two-compartment bioreactor which allows the cell culture, and hence the conditioned media, to be maintained for longer periods of time, for example at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks or more. The system maintains the cells and secreted microparticles within a small cell compartment (approximately 15ml) which is separated from a larger reservoir of medium by a 10kDa semi-permeable membrane. This allows the efficient removal of metabolic waste products while effectively maintaining an extremely high cell density to maximize microparticle

production. Example 9, and Figures 7 and 8, demonstrate that use of a two-compartment bioreactor results in a much higher yield of microparticles than is obtained when a standard cell culture flask (T175 flask) is used.

The microparticles may be separated from other media components based on molecular weight, size, shape, hydrodynamic radius, composition, charge, substrate-ligand interaction, absorbance or scattering of electromagnetic waves, or biological activity. In one embodiment, the conditioned media is filtered using a filter of appropriate size to separate the desired microparticle, for example a 100K MWCO filter. Optionally, the stem cell-conditioned medium is concentrated prior to the isolation of the microparticles by subjecting the concentrated NSC-conditioned medium to size exclusion chromatography. The UV absorbant fractions can then be selected for isolation of the microparticles of interest.

Different microparticles can be isolated from the media by using different isolation techniques and parameters. For example, exosomes have a vesicle density of 1.13–1.19 g/mL and can be isolated by differential centrifugation and sucrose gradient ultracentrifugation at 100,000–200,000g. Microvesicles can be isolated by filtration (100K MWCO) and differential centrifugation at 18,000–20,000g. Membrane particles have a density of 1.04-01.07 g/ml and Exosome-like vesicles have a density of 1.1 g/ml.

A typical production method comprises: culturing stem cells to produce conditioned media; removing cell debris by centrifugation at 1500 rpm; isolating microvesicles (<1000kDa) by ultrafiltration through a 100K MWCO filter or isolating exosomes (30-100nm) by ultracentrifugation at 120,000g; followed by quantification using a BCA protein assay.

Conditionally immortalised stem cells as producer cells for microparticles

In one aspect of the invention, conditionally immortalised stem cells are used to produce microparticles such as microvesicles and/or exosomes. Conditional immortalisation provides a constant supply of clonal cells that produce microparticles such as exosomes. These conditionally immortalised stem cells are typically neural stem cells, but may be a stem cell of any type, for example a haematopoietic stem cell or a mesenchymal stem cell. The conditionally immortalised stem cell may be a $CD34^+$ cell. A method of producing stem cell microparticles is therefore provided, comprising the steps of culturing conditionally-immortalised stem cells and harvesting the microparticles that are produced by the cells. Conditional immortalisation of stem cells is known in the art, as described above; in one embodiment, conditional immortalisation is achieved by introducing c-mycER, which drives cell proliferation only in the presence of the synthetic steroid 4-hydroxytamoxifen (4-OHT). For the avoidance of doubt, this method is not limited to the use of neural stem cells.

The Examples demonstrate the production of exosomes from conditionally-immortalised neural stem cells and CD34+ cord blood cells. This exemplification can readily be applied to other cell types, including mesenchymal stem cells.

When the stem cell used to produce microparticles is a neural stem cell, it may be any of the neural stem cells described herein, for example the CTX0E03 conditionally-immortalised cell line which is clonal, standardised, shows clear safety *in vitro* and *in vivo* and can be manufactured to scale thereby providing a unique resource for stable exosome production. Alternatively, the neural stem cells may be neural retinal stem cell lines, optionally as described in US 7514259.

Microparticles may also be produced from conditionally-immortalised neurosphere initiating stem cells (NS-IC) that are CD45-, CD34-. These cells can initiate neurosphere culture. A neurosphere is an aggregate or cluster of cells which includes neural stem cells and primitive progenitors. NS-IC cells are known in the art, for example as described in EP 1900811 B1 (StemCells Inc.). NS-IC cells are typically $AC133^+$.

In another embodiment, the conditionally immortalised stem cells are oligodendrocyte precursor cells (OPCs). OPCs are precursors to oligodendrocytes and are typically also able to differentiate into astrocytes and, optionally, neurons. OPCs typically express the proteoglycan PDGFRα. OPCs are described, for example, in WO-A-2010/075500 (StemCells Inc.); these OPCs are $PDGFR\alpha^+$ / $CD105^-$ and optionally $CD133^+$.

When the stem cell used to produce microparticles is a mesenchymal stem cell, it may optionally be a conditionally-immortalised adipose-derived stem cell ("ADSC") or a conditionally-immortalised version of the mesenchymal stem cells described in WO-A-2009/105044; these cells are CD29+, CD44+, CD49a+/e+, CD105+, CD166+, CD34-, CD45-.

In a further embodiment, microparticles are produced by conditionally-immortalised human bone marrow derived stem cells expressing CD73, CD90 and CD105 and not expressing CD14, CD19, CD34, CD45 and HLA-DR, wherein at least 50% of the cells of the cell population express glial fibrillary acidic protein (GFAP) and secrete BDNF. Such cells are described in EP-A-2620493 (Brainstorm Cell Therapeutics).

In one embodiment, the conditionally immortalised mesenchymal stem cell is an endometrial regenerative cell ("ERC"). ERCs are known in the art and are typically isolated from menstrual blood. ERCs typically express CD9, CD29, CD41a, CD44, CD59, CD73, CD90 and CD105.

The production of exosomes from non-conditionally-immortalised ERCs is described, for example, in US patent publication number US2013/0195899 (Medistem Inc.).

A further embodiment provides microparticles from conditionally immortalised multipotent adult progenitor cells ("MAPCs"), which are typically derived from bone marrow. MAPCs are known in the art and typically express Oct3 and telomerase. MAPCS are being developed by Athersys Inc. as the "Multistem" product. In one embodiment, MAPCs are human multipotent non-embryonic, non-germ cells that can differentiate into at least one cell type of each of at least two of the endodermal, ectodermal, and mesodermal embryonic lineages, express telomerase, and optionally express Oct-3. These MAPCs have typically undergone at least 10-40 cell doublings in culture (see, for example, US patent 8,147,824; Athersys, Inc.). In another embodiment the MAPCs are a human cell population that express CD90 and CD49c and one or more of sox-9, sox-11, hox-A5, and MSX-1, and optionally express telomerase. These cells typically show that marker profile after having undergone 22 cell doublings in culture.

Another embodiment of mesenchymal stem cells that can be conditionally-immortalised according to the invention are mesenchymal progenitor cells (MPCs). MPCs express SDF-1 (stroma derived factor 1 - a potent stroma derived CXCα chemokine). MPCs can typically differentiate into bone, fat and cartilage. MPCs may typically be isolated by selection for SDF-1 expression, for example using an SDF-1 antibody. MPCs are typically isolated from bone marrow. MPCs are typically positive for at least one marker selected from the group consisting of STRO-1^{bright} VCAM-1^{bright}, THY-1^{bright}, $CD146^{bright}$ and STRO-2^{bright}. Optionally, the MPCs carry at least two markers selected from the group of surface markers specific for MPCs consisting of STRO-1^{bri}, LFA-3, THY-I, VCAM-I, ICAM-I, PECAM-I, P-selectin, L-selectin, CD49a/CD49b/CD29, CD49c/CD29, CD49d/CD29, CD29, CDI 8, CD61, beta-1 integrin, 6-19, thrombomodulin, CDIO, CD13, SCF, PDGF-R, EGF-R, IGFI-R, NGF-R, FGF-R, Leptin-R, RANKL and CD 146 or any combination of these markers. The survival and/or proliferation of the MPC, or their progeny, may be enhanced by exposure to SDF-I or an analog thereof (see, for example, WO2006032075, Angioblast Inc. [now Mesoblast, Inc.]). MPCs are being developed commercially by Mesoblast under the name "Revascor".

Other conditionally-immortalised stem cells from which microparticles, such as exosomes, can be isolated include haematopoietic stem cells, typically CD34+ haematopoietic stem cells, optionally isolated from umbilical cord blood (often referred to as "cord blood cells"). Example 15 and Figure 20A-C demonstrates that Human CD34+ progenitor cells derived from cord blood were successfully conditionally immortalized with a c-mycERTAM lentivirus, and produce exosomes expressing the characteristic marker Alix.

Umbilical cord blood also includes non-haematopoietic stem cells, which can also be conditionally immortalised and used to produce microparticles.

Hematopoietic stem cells are also described in US 7,794,705 (Amorcyte Inc.). These cells are CD34+/CXCR-4+ cells that have CXCR-4-mediated chemotactic activity and are able to form hematopoietic colonies *in vitro*.

Microparticles may also be produced by conditionally-immortalised very small embryonic like stem cells (VSELs) derived from a human, which are typically $CD133^+$ $CXCR4^+$ $CD34^+$ Lin^- $CD45^-$ (for example as described by WO2010039241, NeoStem Inc.). The VSELs are optionally $Oct\text{-}4^+$, $SSEA^+$, $Nanog^+$, or express Oct-4 protein in nuclei and SSEA antigens on the surface.

The conditionally-immortalised stem cell may be a Multipotent Adult Progenitor Cell ("MAPC"). MAPCs are known in the art (see, for example, Reading et al. J Immunol. 2013 May 1;190(9):4542-52).

Induced pluripotent stem (iPS) cells may also be conditionally-immortalised and used to produce exosomes. iPS cells are known in the art, as reviewed by Malik and Rao Methods Mol Biol, 2013; 997-23-33.

Conditionally immortalised differentiated (non-stem) cells as producer cells for microparticles

Conditional immortalisation is not limited to stem cells. Accordingly, in a further aspect of the invention, conditionally immortalised differentiated (i.e. non-stem) cells are used to produce microparticles such as microvesicles and/or exosomes.

Fibroblasts may be conditionally-immortalised and used to produce microparticles such as exosomes. Typically, the fibroblast is a human dermal fibroblast.

Dendritic cells may also be conditionally-immortalised and used to produce microparticles such as exosomes.

Methods of inducing microparticle secretion

The inventors have found that it is possible to increase the production of microparticles by cells, typically stem cells. This finding, which is not limited to neural stem cells and can be used for the production of microparticles from any cell (typically stem cell), allows for an improved yield of microparticles to be obtained from a stem cell culture. This improved yield is particularly advantageous when combined with the continuous supply of microparticles provided by conditionally-immortalised cells.

A first technique to increase the production of microparticles by the (stem) cells is to treat the stem cells with one or more of TGF-β, IFN-γ or TNF-α, typically at between 1 and 25ng/ml e.g. 10ng/ml, for between 12 to 96 hours prior to the removal of conditioned media.

As explained in Example 2 below, the frequency of the occurrence of multivesicular bodies (MVBs) was observed to be altered by the presence of TGF-β, IFN-γ or TNF-α (10ng/ml). The frequency was highest in the presence of TGF-β, followed by IFN-γ, followed by TNF-α. Therefore, adding one or more of TGF-β, IFN-γ or TNF-α to the stem cell culture medium will stimulate the production of microparticles by the cells. The microparticles can then be harvested, by separating the microparticles from other components as described above.

A second technique to increase the production of microparticles by the stem cells is to culture the cells under hypoxic conditions. Culturing cells under hypoxic conditions is well-known to the skilled person, and involves culturing the cells in an atmosphere that has less than atmospheric level of O_2, i.e. less than 21% O_2. This is typically achieved by placing the cells in an incubator that allows oxygen levels to be changed. Hypoxic culture typically involves culturing in an atmosphere containing less than 10% O_2, more typically 5% or less O_2, for example 4% or less, 3% or less, 2% or less, or 1% or less O_2.

The inventors have also realised that co-culturing a stem cell with a different cell type can alter the production of microparticles by the stem cell. The different cell type may be a non-stem cell, i.e. a terminally differentiated cell type. Typically, the different cell type is one with which the stem cell would interact *in vivo*. In one embodiment, neural stem cells are co-cultured with epithelial cells such as endothelial cells, typically Human Umbilical Vein Endothelial Cells (HUVEC). It has been observed that *in vivo*, NSCs and the vasculature interact, with proliferating NSCs being localized in close proximity or adjacent to blood vessels. Receptor tyrosine kinase activation and signal protein secretion has also been observed to be upregulated when NSCs are co-cultured with endothelial cells, again indicating that the vasculature modulates the proliferation capacity of NSCs. Without wishing to be bound by theory, the inventors believe that *in vivo*, there is a pivotal interplay between NSCs and microvessels (i.e. endothelial cells) in the process of tissue regeneration, through amplification of cytokine expression. Microparticles, e.g. exosomes, derived from NSCs (for example CTX0E03 cells) co-cultured with endothelial cells (for example HUVEC) are therefore primed for therapeutic use, because they have been produced in an environment that mimics the *in vivo* environment in which the stem cells and microparticles are active.

Therefore, culturing a stem cell with a different cell type may improve the amount of microparticles produced and/or may refine the content of the microparticles, typically so that the microparticles produced by the stem cells are biased towards an activated state of tissue repair. Accordingly, microparticles produced by stem cells that have been co-cultured with other cells, e.g. NSCs co-cultured with endothelial cells, are advantageous. These microparticles may be obtained by isolation from the co-cultured stem-cell conditioned media, as described herein.

Surprisingly, the present inventors have realised that the amount of microparticles produced by stem cells can be increased greatly simply by culturing stem cells in a multi-compartment bioreactor. This finding is not limited to neural stem cells and applies generally to the culture of all stem cells. Accordingly, one aspect of the invention provides a method of producing microparticles from stem cells that have been cultured in a multi-compartment bioreactor. The cells from which the microparticles are harvested have typically been cultured for at least one week, typically at least 8, 9, 10, 11, 12, 13 or 14 days, for example 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days or more, for example at least three weeks, four weeks, five weeks, six weeks or more. It can be seen from Figure 8 that the increase in microparticle production, week on week, is not merely additive but is exponential. The prolonged culture typically has been observed in the Integra Celline system two-compartment bioreactor (commercially available from Integra Biosciences AG, Zizers, Switzerland) but the findings are not limited to this specific multi-compartment bioreactor; any multi-compartment bioreactor can be used. This culture method can be used to produce microparticles from any stem cell type, including but not limited to neural stem cells and mesenchymal stem cells.

Method of screening for an agent that alters microparticle production

The invention provides a method of screening for an agent that alters the production of a microparticle by a conditionally-immortalised cell, typically a conditionally-immortalised stem cell. This method comprises contacting a conditionally-immortalised (e.g. stem) cell with a candidate agent, typically under conditions suitable for microparticle production, and observing whether (i) the rate of production of microparticles by the contacted conditionally-immortalised cell increases or decreases, or (ii) the characteristics (e.g. size, protein, mRNA or miRNA content) of the microparticles changes, compared to a control stem cell that is not contacted with the agent.

Method for screening total RNA composition of conditioned medium

Following centrifugation (5 min at 1500 rpm), microparticles are collected from conditioned medium through filtration (0.02-0.2µm, or 100K MWCO). Total RNA is obtained using trizol based extraction followed by purification using Qiagen RNaesy mini kit. The extract in water has a 260:280 nm absorbance suggesting that it may be RNA. Total RNA is retro-transcribed with

either a protocol suitable for mRNA (Superscript II RT, Invitrogen) or miRNA (mScript RT kit, Qiagen). Validation of mRNA and miRNA presence is proven by qRT-PCR using primers for ATP5B and YWHAZ for mRNA, and U6B and 15a for miRNA housekeeping genes respectively. The RNA may be assessed by a generic gene expression analysis assay such as an array (micro array or PCR based array), and sequencing.

Kits

The invention provides a kit for use in a method for producing the microparticle of the invention. The kit comprises a cell culture medium, a conditionally-immortalised cell and instructions for producing the microparticle of claim 22 using the kit. Optionally, the kit comprises one or more components of claims 19 or 20. The kit may also comprise a microparticle according to the invention, for use as a control. The control microparticle is optionally lypohilised. The kit may also contain optionally a detection agent suitable for detection of the produced microparticles, for example an antibody that binds specifically to a marker protein that can be used to identify the microparticle.

The invention is further described with reference to the following non-limiting examples.

Examples

Example 1: Preparation of neural stem cells and neural stem cell microparticles for visualisation by electron microscopy.

Method

Embedding CTX0E03 cells for electron microscopy

- 5 x 70% CTX0E03 cultures
- Treat with +/-4OHT, IFNγ, TNFα and TGFβ (all at 10ng for 24hrs)
- Detach cells and fix overnight in 2.5% Gluteraldehyde in 0.1M Cacodylate pH7.4
- Cells spun down 300g
- Buffered osmium 2%, 1.5hrs
- Spin, wash water, overnight
- Uranium acetate 2%, 2hrs
- Spin, wash water, 30mins
- Ethanol gradient 20, 35, 50, 70, 80, 90, 100%, over weekend.
- 100% propylene oxide (PO), 1hr
- Spin, 50% Agar LV resin in PO, 1hr
- 75% LV resin/PO 5hrs

- 100% resin overnight at 60°C
- Cool to RT before cutting (60-80nm), Imaged TEM at 200Kv.

Results

Figure 1A-E shows the electron micrographs of the multivesicular bodies (MVBs) containing exosomes of approximately 30nm – 50nm in diameter. Figure 1F shows microvesicles >100nm in diameter.

Example 2: Production of neural stem cell microparticles from a neural stem cell line.

Method

5 Sub-confluent flasks containing the same culture of CTX0E03 cells were individually treated with either 10ng/ml TGF-β, 10ng/ml IFNγ, or 10ng/ml TNFα alongside full growth media controls with or without the addition of 4OHT. 72 hours after treatment, the cells were collected using trypzean/EDTA, washed and fixed overnight in 2.5% Gluteraldehyde in 0.1M Cacodylate pH7.4 ready for electron microscopy evaluation.

Results

The frequency of the occurrence of multivesicular bodies (MVBs) was observed to be altered by the presence of TGF-β, IFN-γ or TNF-α. The frequency was highest in the presence of TGF-β, followed by IFN-γ, followed by TNF-α.

Conclusion

The production of microparticles from neural stem cells can be stimulated by the addition of the factors TGF-β, IFN-γ or TNF-α. This has the potential for more efficient production of microparticles.

Example 3: Purification, quantification and characterisation of neural stem cell microparticles.

Method

An outline protocol for producing large quantities of microparticles is provided in Figure 2. The main steps are purification, quantification, characterisation, efficacy testing and manufacture.

(1) Purification

Microparticles can be purified from stem cell-conditioned medium by ultracentrifugation, e.g. at 100000 x g for 1-2 hours. Alternative or additional methods for purification of may be used, such as antibody-based methods, e.g. immunoprecipitation, magnetic bead purification, resin-based purification, using specific antibodies.

(2) Quantification

Purified microparticles can be quantified by quantification of total nucleic acid or protein levels, e.g. various PCR or colorimetric protein quantification methods such as such as the BCA assay. Other quantification techniques may alternatively be used, including an electron microscopy grid or an immune-assay using antibodies or antibody fragments that specifically bind to microparticle-specific markers (e.g. ELISA, immunoblotting).

(3) Characterisation

The microparticles can be functionally or structurally characterised. RNA/mRNA/miRNA and protein profiling can be used using methods well known in the art (SDS-PAGE, mass spectrometry, PCR). Constitutively secreted microparticles can be tested and compared to microparticles that have been induced by addition of an inducing agent such as transforming growth factor-beta (TGF-β), interferon-gamma (INF-γ) and/or tumour necrosis factor-alpha (TNF-α).

(4) Therapeutic Efficacy

The efficacy of the microparticles can be tested by *in vitro* and *in vivo* assays. For *in vitro* evaluation, neural stem cell microparticles can be added to cultures of monocytes, PBMCs, endothelial cells and/or fibroblasts and the effect of the microparticles on these cells evaluated. Administration of neural stem cell microparticles to suitable animal models can be used to evaluate the *in vivo* efficacy. Clinical trials can be performed to evaluate safety and outcome of neural stem cell microparticles in human subjects.

(5) Manufacture/Scale-Up

Bioreactors, such as the Integra disposable T1000, can be used for the large-scale manufacture of neural stem cell microparticles. The purified microparticles are then formulated as a therapeutic product.

Example 4: miRNA characterization in CTX0E03 microparticles

Methods

- 3 conditions: CTX0E03 cells in standard culture; microparticles obtained from CTX0E03 cells in standard culture; and purified exosomes derived from CTX0E03 cells in Integra CELLine system (see Examples 7 to 11, below)
- Investigation of miRNA array using qRT-PCR panel (Qiagen) according to manufacturer's instruction. This assay provides high precision and high sensitivity, with data normalization sensitive to method/choice of reference genes. It does not provide genome wide sequencing.

Results: A) List of miRNAs with a cp ≤ 35 found in (i) standard CTX0E03 cells, (ii) filtered conditioned medium (0.02-0.2μm filter) i.e. microparticles and (iii) exosomes derived from Integra CELLine system (preliminary miRNA qRT-PCR miscript array (Qiagen) results).

B) Arithmetic and geometric mean of the reference (housekeeping) genes

A

Mature miRNA	CTX0E03 std culture	CM microparticles	CM exosome Integra
hsa-miR-21-5p	19.52	20.9	20.72
hsa-let-7a-5p	22.64	23.11	22.36
hsa-miR-125b-5p	21.64	23.25	21.74
hsa-miR-9-5p	22.58	23.64	22.94
hsa-miR-92a-3p	23.2	23.94	24.01
hsa-miR-24-3p	23.73	24.24	23.83
hsa-miR-20a-5p	23.45	24.43	25.06
hsa-miR-16-5p	23.14	24.72	24.32
hsa-miR-100-5p	23.28	24.74	23.04
hsa-let-7b-5p	24.67	24.75	23.7
hsa-let-7f-5p	23.93	25.09	23.86
hsa-miR-17-5p	24.56	25.24	26.13
hsa-miR-23b-3p	24.3	25.3	24.13
hsa-miR-106b-5p	24.4	25.41	26.16
hsa-miR-222-3p	23.25	25.49	23.17
hsa-let-7e-5p	24.57	25.58	24.16
hsa-miR-26a-5p	23.4	25.63	24.2
hsa-miR-181a-5p	25.16	25.7	24.32
hsa-miR-125a-5p	23.56	25.75	24.88
hsa-miR-103a-3p	24.65	25.8	25.77
hsa-let-7i-5p	24.37	25.98	24.23
hsa-miR-99a-5p	24.44	26.05	23.44
hsa-let-7c	25.76	26.12	24.07
hsa-let-7g	25.2	26.15	25.17
hsa-miR-195-5p	24.72	26.34	25.67
hsa-miR-93-5p	25.15	26.48	26.06
hsa-miR-22-3p	25.03	26.49	25.66
hsa-miR-20b-5p	26.03	26.86	27.42
hsa-miR-18a-5p	26.71	26.87	29.06
hsa-miR-15b-5p	25.1	26.92	26.43
hsa-let-7d-5p	26.84	26.96	26.52
hsa-miR-424-5p	25.56	27.72	26.66
hsa-miR-15a-5p	26.88	27.89	29.3
hsa-miR-130a-3p	27.23	28.26	28.49
hsa-miR-33a-5p	30.34	28.54	34.18
hsa-miR-128-	26.94	28.64	27.66
hsa-miR-218-5p	27.79	28.68	28.03

hsa-miR-301a-3p	29.53	28.69	31.57
hsa-miR-134	28.3	28.76	28.76
hsa-miR-101-3p	28.44	28.82	31.64
hsa-miR-7-5p	29.71	28.82	30.22
hsa-miR-18b-5p	28.83	28.85	35.47
hsa-miR-185-5p	28.34	28.99	28.13
hsa-miR-378-3p	29.76	29.25	28.97
hsa-miR-132-3p	28.65	29.32	27.72
hsa-miR-345-5p	28.49	29.52	29.66
hsa-miR-219-5p	30.58	29.52	32.7
hsa-miR-127-5p	30.05	29.95	31.11
hsa-miR-146b-5p	30.53	30.54	28.07
hsa-miR-10a-5p	27.1	30.69	28.32
hsa-miR-210	29.85	30.83	30.65
hsa-miR-129-5p	32.51	30.98	31.69
hsa-miR-137	31.46	31.13	30.95
hsa-miR-182-5p	28.34	31.64	31.27
hsa-miR-124-3p	33.38	31.71	33.07
hsa-miR-96-5p	29.77	32.27	34.67
hsa-miR-192-5p	31.42	32.42	32.52
hsa-miR-126-3p	31.73	32.44	32.05
hsa-miR-194-5p	31.11	32.49	31.72
hsa-miR-375	33.77	32.94	30.94
hsa-miR-205-5p	35	33.01	32.72
hsa-miR-183-5p	29.88	33.21	31.74
hsa-miR-10b-5p	29.6	33.22	30.79
hsa-miR-302a-3p	29.67	33.6	31.69
hsa-miR-214-3p	34.19	33.76	32.11
hsa-miR-141-3p	35	33.96	34.51
hsa-miR-302c-3p	31.6	34.29	33.93
hsa-miR-196a-5p	35	34.65	35.75
hsa-miR-150-5p	34.59	34.76	34.59
hsa-miR-155-p	32.04	35.75	32.76

B

	CTX0E03 std culture	CM microparticles	CM exosome Integra
Avg. of Arithmetic Mean	23.54	23.82	24.79
Avg. of Geometric Mean	23.48	23.8	24.62

5

Example 5: CTX0E03 conditioned medium analysis using a protein dot blot

Methods

- Conditioned 24hr and 72 hrs conditioned medium (RMM and ITS medium)
- The collected media has been 'concentrated' by dialysis and the proteins biotinylated (typical total protein concentration appears to be 0.5 mg/ml). The media is then incubated with the Raybiotech L507 human protein arrays (total protein concentration 0.1 mg/ml). Following washing and incubation of the array with HRP-conjugated streptavidin, the presence of proteins is detected by chemiluminescence. The array provides qualitative data (i.e. the protein is present, but no indication of its level of expression compared to other proteins).

Results

Cytokine Name	Cytokine Full Name	Function
EDA-A2	ectodysplasin-A2	May be involved in proper formation of skin appendages
Galectin-3*	Galectin-3	Galactose-specific lectin which binds IgE. May mediate with the alpha-3, beta-1 integrin the stimulation by CSPG4 of endothelial cells migration.
IGFBP-2	Insulin-like growth factor binding proteins 2	IGF-binding proteins prolong the half-life of the IGFs and have been shown to either inhibit or stimulate the growth promoting effects of the IGFs on cell culture.
IGFBP-rp1/IGFBP-7	Insulin-like Growth Factor Binding Protein Related Protein-1 Insulin-like Growth Factor Binding Protein-7	soluble proteins that bind IGFs with high affinity.
IL-1a†	Interleukin 1 alpha	potent mediator of inflammation and immunity
LECT2†	Leukocyte cell-derived chemotaxin-2	Has a neutrophil chemotactic activity. Also a positive regulator of chondrocyte proliferation.
MCP-1†	Monocyte chemoattractant protein 1	plays a role in the recruitment of monocytes to sites of injury and

		infection.
SPARC*	Secreted Protein, Acidic Cysteine-rich-related modular calcium-binding protein 1 [Precursor]	matricellular protein that modulates cell adhesion and proliferation and is thought to function in tissue remodeling and angiogenesis
TIMP-1*	Tissue inhibitor of metalloproteinasess-2	Complexes with metalloproteinases (such as collagenases) and irreversibly inactivates them. Also mediates erythropoiesis in vitro; but, unlike IL-3, it is species-specific, stimulating the growth and differentiation of only human and murine erythroid progenitors.
Thrombospondin-1*	Thrombospondin-1	multimodular secreted protein that associates with the extracellular matrix and possesses a variety of biologic functions, including a potent angiogenic activity.
VEGF*	Vascular endothelial growth factor	Growth factor active in angiogenesis, vasculogenesis and endothelial cell growth.
These proteins show expression in some instances –though may also be present in media.		
EGF R/ErbB1	Epidermal growth factor receptor	Receptor for EGF, but also for other members of the EGF family, as TGF-alpha, amphiregulin, betacellulin, heparin-binding EGF-like growth factor
MDC *	A disintegrin and metalloproteinase domain 11 Metalloproteinase-like, disintegrin-like, and cysteine-rich protein	Probable ligand for integrin in the brain. This is a non catalytic metalloprotease-like protein.

	MDC	
Endostatin*	Endostatin	Angiogenesis inhibitor; inhibits endothelial cell migration but may not effect proliferation. May work in balance with VEGF to maintain level of angiogenesis.
Follistatin	Follistatin	Regulates stem cell renewal versus differentiation by inhibiting pro-differentiation proteins
Csk†	cytoplasmic tyrosine kinase	Activity is required for interleukin 6 (IL-6) induced differentiation. May play a role in the growth and differentiation of hematopoietic cells. May be involved in signal transduction in endocardial and arterial endothelial cells.

* = angiogenesis

† = inflammation

Example 6: Conditioned medium analysis using Human angiogenesis ELISA strips (Signosis)

Method

Human angiogenesis ELISA strips (Signosis) were utilized according to manufacturer's instruction. Fresh RMM medium and 24 hour conditioned CTX0E03 RMM medium were analyzed for 8 angiogenesis cytokines; tumor necrosis factor α (TNFα), insulin-like growth factor 1 (IGF-1), VEGFA, interleukin-6 (IL-6), bFGF, transforming growth factor β 1 (TGFβ1), EGF, and leptin. Individual wells of the strip, coated with each of the primary antibodies directed against the specific angiogenesis cytokines were loaded with test samples. Absorbance was measured by a spectrophotometer at 450 nm. The concentrations of the angiogenesis cytokines were directly proportional to the color intensity of the test sample.

The results are shown in Figure 3.

Example 7: Integra CELLINE – Disposable Bioreactor for the production of Micro particles from CTX0E03 cells.

Efficient micro particle production and harvest from a cell line relies upon maintaining optimal culture conditions for the greatest density of cells. Any restriction in the oxygen or nutrients supplied to the cells or an accumulation of waste metabolic products will limit the life span of the culture, and hence the micro particle production.

The two-compartment CELLine AD 1000 is designed to accommodate adherent cells attached to a matrix inlay within a small cell compartment, separated from a larger media reservoir by means of a 10kDa semi-permeable membrane. This membrane allows a continuous diffusion of nutrients and removal of waste products, while concentrating any micro particles produced by the cell within the smaller cell compartment. Due to the large volume capacity (1 litre) of the media compartment, the system has the potential to maintain high density cultures for longer periods of time without the need for a media change. The production of exosomes from mesothelioma tumour cell cultures is described in Mitchell *et al*, 2008.

Method

In order to obtain optimal performance of the CELLine AD1000, place 25ml of complete growth medium (RMM with growth factors and 4OHT) into the medium compartment of the flask to pre-wet the semi-permeable membrane. Allow the flask to sit for 5 minutes at room temperature before coating the matrix inlay with mouse Laminin by adding 15ml of laminin solution (20µg/ml in DMEM/F12) to the cell compartment for a minimum of 1 hour at 37°C. Remove the laminin solution and add 15ml of warm DMEM/F12 to the cell compartment to remove any excess laminin. Avoiding the matrix inlay drying, slowly introduce approximately $15x10^6$ CTX0E03 cells in a total of 15ml of complete growth medium. Take care to remove any air bubbles from the cell compartment. Carefully add a further 460ml of complete growth medium to the cell compartment before incubating the flask overnight in 5% CO_2 at 37°C. The next day remove the medium from the cell compartment and replace with 15ml of pre warmed growth medium.

Every 7 days harvest the microparticles/medium from the cell compartment. Centrifuge the medium at 1500rpm for 5 minutes to remove any cell debris and store at -80°C. Carefully add another 15ml of pre-warmed complete growth medium in to the cell compartment and 485ml of complete growth medium to the medium compartment and incubate for another 7 days. Microparticles were isolated by 100K MWCO filtration. Repeat as necessary.

Figure 4A shows the amount of protein extracted from 15ml of media containing microparticles purified using the Integra system compared to normal culture conditions (3 days T175). Milligrams of protein measured by BCA assay. Figure 5 shows the corresponding quantity of isolated total RNA measured at 260/280nm.

Marker characterisations indicated that both purified populations (microvesicles and exosomes) express CD63 and CD81 (determined by FACS – Figure 4B). Only the exosomes express the endosomal marker Alix (determined by Western blot, data not shown).

Example 8: Efficacy Assays

(A) Comparison of the function of CTX0E03 conditioned media with the function of purified exosomes from CTX0E03 cells in a wound healing assay.

Method – Wound closure/ scratch assay

- Seed $0.25x10^6$ NHDF (normal human dermal fibroblasts) per well of a 12 well plate and allow to become confluent (24 hours)
- Remove growth factors for 24hrs
- Remove cells (scratch) and incubate with exosomes/conditioned media
- Image effected area over 48hrs
- Estimate area using Image J

Results

	Wound closure (%)		
	0h	24h	48h
CTX0E03 conditioned media	0%	100%	
2ug/ml exosomes	0%	95.4%	100%
Control	0%	48.1%	49.7%

Table 2 - Wound closure/scratch assay representing the migration activity of normal human dermal fibroblasts (NHDF) cultured in CTX0E03 conditioned media or upon the addition of purified exosomes.

Wound closure was calculated as the area covered by cells in relation to the initial wound area, as determined at 0h. Wound closure is expressed as the percentage of the initial wound area at time 0h. These data are also shown, photographically, in Figure 6A.

Figure 6B shows that 10µg CTX0E03 exosomes significantly increase wound closure (as determined in the HDNF scratch/migration assay) after 72 hours, compared to basal conditions (without exosomes).

Further experiments confirmed that exosomes purified (by ultracentrifugation; quantified by BCA protein assay; characterised as >99% positive for CD63 and CD81 and having a greater expression level of Alix compared to the corresponding microparticle fraction) from all time points (weeks 2-6) during continuous culture (using Integra CELLine bioreactors in the presence of growth factors and 4OHT) significantly enhanced fibroblast migration and wound healing, with a peak response between 5-10µg/ml compared to basal conditions. Figure 6C shows the % healed areas for basal conditions, 2µg/ml exosomes, 6 µg/ml exosomes, 20 µg/ml exosomes and an LSGS (low serum growth supplement) positive control. The top panel of Figure 6C shows exosomes isolated from CTX0E03 cells cultured for 2 weeks in the Integra Celline system and the bottom panel of Figure 6C shows exosomes isolated from CTX0E03 cells cultured for 6 weeks in the Integra Celline system. These data show that all doses of all tested NSC exosomes provide increased healing compared to basal conditions, with % healing approaching the positive control (LSGS) after 72 hours.

The data in Figure 6C also show that the exosomes isolated from NSCs cultured for 6 weeks cause faster healing (than 2 week exosomes), with the % healed approaching 100% after only 48 hours, for all doses.

Figure 6D shows the results of an *in vivo* injection wound assay in a mouse, confirming that CTX0E03 cells stimulated wound healing to a statistically-significant degree *in vivo*. This is a simple *in vivo* bioassay which can be used to confirm the efficacy of microparticles *in vivo*.

Conclusion Exosomes released from the human neural stem cell line CTX0E03 enhance fibroblast migration in an *in vitro* model of wound healing, suggesting that exosomes may contribute to the mechanisms by which hNSCs promote repair. Exosomes isolated from cells cultured for 6 weeks show improved wound healing efficacy *in vitro*, compared to exosomes isolated from cells cultured for 2 weeks.

(B) Stimulation of Angiogenesis

A 24 hour assay to detect angiogenesis on primary HUVECs was carried out using an Ibidi µ-slide and automated Wimtube detection and analysis (of tube length and bifurcation points). Microvesicles harvested from Integra flasks at 1, 2, 3, 4 and 6 weeks were added to HUVECs and angiogenesis compared to basal HUVECs (without addition). LSGS (low serum growth supplement) was used as a positive control. The results, depicted in Figure 12, show that neural stem cell microvesicles increase angiogenesis. Further, these data show that a larger increase in angiogenesis is provided by microvesicles harvested after at least 3 weeks of culture (i.e. after 3 weeks, 4 weeks and 6 weeks culture in an Integra celline bioreactor), than is

provided by microvesicles cultured for 1 or 2 weeks. Microvesicles cultured for at least 3 weeks stimulated angiogenesis to a statistically significant level, and a level that approaches that of the positive control. The largest increase in angiogenesis is shown to be provided by microvesicles harvested after 4 weeks; these microvesicles stimulated angiogenesis by the same amount as the positive control.

These data indicate that hNSC microvesicles stimulate angiogenesis.

(C) Stimulation of Neurite Outgrowth

Neurite outgrowth was determined using PC-12 cells though a 1µm insert. After 72 hours, the PC-12 cell bodies were removed and the neurites stained on the underside of the insert. The stain was then extracted and quantified on a spectrophotometer. Microvesicles harvested from Integra flasks at 2 weeks were added to the cells at 0.03µg, 0.3µg and 3µg, each with 100ng/ml NGF (nerve growth factor). Neurite outgrowth was compared to basal cells (without addition). 100ng/ml NGF was used as a control. As shown in Figure 13, the addition of 3µg hNSC microvesicles caused a noticeable increase in neurite outgrowth, compared to the addition of NGF alone.

These data indicate that hNSC microvesicles stimulate neurite outgrowth.

Example 9: Production of exosomes using the Integra CELLine system.

CTX0E03 cells were cultured using the Integra CELLine system and exosomes were purified as described in Example 7. The concentration of exosomes purified from the medium using the CELLine system at the 3 week time point, and as a control a standard T175 system as routinely used in the art, was quantified (using a BCA assay to estimate protein content). Figure 7 shows that the production of exosomes using the Integra CELLine system is increased several fold, compared to using conventional culture (T175 flasks).

Using the Integra CELLine system, CTX0E03 cells were cultured over a 3-week period and medium was harvested at week 1, 2 and 3 for purification and quantification of exosomes, as described in Example 7. Figure 8A shows that the production of microparticles increases exponentially over the 3-week culture period, enabling efficient and large-scale production of microparticles. The concentration of exosomes harvested from a single Integra CELLine flask was then monitored over 1-6 weeks of continuous CTX0E03 culture, with the results shown below and depicted in Figure 8B:

Integra time point	Total quantity of exosomes (ug)	Exosomes ug/ml
Week 1	12	0.80
Week 2	112	7.47
Week 3	88	5.87
Week 4	148	9.87
Week 5	240	16.00
Week 6	440	29.33

These results show that exosome production is surprisingly enhanced when stem cells are cultured in a multi-compartment bioreactor for weeks, typically at least three weeks.

Example 10: Characterisation of phenotype of cells obtained from the Integra CELLine and the standard (T175) culture system.

CTX0E03 cells were cultured using the Integra CELLine bioreactor and standard culture, as described in Example 7. Expression of DCX and GFAP protein markers was confirmed using marker-specific antibodies and fluorescence microscopy.

Expression of DCX, GALC, GFAP, TUBB3, GDNF and IDO markers was detected by qRT-PCR in samples obtained from the cells. Marker expression was compared between microparticles obtained from standard (T175) culture and exosomes obtained from the 3 week cultured Integra CELLine system, assessed against a baseline of the expression level in CTX0E03 cells in standard (T175) culture.

The inventors observed a striking difference in marker expression of cells obtained from the Integra CELLine system as compared to control cells obtained from standard. Markers of partially-differentiated cells were increased several fold in cells cultured in the Integra CELLine system, compared to control cells obtained from standard cultures (Figure 9). Particularly striking changes are increased expression of the markers DCX1 (doublecortin – a marker for entry into the neural lineage), GFAP (glial fibrillary acidic protein – a marker for entry into the astrocytic lineage), GDNF (glial cell-derived neurotrophic factor) and IDO (indoleamine 2,3-dioxygenase). This indicates that in neural stem cells cultured in a two-compartment bioreactor partially differentiate into cells of neural (DCX+) or astrocytic (GFAP+) lineage. The expression of DCX and GFAP in the Integra-cultured cells was confirmed by fluorescence microscopy, demonstrating that CTX0E03 cells cultured using the Integra CELLine bioreactor have a more differentiated neuronal phenotype than standard CTX0E03 cells.

Example 11: Characterisation of miRNA expression profiles of exosomes obtained from Integra CELLine cultures and microparticles obtained from standard (T175) cultures.

CTX0E03 cells were cultured for three weeks using the Integra CELLine culture and in the standard culture in single-compartment T-175 flasks. Exosomes were purified from the Integra culture and microparticles were purified from the standard T-175 culture as described in Example 7. The relative expression levels of various miRNAs expressed in the exosomes and microparticles obtained from either the standard culture or the Integra CELLine system were determined with an miRNA array using qRT-PCR panel (Qiagen) according to manufacturer's instruction, and converted into fold up and down regulation levels as compared to a standard CTX0E03 cell line control group (see Table 3 and Figure 10). These data show a differential miRNA expression profile between exosomes obtained from the Integra CELLine culture system for 3 weeks, microparticles, and cells obtained from the standard single-flask culture.

Table 3: Fold-regulation of miRNAs in microparticles obtained from standard culture or exosomes from the Integra CELLine system, relative to control (CTX0E03 cells).

	Standard Culture (microparticles)	Integra (exosomes)
miRNA	**Fold regulation relative to control (CTX0E03 cells)**	
hsa-miR-146b-5p	-1.0222	10.5805
hsa-let-7c	-1.6954	4.7678
hsa-miR-99a-5p	-3.5349	3.3714
hsa-miR-132-3p	-1.9163	3.088
hsa-miR-378-3p	1.2731	3.0175
hsa-miR-181a-5p	-1.7431	2.9147
hsa-let-7b-5p	-1.4658	2.7574
hsa-miR-100-5p	-3.208	1.977
hsa-let-7e-5p	-2.7101	1.9274
hsa-miR-23b-3p	-2.3322	1.8834
hsa-miR-185-5p	-1.9119	1.8532
hsa-let-7i-5p	-3.5677	1.8404
hsa-let-7a-5p	-1.851	1.7736
hsa-let-7d-5p	-1.5	1.7654
hsa-let-7g-5p	-2.2527	1.7092
hsa-miR-222-3p	-5.8092	1.6779
hsa-let-7f-5p	-2.8712	1.5948
hsa-miR-218-5p	-1.9611	1.5619
hsa-miR-24-3p	-1.6721	1.5511
hsa-miR-9-5p	-2.2475	1.4109
hsa-miR-126-3p	-2.1263	1.203
hsa-miR-134	-1.6567	1.1783
hsa-miR-128	-3.5842	1.0743
hsa-miR-155-5p	-8.8458	1.0425
hsa-miR-22-3p	-3.4782	-1.0023
hsa-miR-26a-5p	-5.3579	-1.0187

hsa-miR-210	-2.3107	-1.0449
hsa-miR-92a-3p	-1.9885	-1.0693
hsa-miR-93-5p	-3.056	-1.1701
hsa-miR-424-5p	-4.9189	-1.2086
hsa-miR-195-5p	-3.8951	-1.2541
hsa-miR-127-5p	-1.1316	-1.2953
hsa-miR-21-5p	-2.8845	-1.3044
hsa-miR-103a-3p	-2.6482	-1.3287
hsa-miR-16-5p	-3.5267	-1.3692
hsa-miR-125a-5p	-5.1159	-1.434
hsa-miR-10a-5p	-14.4701	-1.434
hsa-miR-10b-5p	-15.1194	-1.4373
hsa-miR-345-5p	-2.5521	-1.4406
hsa-miR-130a-3p	-2.6178	-1.5728
hsa-miR-15b-5p	-4.4025	-1.6058
hsa-miR-20b	-2.1312	-1.6096
hsa-miR-20a-5p	-2.3107	-1.8319
hsa-miR-17-5p	-1.9296	-1.8319
hsa-miR-7-5p	-1.5105	-2.042
hsa-miR-106b-5p	-2.4708	-2.1287
hsa-miR-101-3p	1.4794	-2.4453
hsa-miR-302a-3p	-18.0634	-2.4623
hsa-miR-301a-3p	1.4931	-2.5257
hsa-miR-183-5p	-13.9772	-2.5847
hsa-miR-219-5p	1.6994	-2.7321
hsa-miR-18a-5p	-1.4028	-3.2792
hsa-miR-15a-5p	-2.4766	-3.3714
hsa-miR-182-5p	-12.5099	-4.9588
hsa-miR-33a-5p	2.7927	-9.1472
hsa-miR-96-5p	-7.0047	-18.9396
hsa-miR-18b-5p	-1.3519	-49.18

Values were calculated from raw data using the following equations:

$$\Delta CT\ (\text{sample/control}) = \text{Average CT (GOI)} - \text{Average CT (HKG)}$$

$$\text{Fold expression (sample/control)} = 2^{-(\text{Average } \Delta CT)}$$

$$\text{Fold change} = \frac{\text{Fold expression (sample)}}{\text{Fold expression (control)}}$$

$$\text{If (fold change)} > 1 \text{ then (fold regulation)} = \text{(fold change)}$$

$$\text{If (fold change)} < 1 \text{ then (fold regulation)} = -\left(\frac{1}{\text{fold change}}\right)$$

Wherein:

CT = cycle threshold

GOI = gene of interest (investigated miRNA)
HKG = housekeeping genes (reference miRNAs used to normalize the data)

Example 12: Total miRNA analysis

Cells can shuttle RNA into microparticles determined for release into the extracellular space. This allows the conveyance of genetically encoded messages between cells. We here collectively refer to extracellular RNA as 'shuttle RNA'. We aimed to analyze comprehensively non coding RNA species released by CTX0E03 neural stem cells (NSCs) using Next Generation Sequencing.

