NEURAL CELL EXTRACELLULAR VESSICLES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of U.S. Provisional Application No. 62/256,823, filed November 18, 2015, which is hereby incorporated herein by reference in its entirety.

BACKGROUND

Diseases and injuries to the nervous system, including congenital disorders, cancers, degenerative diseases, and spinal cord injury, affect millions of people of all ages. Congenital disorders occur when the brain or spinal cord does not form correctly during development. Cancers of the nervous system result from the uncontrolled spread of aberrant cells. Degenerative diseases occur when the nervous system loses functioning of nerve cells. There is evidence that damage can be reversed by replacing lost cells with new ones derived from cells that can mature into nerve cells, called neural stem cells. However, transplanted stem cells may and often do migrate from the site of implantation and undergo some cell transformation that lead to a teratoma formation. In addition, due to their size, stem cells are often directly injected into the CNS which can induce complications. Invasive CNS surgeries place the patient at risk due to complication that occur during and after delivery, including but not limited to hemorrhages and edema. Stem cells administered systemically often end up being lodged in small capillaries which can induce undesired effects in the lung and may not even reach the disease or injury. Stem cell therapy can also trigger an elicit and adverse immune response.

SUMMARY

Disclosed herein are neural extracellular vesicles (EVs) and methods of using these EVs in the treatment of spinal cord injury, stroke, and traumatic brain injury and neurodegenerative diseases.

The disclosed EVs can be obtained in some embodiments, by culturing neural progenitor (NP) cells that were produced from pluripotent stem cells (e.g. human embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs)) in cell culture medium under conditions and for a time sufficient for the NP cells to produce EVs, and

isolating said EVs from the culture medium. In some embodiments, the NP cells are SOX 1+, SOX 2+, OCT4-, and NESTIN+.

The disclosed EVs can be obtained in some embodiments by culturing neural cells derived directly or indirectly from pluripotent stem cells (PSCs) (e.g. ESCs or iPSCs) in cell culture medium under conditions and for a time sufficient to produce EVs, and isolating said EVs from the culture medium. In some embodiments, the PSC-derived neural cell comprises a glial cell, such as an astrocyte or oligodendrocyte. In some embodiments, the PSC-derived neural cell comprises a neuron. In some embodiments, the PSC-derived neural cell are differentiated from NP cells derived from the hES cells. In some embodiments, the PSC-derived neural cells are differentiated directly from PSCs.

Also disclosed are EVs obtained by culturing astrocytes of any origin in cell culture medium under conditions and for a time sufficient for the astrocytes to produce EVs, and isolating said EVs from the culture medium.

The disclosed EVs can alternatively be obtained in some embodiments, by culturing mesenchymal stem cells (MSCs) that were produced from PSCs in cell culture medium under conditions and for a time sufficient for the MSC cells to produce EVs, and isolating said EVs from the culture medium.

As disclosed herein, EVs produced from hNP cells (also referred to herein as NPEX) had 1653 proteins (see Table 9) that were not identified in EVs from stem-cell-derived astrocytes (also referred to herein as APEX) or mesenchymal stem cells (also referred to herein as MSCEX). Therefore, in some embodiments, the EVs comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400, 1500, 1600 or more protein biomarkers listed in Table 9.

As disclosed herein, EVs produced from APEX had 596 proteins (see Table 8) that were not identified in NPEX or MSCEX. Therefore, in some embodiments, the EVs comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500 or more protein biomarkers listed in Table 8.

As disclosed herein, EVs produced from MSCEX had 536 proteins (see Table 7) that were not identified in APEX or MSCEX. Therefore, in some embodiments, the EVs

comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, or more protein biomarkers listed in Table 7.

In some embodiments, the disclosed EVs are produced from a substantially homogeneous population of cells. In some embodiments, the disclosed EVs are produced from non-transformed cells.

Also disclosed are compositions containing the disclosed EVs. In some embodiments, the composition comprises the disclosed EVs in a biocompatible scaffold, such as a hydrogel. Suitable hydrogels include temperature dependent hydrogels that solidify or set at body temperature, e.g., PLURONICS™; hydrogels crosslinked by ions, e.g., sodium alginate; hydrogels set by exposure to either visible or ultraviolet light, e.g., polyethylene glycol polylactic acid copolymers with acrylate end groups; and hydrogels that are set or solidified upon a change in pH, e.g., TETRONICS™. The hydrogel can, for example, include any of the following: polysaccharides, proteins, polyphosphazenes, poly(oxyethylene)-poly(oxypropylene) block polymers, poly(oxyethylene)-poly(oxypropylene) block polymers of ethylene diamine, poly(acrylic acids), poly(methacrylic acids), copolymers of acrylic acid and methacrylic acid, poly(vinyl acetate), and sulfonated polymers.