Non coding RNAs are divided in two categories (small and long). Small non coding RNA biotypes include ribosomal RNA (rRNA), small nucleolar (snoRNA), small nuclear RNA (snRNA), microRNA (miRNA), miscellaneous other RNA (misc_RNA, e.g. RMRP, vault RNA, metazoa SRP, and RNY), and long non coding RNA biotypes includes long non-coding RNAs (lncRNAs) and large intergenic non-coding RNAs (lincRNAs).

Here, we characterized shuttle RNAs, including small and long non coding RNAs, released from NSC derived exosomes and microvesicles (MV) and compared with the RNA contents of the producer NSCs.

A) Total RNA contents in cells, exosomes and microvesicles identified by Agilent RNA bioanalyser

The RNA in both exosomes and microvesicles mainly consists of small RNA species as shown in Fig. 14. The majority of the nucleotides (nt) was ≤200 as shown against the molecular ladder.

B) RNA composition

Small RNA sequencing libraries were generated to investigate the composition of shuttle and cellular RNA by deep sequencing (Next Generation Sequencing). The results are shown in Figure 15.

C) Deep sequencing of CTX0E03 cell, microvesicle and exosome miRNA expression from standard (T175) cultures.

Deep sequencing is based on the preparation of a cDNA library following by sequencing and provides information regarding the total sequence read out of different miRNAs in the

microvesicles and exosomes. These deep sequence data complement the qRT-PCR array data shown above and provide a comprehensive analysis of the miRNA profile of the cells and microparticles. Unlike the qRT-PCR array analysis, deep sequencing is not restricted to identification of sequences present in the probe array and so the sequences to be identified do not need to be known in advance. Deep sequencing also provides direct read-out and the ability to sequence very short sequences. However, deep sequencing is not suitable for detection of transcripts with low expression.

Method

The presence of a variety of miRNAs in parental cells and their exosomes (30-100μm) and microvesicles (100-1000 μm), purified by differential centrifugation, was identified by deep sequencing, following construction of 1 tagged miRNA library for each sample.

Additionally, specific primers for highly shuttled miRNAs (e.g. hsa-miR-1246) were designed and used in real-time reverse transcription PCR (qRT-PCR) to trace exosomes/microvesicles following *in vivo* implantation.

Deep sequencing was performed by GATC Biotech (Germany) and required the preparation of a tagged miRNA library for each samples followed by sequencing, and miRBase scanning:

- Construction of tagged miRNA libraries (22 to 30 nt)
    - Sequencing libraries were generated by ligation of specific RNA adapter to both 3' and 5' ends for each sample followed by reverse transcription, amplification, and purification of smallRNA libraries (size range of contained smallRNA fraction 22 - 30 nt).

- Sequencing on an Illumina HiSeq 2000 (single read)
    - Sequencing was performed using Illumina HiSeq 2000 (single read). Analysis of one pool could include up to 45,000,000 single read, and each read length is up to 50 bases. Sequencing was quality controlled by using FastQ Files (sequences and quality scores).

- Identification of known miRNAs was performed as followed:
    - RNA adapters were trimmed from resulting sequences and raw data cleaned. Raw data were clustered and for each cluster a number of reads was provided. MiRNAs were identified by miRBase scanning (Ssearch).

Results

Many microvesicle and exosome miRNAs were enriched relative to the cells, indicating that cells specially sort miRNAs for extracellular release. Furthermore, miRNA contents were similar in both exosomes and microvesicles, indicating a common apparatus of selective miRNA uptake in excreted microvesicles. Without wishing to be bound by theory, this may indicate that miRNA content in secreted microvesicles and exosomes can be used as a fingerprint to identify hNSC subtypes.

The deep sequencing analysis therefore identified a unique set of miRNAs in both hNSC exosomes and microvesicles not previously reported. MiRNA content in excreted vesicles is similar, but showed a preferential miRNA uptake compared with hNSC. These findings could support biological effects mediated by shuttle miRNA not previously described for hNSC.

The results are detailed in Tables 4 to 9, below. The data are also depicted in Figure 11, which clearly shows the significantly different miRNA profiles present in the microvesicles and exosomes, compared to the cells. In summary, these data show a massive increase in the amount (read counts) of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532 in microvesicles and exosomes compared to the cells. Large increases are also seen in hsa-miR-4508, hsa-miR-4516, has-miR-3676-5p and hsa-miR-4485. Massive decreases are seen in the amounts (read counts) of certain miRNAs, including hsa-let-7a-5p, has-miR-92b-3p, has-miR-21-5p. hsa-miR-92a-3p, hsa-miR-10a-5p, hsa-100-5p and hsa-99b-5p.

The presence of each of hsa-miR-1246, hsa-miR-4488, hsa-miR-4492, hsa-miR-4508, hsa-miR-4516 and hsa-miR-4532 in the exosomes was validated by qRT-PCR (data not shown).

Plotting the deep sequencing results in the exosomes and microvesicles as relative fold change compared to the cells confirms that hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532 are significantly upregulated in the exosomes and microvesicles compared to the cells. This comparison also shows that miRNA hsa-miR-3195 is the miRNA that is most upregulated, in both exosomes and microvesicles. Although the absolute reads of hsa-miR-3195 are in the range of ~40 for exosomes and microvesicles, there is no hsa-miR-3195 present in the cells.

As noted in Example 11 above, miRNA contents in exosomes, microparticles, and parental cells were also tested and validated using *PCR array* analysis. The following miRNAs were found present by qRT-PCR: hsa-let-7g-5p, hsa-miR-101-3p, hsa-miR-10a-5p, hsa-miR-10b-5p, hsa-miR-125b-5p, hsa-miR-128, hsa-miR-130a-3p, hsa-miR-134, hsa-miR-137, hsa-miR-146b-5p, hsa-miR-15a-5p, hsa-miR-15b-5p, hsa-miR-16-5p, hsa-miR-17-5p, hsa-miR-181a-5p,hsa-miR-

182-5p, hsa-miR-185-5p, hsa-miR-18b-5p, hsa-miR-192-5p, hsa-miR-194-5p, hsa-miR-195-5p, hsa-miR-20a-5p, hsa-miR-20b-5p, hsa-miR-210, hsa-miR-21-5p, hsa-miR-218-5p,hsa-miR-219-5p,hsa-miR-222-3p, hsa-miR-22-3p, hsa-miR-23b-3p, hsa-miR-24-3p,hsa-miR-26a-5p, hsa-miR-301a-3p, hsa-miR-302a-3p,hsa-miR-302c-3p,hsa-miR-345-5p, hsa-miR-378a-3p, hsa-miR-7-5p, hsa-miR-92a-3p,hsa-miR-93-5p,hsa-miR-9-5p,hsa-miR-96-5p, and hsa-miR-99a-5p.

Table 4: Cells EH

Cells: CTX0E03 07EH				
MIRNA	MIRNA.SEQUENCE	SEQ ID NO:	MIRNA LENGTH	READ COUNTS
hsa-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	1	22	75110
hsa-miR-10a-5p	UACCCUGUAGAUCCGAAUUUGUG	2	23	52927
hsa-miR-100-5p	AACCCGUAGAUCCGAACUUGUG	3	22	52451
hsa-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	4	22	39457
hsa-miR-486-5p	UCCUGUACUGAGCUGCCCCGAG	5	22	20310
hsa-miR-27b-3p	UUCACAGUGGCUAAGUUCUGC	6	21	16900
hsa-miR-92a-3p	UAUUGCACUUGUCCCGGCCUGU	7	22	14359
hsa-miR-191-5p	CAACGGAAUCCCAAAAGCAGCUG	8	23	12591
hsa-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA	9	22	11943
hsa-miR-98	UGAGGUAGUAAGUUGUAUUGUU	10	22	11760
hsa-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	11	22	10349
hsa-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	12	22	9900
hsa-miR-92b-3p	UAUUGCACUCGUCCCGGCCUCC	13	22	9794
hsa-miR-127-3p	UCGGAUCCGUCUGAGCUUGGCU	14	22	7064
hsa-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	15	23	6956
hsa-miR-182-5p	UUUGGCAAUGGUAGAACUCACACU	16	24	5531
hsa-let-7c	UGAGGUAGUAGGUUGUAUGGUU	17	22	5103
hsa-miR-379-5p	UGGUAGACUAUGGAACGUAGG	18	21	4746
hsa-miR-146b-5p	UGAGAACUGAAUUCCAUAGGCU	19	22	4552
hsa-miR-21-3p	CAACACCAGUCGAUGGGCUGU	20	21	4089
hsa-miR-1246	AAUGGAUUUUUGGAGCAGG	21	19	3973
hsa-let-7i-5p	UGAGGUAGUAGUUUGUGCUGUU	22	22	3015
hsa-miR-4532	CCCCGGGGAGCCCGGCG	23	17	2847
hsa-miR-183-5p	UAUGGCACUGGUAGAAUUCACU	24	22	2695
hsa-miR-151a-3p	CUAGACUGAAGCUCCUUGAGG	25	21	2681
hsa-miR-501-3p	AAUGCACCCGGGCAAGGAUUCU	26	22	2649
hsa-let-7e-5p	UGAGGUAGGAGGUUGUAUAGUU	27	22	2449
hsa-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	28	22	2435
hsa-miR-16-5p	UAGCAGCACGUAAAUAUUGGCG	29	22	2173
hsa-miR-30a-5p	UGUAAACAUCCUCGACUGGAAG	30	22	2001
hsa-miR-30d-5p	UGUAAACAUCCCCGACUGGAAG	31	22	1977
hsa-miR-409-5p	AGGUUACCCGAGCAACUUUGCAU	32	23	1871
hsa-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	33	22	1826
hsa-miR-4492	GGGGCUGGGCGCGCGCC	34	17	1754
hsa-miR-125a-5p	UCCCUGAGACCCUUUAACCUGUGA	35	24	1451

hsa-miR-222-3p	AGCUACAUCUGGCUACUGGGU	36	21	1422
hsa-miR-151a-5p	UCGAGGAGCUCACAGUCUAGU	37	21	1386
hsa-miR-181b-5p	AACAUUCAUUGCUGUCGGUGGGU	38	23	1382
hsa-miR-221-5p	ACCUGGCAUACAAUGUAGAUUU	39	22	1363
hsa-miR-186-5p	CAAAGAAUUCUCCUUUUGGGCU	40	22	1225
hsa-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUU	41	23	1080
hsa-miR-125b-5p	UCCCUGAGACCCUAACUUGUGA	42	22	1002
hsa-let-7g-5p	UGAGGUAGUAGUUUGUACAGUU	43	22	959
hsa-miR-500a-3p	AUGCACCUGGGCAAGGAUUCUG	44	22	923
hsa-miR-30e-5p	UGUAAACAUCCUUGACUGGAAG	45	22	911
hsa-miR-27a-3p	UUCACAGUGGCUAAGUUCCGC	46	21	867
hsa-miR-409-3p	GAAUGUUGCUCGGUGAACCCCU	47	22	865
hsa-miR-148b-3p	UCAGUGCAUCACAGAACUUUGU	48	22	856
hsa-miR-125b-1-3p	ACGGGUUAGGCUCUUGGGAGCU	49	22	851
hsa-miR-410	AAUAUAACACAGAUGGCCUGU	50	21	848
hsa-miR-381	UAUACAAGGGCAAGCUCUCUGU	51	22	842
hsa-miR-99a-5p	AACCCGUAGAUCCGAUCUUGUG	52	22	773
hsa-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	53	22	765
hsa-miR-148a-3p	UCAGUGCACUACAGAACUUUGU	54	22	702
hsa-miR-23a-3p	AUCACAUUGCCAGGGAUUUCC	55	21	654
hsa-miR-28-3p	CACUAGAUUGUGAGCUCCUGGA	56	22	593
hsa-miR-423-3p	AGCUCGGUCUGAGGCCCCUCAGU	57	23	557
hsa-miR-9-5p	UCUUUGGUUAUCUAGCUGUAUGA	58	23	518
hsa-miR-23b-3p	AUCACAUUGCCAGGGAUUACC	59	21	508
hsa-miR-941	CACCCGGCUGUGUGCACAUGUGC	60	23	492
hsa-miR-4488	AGGGGGCGGGCUCCGGCG	61	18	485
hsa-miR-103a-3p	AGCAGCAUUGUACAGGGCUAUGA	62	23	459
hsa-miR-25-3p	CAUUGCACUUGUCUCGGUCUGA	63	22	436
hsa-miR-889	UUAAUAUCGGACAACCAUUGU	64	21	411
hsa-miR-378a-3p	ACUGGACUUGGAGUCAGAAGG	65	21	410
hsa-miR-30c-5p	UGUAAACAUCCUACACUCUCAGC	66	23	378
hsa-miR-4485	UAACGGCCGCGGUACCCUAA	67	20	358
hsa-miR-125b-2-3p	UCACAAGUCAGGCUCUUGGGAC	68	22	352
hsa-miR-671-3p	UCCGGUUCUCAGGGCUCCACC	69	21	350
hsa-miR-361-5p	UUAUCAGAAUCUCCAGGGGUAC	70	22	337
hsa-miR-30e-3p	CUUUCAGUCGGAUGUUUACAGC	71	22	294
hsa-miR-1271-5p	CUUGGCACCUAGCAAGCACUCA	72	22	288
hsa-miR-589-5p	UGAGAACCACGUCUGCUCUGAG	73	22	282
hsa-miR-374a-5p	UUAUAAUACAACCUGAUAAGUG	74	22	275
hsa-miR-769-5p	UGAGACCUCUGGGUUCUGAGCU	75	22	263
hsa-miR-345-5p	GCUGACUCCUAGUCCAGGGCUC	76	22	249
hsa-miR-30a-3p	CUUUCAGUCGGAUGUUUGCAGC	77	22	236
hsa-miR-15b-5p	UAGCAGCACAUCAUGGUUUACA	78	22	229
hsa-miR-221-3p	AGCUACAUUGUCUGCUGGGUUUC	79	23	225
hsa-miR-31-5p	AGGCAAGAUGCUGGCAUAGCU	80	21	213
hsa-miR-342-3p	UCUCACACAGAAAUCGCACCCGU	81	23	205

hsa-miR-136-3p	CAUCAUCGUCUCAAAUGAGUCU	82	22	203
hsa-miR-493-3p	UGAAGGUCUACUGUGUGCCAGG	83	22	192
hsa-miR-720	UCUCGCUGGGGCCUCCA	84	17	154
hsa-miR-7-5p	UGGAAGACUAGUGAUUUUGUUGU	85	23	154
hsa-miR-130b-3p	CAGUGCAAUGAUGAAAGGGCAU	86	22	150
hsa-miR-192-5p	CUGACCUAUGAAUUGACAGCC	87	21	138
hsa-miR-493-5p	UUGUACAUGGUAGGCUUUCAUU	88	22	115
hsa-miR-204-5p	UUCCCUUUGUCAUCCUAUGCCU	89	22	113
hsa-miR-26b-5p	UUCAAGUAAUUCAGGAUAGGU	90	21	107
hsa-miR-1307-5p	UCGACCGGACCUCGACCGGCU	91	21	105
hsa-let-7d-3p	CUAUACGACCUGCUGCCUUUCU	92	22	103
hsa-miR-340-5p	UUAUAAAGCAAUGAGACUGAUU	93	22	100
hsa-miR-134	UGUGACUGGUUGACCAGAGGGG	94	22	99
hsa-miR-432-5p	UCUUGGAGUAGGUCAUUGGGUGG	95	23	97
hsa-miR-30b-5p	UGUAAACAUCCUACACUCAGCU	96	22	96
hsa-miR-320a	AAAAGCUGGGUUGAGAGGGCGA	97	22	95
hsa-miR-100-3p	CAAGCUUGUAUCUAUAGGUAUG	98	22	94
hsa-miR-744-5p	UGCGGGGCUAGGGCUAACAGCA	99	22	89
hsa-miR-181a-3p	ACCAUCGACCGUUGAUUGUACC	100	22	86
hsa-miR-34a-5p	UGGCAGUGUCUUAGCUGGUUGU	101	22	85
hsa-miR-181a-2-3p	ACCACUGACCGUUGACUGUACC	102	22	81
hsa-miR-190a	UGAUAUGUUUGAUAUAUUAGGU	103	22	79
hsa-miR-132-3p	UAACAGUCUACAGCCAUGGUCG	104	22	78
hsa-miR-181c-5p	AACAUUCAACCUGUCGGUGAGU	105	22	76
hsa-miR-29a-3p	UAGCACCAUCUGAAAUCGGUUA	106	22	75
hsa-miR-301a-3p	CAGUGCAAUAGUAUUGUCAAAGC	107	23	75
hsa-miR-411-5p	UAGUAGACCGUAUAGCGUACG	108	21	75
hsa-miR-128	UCACAGUGAACCGGUCUCUUU	109	21	74
hsa-miR-4516	GGGAGAAGGGUCGGGGC	110	17	74
hsa-miR-425-5p	AAUGACACGAUCACUCCCGUUGA	111	23	72
hsa-miR-130b-5p	ACUCUUUCCCUGUUGCACUAC	112	21	71
hsa-miR-130a-3p	CAGUGCAAUGUUAAAAGGGCAU	113	22	67
hsa-miR-30d-3p	CUUUCAGUCAGAUGUUUGCUGC	114	22	65
hsa-miR-654-5p	UGGUGGGCCGCAGAACAUGUGC	115	22	65
hsa-miR-93-5p	CAAAGUGCUGUUCGUGCAGGUAG	116	23	65
hsa-miR-487b	AAUCGUACAGGGUCAUCCACUU	117	22	63
hsa-miR-484	UCAGGCUCAGUCCCCUCCCGAU	118	22	62
hsa-miR-24-3p	UGGCUCAGUUCAGCAGGAACAG	119	22	61
hsa-miR-4677-3p	UCUGUGAGACCAAAGAACUACU	120	22	61
hsa-miR-149-5p	UCUGGCUCCGUGUCUUCACUCCC	121	23	56
hsa-miR-197-3p	UUCACCACCUUCUCCACCCAGC	122	22	56
hsa-miR-96-5p	UUUGGCACUAGCACAUUUUUGCU	123	23	56
hsa-miR-1307-3p	ACUCGGCGUGGCGUCGGUCGUG	124	22	55
hsa-miR-34c-5p	AGGCAGUGUAGUUAGCUGAUUGC	125	23	53
hsa-miR-370	GCCUGCUGGGGUGGAACCUGGU	126	22	52
hsa-miR-148b-5p	AAGUUCUGUUAUACACUCAGGC	127	22	51

hsa-miR-335-5p	UCAAGAGCAAUAACGAAAAAUGU	128	23	51
hsa-miR-4461	GAUUGAGACUAGUAGGGCUAGGC	129	23	50
hsa-miR-27a-5p	AGGGCUUAGCUGCUUGUGAGCA	130	22	49
hsa-miR-363-3p	AAUUGCACGGUAUCCAUCUGUA	131	22	47
hsa-miR-431-5p	UGUCUUGCAGGCCGUCAUGCA	132	21	47
hsa-miR-877-5p	GUAGAGGAGAUGGCGCAGGG	133	20	46
hsa-miR-550a-5p	AGUGCCUGAGGGAGUAAGAGCCC	134	23	45
hsa-miR-4508	GCGGGGCUGGGCGCGCG	135	17	44
hsa-miR-541-3p	UGGUGGGCACAGAAUCUGGACU	136	22	42
hsa-miR-135b-5p	UAUGGCUUUUCAUUCCUAUGUGA	137	23	40
hsa-miR-140-3p	UACCACAGGGUAGAACCACGG	138	21	39
hsa-miR-362-5p	AAUCCUUGGAACCUAGGUGUGAGU	139	24	37
hsa-miR-455-3p	GCAGUCCAUGGGCAUAUACAC	140	21	37
hsa-miR-758	UUUGUGACCUGGUCCACUAACC	141	22	37
hsa-miR-101-3p	UACAGUACUGUGAUAACUGAA	142	21	36
hsa-miR-374b-5p	AUAUAAUACAACCUGCUAAGUG	143	22	36
hsa-miR-148a-5p	AAAGUUCUGAGACACUCCGACU	144	22	35
hsa-miR-17-5p	CAAAGUGCUUACAGUGCAGGUAG	145	23	35
hsa-miR-20a-5p	UAAAGUGCUUAUAGUGCAGGUAG	146	23	35
hsa-miR-874	CUGCCCUGGCCCGAGGGACCGA	147	22	35
hsa-miR-193b-3p	AACUGGCCCUCAAAGUCCCGCU	148	22	34
hsa-miR-548ah-3p	CAAAAACUGCAGUUACUUUUGC	149	22	34
hsa-miR-539-3p	AUCAUACAAGGACAAUUUCUUU	150	22	33
hsa-miR-421	AUCAACAGACAUUAAUUGGGCGC	151	23	31
hsa-miR-28-5p	AAGGAGCUCACAGUCUAUUGAG	152	22	30
hsa-miR-485-3p	GUCAUACACGGCUCUCCUCUCU	153	22	29
hsa-miR-2467-5p	UGAGGCUCUGUUAGCCUUGGCUC	154	23	26
hsa-miR-4449	CGUCCCGGGGCUGCGCGAGGCA	155	22	26
hsa-miR-24-2-5p	UGCCUACUGAGCUGAAACACAG	156	22	25
hsa-miR-181d	AACAUUCAUUGUUGUCGGUGGGU	157	23	24
hsa-miR-323a-3p	CACAUUACACGGUCGACCUCU	158	21	24
hsa-miR-106b-3p	CCGCACUGUGGGUACUUGCUGC	159	22	23
hsa-miR-125a-3p	ACAGGUGAGGUUCUUGGGAGCC	160	22	23
hsa-miR-330-5p	UCUCUGGGCCUGUGUCUUAGGC	161	22	23
hsa-miR-1275	GUGGGGGAGAGGCUGUC	162	17	22
hsa-miR-19b-3p	UGUGCAAAUCCAUGCAAAACUGA	163	23	22
hsa-miR-301b	CAGUGCAAUGAUAUUGUCAAAGC	164	23	21
hsa-miR-485-5p	AGAGGCUGGCCGUGAUGAAUUC	165	22	21
hsa-miR-29b-3p	UAGCACCAUUUGAAAUCAGUGUU	166	23	20
hsa-miR-3158-3p	AAGGGCUUCCUCUCUGCAGGAC	167	22	20
hsa-miR-431-3p	CAGGUCGUCUUGCAGGGCUUCU	168	22	20
hsa-miR-454-3p	UAGUGCAAUAUUGCUUAUAGGGU	169	23	20
hsa-miR-106b-5p	UAAAGUGCUGACAGUGCAGAU	170	21	19
hsa-miR-1973	ACCGUGCAAAGGUAGCAUA	171	19	19
hsa-miR-31-3p	UGCUAUGCCAACAUAUUGCCAU	172	22	19
hsa-miR-374a-3p	CUUAUCAGAUUGUAUUGUAAUU	173	22	19

hsa-miR-433	AUCAUGAUGGGCUCCUCGGUGU	174	22	19
hsa-miR-4417	GGUGGGCUUCCCGGAGGG	175	18	19
hsa-miR-143-3p	UGAGAUGAAGCACUGUAGCUC	176	21	18
hsa-miR-19a-3p	UGUGCAAAUCUAUGCAAAACUGA	177	23	18
hsa-miR-532-5p	CAUGCCUUGAGUGUAGGACCGU	178	22	18
hsa-miR-561-5p	AUCAAGGAUCUUAAACUUUGCC	179	22	18
hsa-miR-663b	GGUGGCCCGGCCGUGCCUGAGG	180	22	18
hsa-miR-1301	UUGCAGCUGCCUGGGAGUGACUUC	181	24	17
hsa-miR-299-3p	UAUGUGGGAUGGUAAACCGCUU	182	22	17
hsa-miR-9-3p	AUAAAGCUAGAUAACCGAAAGU	183	22	17
hsa-miR-17-3p	ACUGCAGUGAAGGCACUUGUAG	184	22	15
hsa-miR-376c	AACAUAGAGGAAAUUCCACGU	185	21	15
hsa-miR-424-5p	CAGCAGCAAUUCAUGUUUUGAA	186	22	15
hsa-miR-660-5p	UACCCAUUGCAUAUCGGAGUUG	187	22	15
hsa-miR-153	UUGCAUAGUCACAAAAGUGAUC	188	22	14
hsa-miR-3605-5p	UGAGGAUGGAUAGCAAGGAAGCC	189	23	14
hsa-miR-3687	CCCGGACAGGCGUUCGUGCGACGU	190	24	14
hsa-miR-4284	GGGCUCACAUCACCCCAU	191	18	14
hsa-miR-455-5p	UAUGUGCCUUUGGACUACAUCG	192	22	14
hsa-miR-543	AAACAUUCGCGGUGCACUUCUU	193	22	14
hsa-miR-1276	UAAAGAGCCCUGUGGAGACA	194	20	13
hsa-miR-330-3p	GCAAAGCACACGGCCUGCAGAGA	195	23	13
hsa-miR-369-3p	AAUAAUACAUGGUUGAUCUUU	196	21	13
hsa-miR-4786-5p	UGAGACCAGGACUGGAUGCACC	197	22	13
hsa-miR-548k	AAAAGUACUUGCGGAUUUUGCU	198	22	13
hsa-miR-1226-3p	UCACCAGCCCUGUGUUCCCUAG	199	22	12
hsa-miR-188-3p	CUCCCACAUGCAGGGUUUGCA	200	21	12
hsa-miR-27b-5p	AGAGCUUAGCUGAUUGGUGAAC	201	22	12
hsa-miR-377-5p	AGAGGUUGCCCUUGGUGAAUUC	202	22	12
hsa-miR-487a	AAUCAUACAGGGACAUCCAGUU	203	22	12
hsa-miR-92a-1-5p	AGGUUGGGAUCGGUUGCAAUGCU	204	23	12
hsa-miR-135b-3p	AUGUAGGGCUAAAAGCCAUGGG	205	22	11
hsa-miR-218-5p	UUGUGCUUGAUCUAACCAUGU	206	21	11
hsa-miR-3943	UAGCCCCCAGGCUUCACUUGGCG	207	23	11
hsa-miR-92b-5p	AGGGACGGGACGCGGUGCAGUG	208	22	11
hsa-miR-1185-1-3p	AUAUACAGGGGGAGACUCUUAU	209	22	10
hsa-miR-1273g-3p	ACCACUGCACUCCAGCCUGAG	210	21	10
hsa-miR-2355-5p	AUCCCCAGAUACAAUGGACAA	211	21	10
hsa-miR-23a-5p	GGGGUUCCUGGGGAUGGGAUUU	212	22	10
hsa-miR-30c-1-3p	CUGGGAGAGGGUUGUUUACUCC	213	22	10
hsa-miR-329	AACACACCUGGUUAACCUCUUU	214	22	10
hsa-miR-337-3p	CUCCUAUAUGAUGCCUUUCUUC	215	22	10
hsa-miR-3609	CAAAGUGAUGAGUAAUACUGGCUG	216	24	10
hsa-miR-378a-5p	CUCCUGACUCCAGGUCCUGUGU	217	22	10
hsa-miR-3929	GAGGCUGAUGUGAGUAGACCACU	218	23	10
hsa-miR-4745-5p	UGAGUGGGGCUCCCGGGACGGCG	219	23	10

hsa-miR-5096	GUUUCACCAUGUUGGUCAGGC	220	21	10
hsa-miR-656	AAUAUUAUACAGUCAACCUCU	221	21	10
hsa-let-7a-3p	CUAUACAAUCUACUGUCUUUC	222	21	9
hsa-miR-15a-5p	UAGCAGCACAUAAUGGUUUGUG	223	22	9
hsa-miR-185-5p	UGGAGAGAAAGGCAGUUCCUGA	224	22	9
hsa-miR-25-5p	AGGCGGAGACUUGGGCAAUUG	225	21	9
hsa-miR-3065-5p	UCAACAAAAUCACUGAUGCUGGA	226	23	9
hsa-miR-3176	ACUGGCCUGGGACUACCGG	227	19	9
hsa-miR-339-3p	UGAGCGCCUCGACGACAGAGCCG	228	23	9
hsa-miR-374b-3p	CUUAGCAGGUUGUAUUAUCAUU	229	22	9
hsa-miR-4435	AUGGCCAGAGCUCACACAGAGG	230	22	9
hsa-miR-4448	GGCUCCUUGGUCUAGGGGUA	231	20	9
hsa-miR-4497	CUCCGGGACGGCUGGGC	232	17	9
hsa-miR-4521	GCUAAGGAAGUCCUGUGCUCAG	233	22	9
hsa-miR-539-5p	GGAGAAAUUAUCCUUGGUGUGU	234	22	9
hsa-miR-548ah-5p	AAAAGUGAUUGCAGUGUUUG	235	20	9
hsa-miR-1910	CCAGUCCUGUGCCUGCCGCCU	236	21	8
hsa-miR-376a-3p	AUCAUAGAGGAAAAUCCACGU	237	21	8
hsa-miR-382-5p	GAAGUUGUUCGUGGUGGAUUCG	238	22	8
hsa-miR-3940-3p	CAGCCCGGAUCCCAGCCCACUU	239	22	8
hsa-miR-494	UGAAACAUACACGGGAAACCUC	240	22	8
hsa-miR-495	AAACAAACAUGGUGCACUUCUU	241	22	8
hsa-miR-545-3p	UCAGCAAACAUUUAUUGUGUGC	242	22	8
hsa-miR-99b-3p	CAAGCUCGUGUCUGUGGGUCCG	243	22	8
hsa-miR-1197	UAGGACACAUGGUCUACUUCU	244	21	7
hsa-miR-181b-3p	CUCACUGAACAAUGAAUGCAA	245	21	7
hsa-miR-212-5p	ACCUUGGCUCUAGACUGCUUACU	246	23	7
hsa-miR-3200-3p	CACCUUGCGCUACUCAGGUCUG	247	22	7
hsa-miR-340-3p	UCCGUCUCAGUUACUUUAUAGC	248	22	7
hsa-miR-3607-5p	GCAUGUGAUGAAGCAAAUCAGU	249	22	7
hsa-miR-361-3p	UCCCCCAGGUGUGAUUCUGAUUU	250	23	7
hsa-miR-3656	GGCGGGUGCGGGGGUGG	251	17	7
hsa-miR-532-3p	CCUCCCACACCCAAGGCUUGCA	252	22	7
hsa-miR-574-3p	CACGCUCAUGCACACACCCACA	253	22	7
hsa-miR-107	AGCAGCAUUGUACAGGGCUAUCA	254	23	6
hsa-miR-127-5p	CUGAAGCUCAGAGGGCUCUGAU	255	22	6
hsa-miR-18a-5p	UAAGGUGCAUCUAGUGCAGAUAG	256	23	6
hsa-miR-26a-2-3p	CCUAUUCUUGAUUACUUGUUUC	257	22	6
hsa-miR-296-5p	AGGGCCCCCCCUCAAUCCUGU	258	21	6
hsa-miR-3648	AGCCGCGGGGAUCGCCGAGGG	259	21	6
hsa-miR-382-3p	AAUCAUUCACGGACAACACUU	260	21	6
hsa-miR-3939	UACGCGCAGACCACAGGAUGUC	261	22	6
hsa-miR-432-3p	CUGGAUGGCUCCUCCAUGUCU	262	21	6
hsa-miR-4423-5p	AGUUGCCUUUUUGUUCCCAUGC	263	22	6
hsa-miR-4466	GGGUGCGGGCCGGCGGGG	264	18	6
hsa-miR-454-5p	ACCCUAUCAAUAUUGUCUCUGC	265	22	6

hsa-miR-4746-5p	CCGGUCCCAGGAGAACCUGCAGA	266	23	6
hsa-miR-496	UGAGUAUUACAUGGCCAAUCUC	267	22	6
hsa-miR-548o-3p	CCAAAACUGCAGUUACUUUUGC	268	22	6
hsa-miR-1248	ACCUUCUUGUAUAAGCACUGUGCUAAA	269	27	5
hsa-miR-1254	AGCCUGGAAGCUGGAGCCUGCAGU	270	24	5
hsa-miR-1296	UUAGGGCCCUGGCUCCAUCUCC	271	22	5
hsa-miR-136-5p	ACUCCAUUUGUUUUGAUGAUGGA	272	23	5
hsa-miR-199a-5p	CCCAGUGUUCAGACUACCUGUUC	273	23	5
hsa-miR-296-3p	GAGGGUUGGGUGGAGGCUCUCC	274	22	5
hsa-miR-3177-3p	UGCACGGCACUGGGGACACGU	275	21	5
hsa-miR-324-3p	ACUGCCCCAGGUGCUGCUGG	276	20	5
hsa-miR-337-5p	GAACGGCUUCAUACAGGAGUU	277	21	5
hsa-miR-342-5p	AGGGGUGCUAUCUGUGAUUGA	278	21	5
hsa-miR-365b-3p	UAAUGCCCCUAAAAAUCCUUAU	279	22	5
hsa-miR-3676-5p	AGGAGAUCCUGGGUU	280	15	5
hsa-miR-502-3p	AAUGCACCUGGGCAAGGAUUCA	281	22	5
hsa-miR-505-3p	CGUCAACACUUGCUGGUUUCCU	282	22	5
hsa-miR-550a-3p	UGUCUUACUCCCUCAGGCACAU	283	22	5
hsa-miR-5587-3p	GCCCCGGGCAGUGUGAUCAUC	284	21	5
hsa-miR-641	AAAGACAUAGGAUAGAGUCACCUC	285	24	5
hsa-miR-655	AUAAUACAUGGUUAACCUCUUU	286	22	5
hsa-miR-664-3p	UAUUCAUUUAUCCCCAGCCUACA	287	23	5
hsa-miR-671-5p	AGGAAGCCCUGGAGGGGCUGGAG	288	23	5
hsa-miR-760	CGGCUCUGGGUCUGUGGGGA	289	20	5
hsa-let-7e-3p	CUAUACGGCCUCCUAGCUUUCC	290	22	4
hsa-miR-1268a	CGGGCGUGGUGGUGGGGG	291	18	4
hsa-miR-1273f	GGAGAUGGAGGUUGCAGUG	292	19	4
hsa-miR-1286	UGCAGGACCAAGAUGAGCCCU	293	21	4
hsa-miR-1291	UGGCCCUGACUGAAGACCAGCAGU	294	24	4
hsa-miR-141-3p	UAACACUGUCUGGUAAAGAUGG	295	22	4
hsa-miR-1468	CUCCGUUUGCCUGUUUCGCUG	296	21	4
hsa-miR-328	CUGGCCCUCUCUGCCCUUCCGU	297	22	4
hsa-miR-424-3p	CAAAACGUGAGGCGCUGCUAU	298	21	4
hsa-miR-4454	GGAUCCGAGUCACGGCACCA	299	20	4
hsa-miR-4463	GAGACUGGGGUGGGGCC	300	17	4
hsa-miR-4671-3p	UUAGUGCAUAGUCUUUGGUCU	301	21	4
hsa-miR-4775	UUAAUUUUUUGUUUCGGUCACU	302	22	4
hsa-miR-500a-5p	UAAUCCUUGCUACCUGGGUGAGA	303	23	4
hsa-miR-548b-5p	AAAAGUAAUUGUGGUUUUGGCC	304	22	4
hsa-miR-573	CUGAAGUGAUGUGUAACUGAUCAG	305	24	4
hsa-miR-576-5p	AUUCUAAUUUCUCCACGUCUUU	306	22	4
hsa-miR-625-3p	GACUAUAGAACUUUCCCCCUCA	307	22	4
hsa-miR-652-3p	AAUGGCGCCACUAGGGUUGUG	308	21	4
hsa-miR-665	ACCAGGAGGCUGAGGCCCCU	309	20	4
hsa-miR-766-3p	ACUCCAGCCCCACAGCCUCAGC	310	22	4
hsa-miR-935	CCAGUUACCGCUUCCGCUACCGC	311	23	4

hsa-miR-937	AUCCGCGCUCUGACUCUCUGCC	312	22	4
hsa-miR-1180	UUUCCGGCUCGCGUGGGUGUGU	313	22	3
hsa-miR-1185-2-3p	AUAUACAGGGGGAGACUCUCAU	314	22	3
hsa-miR-132-5p	ACCGUGGCUUUCGAUUGUUACU	315	22	3
hsa-miR-16-2-3p	CCAAUAUUACUGUGCUGCUUUA	316	22	3
hsa-miR-20b-5p	CAAAGUGCUCAUAGUGCAGGUAG	317	23	3
hsa-miR-2116-3p	CCUCCCAUGCCAAGAACUCCC	318	21	3
hsa-miR-299-5p	UGGUUUACCGUCCCACAUACAU	319	22	3
hsa-miR-30b-3p	CUGGGAGGUGGAUGUUUACUUC	320	22	3
hsa-miR-30c-2-3p	CUGGGAGAAGGCUGUUUACUCU	321	22	3
hsa-miR-3187-3p	UUGGCCAUGGGGCUGCGCGG	322	20	3
hsa-miR-3615	UCUCUCGGCUCCUCGCGGCUC	323	21	3
hsa-miR-3620	UCACCCUGCAUCCCGCACCCAG	324	22	3
hsa-miR-3654	GACUGGACAAGCUGAGGAA	325	19	3
hsa-miR-3662	GAAAAUGAUGAGUAGUGACUGAUG	326	24	3
hsa-miR-3681-5p	UAGUGGAUGAUGCACUCUGUGC	327	22	3
hsa-miR-4286	ACCCCACUCCUGGUACC	328	17	3
hsa-miR-4640-3p	CACCCCCUGUUUCCUGGCCCAC	329	22	3
hsa-miR-4717-3p	ACACAUGGGUGGCUGUGGCCU	330	21	3
hsa-miR-542-3p	UGUGACAGAUUGAUAACUGAAA	331	22	3
hsa-miR-5584-5p	CAGGGAAAUGGGAAGAACUAGA	332	22	3
hsa-miR-570-3p	CGAAAACAGCAAUUACCUUUGC	333	22	3
hsa-miR-574-5p	UGAGUGUGUGUGUGAGUGUGU	334	23	3
hsa-miR-628-3p	UCUAGUAAGAGUGGCAGUCGA	335	21	3
hsa-miR-654-3p	UAUGUCUGCUGACCAUCACCUU	336	22	3
hsa-miR-769-3p	CUGGGAUCUCCGGGGUCUUGGUU	337	23	3
hsa-miR-943	CUGACUGUUGCCGUCCUCCAG	338	21	3
hsa-let-7b-3p	CUAUACAACCUACUGCCUUCCC	339	22	2
hsa-miR-1244	AAGUAGUUGGUUUGUAUGAGAUGGUU	340	26	2
hsa-miR-1255a	AGGAUGAGCAAAGAAAGUAGAUU	341	23	2
hsa-miR-1273e	UUGCUUGAACCCAGGAAGUGGA	342	22	2
hsa-miR-1289	UGGAGUCCAGGAAUCUGCAUUUU	343	23	2
hsa-miR-152	UCAGUGCAUGACAGAACUUGG	344	21	2
hsa-miR-194-5p	UGUAACAGCAACUCCAUGUGGA	345	22	2
hsa-miR-195-5p	UAGCAGCACAGAAAUAUUGGC	346	21	2
hsa-miR-200c-3p	UAAUACUGCCGGGUAAUGAUGGA	347	23	2
hsa-miR-212-3p	UAACAGUCUCCAGUCACGGCC	348	21	2
hsa-miR-222-5p	CUCAGUAGCCAGUGUAGAUCCU	349	22	2
hsa-miR-3065-3p	UCAGCACCAGGAUAUUGUUGGAG	350	23	2
hsa-miR-3115	AUAUGGGUUUACUAGUUGGU	351	20	2
hsa-miR-3126-5p	UGAGGGACAGAUGCCAGAAGCA	352	22	2
hsa-miR-3174	UAGUGAGUUAGAGAUGCAGAGCC	353	23	2
hsa-miR-324-5p	CGCAUCCCCUAGGGCAUUGGUGU	354	23	2
hsa-miR-33a-5p	GUGCAUUGUAGUUGCAUUGCA	355	21	2
hsa-miR-3677-3p	CUCGUGGGCUCUGGCCACGGCC	356	22	2
hsa-miR-369-5p	AGAUCGACCGUGUUAUAUUCGC	357	22	2

hsa-miR-425-3p	AUCGGGAAUGUCGUGUCCGCCC	358	22	2
hsa-miR-4426	GAAGAUGGACGUACUUU	359	17	2
hsa-miR-4467	UGGCGGCGGUAGUUAUGGGCUU	360	22	2
hsa-miR-4482-3p	UUUCUAUUUCUCAGUGGGGCUC	361	22	2
hsa-miR-4515	AGGACUGGACUCCCGGCAGCCC	362	22	2
hsa-miR-4792	CGGUGAGCGCUCGCUGGC	363	18	2
hsa-miR-659-5p	AGGACCUUCCCUGAACCAAGGA	364	22	2
hsa-miR-663a	AGGCGGGGCGCCGCGGGACCGC	365	22	2
hsa-miR-940	AAGGCAGGGCCCCCGCUCCCC	366	21	2
hsa-miR-99a-3p	CAAGCUCGCUUCUAUGGGUCUG	367	22	2
hsa-miR-1185-5p	AGAGGAUACCCUUUGUAUGUU	368	21	1
hsa-miR-1225-3p	UGAGCCCCUGUGCCGCCCCCAG	369	22	1
hsa-miR-1237	UCCUUCUGCUCCGUCCCCCAG	370	21	1
hsa-miR-1252	AGAAGGAAAUUGAAUUCAUUUA	371	22	1
hsa-miR-1257	AGUGAAUGAUGGGUUCUGACC	372	21	1
hsa-miR-1260b	AUCCCACCACUGCCACCAU	373	19	1
hsa-miR-1273d	GAACCCAUGAGGUUGAGGCUGCAGU	374	25	1
hsa-miR-1290	UGGAUUUUUGGAUCAGGGA	375	19	1
hsa-miR-1306-3p	ACGUUGGCUCUGGUGGUG	376	18	1
hsa-miR-1321	CAGGGAGGUGAAUGUGAU	377	18	1
hsa-miR-1343	CUCCUGGGGCCCGCACUCUCGC	378	22	1
hsa-miR-138-5p	AGCUGGUGUUGUGAAUCAGGCCG	379	23	1
hsa-miR-140-5p	CAGUGGUUUUACCCUAUGGUAG	380	22	1
hsa-miR-146b-3p	UGCCCUGUGGACUCAGUUCUGG	381	22	1
hsa-miR-186-3p	GCCCAAAGGUGAAUUUUUUGGG	382	22	1
hsa-miR-1908	CGGCGGGGACGGCGAUUGGUC	383	21	1
hsa-miR-1915-3p	CCCCAGGGCGACGCGGCGGG	384	20	1
hsa-miR-1915-5p	ACCUUGCCUUGCUGCCCGGGCC	385	22	1
hsa-miR-193a-3p	AACUGGCCUACAAAGUCCCAGU	386	22	1
hsa-miR-19b-1-5p	AGUUUUGCAGGUUUGCAUCCAGC	387	23	1
hsa-miR-208b	AUAAGACGAACAAAAGGUUUGU	388	22	1
hsa-miR-2110	UUGGGGAAACGGCCGCUGAGUG	389	22	1
hsa-miR-219-1-3p	AGAGUUGAGUCUGGACGUCCCG	390	22	1
hsa-miR-26b-3p	CCUGUUCUCCAUUACUUGGCUC	391	22	1
hsa-miR-2964a-3p	AGAAUUGCGUUUGGACAAUCAGU	392	23	1
hsa-miR-29a-5p	ACUGAUUUCUUUUGGUGUUCAG	393	22	1
hsa-miR-3126-3p	CAUCUGGCAUCCGUCACACAGA	394	22	1
hsa-miR-3130-3p	GCUGCACCGGAGACUGGGUAA	395	21	1
hsa-miR-3130-5p	UACCCAGUCUCCGGUGCAGCC	396	21	1
hsa-miR-3140-5p	ACCUGAAUUACCAAAAGCUUU	397	21	1
hsa-miR-3155a	CCAGGCUCUGCAGUGGGAACU	398	21	1
hsa-miR-3157-3p	CUGCCCUAGUCUAGCUGAAGCU	399	22	1
hsa-miR-3180-3p	UGGGGCGGAGCUUCCGGAGGCC	400	22	1
hsa-miR-323b-5p	AGGUUGUCCGUGGUGAGUUCGCA	401	23	1
hsa-miR-339-5p	UCCCUGUCCUCCAGGAGCUCACG	402	23	1
hsa-miR-34a-3p	CAAUCAGCAAGUAUACUGCCCU	403	22	1

hsa-miR-34b-3p	CAAUCACUAACUCCACUGCCAU	404	22	1
hsa-miR-34c-3p	AAUCACUAACCACACGGCCAGG	405	22	1
hsa-miR-3658	UUUAAGAAAACACCAUGGAGAU	406	22	1
hsa-miR-365a-5p	AGGGACUUUUGGGGGCAGAUGUG	407	23	1
hsa-miR-3676-3p	CCGUGUUUCCCCCACGCUUU	408	20	1
hsa-miR-3691-5p	AGUGGAUGAUGGAGACUCGGUAC	409	23	1
hsa-miR-376a-5p	GUAGAUUCUCCUUCUAUGAGUA	410	22	1
hsa-miR-378g	ACUGGGCUUGGAGUCAGAAG	411	20	1
hsa-miR-3909	UGUCCUCUAGGGCCUGCAGUCU	412	22	1
hsa-miR-3928	GGAGGAACCUUGGAGCUUCGGC	413	22	1
hsa-miR-3942-3p	UUUCAGAUAACAGUAUUACAU	414	21	1
hsa-miR-3944-5p	UGUGCAGCAGGCCAACCGAGA	415	21	1
hsa-miR-3960	GGCGGCGGCGGAGGCGGGGG	416	20	1
hsa-miR-4326	UGUUCCUCUGUCUCCCAGAC	417	20	1
hsa-miR-4444	CUCGAGUUGGAAGAGGCG	418	18	1
hsa-miR-4450	UGGGGAUUUGGAGAAGUGGUGA	419	22	1
hsa-miR-4642	AUGGCAUCGUCCCCUGGUGGCU	420	22	1
hsa-miR-4668-5p	AGGGAAAAAAAAAAGGAUUUGUC	421	23	1
hsa-miR-4673	UCCAGGCAGGAGCCGGACUGGA	422	22	1
hsa-miR-4688	UAGGGGCAGCAGAGGACCUGGG	423	22	1
hsa-miR-4700-3p	CACAGGACUGACUCCUCACCCCAGUG	424	26	1
hsa-miR-4731-3p	CACACAAGUGGCCCCCAACACU	425	22	1
hsa-miR-4749-3p	CGCCCCUCCUGCCCCCACAG	426	20	1
hsa-miR-4769-5p	GGUGGGAUGGAGAGAAGGUAUGAG	427	24	1
hsa-miR-4800-5p	AGUGGACCGAGGAAGGAAGGA	428	21	1
hsa-miR-491-5p	AGUGGGGAACCCUUCCAUGAGG	429	22	1
hsa-miR-501-5p	AAUCCUUUGUCCCUGGGUGAGA	430	22	1
hsa-miR-5092	AAUCCACGCUGAGCUUGGCAUC	431	22	1
hsa-miR-541-5p	AAAGGAUUCUGCUGUCGGUCCCACU	432	25	1
hsa-miR-542-5p	UCGGGGAUCAUCAUGUCACGAGA	433	23	1
hsa-miR-551b-3p	GCGACCCAUACUUGGUUUCAG	434	21	1
hsa-miR-5690	UCAGCUACUACCUCUAUUAGG	435	21	1
hsa-miR-577	UAGAUAAAAUAUUGGUACCUG	436	21	1
hsa-miR-584-3p	UCAGUUCCAGGCCAACCAGGCU	437	22	1
hsa-miR-589-3p	UCAGAACAAAUGCCGGUUCCCAGA	438	24	1
hsa-miR-616-5p	ACUCAAAACCCUUCAGUGACUU	439	22	1
hsa-miR-628-5p	AUGCUGACAUAUUUACUAGAGG	440	22	1
hsa-miR-629-5p	UGGGUUUACGUUGGGAGAACU	441	21	1
hsa-miR-644b-3p	UUCAUUUGCCUCCCAGCCUACA	442	22	1
hsa-miR-664-5p	ACUGGCUAGGGAAAAUGAUUGGAU	443	24	1
hsa-miR-922	GCAGCAGAGAAUAGGACUACGUC	444	23	1