In some embodiments, the composition comprising the disclosed EVs further comprises one more neurotrophic agents. The composition can further comprises one or more agents selected from the group consisting of leukemia inhibitory factor (LIF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CTNF), epidermal growth factor receptor (EGF), basic fibroblast growth factor (bFGF), FGF-6, glial-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CTNF), granulocyte colony-stimulating factor (GCSF), hepatocyte growth factor (HGF), IFN-γ, insulin-like growth factor binding protein (IGFBP-2), IGFBP-6, IL-1ra, IL-6, IL-8, monocyte chemotactic protein (MCP-1), mononuclear phagocyte colony-stimulating factor (M-CSF), neurotrophic factors (NT3), tissue inhibitor of metalloproteinases (TIMP-1), TIMP-2, tumor necrosis factor (TNF-β), vascular endothelial growth factor (VEGF), VEGF-D, urokinase plasminogen activator receptor (uPAR), bone morphogenetic protein 4 (BMP4), IL1-a, IL-3, leptin, stem cell factor (SCF), stromal cell-derived factor-1 (SDF-

1), platelet derived growth factor-BB (PDGFBB), transforming growth factors beta (TGFβ-1) and TGFβ-3.

In some embodiments, the composition comprising the disclosed EVs further comprises a protease inhibitor, RNAse inhibitor, or combination thereof.

Also disclosed is a method of treating a subject with a with a spinal cord injury, stroke, traumatic brain injury or a neurodegenerative disease comprising administering to the subject an effective amount of a composition containing a neural EVs disclosed herein. In some embodiments, the neurodegenerative disease is Alzheimer's disease, Parkinson's disease, a Parkinson's-related disorder, Huntington's disease, prion disease, motor neuron disease (MND), spinocerebellar ataxia (SCA) or spinal muscular atrophy (SMA).

There are several protein families represented in the contents of the disclosed EV that could be beneficial in the context of several age related diseases. These include catalytically active enzymes like metalloproteases, several calcium-mediated signaling proteins, and other ion channels. Several DNA and RNA polymerase subunits are present as well as ubiquitin ligases, and proteasome subunits. Therefore, also disclosed is a method of treating a subject with a protein homeostasis disorder or a proteinopathy comprising administering to the subject an effective amount of a composition containing a neural EVs disclosed herein.

Also disclosed is the use of a composition containing a neural EVs in the manufacture of a medicament for treating a patient or subject with a spinal cord injury, who has suffered a stroke or traumatic brain injury or has a neurodegenerative disease.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1 illustrates potential sources of cells from which extracellular vesicles (EVs) (e.g. exosomes) may be obtained.

Figure 2 is an ultrastructural analysis indicating that multivesicular bodies (MVBs) which contain EVs are common in neural progenitors (NPs). Traditionally described as "vesicles containing smaller spherical and ellipsoidal vesicles and other inclusions described as filaments, granules, irregular dense masses, and membrane components", are apparent near the limiting membrane of NPs. Also as reported, the vesicles were frequently found in clusters of 3 or more vesicles (panels A, B). The inset from panel B is shown in panel C and this MVB actual has a vesicle budding inward into the larger multivesicular body, supporting a role for these vesicles in protein recycling from the plasma membrane. These vesicles do appear to bind with the plasma membrane, releasing EVs into the extracellular space (panels D, E). Previous reports indicate that the vesicles can coalesce, and this seems common in NPs, and can be seen in most cells with clusters of MVBs (panels A, F, G). Panel H is a transmission electron microscopic (TEM) image of purified EVs from NPs.

Figures 3A to 3D show that EVs can be purified and detected by nanoparticle tracking analysis. Figure 3A shows proteins from exosomes separated by SDS-PAGE and gels stained with coomassie stain. Protein profiles from EVs overlapped but was distinctive from the cell pellet, supporting that cargoes are specifically trafficked to EVs. Figure 3B shows that protein content when compared by BCA Assay reveals that amount of protein in the profile changes when cells are exposed to stressful conditions, like nutrient deprivation. Figures 3C and 3D show NanoSight analysis of purified EVs from neural progenitor cells (Fig. 3C) and astrocytes (Fig. 3D). These EVs show overlapping but different size profiles, with both types of cells producing a peak indicating 55 nm vesicles, and ranging from 25-250 nm.