Table 5: Cells EI

CELLS - CTX0E03 07EI				
MIRNA	MIRNA.SEQUENCE	SEQ ID NO:	MIRNA LENGTH	READ COUNTS

hsa-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	1	22	305060
hsa-miR-92b-3p	UAUUGCACUCGUCCCGGCCUCC	13	22	242715
hsa-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA	9	22	154626
hsa-miR-92a-3p	UAUUGCACUUGUCCCGGCCUGU	7	22	137412
hsa-miR-127-3p	UCGGAUCCGUCUGAGCUUGGCU	14	22	110806
hsa-miR-100-5p	AACCCGUAGAUCCGAACUUGUG	3	22	109290
hsa-miR-27b-3p	UUCACAGUGGCUAAGUUCUGC	6	21	91902
hsa-miR-191-5p	CAACGGAAUCCCAAAAGCAGCUG	8	23	89150
hsa-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	12	22	88724
hsa-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	4	22	87399
hsa-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	11	22	78395
hsa-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	15	23	47686
hsa-miR-486-5p	UCCUGUACUGAGCUGCCCCGAG	5	22	41639
hsa-miR-30a-5p	UGUAAACAUCCUCGACUGGAAG	30	22	35465
hsa-miR-98	UGAGGUAGUAAGUUGUAUUGUU	10	22	30440
hsa-miR-151a-3p	CUAGACUGAAGCUCCUUGAGG	25	21	29047
hsa-miR-21-3p	CAACACCAGUCGAUGGGCUGU	20	21	27733
hsa-miR-30d-5p	UGUAAACAUCCCCGACUGGAAG	31	22	27307
hsa-let-7c	UGAGGUAGUAGGUUGUAUGGUU	17	22	27224
hsa-miR-10a-5p	UACCCUGUAGAUCCGAAUUUGUG	2	23	26908
hsa-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	33	22	26456
hsa-miR-182-5p	UUUGGCAAUGGUAGAACUCACACU	16	24	25885
hsa-miR-222-3p	AGCUACAUCUGGCUACUGGGU	36	21	22187
hsa-miR-125a-5p	UCCCUGAGACCCUUUAACCUGUGA	35	24	20960
hsa-miR-16-5p	UAGCAGCACGUAAAUAUUGGCG	29	22	19856
hsa-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	28	22	19774
hsa-miR-151a-5p	UCGAGGAGCUCACAGUCUAGU	37	21	19773
hsa-let-7e-5p	UGAGGUAGGAGGUUGUAUAGUU	27	22	19035
hsa-miR-125b-5p	UCCCUGAGACCCUAACUUGUGA	42	22	17965
hsa-let-7i-5p	UGAGGUAGUAGUUUGUGCUGUU	22	22	17802
hsa-let-7g-5p	UGAGGUAGUAGUUUGUACAGUU	43	22	15467
hsa-miR-409-3p	GAAUGUUGCUCGGUGAACCCCU	47	22	14133
hsa-miR-30e-5p	UGUAAACAUCCUUGACUGGAAG	45	22	13889
hsa-miR-181b-5p	AACAUUCAUUGCUGUCGGUGGGU	38	23	12606
hsa-miR-186-5p	CAAAGAAUUCUCCUUUUGGGCU	40	22	12441
hsa-miR-381	UAUACAAGGGCAAGCUCUCUGU	51	22	9851
hsa-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUU	41	23	8893
hsa-miR-30c-5p	UGUAAACAUCCUACACUCUCAGC	66	23	8737
hsa-miR-410	AAUAUAACACAGAUGGCCUGU	50	21	8509
hsa-miR-146b-5p	UGAGAACUGAAUUCCAUAGGCU	19	22	8434
hsa-miR-654-3p	UAUGUCUGCUGACCAUCACCUU	336	22	8392
hsa-miR-9-5p	UCUUUGGUUAUCUAGCUGUAUGA	58	23	7957
hsa-miR-28-3p	CACUAGAUUGUGAGCUCCUGGA	56	22	7767
hsa-miR-148a-3p	UCAGUGCACUACAGAACUUUGU	54	22	6599
hsa-miR-379-5p	UGGUAGACUAUGGAACGUAGG	18	21	6135
hsa-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	53	22	5972

hsa-miR-183-5p	UAUGGCACUGGUAGAAUUCACU	24	22	5477
hsa-miR-25-3p	CAUUGCACUUGUCUCGGUCUGA	63	22	5303
hsa-miR-423-3p	AGCUCGGUCUGAGGCCCCUCAGU	57	23	5225
hsa-miR-889	UUAAUAUCGGACAACCAUUGU	64	21	4597
hsa-miR-221-5p	ACCUGGCAUACAAUGUAGAUUU	39	22	4379
hsa-miR-125b-1-3p	ACGGGUUAGGCUCUUGGGAGCU	49	22	4192
hsa-miR-409-5p	AGGUUACCCGAGCAACUUUGCAU	32	23	3970
hsa-miR-4492	GGGGCUGGGCGCGCGCC	34	17	3864
hsa-miR-148b-3p	UCAGUGCAUCACAGAACUUUGU	48	22	3593
hsa-miR-103a-3p	AGCAGCAUUGUACAGGGCUAUGA	62	23	3518
hsa-miR-1271-5p	CUUGGCACCUAGCAAGCACUCA	72	22	3477
hsa-miR-136-3p	CAUCAUCGUCUCAAAUGAGUCU	82	22	3373
hsa-miR-769-5p	UGAGACCUCUGGGUUCUGAGCU	75	22	2957
hsa-miR-4532	CCCCGGGGAGCCCGGCG	23	17	2915
hsa-miR-378a-3p	ACUGGACUUGGAGUCAGAAGG	65	21	2895
hsa-miR-99a-5p	AACCCGUAGAUCCGAUCUUGUG	52	22	2767
hsa-miR-221-3p	AGCUACAUUGUCUGCUGGGUUUC	79	23	2764
hsa-miR-30e-3p	CUUUCAGUCGGAUGUUUACAGC	71	22	2441
hsa-miR-26b-5p	UUCAAGUAAUUCAGGAUAGGU	90	21	2432
hsa-miR-4488	AGGGGGCGGGCUCCGGCG	61	18	2391
hsa-miR-27a-3p	UUCACAGUGGCUAAGUUCCGC	46	21	2385
hsa-miR-23b-3p	AUCACAUUGCCAGGGAUUACC	59	21	2316
hsa-miR-500a-3p	AUGCACCUGGGCAAGGAUUCUG	44	22	2144
hsa-miR-941	CACCCGGCUGUGUGCACAUGUGC	60	23	2114
hsa-miR-23a-3p	AUCACAUUGCCAGGGAUUUCC	55	21	2086
hsa-miR-30a-3p	CUUUCAGUCGGAUGUUUGCAGC	77	22	2045
hsa-miR-30b-5p	UGUAAACAUCCUACACUCAGCU	96	22	1936
hsa-miR-501-3p	AAUGCACCCGGGCAAGGAUUCU	26	22	1895
hsa-miR-130b-3p	CAGUGCAAUGAUGAAAGGGCAU	86	22	1862
hsa-miR-1246	AAUGGAUUUUUGGAGCAGG	21	19	1783
hsa-miR-140-3p	UACCACAGGGUAGAACCACGG	138	21	1735
hsa-miR-31-5p	AGGCAAGAUGCUGGCAUAGCU	80	21	1705
hsa-miR-493-3p	UGAAGGUCUACUGUGUGCCAGG	83	22	1698
hsa-miR-181c-5p	AACAUUCAACCUGUCGGUGAGU	105	22	1554
hsa-miR-93-5p	CAAAGUGCUGUUCGUGCAGGUAG	116	23	1492
hsa-miR-181a-2-3p	ACCACUGACCGUUGACUGUACC	102	22	1491
hsa-miR-15b-5p	UAGCAGCACAUCAUGGUUUACA	78	22	1465
hsa-miR-7-5p	UGGAAGACUAGUGAUUUUGUUGU	85	23	1460
hsa-miR-192-5p	CUGACCUAUGAAUUGACAGCC	87	21	1453
hsa-miR-425-5p	AAUGACACGAUCACUCCCGUUGA	111	23	1432
hsa-miR-204-5p	UUCCCUUUGUCAUCCUAUGCCU	89	22	1378
hsa-miR-340-5p	UUAUAAAGCAAUGAGACUGAUU	93	22	1360
hsa-miR-190a	UGAUAUGUUUGAUAUAUUAGGU	103	22	1305
hsa-miR-34a-5p	UGGCAGUGUCUUAGCUGGUUGU	101	22	1283
hsa-miR-20a-5p	UAAAGUGCUUAUAGUGCAGGUAG	146	23	1257
hsa-miR-29a-3p	UAGCACCAUCUGAAAUCGGUUA	106	22	1206

hsa-miR-361-5p	UUAUCAGAAUCUCCAGGGGUAC	70	22	1173
hsa-miR-671-3p	UCCGGUUCUCAGGGCUCCACC	69	21	1166
hsa-miR-411-5p	UAGUAGACCGUAUAGCGUACG	108	21	1130
hsa-miR-589-5p	UGAGAACCACGUCUGCUCUGAG	73	22	1067
hsa-miR-130a-3p	CAGUGCAAUGUUAAAAGGGCAU	113	22	1020
hsa-miR-320a	AAAAGCUGGGUUGAGAGGGCGA	97	22	994
hsa-miR-149-5p	UCUGGCUCCGUGUCUUCACUCCC	121	23	948
hsa-miR-335-5p	UCAAGAGCAAUAACGAAAAAUGU	128	23	945
hsa-miR-134	UGUGACUGGUUGACCAGAGGGG	94	22	941
hsa-miR-17-5p	CAAAGUGCUUACAGUGCAGGUAG	145	23	939
hsa-miR-493-5p	UUGUACAUGGUAGGCUUUCAUU	88	22	876
hsa-miR-34c-5p	AGGCAGUGUAGUUAGCUGAUUGC	125	23	846
hsa-miR-484	UCAGGCUCAGUCCCCUCCCGAU	118	22	835
hsa-miR-181a-3p	ACCAUCGACCGUUGAUUGUACC	100	22	803
hsa-miR-24-3p	UGGCUCAGUUCAGCAGGAACAG	119	22	740
hsa-miR-128	UCACAGUGAACCGGUCUCUUU	109	21	707
hsa-miR-342-3p	UCUCACACAGAAAUCGCACCCGU	81	23	698
hsa-miR-454-3p	UAGUGCAAUAUUGCUUAUAGGGU	169	23	690
hsa-miR-1307-5p	UCGACCGGACCUCGACCGGCU	91	21	616
hsa-miR-487b	AAUCGUACAGGGUCAUCCACUU	117	22	590
hsa-miR-130b-5p	ACUCUUUCCCUGUUGCACUAC	112	21	568
hsa-miR-197-3p	UUCACCACCUUCUCCACCCAGC	122	22	544
hsa-miR-432-5p	UCUUGGAGUAGGUCAUUGGGUGG	95	23	542
hsa-miR-374a-5p	UUAUAAUACAACCUGAUAAGUG	74	22	537
hsa-miR-345-5p	GCUGACUCCUAGUCCAGGGCUC	76	22	527
hsa-miR-744-5p	UGCGGGGCUAGGGCUAACAGCA	99	22	515
hsa-miR-376c	AACAUAGAGGAAAUUCCACGU	185	21	506
hsa-miR-181d	AACAUUCAUUGUUGUCGGUGGGU	157	23	497
hsa-miR-363-3p	AAUUGCACGGUAUCCAUCUGUA	131	22	493
hsa-miR-539-3p	AUCAUACAAGGACAAUUUCUUU	150	22	493
hsa-miR-758	UUUGUGACCUGGUCCACUAACC	141	22	477
hsa-miR-323a-3p	CACAUUACACGGUCGACCUCU	158	21	443
hsa-miR-107	AGCAGCAUUGUACAGGGCUAUCA	254	23	431
hsa-miR-720	UCUCGCUGGGGCCUCCA	84	17	427
hsa-miR-654-5p	UGGUGGGCCGCAGAACAUGUGC	115	22	409
hsa-miR-370	GCCUGCUGGGGUGGAACCUGGU	126	22	406
hsa-miR-421	AUCAACAGACAUUAAUUGGGCGC	151	23	399
hsa-miR-30d-3p	CUUUCAGUCAGAUGUUUGCUGC	114	22	358
hsa-miR-148b-5p	AAGUUCUGUUAUACACUCAGGC	127	22	354
hsa-miR-1301	UUGCAGCUGCCUGGGAGUGACUUC	181	24	346
hsa-miR-374b-5p	AUAUAAUACAACCUGCUAAGUG	143	22	339
hsa-miR-125b-2-3p	UCACAAGUCAGGCUCUUGGGAC	68	22	333
hsa-miR-28-5p	AAGGAGCUCACAGUCUAUUGAG	152	22	332
hsa-miR-495	AAACAAACAUGGUGCACUUCUU	241	22	321
hsa-miR-15a-5p	UAGCAGCACAUAAUGGUUUGUG	223	22	320
hsa-miR-100-3p	CAAGCUUGUAUCUAUAGGUAUG	98	22	314

hsa-miR-193b-3p	AACUGGCCCUCAAAGUCCCGCU	148	22	305
hsa-miR-330-5p	UCUCUGGGCCUGUGUCUUAGGC	161	22	303
hsa-miR-376a-3p	AUCAUAGAGGAAAAUCCACGU	237	21	298
hsa-miR-135b-5p	UAUGGCUUUUCAUUCCUAUGUGA	137	23	289
hsa-miR-301a-3p	CAGUGCAAUAGUAUUGUCAAAGC	107	23	280
hsa-miR-218-5p	UUGUGCUUGAUCUAACCAUGU	206	21	276
hsa-miR-143-3p	UGAGAUGAAGCACUGUAGCUC	176	21	256
hsa-miR-27b-5p	AGAGCUUAGCUGAUUGGUGAAC	201	22	255
hsa-miR-369-3p	AAUAAUACAUGGUUGAUCUUU	196	21	255
hsa-miR-877-5p	GUAGAGGAGAUGGCGCAGGG	133	20	249
hsa-miR-19b-3p	UGUGCAAAUCCAUGCAAAACUGA	163	23	246
hsa-miR-424-5p	CAGCAGCAAUUCAUGUUUUGAA	186	22	245
hsa-miR-660-5p	UACCCAUUGCAUAUCGGAGUUG	187	22	244
hsa-miR-532-5p	CAUGCCUUGAGUGUAGGACCGU	178	22	238
hsa-miR-299-3p	UAUGUGGGAUGGUAAACCGCUU	182	22	235
hsa-miR-431-3p	CAGGUCGUCUUGCAGGGCUUCU	168	22	231
hsa-miR-374a-3p	CUUAUCAGAUUGUAUUGUAAUU	173	22	220
hsa-miR-148a-5p	AAAGUUCUGAGACACUCCGACU	144	22	214
hsa-miR-4516	GGGAGAAGGGUCGGGGC	110	17	207
hsa-miR-92b-5p	AGGGACGGGACGCGGUGCAGUG	208	22	206
hsa-miR-16-2-3p	CCAAUAUUACUGUGCUGCUUUA	316	22	202
hsa-miR-101-3p	UACAGUACUGUGAUAACUGAA	142	21	201
hsa-let-7a-3p	CUAUACAAUCUACUGUCUUUC	222	21	199
hsa-miR-4485	UAACGGCCGCGGUACCCUAA	67	20	195
hsa-miR-455-3p	GCAGUCCAUGGGCAUAUACAC	140	21	192
hsa-miR-185-5p	UGGAGAGAAAGGCAGUUCCUGA	224	22	188
hsa-miR-1185-1-3p	AUAUACAGGGGGAGACUCUUAU	209	22	187
hsa-miR-1197	UAGGACACAUGGUCUACUUCU	244	21	185
hsa-miR-106b-3p	CCGCACUGUGGGUACUUGCUGC	159	22	178
hsa-miR-24-2-5p	UGCCUACUGAGCUGAAACACAG	156	22	178
hsa-miR-4677-3p	UCUGUGAGACCAAAGAACUACU	120	22	177
hsa-miR-380-3p	UAUGUAAUAUGGUCCACAUCUU	445	22	174
hsa-miR-548k	AAAAGUACUUGCGGAUUUUGCU	198	22	171
hsa-miR-1307-3p	ACUCGGCGUGGCGUCGGUCGUG	124	22	169
hsa-miR-485-3p	GUCAUACACGGCUCUCCUCUCU	153	22	168
hsa-miR-494	UGAAACAUACACGGGAAACCUC	240	22	165
hsa-miR-17-3p	ACUGCAGUGAAGGCACUUGUAG	184	22	163
hsa-miR-561-5p	AUCAAGGAUCUUAAACUUUGCC	179	22	160
hsa-miR-27a-5p	AGGGCUUAGCUGCUUGUGAGCA	130	22	158
hsa-miR-874	CUGCCCUGGCCCGAGGGACCGA	147	22	151
hsa-miR-9-3p	AUAAAGCUAGAUAACCGAAAGU	183	22	151
hsa-miR-96-5p	UUUGGCACUAGCACAUUUUUGCU	123	23	151
hsa-miR-656	AAUAUUAUACAGUCAACCUCU	221	21	147
hsa-miR-379-3p	UAUGUAACAUGGUCCACUAACU	446	22	145
hsa-miR-382-5p	GAAGUUGUUCGUGGUGGAUUCG	238	22	144
hsa-miR-541-3p	UGGUGGGCACAGAAUCUGGACU	136	22	141

hsa-miR-337-3p	CUCCUAUAUGAUGCCUUUCUUC	215	22	139
hsa-miR-15b-3p	CGAAUCAUUAUUUGCUGCUCUA	447	22	137
hsa-miR-20b-5p	CAAAGUGCUCAUAGUGCAGGUAG	317	23	136
hsa-miR-329	AACACACCUGGUUAACCUCUUU	214	22	136
hsa-miR-3676-5p	AGGAGAUCCUGGGUU	280	15	134
hsa-miR-543	AAACAUUCGCGGUGCACUUCUU	193	22	134
hsa-miR-365b-3p	UAAUGCCCCUAAAAAUCCUUAU	279	22	133
hsa-miR-125a-3p	ACAGGUGAGGUUCUUGGGAGCC	160	22	131
hsa-miR-3065-5p	UCAACAAAAUCACUGAUGCUGGA	226	23	130
hsa-miR-1296	UUAGGGCCCUGGCUCCAUCUCC	271	22	126
hsa-miR-935	CCAGUUACCGCUUCCGCUACCGC	311	23	118
hsa-miR-132-3p	UAACAGUCUACAGCCAUGGUCG	104	22	116
hsa-miR-4284	GGGCUCACAUCACCCCAU	191	18	116
hsa-miR-487a	AAUCAUACAGGGACAUCCAGUU	203	22	113
hsa-miR-574-5p	UGAGUGUGUGUGUGUGAGUGUGU	334	23	113
hsa-miR-301b	CAGUGCAAUGAUAUUGUCAAAGC	164	23	111
hsa-miR-548o-3p	CCAAAACUGCAGUUACUUUUGC	268	22	105
hsa-miR-18a-5p	UAAGGUGCAUCUAGUGCAGAUAG	256	23	104
hsa-miR-485-5p	AGAGGCUGGCCGUGAUGAAUUC	165	22	104
hsa-miR-548ah-5p	AAAAGUGAUUGCAGUGUUUG	235	20	103
hsa-miR-361-3p	UCCCCCAGGUGUGAUUCUGAUUU	250	23	101
hsa-miR-433	AUCAUGAUGGGCUCCUCGGUGU	174	22	101
hsa-miR-337-5p	GAACGGCUUCAUACAGGAGUU	277	21	100
hsa-miR-1276	UAAAGAGCCCUGUGGAGACA	194	20	99
hsa-miR-30c-1-3p	CUGGGAGAGGGUUGUUUACUCC	213	22	99
hsa-miR-31-3p	UGCUAUGCCAACAUAUUGCCAU	172	22	96
hsa-miR-424-3p	CAAAACGUGAGGCGCUGCUAU	298	21	96
hsa-miR-550a-5p	AGUGCCUGAGGGAGUAAGAGCCC	134	23	95
hsa-miR-4454	GGAUCCGAGUCACGGCACCA	299	20	94
hsa-miR-541-5p	AAAGGAUUCUGCUGUCGGUCCCACU	432	25	92
hsa-miR-106b-5p	UAAAGUGCUGACAGUGCAGAU	170	21	89
hsa-miR-153	UUGCAUAGUCACAAAAGUGAUC	188	22	88
hsa-miR-135b-3p	AUGUAGGGCUAAAAGCCAUGGG	205	22	87
hsa-miR-574-3p	CACGCUCAUGCACACACCCACA	253	22	87
hsa-miR-1226-3p	UCACCAGCCCUGUGUUCCCUAG	199	22	85
hsa-miR-576-5p	AUUCUAAUUUCUCCACGUCUUU	306	22	84
hsa-miR-127-5p	CUGAAGCUCAGAGGGCUCUGAU	255	22	83
hsa-miR-155-5p	UUAAUGCUAAUCGUGAUAGGGGU	448	23	83
hsa-miR-3176	ACUGGCCUGGGACUACCGG	227	19	83
hsa-miR-382-3p	AAUCAUUCACGGACAACACUU	260	21	83
hsa-miR-1275	GUGGGGGAGAGGCUGUC	162	17	82
hsa-miR-671-5p	AGGAAGCCCUGGAGGGGCUGGAG	288	23	82
hsa-miR-23a-5p	GGGGUUCCUGGGGAUGGGAUUU	212	22	81
hsa-miR-25-5p	AGGCGGAGACUUGGGCAAUUG	225	21	80
hsa-miR-641	AAAGACAUAGGAUAGAGUCACCUC	285	24	80
hsa-miR-19a-3p	UGUGCAAAUCUAUGCAAAACUGA	177	23	79

hsa-miR-377-3p	AUCACACAAAGGCAACUUUUGU	449	22	78
hsa-miR-454-5p	ACCCUAUCAAUAUUGUCUCUGC	265	22	78
hsa-miR-496	UGAGUAUUACAUGGCCAAUCUC	267	22	78
hsa-miR-29b-3p	UAGCACCAUUUGAAAUCAGUGUU	166	23	77
hsa-miR-26a-2-3p	CCUAUUCUUGAUUACUUGUUUC	257	22	76
hsa-miR-1260b	AUCCCACCACUGCCACCAU	373	19	74
hsa-miR-2467-5p	UGAGGCUCUGUUAGCCUUGGCUC	154	23	74
hsa-miR-377-5p	AGAGGUUGCCCUUGGUGAAUUC	202	22	74
hsa-miR-330-3p	GCAAAGCACACGGCCUGCAGAGA	195	23	73
hsa-miR-1180	UUUCCGGCUCGCGUGGGUGUGU	313	22	71
hsa-miR-99b-3p	CAAGCUCGUGUCUGUGGGUCCG	243	22	71
hsa-miR-299-5p	UGGUUUACCGUCCCACAUACAU	319	22	69
hsa-miR-374b-3p	CUUAGCAGGUUGUAUUAUCAUU	229	22	69
hsa-miR-4746-5p	CCGGUCCCAGGAGAACCUGCAGA	266	23	69
hsa-miR-331-3p	GCCCCUGGGCCUAUCCUAGAA	450	21	68
hsa-miR-340-3p	UCCGUCUCAGUUACUUUAUAGC	248	22	68
hsa-miR-92a-1-5p	AGGUUGGGAUCGGUUGCAAUGCU	204	23	68
hsa-miR-542-3p	UGUGACAGAUUGAUAACUGAAA	331	22	66
hsa-miR-431-5p	UGUCUUGCAGGCCGUCAUGCA	132	21	65
hsa-miR-1254	AGCCUGGAAGCUGGAGCCUGCAGU	270	24	61
hsa-miR-3158-3p	AAGGGCUUCCUCUCUGCAGGAC	167	22	61
hsa-miR-362-5p	AAUCCUUGGAACCUAGGUGUGAGU	139	24	61
hsa-miR-30c-2-3p	CUGGGAGAAGGCUGUUUACUCU	321	22	59
hsa-miR-4461	GAUUGAGACUAGUAGGGCUAGGC	129	23	59
hsa-miR-3200-3p	CACCUUGCGCUACUCAGGUCUG	247	22	57
hsa-miR-215	AUGACCUAUGAAUUGACAGAC	451	21	56
hsa-miR-1185-5p	AGAGGAUACCCUUUGUAUGUU	368	21	55
hsa-miR-328	CUGGCCCUCUCUGCCCUUCCGU	297	22	55
hsa-miR-655	AUAAUACAUGGUUAACCUCUUU	286	22	55
hsa-miR-181b-3p	CUCACUGAACAAUGAAUGCAA	245	21	54
hsa-miR-376b	AUCAUAGAGGAAAAUCCAUGUU	452	22	54
hsa-miR-486-3p	CGGGGCAGCUCAGUACAGGAU	453	21	54
hsa-miR-760	CGGCUCUGGGUCUGUGGGGA	289	20	54
hsa-miR-3909	UGUCCUCUAGGGCCUGCAGUCU	412	22	53
hsa-miR-4508	GCGGGGCUGGGCGCGCG	135	17	53
hsa-miR-4521	GCUAAGGAAGUCCUGUGCUCAG	233	22	53
hsa-let-7e-3p	CUAUACGGCCUCCUAGCUUUCC	290	22	52
hsa-miR-455-5p	UAUGUGCCUUUGGACUACAUCG	192	22	52
hsa-miR-93-3p	ACUGCUGAGCUAGCACUUCCCG	454	22	51
hsa-miR-151b	UCGAGGAGCUCACAGUCU	455	18	49
hsa-miR-887	GUGAACGGGCGCCAUCCCGAGG	456	22	49
hsa-miR-152	UCAGUGCAUGACAGAACUUGG	344	21	48
hsa-miR-324-3p	ACUGCCCCAGGUGCUGCUGG	276	20	48
hsa-miR-1266	CCUCAGGGCUGUAGAACAGGGCU	457	23	47
hsa-miR-302b-3p	UAAGUGCUUCCAUGUUUUAGUAG	458	23	47
hsa-miR-548e	AAAAACUGAGACUACUUUUGCA	459	22	47

hsa-miR-502-3p	AAUGCACCUGGGCAAGGAUUCA	281	22	46
hsa-miR-302d-3p	UAAGUGCUUCCAUGUUUGAGUGU	460	23	45
hsa-miR-3943	UAGCCCCCAGGCUUCACUUGGCG	207	23	45
hsa-miR-1286	UGCAGGACCAAGAUGAGCCCU	293	21	44
hsa-miR-3605-5p	UGAGGAUGGAUAGCAAGGAAGCC	189	23	44
hsa-miR-505-3p	CGUCAACACUUGCUGGUUUCCU	282	22	44
hsa-miR-3615	UCUCUCGGCUCCUCGCGGCUC	323	21	43
hsa-miR-4435	AUGGCCAGAGCUCACACAGAGG	230	22	43
hsa-miR-598	UACGUCAUCGUUGUCAUCGUCA	461	22	43
hsa-miR-126-5p	CAUUAUUACUUUUGGUACGCG	462	21	42
hsa-miR-4671-3p	UUAGUGCAUAGUCUUUGGUCU	301	21	41
hsa-miR-652-3p	AAUGGCGCCACUAGGGUUGUG	442	21	41
hsa-miR-3687	CCCGGACAGGCGUUCGUGCGACGU	190	24	40
hsa-miR-4286	ACCCCACUCCUGGUACC	328	17	40
hsa-miR-590-3p	UAAUUUUAUGUAUAAGCUAGU	463	21	40
hsa-miR-1285-3p	UCUGGGCAACAAAGUGAGACCU	464	22	39
hsa-miR-2355-5p	AUCCCCAGAUACAAUGGACAA	593	21	38
hsa-miR-550a-3p	UGUCUUACUCCCUCAGGCACAU	283	22	38
hsa-let-7d-3p	CUAUACGACCUGCUGCCUUUCU	92	22	37
hsa-miR-136-5p	ACUCCAUUUGUUUUGAUGAUGGA	272	23	37
hsa-miR-1468	CUCCGUUUGCCUGUUUCGCUG	296	21	37
hsa-miR-3609	CAAAGUGAUGAGUAAUACUGGCUG	216	24	37
hsa-miR-548b-5p	AAAAGUAAUUGUGGUUUUGGCC	304	22	37
hsa-miR-664-3p	UAUUCAUUUAUCCCCAGCCUACA	287	23	37
hsa-miR-99a-3p	CAAGCUCGCUUCUAUGGGUCUG	367	22	37
hsa-miR-532-3p	CCUCCCACACCCAAGGCUUGCA	252	22	36
hsa-miR-10b-5p	UACCCUGUAGAACCGAAUUUGUG	465	23	33
hsa-miR-369-5p	AGAUCGACCGUGUUAUAUUCGC	357	22	33
hsa-miR-3161	CUGAUAAGAACAGAGGCCCAGAU	466	23	32
hsa-miR-3940-3p	CAGCCCGGAUCCCAGCCCACUU	239	22	32
hsa-miR-663b	GGUGGCCCGGCCGUGCCUGAGG	180	22	32
hsa-miR-219-2-3p	AGAAUUGUGGCUGGACAUCUGU	467	22	31
hsa-miR-2277-5p	AGCGCGGGCUGAGCGCUGCCAGUC	735	24	31
hsa-miR-4448	GGCUCCUUGGUCUAGGGGUA	231	20	31
hsa-miR-339-5p	UCCCUGUCCUCCAGGAGCUCACG	402	23	30
hsa-miR-3613-5p	UGUUGUACUUUUUUUUUUGUUC	469	22	30
hsa-miR-4775	UUAAUUUUUUGUUUCGGUCACU	302	22	30
hsa-miR-212-5p	ACCUUGGCUCUAGACUGCUUACU	246	23	29
hsa-miR-324-5p	CGCAUCCCCUAGGGCAUUGGUGU	354	23	27
hsa-miR-4326	UGUUCCUCUGUCUCCCAGAC	417	20	27
hsa-miR-582-3p	UAACUGGUUGAACAACUGAACC	470	22	27
hsa-miR-34a-3p	CAAUCAGCAAGUAUACUGCCCU	403	22	26
hsa-miR-106a-5p	AAAAGUGCUUACAGUGCAGGUAG	471	23	25
hsa-miR-4745-5p	UGAGUGGGGCUCCCGGGACGGCG	219	23	25
hsa-miR-769-3p	CUGGGAUCUCCGGGGUCUUGGUU	337	23	25
hsa-miR-1268a	CGGGCGUGGUGGUGGGGG	291	18	24

hsa-miR-154-3p	AAUCAUACACGGUUGACCUAUU	472	22	24
hsa-miR-188-3p	CUCCCACAUGCAGGGUUUGCA	200	21	24
hsa-miR-29c-3p	UAGCACCAUUUGAAAUCGGUUA	473	22	24
hsa-miR-539-5p	GGAGAAAUUAUCCUUGGUGUGU	234	22	24
hsa-miR-766-3p	ACUCCAGCCCCACAGCCUCAGC	310	22	24
hsa-miR-30b-3p	CUGGGAGGUGGAUGUUUACUUC	320	22	23
hsa-miR-3177-3p	UGCACGGCACUGGGGACACGU	275	21	23
hsa-miR-191-3p	GCUGCGCUUGGAUUUCGUCCCC	474	22	22
hsa-miR-296-3p	GAGGGUUGGGUGGAGGCUCUCC	274	22	22
hsa-miR-296-5p	AGGGCCCCCCCUCAAUCCUGU	258	21	22
hsa-miR-339-3p	UGAGCGCCUCGACGACAGAGCCG	228	23	22
hsa-miR-501-5p	AAUCCUUUGUCCCUGGGUGAGA	430	22	22
hsa-miR-200b-3p	UAAUACUGCCUGGUAAUGAUGA	475	22	21
hsa-miR-212-3p	UAACAGUCUCCAGUCACGGCC	348	21	21
hsa-miR-26b-3p	CCUGUUCUCCAUUACUUGGCUC	391	22	21
hsa-miR-665	ACCAGGAGGCUGAGGCCCCU	309	20	21
hsa-miR-668	UGUCACUCGGCUCGGCCCACUAC	476	23	21
hsa-miR-146a-5p	UGAGAACUGAAUUCCAUGGGUU	477	22	20
hsa-miR-1973	ACCGUGCAAAGGUAGCAUA	171	19	20
hsa-miR-210	CUGUGCGUGUGACAGCGGCUGA	478	22	20
hsa-miR-3607-5p	GCAUGUGAUGAAGCAAAUCAGU	249	22	20
hsa-miR-378a-5p	CUCCUGACUCCAGGUCCUGUGU	217	22	20
hsa-miR-4449	CGUCCCGGGGCUGCGCGAGGCA	155	22	20
hsa-miR-138-5p	AGCUGGUGUUGUGAAUCAGGCCG	379	23	19
hsa-miR-146b-3p	UGCCCUGUGGACUCAGUUCUGG	381	22	18
hsa-miR-3065-3p	UCAGCACCAGGAUAUUGUUGGAG	350	23	18
hsa-miR-4417	GGUGGGCUUCCCGGAGGG	175	18	18
hsa-miR-497-5p	CAGCAGCACACUGUGGUUUGU	479	21	18
hsa-miR-500a-5p	UAAUCCUUGCUACCUGGGUGAGA	303	23	18
hsa-miR-625-3p	GACUAUAGAACUUUCCCCCUCA	307	22	18
hsa-miR-628-3p	UCUAGUAAGAGUGGCAGUCGA	335	21	18
hsa-miR-1343	CUCCUGGGGCCCGCACUCUCGC	378	22	17
hsa-miR-3648	AGCCGCGGGGAUCGCCGAGGG	259	21	17
hsa-miR-432-3p	CUGGAUGGCUCCUCCAUGUCU	262	21	17
hsa-miR-4482-3p	UUUCUAUUUCUCAGUGGGGCUC	361	22	17
hsa-miR-542-5p	UCGGGGAUCAUCAUGUCACGAGA	433	23	17
hsa-miR-551b-3p	GCGACCCAUACUUGGUUUCAG	434	21	17
hsa-miR-7-1-3p	CAACAAAUCACAGUCUGCCAUA	480	22	17
hsa-miR-219-1-3p	AGAGUUGAGUCUGGACGUCCCG	390	22	16
hsa-miR-3656	GGCGGGUGCGGGGGUGG	251	17	16
hsa-miR-3661	UGACCUGGGACUCGGACAGCUG	481	22	16
hsa-miR-411-3p	UAUGUAACACGGUCCACUAACC	482	22	16
hsa-miR-5096	GUUUCACCAUGUUGGUCAGGC	220	21	16
hsa-miR-577	UAGAUAAAAUAUUGGUACCUG	436	21	16
hsa-let-7i-3p	CUGCGCAAGCUACUGCCUUGCU	483	22	15
hsa-miR-132-5p	ACCGUGGCUUUCGAUUGUUACU	315	22	15

hsa-miR-140-5p	CAGUGGUUUUACCCUAUGGUAG	380	22	15
hsa-miR-195-5p	UAGCAGCACAGAAAUAUUGGC	346	21	15
hsa-miR-3187-3p	UUGGCCAUGGGGCUGCGCGG	322	20	15
hsa-miR-342-5p	AGGGGUGCUAUCUGUGAUUGA	278	21	15
hsa-miR-34b-3p	CAAUCACUAACUCCACUGCCAU	404	22	15
hsa-miR-4661-5p	AACUAGCUCUGUGGAUCCUGAC	484	22	15
hsa-miR-584-5p	UUAUGGUUUGCCUGGGACUGAG	485	22	15
hsa-miR-744-3p	CUGUUGCCACUAACCUCAACCU	486	22	15
hsa-miR-770-5p	UCCAGUACCACGUGUCAGGGCCA	487	23	15
hsa-miR-3677-3p	CUCGUGGGCUCUGGCCACGGCC	356	22	14
hsa-miR-425-3p	AUCGGGAAUGUCGUGUCCGCCC	358	22	14
hsa-miR-548ah-3p	CAAAAACUGCAGUUACUUUUGC	149	22	14
hsa-miR-5699	UCCUGUCUUUCCUUGUUGGAGC	488	22	14
hsa-miR-582-5p	UUACAGUUGUUCAACCAGUUACU	489	23	14
hsa-miR-1185-2-3p	AUAUACAGGGGGAGACUCUCAU	314	22	13
hsa-miR-1249	ACGCCCUUCCCCCCCUUCUUCA	490	22	13
hsa-miR-1255a	AGGAUGAGCAAAGAAAGUAGAUU	341	23	13
hsa-miR-1910	CCAGUCCUGUGCCUGCCGCCU	236	21	13
hsa-miR-301a-5p	GCUCUGACUUUAUUGCACUACU	491	22	13
hsa-miR-5001-3p	UUCUGCCUCUGUCCAGGUCCUU	492	22	13
hsa-miR-5094	AAUCAGUGAAUGCCUUGAACCU	493	22	13
hsa-miR-628-5p	AUGCUGACAUAUUUACUAGAGG	440	22	13
hsa-miR-629-5p	UGGGUUUACGUUGGGAGAACU	441	21	13
hsa-miR-937	AUCCGCGCUCUGACUCUCUGCC	312	22	13
hsa-miR-940	AAGGCAGGGCCCCCGCUCCCC	366	21	13
hsa-miR-1248	ACCUUCUUGUAUAAGCACUGUGCUAAA	269	27	12
hsa-miR-194-5p	UGUAACAGCAACUCCAUGUGGA	345	22	12
hsa-miR-199b-3p	ACAGUAGUCUGCACAUUGGUUA	494	22	12
hsa-miR-22-5p	AGUUCUUCAGUGGCAAGCUUUA	495	22	12
hsa-miR-3605-3p	CCUCCGUGUUACCUGUCCUCUAG	496	23	12
hsa-miR-3654	GACUGGACAAGCUGAGGAA	325	19	12
hsa-miR-504	AGACCCUGGUCUGCACUCUAUC	497	22	12
hsa-miR-1291	UGGCCCUGACUGAAGACCAGCAGU	294	24	11
hsa-miR-1299	UUCUGGAAUUCUGUGUGAGGGA	498	22	11
hsa-miR-188-5p	CAUCCCUUGCAUGGUGGAGGG	499	21	11
hsa-miR-222-5p	CUCAGUAGCCAGUGUAGAUCCU	349	22	11
hsa-miR-331-5p	CUAGGUAUGGUCCCAGGGAUCC	500	22	11
hsa-miR-3939	UACGCGCAGACCACAGGAUGUC	261	22	11
hsa-miR-154-5p	UAGGUUAUCCGUGUUGCCUUCG	501	22	10
hsa-miR-18a-3p	ACUGCCCUAAGUGCUCCUUCUGG	502	23	10
hsa-miR-1908	CGGCGGGGACGGCGAUUGGUC	383	21	10
hsa-miR-200c-3p	UAAUACUGCCGGGUAAUGAUGGA	347	23	10
hsa-miR-2116-3p	CCUCCCAUGCCAAGAACUCCC	318	21	10
hsa-miR-302a-3p	UAAGUGCUUCCAUGUUUUGGUGA	503	23	10
hsa-miR-3174	UAGUGAGUUAGAGAUGCAGAGCC	353	23	10
hsa-miR-326	CCUCUGGGCCCUUCCUCCAG	504	20	10

hsa-let-7g-3p	CUGUACAGGCCACUGCCUUGC	505	21	9
hsa-miR-141-3p	UAACACUGUCUGGUAAAGAUGG	295	22	9
hsa-miR-24-1-5p	UGCCUACUGAGCUGAUAUCAGU	506	22	9
hsa-miR-3115	AUAUGGGUUUACUAGUUGGU	351	20	9
hsa-miR-3180-3p	UGGGGCGGAGCUUCCGGAGGCC	400	22	9
hsa-miR-33a-5p	GUGCAUUGUAGUUGCAUUGCA	355	21	9
hsa-miR-34c-3p	AAUCACUAACCACACGGCCAGG	405	22	9
hsa-miR-3929	GAGGCUGAUGUGAGUAGACCACU	218	23	9
hsa-miR-4517	AAAUAUGAUGAAACUCACAGCUGAG	507	25	9
hsa-miR-576-3p	AAGAUGUGGAAAAAUUGGAAUC	508	22	9
hsa-miR-1229	CUCUCACCACUGCCCUCCCACAG	509	23	8
hsa-miR-1289	UGGAGUCCAGGAAUCUGCAUUUU	343	23	8
hsa-miR-1915-5p	ACCUUGCCUUGCUGCCCGGGCC	385	22	8
hsa-miR-23b-5p	UGGGUUCCUGGCAUGCUGAUUU	510	22	8
hsa-miR-302a-5p	ACUUAAACGUGGAUGUACUUGCU	511	23	8
hsa-miR-3938	AAUUCCCUUGUAGAUAACCCGG	512	22	8
hsa-miR-4466	GGGUGCGGGCCGGCGGGG	264	18	8
hsa-miR-4786-5p	UGAGACCAGGACUGGAUGCACC	197	22	8
hsa-miR-589-3p	UCAGAACAAAUGCCGGUUCCCAGA	438	24	8
hsa-miR-616-5p	ACUCAAAACCCUUCAGUGACUU	439	22	8
hsa-miR-943	CUGACUGUUGCCGUCCUCCAG	338	21	8
hsa-miR-1237	UCCUUCUGCUCCGUCCCCCAG	370	21	7
hsa-miR-1915-3p	CCCCAGGGCGACGCGGCGGG	384	20	7
hsa-miR-3620	UCACCCUGCAUCCCGCACCCAG	324	22	7
hsa-miR-3691-5p	AGUGGAUGAUGGAGACUCGGUAC	409	23	7
hsa-miR-4426	GAAGAUGGACGUACUUU	359	17	7
hsa-let-7a-2-3p	CUGUACAGCCUCCUAGCUUUCC	513	22	6
hsa-miR-10a-3p	CAAAUUCGUAUCUAGGGGAAUA	514	22	6
hsa-miR-1287	UGCUGGAUCAGUGGUUCGAGUC	515	22	6
hsa-miR-145-5p	GUCCAGUUUUCCCAGGAAUCCCU	516	23	6
hsa-miR-29b-1-5p	GCUGGUUUCAUAUGGUGGUUUAGA	517	24	6
hsa-miR-3128	UCUGGCAAGUAAAAAACUCUCAU	518	23	6
hsa-miR-33b-5p	GUGCAUUGCUGUUGCAUUGC	519	20	6
hsa-miR-3681-5p	UAGUGGAUGAUGCACUCUGUGC	327	22	6
hsa-miR-3685	UUUCCUACCCUACCUGAAGACU	520	22	6
hsa-miR-3918	ACAGGGCCGCAGAUGGAGACU	521	21	6
hsa-miR-551b-5p	GAAAUCAAGCGUGGGUGAGACC	522	22	6
hsa-miR-1273f	GGAGAUGGAGGUUGCAGUG	292	19	5
hsa-miR-1273g-3p	ACCACUGCACUCCAGCCUGAG	210	21	5
hsa-miR-1304-5p	UUUGAGGCUACAGUGAGAUGUG	523	22	5
hsa-miR-1538	CGGCCCGGGCUGCUGCUGUUCCU	524	23	5
hsa-miR-181c-3p	AACCAUCGACCGUUGAGUGGAC	525	22	5
hsa-miR-193a-5p	UGGGUCUUUGCGGGCGAGAUGA	526	22	5
hsa-miR-208b	AUAAGACGAACAAAAGGUUUGU	388	22	5
hsa-miR-219-5p	UGAUUGUCCAAACGCAAUUCU	527	21	5
hsa-miR-3159	UAGGAUUACAAGUGUCGGCCAC	528	22	5

hsa-miR-3173-5p	UGCCCUGCCUGUUUUCUCCUUU	529	22	5
hsa-miR-3175	CGGGGAGAGAACGCAGUGACGU	530	22	5
hsa-miR-3200-5p	AAUCUGAGAAGGCGCACAAGGU	531	22	5
hsa-miR-3662	GAAAAUGAUGAGUAGUGACUGAUG	326	24	5
hsa-miR-3928	GGAGGAACCUUGGAGCUUCGGC	413	22	5
hsa-miR-4709-3p	UUGAAGAGGAGGUGCUCUGUAGC	532	23	5
hsa-miR-4787-3p	GAUGCGCCGCCCACUGCCCCGCGC	533	24	5
hsa-miR-499a-5p	UUAAGACUUGCAGUGAUGUUU	534	21	5
hsa-miR-545-3p	UCAGCAAACAUUUAUUGUGUGC	242	22	5
hsa-miR-548u	CAAAGACUGCAAUUACUUUUGCG	535	23	5
hsa-miR-659-5p	AGGACCUUCCCUGAACCAAGGA	364	22	5
hsa-miR-1257	AGUGAAUGAUGGGUUCUGACC	372	21	4
hsa-miR-1292	UGGGAACGGGUUCCGGCAGACGCUG	536	25	4
hsa-miR-1914-5p	CCCUGUGCCCGGCCCACUUCUG	537	22	4
hsa-miR-195-3p	CCAAUAUUGGCUGUGCUGCUCC	538	22	4
hsa-miR-2110	UUGGGGAAACGGCCGCUGAGUG	389	22	4
hsa-miR-302c-5p	UUUAACAUGGGGGUACCUGCUG	539	22	4
hsa-miR-3126-3p	CAUCUGGCAUCCGUCACACAGA	394	22	4
hsa-miR-3126-5p	UGAGGGACAGAUGCCAGAAGCA	352	22	4
hsa-miR-3150a-5p	CAACCUCGACGAUCUCCUCAGC	540	22	4
hsa-miR-3157-3p	CUGCCCUAGUCUAGCUGAAGCU	399	22	4
hsa-miR-323b-3p	CCCAAUACACGGUCGACCUCUU	541	22	4
hsa-miR-335-3p	UUUUUCAUUAUUGCUCCUGACC	542	22	4
hsa-miR-3607-3p	ACUGUAAACGCUUUCUGAUG	543	20	4
hsa-miR-3653	CUAAGAAGUUGACUGAAG	544	18	4
hsa-miR-3663-3p	UGAGCACCACACAGGCCGGGCGC	545	23	4
hsa-miR-376a-5p	GUAGAUUCUCCUUCUAUGAGUA	410	22	4
hsa-miR-4423-3p	AUAGGCACCAAAAAGCAACAA	662	21	4
hsa-miR-4423-5p	AGUUGCCUUUUUGUUCCCAUGC	263	22	4
hsa-miR-4463	GAGACUGGGGUGGGGCC	300	17	4
hsa-miR-449a	UGGCAGUGUAUUGUUAGCUGGU	547	22	4
hsa-miR-4511	GAAGAACUGUUGCAUUUGCCCU	548	22	4
hsa-miR-4640-3p	CACCCCCUGUUUCCUGGCCCAC	329	22	4
hsa-miR-4800-3p	CAUCCGUCCGUCUGUCCAC	549	19	4
hsa-miR-505-5p	GGGAGCCAGGAAGUAUUGAUGU	550	22	4
hsa-miR-548a-3p	CAAAACUGGCAAUUACUUUUGC	551	22	4
hsa-miR-570-3p	CGAAAACAGCAAUUACCUUUGC	333	22	4
hsa-miR-663a	AGGCGGGGCGCCGCGGGACCGC	365	22	4
hsa-miR-877-3p	UCCUCUUCUCCCUCCUCCCAG	552	21	4
hsa-miR-103a-2-5p	AGCUUCUUUACAGUGCUGCCUUG	553	23	3
hsa-miR-1268b	CGGGCGUGGUGGUGGGGGUG	554	20	3
hsa-miR-1270	CUGGAGAUAUGGAAGAGCUGUGU	555	23	3
hsa-miR-1293	UGGGUGGUCUGGAGAUUUGUGC	556	22	3
hsa-miR-1322	GAUGAUGCUGCUGAUGCUG	557	19	3
hsa-miR-150-5p	UCUCCCAACCCUUGUACCAGUG	558	22	3
hsa-miR-190b	UGAUAUGUUUGAUAUUGGGUU	559	21	3

hsa-miR-193a-3p	AACUGGCCUACAAAGUCCCAGU	386	22	3
hsa-miR-193b-5p	CGGGGUUUUGAGGGCGAGAUGA	560	22	3
hsa-miR-199a-5p	CCCAGUGUUCAGACUACCUGUUC	273	23	3
hsa-miR-20a-3p	ACUGCAUUAUGAGCACUUAAAG	561	22	3
hsa-miR-216a	UAAUCUCAGCUGGCAACUGUGA	562	22	3
hsa-miR-2682-5p	CAGGCAGUGACUGUUCAGACGUC	563	23	3
hsa-miR-2964a-5p	AGAUGUCCAGCCACAAUUCUCG	564	22	3
hsa-miR-3177-5p	UGUGUACACACGUGCCAGGCGCU	565	23	3
hsa-miR-320c	AAAAGCUGGGUUGAGAGGGU	566	20	3
hsa-miR-323a-5p	AGGUGGUCCGUGGCGCGUUCGC	567	22	3
hsa-miR-3622a-5p	CAGGCACGGGAGCUCAGGUGAG	568	22	3
hsa-miR-3912	UAACGCAUAAUAUGGACAUGU	569	21	3
hsa-miR-3934	UCAGGUGUGGAAACUGAGGCAG	570	22	3
hsa-miR-3942-3p	UUUCAGAUAACAGUAUUACAU	414	21	3
hsa-miR-3942-5p	AAGCAAUACUGUUACCUGAAAU	571	22	3
hsa-miR-4523	GACCGAGAGGGCCUCGGCUGU	572	21	3
hsa-miR-4640-5p	UGGGCCAGGGAGCAGCUGGUGGG	573	23	3
hsa-miR-4671-5p	ACCGAAGACUGUGCGCUAAUCU	574	22	3
hsa-miR-4709-5p	ACAACAGUGACUUGCUCUCCAA	575	22	3
hsa-miR-4731-3p	CACACAAGUGGCCCCCAACACU	425	22	3
hsa-miR-4731-5p	UGCUGGGGGCCACAUGAGUGUG	576	22	3
hsa-miR-4762-5p	CCAAAUCUUGAUCAGAAGCCU	577	21	3
hsa-miR-5010-5p	AGGGGGAUGGCAGAGCAAAAUU	578	22	3
hsa-miR-502-5p	AUCCUUGCUAUCUGGGUGCUA	579	21	3
hsa-miR-548d-5p	AAAAGUAAUUGUGGUUUUUGCC	580	22	3
hsa-miR-548i	AAAAGUAAUUGCGGAUUUUGCC	581	22	3
hsa-miR-548j	AAAAGUAAUUGCGGUCUUUGGU	582	22	3
hsa-miR-5587-3p	GCCCCGGGCAGUGUGAUCAUC	284	21	3
hsa-miR-1225-3p	UGAGCCCCUGUGCCGCCCCCAG	369	22	2
hsa-miR-1227	CGUGCCACCCUUUUCCCCAG	583	20	2
hsa-miR-1252	AGAAGGAAAUUGAAUUCAUUUA	371	22	2
hsa-miR-1280	UCCCACCGCUGCCACCC	584	17	2
hsa-miR-1288	UGGACUGCCCUGAUCUGGAGA	585	21	2
hsa-miR-1303	UUUAGAGACGGGGUCUUGCUCU	586	22	2
hsa-miR-1306-3p	ACGUUGGCUCUGGUGGUG	376	18	2
hsa-miR-139-5p	UCUACAGUGCACGUGUCUCCAG	587	22	2
hsa-miR-149-3p	AGGGAGGGACGGGGGCUGUGC	588	21	2
hsa-miR-16-1-3p	CCAGUAUUAACUGUGCUGCUGA	589	22	2
hsa-miR-1909-5p	UGAGUGCCGGUGCCUGCCCUG	590	21	2
hsa-miR-224-5p	CAAGUCACUAGUGGUUCCGUU	591	21	2
hsa-miR-2276	UCUGCAAGUGUCAGAGGCGAGG	592	22	2
hsa-miR-2355-3p	AUUGUCCUUGCUGUUUGGAGAU	468	22	2
hsa-miR-2964a-3p	AGAAUUGCGUUUGGACAAUCAGU	392	23	2
hsa-miR-29c-5p	UGACCGAUUUCUCCUGGUGUUC	594	22	2
hsa-miR-3074-3p	GAUAUCAGCUCAGUAGGCACCG	595	22	2
hsa-miR-3120-3p	CACAGCAAGUGUAGACAGGCA	596	21	2

hsa-miR-3130-5p	UACCCAGUCUCCGGUGCAGCC	396	21	2
hsa-miR-3140-3p	AGCUUUUGGGAAUUCAGGUAGU	597	22	2
hsa-miR-3155a	CCAGGCUCUGCAGUGGGAACU	398	21	2
hsa-miR-3163	UAUAAAAUGAGGGCAGUAAGAC	598	22	2
hsa-miR-3167	AGGAUUUCAGAAAUACUGGUGU	599	22	2
hsa-miR-363-5p	CGGGUGGAUCACGAUGCAAUUU	600	22	2
hsa-miR-3676-3p	CCGUGUUUCCCCCACGCUUU	408	20	2
hsa-miR-378g	ACUGGGCUUGGAGUCAGAAG	411	20	2
hsa-miR-4467	UGGCGGCGGUAGUUAUGGGCUU	360	22	2
hsa-miR-4498	UGGGCUGGCAGGGCAAGUGCUG	601	22	2
hsa-miR-4654	UGUGGGAUCUGGAGGCAUCUGG	420	22	2
hsa-miR-4659a-3p	UUUCUUCUUAGACAUGGCAACG	603	22	2
hsa-miR-4662a-5p	UUAGCCAAUUGUCCAUCUUUAG	604	22	2
hsa-miR-4683	UGGAGAUCCAGUGCUCGCCCGAU	605	23	2
hsa-miR-4738-3p	UGAAACUGGAGCGCCUGGAGGA	606	22	2
hsa-miR-4746-3p	AGCGGUGCUCCUGCGGGCCGA	607	21	2
hsa-miR-4748	GAGGUUUGGGGAGGAUUUGCU	608	21	2
hsa-miR-4792	CGGUGAGCGCUCGCUGGC	363	18	2
hsa-miR-491-5p	AGUGGGGAACCCUUCCAUGAGG	429	22	2
hsa-miR-5000-3p	UCAGGACACUUCUGAACUUGGA	609	22	2
hsa-miR-503	UAGCAGCGGGAACAGUUCUGCAG	610	23	2
hsa-miR-5189	UCUGGGCACAGGCGGAUGGACAGG	611	24	2
hsa-miR-548aq-3p	CAAAAACUGCAAUUACUUUUGC	612	22	2
hsa-miR-548av-3p	AAAACUGCAGUUACUUUUGC	613	20	2
hsa-miR-5584-5p	CAGGGAAAUGGGAAGAACUAGA	332	22	2
hsa-miR-5690	UCAGCUACUACCUCUAUUAGG	435	21	2
hsa-miR-573	CUGAAGUGAUGUGUAACUGAUCAG	305	24	2
hsa-miR-597	UGUGUCACUCGAUGACCACUGU	614	22	2
hsa-miR-622	ACAGUCUGCUGAGGUUGGAGC	615	21	2
hsa-miR-636	UGUGCUUGCUCGUCCCGCCCGCA	616	23	2
hsa-miR-1193	GGGAUGGUAGACCGGUGACGUGC	617	23	1
hsa-miR-1224-3p	CCCCACCUCCUCUCUCCUCAG	618	21	1
hsa-miR-122-5p	UGGAGUGUGACAAUGGUGUUUG	720	22	1
hsa-miR-1228-5p	GUGGGCGGGGGCAGGUGUGUG	620	21	1
hsa-miR-1244	AAGUAGUUGGUUUGUAUGAGAUGGUU	340	26	1
hsa-miR-1247-5p	ACCCGUCCCGUUCGUCCCCGGA	621	22	1
hsa-miR-1255b-5p	CGGAUGAGCAAAGAAAGUGGUU	622	22	1
hsa-miR-1269b	CUGGACUGAGCCAUGCUACUGG	623	22	1
hsa-miR-1272	GAUGAUGAUGGCAGCAAAUUCUGAAA	624	26	1
hsa-miR-1273c	GGCGACAAAACGAGACCCUGUC	625	22	1
hsa-miR-1273e	UUGCUUGAACCCAGGAAGUGGA	342	22	1
hsa-miR-1282	UCGUUUGCCUUUUUCUGCUU	626	20	1
hsa-miR-1290	UGGAUUUUUGGAUCAGGGA	375	19	1
hsa-miR-1294	UGUGAGGUUGGCAUUGUUGUCU	627	22	1
hsa-miR-1306-5p	CCACCUCCCCUGCAAACGUCCA	628	22	1
hsa-miR-1321	CAGGGAGGUGAAUGUGAU	377	18	1

hsa-miR-135a-5p	UAUGGCUUUUUAUUCCUAUGUGA	629	23	1
hsa-miR-137	UUAUUGCUUAAGAAUACGCGUAG	630	23	1
hsa-miR-142-5p	CAUAAAGUAGAAAGCACUACU	631	21	1
hsa-miR-143-5p	GGUGCAGUGCUGCAUCUCUGGU	632	22	1
hsa-miR-15a-3p	CAGGCCAUAUUGUGCUGCCUCA	633	22	1
hsa-miR-186-3p	GCCCAAAGGUGAAUUUUUUGGG	382	22	1
hsa-miR-192-3p	CUGCCAAUUCCAUAGGUCACAG	634	22	1
hsa-miR-19b-1-5p	AGUUUUGCAGGUUUGCAUCCAGC	387	23	1
hsa-miR-200a-3p	UAACACUGUCUGGUAACGAUGU	635	22	1
hsa-miR-204-3p	GCUGGGAAGGCAAAGGGACGU	636	21	1
hsa-miR-214-3p	ACAGCAGGCACAGACAGGCAGU	637	22	1
hsa-miR-29a-5p	ACUGAUUUCUUUUGGUGUUCAG	393	22	1
hsa-miR-3064-5p	UCUGGCUGUUGUGGUGUGCAA	638	21	1
hsa-miR-3116	UGCCUGGAACAUAGUAGGGACU	639	22	1
hsa-miR-3125	UAGAGGAAGCUGUGGAGAGA	640	20	1
hsa-miR-3127-3p	UCCCCUUCUGCAGGCCUGCUGG	641	22	1
hsa-miR-3130-3p	GCUGCACCGGAGACUGGGUAA	395	21	1
hsa-miR-3140-5p	ACCUGAAUUACCAAAAGCUUU	397	21	1
hsa-miR-3157-5p	UUCAGCCAGGCUAGUGCAGUCU	642	22	1
hsa-miR-3179	AGAAGGGGUGAAAUUUAAACGU	643	22	1
hsa-miR-3181	AUCGGGCCCUCGGCGCCGG	644	19	1
hsa-miR-3187-5p	CCUGGGCAGCGUGUGGCUGAAGG	645	23	1
hsa-miR-3190-5p	UCUGGCCAGCUACGUCCCCA	646	20	1
hsa-miR-3198	GUGGAGUCCUGGGGAAUGGAGA	647	22	1
hsa-miR-320b	AAAAGCUGGGUUGAGAGGGCAA	648	22	1
hsa-miR-323b-5p	AGGUUGUCCGUGGUGAGUUCGCA	401	23	1
hsa-miR-3591-5p	UUUAGUGUGAUAAUGGCGUUUGA	649	23	1
hsa-miR-3619-5p	UCAGCAGGCAGGCUGGUGCAGC	650	22	1
hsa-miR-3659	UGAGUGUUGUCUACGAGGGCA	651	21	1
hsa-miR-3674	AUUGUAGAACCUAAGAUUGGCC	652	22	1
hsa-miR-3679-3p	CUUCCCCCCAGUAAUCUUCAUC	653	22	1
hsa-miR-375	UUUGUUCGUUCGGCUCGCGUGA	654	22	1
hsa-miR-378b	ACUGGACUUGGAGGCAGAA	655	19	1
hsa-miR-3908	GAGCAAUGUAGGUAGACUGUUU	656	22	1
hsa-miR-3911	UGUGUGGAUCCUGGAGGAGGCA	657	22	1
hsa-miR-3913-5p	UUUGGGACUGAUCUUGAUGUCU	658	22	1
hsa-miR-3917	GCUCGGACUGAGCAGGUGGG	659	20	1
hsa-miR-3944-3p	UUCGGGCUGGCCUGCUGCUCCGG	660	23	1
hsa-miR-429	UAAUACUGUCUGGUAAAACCGU	661	22	1
hsa-miR-4421	ACCUGUCUGUGGAAAGGAGCUA	718	22	1
hsa-miR-4443	UUGGAGGCGUGGGUUUU	663	17	1
hsa-miR-4459	CCAGGAGGCGGAGGAGGUGGAG	664	22	1
hsa-miR-4473	CUAGUGCUCUCCGUUACAAGUA	665	22	1
hsa-miR-4479	CGCGCGGCCGUGCUCGGAGCAG	666	22	1
hsa-miR-4497	CUCCGGGACGGCUGGGC	232	17	1
hsa-miR-4504	UGUGACAAUAGAGAUGAACAUG	667	22	1

hsa-miR-4520b-3p	UUUGGACAGAAAACACGCAGGU	668	22	1
hsa-miR-452-5p	AACUGUUUGCAGAGGAAACUGA	669	22	1
hsa-miR-4636	AACUCGUGUUCAAAGCCUUUAG	670	22	1
hsa-miR-4659b-3p	UUUCUUCUUAGACAUGGCAGCU	671	22	1
hsa-miR-4664-3p	CUUCCGGUCUGUGAGCCCCGUC	672	22	1
hsa-miR-4665-5p	CUGGGGGACGCGUGAGCGCGAGC	673	23	1
hsa-miR-4666a-5p	AUACAUGUCAGAUUGUAUGCC	674	21	1
hsa-miR-4673	UCCAGGCAGGAGCCGGACUGGA	422	22	1
hsa-miR-4681	AACGGGAAUGCAGGCUGUAUCU	675	22	1
hsa-miR-4682	UCUGAGUUCCUGGAGCCUGGUCU	676	23	1
hsa-miR-4690-5p	GAGCAGGCGAGGCUGGGCUGAA	677	22	1
hsa-miR-4699-5p	AGAAGAUUGCAGAGUAAGUUCC	678	22	1
hsa-miR-4700-3p	CACAGGACUGACUCCUCACCCCAGUG	424	26	1
hsa-miR-4706	AGCGGGGAGGAAGUGGGCGCUGCUU	679	25	1
hsa-miR-4721	UGAGGGCUCCAGGUGACGGUGG	680	22	1
hsa-miR-4728-3p	CAUGCUGACCUCCCUCCUGCCCCAG	681	25	1
hsa-miR-4742-5p	UCAGGCAAAGGGAUAUUUACAGA	682	23	1
hsa-miR-4747-3p	AAGGCCCGGGCUUUCCUCCCAG	683	22	1
hsa-miR-4749-5p	UGCGGGGACAGGCCAGGGCAUC	684	22	1
hsa-miR-4755-3p	AGCCAGGCUCUGAAGGGAAAGU	685	22	1
hsa-miR-4763-5p	CGCCUGCCCAGCCCUCCUGCU	686	21	1
hsa-miR-4766-3p	AUAGCAAUUGCUCUUUUGGAA	687	21	1
hsa-miR-4781-3p	AAUGUUGGAAUCCUCGCUAGAG	688	22	1
hsa-miR-4793-3p	UCUGCACUGUGAGUUGGCUGGCU	689	23	1
hsa-miR-488-3p	UUGAAAGGCUAUUUCUUGGUC	690	21	1
hsa-miR-4999-5p	UGCUGUAUUGUCAGGUAGUGA	691	21	1
hsa-miR-5001-5p	AGGGCUGGACUCAGCGGCGGAGCU	692	24	1
hsa-miR-5002-5p	AAUUUGGUUUCUGAGGCACUUAGU	693	24	1
hsa-miR-5004-5p	UGAGGACAGGGCAAAUUCACGA	694	22	1
hsa-miR-5006-3p	UUUCCCUUUCCAUCCUGGCAG	695	21	1
hsa-miR-5088	CAGGGCUCAGGGAUUGGAUGGAG	696	23	1
hsa-miR-544a	AUUCUGCAUUUUUAGCAAGUUC	697	22	1
hsa-miR-548al	AACGGCAAUGACUUUUGUACCA	698	22	1
hsa-miR-548aq-5p	GAAAGUAAUUGCUGUUUUUGCC	699	22	1
hsa-miR-548at-5p	AAAAGUUAUUGCGGUUUUGGCU	700	22	1
hsa-miR-548au-5p	AAAAGUAAUUGCGGUUUUUGC	701	21	1
hsa-miR-548b-3p	CAAGAACCUCAGUUGCUUUUGU	702	22	1
hsa-miR-556-3p	AUAUUACCAUUAGCUCAUCUUU	703	22	1
hsa-miR-5582-3p	UAAAACUUUAAGUGUGCCUAGG	704	22	1
hsa-miR-5586-3p	CAGAGUGACAAGCUGGUUAAAG	705	22	1
hsa-miR-5588-5p	ACUGGCAUUAGUGGGACUUUU	706	21	1
hsa-miR-5683	UACAGAUGCAGAUUCUCUGACUUC	707	24	1
hsa-miR-5696	CUCAUUUAAGUAGUCUGAUGCC	708	22	1
hsa-miR-5701	UUAUUGUCACGUUCUGAUU	709	19	1
hsa-miR-5706	UUCUGGAUAACAUGCUGAAGCU	710	22	1
hsa-miR-592	UUGUGUCAAUAUGCGAUGAUGU	711	22	1

hsa-miR-603	CACACACUGCAAUUACUUUUGC	712	22	1
hsa-miR-624-3p	CACAAGGUAUUGGUAUUACCU	713	21	1
hsa-miR-885-5p	UCCAUUACACUACCCUGCCUCU	714	22	1
hsa-miR-933	UGUGCGCAGGGAGACCUCUCCC	715	22	1

Table 6: Microvesicles EI

MICROVESICLES CTX0E0307EI				
MIRNA	MIRNA.SEQUENCE	SEQ ID NO:	MIRNA LENGTH	READ COUNTS
hsa-miR-1246	AAUGGAUUUUUGGAGCAGG	21	19	32723
hsa-miR-4492	GGGGCUGGGCGCGCGCC	34	17	16225
hsa-miR-4488	AGGGGGCGGGCUCCGGCG	61	18	12878
hsa-miR-4532	CCCCGGGGAGCCCGGCG	23	17	6746
hsa-miR-4508	GCGGGGCUGGGCGCGCG	135	17	531
hsa-miR-4516	GGGAGAAGGGUCGGGGC	110	17	500
hsa-miR-3676-5p	AGGAGAUCCUGGGUU	280	15	357
hsa-miR-4485	UAACGGCCGCGGUACCCUAA	67	20	44
hsa-miR-4497	CUCCGGGACGGCUGGGC	232	17	43
hsa-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA	9	22	33
hsa-miR-3195	CGCGCCGGGCCCGGGUU	716	17	28
hsa-miR-3648	AGCCGCGGGGAUCGCCGAGGG	259	21	26
hsa-miR-663b	GGUGGCCCGGCCGUGCCUGAGG	180	22	24
hsa-miR-3656	GGCGGGUGCGGGGGUGG	251	17	19
hsa-miR-3687	CCCGGACAGGCGUUCGUGCGACGU	190	24	19
hsa-miR-4466	GGGUGCGGGCCGGCGGGG	264	18	19
hsa-miR-4792	CGGUGAGCGCUCGCUGGC	363	18	19
hsa-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	4	22	18
hsa-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	1	22	15
hsa-miR-1290	UGGAUUUUUGGAUCAGGGA	375	19	7
hsa-miR-1291	UGGCCCUGACUGAAGACCAGCAGU	294	24	7
hsa-miR-182-5p	UUUGGCAAUGGUAGAACUCACACU	16	24	7
hsa-miR-5096	GUUUCACCAUGUUGGUCAGGC	220	21	7
hsa-miR-1273f	GGAGAUGGAGGUUGCAGUG	292	19	5
hsa-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	12	22	5
hsa-miR-4284	GGGCUCACAUCACCCCAU	191	18	5
hsa-miR-92b-3p	UAUUGCACUCGUCCCGGCCUCC	13	22	5
hsa-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	28	22	4
hsa-let-7c	UGAGGUAGUAGGUUGUAUGGUU	17	22	4
hsa-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	11	22	4
hsa-miR-100-5p	AACCCGUAGAUCCGAACUUGUG	3	22	4
hsa-miR-1248	ACCUUCUUGUAUAAGCACUGUGCUAAA	269	27	4
hsa-miR-1973	ACCGUGCAAAGGUAGCAUA	171	19	4
hsa-miR-21-3p	CAACACCAGUCGAUGGGCUGU	20	21	4
hsa-miR-3654	GACUGGACAAGCUGAGGAA	325	19	4
hsa-miR-92a-3p	UAUUGCACUUGUCCCGGCCUGU	7	22	4

hsa-miR-1273g-3p	ACCACUGCACUCCAGCCUGAG	210	21	3
hsa-miR-23b-3p	AUCACAUUGCCAGGGAUUACC	59	21	3
hsa-miR-3609	CAAAGUGAUGAGUAAUACUGGCUG	216	24	3
hsa-miR-3615	UCUCUCGGCUCCUCGCGGCUC	323	21	3
hsa-miR-3653	CUAAGAAGUUGACUGAAG	544	18	3
hsa-miR-3960	GGCGGCGGCGGAGGCGGGGG	416	20	3
hsa-miR-4448	GGCUCCUUGGUCUAGGGGUA	231	20	3
hsa-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	92	22	2
hsa-miR-16-5p	UAGCAGCACGUAAAUAUUGGCG	29	22	2
hsa-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	15	23	2
hsa-miR-181b-5p	AACAUUCAUUGCUGUCGGUGGGU	38	23	2
hsa-miR-222-3p	AGCUACAUCUGGCUACUGGGU	36	21	2
hsa-miR-24-3p	UGGCUCAGUUCAGCAGGAACAG	119	22	2
hsa-miR-3196	CGGGGCGGCAGGGGCCUC	717	18	2
hsa-miR-4419b	GAGGCUGAAGGAAGAUGG	718	18	2
hsa-miR-4461	GAUUGAGACUAGUAGGGCUAGGC	129	23	2
hsa-miR-4486	GCUGGGCGAGGCUGGCA	719	17	2
hsa-miR-663a	AGGCGGGGCGCCGCGGGACCGC	365	22	2
hsa-miR-9-5p	UCUUUGGUUAUCUAGCUGUAUGA	58	23	2
hsa-let-7i-3p	CUGCGCAAGCUACUGCCUUGCU	483	22	1
hsa-let-7i-5p	UGAGGUAGUAGUUUGUGCUGUU	22	22	1
hsa-miR-1225-5p	GUGGGUACGGCCCAGUGGGGGG	720	22	1
hsa-miR-1244	AAGUAGUUGGUUUGUAUGAGAUGGUU	340	26	1
hsa-miR-125b-5p	UCCCUGAGACCCUAACUUGUGA	42	22	1
hsa-miR-1275	GUGGGGGAGAGGCUGUC	162	17	1
hsa-miR-1280	UCCCACCGCUGCCACCC	584	17	1
hsa-miR-134	UGUGACUGGUUGACCAGAGGGG	94	22	1
hsa-miR-149-5p	UCUGGCUCCGUGUCUUCACUCCC	121	23	1
hsa-miR-191-5p	CAACGGAAUCCCAAAAGCAGCUG	8	23	1
hsa-miR-221-3p	AGCUACAUUGUCUGCUGGGUUUC	79	23	1
hsa-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	33	22	1
hsa-miR-26b-5p	UUCAAGUAAUUCAGGAUAGGU	90	21	1
hsa-miR-30c-5p	UGUAAACAUCCUACACUCUCAGC	66	23	1
hsa-miR-30d-5p	UGUAAACAUCCCCGACUGGAAG	31	22	1
hsa-miR-3182	GCUUCUGUAGUGUAGUC	721	17	1
hsa-miR-320a	AAAAGCUGGGUUGAGAGGGCGA	97	22	1
hsa-miR-34a-5p	UGGCAGUGUCUUAGCUGGUUGU	101	22	1
hsa-miR-3607-3p	ACUGUAAACGCUUUCUGAUG	543	20	1
hsa-miR-361-5p	UUAUCAGAAUCUCCAGGGGUAC	70	22	1
hsa-miR-3652	CGGCUGGAGGUGUGAGGA	722	18	1
hsa-miR-409-3p	GAAUGUUGCUCGGUGAACCCCU	47	22	1
hsa-miR-423-3p	AGCUCGGUCUGAGGCCCCUCAGU	57	23	1
hsa-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUU	41	23	1
hsa-miR-432-5p	UCUUGGAGUAGGUCAUUGGGUGG	95	23	1
hsa-miR-4417	GGUGGGCUUCCCGGAGGG	175	18	1
hsa-miR-4426	GAAGAUGGACGUACUUU	359	17	1

hsa-miR-4449	CGUCCCGGGGCUGCGCGAGGCA	155	22	1
hsa-miR-4800-3p	CAUCCGUCCGUCUGUCCAC	549	19	1
hsa-miR-484	UCAGGCUCAGUCCCCUCCCGAU	118	22	1
hsa-miR-486-5p	UCCUGUACUGAGCUGCCCCGAG	5	22	1
hsa-miR-493-3p	UGAAGGUCUACUGUGUGCCAGG	83	22	1
hsa-miR-5095	UUACAGGCGUGAACCACCGCG	723	21	1
hsa-miR-556-3p	AUAUUACCAUUAGCUCAUCUUU	703	22	1
hsa-miR-644b-5p	UGGGCUAAGGGAGAUGAUUGGGUA	724	24	1
hsa-miR-664-5p	ACUGGCUAGGGAAAAUGAUUGGAU	443	24	1
hsa-miR-760	CGGCUCUGGGUCUGUGGGGA	289	20	1
hsa-miR-941	CACCCGGCUGUGUGCACAUGUGC	60	23	1
hsa-miR-98	UGAGGUAGUAAGUUGUAUUGUU	10	22	1
hsa-miR-99a-5p	AACCCGUAGAUCCGAUCUUGUG	52	22	1

Table 7: Exosomes EI

EXOSOMES CTX0E0307EI				
MIRNA	MIRNA.SEQUENCE	SEQ ID NO:	MIRNA LENGTH	READ COUNTS
hsa-miR-1246	AAUGGAUUUUUGGAGCAGG	21	19	83958
hsa-miR-4492	GGGGCUGGGCGCGCGCC	34	17	22482
hsa-miR-4488	AGGGGGCGGGCUCCGGCG	61	18	20618
hsa-miR-4532	CCCCGGGGAGCCCGGCG	23	17	6419
hsa-miR-4516	GGGAGAAGGGUCGGGGC	110	17	904
hsa-miR-4508	GCGGGGCUGGGCGCGCG	135	17	723
hsa-miR-3676-5p	AGGAGAUCCUGGGUU	280	15	174
hsa-miR-4485	UAACGGCCGCGGUACCCUAA	67	20	43
hsa-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA	9	22	41
hsa-miR-4497	CUCCGGGACGGCUGGGC	232	17	28
hsa-miR-663b	GGUGGCCCGGCCGUGCCUGAGG	180	22	26
hsa-miR-4792	CGGUGAGCGCUCGCUGGC	363	18	24
hsa-miR-4454	GGAUCCGAGUCACGGCACCA	299	20	22
hsa-miR-1291	UGGCCCUGACUGAAGACCAGCAGU	294	24	17
hsa-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	12	22	17
hsa-miR-3195	CGCGCCGGGCCCGGGUU	716	17	17
hsa-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	1	22	15
hsa-miR-182-5p	UUUGGCAAUGGUAGAACUCACACU	16	24	15
hsa-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	4	22	15
hsa-miR-5096	GUUUCACCAUGUUGGUCAGGC	220	21	14
hsa-miR-3648	AGCCGCGGGGAUCGCCGAGGG	259	21	13
hsa-miR-3654	GACUGGACAAGCUGAGGAA	325	19	13
hsa-miR-4466	GGGUGCGGGCCGGCGGGG	264	18	12
hsa-miR-3687	CCCGGACAGGCGUUCGUGCGACGU	190	24	11
hsa-miR-4284	GGGCUCACAUCACCCCAU	191	18	11
hsa-miR-3656	GGCGGGUGCGGGGGUGG	251	17	10
hsa-miR-3609	CAAAGUGAUGAGUAAUACUGGCUG	216	24	8

hsa-miR-644b-5p	UGGGCUAAGGGAGAUGAUUGGGUA	724	24	8
hsa-miR-664-5p	ACUGGCUAGGGAAAAUGAUUGGAU	443	24	8
hsa-miR-92a-3p	UAUUGCACUUGUCCCGGCCUGU	7	22	7
hsa-miR-92b-3p	UAUUGCACUCGUCCCGGCCUCC	13	22	7
hsa-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	28	22	6
hsa-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	11	22	6
hsa-miR-127-3p	UCGGAUCCGUCUGAGCUUGGCU	14	22	6
hsa-miR-1290	UGGAUUUUUGGAUCAGGGA	375	19	6
hsa-miR-4449	CGUCCCGGGGCUGCGCGAGGCA	155	22	6
hsa-miR-4461	GAUUGAGACUAGUAGGGCUAGGC	129	23	6
hsa-miR-100-5p	AACCCGUAGAUCCGAACUUGUG	3	22	5
hsa-miR-1248	ACCUUCUUGUAUAAGCACUGUGCUAAA	269	27	5
hsa-miR-1973	ACCGUGCAAAGGUAGCAUA	171	19	5
hsa-miR-3653	CUAAGAAGUUGACUGAAG	544	18	5
hsa-miR-4417	GGUGGGCUUCCCGGAGGG	175	18	5
hsa-miR-125b-5p	UCCCUGAGACCCUAACUUGUGA	42	22	4
hsa-miR-151a-3p	CUAGACUGAAGCUCCUUGAGG	25	21	4
hsa-miR-16-5p	UAGCAGCACGUAAAUAUUGGCG	29	22	4
hsa-miR-21-3p	CAACACCAGUCGAUGGGCUGU	20	21	4
hsa-miR-23a-3p	AUCACAUUGCCAGGGAUUUCC	55	21	4
hsa-miR-4419b	GAGGCUGAAGGAAGAUGG	718	18	4
hsa-miR-1273f	GGAGAUGGAGGUUGCAGUG	292	19	3
hsa-miR-1273g-3p	ACCACUGCACUCCAGCCUGAG	210	21	3
hsa-miR-181b-5p	AACAUUCAUUGCUGUCGGUGGGU	38	23	3
hsa-miR-221-3p	AGCUACAUUGUCUGCUGGGUUUC	79	23	3
hsa-miR-3615	UCUCUCGGCUCCUCGCGGCUC	323	21	3
hsa-miR-9-5p	UCUUUGGUUAUCUAGCUGUAUGA	58	23	3
hsa-let-7c	UGAGGUAGUAGGUUGUAUGGUU	17	22	2
hsa-let-7e-5p	UGAGGUAGGAGGUUGUAUAGUU	27	22	2
hsa-let-7i-5p	UGAGGUAGUAGUUUGUGCUGUU	22	22	2
hsa-miR-103a-3p	AGCAGCAUUGUACAGGGCUAUGA	62	23	2
hsa-miR-106b-5p	UAAAGUGCUGACAGUGCAGAU	170	21	2
hsa-miR-1273e	UUGCUUGAACCCAGGAAGUGGA	342	22	2
hsa-miR-221-5p	ACCUGGCAUACAAUGUAGAUUU	39	22	2
hsa-miR-222-3p	AGCUACAUCUGGCUACUGGGU	36	21	2
hsa-miR-30d-5p	UGUAAACAUCCCCGACUGGAAG	31	22	2
hsa-miR-3960	GGCGGCGGCGGAGGCGGGGG	416	20	2
hsa-let-7d-3p	CUAUACGACCUGCUGCCUUUCU	92	22	1
hsa-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	53	22	1
hsa-let-7g-5p	UGAGGUAGUAGUUUGUACAGUU	43	22	1
hsa-let-7i-3p	CUGCGCAAGCUACUGCCUUGCU	483	22	1
hsa-miR-10a-5p	UACCCUGUAGAUCCGAAUUUGUG	2	23	1
hsa-miR-1181	CCGUCGCCGCCACCCGAGCCG	725	21	1
hsa-miR-1225-3p	UGAGCCCCUGUGCCGCCCCCAG	369	22	1
hsa-miR-1244	AAGUAGUUGGUUUGUAUGAGAUGGUU	340	26	1
hsa-miR-125a-5p	UCCCUGAGACCCUUUAACCUGUGA	35	24	1

hsa-miR-1296	UUAGGGCCCUGGCUCCAUCUCC	271	22	1
hsa-miR-1307-5p	UCGACCGGACCUCGACCGGCU	91	21	1
hsa-miR-146b-5p	UGAGAACUGAAUUCCAUAGGCU	19	22	1
hsa-miR-149-5p	UCUGGCUCCGUGUCUUCACUCCC	121	23	1
hsa-miR-151a-5p	UCGAGGAGCUCACAGUCUAGU	37	21	1
hsa-miR-15b-5p	UAGCAGCACAUCAUGGUUUACA	78	22	1
hsa-miR-181a-2-3p	ACCACUGACCGUUGACUGUACC	102	22	1
hsa-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	15	23	1
hsa-miR-191-5p	CAACGGAAUCCCAAAAGCAGCUG	8	23	1
hsa-miR-198	GGUCCAGAGGGGAGAUAGGUUC	726	22	1
hsa-miR-204-5p	UUCCCUUUGUCAUCCUAUGCCU	89	22	1
hsa-miR-20a-5p	UAAAGUGCUUAUAGUGCAGGUAG	146	23	1
hsa-miR-219-5p	UGAUUGUCCAAACGCAAUUCU	527	21	1
hsa-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	33	22	1
hsa-miR-23b-3p	AUCACAUUGCCAGGGAUUACC	59	21	1
hsa-miR-26b-3p	CCUGUUCUCCAUUACUUGGCUC	391	22	1
hsa-miR-299-5p	UGGUUUACCGUCCCACAUACAU	319	22	1
hsa-miR-29a-3p	UAGCACCAUCUGAAAUCGGUUA	106	22	1
hsa-miR-30e-3p	CUUUCAGUCGGAUGUUUACAGC	71	22	1
hsa-miR-31-3p	UGCUAUGCCAACAUAUUGCCAU	172	22	1
hsa-miR-3198	GUGGAGUCCUGGGGAAUGGAGA	647	22	1
hsa-miR-323a-3p	CACAUUACACGGUCGACCUCU	158	21	1
hsa-miR-342-3p	UCUCACACAGAAAUCGCACCCGU	81	23	1
hsa-miR-3607-3p	ACUGUAAACGCUUUCUGAUG	543	20	1
hsa-miR-3651	CAUAGCCCGGUCGCUGGUACAUGA	727	24	1
hsa-miR-378a-3p	ACUGGACUUGGAGUCAGAAGG	65	21	1
hsa-miR-379-5p	UGGUAGACUAUGGAACGUAGG	18	21	1
hsa-miR-423-3p	AGCUCGGUCUGAGGCCCCUCAGU	57	23	1
hsa-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUU	41	23	1
hsa-miR-425-5p	AAUGACACGAUCACUCCCGUUGA	111	23	1
hsa-miR-4258	CCCCGCCACCGCCUUGG	728	17	1
hsa-miR-4426	GAAGAUGGACGUACUUU	359	17	1
hsa-miR-4443	UUGGAGGCGUGGGUUUU	663	17	1
hsa-miR-4448	GGCUCCUUGGUCUAGGGGUA	231	20	1
hsa-miR-4697-3p	UGUCAGUGACUCCUGCCCCUUGGU	729	24	1
hsa-miR-4700-3p	CACAGGACUGACUCCUCACCCCAGUG	424	26	1
hsa-miR-4700-5p	UCUGGGGAUGAGGACAGUGUGU	730	22	1
hsa-miR-4797-3p	UCUCAGUAAGUGGCACUCUGU	731	21	1
hsa-miR-484	UCAGGCUCAGUCCCCUCCCGAU	118	22	1
hsa-miR-486-5p	UCCUGUACUGAGCUGCCCCGAG	5	22	1
hsa-miR-494	UGAAACAUACACGGGAAACCUC	240	22	1
hsa-miR-500a-5p	UAAUCCUUGCUACCUGGGUGAGA	303	23	1
hsa-miR-644b-3p	UUCAUUUGCCUCCCAGCCUACA	442	22	1
hsa-miR-663a	AGGCGGGGCGCCGCGGGACCGC	365	22	1