Figure 4 shows differentiated neural cells internalize DiI-labeled EVs from neural progenitor cells. By adding 10 uM DiI to the cellular supernatant for 30 minutes prior to the final EVs spin and PBS wash, it was possible to label EVs. When added into the culture medium of differentiated cells, uptake of EVs was evident within 5 minutes.

Figures 5A and 5B show EVs from neural progenitors protect more differentiated neural cells from starvation stress. Figure 5A shows EVs harvested by ultrafiltration from neural progenitor cells (NPs), astrocytes, or human umbilical MSCs. Protein content was measured by BCA, and EVs were serially diluted and transferred in equal volumes

phosphate buffered serum (PBS) into wells containing NeuroNet cells (6-8 week differentiated). Cells were subjected to starvation stress for 10 days, when cells were fixed, and stained for β-III tubulin (Tuj). The center 20 fields of view per well were imaged using the Cellomics Arrayscan (representative images from 4 technical reps shown). Figure 5B shows NP and Astrocyte EVs protected the cells from starvations stress, and largely maintained integrity of the monolayer and extensions. While more cells and debris are present in the MSC treated wells, the cells had largely lost their neural morphology. Few cells were still detectable in the wells that received only PBS. NP and Astrocyte EVs samples had higher protein concentrations, so were treated with 50 µg protein/well. Protein was limiting in the MSC samples, so 6.25 was the highest concentration possible, but still appeared to kill the cells in a concentration dependent way, so it is unlikely that the higher doses (50, 25, or 12.5 µg/well) would produce a different result.

Figures 6A to 6C show indium-111 labeled EVs can be found in proximity of stroke tissue within 1 hour of injection. Figures 6A to 6C show biodistribution of indium-111 labeled EVs (Fig. 6B, 6C) compared to free indium (Fig. 6A), which indicates that EVs are present in the brain in proximity of the stroke within 1 hour of injection either when injected immediately following stroke (Fig. 6B circles, left panels), or 24 hours after the stroke occurred (Fig 6C, circles, left panels). Regardless of the timing of the initial injection, EVs were largely cleared from the area 24 hours after injection (Figs. 6B, 6C; circles, right panels) although a smaller amount of radioactivity was still detectable, likely indicating EVs were metabolized by surrounding tissues.

Figure 7 shows biodistribution of DiR labeled EVs in piglet brain. DiR labeled EVs (approximately 2.7×10^{10} vesicles/kg) were detectable from both the dorsal and ventral via direct delivery into the brain parenchyma by stereotaxic injection (top panels), and into the CSF in the subarachnoid space (lower panels). Fluorescence was detectable in the dorsal and ventral aspects of the brain in both instances, but more pronounced in the dorsal region when injected IP (top panels), and ventral areas of the brain following CSF injection (lower panels).

Figures 8A to 8E show treatment using EVs derived from neural cells improves infarct size and functional outcomes in the mouse embolic stroke model. APEX,

MSCEX, PBS, and NPEX aliquots were provided to blinded investigators for injection into mice following induction of embolic stroke (3 repeated doses of approximately 2.7 x 10^{11} vesicles/kg at 2, 14, and 28 hours after stroke). TTC staining of brains harvested 96 hours post-stroke revealed substantially decreased infarct size following NPEX or APEX treatment while MSCEX had no effect (Fig. 8A, 8C). NPEX and APEX also decreased mortality over the course of the study with over 40% of control and MSCEX treated mice succumbing to complications over the course of the study while approximately 25-30% of APEX and NPEX treated animals were lost (Fig. 8B). Phenotypic benefits including improved sensory capacity detected by adhesive tape test (Fig. 8E), and fewer neurological deficits as summarized by neurological deficit score (Fig. 8D) were also noted in APEX and NPEX treated animals.

Figures 9A to 9C show EVs derived from neural cells modulate the immune response following stroke. Blood sample flow cytometry 96 hours post-stroke indicates that APEX and NPEX increase regulatory T-cells relative to MSCEX and control (vehicle) treated groups (Fig. 9A), decrease inflammatory T-helper cells (Fig. 9B), and increase anti-inflammatory M2 macrophages in the circulation (Fig. 9C).

Figures 10A to 10C show NPEX treatment results in decreased infarct volume within 28 ± 4 hours post-stroke as measured by MRI. Animals subjected to stroke received either NPEX (approximately 2.7 x 10^{10} vesicles/kg) or PBS (vehicle) at 2, 14, and 24 hours post-stroke. While anesthetized, animals were also subjected to MRI analysis. NPEX treated animals had substantially reduced infarct volume compared to those that received PBS (Figs. A-C). When the size difference between the ipsilateral and contralateral sides was evaluated, there was less difference between hemispheres in the NPEX group, indicating less edema and swelling as compared to controls.