Table 8: Microvesicles EH

MICROVESICLES CTX0E03 07EH				
MIRNA	MIRNA.SEQUENCE	SEQ ID NO:	MIRNA LENGTH	READ COUNTS
hsa-miR-1246	AAUGGAUUUUUGGAGCAGG	21	19	78791
hsa-miR-4492	GGGGCUGGGCGCGCGCC	34	17	6012
hsa-miR-4532	CCCCGGGGAGCCCGGCG	23	17	3410
hsa-miR-4488	AGGGGGCGGGCUCCGGCG	61	18	1737
hsa-miR-4485	UAACGGCCGCGGUACCCUAA	67	20	319
hsa-miR-4508	GCGGGGCUGGGCGCGCG	135	17	221
hsa-miR-4516	GGGAGAAGGGUCGGGGC	110	17	114
hsa-miR-4466	GGGUGCGGGCCGGCGGGG	264	18	61
hsa-miR-4497	CUCCGGGACGGCUGGGC	232	17	51
hsa-miR-3195	CGCGCCGGGCCCGGGUU	716	17	41
hsa-miR-1973	ACCGUGCAAAGGUAGCAUA	171	19	30
hsa-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA	9	22	22
hsa-miR-4284	GGGCUCACAUCACCCCAU	191	18	20
hsa-miR-4792	CGGUGAGCGCUCGCUGGC	363	18	12
hsa-miR-92a-3p	UAUUGCACUUGUCCCGGCCUGU	7	22	12
hsa-miR-1291	UGGCCCUGACUGAAGACCAGCAGU	294	24	11
hsa-miR-3676-5p	AGGAGAUCCUGGGUU	280	15	10
hsa-miR-100-5p	AACCCGUAGAUCCGAACUUGUG	3	22	8
hsa-miR-3656	GGCGGGUGCGGGGGUGG	251	17	8
hsa-miR-663b	GGUGGCCCGGCCGUGCCUGAGG	180	22	8
hsa-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	1	22	7
hsa-miR-1290	UGGAUUUUUGGAUCAGGGA	375	19	7
hsa-miR-3687	CCCGGACAGGCGUUCGUGCGACGU	190	24	7
hsa-miR-4461	GAUUGAGACUAGUAGGGCUAGGC	52	23	6
hsa-miR-664-5p	ACUGGCUAGGGAAAAUGAUUGGAU	91	24	6
hsa-miR-92b-3p	UAUUGCACUCGUCCCGGCCUCC	13	22	6
hsa-miR-125b-5p	UCCCUGAGACCCUAACUUGUGA	42	22	5
hsa-miR-3653	CUAAGAAGUUGACUGAAG	544	18	5
hsa-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	11	22	4
hsa-miR-16-5p	UAGCAGCACGUAAAUAUUGGCG	29	22	4
hsa-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	15	23	4
hsa-miR-3609	CAAAGUGAUGAGUAAUACUGGCUG	216	24	4
hsa-miR-9-5p	UCUUUGGUUAUCUAGCUGUAUGA	58	23	4
hsa-let-7c	UGAGGUAGUAGGUUGUAUGGUU	17	22	3
hsa-miR-1244	AAGUAGUUGGUUUGUAUGAGAUGGUU	59	26	3
hsa-miR-127-3p	UCGGAUCCGUCUGAGCUUGGCU	14	22	3
hsa-miR-181b-5p	AACAUUCAUUGCUGUCGGUGGGU	38	23	3
hsa-miR-21-3p	CAACACCAGUCGAUGGGCUGU	20	21	3
hsa-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	12	22	3
hsa-miR-30c-5p	UGUAAACAUCCUACACUCUCAGC	66	23	3

hsa-miR-3960	GGCGGCGGCGGAGGCGGGGG	416	20	3
hsa-miR-485-3p	GUCAUACACGGCUCUCCUCUCU	153	22	3
hsa-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	28	22	2
hsa-let-7g-5p	UGAGGUAGUAGUUUGUACAGUU	43	22	2
hsa-miR-1273f	GGAGAUGGAGGUUGCAGUG	292	19	2
hsa-miR-151a-3p	CUAGACUGAAGCUCCUUGAGG	25	21	2
hsa-miR-182-5p	UUUGGCAAUGGUAGAACUCACACU	16	24	2
hsa-miR-191-5p	CAACGGAAUCCCAAAAGCAGCUG	8	23	2
hsa-miR-197-3p	UUCACCACCUUCUCCACCCAGC	122	22	2
hsa-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUU	41	23	2
hsa-miR-4468	AGAGCAGAAGGAUGAGAU	732	18	2
hsa-miR-644b-5p	UGGGCUAAGGGAGAUGAUUGGGUA	724	24	2
hsa-miR-93-5p	CAAAGUGCUGUUCGUGCAGGUAG	116	23	2
hsa-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	92	22	1
hsa-miR-1225-3p	UGAGCCCCUGUGCCGCCCCCAG	369	22	1
hsa-miR-1254	AGCCUGGAAGCUGGAGCCUGCAGU	270	24	1
hsa-miR-1273g-3p	ACCACUGCACUCCAGCCUGAG	210	21	1
hsa-miR-1275	GUGGGGGAGAGGCUGUC	162	17	1
hsa-miR-1296	UUAGGGCCCUGGCUCCAUCUCC	271	22	1
hsa-miR-1307-5p	UCGACCGGACCUCGACCGGCU	91	21	1
hsa-miR-134	UGUGACUGGUUGACCAGAGGGG	94	22	1
hsa-miR-15b-5p	UAGCAGCACAUCAUGGUUUACA	78	22	1
hsa-miR-17-5p	CAAAGUGCUUACAGUGCAGGUAG	145	23	1
hsa-miR-1972	UCAGGCCAGGCACAGUGGCUCA	733	22	1
hsa-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	33	22	1
hsa-miR-25-3p	CAUUGCACUUGUCUCGGUCUGA	63	22	1
hsa-miR-27b-3p	UUCACAGUGGCUAAGUUCUGC	6	21	1
hsa-miR-3065-5p	UCAACAAAAUCACUGAUGCUGGA	226	23	1
hsa-miR-30d-5p	UGUAAACAUCCCCGACUGGAAG	31	22	1
hsa-miR-320a	AAAAGCUGGGUUGAGAGGGCGA	97	22	1
hsa-miR-342-3p	UCUCACACAGAAAUCGCACCCGU	81	23	1
hsa-miR-3648	AGCCGCGGGGAUCGCCGAGGG	259	21	1
hsa-miR-3652	CGGCUGGAGGUGUGAGGA	722	18	1
hsa-miR-376c	AACAUAGAGGAAAUUCCACGU	185	21	1
hsa-miR-378a-3p	ACUGGACUUGGAGUCAGAAGG	65	21	1
hsa-miR-409-3p	GAAUGUUGCUCGGUGAACCCCU	47	22	1
hsa-miR-433	AUCAUGAUGGGCUCCUCGGUGU	174	22	1
hsa-miR-4417	GGUGGGCUUCCCGGAGGG	175	18	1
hsa-miR-4448	GGCUCCUUGGUCUAGGGGUA	231	20	1
hsa-miR-4454	GGAUCCGAGUCACGGCACCA	299	20	1
hsa-miR-454-3p	UAGUGCAAUAUUGCUUAUAGGGU	169	23	1
hsa-miR-4800-3p	CAUCCGUCCGUCUGUCCAC	549	19	1
hsa-miR-493-3p	UGAAGGUCUACUGUGUGCCAGG	83	22	1
hsa-miR-5095	UUACAGGCGUGAACCACCGCG	723	21	1
hsa-miR-574-3p	CACGCUCAUGCACACACCCACA	253	22	1
hsa-miR-665	ACCAGGAGGCUGAGGCCCCU	309	20	1

hsa-miR-720	UCUCGCUGGGGCCUCCA	84	17	1
hsa-miR-99a-5p	AACCCGUAGAUCCGAUCUUGUG	52	22	1
hsa-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	4	22	1

Table 9: Exosomes EH

EXOSOMES CTX0E03 07EH				
MIRNA	MIRNA.SEQUENCE	SEQ ID NO:	MIRNA LENGTH	READ COUNTS
hsa-miR-1246	AAUGGAUUUUUGGAGCAGG	21	19	111092
hsa-miR-4492	GGGGCUGGGCGCGCGCC	34	17	5188
hsa-miR-4532	CCCCGGGGAGCCCGGCG	23	17	3368
hsa-miR-4488	AGGGGGCGGGCUCCGGCG	61	18	1389
hsa-miR-4485	UAACGGCCGCGGUACCCUAA	67	20	386
hsa-miR-4508	GCGGGGCUGGGCGCGCG	135	17	188
hsa-miR-4516	GGGAGAAGGGUCGGGGC	110	17	135
hsa-miR-4497	CUCCGGGACGGCUGGGC	232	17	73
hsa-miR-1973	ACCGUGCAAAGGUAGCAUA	171	19	50
hsa-miR-3195	CGCGCCGGGCCCGGGUU	716	17	48
hsa-miR-4466	GGGUGCGGGCCGGCGGGG	264	18	43
hsa-let-7a-5p	UGAGGUAGUAGGUUGUAUAGUU	1	22	20
hsa-miR-99b-5p	CACCCGUAGAACCGACCUUGCG	4	22	19
hsa-miR-21-5p	UAGCUUAUCAGACUGAUGUUGA	9	22	18
hsa-miR-92a-3p	UAUUGCACUUGUCCCGGCCUGU	7	22	18
hsa-miR-3676-5p	AGGAGAUCCUGGGUU	280	15	17
hsa-miR-4792	CGGUGAGCGCUCGCUGGC	363	18	15
hsa-miR-664-5p	ACUGGCUAGGGAAAAUGAUUGGAU	443	24	13
hsa-miR-100-5p	AACCCGUAGAUCCGAACUUGUG	3	22	11
hsa-miR-1291	UGGCCCUGACUGAAGACCAGCAGU	294	24	10
hsa-miR-16-5p	UAGCAGCACGUAAAUAUUGGCG	29	22	10
hsa-miR-4284	GGGCUCACAUCACCCCAU	191	18	10
hsa-miR-663b	GGUGGCCCGGCCGUGCCUGAGG	180	22	9
hsa-miR-25-3p	CAUUGCACUUGUCUCGGUCUGA	63	22	8
hsa-miR-3656	GGCGGGUGCGGGGGUGG	251	17	8
hsa-miR-181a-5p	AACAUUCAACGCUGUCGGUGAGU	15	23	7
hsa-miR-26a-5p	UUCAAGUAAUCCAGGAUAGGCU	12	22	6
hsa-miR-3654	GACUGGACAAGCUGAGGAA	325	19	6
hsa-miR-644b-5p	UGGGCUAAGGGAGAUGAUUGGGUA	724	24	6
hsa-let-7b-5p	UGAGGUAGUAGGUUGUGUGGUU	28	22	5
hsa-let-7f-5p	UGAGGUAGUAGAUUGUAUAGUU	11	22	5
hsa-miR-1290	UGGAUUUUUGGAUCAGGGA	375	19	5
hsa-miR-4426	GAAGAUGGACGUACUUU	359	17	5
hsa-miR-5096	GUUUCACCAUGUUGGUCAGGC	220	21	5
hsa-miR-125b-5p	UCCCUGAGACCCUAACUUGUGA	42	22	4
hsa-miR-1273f	GGAGAUGGAGGUUGCAGUG	292	19	4
hsa-miR-191-5p	CAACGGAAUCCCAAAAGCAGCUG	8	23	4

hsa-miR-22-3p	AAGCUGCCAGUUGAAGAACUGU	33	22	4
hsa-miR-3609	CAAAGUGAUGAGUAAUACUGGCUG	216	24	4
hsa-miR-3687	CCCGGACAGGCGUUCGUGCGACGU	190	24	4
hsa-miR-93-5p	CAAAGUGCUGUUCGUGCAGGUAG	116	23	4
hsa-miR-1248	ACCUUCUUGUAUAAGCACUGUGCUAAA	269	27	3
hsa-miR-1273g-3p	ACCACUGCACUCCAGCCUGAG	210	21	3
hsa-miR-151a-3p	CUAGACUGAAGCUCCUUGAGG	25	21	3
hsa-miR-182-5p	UUUGGCAAUGGUAGAACUCACACU	16	24	3
hsa-miR-221-3p	AGCUACAUUGUCUGCUGGGUUUC	79	23	3
hsa-miR-222-3p	AGCUACAUCUGGCUACUGGGU	36	21	3
hsa-miR-29a-3p	UAGCACCAUCUGAAAUCGGUUA	106	22	3
hsa-miR-4461	GAUUGAGACUAGUAGGGCUAGGC	129	23	3
hsa-miR-486-5p	UCCUGUACUGAGCUGCCCCGAG	5	22	3
hsa-miR-92b-3p	UAUUGCACUCGUCCCGGCCUCC	13	22	3
hsa-miR-9-5p	UCUUUGGUUAUCUAGCUGUAUGA	58	23	3
hsa-miR-98	UGAGGUAGUAAGUUGUAUUGUU	10	22	3
hsa-let-7d-5p	AGAGGUAGUAGGUUGCAUAGUU	53	22	2
hsa-miR-134	UGUGACUGGUUGACCAGAGGGG	94	22	2
hsa-miR-151a-5p	UCGAGGAGCUCACAGUCUAGU	37	21	2
hsa-miR-15b-5p	UAGCAGCACAUCAUGGUUUACA	78	22	2
hsa-miR-30a-5p	UGUAAACAUCCUCGACUGGAAG	30	22	2
hsa-miR-3124-3p	ACUUUCCUCACUCCCGUGAAGU	734	22	2
hsa-miR-3653	CUAAGAAGUUGACUGAAG	544	18	2
hsa-let-7c	UGAGGUAGUAGGUUGUAUGGUU	17	22	1
hsa-let-7d-3p	CUAUACGACCUGCUGCCUUUCU	92	22	1
hsa-let-7g-5p	UGAGGUAGUAGUUUGUACAGUU	43	22	1
hsa-let-7i-5p	UGAGGUAGUAGUUUGUGCUGUU	22	22	1
hsa-miR-103a-3p	AGCAGCAUUGUACAGGGCUAUGA	62	23	1
hsa-miR-106b-5p	UAAAGUGCUGACAGUGCAGAU	170	21	1
hsa-miR-1244	AAGUAGUUGGUUUGUAUGAGAUGGUU	340	26	1
hsa-miR-128	UCACAGUGAACCGGUCUCUUU	109	21	1
hsa-miR-1285-3p	UCUGGGCAACAAAGUGAGACCU	464	22	1
hsa-miR-1307-3p	ACUCGGCGUGGCGUCGGUCGUG	124	22	1
hsa-miR-140-3p	UACCACAGGGUAGAACCACGG	138	21	1
hsa-miR-148b-3p	UCAGUGCAUCACAGAACUUUGU	48	22	1
hsa-miR-181b-5p	AACAUUCAUUGCUGUCGGUGGGU	38	23	1
hsa-miR-193a-3p	AACUGGCCUACAAAGUCCCAGU	386	22	1
hsa-miR-1972	UCAGGCCAGGCACAGUGGCUCA	733	22	1
hsa-miR-21-3p	CAACACCAGUCGAUGGGCUGU	20	21	1
hsa-miR-2277-3p	UGACAGCGCCCUGCCUGGCUC	735	21	1
hsa-miR-23a-3p	AUCACAUUGCCAGGGAUUUCC	55	21	1
hsa-miR-23b-3p	AUCACAUUGCCAGGGAUUACC	59	21	1
hsa-miR-24-3p	UGGCUCAGUUCAGCAGGAACAG	119	22	1
hsa-miR-27a-3p	UUCACAGUGGCUAAGUUCCGC	46	21	1
hsa-miR-27b-3p	UUCACAGUGGCUAAGUUCUGC	6	21	1
hsa-miR-299-3p	UAUGUGGGAUGGUAAACCGCUU	182	22	1

hsa-miR-30b-5p	UGUAAACAUCCUACACUCAGCU	96	22	1
hsa-miR-30c-5p	UGUAAACAUCCUACACUCUCAGC	66	23	1
hsa-miR-31-3p	UGCUAUGCCAACAUAUUGCCAU	172	22	1
hsa-miR-3196	CGGGGCGGCAGGGGCCUC	717	18	1
hsa-miR-3198	GUGGAGUCCUGGGGAAUGGAGA	647	22	1
hsa-miR-320a	AAAAGCUGGGUUGAGAGGGCGA	97	22	1
hsa-miR-329	AACACACCUGGUUAACCUCUUU	214	22	1
hsa-miR-339-5p	UCCCUGUCCUCCAGGAGCUCACG	402	23	1
hsa-miR-34a-5p	UGGCAGUGUCUUAGCUGGUUGU	101	22	1
hsa-miR-3607-5p	GCAUGUGAUGAAGCAAAUCAGU	249	22	1
hsa-miR-3648	AGCCGCGGGGAUCGCCGAGGG	259	21	1
hsa-miR-376c	AACAUAGAGGAAAUUCCACGU	185	21	1
hsa-miR-3960	GGCGGCGGCGGAGGCGGGGG	416	20	1
hsa-miR-411-3p	UAUGUAACACGGUCCACUAACC	482	22	1
hsa-miR-423-3p	AGCUCGGUCUGAGGCCCCUCAGU	57	23	1
hsa-miR-423-5p	UGAGGGGCAGAGAGCGAGACUUU	41	23	1
hsa-miR-4417	GGUGGGCUUCCCGGAGGG	175	18	1
hsa-miR-4444	CUCGAGUUGGAAGAGGCG	418	18	1
hsa-miR-4499	AAGACUGAGAGGAGGGA	736	17	1
hsa-miR-4521	GCUAAGGAAGUCCUGUGCUCAG	233	22	1
hsa-miR-4680-5p	AGAACUCUUGCAGUCUUAGAUGU	737	23	1
hsa-miR-4709-5p	ACAACAGUGACUUGCUCUCCAA	575	22	1
hsa-miR-501-3p	AAUGCACCCGGGCAAGGAUUCU	26	22	1
hsa-miR-644b-3p	UUCAUUUGCCUCCCAGCCUACA	442	22	1
hsa-miR-654-3p	UAUGUCUGCUGACCAUCACCUU	336	22	1
hsa-miR-9-3p	AUAAAGCUAGAUAACCGAAAGU	183	22	1
hsa-miR-940	AAGGCAGGGCCCCCGCUCCCC	366	21	1
hsa-miR-99a-5p	AACCCGUAGAUCCGAUCUUGUG	52	22	1

D) Identification of top ranking coding and non-coding RNAs by GENCODE analysis performed in exosomes, MV and producer cells

CTX0E0307EH cells	CTX0E0307EH EXO	CTX0E0307E H MV	CTX0E0307EI cells	CTX0E0307EIE XO	CTX0E0307EI MV
18741941	12678688	10876797	22116110	16311289	835970

Table 10: Total number of sequence reads identified by using GENCODE in each tested samples

Using GENCODE database analysis of the sequence results, seven putative novel miRNA sequences were identified in exosomes (EXO), microvesicles (MV) and producer cells, as shown in Table 11. (nb CTX0E03 07EI MV reads are misrepresented due to the lower amount of starting material – see Table 10). These data are shown graphically in Figure 16, which

shows that these sequences are preferentially shuttled into exosomes and microvesicles compared to the cells.

Gene Symbol	Transcript ID	Length	Type of RNA	CTX0E0307E H cells	CTX0E0307E H EXO	CTX0E0307E H MV	CTX0E0307E I cells	CTX0E0307E I EXO	CTX0E0307EI MV
AC079949.1	AC079949.1-201	57	Novel miRNA	2629	27006	14873	2425	11433	848
AP000318.1	AP000318.1-201	64	Novel miRNA	1353	9379	11002	7469	2953	419
AL161626.1	AL161526.1-201	57	Novel miRNA	471	4450	3712	291	1263	129
AC004943.1	AC004943.1-201	81	Novel miRNA	24	81	43	23	94	5
AL121897.1	AL121897.1-201	89	Novel miRNA	6	22	14	2	30	3

Table 11: Identification of putative novel miRNA sequences using GENCODE in exosomes (EXO), microvesicles (MV) and producer cells. CTX0E03 07EI MV reads are misrepresented due to the lower amount of starting material (table 1). The transcript IDs are taken from the Ensembl database (www.ensembl.org).

Validation and of novel miRNAs

AC079949.1-201 (SEQ ID NO:738)

Gene: AC079949.1 ENSG00000239776
>12 dna:chromosome chromosome:GRCh37:12:127650616:127650672:1

GGCCGCGCCCCGTTTCCCAGGACAAAGGGCACTCCGCACCGGACCCTGGTCCCAGCG

For AC079949.1-201 putative mature miRNA, **gaccaggguccggugcggagug (SEQ ID NO:745)** was identified as the possible 5' stem mature miRNA using http://mirna.imbb.forth.gr/MatureBayes.html, a tool for finding mature miRNA within a miRNA precursor sequence using a Naive Bays classifier. Its presence validation was performed using AGGGTCCGGTGCGGAGT (SEQ ID NO:746) primer sequence. This sequence was entered in mirbase (http://www.mirbase.org/) and the following miRNA was found with similar sequence: *Bos taurus* miR-2887-1 (Accession No. MIMAT0013845).

bta-miR-2887 : 9-20 (SEQ ID NO:747)

```
AC079949 (5)          2  ggguccggugcg  13
                            ||||||||||||
bta-miR-2887          9  ggguccggugcg  20
```

The presence of this novel miRNA was tested by qRT-PCR on purified exosomes retro transcribed miRNA.

The same analysis was performed using the 3' stem of AC079949, sequence TGCGGAGTGCCCTTTGTCCT (SEQ ID NO:748), but in this case no similar miRNA was identified in mirbase.

AP000318.1-201 (SEQ ID NO:739)

Gene: AP000318.1 ENSG00000266007
>21 dna:chromosome chromosome:GRCh37:21:35677430:35677493:1

CCCACTCCCTGGCGCCGCTTGTGGAGGGCCCAAGTCCTTCTGATTGAGGCCCAACCCGTGGAAG

For AP000318.1-201 putative mature miRNA, **ggagggcccaaguccuucugau** (SEQ ID NO:744) was identified as the possible 5' stem mature miRNA. Its presence validation was performed using GGAGGGCCCAAGTCCTTCTGAT (SEQ ID NO:749) primer sequence. *Caenorhabditis remanei* miR-55 stem-loop was identified as similar miRNA. Primer validation was again carried out by qRT-PCR.

crm-miR-55-5p : 4-17 (SEQ ID NO:750)

```
AP000318.1          20  cccaaguccuucug  7
                        ||||||| ||||||
crm-miR-55-5p        4  cccaagugcuucug  17
```

AL161626.1-201 (SEQ ID NO:740)

Gene: AL161626.1 ENSG00000241781
>9 dna:chromosome chromosome:GRCh37:9:79186731:79186787:1

CGCCGGGACCGGGGTCCGGGGCGGAGTGCCCTTCCTCCTGGGAAACGGGGTGCGGC

For AL161626.1-201 putative mature miRNA, **ggcggagugcccuucuuccugg (SEQ ID NO:743)** was identified as the possible 5' stem mature miRNA. Its presence validation was performed using CGGAGTGCCCTTCTTCCT (SEQ ID NO:751) primer sequence. *Zea mays* miR164c stem-loop and *Achypodium distachyon* miR164f stem-loop were identified as similar miRNA. Primer validation was again carried out by qRT-PCR.

zma-miR164c-3p : 4-15 (SEQ ID NO:752)

```
AL161626.1           5  gugcccuucuuc  16
                        ||||||||||||
zma-miR164c-3p       4  gugcccuucuuc  15
```

AC004943.1 (SEQ ID NO:741)

Gene: AC004943.1 ENSG00000265573
>16 dna:chromosome chromosome:GRCh37:16:72821592:72821672:-1

GCTTCACGTCCCCACCGGCGGCGGCGGCGGTGGCAGTGGCGGCGGCGGCGGCGGTGGCGG
CGGCGGCGGCGGCGGCGGCTC

AL121897.1 (SEQ ID NO:742)

Gene: AL121897.1 ENSG00000264308
>20 dna:chromosome chromosome:GRCh37:20:30865503:30865591:1

GCCGCCCCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCGCCCGCTTTCGGCTCGGG
CCTCAGGTGAGTCGGAGGGGCCGGGCGCC

Miscellaneous RNA (misc_RNA), including novel putative

Misc_RNA is short for miscellaneous RNA, a general term for a series of miscellaneous small RNA. Miscellaneous transcript feature are not defined by other RNA keys.

List of top ranking previously known and novel misc_RNAs identified using GENCODE sequence data set:

Gene Symbol	Transcript ID	Length	Type of RNA	CTX0E0307EH cells	CTX0E0307EH EXO	CTX0E0307EH MV	CTX0E0307EI cells	CTX0E0307EI EXO	CTX0E0307EI MV
RPPH1	RPPH1-201	333	misc RNA	76	2229	1785	0	1077	197
RMRP	RMRP-201	264	misc RNA	139	1803	1443	191	659	87
RPPH1	RPPH1-001	638	misc RNA	182	931	1372	795	2017	157
VTRNA1-1	VTRNA1-1-201	99	misc RNA	43	720	52	247	210	9
Y_RNA	Y_RNA.321-201	93	Novel misc RN	159	196	661	960	903	217
Y_RNA	Y_RNA.725-201	95	Novel misc RN	1092	18	74	1005	39	11
Y_RNA	Y_RNA.125-201	96	Novel misc RN	1079	15	58	906	27	12
Y_RNA	Y_RNA.118-201	99	Novel misc RN	134	12	9	156	45	7
Y_RNA	Y_RNA.394-201	109	Novel misc RN	9	9	7	33	13	1
Y_RNA	Y_RNA.687-201	111	Novel misc RN	36	6	15	103	41	10
Y_RNA	Y_RNA.144-201	102	Novel misc RN	129	5	21	187	84	5
Y_RNA	Y_RNA.337-201	105	Novel misc RN	7	4	0	15	4	0
Y_RNA	Y_RNA.413-201	97	Novel misc RN	136	4	8	125	46	3
Y_RNA	Y_RNA.30-201	103	Novel misc RN	74	3	3	62	21	2

Table 12: Identification of misc_RNA, including putative novel misc_RNA, sequences using GENCODE in exosomes (EXO), microvesicles (MV) and producer cells. (CTX0E03 07EI MV reads are misrepresented due to the lower amount of starting material - Table 10). The transcript IDs are taken from the Ensembl database (www.ensembl.org).

Among the misc_RNA the following sequences were found preferentially down or up shuttled in exosomes and MV: RPHI, RMRP, and VTRNA1-1 up shuttled and Y_RNA.725-201, and Y_RNA.125-201 down respectively. RPHI is a ribonuclease P RNA component H1. RMRP gene

encodes the RNA component of mitochondrial RNA processing endoribonuclease, which cleaves mitochondrial RNA at a priming site of mitochondrial DNA replication. This RNA also interacts with the telomerase reverse transcriptase catalytic subunit to form a distinct ribonucleoprotein complex that has RNA-dependent RNA polymerase activity and produces double-stranded RNAs that can be processed into small interfering RNA. VTRNA1-1 is vault RNA component 1. Vaults are large cytoplasmic ribonucleoproteins and they are composed of a major vault protein, MVP, 2 minor vault proteins, TEP1 and PARP4, and a non-translated RNA component, VTRNA1-1. Y_RNA.725-201, and Y_RNA.125-201 are novel misc_RNAs and their function is not defined.

Metazoa miscellaneous RNA

The signal recognition particle RNA, also known as 7SL, 6S, ffs, or 4.5S RNA, is the RNA component of the signal recognition particle (SRP) ribonucleoprotein complex. SRP is a universally conserved ribonucleoprotein that directs the traffic of proteins within the cell and allows them to be secreted. The SRP RNA, together with one or more SRP proteins contributes to the binding and release of the signal peptide. The RNA and protein components of this complex are highly conserved but do vary between the different kingdoms of life.

List of top ranking Metazoa misc_RNAs identified using GENCODE sequence data set:

Gene Symbol	Transcript ID	Length	Type of RNA	CTX0E0307EH cells	CTX0E0307EH EXO	CTX0E0307EH MV	CTX0E0307EI cells	CTX0E0307EI EXO	CTX0E0307EI MV
Metazoa_SRP	Metazoa_SRP.791-201	288	Metazoan signal recogn	679	2324	2058	771	2698	465
Metazoa_SRP	Metazoa_SRP.561-201	294	Metazoan signal recogn	634	2006	1683	744	2147	432
Metazoa_SRP	Metazoa_SRP.864-201	297	Metazoan signal recogn	252	1884	1544	78	170	148
Metazoa_SRP	Metazoa_SRP.824-201	297	Metazoan signal recogn	438	881	958	505	1860	342
Metazoa_SRP	Metazoa_SRP.72-201	278	Metazoan signal recogn	441	630	631	494	2184	349
Metazoa_SRP	Metazoa_SRP.151-201	307	Metazoan signal recogn	377	464	470	432	1431	265
Metazoa_SRP	Metazoa_SRP.208-201	277	Metazoan signal recogn	382	410	431	422	1104	242
Metazoa_SRP	Metazoa_SRP.501-201	280	Metazoan signal recogn	265	272	266	235	434	44
Metazoa_SRP	Metazoa_SRP.682-201	298	Metazoan signal recogn	12	52	21	10	13	2

Table 13: Identification signal recognition particle RNA (misc_RNA) sequences using GENCODE in exosomes (EXO), microvesicles (MV) and producer cells. The transcript IDs are taken from the Ensembl database (www.ensembl.org).

RRNA (ribosomal RNA)

Ribosomal RNA (rRNA) forms part of the protein-synthesizing organelle known as a ribosome and that is exported to the cytoplasm to help translate the information in messenger RNA (mRNA) into protein. Eukaryotic ribosome (80S) rRNA components are: large unit (rRNA 5S, 5.8S, and 28S) small unit (rRNA 18S). Both rRNA 28S and 5.8S are selectively up-shuttled in exosomes and MV.

List of top ranking rRNA identified using GENCODE sequence data set:

Gene Symbol	Transcript ID	Length	Type of RNA	CTX0E0307EH cells	CTX0E0307EH EXO	CTX0E0307EH MV	CTX0E0307EI cells	CTX0E0307EI EXO	CTX0E0307EI MV
RNA5-8SP6	RNA5-8SP6-201	152	rRNA	205008	1148190	706558	213187	135909	14732
RNA28S5	RNA28S5-001	432	rRNA	86111	458585	516754	62829	390237	47483
RNA18S5	RNA18S5-001	599	rRNA	74634	52055	61639	116874	138484	14616
RNA5-8SP2	RNA5-8SP2-201	152	rRNA	6488	1719	1540	9231	3112	149
RNA5-8SP5	RNA5-8SP5-201	152	rRNA	2794	7393	3924	7314	3579	232

Table 14: Identification rRNA sequences using GENCODE in exosomes (EXO), microvesicles (MV) and producer cells. The transcript IDs are taken from the Ensembl database (www.ensembl.org).

Small nucleolar RNA: snoRNA

Small nucleolar RNAs (snoRNAs) are a class of small RNA molecules that primarily guides chemical modifications of other RNAs, mainly ribosomal RNAs, transfer RNAs and small nuclear RNAs. There are two main classes of snoRNA, the C/D box snoRNAs which are associated with methylation, and the H/ACA box snoRNAs which are associated with pseudouridylation.

List of top ranking snoRNA identified using GENCODE sequence data set:

Gene Symbol	Transcript ID	Length	Type of RNA	CTX0E0307EH cells	CTX0E0307EH EXO	CTX0E0307EH MV	CTX0E0307EI cells	CTX0E0307EI EXO	CTX0E0307EI MV
SNORD3A	SNORD3A-201	216	snoRNA	1433	2085	1621	906	1732	120
SNORD3C	SNORD3C-201	216	snoRNA	1169	1702	1220	639	1176	86
SNORD29	SNORD29-201	65	snoRNA	28130	1633	1070	36677	1752	45
SNORD83B	SNORD83B-201	93	snoRNA	1835	675	487	638	575	29
SNORD30	SNORD30-201	70	snoRNA	29743	254	244	29071	283	24

Table 15: Identification of snoRNA sequences using GENCODE in exosomes (EXO), microvesicles (MV) and producer cells. The transcript IDs are taken from the Ensembl database (www.ensembl.org).

Small nuclear RNA (snRNA)

Small nuclear ribonucleic acid (snRNA), also commonly referred to as U-RNA, is a class of small RNA molecules that make up the major spliceosome are named U1, U2, U4, U5, and U6, and participate in several RNA-RNA and RNA-protein interactions. Their primary function is in the processing of pre-mRNA (hnRNA) in the nucleus. They have also been shown to aide in the regulation of transcription factors (7SK RNA) or RNA polymerase II (B2 RNA), and maintaining the telomeres.

List of top ranking snRNA identified using GENCODE sequence data set:

Gene Symbol	Transcript ID	Length	Type of RNA	CTX0E0307EH cells	CTX0E0307EH EXO	CTX0E0307EH MV	CTX0E0307EI cells	CTX0E0307EI EXO	CTX0E0307EI MV
U2	U2.38-201	191	snRNA	1354	71596	49223	751	35290	1919
U2	U2.6-201	192	snRNA	834	15561	13594	303	8146	272
U1	U1.81-201	164	snRNA	584	10901	7307	91	3197	121
U1	U1.90-201	167	snRNA	533	9927	6689	48	2187	84
U2	U2.7-201	191	snRNA	201	9267	3109	288	6736	262

Table 16A: Identification of snRNA sequences using GENCODE in exosomes (EXO), microvesicles (MV) and producer cells. The transcript IDs are taken from the Ensembl database (www.ensembl.org).

LincRNA and novel lincRNA

Large intergenic non-coding RNAs (lincRNAs) are emerging as key regulators of diverse cellular processes. Determining the function of individual lincRNAs remains a challenge. Long non-coding RNAs (long ncRNAs, lncRNA) are non-protein coding transcripts longer than 200 nucleotides.

List of top ranking previously known and novel lincRNAs identified using GENCODE sequence data set:

Gene Symbol	Transcript ID	Length	Type of RNA	CTX0E0307EH cells	CTX0E0307EH EXO	CTX0E0307EH MV	CTX0E0307EI cells	CTX0E0307EI EXO	CTX0E0307EI MV
RP11-108M9.3	RP11-108M9.3-0(	1761	Novel lincRNA	244	159	240	539	324	45
RP11-329L6.1	RP11-329L6.1-00	507	Novel lincRNA	19	70	41	29	84	2
RP11-160E2.6	RP11-160E2.6-00	637	Novel lincRNA	228	67	115	489	74	6
AC004528.3	AC004528.3-001	107	Novel lincRNA	16	58	46	14	55	4
MALAT1	MALAT1-201	4585	lincRNA	150	308	234	26	182	12
GAS5	GAS5-007	2743	lincRNA	12024	215	120	46501	875	13

Table 16B: Identification of lincRNA and putative novel lincRNA sequences using GENCODE in exosomes (EXO), microvesicles (MV) and producer cells. The transcript IDs are taken from the Ensembl database (www.ensembl.org).

GAS5 lincRNA is highly expressed in cell producer compared to in exosomes and microvesicles (down shuttled in both exosomes and MV).

mRNA

Coding sequencing mRNA were also identified.

Gene Symbol	Transcript ID	Length	Type of RNA	CTX0E0307EH cells	CTX0E0307EH EXO	CTX0E0307EH MV	CTX0E0307EI cells	CTX0E0307EI EXO	CTX0E0307EI MV
EEF2	EEF2-201	9407	mRNA	710	578	449	1155	471	33
MTRNR2L8	MTRNR2L8-201	1290	mRNA	1383	548	642	1323	258	15
NES	NES-001	8635	mRNA	668	406	234	1448	267	20
VIM	VIM-001	8316	mRNA	563	911	501	1500	618	36

Table 17: Identification of mRNA sequences using GENCODE in exosomes (EXO), microvesicles (MV) and producer cells. The transcript IDs are taken from the Ensembl database (www.ensembl.org).

Example 12: Conclusion

The main scope of the deep sequence analysis was to identify their miRNA components in neural stem cell-derived vesicles (exosomes and microvesicles). This analysis identified a new set of known and novel miRNAs that are preferentially shuttled into both exosomes and MV. Among the identified miRNAs already included in mirbase database were hsa-miR-1246, hsa-miR-4488, hsa-miR-4492, hsa-miR-4508, hsa-miR-4516, hsa-miR-4532, and among the novel miRNAs were AC079949.1, AP000318.1, AL161626.1, AC004943.1, AL121897.1. Top ranking shuttled miRNAs, including novel ones were validated by qRT-PCR in exosomes.

The size distribution of shuttle RNA, as shown here, is mostly in the range of 20 to 200 nt and other RNA species are released by cells into the extracellular space. By deep sequencing and GENCODE sequence set analysis we found a greater complexity and diversity of non-coding RNA transcripts. We extended this analysis with detailed evaluation and this led to the discovery of preferentially up (defined as log2 fold change ≥ 2) and down (defined as log2 fold change ≤ -2) shuttle of other non-coding RNAs in both exosomes and microvesicles. Differentially shuttled non coding RNA were found in almost all the non-coding RNA subtypes, ribosomal RNA (rRNA), small nucleolar (snoRNA), small nuclear RNA (snRNA), microRNA (miRNA), miscellaneous other RNA (misc_RNA, e.g. RMRP, vault RNA, metazoa SRP, and RNY), and large intergenic non-coding RNAs (lincRNAs).

The unequal distribution of the detected RNA species over cellular and shuttle RNA, combined with increasing evidence for their role in gene regulation strongly suggest that cells specifically release these RNAs to modify the function of target cells.

Example 13: Proteomic analysis

Methods

Exosomes and microvesicle fractions were prepared from a CTX0E03 cell Integra culture (week 2), using differential ultracentrifugation. Exosomes and microvesicles were disrupted in modified RIPA buffer (50mM Tris HCl, pH 8.0, 150mM NaCl, 1% SDS, 0.1% Triton X100, 10mM DTT, 1x Complete protease inhibitor (Roche) and 1x PhosStop phosphatase inhibitor (Roche)) and subjected to manual shearing using a 1mL tuberculin syringe and 25 gauge needle. Samples were re-quantitated post disruption using the Qubit fluorometer (Invitrogen). 20µg of each sample was loaded onto a 4-12% SDS-PAGE gel (Novex, Invitrogen). The gel was excised into forty segments per lane and gel slices were processed using a robot (ProGest, DigiLab) with the following protocol:

a) wash with 25mM ammonium bicarbonate followed by acetonitrile;

b) reduce with 10mM dithiothreitol at 60°C followed by alkylation with 50mM iodoacetamide at room temperature;

c) digest with trypsin (Promega) at 37°C for 4h;

d) quench with formic acid;

e) the supernatant was analysed by mass spectrometry directly without further processing.

Mass Spectrometry

Each gel digest was analysed by nano LC/MS/MS with a Waters NanoAcquity HPLC system interfaced to a ThermoFisher Q Exactive. Peptides were loaded on a trapping column and eluted over a 75µm analytical column at 350nL/min; both columns were packed with Jupiter Proteo resin (Phenomenex). The mass spectrometer was operated in data-dependent mode, with MS and MS/MS performed in the Orbitrap at 70,000 FWHM and 17,500 FWHM resolution, respectively.

Exosomes

2572 proteins were identified by Mass spectrometry in exosomes purified by ultracentrifugation. The exosomes were isolated from the initial stages of an Integra culture (week 2). The gene names and corresponding SWISSPROT accession numbers (in brackets) of all 2572 proteins are listed in Table 18 (in alphabetical order of gene name) and the 100 most abundant proteins are listed in Table 19, in order of decreasing abundance. The characteristic exosome markers CD9, CD81 and Alix (also known as PDCD6IP) are present in the most abundant 100 proteins.

A1BG (P04217), A2M (P01023), AACS (Q86V21), AAMP (Q13685), AARS (P49588), AARSD1 (Q9BTE6), AASDHPPT (Q9NRN7), ABCA3 (Q99758), ABCE1 (P61221), ABCF1 (Q8NE71), ABCF3 (Q9NUQ8), ABHD10 (Q9NUJ1), ABHD14B (Q96IU4), ABI1 (Q8IZP0), ABR (Q12979), ACAA2 (P42765), ACACA (Q13085), ACADVL (P49748), ACAP2 (Q15057), ACAT1 (P24752), ACAT2 (Q9BWD1), ACBD7 (Q8N6N7), ACLY (P53396), ACO1 (P21399), ACO2 (Q99798), ACOT1 (Q86TX2), ACOT13 (Q9NPJ3), ACOT7 (O00154), ACP1 (P24666), ACSL1 (P33121), ACSL3 (O95573), ACSL4 (O60488), ACSS2 (Q9NR19), ACTC1 (P68032), ACTG1 (P63261), ACTL6A (O96019), ACTN1 (P12814), ACTN4 (O43707), ACTR10 (Q9NZ32), ACTR1A (P61163), ACTR1B (P42025), ACTR2 (P61160), ACTR3 (P61158), ADAM10 (O14672), ADAM12 (O43184), ADAMTS15 (Q8TE58), ADAMTS16 (Q8TE57), ADAR (P55265), ADAT2 (Q7Z6V5), ADH5 (P11766), ADI1 (Q9BV57), ADK (P55263), ADRBK1 (P25098), ADRM1 (Q16186), ADSL (P30566), ADSS (P30520), AEBP1 (Q8IUX7), AFM (P43652), AGL (P35573), AGRN (O00468), AGT (P01019), AHCY (P23526), AHCYL1 (O43865), AHNAK (Q09666),

AHSA1 (O95433), AHSG (P02765), AIDA (Q96BJ3), AIFM1 (O95831), AIMP1 (Q12904), AIMP2 (Q13155), AIP (O00170), AK1 (P00568), AK3 (Q9UIJ7), AK4 (P27144), AKAP12 (Q02952), AKAP9 (Q99996), AKR1A1 (P14550), AKR1B1 (P15121), AKR1C1 (Q04828), AKR7A2 (O43488), AKR7A3 (O95154), AKT1 (P31749), ALCAM (Q13740), ALDH16A1 (Q8IZ83), ALDH3A1 (P30838), ALDH7A1 (P49419), ALDH9A1 (P49189), ALDOA (P04075), ALDOC (P09972), ALKBH2 (Q6NS38), ALKBH4 (Q9NXW9), AMBP (P02760), AMDHD2 (Q9Y303), AMPD2 (Q01433), AMZ2 (Q86W34), ANAPC1 (Q9H1A4), ANAPC4 (Q9UJX5), ANAPC5 (Q9UJX4), ANAPC7 (Q9UJX3), ANKFY1 (Q9P2R3), ANKRD28 (O15084), ANP32A (P39687), ANP32B (Q92688), ANP32E (Q9BTT0), ANXA1 (P04083), ANXA2 (P07355), ANXA4 (P09525), ANXA5 (P08758), ANXA6 (P08133), ANXA7 (P20073), AP1B1 (Q10567), AP1G1 (O43747), AP1M1 (Q9BXS5), AP1S1 (P61966), AP1S2 (P56377), AP2A1 (O95782), AP2A2 (O94973), AP2B1 (P63010), AP2M1 (Q96CW1), AP2S1 (P53680), AP3B1 (O00203), AP3D1 (O14617), AP3M1 (Q9Y2T2), AP3S1 (Q92572), AP3S2 (P59780), AP4S1 (Q9Y587), APEH (P13798), APEX1 (P27695), API5 (Q9BZZ5), APIP (Q96GX9), APOA1 (P02647), APOA1BP (Q8NCW5), APOA2 (P02652), APOBEC3C (Q9NRW3), APOC2 (P02655), APOD (P05090), APOH (P02749), APOM (O95445), APPL1 (Q9UKG1), APRT (P07741), AQR (O60306), ARCN1 (P48444), ARF1 (P84077), ARF4 (P18085), ARF5 (P84085), ARF6 (P62330), ARFIP1 (P53367), ARFIP2 (P53365), ARHGAP1 (Q07960), ARHGAP12 (Q8IWW6), ARHGDIA (P52565), ARHGEF1 (Q92888), ARHGEF10 (O15013), ARHGEF7 (Q14155), ARIH1 (Q9Y4X5), ARIH2 (O95376), ARL1 (P40616), ARL2 (P36404), ARL3 (P36405), ARL6IP1 (Q15041), ARL8B (Q9NVJ2), ARMC10 (Q8N2F6), ARMC6 (Q6NXE6), ARMC8 (Q8IUR7), ARMC9 (Q7Z3E5), ARMCX3 (Q9UH62), ARPC1A (Q92747), ARPC1B (O15143), ARPC2 (O15144), ARPC3 (O15145), ARPC4 (P59998), ARPC5 (O15511), ARPC5L (Q9BPX5), ARRDC1 (Q8N5I2), ASB6 (Q9NWX5), ASCC1 (Q8N9N2), ASCC2 (Q9H1I8), ASCC3 (Q8N3C0), ASF1A (Q9Y294), ASH2L (Q9UBL3), ASMTL (O95671), ASNA1 (O43681), ASNS (P08243), ASS1 (P00966), ATG16L1 (Q676U5), ATG3 (Q9NT62), ATG4B (Q9Y4P1), ATG7 (O95352), ATIC (P31939), ATL3 (Q6DD88), ATM (Q13315), ATOX1 (O00244), ATP1A1 (P05023), ATP1B1 (P05026), ATP1B3 (P54709), ATP2B1 (P20020), ATP2B4 (P23634), ATP5B (P06576), ATP5E (P56381), ATP5I (P56385), ATP6AP2 (O75787), ATP6V0D1 (P61421), ATP6V1A (P38606), ATP6V1B2 (P21281), ATP6V1C1 (P21283), ATP6V1D (Q9Y5K8), ATP6V1E1 (P36543), ATP6V1G1 (O75348), ATP6V1H (Q9UI12), ATR (Q13535), ATRN (O75882), ATXN10 (Q9UBB4), B2M (P61769), B3GAT3 (O94766), B3GNT1 (O43505), B4GALT7 (Q9UBV7), BAG2 (O95816), BAIAP2 (Q9UQB8), BANF1 (O75531), BAT1 (Q13838), BAT3 (P46379), BBOX1 (O75936), BCAS2 (O75934), BCAT1 (P54687), BCCIP (Q9P287), BCL2L13 (Q9BXK5), BCLAF1 (Q9NYF8), BDH2 (Q9BUT1), BICD2 (Q8TD16), BLOC1S1 (P78537), BLVRA (P53004), BLVRB (P30043), BMP1 (P13497), BOLA2 (Q9H3K6), BPGM (P07738), BPHL (Q86WA6), BPNT1 (O95861), BRCC3 (P46736), BRE (Q9NXR7), BROX (Q5VW32), BRP16L

(P0CB43), BSG (P35613), BST1 (Q10588), BTAF1 (O14981), BUB3 (O43684), BUD31 (P41223), BYSL (Q13895), BZW1 (Q7L1Q6), BZW2 (Q9Y6E2), C10orf119 (Q9BTE3), C10orf58 (Q9BRX8), C10orf76 (Q5T2E6), C11orf54 (Q9H0W9), C11orf68 (Q9H3H3), C12orf10 (Q9HB07), C14orf149 (Q96EM0), C14orf166 (Q9Y224), C15orf58 (Q6ZNW5), C16orf13 (Q96S19), C16orf80 (Q9Y6A4), C1D (Q13901), C1orf123 (Q9NWV4), C1orf50 (Q9BV19), C1orf57 (Q9BSD7), C1RL (Q9NZP8), C20orf11 (Q9NWU2), C20orf27 (Q9GZN8), C20orf4 (Q9Y312), C21orf59 (P57076), C22orf25 (Q6ICL3), C22orf28 (Q9Y3I0), C2orf29 (Q9UKZ1), C2orf79 (Q6GMV3), C3orf10 (Q8WUW1), C3orf26 (Q9BQ75), C3orf75 (Q0PNE2), C4orf27 (Q9NWY4), C4orf41 (Q7Z392), C5orf32 (Q9H1C7), C6orf130 (Q9Y530), C6orf211 (Q9H993), C7orf25 (Q9BPX7), C7orf28B (P86790), C7orf41 (Q8N3F0), C7orf59 (Q0VGL1), C9orf142 (Q9BUH6), C9orf23 (Q8N5L8), C9orf41 (Q8N4J0), C9orf64 (Q5T6V5), CA11 (O75493), CAB39 (Q9Y376), CACNA2D1 (P54289), CACYBP (Q9HB71), CAD (P27708), CADM1 (Q9BY67), CADM4 (Q8NFZ8), CALB1 (P05937), CALD1 (Q05682), CALM1 (P62158), CAMK2D (Q13557), CAND1 (Q86VP6), CAP1 (Q01518), CAPN1 (P07384), CAPN2 (P17655), CAPN5 (O15484), CAPNS1 (P04632), CAPS (Q13938), CAPZA1 (P52907), CAPZA2 (P47755), CAPZB (P47756), CARHSP1 (Q9Y2V2), CARKD (Q8IW45), CARM1 (Q86X55), CARS (P49589), CASK (O14936), CASP3 (P42574), CASP6 (P55212), CAT (P04040), CBFB (Q13951), CBR1 (P16152), CBR3 (O75828), CBS (P35520), CBWD2 (Q8IUF1), CBX1 (P83916), CBX3 (Q13185), CBX5 (P45973), CC2D1A (Q6P1N0), CC2D1B (Q5T0F9), CCAR1 (Q8IX12), CCBL1 (Q16773), CCBL2 (Q6YP21), CCDC22 (O60826), CCDC25 (Q86WR0), CCDC53 (Q9Y3C0), CCDC56 (Q9Y2R0), CCDC93 (Q567U6), CCNC (P24863), CCND2 (P30279), CCNH (P51946), CCT2 (P78371), CCT3 (P49368), CCT4 (P50991), CCT5 (P48643), CCT6A (P40227), CCT7 (Q99832), CCT8 (P50990), CD109 (Q6YHK3), CD151 (P48509), CD276 (Q5ZPR3), CD44 (P16070), CD47 (Q08722), CD59 (P13987), CD63 (P08962), CD81 (P60033), CD9 (P21926), CD99 (P14209), CDC16 (Q13042), CDC23 (Q9UJX2), CDC27 (P30260), CDC34 (P49427), CDC37 (Q16543), CDC40 (O60508), CDC42 (P60953), CDC5L (Q99459), CDCP1 (Q9H5V8), CDH2 (P19022), CDK1 (P06493), CDK2 (P24941), CDK2AP2 (O75956), CDK4 (P11802), CDK5 (Q00535), CDK5RAP3 (Q96JB5), CDK7 (P50613), CDKN2A (P42771), CDKN2AIP (Q9NXV6), CELSR1 (Q9NYQ6), CELSR2 (Q9HCU4), CEP57 (Q86XR8), CFL1 (P23528), CFL2 (Q9Y281), CHAC2 (Q8WUX2), CHAF1B (Q13112), CHD4 (Q14839), CHEK2 (O96017), CHERP (Q8IWX8), CHID1 (Q9BWS9), CHML (P26374), CHMP1B (Q7LBR1), CHMP2A (O43633), CHMP4A (Q9BY43), CHMP4B (Q9H444), CHMP6 (Q96FZ7), CHORDC1 (Q9UHD1), CHP (Q99653), CHRAC1 (Q9NRG0), CHST14 (Q8NCH0), CHST3 (Q7LGC8), CHURC1 (Q8WUH1), CIAO1 (O76071), CIAPIN1 (Q6FI81), CIRH1A (Q969X6), CKAP5 (Q14008), CKB (P12277), CLASP1 (Q7Z460), CLDN3 (O15551), CLEC18B (Q6UXF7), CLIC1 (O00299), CLIC4 (Q9Y696), CLLD6 (Q5W111), CLNS1A (P54105), CLP1 (Q92989), CLPB (Q9H078), CLTA (P09496), CLTC (Q00610), CLU (P10909), CMAS (Q8NFW8), CMBL (Q96DG6), CMPK1

(P30085), CNBP (P62633), CNDP2 (Q96KP4), CNN2 (Q99439), CNN3 (Q15417), CNOT1 (A5YKK6), CNOT10 (Q9H9A5), CNOT6L (Q96LI5), CNOT7 (Q9UIV1), CNP (P09543), COASY (Q13057), COBRA1 (Q8WX92), COG1 (Q8WTW3), COG2 (Q14746), COG3 (Q96JB2), COG4 (Q9H9E3), COG5 (Q9UP83), COG6 (Q9Y2V7), COG7 (P83436), COG8 (Q96MW5), COL11A1 (P12107), COL14A1 (Q05707), COL6A1 (P12109), COMMD1 (Q8N668), COMMD10 (Q9Y6G5), COMMD2 (Q86X83), COMMD3 (Q9UBI1), COMMD4 (Q9H0A8), COMMD5 (Q9GZQ3), COMMD6 (Q7Z4G1), COMMD7 (Q86VX2), COMMD8 (Q9NX08), COMMD9 (Q9P000), COMT (P21964), COPA (P53621), COPB1 (P53618), COPB2 (P35606), COPE (O14579), COPG (Q9Y678), COPG2 (Q9UBF2), COPS2 (P61201), COPS3 (Q9UNS2), COPS4 (Q9BT78), COPS5 (Q92905), COPS6 (Q7L5N1), COPS7A (Q9UBW8), COPS7B (Q9H9Q2), COPS8 (Q99627), COPZ1 (P61923), CORO1A (P31146), CORO1B (Q9BR76), CORO1C (Q9ULV4), CORO2B (Q9UQ03), CORO7 (P57737), COTL1 (Q14019), COX5A (P20674), COX5B (P10606), COX6C (P09669), COX7A2 (P14406), CP (P00450), CPD (O75976), CPN2 (P22792), CPNE1 (Q99829), CPNE3 (O75131), CPNE7 (Q9UBL6), CPSF1 (Q10570), CPSF2 (Q9P2I0), CPSF3 (Q9UKF6), CPSF7 (Q8N684), CPXM1 (Q96SM3), CRIP2 (P52943), CRK (P46108), CRLF3 (Q8IUI8), CRTAP (O75718), CRYAB (P02511), CRYM (Q14894), CRYZ (Q08257), CRYZL1 (O95825), CS (O75390), CSDE1 (O75534), CSE1L (P55060), CSK (P41240), CSNK1A1 (P48729), CSNK2A1 (P68400), CSNK2B (P67870), CSRP1 (P21291), CSRP2 (Q16527), CSTB (P04080), CSTF1 (Q05048), CSTF2T (Q9H0L4), CSTF3 (Q12996), CTBP1 (Q13363), CTBP2 (P56545), CTNNA1 (P35221), CTNNB1 (P35222), CTNNBL1 (Q8WYA6), CTNND1 (O60716), CTPS (P17812), CTPS2 (Q9NRF8), CTR9 (Q6PD62), CTSC (P53634), CTSD (P07339), CTSF (Q9UBX1), CTSL2 (O60911), CTU1 (Q7Z7A3), CTU2 (Q2VPK5), CUL1 (Q13616), CUL2 (Q13617), CUL3 (Q13618), CUL4A (Q13619), CUL4B (Q13620), CUL5 (Q93034), CWF19L1 (Q69YN2), CXADR (P78310), CXorf26 (Q9BVG4), CYB5A (P00167), CYCS (P99999), CYFIP1 (Q7L576), CYFIP2 (Q96F07), CYR61 (O00622), DAG1 (Q14118), DAK (Q3LXA3), DARS (P14868), DAZAP1 (Q96EP5), DBI (P07108), DBN1 (Q16643), DBNL (Q9UJU6), DBR1 (Q9UK59), DCAF7 (P61962), DCAF8 (Q5TAQ9), DCD (P81605), DCK (P27707), DCLK1 (O15075), DCPS (Q96C86), DCTD (P32321), DCTN1 (Q14203), DCTN2 (Q13561), DCTN3 (O75935), DCTN4 (Q9UJW0), DCTN5 (Q9BTE1), DCTN6 (O00399), DCUN1D1 (Q96GG9), DCUN1D5 (Q9BTE7), DCXR (Q7Z4W1), DDA1 (Q9BW61), DDAH2 (O95865), DDB1 (Q16531), DDB2 (Q92466), DDI2 (Q5TDH0), DDR1 (Q08345), DDT (P30046), DDX1 (Q92499), DDX17 (Q92841), DDX19A (Q9NUU7), DDX21 (Q9NR30), DDX23 (Q9BUQ8), DDX39 (O00148), DDX3X (O00571), DDX5 (P17844), DDX51 (Q8N8A6), DDX6 (P26196), DECR1 (Q16698), DEF (Q68CQ4), DEFA1 (P59665), DENR (O43583), DERA (Q9Y315), DFFA (O00273), DHFR (P00374), DHPS (P49366), DHRS1 (Q96LJ7), DHRS11 (Q6UWP2), DHRS4 (Q9BTZ2), DHX15 (O43143), DHX16 (O60231), DHX29 (Q7Z478), DHX36 (Q9H2U1), DHX9 (Q08211), DIAPH1 (O60610), DIAPH2 (O60879), DIMT1L (Q9UNQ2), DIP2B

(Q9P265), DIP2C (Q9Y2E4), DIS3 (Q9Y2L1), DIS3L2 (Q8IYB7), DKC1 (O60832), DLG1 (Q12959), DNAH17 (Q9UFH2), DNAJA1 (P31689), DNAJA2 (O60884), DNAJB1 (P25685), DNAJB4 (Q9UDY4), DNAJC13 (O75165), DNAJC3 (Q13217), DNAJC7 (Q99615), DNASE1L1 (P49184), DNM1 (Q05193), DNM1L (O00429), DNM2 (P50570), DNPEP (Q9ULA0), DOCK1 (Q14185), DOCK4 (Q8N1I0), DOCK5 (Q9H7D0), DOCK7 (Q96N67), DOHH (Q9BU89), DOM3Z (O77932), DPCD (Q9BVM2), DPH1 (Q9BZG8), DPH2 (Q9BQC3), DPH5 (Q9H2P9), DPM1 (O60762), DPP3 (Q9NY33), DPP9 (Q86TI2), DPY30 (Q9C005), DPYSL2 (Q16555), DPYSL3 (Q14195), DPYSL4 (O14531), DPYSL5 (Q9BPU6), DRG1 (Q9Y295), DRG2 (P55039), DSG1 (Q02413), DSP (P15924), DST (Q03001), DSTN (P60981), DTD1 (Q8TEA8), DTYMK (P23919), DUS2L (Q9NX74), DUSP12 (Q9UNI6), DUSP23 (Q9BVJ7), DUSP3 (P51452), DYM (Q7RTS9), DYNC1H1 (Q14204), DYNC1I2 (Q13409), DYNC1LI1 (Q9Y6G9), DYNC1LI2 (O43237), DYNC2H1 (Q8NCM8), DYNLL1 (P63167), DYNLL2 (Q96FJ2), DYNLRB1 (Q9NP97), DYNLT1 (P63172), ECHDC1 (Q9NTX5), ECHDC3 (Q96DC8), ECHS1 (P30084), ECM29 (Q5VYK3), EDC4 (Q6P2E9), EEA1 (Q15075), EEF1A1 (P68104), EEF1B2 (P24534), EEF1D (P29692), EEF1E1 (O43324), EEF1G (P26641), EEF2 (P13639), EEFSEC (P57772), EFEMP2 (O95967), EFHD2 (Q96C19), EFNB2 (P52799), EFTUD1 (Q7Z2Z2), EFTUD2 (Q15029), EGFR (P00533), EHD1 (Q9H4M9), EHD2 (Q9NZN4), EHD4 (Q9H223), EIF1 (P41567), EIF1AX (P47813), EIF2A (Q9BY44), EIF2AK2 (P19525), EIF2B1 (Q14232), EIF2B2 (P49770), EIF2B3 (Q9NR50), EIF2B4 (Q9UI10), EIF2B5 (Q13144), EIF2C2 (Q9UKV8), EIF2S1 (P05198), EIF2S2 (P20042), EIF2S3 (P41091), EIF3A (Q14152), EIF3B (P55884), EIF3C (Q99613), EIF3D (O15371), EIF3E (P60228), EIF3F (O00303), EIF3G (O75821), EIF3H (O15372), EIF3I (Q13347), EIF3J (O75822), EIF3K (Q9UBQ5), EIF3L (Q9Y262), EIF3M (Q7L2H7), EIF4A1 (P60842), EIF4A2 (Q14240), EIF4A3 (P38919), EIF4E (P06730), EIF4E2 (O60573), EIF4G1 (Q04637), EIF4G2 (P78344), EIF4G3 (O43432), EIF4H (Q15056), EIF5 (P55010), EIF5A (P63241), EIF5B (O60841), EIF6 (P56537), ELAC2 (Q9BQ52), ELAVL1 (Q15717), ELMO2 (Q96JJ3), ELP2 (Q6IA86), ELP3 (Q9H9T3), EMG1 (Q92979), EMILIN1 (Q9Y6C2), EML1 (O00423), EML2 (O95834), EML3 (Q32P44), EML4 (Q9HC35), ENAH (Q8N8S7), ENO1 (P06733), ENO2 (P09104), ENOPH1 (Q9UHY7), ENY2 (Q9NPA8), EPB41L2 (O43491), EPB41L3 (Q9Y2J2), EPHA2 (P29317), EPHB3 (P54753), EPHX1 (P07099), EPM2AIP1 (Q7L775), EPRS (P07814), ERH (P84090), ERI1 (Q8IV48), ERI3 (O43414), ERP44 (Q9BS26), ESD (P10768), ESYT1 (Q9BSJ8), ETF1 (P62495), ETFA (P13804), ETFB (P38117), EXOC1 (Q9NV70), EXOC2 (Q96KP1), EXOC3 (O60645), EXOC4 (Q96A65), EXOC5 (O00471), EXOC6 (Q8TAG9), EXOC7 (Q9UPT5), EXOC8 (Q8IYI6), EXOSC1 (Q9Y3B2), EXOSC2 (Q13868), EXOSC3 (Q9NQT5), EXOSC4 (Q9NPD3), EXOSC5 (Q9NQT4), EXOSC6 (Q5RKV6), EXOSC7 (Q15024), EXOSC8 (Q96B26), EXOSC9 (Q06265), EXTL3 (O43909), EYA3 (Q99504), EZR (P15311), F3 (P13726), F8 (P00451), F8A1 (P23610), FABP5 (Q01469), FABP7 (O15540), FADD (Q13158), FAF1 (Q9UNN5), FAH (P16930), FAHD2A (Q96GK7),

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(Q9NR31), SARM1 (Q6SZW1), SARS (P49591), SART3 (Q15020), SBDS (Q9Y3A5), SBF1 (O95248), SCARB1 (Q8WTV0), SCARB2 (Q14108), SCFD1 (Q8WVM8), SCLY (Q96I15), SCP2 (P22307), SCPEP1 (Q9HB40), SCRG1 (O75711), SCRIB (Q14160), SCRN1 (Q12765), SCRN2 (Q96FV2), SCYL1 (Q96KG9), SCYL2 (Q6P3W7), SDC1 (P18827), SDC2 (P34741), SDCBP (O00560), SDF4 (Q9BRK5), SDHA (P31040), SDK1 (Q7Z5N4), SDSL (Q96GA7), SEC11A (P67812), SEC13 (P55735), SEC22B (O75396), SEC23A (Q15436), SEC23B (Q15437), SEC23IP (Q9Y6Y8), SEC24A (O95486), SEC24B (O95487), SEC24C (P53992), SEC24D (O94855), SEC31A (O94979), SEH1L (Q96EE3), SELH (Q8IZQ5), SEMA3A (Q14563), SEPSECS (Q9HD40), 40787 (Q9NVA2), 37500 (Q15019), 38596 (Q99719), 39326 (Q16181), 39692 (Q92599), 40057 (Q9UHD8), SERBP1 (Q8NC51), SERPINA1 (P01009), SERPINA3 (P01011), SERPINA7 (P05543), SERPINB6 (P35237), SERPINB8 (P50452), SERPINE1 (P05121), SERPINE2 (P07093), SERPING1 (P05155), SERPINH1 (P50454), SETD3 (Q86TU7), SETD7 (Q8WTS6), SF3A1 (Q15459), SF3A2 (Q15428), SF3A3 (Q12874), SF3B1 (O75533), SF3B14 (Q9Y3B4), SF3B2 (Q13435), SF3B3 (Q15393), SF3B4 (Q15427), SF3B5 (Q9BWJ5), SFPQ (P23246), SFRP4 (Q6FHJ7), SGTA (O43765), SH3BP4 (Q9P0V3), SH3GL1 (Q99961), SH3GLB1 (Q9Y371), SHBG (P04278), SHC1 (P29353), SHMT1 (P34896), SHMT2 (P34897), SHOC2 (Q9UQ13), SHPK (Q9UHJ6), SKIV2L (Q15477), SKIV2L2 (P42285), SKP1 (P63208), SLC16A1 (P53985), SLC1A3 (P43003), SLC1A5 (Q15758), SLC29A1 (Q99808), SLC2A1 (P11166), SLC31A1 (O15431), SLC3A2 (P08195), SLC44A2 (Q8IWA5), SLC5A3 (P53794), SLC7A5 (Q01650), SLC9A3R1 (O14745), SLC9A3R2 (Q15599), SLIRP (Q9GZT3), SMAD4 (Q13485), SMARCA4 (P51532), SMARCA5 (O60264), SMARCC1 (Q92922), SMARCC2 (Q8TAQ2), SMARCD1 (Q96GM5), SMARCD2 (Q92925), SMARCE1 (Q969G3), SMC1A (Q14683), SMC2 (O95347), SMC3 (Q9UQE7), SMC4 (Q9NTJ3), SMC5 (Q8IY18), SMC6 (Q96SB8), SMCHD1 (A6NHR9), SMEK1 (Q6IN85), SMS (P52788), SMU1 (Q2TAY7), SMYD5 (Q6GMV2), SNAP23 (O00161), SNAPIN (O95295), SND1 (Q7KZF4), SNF8 (Q96H20), SNRNP200 (O75643), SNRNP40 (Q96DI7), SNRPA1 (P09661), SNRPB (P14678), SNRPD1 (P62314), SNRPD2 (P62316), SNRPD3 (P62318), SNRPE (P62304), SNRPF (P62306), SNRPG (P62308), SNTB1 (Q13884), SNUPN (O95149), SNX1 (Q13596), SNX12 (Q9UMY4), SNX17 (Q15036), SNX18 (Q96RF0), SNX2 (O60749), SNX27 (Q96L92), SNX3 (O60493), SNX5 (Q9Y5X3), SNX6 (Q9UNH7), SNX8 (Q9Y5X2), SNX9 (Q9Y5X1), SOD1 (P00441), SORD (Q00796), SORT1 (Q99523), SPAG9 (O60271), SPC24 (Q8NBT2), SPC25 (Q9HBM1), SPG21 (Q9NZD8), SPR (P35270), SPRYD4 (Q8WW59), SPTAN1 (Q13813), SPTBN1 (Q01082), SPTBN2 (O15020), SRGAP2 (O75044), SRI (P30626), SRM (P19623), SRP14 (P37108), SRP19 (P09132), SRP54 (P61011), SRP68 (Q9UHB9), SRP72 (O76094), SRP9 (P49458), SRPX (P78539), SRPX2 (O60687), SRR (Q9GZT4), SRRT (Q9BXP5), SRSF1 (Q07955), SRSF11 (Q05519), SRSF2 (Q01130), SRSF3 (P84103), SRSF6 (Q13247), SRSF7 (Q16629), SRSF9 (Q13242), SRXN1 (Q9BYN0), SSB (P05455), SSBP1 (Q04837), SSRP1

(Q08945), SSSCA1 (O60232), ST13 (P50502), STAG2 (Q8N3U4), STAM (Q92783), STAMBP (O95630), STAT1 (P42224), STAT3 (P40763), STIP1 (P31948), STK24 (Q9Y6E0), STK25 (O00506), STK38L (Q9Y2H1), STOM (P27105), STON2 (Q8WXE9), STRAP (Q9Y3F4), STUB1 (Q9UNE7), STX12 (Q86Y82), STX4 (Q12846), STX5 (Q13190), STX7 (O15400), STXBP1 (P61764), STXBP3 (O00186), STYX (Q8WUJ0), SUB1 (P53999), SUDS3 (Q9H7L9), SUGT1 (Q9Y2Z0), SUMO1 (P63165), SUPT16H (Q9Y5B9), SUPT4H1 (P63272), SUPT5H (O00267), SUPT6H (Q7KZ85), SVEP1 (Q4LDE5), SWAP70 (Q9UH65), SYMPK (Q92797), SYNCRIP (O60506), SYNE1 (Q8NF91), SYNE2 (Q8WXH0), SYNGR2 (O43760), SYNJ2BP (P57105), TAB1 (Q15750), TAF9 (Q9Y3D8), TAF9 (Q16594), TAGLN (Q01995), TAGLN2 (P37802), TALDO1 (P37837), TARDBP (Q13148), TARS (P26639), TATDN1 (Q6P1N9), TAX1BP3 (O14907), TBC1D13 (Q9NVG8), TBC1D15 (Q8TC07), TBC1D23 (Q9NUY8), TBC1D24 (Q9ULP9), TBC1D4 (O60343), TBC1D9B (Q66K14), TBCA (O75347), TBCB (Q99426), TBCD (Q9BTW9), TBCE (Q15813), TBL1XR1 (Q9BZK7), TCEA1 (P23193), TCEB1 (Q15369), TCEB2 (Q15370), TCERG1 (O14776), TCP1 (P17987), TDP2 (O95551), TEP1 (Q99973), TEX10 (Q9NXF1), TF (P02787), TFCP2 (Q12800), TFG (Q92734), TFRC (P02786), TGFB1 (P01137), TGFB2 (P61812), TGFBI (Q15582), TGM1 (P22735), TH1L (Q8IXH7), THBS1 (P07996), THBS3 (P49746), THG1L (Q9NWX6), THOC2 (Q8NI27), THOC3 (Q96J01), THOC5 (Q13769), THOC6 (Q86W42), THOC7 (Q6I9Y2), THOP1 (P52888), THUMPD1 (Q9NXG2), THY1 (P04216), THYN1 (Q9P016), TIA1 (P31483), TIGAR (Q9NQ88), TIMM13 (Q9Y5L4), TIMM50 (Q3ZCQ8), TIMM8B (Q9Y5J9), TIMM9 (Q9Y5J7), TIMP1 (P01033), TIPRL (O75663), TKT (P29401), TLN1 (Q9Y490), TLN2 (Q9Y4G6), TM9SF2 (Q99805), TM9SF3 (Q9HD45), TMED10 (P49755), TMED2 (Q15363), TMED7 (Q9Y3B3), TMED9 (Q9BVK6), TMEM167A (Q8TBQ9), TMEM2 (Q9UHN6), TMEM50B (P56557), TMEM87A (Q8NBN3), TMOD3 (Q9NYL9), TNC (P24821), TNPO1 (Q92973), TNPO2 (O14787), TNPO3 (Q9Y5L0), TOLLIP (Q9H0E2), TOMM20 (Q15388), TOMM22 (Q9NS69), TOMM34 (Q15785), TOMM5 (Q8N4H5), TOMM70A (O94826), TOP1 (P11387), TOP2B (Q02880), TOR1B (O14657), TP53BP1 (Q12888), TP53RK (Q96S44), TPI1 (P60174), TPM3 (P06753), TPM3L (A6NL28), TPM4 (P67936), TPMT (P51580), TPP1 (O14773), TPP2 (P29144), TPR (P12270), TPRG1L (Q5T0D9), TPRKB (Q9Y3C4), TPT1 (P13693), TRAF2 (Q12933), TRAP1 (Q12931), TRAPPC1 (Q9Y5R8), TRAPPC2L (Q9UL33), TRAPPC3 (O43617), TRAPPC4 (Q9Y296), TRAPPC5 (Q8IUR0), TRAPPC6A (O75865), TRAPPC6B (Q86SZ2), TRIM22 (Q8IYM9), TRIM25 (Q14258), TRIM28 (Q13263), TRIP12 (Q14669), TRIP13 (Q15645), TRIP6 (Q15654), TRMT1 (Q9NXH9), TRMT112 (Q9UI30), TRMT5 (Q32P41), TRMT6 (Q9UJA5), TRMT61A (Q96FX7), TRNT1 (Q96Q11), TROVE2 (P10155), TRRAP (Q9Y4A5), TSG101 (Q99816), TSKU (Q8WUA8), TSPAN14 (Q8NG11), TSPAN4 (O14817), TSPAN5 (P62079), TSPAN6 (O43657), TSPAN9 (O75954), TSSC1 (Q53HC9), TSTA3 (Q13630), TTC1 (Q99614), TTC37 (Q6PGP7), TTC38 (Q5R3I4), TTC5 (Q8N0Z6), TTC9C (Q8N5M4), TTL (Q8NG68), TTLL12 (Q14166), TTN

(Q8WZ42), TTR (P02766), TTYH1 (Q9H313), TTYH2 (Q9BSA4), TTYH3 (Q9C0H2), TUBA1B (P68363), TUBA1C (Q9BQE3), TUBB (P07437), TUBB2A (Q13885), TUBB2B (Q9BVA1), TUBB2C (P68371), TUBB3 (Q13509), TUBB4 (P04350), TUBB6 (Q9BUF5), TUBG1 (P23258), TUBGCP2 (Q9BSJ2), TUBGCP3 (Q96CW5), TWF1 (Q12792), TWF2 (Q6IBS0), TXN (P10599), TXNDC17 (Q9BRA2), TXNDC9 (O14530), TXNL1 (O43396), TXNL4B (Q9NX01), TXNRD1 (Q16881), TYMS (P04818), U2AF1 (Q01081), U2AF2 (P26368), UAP1 (Q16222), UBA1 (P22314), UBA2 (Q9UBT2), UBA3 (Q8TBC4), UBA5 (Q9GZZ9), UBA6 (A0AVT1), UBE2D1 (P51668), UBE2D3 (P61077), UBE2E1 (P51965), UBE2G2 (P60604), UBE2I (P63279), UBE2J2 (Q8N2K1), UBE2K (P61086), UBE2L3 (P68036), UBE2M (P61081), UBE2N (P61088), UBE2O (Q9C0C9), UBE2V1 (Q13404), UBE2V2 (Q15819), UBE2Z (Q9H832), UBE3A (Q05086), UBE4A (Q14139), UBE4B (O95155), UBL3 (O95164), UBL4A (P11441), UBL5 (Q9BZL1), UBR1 (Q8IWV7), UBR4 (Q5T4S7), UBTD1 (Q9HAC8), UBXN1 (Q04323), UCHL1 (P09936), UCHL3 (P15374), UCHL5 (Q9Y5K5), UCK2 (Q9BZX2), UFC1 (Q9Y3C8), UFD1L (Q92890), UFSP2 (Q9NUQ7), UGDH (O60701), UGP2 (Q16851), UMPS (P11172), UNC119B (A6NIH7), UNC45A (Q9H3U1), UPF1 (Q92900), UPP1 (Q16831), UROD (P06132), UROS (P10746), USO1 (O60763), USP10 (Q14694), USP11 (P51784), USP14 (P54578), USP15 (Q9Y4E8), USP24 (Q9UPU5), USP39 (Q53GS9), USP5 (P45974), USP7 (Q93009), USP9X (Q93008), UTP15 (Q8TED0), UXS1 (Q8NBZ7), UXT (Q9UBK9), VAC14 (Q08AM6), VAMP3 (Q15836), VAMP5 (O95183), VAPA (Q9P0L0), VAPB (O95292), VARS (P26640), VASN (Q6EMK4), VASP (P50552), VAT1 (Q99536), VAV2 (P52735), VBP1 (P61758), VCAN (P13611), VCL (P18206), VCP (P55072), VIM (P08670), VPRBP (Q9Y4B6), VPS11 (Q9H270), VPS13C (Q709C8), VPS16 (Q9H269), VPS18 (Q9P253), VPS24 (Q9Y3E7), VPS25 (Q9BRG1), VPS26A (O75436), VPS26B (Q4G0F5), VPS28 (Q9UK41), VPS29 (Q9UBQ0), VPS33A (Q96AX1), VPS33B (Q9H267), VPS35 (Q96QK1), VPS36 (Q86VN1), VPS37B (Q9H9H4), VPS39 (Q96JC1), VPS45 (Q9NRW7), VPS4A (Q9UN37), VPS4B (O75351), VPS53 (Q5VIR6), VRK1 (Q99986), VTA1 (Q9NP79), VWA1 (Q6PCB0), VWA5A (O00534), WARS (P23381), WASF1 (Q92558), WASL (O00401), WDFY1 (Q8IWB7), WDR1 (O75083), WDR11 (Q9BZH6), WDR12 (Q9GZL7), WDR18 (Q9BV38), WDR26 (Q9H7D7), WDR33 (Q9C0J8), WDR4 (P57081), WDR43 (Q15061), WDR45L (Q5MNZ6), WDR48 (Q8TAF3), WDR5 (P61964), WDR54 (Q9H977), WDR55 (Q9H6Y2), WDR59 (Q6PJI9), WDR6 (Q9NNW5), WDR61 (Q9GZS3), WDR73 (Q6P4I2), WDR77 (Q9BQA1), WDR82 (Q6UXN9), WDR91 (A4D1P6), WDR92 (Q96MX6), WNK1 (Q9H4A3), XPNPEP1 (Q9NQW7), XPO1 (O14980), XPO4 (Q9C0E2), XPO5 (Q9HAV4), XPO6 (Q96QU8), XPO7 (Q9UIA9), XPOT (O43592), XRCC1 (P18887), XRCC5 (P13010), XRCC6 (P12956), XRN2 (Q9H0D6), YARS (P54577), YBX1 (P67809), YEATS4 (O95619), YES1 (P07947), YIPF4 (Q9BSR8), YKT6 (O15498), YPEL5 (P62699), YRDC (Q86U90), YTHDF2 (Q9Y5A9), YWHAB (P31946), YWHAE (P62258), YWHAG (P61981), YWHAH (Q04917), YWHAQ (P27348), YWHAZ (P63104), ZC3HAV1L

(Q96H79), ZCCHC3 (Q9NUD5), ZER1 (Q7Z7L7), ZFPL1 (O95159), ZFR (Q96KR1), ZMAT2 (Q96NC0), ZNF259 (O75312), ZW10 (O43264), ZWILCH (Q9H900), ZYG11B (Q9C0D3), ZYX (Q15942), ZZEF1 (O43149).

Table 18: Gene names and SWISSPROT accession numbers of all 2572 proteins identified in CTX0E03 exosomes (listed in alphabetical order of gene name).

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Identified proteins	Accession number
Actin, cytoplasmic 2	P63261
Glyceraldehyde-3-phosphate dehydrogenase	P04406
Histone H4	P62805
Pyruvate kinase isozymes M1/M2	P14618
Alpha-enolase	P06733
Heat shock protein HSP 90-beta	P08238
Ubiquitin-40S ribosomal protein S27a	P62979
Heat shock cognate 71 kDa protein	P11142
Haptoglobin	P00738
Heat shock protein HSP 90-alpha	P07900
Phosphoglycerate kinase 1	P00558
Actin, alpha cardiac muscle 1	P68032
40S ribosomal protein S3	P23396
Elongation factor 1-alpha 1	P68104
GTP-binding nuclear protein Ran	P62826
Histone H2B type 1-M	Q99879
Peptidyl-prolyl cis-trans isomerase A	P62937
Profilin-1	P07737
Elongation factor 2	P13639
Fatty acid synthase	P49327
Tubulin beta-2C chain	P68371
Tubulin alpha-1B chain	P68363
Tubulin beta chain	P07437
40S ribosomal protein S11	P62280
Eukaryotic initiation factor 4A-I	P60842
T-complex protein 1 subunit theta	P50990
14-3-3 protein theta	P27348
40S ribosomal protein S18	P62269
Tubulin beta-3 chain	Q13509
T-complex protein 1 subunit beta	P78371
40S ribosomal protein S16	P62249
Heat shock 70 kDa protein 1A/1B	P08107
Histone H3.2	Q71DI3
Transketolase	P29401
40S ribosomal protein SA	P08865

Clusterin	P10909
Fatty acid-binding protein, brain	O15540
Hemopexin	P02790
T-complex protein 1 subunit gamma	P49368
Tubulin beta-2B chain	Q9BVA1
Adenosylhomocysteinase	P23526
T-complex protein 1 subunit eta	Q99832
40S ribosomal protein S15a	P62244
T-complex protein 1 subunit delta	P50991
Vimentin	P08670
Guanine nucleotide-binding protein subunit beta-2-like 1	P63244
Dihydropyrimidinase-related protein 3	Q14195
Elongation factor 1-gamma	P26641
Fascin	Q16658
Creatine kinase B-type	P12277
X-ray repair cross-complementing protein 5	P13010
40S ribosomal protein S2	P15880
Histone H2A type 2-A	Q6FI13
40S ribosomal protein S4, X isoform	P62701
14-3-3 protein zeta/delta	P63104
Heterogeneous nuclear ribonucleoprotein A1	P09651
CD81 antigen	P60033
Keratin, type I cytoskeletal 14	P02533
ATP-citrate synthase	P53396
40S ribosomal protein S9	P46781
Transgelin-2	P37802
Fructose-bisphosphate aldolase A	P04075
Ubiquitin-like modifier-activating enzyme 1	P22314
Peroxiredoxin-1	Q06830
40S ribosomal protein S5	P46782
T-complex protein 1 subunit epsilon	P48643
60S ribosomal protein L30	P62888
T-complex protein 1 subunit alpha	P17987
60S ribosomal protein L12	P30050
Cofilin-1	P23528
Heterogeneous nuclear ribonucleoproteins A2/B1	P22626
Eukaryotic translation initiation factor 5A-1	P63241
Phosphoglycerate mutase 1	P18669
Clathrin heavy chain 1	Q00610
Dihydropyrimidinase-related protein 2	Q16555
60S ribosomal protein L35a	P18077
T-complex protein 1 subunit zeta	P40227
Carbonyl reductase [NADPH] 1	P16152
40S ribosomal protein S3a	P61247
Ferritin heavy chain	P02794

Annexin A2	P07355
Myosin light polypeptide 6	P60660
Major vault protein	Q14764
Heterogeneous nuclear ribonucleoprotein D0	Q14103
60S acidic ribosomal protein P0	P05388
X-ray repair cross-complementing protein 6	P12956
40S ribosomal protein S20	P60866
Protein arginine N-methyltransferase 1	Q99873
40S ribosomal protein S10	P46783
Transaldolase	P37837
Histone H2B type 1-	P23527
Triosephosphate isomerase	P60174
Protein S100-A6	P06703
40S ribosomal protein S17	P08708
CD9 antigen	P21926
Filamin-A	P21333
Peptidyl-prolyl cis-trans isomerase FKBP4	Q02790
Programmed cell death 6-interacting protein	Q8WUM4
Glutathione S-transferase P	P09211
14-3-3 protein epsilon	P62258

Table 19: 100 most abundant proteins (name and SwissProt accession number) observed in CTX0E03 exosomes

Microvesicles

2940 proteins were identified by Mass spectrometry in Microvesicles isolated from the initial stages of an Integra culture (week 2) and purified by centrifugation at 10,000 x g. The gene names and corresponding SWISSPROT accession numbers (in brackets) of all 2940 proteins are listed in Table 20 (in alphabetical order of gene name) and the 100 most abundant proteins are listed in Table 21, in order of decreasing abundance.

A1BG (P04217), AACS (Q86V21), AAMP (Q13685), AARS (P49588), AARSD1 (Q9BTE6), AASDHPPT (Q9NRN7), ABCA3 (Q99758), ABCC1 (P33527), ABCC4 (O15439), ABCE1 (P61221), ABCF1 (Q8NE71), ABCF2 (Q9UG63), ABCF3 (Q9NUQ8), ABHD14B (Q96IU4), ABI1 (Q8IZP0), ABR (Q12979), ACAA1 (P09110), ACAA2 (P42765), ACACA (Q13085), ACADM (P11310), ACADVL (P49748), ACAT1 (P24752), ACAT2 (Q9BWD1), ACBD6 (Q9BR61), ACBD7 (Q8N6N7), ACLY (P53396), ACO1 (P21399), ACO2 (Q99798), ACOT1 (Q86TX2), ACOT13 (Q9NPJ3), ACOT7 (O00154), ACOX1 (Q15067), ACOX3 (O15254), ACP1 (P24666), ACSL1 (P33121), ACSL3 (O95573), ACSL4 (O60488), ACSS2 (Q9NR19), ACTC1 (P68032), ACTG1 (P63261), ACTL6A (O96019), ACTN1 (P12814), ACTN4 (O43707), ACTR10 (Q9NZ32),

ACTR1A (P61163), ACTR1B (P42025), ACTR2 (P61160), ACTR3 (P61158), ACY1 (Q03154), ADAM10 (O14672), ADAM9 (Q13443), ADAMTS15 (Q8TE58), ADAMTS16 (Q8TE57), ADAR (P55265), ADD1 (P35611), ADD3 (Q9UEY8), ADH5 (P11766), ADK (P55263), ADO (Q96SZ5), ADPRH (P54922), ADRBK1 (P25098), ADRM1 (Q16186), ADSL (P30566), ADSS (P30520), AEBP1 (Q8IUX7), AFM (P43652), AGL (P35573), AGPS (O00116), AGRN (O00468), AHCY (P23526), AHCYL1 (O43865), AHNAK (Q09666), AHNAK2 (Q8IVF2), AHSA1 (O95433), AHSG (P02765), AIDA (Q96BJ3), AIFM1 (O95831), AIMP1 (Q12904), AIMP2 (Q13155), AIP (O00170), AK1 (P00568), AK2 (P54819), AK3 (Q9UIJ7), AK4 (P27144), AKAP12 (Q02952), AKAP9 (Q99996), AKR1A1 (P14550), AKR1B1 (P15121), AKR1C1 (Q04828), AKR7A2 (O43488), AKR7A3 (O95154), AKT1 (P31749), ALCAM (Q13740), ALDH16A1 (Q8IZ83), ALDH18A1 (P54886), ALDH2 (P05091), ALDH3A1 (P30838), ALDH7A1 (P49419), ALDH9A1 (P49189), ALDOA (P04075), ALDOC (P09972), ALKBH2 (Q6NS38), ALOX12B (O75342), AMDHD2 (Q9Y303), AMPD2 (Q01433), ANAPC1 (Q9H1A4), ANAPC4 (Q9UJX5), ANAPC5 (Q9UJX4), ANAPC7 (Q9UJX3), ANKFY1 (Q9P2R3), ANKRD17 (O75179), ANKRD28 (O15084), ANKRD52 (Q8NB46), ANP32A (P39687), ANP32B (Q92688), ANP32E (Q9BTT0), ANXA1 (P04083), ANXA11 (P50995), ANXA2 (P07355), ANXA3 (P12429), ANXA4 (P09525), ANXA5 (P08758), ANXA6 (P08133), ANXA7 (P20073), AP1B1 (Q10567), AP1G1 (O43747), AP1M1 (Q9BXS5), AP1S2 (P56377), AP2A1 (O95782), AP2A2 (O94973), AP2B1 (P63010), AP2M1 (Q96CW1), AP2S1 (P53680), AP3B1 (O00203), AP3D1 (O14617), AP3M1 (Q9Y2T2), AP3S1 (Q92572), AP4S1 (Q9Y587), APEH (P13798), APEX1 (P27695), API5 (Q9BZZ5), APIP (Q96GX9), APMAP (Q9HDC9), APOA2 (P02652), APOBEC3C (Q9NRW3), APOH (P02749), APOL2 (Q9BQE5), APPL1 (Q9UKG1), APRT (P07741), AQR (O60306), ARAF (P10398), ARCN1 (P48444), ARF1 (P84077), ARF4 (P18085), ARF6 (P62330), ARFGAP2 (Q8N6H7), ARFIP1 (P53367), ARFIP2 (P53365), ARG1 (P05089), ARHGAP1 (Q07960), ARHGAP5 (Q13017), ARHGDIA (P52565), ARHGEF1 (Q92888), ARHGEF10 (O15013), ARHGEF6 (Q15052), ARHGEF7 (Q14155), ARIH1 (Q9Y4X5), ARIH2 (O95376), ARL1 (P40616), ARL2 (P36404), ARL3 (P36405), ARL6IP1 (Q15041), ARL8A (Q96BM9), ARL8B (Q9NVJ2), ARMC10 (Q8N2F6), ARMC6 (Q6NXE6), ARMC8 (Q8IUR7), ARMC9 (Q7Z3E5), ARPC1A (Q92747), ARPC1B (O15143), ARPC2 (O15144), ARPC3 (O15145), ARPC4 (P59998), ARPC5 (O15511), ARPC5L (Q9BPX5), ASAH1 (Q13510), ASCC1 (Q8N9N2), ASCC3 (Q8N3C0), ASMTL (O95671), ASNA1 (O43681), ASNS (P08243), ASPSCR1 (Q9BZE9), ASS1 (P00966), ATAD3A (Q9NVI7), ATE1 (O95260), ATG101 (Q9BSB4), ATG16L1 (Q676U5), ATG3 (Q9NT62), ATG4B (Q9Y4P1), ATG7 (O95352), ATIC (P31939), ATL3 (Q6DD88), ATM (Q13315), ATOX1 (O00244), ATP1A1 (P05023), ATP1B1 (P05026), ATP1B3 (P54709), ATP2A2 (P16615), ATP2B1 (P20020), ATP2B4 (P23634), ATP5A1 (P25705), ATP5B (P06576), ATP5C1 (P36542), ATP5E (P56381), ATP5F1 (P24539), ATP5H (O75947), ATP5I (P56385), ATP5L (O75964), ATP5O (P48047), ATP6AP1 (Q15904), ATP6AP2 (O75787), ATP6V0A1 (Q93050),

ATP6V0D1 (P61421), ATP6V1A (P38606), ATP6V1B2 (P21281), ATP6V1C1 (P21283), ATP6V1D (Q9Y5K8), ATP6V1E1 (P36543), ATP6V1G1 (O75348), ATP6V1H (Q9UI12), ATR (Q13535), ATRN (O75882), ATXN10 (Q9UBB4), B2M (P61769), B3GAT3 (O94766), B3GNT1 (O43505), BAG2 (O95816), BAG5 (Q9UL15), BAIAP2 (Q9UQB8), BANF1 (O75531), BAT1 (Q13838), BAT3 (P46379), BCAM (P50895), BCAS2 (O75934), BCAT1 (P54687), BCCIP (Q9P287), BCL2L12 (Q9HB09), BDH2 (Q9BUT1), BICD2 (Q8TD16), BLMH (Q13867), BLVRA (P53004), BLVRB (P30043), BMP1 (P13497), BOLA2 (Q9H3K6), BOP1 (Q14137), BPGM (P07738), BPNT1 (O95861), BRCC3 (P46736), BRE (Q9NXR7), BRIX1 (Q8TDN6), BROX (Q5VW32), BRP16L (P0CB43), BSG (P35613), BST1 (Q10588), BTAF1 (O14981), BUB3 (O43684), BUD31 (P41223), BYSL (Q13895), BZW1 (Q7L1Q6), BZW2 (Q9Y6E2), C10orf119 (Q9BTE3), C10orf58 (Q9BRX8), C10orf76 (Q5T2E6), C11orf54 (Q9H0W9), C11orf68 (Q9H3H3), C12orf10 (Q9HB07), C12orf57 (Q99622), C14orf149 (Q96EM0), C14orf166 (Q9Y224), C14orf21 (Q86U38), C15orf58 (Q6ZNW5), C16orf13 (Q96S19), C16orf61 (Q9NRP2), C16orf80 (Q9Y6A4), C18orf21 (Q32NC0), C18orf8 (Q96DM3), C1orf123 (Q9NWV4), C1orf128 (Q9GZP4), C1orf57 (Q9BSD7), C20orf11 (Q9NWU2), C20orf4 (Q9Y312), C21orf33 (P30042), C21orf59 (P57076), C22orf28 (Q9Y3I0), C3orf10 (Q8WUW1), C3orf26 (Q9BQ75), C3orf75 (Q0PNE2), C4orf27 (Q9NWY4), C4orf41 (Q7Z392), C4orf43 (Q96EY4), C5orf33 (Q4G0N4), C6orf211 (Q9H993), C7orf28B (P86790), C7orf50 (Q9BRJ6), C7orf59 (Q0VGL1), C8orf33 (Q9H7E9), C9orf142 (Q9BUH6), C9orf23 (Q8N5L8), C9orf41 (Q8N4J0), C9orf64 (Q5T6V5), CA11 (O75493), CA12 (O43570), CA2 (P00918), CAB39 (Q9Y376), CACNA2D1 (P54289), CACYBP (Q9HB71), CAD (P27708), CADM1 (Q9BY67), CADM4 (Q8NFZ8), CALB1 (P05937), CALD1 (Q05682), CALM1 (P62158), CALR (P27797), CALU (O43852), CAMK1 (Q14012), CAMK2D (Q13557), CAMKV (Q8NCB2), CAND1 (Q86VP6), CANX (P27824), CAP1 (Q01518), CAPN1 (P07384), CAPN2 (P17655), CAPN5 (O15484), CAPN7 (Q9Y6W3), CAPNS1 (P04632), CAPRIN1 (Q14444), CAPS (Q13938), CAPZA1 (P52907), CAPZA2 (P47755), CAPZB (P47756), CARHSP1 (Q9Y2V2), CARKD (Q8IW45), CARM1 (Q86X55), CARS (P49589), CASK (O14936), CASP14 (P31944), CASP3 (P42574), CASP7 (P55210), CAT (P04040), CBFB (Q13951), CBR1 (P16152), CBR3 (O75828), CBS (P35520), CBX1 (P83916), CBX3 (Q13185), CBX5 (P45973), CC2D1A (Q6P1N0), CCAR1 (Q8IX12), CCBL2 (Q6YP21), CCDC102B (Q68D86), CCDC22 (O60826), CCDC25 (Q86WR0), CCDC93 (Q567U6), CCND2 (P30279), CCNY (Q8ND76), CCT2 (P78371), CCT3 (P49368), CCT4 (P50991), CCT5 (P48643), CCT6A (P40227), CCT7 (Q99832), CCT8 (P50990), CD109 (Q6YHK3), CD151 (P48509), CD276 (Q5ZPR3), CD44 (P16070), CD46 (P15529), CD47 (Q08722), CD58 (P19256), CD59 (P13987), CD63 (P08962), CD81 (P60033), CD9 (P21926), CD97 (P48960), CD99 (P14209), CDC123 (O75794), CDC16 (Q13042), CDC23 (Q9UJX2), CDC34 (P49427), CDC37 (Q16543), CDC40 (O60508), CDC42 (P60953), CDC42BPB (Q9Y5S2), CDC5L (Q99459), CDCP1 (Q9H5V8), CDH2 (P19022), CDK1 (P06493), CDK2

(P24941), CDK4 (P11802), CDK5 (Q00535), CDK5RAP3 (Q96JB5), CDK7 (P50613), CDKN2A (P42771), CDKN2AIP (Q9NXV6), CECR5 (Q9BXW7), CELF1 (Q92879), CELSR1 (Q9NYQ6), CELSR2 (Q9HCU4), CFL1 (P23528), CFL2 (Q9Y281), CHCHD3 (Q9NX63), CHD4 (Q14839), CHEK2 (O96017), CHERP (Q8IWX8), CHID1 (Q9BWS9), CHMP1A (Q9HD42), CHMP1B (Q7LBR1), CHMP2A (O43633), CHMP4A (Q9BY43), CHMP4B (Q9H444), CHMP5 (Q9NZZ3), CHMP6 (Q96FZ7), CHN1 (P15882), CHORDC1 (Q9UHD1), CHP (Q99653), CHRAC1 (Q9NRG0), CHST3 (Q7LGC8), CIAO1 (O76071), CIAPIN1 (Q6FI81), CIRBP (Q14011), CIRH1A (Q969X6), CISD2 (Q8N5K1), CKAP4 (Q07065), CKAP5 (Q14008), CKB (P12277), CLASP1 (Q7Z460), CLIC1 (O00299), CLIC4 (Q9Y696), CLLD6 (Q5W111), CLNS1A (P54105), CLPB (Q9H078), CLTA (P09496), CLTC (Q00610), CLTCL1 (P53675), CLU (P10909), CMBL (Q96DG6), CMC1 (Q7Z7K0), CMPK1 (P30085), CMTM6 (Q9NX76), CNBP (P62633), CNDP2 (Q96KP4), CNN2 (Q99439), CNN3 (Q15417), CNNM3 (Q8NE01), CNOT1 (A5YKK6), CNOT10 (Q9H9A5), CNOT6L (Q96LI5), CNP (P09543), COASY (Q13057), COBRA1 (Q8WX92), COG1 (Q8WTW3), COG3 (Q96JB2), COG4 (Q9H9E3), COG5 (Q9UP83), COG6 (Q9Y2V7), COL11A1 (P12107), COL14A1 (Q05707), COL18A1 (P39060), COL6A1 (P12109), COMMD10 (Q9Y6G5), COMMD2 (Q86X83), COMMD3 (Q9UBI1), COMMD5 (Q9GZQ3), COMMD8 (Q9NX08), COMMD9 (Q9P000), COMT (P21964), COPA (P53621), COPB1 (P53618), COPB2 (P35606), COPE (O14579), COPG (Q9Y678), COPG2 (Q9UBF2), COPS2 (P61201), COPS3 (Q9UNS2), COPS4 (Q9BT78), COPS5 (Q92905), COPS6 (Q7L5N1), COPS7A (Q9UBW8), COPS7B (Q9H9Q2), COPS8 (Q99627), CORO1B (Q9BR76), CORO1C (Q9ULV4), CORO2B (Q9UQ03), CORO7 (P57737), COTL1 (Q14019), COX4NB (O43402), COX5A (P20674), COX5B (P10606), COX6C (P09669), CP (P00450), CPD (O75976), CPNE1 (Q99829), CPNE2 (Q96FN4), CPNE3 (O75131), CPNE4 (Q96A23), CPNE7 (Q9UBL6), CPOX (P36551), CPSF1 (Q10570), CPSF2 (Q9P2I0), CPSF3 (Q9UKF6), CPSF3L (Q5TA45), CPSF6 (Q16630), CPSF7 (Q8N684), CPXM1 (Q96SM3), CRABP2 (P29373), CRIP2 (P52943), CRK (P46108), CRLF3 (Q8IUI8), CRNKL1 (Q9BZJ0), CRTAP (O75718), CRYAB (P02511), CRYM (Q14894), CRYZ (Q08257), CRYZL1 (O95825), CS (O75390), CSDE1 (O75534), CSE1L (P55060), CSK (P41240), CSNK1A1 (P48729), CSNK2A1 (P68400), CSNK2A2 (P19784), CSNK2B (P67870), CSRP1 (P21291), CSRP2 (Q16527), CSTB (P04080), CSTF1 (Q05048), CSTF2T (Q9H0L4), CSTF3 (Q12996), CTBP1 (Q13363), CTBP2 (P56545), CTNNA1 (P35221), CTNNAL1 (Q9UBT7), CTNNB1 (P35222), CTNNBL1 (Q8WYA6), CTNND1 (O60716), CTPS (P17812), CTPS2 (Q9NRF8), CTR9 (Q6PD62), CTSC (P53634), CTSD (P07339), CTSF (Q9UBX1), CTSL2 (O60911), CTTN (Q14247), CTU1 (Q7Z7A3), CUL1 (Q13616), CUL2 (Q13617), CUL3 (Q13618), CUL4A (Q13619), CUL4B (Q13620), CUL5 (Q93034), CUL7 (Q14999), CXADR (P78310), CXCL14 (O95715), CXorf26 (Q9BVG4), CXorf38 (Q8TB03), CYB5R3 (P00387), CYC1 (P08574), CYCS (P99999), CYFIP1 (Q7L576), CYFIP2 (Q96F07), CYR61 (O00622), DAB1 (O75553), DAD1 (P61803), DAG1 (Q14118), DAK (Q3LXA3), DAPK3 (O43293), DARS (P14868), DAZAP1

(Q96EP5), DBI (P07108), DBN1 (Q16643), DBNL (Q9UJU6), DCAF7 (P61962), DCAF8 (Q5TAQ9), DCBLD2 (Q96PD2), DCK (P27707), DCLK1 (O15075), DCPS (Q96C86), DCTD (P32321), DCTN1 (Q14203), DCTN2 (Q13561), DCTN3 (O75935), DCTN4 (Q9UJW0), DCTN5 (Q9BTE1), DCTN6 (O00399), DCUN1D1 (Q96GG9), DCUN1D3 (Q8IWE4), DCUN1D5 (Q9BTE7), DCXR (Q7Z4W1), DDA1 (Q9BW61), DDAH1 (O94760), DDAH2 (O95865), DDB1 (Q16531), DDB2 (Q92466), DDI2 (Q5TDH0), DDOST (P39656), DDR1 (Q08345), DDT (P30046), DDX1 (Q92499), DDX17 (Q92841), DDX18 (Q9NVP1), DDX19A (Q9NUU7), DDX20 (Q9UHI6), DDX21 (Q9NR30), DDX23 (Q9BUQ8), DDX24 (Q9GZR7), DDX27 (Q96GQ7), DDX39 (O00148), DDX3X (O00571), DDX46 (Q7L014), DDX47 (Q9H0S4), DDX49 (Q9Y6V7), DDX5 (P17844), DDX50 (Q9BQ39), DDX51 (Q8N8A6), DDX52 (Q9Y2R4), DDX54 (Q8TDD1), DDX55 (Q8NHQ9), DDX56 (Q9NY93), DDX6 (P26196), DECR1 (Q16698), DECR2 (Q9NUI1), DEF (Q68CQ4), DEK (P35659), DENR (O43583), DERA (Q9Y315), DFFA (O00273), DFFB (O76075), DHCR24 (Q15392), DHCR7 (Q9UBM7), DHFR (P00374), DHPS (P49366), DHRS11 (Q6UWP2), DHRS4 (Q9BTZ2), DHX15 (O43143), DHX16 (O60231), DHX29 (Q7Z478), DHX30 (Q7L2E3), DHX32 (Q7L7V1), DHX36 (Q9H2U1), DHX37 (Q8IY37), DHX38 (Q92620), DHX9 (Q08211), DIAPH1 (O60610), DIAPH2 (O60879), DIMT1L (Q9UNQ2), DIP2A (Q14689), DIP2B (Q9P265), DIP2C (Q9Y2E4), DIS3 (Q9Y2L1), DIS3L2 (Q8IYB7), DKC1 (O60832), DLAT (P10515), DLD (P09622), DLG1 (Q12959), DLGAP4 (Q9Y2H0), DLST (P36957), DMD (P11532), DNAJA1 (P31689), DNAJA2 (O60884), DNAJB1 (P25685), DNAJB11 (Q9UBS4), DNAJB4 (Q9UDY4), DNAJB6 (O75190), DNAJC13 (O75165), DNAJC2 (Q99543), DNAJC3 (Q13217), DNAJC7 (Q99615), DNASE1L1 (P49184), DNM1 (Q05193), DNM1L (O00429), DNM2 (P50570), DNMT1 (P26358), DNPEP (Q9ULA0), DOCK1 (Q14185), DOCK4 (Q8N1I0), DOCK5 (Q9H7D0), DOCK7 (Q96N67), DOCK9 (Q9BZ29), DOHH (Q9BU89), DPCD (Q9BVM2), DPH2 (Q9BQC3), DPH5 (Q9H2P9), DPM1 (O60762), DPM3 (Q9P2X0), DPP3 (Q9NY33), DPP9 (Q86TI2), DPY30 (Q9C005), DPYSL2 (Q16555), DPYSL3 (Q14195), DPYSL4 (O14531), DPYSL5 (Q9BPU6), DRG1 (Q9Y295), DRG2 (P55039), DSC1 (Q08554), DSG1 (Q02413), DSP (P15924), DST (Q03001), DSTN (P60981), DTD1 (Q8TEA8), DTNA (Q9Y4J8), DTYMK (P23919), DUS2L (Q9NX74), DUS3L (Q96G46), DUSP12 (Q9UNI6), DUSP3 (P51452), DYM (Q7RTS9), DYNC1H1 (Q14204), DYNC1I2 (Q13409), DYNC1LI1 (Q9Y6G9), DYNC1LI2 (O43237), DYNC2H1 (Q8NCM8), DYNLL1 (P63167), DYNLL2 (Q96FJ2), DYNLRB1 (Q9NP97), DYNLT1 (P63172), EBNA1BP2 (Q99848), ECE1 (P42892), ECHDC1 (Q9NTX5), ECHS1 (P30084), ECM29 (Q5VYK3), EDC3 (Q96F86), EDC4 (Q6P2E9), EEA1 (Q15075), EEF1A1 (P68104), EEF1B2 (P24534), EEF1D (P29692), EEF1E1 (O43324), EEF1G (P26641), EEF2 (P13639), EEF2K (O00418), EEFSEC (P57772), EFEMP2 (O95967), EFHD2 (Q96C19), EFTUD1 (Q7Z2Z2), EFTUD2 (Q15029), EGFR (P00533), EHD1 (Q9H4M9), EHD2 (Q9NZN4), EHD3 (Q9NZN3), EHD4 (Q9H223), EIF1AX (P47813), EIF2A (Q9BY44), EIF2AK2 (P19525), EIF2AK4 (Q9P2K8), EIF2B1 (Q14232), EIF2B2 (P49770), EIF2B3 (Q9NR50), EIF2B4

(Q9UI10), EIF2B5 (Q13144), EIF2C1 (Q9UL18), EIF2C2 (Q9UKV8), EIF2S1 (P05198), EIF2S2 (P20042), EIF2S3 (P41091), EIF3A (Q14152), EIF3B (P55884), EIF3C (Q99613), EIF3D (O15371), EIF3E (P60228), EIF3F (O00303), EIF3G (O75821), EIF3H (O15372), EIF3I (Q13347), EIF3J (O75822), EIF3K (Q9UBQ5), EIF3L (Q9Y262), EIF3M (Q7L2H7), EIF4A1 (P60842), EIF4A2 (Q14240), EIF4A3 (P38919), EIF4E (P06730), EIF4G1 (Q04637), EIF4G2 (P78344), EIF4H (Q15056), EIF5 (P55010), EIF5A (P63241), EIF5B (O60841), EIF6 (P56537), ELAC2 (Q9BQ52), ELAVL1 (Q15717), ELMO2 (Q96JJ3), ELP2 (Q6IA86), ELP3 (Q9H9T3), EMD (P50402), EMG1 (Q92979), EML1 (O00423), EML2 (O95834), EML3 (Q32P44), EML4 (Q9HC35), ENAH (Q8N8S7), ENC1 (O14682), ENO1 (P06733), ENO2 (P09104), ENOPH1 (Q9UHY7), ENY2 (Q9NPA8), EPB41L2 (O43491), EPB41L3 (Q9Y2J2), EPDR1 (Q9UM22), EPHA2 (P29317), EPHB2 (P29323), EPHB3 (P54753), EPHB4 (P54760), EPHX1 (P07099), EPM2AIP1 (Q7L775), EPN1 (Q9Y6I3), EPRS (P07814), ERBB2IP (Q96RT1), ERGIC1 (Q969X5), ERH (P84090), ERI1 (Q8IV48), ERI3 (O43414), ERLIN2 (O94905), ERO1L (Q96HE7), ERP29 (P30040), ERP44 (Q9BS26), ESD (P10768), ESYT1 (Q9BSJ8), ETF1 (P62495), ETFA (P13804), ETFB (P38117), EXOC1 (Q9NV70), EXOC2 (Q96KP1), EXOC3 (O60645), EXOC4 (Q96A65), EXOC5 (O00471), EXOC6 (Q8TAG9), EXOC6B (Q9Y2D4), EXOC7 (Q9UPT5), EXOC8 (Q8IYI6), EXOSC1 (Q9Y3B2), EXOSC10 (Q01780), EXOSC2 (Q13868), EXOSC3 (Q9NQT5), EXOSC4 (Q9NPD3), EXOSC5 (Q9NQT4), EXOSC6 (Q5RKV6), EXOSC7 (Q15024), EXOSC8 (Q96B26), EXOSC9 (Q06265), EZR (P15311), F11R (Q9Y624), F8 (P00451), F8A1 (P23610), FABP5 (Q01469), FABP7 (O15540), FADD (Q13158), FAH (P16930), FAHD1 (Q6P587), FAHD2A (Q96GK7), FAM115A (Q9Y4C2), FAM120A (Q9NZB2), FAM125A (Q96EY5), FAM127A (A6ZKI3), FAM129A (Q9BZQ8), FAM129B (Q96TA1), FAM136A (Q96C01), FAM175B (Q15018), FAM3C (Q92520), FAM45B (Q6NSW5), FAM49B (Q9NUQ9), FAM82B (Q96DB5), FAM84B (Q96KN1), FAM96B (Q9Y3D0), FAM98A (Q8NCA5), FAM98B (Q52LJ0), FANCI (Q9NVI1), FAR1 (Q8WVX9), FARP1 (Q9Y4F1), FARP2 (O94887), FARSA (Q9Y285), FARSB (Q9NSD9), FAS (P25445), FASN (P49327), FAT1 (Q14517), FAU (P62861), FBL (P22087), FBLN2 (P98095), FBN1 (P35555), FBN2 (P35556), FBXL18 (Q96ME1), FBXO21 (O94952), FBXO22 (Q8NEZ5), FBXW11 (Q9UKB1), FCF1 (Q9Y324), FDFT1 (P37268), FDPS (P14324), FDXR (P22570), FEN1 (P39748), FERMT1 (Q9BQL6), FERMT2 (Q96AC1), FFR (Q9UID3), FGFBP3 (Q8TAT2), FH (P07954), FHL1 (Q13642), FHL2 (Q14192), FHL3 (Q13643), FIBP (O43427), FKBP10 (Q96AY3), FKBP1A (P62942), FKBP2 (P26885), FKBP3 (Q00688), FKBP4 (Q02790), FKBP5 (Q13451), FLG (P20930), FLG2 (Q5D862), FLII (Q13045), FLNA (P21333), FLNB (O75369), FLNC (Q14315), FLOT1 (O75955), FLOT2 (Q14254), FMNL2 (Q96PY5), FN3K (Q9H479), FN3KRP (Q9HA64), FNTA (P49354), FNTB (P49356), FOLR1 (P15328), FREM2 (Q5SZK8), FRG1 (Q14331), FRMD5 (Q7Z6J6), FRMD8 (Q9BZ67), FRYL (O94915), FSCN1 (Q16658), FSD1 (Q9BTV5), FTH1 (P02794), FTL (P02792), FTO (Q9C0B1), FTSJD2 (Q8N1G2), FUBP1 (Q96AE4), FUBP3

(Q96I24), FUCA2 (Q9BTY2), FUK (Q8N0W3), FUS (P35637), FXR1 (P51114), FXR2 (P51116), FYCO1 (Q9BQS8), FYN (P06241), G3BP1 (Q13283), G3BP2 (Q9UN86), G6PD (P11413), GAA (P10253), GALK1 (P51570), GALK2 (Q01415), GALNT1 (Q10472), GALNT2 (Q10471), GALNT7 (Q86SF2), GAN (Q9H2C0), GANAB (Q14697), GAP43 (P17677), GAPDH (P04406), GAPVD1 (Q14C86), GAR1 (Q9NY12), GARS (P41250), GART (P22102), GATSL2 (A6NHX0), GBA (P04062), GBE1 (Q04446), GBF1 (Q92538), GCDH (Q92947), GCLC (P48506), GCLM (P48507), GCN1L1 (Q92616), GDI1 (P31150), GDI2 (P50395), GEMIN4 (P57678), GEMIN5 (Q8TEQ6), GEMIN6 (Q8WXD5), GET4 (Q7L5D6), GFAP (P14136), GFM1 (Q96RP9), GFPT1 (Q06210), GFPT2 (O94808), GGCT (O75223), GGPS1 (O95749), GINS1 (Q14691), GINS2 (Q9Y248), GINS4 (Q9BRT9), GIPC1 (O14908), GIT1 (Q9Y2X7), GLA (P06280), GLB1L2 (Q8IW92), GLE1 (Q53GS7), GLG1 (Q92896), GLIPR2 (Q9H4G4), GLMN (Q92990), GLO1 (Q04760), GLOD4 (Q9HC38), GLRX (P35754), GLRX3 (O76003), GLT25D1 (Q8NBJ5), GLT25D2 (Q8IYK4), GLTP (Q9NZD2), GLUD1 (P00367), GLUL (P15104), GMDS (O60547), GMFB (P60983), GMPPA (Q96IJ6), GMPPB (Q9Y5P6), GMPR (P36959), GMPR2 (Q9P2T1), GMPS (P49915), GNA11 (P29992), GNA12 (Q03113), GNA13 (Q14344), GNAI1 (P63096), GNAI2 (P04899), GNAI3 (P08754), GNAQ (P50148), GNAS (Q5JWF2), GNB1 (P62873), GNB1L (Q9BYB4), GNB2 (P62879), GNB2L1 (P63244), GNB4 (Q9HAV0), GNE (Q9Y223), GNG10 (P50151), GNG12 (Q9UBI6), GNG4 (P50150), GNG5 (P63218), GNL3 (Q9BVP2), GNPDA1 (P46926), GNPNAT1 (Q96EK6), GOLGA7 (Q7Z5G4), GOLM1 (Q8NBJ4), GOLPH3 (Q9H4A6), GORASP2 (Q9H8Y8), GOT1 (P17174), GOT2 (P00505), GPC1 (P35052), GPC4 (O75487), GPC6 (Q9Y625), GPD1L (Q8N335), GPHN (Q9NQX3), GPI (P06744), GPM6A (P51674), GPN1 (Q9HCN4), GPR50 (Q13585), GPR56 (Q9Y653), GPS1 (Q13098), GPSM1 (Q86YR5), GPX1 (P07203), GPX4 (P36969), GRB2 (P62993), GRHPR (Q9UBQ7), GRP (Q3ZCW2), GRWD1 (Q9BQ67), GSDMA (Q96QA5), GSK3A (P49840), GSK3B (P49841), GSN (P06396), GSPT1 (P15170), GSR (P00390), GSS (P48637), GSTK1 (Q9Y2Q3), GSTM2 (P28161), GSTM3 (P21266), GSTM4 (Q03013), GSTO1 (P78417), GSTP1 (P09211), GSTT2 (P0CG29), GSTZ1 (O43708), GTF2E2 (P29084), GTF2F2 (P13984), GTF2H3 (Q13889), GTF2I (P78347), GTF3C2 (Q8WUA4), GTF3C3 (Q9Y5Q9), GTF3C4 (Q9UKN8), GTPBP1 (O00178), GTPBP4 (Q9BZE4), GUK1 (Q16774), GYG1 (P46976), GYS1 (P13807), H1F0 (P07305), H1FX (Q92522), H2AFX (P16104), H2AFY (O75367), H2AFZ (P0C0S5), HADH (Q16836), HADHA (P40939), HARS (P12081), HAT1 (O14929), HAUS3 (Q68CZ6), HAUS4 (Q9H6D7), HBA1 (P69905), HBB (P68871), HBS1L (Q9Y450), HBXIP (O43504), HCFC1 (P51610), HDAC1 (Q13547), HDAC2 (Q92769), HDDC2 (Q7Z4H3), HDGF (P51858), HDGFRP2 (Q7Z4V5), HDHD2 (Q9H0R4), HDLBP (Q00341), HEATR1 (Q9H583), HEATR2 (Q86Y56), HEBP1 (Q9NRV9), HECTD3 (Q5T447), HERC4 (Q5GLZ8), HEXB (P07686), HGS (O14964), HHIP (Q96QV1), HINT1 (P49773), HINT2 (Q9BX68), HINT3 (Q9NQE9), HIP1R (O75146), HIST1H1B (P16401), HIST1H1C (P16403), HIST1H1D (P16402), HIST1H1E (P10412), HIST1H2AD

(P20671), HIST1H2BJ (P06899), HIST1H2BM (Q99879), HIST1H2BO (P23527), HIST1H4A (P62805), HIST2H2AA3 (Q6FI13), HIST2H2AB (Q8IUE6), HIST2H2BE (Q16778), HIST2H3A (Q71DI3), HIST3H2BB (Q8N257), HK1 (P19367), HK2 (P52789), HLA-A (P30443), HLA-A (P01892), HLA-B (P03989), HMGA1 (P17096), HMGB1 (P09429), HMGB2 (P26583), HMGCL (P35914), HMGCS1 (Q01581), HMGN1 (P05114), HMGN2 (P05204), HMGN4 (O00479), HNRNPA0 (Q13151), HNRNPA1 (P09651), HNRNPA2B1 (P22626), HNRNPA3 (P51991), HNRNPAB (Q99729), HNRNPC (P07910), HNRNPD (Q14103), HNRNPF (P52597), HNRNPH1 (P31943), HNRNPH2 (P55795), HNRNPH3 (P31942), HNRNPK (P61978), HNRNPL (P14866), HNRNPM (P52272), HNRNPR (O43390), HNRNPU (Q00839), HNRNPUL1 (Q9BUJ2), HNRNPUL2 (Q1KMD3), HNRPDL (O14979), HNRPLL (Q8WVV9), HOOK3 (Q86VS8), HP (P00738), HP1BP3 (Q5SSJ5), HPCAL1 (P37235), HPRT1 (P00492), HPX (P02790), HRAS (P01112), HRNR (Q86YZ3), HSD17B10 (Q99714), HSD17B12 (Q53GQ0), HSD17B4 (P51659), HSDL2 (Q6YN16), HSP90AA1 (P07900), HSP90AB1 (P08238), HSP90B1 (P14625), HSPA12A (O43301), HSPA14 (Q0VDF9), HSPA1A (P08107), HSPA4 (P34932), HSPA4L (O95757), HSPA5 (P11021), HSPA8 (P11142), HSPA9 (P38646), HSPB1 (P04792), HSPBP1 (Q9NZL4), HSPD1 (P10809), HSPE1 (P61604), HSPG2 (P98160), HSPH1 (Q92598), HTRA1 (Q92743), HTT (P42858), HUWE1 (Q7Z6Z7), HYOU1 (Q9Y4L1), IARS (P41252), ICAM1 (P05362), IDE (P14735), IDH1 (O75874), IDH2 (P48735), IDH3A (P50213), IDI1 (Q13907), IFI16 (Q16666), IFIT5 (Q13325), IFITM3 (Q01628), IFRD2 (Q12894), IFT172 (Q9UG01), IGF1R (P08069), IGF2BP2 (Q9Y6M1), IGF2BP3 (O00425), IGF2R (P11717), IGFBP3 (P17936), IGFBP5 (P24593), IGHG1 (P01857), IGHG2 (P01859), IGSF3 (O75054), IGSF8 (Q969P0), IKBKAP (O95163), IKBKB (O14920), IL1RAP (Q9NPH3), ILF2 (Q12905), ILF3 (Q12906), ILK (Q13418), ILKAP (Q9H0C8), IMMT (Q16891), IMP3 (Q9NV31), IMPA1 (P29218), IMPA2 (O14732), IMPAD1 (Q9NX62), IMPDH1 (P20839), IMPDH2 (P12268), INA (Q16352), INF2 (Q27J81), INPP1 (P49441), INPPL1 (O15357), INTS10 (Q9NVR2), INTS3 (Q68E01), INTS7 (Q9NVH2), INTS8 (Q75QN2), IPO11 (Q9UI26), IPO4 (Q8TEX9), IPO5 (O00410), IPO7 (O95373), IPO8 (O15397), IPO9 (Q96P70), IQGAP1 (P46940), IRF2BP2 (Q7Z5L9), IRF3 (Q14653), IRGQ (Q8WZA9), ISOC1 (Q96CN7), ISYNA1 (Q9NPH2), ITFG3 (Q9H0X4), ITGA2 (P17301), ITGA3 (P26006), ITGA4 (P13612), ITGA5 (P08648), ITGA6 (P23229), ITGA7 (Q13683), ITGAV (P06756), ITGB1 (P05556), ITGB1BP1 (O14713), ITGB3 (P05106), ITGB4 (P16144), ITGB5 (P18084), ITGB8 (P26012), ITPA (Q9BY32), JAM3 (Q9BX67), JUP (P14923), KARS (Q15046), KATNB1 (Q9BVA0), KBTBD6 (Q86V97), KCTD21 (Q4G0X4), KDM1A (O60341), KEAP1 (Q14145), KHDRBS1 (Q07666), KHSRP (Q92945), KIAA0020 (Q15397), KIAA0090 (Q8N766), KIAA0174 (P53990), KIAA0196 (Q12768), KIAA0664 (O75153), KIAA0776 (O94874), KIAA1033 (Q2M389), KIAA1279 (Q96EK5), KIAA1598 (A0MZ66), KIAA1797 (Q5VW36), KIAA1949 (Q6NYC8), KIAA1967 (Q8N163), KIDINS220 (Q9ULH0), KIF1A (Q12756), KIF2A (O00139), KIF5B (P33176), KIF5C (O60282), KLC1 (Q07866), KLHDC4 (Q8TBB5), KLHL13

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(P49902), NT5C3L (Q969T7), NT5E (P21589), NTN1 (O95631), NUBP1 (P53384), NUBP2 (Q9Y5Y2), NUCB1 (Q02818), NUCKS1 (Q9H1E3), NUDC (Q9Y266), NUDCD1 (Q96RS6), NUDCD2 (Q8WVJ2), NUDT1 (P36639), NUDT10 (Q8NFP7), NUDT16 (Q96DE0), NUDT16L1 (Q9BRJ7), NUDT21 (O43809), NUDT4 (Q9NZJ9), NUDT5 (Q9UKK9), NUMA1 (Q14980), NUP188 (Q5SRE5), NUP210 (Q8TEM1), NUP37 (Q8NFH4), NUP43 (Q8NFH3), NUP54 (Q7Z3B4), NUP62 (P37198), NUP85 (Q9BW27), NUP88 (Q99567), NUP93 (Q8N1F7), NUTF2 (P61970), NXF1 (Q9UBU9), NXN (Q6DKJ4), NXT1 (Q9UKK6), OAT (P04181), OBSL1 (O75147), OCRL (Q01968), ODR4 (Q5SWX8), ODZ2 (Q9NT68), ODZ3 (Q9P273), OGFOD1 (Q8N543), OGT (O15294), OLA1 (Q9NTK5), OLFML3 (Q9NRN5), OPA1 (O60313), ORC3 (Q9UBD5), OSBP (P22059), OSBPL6 (Q9BZF3), OSGEP (Q9NPF4), OTUB1 (Q96FW1), OVCA2 (Q8WZ82), OXCT1 (P55809), OXSR1 (O95747), P4HA1 (P13674), P4HB (P07237), PA2G4 (Q9UQ80), PAAF1 (Q9BRP4), PABPC1 (P11940), PABPC4 (Q13310), PABPN1 (Q86U42), PACSIN2 (Q9UNF0), PACSIN3 (Q9UKS6), PAF1 (Q8N7H5), PAFAH1B1 (P43034), PAFAH1B2 (P68402), PAFAH1B3 (Q15102), PAICS (P22234), PAIP1 (Q9H074), PAK1IP1 (Q9NWT1), PAK2 (Q13177), PALD (Q9ULE6), PALLD (Q8WX93), PANK4 (Q9NVE7), PAPOLA (P51003), PAPSS1 (O43252), PARK7 (Q99497), PARN (O95453), PARP1 (P09874), PARP4 (Q9UKK3), PARVA (Q9NVD7), PBLD (P30039), PCBD1 (P61457), PCBP1 (Q15365), PCBP2 (Q15366), PCDHB2 (Q9Y5E7), PCDHGC3 (Q9UN70), PCID2 (Q5JVF3), PCMT1 (P22061), PCNA (P12004), PCOLCE2 (Q9UKZ9), PCYOX1 (Q9UHG3), PCYOX1L (Q8NBM8), PCYT2 (Q99447), PDCD10 (Q9BUL8), PDCD11 (Q14690), PDCD4 (Q53EL6), PDCD5 (O14737), PDCD6 (O75340), PDCD6IP (Q8WUM4), PDCL3 (Q9H2J4), PDDC1 (Q8NB37), PDE12 (Q6L8Q7), PDGFRA (P16234), PDIA3 (P30101), PDIA4 (P13667), PDIA5 (Q14554), PDIA6 (Q15084), PDLIM1 (O00151), PDLIM4 (P50479), PDLIM5 (Q96HC4), PDLIM7 (Q9NR12), PDRO (Q6IAA8), PDS5A (Q29RF7), PDS5B (Q9NTI5), PDXK (O00764), PDXP (Q96GD0), PEA15 (Q15121), PEBP1 (P30086), PECI (O75521), PEF1 (Q9UBV8), PELO (Q9BRX2), PELP1 (Q8IZL8), PEPD (P12955), PES1 (O00541), PFAS (O15067), PFDN1 (O60925), PFDN2 (Q9UHV9), PFDN4 (Q9NQP4), PFDN5 (Q99471), PFDN6 (O15212), PFKL (P17858), PFKM (P08237), PFKP (Q01813), PFN1 (P07737), PFN2 (P35080), PGAM1 (P18669), PGAM5 (Q96HS1), PGD (P52209), PGGT1B (P53609), PGK1 (P00558), PGLS (O95336), PGLYRP2 (Q96PD5), PGM1 (P36871), PGM2L1 (Q6PCE3), PGM3 (O95394), PGP (A6NDG6), PGRMC1 (O00264), PGRMC2 (O15173), PHB (P35232), PHB2 (Q99623), PHF5A (Q7RTV0), PHF6 (Q8IWS0), PHGDH (O43175), PHKB (Q93100), PHLDA1 (Q8WV24), PHLDA3 (Q9Y5J5), PHLDB1 (Q86UU1), PHPT1 (Q9NRX4), PI15 (O43692), PI4KA (P42356), PICALM (Q13492), PIGT (Q969N2), PIK3CA (P42336), PIK3R4 (Q99570), PIN1 (Q13526), PIP4K2A (P48426), PIP4K2B (P78356), PIP4K2C (Q8TBX8), PIPOX (Q9P0Z9), PIPSL (A2A3N6), PITPNB (P48739), PKM2 (P14618), PKP1 (Q13835), PLAA (Q9Y263), PLCB3 (Q01970), PLCD1 (P51178), PLCD3 (Q8N3E9), PLCG1 (P19174), PLCG2 (P16885), PLD3 (Q8IV08), PLEC

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(P29353), SHMT1 (P34896), SHMT2 (P34897), SHOC2 (Q9UQ13), SHPK (Q9UHJ6), SIRT5 (Q9NXA8), SKIV2L (Q15477), SKIV2L2 (P42285), SKP1 (P63208), SLC12A2 (P55011), SLC12A4 (Q9UP95), SLC16A1 (P53985), SLC1A3 (P43003), SLC1A5 (Q15758), SLC25A10 (Q9UBX3), SLC25A11 (Q02978), SLC25A13 (Q9UJS0), SLC25A22 (Q9H936), SLC25A3 (Q00325), SLC25A5 (P05141), SLC25A6 (P12236), SLC26A2 (P50443), SLC29A1 (Q99808), SLC29A2 (Q14542), SLC2A1 (P11166), SLC30A1 (Q9Y6M5), SLC38A1 (Q9H2H9), SLC3A2 (P08195), SLC44A2 (Q8IWA5), SLC4A2 (P04920), SLC4A7 (Q9Y6M7), SLC5A3 (P53794), SLC5A6 (Q9Y289), SLC6A8 (P48029), SLC7A1 (P30825), SLC7A5 (Q01650), SLC9A3R1 (O14745), SLC9A3R2 (Q15599), SLIRP (Q9GZT3), SLK (Q9H2G2), SMAD1 (Q15797), SMAD2 (Q15796), SMARCA4 (P51532), SMARCA5 (O60264), SMARCB1 (Q12824), SMARCC1 (Q92922), SMARCC2 (Q8TAQ2), SMARCD2 (Q92925), SMC1A (Q14683), SMC2 (O95347), SMC3 (Q9UQE7), SMC4 (Q9NTJ3), SMC5 (Q8IY18), SMCHD1 (A6NHR9), SMEK1 (Q6IN85), SMG1 (Q96Q15), SMN1 (Q16637), SMS (P52788), SMU1 (Q2TAY7), SMYD3 (Q9H7B4), SMYD5 (Q6GMV2), SNAP23 (O00161), SND1 (Q7KZF4), SNF8 (Q96H20), SNRNP200 (O75643), SNRNP40 (Q96DI7), SNRNP70 (P08621), SNRPA1 (P09661), SNRPB (P14678), SNRPB2 (P08579), SNRPD1 (P62314), SNRPD2 (P62316), SNRPD3 (P62318), SNRPE (P62304), SNRPF (P62306), SNRPG (P62308), SNTB1 (Q13884), SNTB2 (Q13425), SNX1 (Q13596), SNX12 (Q9UMY4), SNX17 (Q15036), SNX18 (Q96RF0), SNX2 (O60749), SNX27 (Q96L92), SNX3 (O60493), SNX5 (Q9Y5X3), SNX6 (Q9UNH7), SNX9 (Q9Y5X1), SOD1 (P00441), SOD2 (P04179), SORD (Q00796), SORT1 (Q99523), SPATS2L (Q9NUQ6), SPC24 (Q8NBT2), SPCS2 (Q15005), SPCS3 (P61009), SPG21 (Q9NZD8), SPIN1 (Q9Y657), SPR (P35270), SPRR1B (P22528), SPRR2E (P22531), SPTAN1 (Q13813), SPTBN1 (Q01082), SPTBN2 (O15020), SR140 (O15042), SRBD1 (Q8N5C6), SRCRL (A1L4H1), SRGAP2 (O75044), SRI (P30626), SRM (P19623), SRP14 (P37108), SRP19 (P09132), SRP54 (P61011), SRP68 (Q9UHB9), SRP72 (O76094), SRP9 (P49458), SRPK1 (Q96SB4), SRPR (P08240), SRPRB (Q9Y5M8), SRPX (P78539), SRPX2 (O60687), SRR (Q9GZT4), SRRM1 (Q8IYB3), SRRM2 (Q9UQ35), SRRT (Q9BXP5), SRSF1 (Q07955), SRSF10 (O75494), SRSF11 (Q05519), SRSF2 (Q01130), SRSF3 (P84103), SRSF5 (Q13243), SRSF6 (Q13247), SRSF7 (Q16629), SRSF9 (Q13242), SRXN1 (Q9BYN0), SSB (P05455), SSBP1 (Q04837), SSR1 (P43307), SSR3 (Q9UNL2), SSRP1 (Q08945), SSSCA1 (O60232), SSU72 (Q9NP77), ST13 (P50502), STAG1 (Q8WVM7), STAM (Q92783), STAMBP (O95630), STAT1 (P42224), STAT2 (P52630), STAT3 (P40763), STAU1 (O95793), STIP1 (P31948), STK10 (O94804), STK24 (Q9Y6E0), STK25 (O00506), STK38 (Q15208), STK38L (Q9Y2H1), STOM (P27105), STOML2 (Q9UJZ1), STON2 (Q8WXE9), STRAP (Q9Y3F4), STT3A (P46977), STUB1 (Q9UNE7), STX12 (Q86Y82), STX4 (Q12846), STX5 (Q13190), STXBP1 (P61764), STXBP3 (O00186), STYX (Q8WUJ0), SUB1 (P53999), SUCLA2 (Q9P2R7), SUCLG2 (Q96I99), SUGT1 (Q9Y2Z0), SULF2 (Q8IWU5), SUMO1 (P63165), SUPT16H (Q9Y5B9), SUPT4H1 (P63272),

SUPT5H (O00267), SUPT6H (Q7KZ85), SUSD5 (O60279), SVEP1 (Q4LDE5), SVIL (O95425), SWAP70 (Q9UH65), SYMPK (Q92797), SYNCRIP (O60506), SYNGR2 (O43760), SYNJ2BP (P57105), SYNM (O15061), SYPL1 (Q16563), TAB1 (Q15750), TAF9 (Q9Y3D8), TAGLN (Q01995), TAGLN2 (P37802), TALDO1 (P37837), TAOK1 (Q7L7X3), TARDBP (Q13148), TARS (P26639), TATDN1 (Q6P1N9), TAX1BP3 (O14907), TBC1D13 (Q9NVG8), TBC1D15 (Q8TC07), TBC1D23 (Q9NUY8), TBC1D24 (Q9ULP9), TBC1D4 (O60343), TBC1D9B (Q66K14), TBCA (O75347), TBCB (Q99426), TBCC (Q15814), TBCD (Q9BTW9), TBCE (Q15813), TBK1 (Q9UHD2), TBL1XR1 (Q9BZK7), TBL2 (Q9Y4P3), TBL3 (Q12788), TBPL1 (P62380), TCEA1 (P23193), TCEB1 (Q15369), TCEB2 (Q15370), TCERG1 (O14776), TCF25 (Q9BQ70), TCP1 (P17987), TELO2 (Q9Y4R8), TEX10 (Q9NXF1), TEX15 (Q9BXT5), TF (P02787), TFCP2 (Q12800), TFG (Q92734), TFRC (P02786), TGFB1 (P01137), TGFB2 (P61812), TGFBI (Q15582), TGFBRAP1 (Q8WUH2), TGM1 (P22735), TGM3 (Q08188), TH1L (Q8IXH7), THBS1 (P07996), THBS3 (P49746), THG1L (Q9NWX6), THOC2 (Q8NI27), THOC3 (Q96J01), THOC5 (Q13769), THOC6 (Q86W42), THOC7 (Q6I9Y2), THOP1 (P52888), THTPA (Q9BU02), THUMPD1 (Q9NXG2), THUMPD3 (Q9BV44), THY1 (P04216), THYN1 (Q9P016), TIA1 (P31483), TIAL1 (Q01085), TIGAR (Q9NQ88), TIMM13 (Q9Y5L4), TIMM44 (O43615), TIMM50 (Q3ZCQ8), TIMM8A (O60220), TIMM8B (Q9Y5J9), TIMM9 (Q9Y5J7), TIMP2 (P16035), TIPRL (O75663), TJP1 (Q07157), TKT (P29401), TLN1 (Q9Y490), TLN2 (Q9Y4G6), TM9SF3 (Q9HD45), TMED10 (P49755), TMED2 (Q15363), TMED5 (Q9Y3A6), TMED7 (Q9Y3B3), TMED9 (Q9BVK6), TMEFF2 (Q9UIK5), TMEM132A (Q24JP5), TMEM2 (Q9UHN6), TMEM30A (Q9NV96), TMEM33 (P57088), TMOD3 (Q9NYL9), TMPO (P42166), TMX1 (Q9H3N1), TNC (P24821), TNKS1BP1 (Q9C0C2), TNPO1 (Q92973), TNPO2 (O14787), TNPO3 (Q9Y5L0), TOM1L2 (Q6ZVM7), TOMM20 (Q15388), TOMM34 (Q15785), TOMM5 (Q8N4H5), TOMM70A (O94826), TOP1 (P11387), TOP2A (P11388), TOP2B (Q02880), TP53I3 (Q53FA7), TP53RK (Q96S44), TPBG (Q13641), TPD52 (P55327), TPI1 (P60174), TPM1 (P09493), TPM2 (P07951), TPM3 (P06753), TPM3L (A6NL28), TPM4 (P67936), TPP2 (P29144), TPT1 (P13693), TRA2A (Q13595), TRA2B (P62995), TRAF2 (Q12933), TRAP1 (Q12931), TRAPPC1 (Q9Y5R8), TRAPPC2L (Q9UL33), TRAPPC3 (O43617), TRAPPC4 (Q9Y296), TRAPPC5 (Q8IUR0), TRIM16 (O95361), TRIM22 (Q8IYM9), TRIM25 (Q14258), TRIM26 (Q12899), TRIM28 (Q13263), TRIM47 (Q96LD4), TRIM5 (Q9C035), TRIO (O75962), TRIP13 (Q15645), TRIP6 (Q15654), TRMT1 (Q9NXH9), TRMT112 (Q9UI30), TRMT5 (Q32P41), TRMT6 (Q9UJA5), TRMT61A (Q96FX7), TRNT1 (Q96Q11), TROVE2 (P10155), TRRAP (Q9Y4A5), TSG101 (Q99816), TSKU (Q8WUA8), TSN (Q15631), TSPAN14 (Q8NG11), TSPAN6 (O43657), TSR1 (Q2NL82), TSSC1 (Q53HC9), TSTA3 (Q13630), TTC1 (Q99614), TTC15 (Q8WVT3), TTC27 (Q6P3X3), TTC37 (Q6PGP7), TTC38 (Q5R3I4), TTC7B (Q86TV6), TTC9C (Q8N5M4), TTL (Q8NG68), TTLL12 (Q14166), TTN (Q8WZ42), TTYH1 (Q9H313), TTYH3 (Q9C0H2), TUBA1B (P68363), TUBA4A (P68366), TUBB (P07437), TUBB2B

(Q9BVA1), TUBB2C (P68371), TUBB3 (Q13509), TUBB6 (Q9BUF5), TUBG1 (P23258), TUBGCP2 (Q9BSJ2), TUBGCP3 (Q96CW5), TUFM (P49411), TWF1 (Q12792), TWF2 (Q6IBS0), TXN (P10599), TXNDC17 (Q9BRA2), TXNDC5 (Q8NBS9), TXNDC9 (O14530), TXNL1 (O43396), TXNRD1 (Q16881), TYK2 (P29597), TYMS (P04818), U2AF1 (Q01081), U2AF2 (P26368), UAP1 (Q16222), UBA1 (P22314), UBA2 (Q9UBT2), UBA3 (Q8TBC4), UBA52 (P62987), UBA6 (A0AVT1), UBE2D1 (P51668), UBE2D3 (P61077), UBE2E1 (P51965), UBE2G2 (P60604), UBE2I (P63279), UBE2J2 (Q8N2K1), UBE2K (P61086), UBE2L3 (P68036), UBE2M (P61081), UBE2N (P61088), UBE2O (Q9C0C9), UBE2S (Q16763), UBE2V1 (Q13404), UBE2V2 (Q15819), UBE3A (Q05086), UBE3C (Q15386), UBE4A (Q14139), UBE4B (O95155), UBFD1 (O14562), UBL3 (O95164), UBL4A (P11441), UBL5 (Q9BZL1), UBLCP1 (Q8WVY7), UBP1 (Q9NZI7), UBQLN2 (Q9UHD9), UBR1 (Q8IWV7), UBR4 (Q5T4S7), UBTD1 (Q9HAC8), UBXN1 (Q04323), UBXN6 (Q9BZV1), UCHL1 (P09936), UCHL3 (P15374), UCHL5 (Q9Y5K5), UCK2 (Q9BZX2), UFC1 (Q9Y3C8), UFD1L (Q92890), UGDH (O60701), UGGT1 (Q9NYU2), UGP2 (Q16851), ULK3 (Q6PHR2), UMPS (P11172), UNC119B (A6NIH7), UNC45A (Q9H3U1), UPF1 (Q92900), UPP1 (Q16831), UQCRC1 (P31930), UQCRC2 (P22695), UQCRFS1 (P47985), URB1 (O60287), URB2 (Q14146), UROD (P06132), UROS (P10746), USO1 (O60763), USP10 (Q14694), USP11 (P51784), USP13 (Q92995), USP14 (P54578), USP15 (Q9Y4E8), USP24 (Q9UPU5), USP39 (Q53GS9), USP5 (P45974), USP7 (Q93009), USP9X (Q93008), UTP15 (Q8TED0), UTP18 (Q9Y5J1), UTP20 (O75691), UTP6 (Q9NYH9), UTRN (P46939), UXS1 (Q8NBZ7), UXT (Q9UBK9), VAC14 (Q08AM6), VAMP3 (Q15836), VAMP5 (O95183), VAPA (Q9P0L0), VAPB (O95292), VARS (P26640), VASP (P50552), VAT1 (Q99536), VAV2 (P52735), VBP1 (P61758), VCAN (P13611), VCL (P18206), VCP (P55072), VDAC1 (P21796), VDAC2 (P45880), VDAC3 (Q9Y277), VIM (P08670), VPRBP (Q9Y4B6), VPS11 (Q9H270), VPS13A (Q96RL7), VPS13C (Q709C8), VPS16 (Q9H269), VPS18 (Q9P253), VPS24 (Q9Y3E7), VPS25 (Q9BRG1), VPS26A (O75436), VPS26B (Q4G0F5), VPS28 (Q9UK41), VPS29 (Q9UBQ0), VPS33A (Q96AX1), VPS33B (Q9H267), VPS35 (Q96QK1), VPS36 (Q86VN1), VPS37B (Q9H9H4), VPS39 (Q96JC1), VPS41 (P49754), VPS45 (Q9NRW7), VPS4A (Q9UN37), VPS4B (O75351), VPS53 (Q5VIR6), VPS8 (Q8N3P4), VRK1 (Q99986), VTA1 (Q9NP79), VWA1 (Q6PCB0), VWA5A (O00534), WARS (P23381), WASF2 (Q9Y6W5), WASL (O00401), WBSCR22 (O43709), WDFY1 (Q8IWB7), WDR1 (O75083), WDR11 (Q9BZH6), WDR12 (Q9GZL7), WDR18 (Q9BV38), WDR26 (Q9H7D7), WDR3 (Q9UNX4), WDR36 (Q8NI36), WDR4 (P57081), WDR43 (Q15061), WDR45L (Q5MNZ6), WDR48 (Q8TAF3), WDR5 (P61964), WDR54 (Q9H977), WDR6 (Q9NNW5), WDR61 (Q9GZS3), WDR73 (Q6P4I2), WDR74 (Q6RFH5), WDR75 (Q8IWA0), WDR77 (Q9BQA1), WDR82 (Q6UXN9), WDR92 (Q96MX6), WHSC2 (Q9H3P2), WRNIP1 (Q96S55), XP32 (Q5T750), XPC (Q01831), XPNPEP1 (Q9NQW7), XPO1 (O14980), XPO4 (Q9C0E2), XPO5 (Q9HAV4), XPO6 (Q96QU8), XPO7 (Q9UIA9), XPOT (O43592), XRCC1 (P18887), XRCC5

(P13010), XRCC6 (P12956), XRN2 (Q9H0D6), YARS (P54577), YBX1 (P67809), YES1 (P07947), YKT6 (O15498), YRDC (Q86U90), YTHDC1 (Q96MU7), YTHDF2 (Q9Y5A9), YWHAB (P31946), YWHAE (P62258), YWHAG (P61981), YWHAH (Q04917), YWHAQ (P27348), YWHAZ (P63104), ZC3H15 (Q8WU90), ZC3HAV1 (Q7Z2W4), ZC3HAV1L (Q96H79), ZCCHC3 (Q9NUD5), ZFAND1 (Q8TCF1), ZFR (Q96KR1), ZMAT2 (Q96NC0), ZNF259 (O75312), ZNF326 (Q5BKZ1), ZNF330 (Q9Y3S2), ZNF622 (Q969S3), ZNF765 (Q7L2R6), ZNFX1 (Q9P2E3), ZW10 (O43264), ZWILCH (Q9H900), ZYG11B (Q9C0D3), ZYX (Q15942).

Table 20: Gene names and SWISSPROT accession numbers of all 2940 proteins identified in CTX0E03 microvesicles (listed in alphabetical order of gene name).

Identified proteins	Accession number
Actin, cytoplasmic 2	P63261
Histone H4	P62805
Histone H2B	Q99879
Histone H3.2	Q71DI3
Histone H2B type 1	P23527
Glyceraldehyde-3-phosphate dehydrogenase	P04406
Histone H2A type 2-A	Q6FI13
Ubiquitin-40S ribosomal protein S27a	P62979
Annexin A2	P07355
Alpha-enolase	P06733
Pyruvate kinase isozymes M1/M2	P14618
60S ribosomal protein L6	Q02878
Histone H2B type 2-E	Q16778
Heat shock cognate 71 kDa protein	P11142
Actin, alpha cardiac muscle 1	P68032
Heat shock protein HSP 90-beta	P08238
Histone H2B type 1-J	P06899
Elongation factor 1-alpha 1	P68104
Tubulin beta-2C chain	P68371
60S ribosomal protein L18	Q07020
Tubulin beta chain	P07437
40S ribosomal protein S2	P15880
40S ribosomal protein S11	P62280
Histone H2B type 3-B	Q8N257
Tubulin alpha-1B chain	P68363
40S ribosomal protein S3	P23396
40S ribosomal protein S3a	P61247
Histone H2A type 1-D	P20671
Elongation factor 2	P13639
Heat shock protein HSP 90-alpha	P07900

GTP-binding nuclear protein Ran	P62826
60S ribosomal protein L4	P36578
40S ribosomal protein S9	P46781
Profilin-1	P07737
60S ribosomal protein L13a	P40429
Phosphoglycerate kinase 1	P00558
Fatty acid synthase	P49327
Annexin A1	P04083
Histone H2A.Z	P0C0S5
Vimentin	P08670
40S ribosomal protein S6	P62753
Moesin	P26038
Peptidyl-prolyl cis-trans isomerase A	P62937
60S ribosomal protein L26	P61254
60S ribosomal protein L3	P39023
40S ribosomal protein S8	P62241
60S ribosomal protein L28	P46779
Ezrin	P15311
40S ribosomal protein S4, X isoform	P62701
60S ribosomal protein L7a	P62424
60S ribosomal protein L13	P26373
60S ribosomal protein L7	P18124
40S ribosomal protein S23	P62266
60S ribosomal protein L5	P46777
Eukaryotic initiation factor 4A-I	P60842
40S ribosomal protein S24	P62847
Tubulin beta-2B chain	Q9BVA1
60S ribosomal protein L8	P62917
60S ribosomal protein L15	P61313
60S ribosomal protein L10	P27635
Peroxiredoxin-1	Q06830
Keratin, type I cytoskeletal 14	P02533
14-3-3 protein theta	P27348
40S ribosomal protein S18	P62269
Transketolase	P29401
60S ribosomal protein L24	P83731
Histone H1.5	P16401
Cofilin-1	P23528
Dihydropyrimidinase-related protein 3	Q14195
60S ribosomal protein L21	P46778
60S ribosomal protein L36	Q9Y3U8
Sodium/potassium-transporting ATPase subunit alpha-1	P05023
40S ribosomal protein S16	P62249
T-complex protein 1 subunit gamma	P49368
Heterogeneous nuclear ribonucleoprotein A1	P09651

60S ribosomal protein L14	P50914
Heat shock 70 kDa protein 1A/1B	P08107
T-complex protein 1 subunit theta	P50990
60S ribosomal protein L30	P62888
Protein S100-A6	P06703
40S ribosomal protein SA	P08865
CD44 antigen	P16070
60S ribosomal protein L35a	P18077
Tubulin beta-3 chain	Q13509
T-complex protein 1 subunit delta	P50991
4F2 cell-surface antigen heavy chain	P08195
T-complex protein 1 subunit beta	P78371
Myosin-9	P35579
Adenosylhomocysteinase	P23526
Filamin-A	P21333
Fatty acid-binding protein, brain	O15540
Myristoylated alanine-rich C-kinase substrate	P29966
T-complex protein 1 subunit eta	Q99832
Fascin	Q16658
Fructose-bisphosphate aldolase A	P04075
60S ribosomal protein L27	P61353
60S ribosomal protein L17	P18621
Heterogeneous nuclear ribonucleoproteins A2/B1	P22626
60S ribosomal protein L10a	P62906
60S ribosomal protein L35	P42766

Table 21: 100 most abundant proteins (name and SwissProt accession number) in CTX0E03 microvesicles

Discussion of proteomic data

CD63 (also known as MLA1 and TSPAN30), TSG101 (also known as ESCRT-I complex subunit TSG101), CD109 (also known as 150 kDa TGF-beta-1-binding protein) and thy-1 (also known as CD90) were detected in both exosomes and microvesicles.

Other tetraspanins were also detected: Tetraspanin-4, -5, -6, -9 and 14 were detected in the exosome fraction; tetraspanins-6 and -14 were detected in the microvesicles.

CD133 (also known as AC133, Prominin-1, PROM1, PROML1 and MSTP061) was detected in the exosomes but not the microvesicles.

CD53 (also known as MOX44 and TSPAN25), CD82 (also known as KAI1, SAR2, ST6 and TSPAN27), CD37 (also known as TSPAN26) and CD40 ligand (also known as CD40LG, CD40L and TNFSF5) were not detected in the exosomes or the microvesicles.

Nestin, GFAP and tubulin beta-3 chain (also known as TUBB3) were detected in both the exosome and microvesicle fractions, with tubulin beta-3 chain being particularly prominent within the top 100 proteins in both fractions. Sox2, DCX, GALC, GDNF and IDO were not detected.

Selectins and TNFRI (also known as TNF receptor 1, TNFRSF1A, TNFAR and TNFR1) were not detected.

Integrin alpha-2, -3, -4, -5, -6, -7, -V and integrin beta-1, -4 and -8 were detected in both exosome and microvesicle fractions. Integrin beta-3 and -5 were detected in the microvesicles only.

MHC Class I antigens (*e.g.* HLA_A1, HLA-A2 and HLA-B27) were detected in both the exosomes and microvesicles.

Cell-adhesion molecules (*e.g.* CADM1, CADM4, ICAM1, JAM3, L1CAM, NCAM) were detected in both the exosomes and microvesicles.

Cytoskeletal proteins (*e.g.* actin, vimentin, keratins, catenins, dystroglucan, neurofilament polypeptide, microtubule-associated protein, tubulin, desmoplaktin, plectin, plakophilin, septin, spectrin, talin, vinculin and zyxin) were detected in both the exosome and microvesicle fractions.

GTPases, clathrin, chaperones, heat-shock proteins (*e.g.* Hsp90, Hsp70), splicing factors, translation factors, annexins and growth factors (*e.g.* TGF-beta) were detected in both the exosomes and microvesicles.

Galectin-3, TIMP-1, thrombosponding-1, EGF receptor and CSK were detected in both the exosomes and microvesicles.

Figure 18 compares the proteomic data from the exosomes and microvesicles. Figure 18A illustrates the number of unique proteins within each micro particle population, isolated from week 2 Integra culture system. Figure 18B compares the biological processes associated with the identified proteins within each micro particle population, isolated from week 2 Integra

system. The proteins identified within exosomes and microvesicles are associated with very similar biological processes.

Proteins associated with biotin metabolism were only found in exosomes and proteins involved in tryptophan biosynthesis and taurine/alpha-linolenic acid metabolism were only identified in microvesicles.

Figure 18C compares the CTX0E03 proteome to the Mesenchymal Stem Cell exosome proteome disclosed in Lai et al 2012, in which a total of 857 proteins were identified in exosomes released from mesenchymal stem cells.

Figure 18D compares the biological processes associated with the identified proteins within the MSC derived exosomes (Lim 2012) with the neural stem cell derived exosomes of the invention. The three biological processes found to be associated with the MSC derived exosomes only are (in decreasing order of significance): Asthma; phenylalanine, tyrosine and tryptophan biosynthesis; and primary immunodeficiency. The thirty biological processes found to be associated only with the neural stem cell derived exosomes are shown in Figure 19; the most significant biological function identified relates to RNA polymerase.

A further comparison of the 197 biological processes shared by both MSC derived exosomes and NSC derived exosomes shows that NSC exosomes contain notably more processes involved in RNA degradation, the Ribosome and spliceosomes, when compared to MSC exosomes.

The above comparison indicates a number of significant differences between NSC derived exosomes and MSC derived exosomes (as characterised by Lim *et al* 2012). The 4 most significant biological differences identified as present in NSC exosomes compared to being very low/absent in those identified by the Lim's group, all involve proteins associated with the production, packaging, function and degradation of genetic material, i.e RNA polymerase, RNA degradation, Ribosome and spliceosomes.

Example 14: Size distribution of Microparticles

NanoSight analysis was undertaken to determine the particle size and concentration of microvesicles ("mv1" to "mv6") and exosomes ("exo1" to "exo6") isolated from CTX0E03 cells cultured in the Integra Celline system for 1, 2, 3, 4, 5 and 6 weeks. All results are based on 5 replicate measurements.

Particle size distribution was measured using Nanoparticle Tracking Analysis (NTA). NTA detects the movement of particles in solution and relates it to particle size. Mode and median particle size was calculated for all samples. Exosome samples were analysed using the most sensitive camera settings in order to capture the smallest vesicles. Microvesicle samples were analysed using less sensitive camera settings to prevent over exposure of the larger vesicles. As a result, some smaller vesicles were not detected in the samples. Although smaller vesicles were present in the MV samples, these represent a small percentage of the sample in terms of mass.

A proportion of Exo1 was labelled with a fluorescent membrane-specific dye (CellMask™) and a combination of NTA analysis with the CellMask™ labelling confirmed that the events detected by NTA correspond to membrane vesicles (data not shown).

The results are shown in Table 22 below, and in Figure 17.

The exosomes show a drop in size at week six, from a mode of approximately 110nm to approximately 70nm, or from a median of approximately 130nm to approximately 75nm. The overall size range, from 70nm to 150nm, is consistent with the size of exosomes from other cell types, described in the art. The observed reduction in size of the exosomes to around 70nm diameter after culturing the cells for 6 weeks correlates with the increased efficacy of exosomes isolated from CTX0E03 cells that have been cultured in a multi-compartment bioreactor for 6 weeks correlates, as reported in Example 8 and Figure 6.

It is also noted that the concentration of microvesicles and exosomes decreases over the six week period of Figure 17, broadly mirroring the improved efficacy observed over time.

The microvesicles are, as expected, larger, with a mode diameter of approximately 150nm – 200nm, or a median diameter of approximately 180nm – 350nm.

Sample	Count	Dilution	Concentration $x10^{12}$/ml	Mode (nm)	Median (nm)
Exo1 (1)	5.204	10000	**32.26**	**107**	**151**
Exo1 (2)	1.734	10000	**10.75**	**135**	**164**
Exo1 (3)	6.55	10000	**40.61**	**108**	**128**
Exo2	14.33	10000	**88.85**	**118**	**153**
Exo3 (1)*	2.52	10000	**15.62**	**89**	**115**
Exo3 (2)	10.06	10000	**62.37**	**115**	**146**

Exo3 (3)	8.98	10000	**55.68**	**128**	**147**
Exo4 (1)	3.04	10000	**18.85**	**111**	**136**
Exo4 (2)	2.89	10000	**17.92**	**110**	**120**
Exo4 (3)	2.77	10000	**17.17**	**116**	**134**
Exo5 (1)	2.34	100	**0.15**	**99**	**117**
Exo5 (2)	2.02	100	**0.13**	**102**	**124**
Exo 5 (3)	2.08	100	**0.13**	**116**	**127**
Exo6 (1)	1.45	100	**0.09**	**68**	**74**
Exo6 (2)	1.19	100	**0.07**	**69**	**75**
MV1 (1)	9.314	200	**1.15**	**183**	**212**
MV1 (2)	10.76	200	**1.33**	**161**	**214**
MV1 (3)	10.738	200	**1.33**	**173**	**198**
MV2	5.89	1000	**3.65**	**177**	**194**
MV3 (1)*	5.68	2000	**7.04**	**150**	**186**
MV3 (2)	11.5	2000	**14.26**	**221**	**351**
MV3 (3)	9.57	2000	**11.87**	**214**	**270**
MV4 (1)	4.894	400	**1.21**	**209**	**240**
MV4 (2)	2.934	1000	**1.82**	**195**	**212**
MV4 (3)	2.55	1000	**1.58**	**184**	**221**
MV5 (1)	1.086	200	**0.13**	**164**	**237**
MV5 (2)	1.458	200	**0.18**	**205**	**205**
MV 5 (3)	1.3	200	**0.16**	**219**	**210**
MV6 (1)	0.346	200	**0.04**	**171**	**186**
MV6 (2)	0.37	200	**0.05**	**168**	**212**
Media	0.14	10	**0.00**	**100**	**149**

* large aggregates.

Table 22: Size distribution of CTX0E03 microvesicles and exosomes.

Example 15: Exosomes produced by human CD34+ progenitor cells derived from cord blood conditionally immortalized with a c-mycERTAM lentivirus.

Human CD34+ progenitor cells derived from cord blood were conditionally immortalized with a c-mycERTAM lentivirus. qRT-PCR confirmed the presence of c-mycERTAM mRNA in lentivirus infected human CD34+ progenitor derived from cord blood (as shown in Figure 20A).

Western Blot analysis of exosomes from cell culture supernatants was then performed. The analysis of samples was done as specified below:

1. Concentration of exosomes from two cell supernatant samples, 1 ml volume each, using exosome capture immunobeads;

2. SDS-PAGE and WB analysis for expression of common exosome associated proteins (Alix and HSP70) including normalisation control and reference sample with known expression of analysed markers and known protein content.

Material analysed:

Aliquots of supernatant from cell culture contained three 1.5 ml vials isolated from CD34 and conditionally immortalised CD34 c-mycERTAM cells, stored at -80°C until processing.

Description of the activity:

Exosomes are captured and concentrated from precleared supernatants by incubation with exosome capture immunobeads ON at 4°C.

After immunobeads recovery, remaining supernatant weas ultracentrifuged 2 hours at 120.000 x g to precipitate residual exosomes (if any) and check efficiency of immunocapturing.

Total IP and UC pellets, corresponding each to 1ml of original supernatant samples, were lysed and loaded on gel and analyzed by WB for Alix (a protein involved in the concentration and sorting of cargo proteins at the multivesicular body level, and incorporation into IL vesicles, ubiquitoussly expressed in all exosomes) and HSP70 (molecular chaperone facilitating the assembly of multi-protein complexes, participate in the translocation of polypeptides across cell membranes, expressed on exosomes from most epithelial like human cells).

Concentrated supernatants were too dense and thus not suitable for WB analysis.

Overall results of the analysis:

Control sample: We first applied the protocol to a control sample, supernatant derived from a human cell culture, showing that 1 mL of sample is sufficient to obtain high expression signal.

We harvested control sample supernatant from 72 hours old cell culture at 80% confluence, in a way that 1 ml of conditioned medium corresponded to $1,1x10^6$ cells with a total yield of 8.3 µg total exosomes protein concentration /ml supernatant.

As a reference to estimate band's density we loaded three different concentrations of exosomes purified from the same human cell culture supernatant.

As expected immunoprecipitated sample (from 1 ml of supernatant) yields a signal comparable to 5-10 µg of purified exosomes. This result is shown in Figure 20B.

Sample: cell culture supernatant

CD34
CD34 cmycERTAM

Exosomes from sample supernatants were successfully concentrated using exosome capturing immunobeads (based on binding tetraspanins as common exosomal markers).

Samples loaded after Immunoprecipitation (IP) shows Alix expression corresponding to overall yield of less than 1 µg of exosomes while no clear differences can be appreciated between two samples: both CD34+ and CD34+ c-MycERTam cells produce exosomes. A different method should be used for accurate quantitative comparison. Samples appear negative for HSP70 expression (possibly due to tissue/cell type). These results are shown in Figure 20C.

Used immunobeads have previously shown to precipitate total exosomes from cell supernatant as confirmed by absence of signal after ultracentrifugation (UC) of residual supernatants. The same was confirmed also for analyzed sample.

Embodiments of the invention comprise:

1. A neural stem cell microparticle.
2. The neural stem cell microparticle of embodiment 1, wherein the microparticle is an exosome, microvesicle, membrane particle, membrane vesicle, exosome-like vesicle, ectosome-like vesicle, ectosome or exovesicle.
3. The neural stem cell microparticle of embodiments 1 or 2, wherein the microparticle is derived from a neural stem cell line.
4. The neural stem cell microparticle of embodiment 3, wherein the neural stem cell line is conditionally-immortalised and/or grown in serum free medium.
5. The neural stem cell microparticle of embodiment 4, wherein the neural stem cell line is CTX0E03 having ECACC Accession No. 04091601, STR0C05 having ECACC Accession No.04110301 and HPC0A07 having ECACC Accession No.04092302.
6. The neural stem cell microparticle of any preceding embodiment, 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.
7. The neural stem cell microparticle of any preceding embodiment, comprising RNA.
8. The neural stem cell microparticle of embodiment 7, wherein the RNA is mRNA and/or miRNA.
9. The neural stem cell microparticle of embodiment 8, wherein the microparticle comprises one, two, three or four of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532.
10. The neural stem cell microparticle of any preceding embodiment, comprising one or more of:
    (a) a lipid selected from ceramide, cholesterol, sphingomyelin, phosphatidylserine, phosphatidylinositol, and/or phosphatidylcholine;
    (b) miRNA, optionally 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.

11. The neural stem cell microparticle of any preceding embodiment, comprising at least 10 of the proteins present in Table 19 or Table 21.
12. The neural stem cell microparticle of any preceding embodiment, comprising at least one biological activity of a neural stem cell or a neural stem cell-conditioned medium.
13. The neural stem cell microparticle of embodiment 12, wherein the at least one biological activity is regenerative activity.
14. The neural stem cell microparticle of any preceding embodiment, for use in therapy.
15. The neural stem cell microparticle of embodiment 14, wherein the therapy is regenerative therapy.
16. The neural stem cell microparticle of embodiments 14 or 15, wherein the therapy is for a
    (i) Neurological disorder, disease or deficit, such as Parkinson's, Alzheimer's, Stroke, or ALS;
    (ii) Lysosomal storage disorder;
    (iii) Cardiovascular disorder, 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 disorder, such as Diabetes (I or II), rheumatoid arthritis, osteoarthritis, lupus, Crohn's disease, Irritable Bowel Disease, or Graft versus Host Disease;
    (vi) Psychiatric disorder, such as: Depression, Bipolar, Schizophrenia or an Autistic syndrome disorder such as Autism, Asperger's syndrome or Rett Syndrome;
    (vii) Blindness-causing disease of the retina, such as Age-related macular degeneration, Stargardt disease, diabetic retinopathy, or retinitis pigmentosa; and
    (viii) Demyelinating disease, such as multiple sclerosis, 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.
17. The neural stem cell microparticle of embodiments 14-16, wherein the therapy improves functional and/or cognitive recovery.
18. The neural stem cell microparticle of embodiments 14-17, wherein the therapy is of stroke, peripheral arterial disease or blindness-causing diseases of the retina.
19. The neural stem cell microparticle of embodiments 14 to 17, 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.

20. Use of a neural stem cell microparticle according to any preceding embodiment, in the manufacture of a medicament for the treatment of a disease.
21. A method of producing a neural stem cell microparticle as defined in embodiments 1-13, comprising isolating a microparticle from a neural stem cell-conditioned medium.
22. 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.
23. A method according to embodiment 22, wherein the stem cell is a neural stem cell, optionally as defined in any of embodiments 3 to 5.
24. A method according to embodiment 22(i) or embodiment 23 when dependent upon embodiment 22(i), 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).
25. A method according to embodiment 22(iii), embodiment 23 or 24 when dependent upon embodiment 22(iii), wherein the different cell type is an endothelial cell.
26. A microparticle obtainable by the method of any of embodiments 22-25.
27. A composition comprising a microparticle according to any of embodiments 1-13 or 26 and a pharmaceutically acceptable excipient, carrier or diluent.
28. A kit for use in a method for producing the microparticle of any of embodiments 1-13 or 26 comprising: (a) a medium; (b) a neural stem cell; (c) optionally the one or more components of embodiments 22 to 24; (d) optionally the microparticle of any of embodiments 1-13 or 26 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 of any of embodiments 1-13 or 26 using the kit.
29. A method of screening for an agent that alters the rate of production of a microparticle by a stem cell, comprising contacting a stem cell with a candidate agent and observing whether the rate production of microparticles by the contacted stem cell increases or decreases compared to a control.
30. A method of producing a stem cell microparticle, comprising:
    i. culturing the stem cells in an environment that allows stem cell differentiation; and
    ii. collecting the microparticles that are produced by the cells.

31. The method of embodiment 30, wherein an environment that allows stem cell differentiation is culture in a multi-compartment bioreactor, for example wherein the bioreactor contains at least two compartments separated by one or more membranes or barriers that separate the compartment containing the cells from one or more compartments containing gas and/or culture medium.
32. The method of embodiment 31, wherein the culture is for more than seven days.
33. The method of any one of embodiments 30-32, comprising isolating a microparticle from a stem cell-conditioned medium.
34. The method of embodiment 33, wherein the stem cell-conditioned medium comprises one or more additive components or agents which stimulate the release of microparticles by the stem cells into the medium.
35. The method of embodiment 34, wherein the one or more components are selected from transforming growth factor-beta (TGF-β), interferon-gamma (INF-γ) and/or tumour necrosis factor-alpha (TNF-α).
36. The method of any one of embodiments 33-35, wherein the stem cells were cultured under hypoxic conditions.
37. The method of any one of embodiments 33-36, wherein the stem cells were co-cultured with a different cell type.
38. The method of embodiment 37, wherein the different cell type is an endothelial cell.
39. The method of any one of embodiments 30 to 38, wherein the stem cell is a neural stem cell.
40. The method of embodiment 39, wherein the stem cell is a neural stem cell line.
41. The method of embodiment 40, wherein the neural stem cell line is conditionally-immortalised.
42. The method of embodiments 40 or 41, wherein the neural stem cell line is CTX0E03 having ECACC Accession No. 04091601, STR0C05 having ECACC Accession No.04110301, or HPC0A07 having ECACC Accession No.04092302.
43. The method of any one of embodiments 40-42, wherein the neural stem cell line is grown in serum-free medium.
44. The method of any one of embodiments 39-43, wherein the neural stem cell expresses one or more of the markers: Nestin, Sox2, GFAP, βIII tubulin, DCX, GALC, TUBB3, GDNF and IDO.
45. The method of any one of embodiments 39-44, wherein the microparticle is an exosome and the exosome expresses one or more of: DCX, GFAP, GALC, TUBB3, GDNF and IDO.
46. The method of any one of embodiments 30 to 45, wherein at least two, three, four, five, six or seven miRNAs are up or down regulated in the microparticle compared to in the

corresponding stem cells cultured in standard T-175 flasks, as calculated by Fold Regulation.

47. The method of any one of embodiments 30 to 46, wherein the microparticle is an exosome and the exosome expresses one, two, three, four, five, six, seven, eight, nine, ten or more or more of the following miRNAs at a higher level than is expressed in the corresponding stem cells cultured in standard T-175 flasks, as calculated by Fold Regulation: hsa-miR-146b-5p; hsa-let-7c; hsa-miR-99a; hsa-miR-132; hsa-miR-378; hsa-miR-181a; hsa-let-7b; hsa-miR-100; hsa-let-7e; hsa-miR-23b; hsa-miR-185; hsa-let-7i; hsa-let-7a; hsa-let-7d; hsa-let-7g; hsa-miR-222; hsa-let-7f; hsa-miR-218; hsa-miR-24; hsa-miR-9; hsa-miR-126; hsa-miR-134; hsa-miR-128; and hsa-miR-155.
48. The method of any one of embodiments 30 to 47, wherein the microparticle is an exosome and the exosome expresses one, two, three, four, five, six, seven, eight, nine, ten or more of the following miRNAs at a lower level than is expressed in the corresponding stem cells cultured in standard T-175 flasks, as calculated by Fold Regulation: hsa-miR-22; hsa-miR-26a; hsa-miR-210; hsa-miR-92a; hsa-miR-93; hsa-miR-424; hsa-miR-195; hsa-miR-127-5p; hsa-miR-21; hsa-miR-103a; hsa-miR-16; hsa-miR-125a-5p; hsa-miR-10a; hsa-miR-10b; hsa-miR-345; hsa-miR-130a; hsa-miR-15b; hsa-miR-20b; hsa-miR-20a; hsa-miR-17; hsa-miR-7; hsa-miR-106b; hsa-miR-101; hsa-miR-302a; hsa-miR-301a; hsa-miR-183; hsa-miR-219-5p; hsa-miR-18a; hsa-miR-15a; hsa-miR-182; hsa-miR-33a; hsa-miR-96; and hsa-miR-18b.
49. The method of any of embodiments 30 to 48, wherein the microparticle comprises one, two, three or four of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532.
50. The method of any one of embodiments 30 to 49, further comprising loading the isolated or purified microparticle with one or more exogenous nucleic acids, lipids, proteins, drugs or prodrugs.
51. The method of embodiment 50, wherein the exogenous nucleic acid is siRNA capable of silencing one or more pathological genes.
52. A microparticle obtainable by the method of any one of embodiments 30-51.
53. A microparticle which is an exosome and the exosome expresses one or more of: DCX, GFAP, GALC, TUBB3, GDNF and IDO.
54. The microparticle of any one of embodiments 52-53, wherein the exosome expresses one, two, three, four, five, six, seven, eight, nine, ten or more or more of the following miRNAs at a higher level than is expressed in the corresponding stem cells cultured in standard T-175 flasks, as calculated by Fold Regulation: hsa-miR-146b-5p; hsa-let-7c; hsa-miR-99a; hsa-miR-132; hsa-miR-378; hsa-miR-181a; hsa-let-7b; hsa-miR-100; hsa-let-7e; hsa-miR-23b; hsa-miR-185; hsa-let-7i; hsa-let-7a; hsa-let-7d; hsa-let-7g; hsa-miR-222; hsa-let-7f; hsa-miR-218; hsa-miR-24; hsa-miR-9; hsa-miR-126; hsa-miR-134; hsa-miR-128; and hsa-miR-155.

55. The microparticle of any one of embodiments 52-54, wherein the exosome expresses one, two, three, four, five, six, seven, eight, nine, ten or more of the following miRNAs at a lower level than is expressed in the corresponding stem cells cultured in standard T-175 flasks, as calculated by Fold Regulation: hsa-miR-22; hsa-miR-26a; hsa-miR-210; hsa-miR-92a; hsa-miR-93; hsa-miR-424; hsa-miR-195; hsa-miR-127-5p; hsa-miR-21; hsa-miR-103a; hsa-miR-16; hsa-miR-125a-5p; hsa-miR-10a; hsa-miR-10b; hsa-miR-345; hsa-miR-130a; hsa-miR-15b; hsa-miR-20b; hsa-miR-20a; hsa-miR-17; hsa-miR-7; hsa-miR-106b; hsa-miR-101; hsa-miR-302a; hsa-miR-301a; hsa-miR-183; hsa-miR-219-5p; hsa-miR-18a; hsa-miR-15a; hsa-miR-182; hsa-miR-33a; hsa-miR-96; and hsa-miR-18b.
56. The microparticle any one of embodiments 52-55, wherein the microparticle comprises one, two, three or four of hsa-miR-1246, hsa-miR-4492, hsa-miR-4488 and hsa-miR-4532.
57. The microparticle of any one of embodiments 52-56, for use in therapy.
58. The microparticle or embodiment 57, wherein the therapy is for a:
    i. Neurological disorder, disease or deficit, such as Parkinson's, Alzheimer's, Stroke, or ALS;
    ii. Lysosomal storage disorder;
    iii. Cardiovascular disorder, 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 disorder, such as Diabetes (I or II), rheumatoid arthritis, osteoarthritis, lupus, Crohn's disease, Irritable Bowel Disease, or Graft versus Host Disease;
    vi. Psychiatric disorder, such as: Depression, Bipolar, Schizophrenia or an Autistic syndrome disorder such as Autism, Asperger's syndrome or Rett Syndrome;
    vii. Blindness-causing disease of the retina, such as Age-related macular degeneration, Stargardt disease, diabetic retinopathy, or retinitis pigmentosa; or
    viii. Demyelinating disease, 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.
59. A composition comprising the microparticle of any one of embodiments 52-56 and a stem cell, optionally wherein the stem cell is the stem cell from which the microparticle is derived, for example wherein the stem cell is CTX0E03 having ECACC Accession No. 04091601.

60. The composition of embodiment 59, for use in therapy.

61. The composition of embodiment 60, wherein the stem cell and the microparticle are administered:

    i. together in a single pharmaceutical composition;

    ii. contemporaneously or simultaneously but separately; or

    iii. separately and sequentially, for example wherein the duration between the administration of the cell and microparticle is one hour, one day, one week, two weeks or more.

62. The composition of any one of embodiments 60-61, wherein the therapy induces tolerance, typically immunotolerance, in a host that is to receive the stem cells from which the microparticle is derived; or wherein tolerance to the stem cells is increased by administering stem cells together with the microparticles.

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CLAIMS

1. Use of a conditionally-immortalised cell to produce microparticles, wherein the conditionally-immortalised cell is:
   (i) a mesenchymal stem cell, optionally selected from a bone marrow derived stem cell, an endometrial regenerative cell, a mesenchymal progenitor cell, an adipose derived stem cell or a multipotent adult progenitor cell;
   (ii) a neural stem cell selected from a neurosphere initiating stem cell or an oligodendrocyte precursor cell;
   (iii) a haematopoietic stem cell, optionally a CD34+ cell and/or isolated from umbilical cord blood, or optionally a CD34+/CXCR4+ cell;
   (iv) a non-haematopoietic umbilical cord blood stem cell;
   (v) a very small embryonic like stem cell (VSEL);
   (vi) an induced pluripotent stem (iPS) cell;
   (vii) a fibroblast; or
   (viii) a dendritic cell.
2. The use according to claim 1, wherein the cell comprises c-mycER.
3. The use of claim 1 or claim 2, wherein the microparticle is an exosome, microvesicle, membrane particle, membrane vesicle, exosome-like vesicle, ectosome-like vesicle, ectosome or exovesicle.
4. The use according to any preceding claim, wherein the cell is as defined in claim 1(i), 1(ii), 1(iii), 1(iv), 1(v) or 1(vi) and is from a stem cell line.
5. The use of claim 4, wherein the stem cell line is grown in serum free medium.
6. The use 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.
7. The use of any preceding claim, wherein the microparticle comprises RNA.
8. The use of claim 7, wherein the RNA is mRNA and/or miRNA.
9. A method of producing a microparticle, comprising isolating a microparticle from a conditionally-immortalised cell-conditioned medium, wherein the cell is as defined in claim 1 or claim 2.

10. A method of producing a microparticle according to claim 9, wherein:

(i) the cell-conditioned medium comprises one or more of transforming growth factor-beta (TGF-β), interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α), which induce the release of microparticles by the stem cells into the medium;

(ii) the cells were cultured under hypoxic conditions;

(iii) the cells were co-cultured with a different cell type;

(iv) the cells were cultured in a multi-compartment bioreactor; and/or

(v) the cells were stem cells that were partially-differentiated.

11. A kit when used in the method of claim 9 comprising: (a) a medium; (b) a conditionally-immortalised cell as defined in claim 1; (c) optionally one or more of transforming growth factor-beta (TGF-β), interferon-gamma (IFN-γ) and tumour necrosis factor-alpha (TNF-α); (d) optionally a microparticle obtainable by the method of claim 9 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 using the kit.

12. A method of screening for an agent that alters the rate of production of a microparticle by a conditionally-immortalised cell, comprising contacting a conditionally immortalised cell as defined in claim 1 with a candidate agent and observing whether the rate production of microparticles by the contacted conditionally-immortalised cell increases or decreases compared to a control.