Figure 11 shows NPEX treatment improves molecular deficits 12 weeks after stroke. T2 and T2 flair images both indicate less detectable damage in NPEX treated pigs 12 weeks post-stroke. The absence (death) of tissue was significantly reduced at the 12 week timepoint and areas of density incongruent with host tissue were far less evident in treated animals.

Figure 12 is a Venn diagram showing the number of proteins unique to, and shared by NPEX, APEX, and MSCEX EVs.

DETAILED DESCRIPTION

Definitions

In accordance with the present invention there may be employed conventional cell culture methods, chemical synthetic methods and other biological and pharmaceutical techniques within the skill of the art. Such techniques are well-known and are otherwise explained fully in the literature.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise (such as in the case of a group containing a number of carbon atoms in which case each carbon atom number falling within the range is provided), between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described.

It is to be noted that as used herein and in the appended claims, the singular forms "a," "and" and "the" include plural references unless the context clearly dictates otherwise.

Furthermore, the following terms shall have the definitions set out below. It is understood that in the event a specific term is not defined herein below, that term shall have a meaning within its typical use within context by those of ordinary skill in the art.

The term “subject” refers to any individual who is the target of administration or treatment. The subject can be a vertebrate, for example, a mammal. Thus, the subject can be a human or veterinary patient. The term “patient” refers to a subject under the treatment of a clinician, e.g., physician.

The term "therapeutically effective" refers to the amount of the composition used is of sufficient quantity to ameliorate one or more causes or symptoms of a disease or disorder. Such amelioration only requires a reduction or alteration, not necessarily elimination.

The term "pharmaceutically acceptable" refers 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 problems or complications commensurate with a reasonable benefit/risk ratio.

The terms "treat", "treating", and "treatment", etc., as used herein, refer to any action providing a benefit to a patient at risk for or afflicted by a disease state, condition or deficiency which may be improved using cellular compositions according to the present invention. Treating a condition includes improving the condition through lessening or suppression of at least one symptom, delay in progression of the effects of the disease state or condition, including the prevention or delay in the onset of effects of the disease state or condition, etc. In the present application, treatment can involve reducing the impact of a spinal cord injury or stroke, including reversing and/or inhibiting the effects of such injury, reversing, improving, inhibiting and/or stabilizing a neurodegenerative disease such that the disease improves and/or does not progress or worsen. The term "prophylactic" is used to describe a method which "reduces the likelihood" that a particular result will occur, often the progression and/or worsening of a disease state and/or condition.

Standard techniques for growing cells, separating cells, and where relevant, cloning, DNA isolation, amplification and purification, for enzymatic reactions involving DNA ligase, DNA polymerase, restriction endonucleases and the like, and various separation techniques are those known and commonly employed by those skilled in the art. A number of standard techniques are described in Sambrook *et al.*, 1989 Molecular Cloning, Second Edition, Cold Spring Harbor Laboratory, Plainview, New York; Maniatis *et al.*, 1982 Molecular Cloning, Cold Spring Harbor Laboratory, Plainview, New York; Wu (Ed.) 1993 Meth. Enzymol. 218, Part I; Wu (Ed.) 1979 Meth. Enzymol. 68; Wu et al., (Eds.) 1983 Meth. Enzymol. 100 and 101; Grossman and Moldave (Eds.)

1980 Meth. Enzymol. 65; Miller (Ed.) 1972 Experiments in Molecular Genetics, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York; Old and Primrose, 1981 Principles of Gene Manipulation, University of California Press, Berkeley; Schleif and Wensink, 1982 Practical Methods in Molecular Biology; Glover (Ed.) 1985 DNA Cloning Vol. I and II, IRL Press, Oxford, UK; Hames and Higgins (Eds.) 1985 Nucleic Acid Hybridization, IRL Press, Oxford, UK; and Setlow and Hollaender 1979 Genetic Engineering: Principles and Methods, Vols. 1-4, Plenum Press, New York. Abbreviations and nomenclature, where employed, are deemed standard in the field and commonly used in professional journals such as those cited herein.

The term "human Pluripotent Stem Cells", of which "human Embryonic Stem Cells" (hESCs) and human induced pluripotent stem cells (hiPSCs) are a subset, are derived from pre-embryonic, embryonic, fetal tissue or adult stem cells (in the case of human induced pluripotent stem cells) at any time after fertilization, and have the characteristic of being capable under appropriate conditions of producing progeny of several different cell types, especially including neuronal stem and progenitors, neural crest cells, mesenchymal stem cells (MSCs) and related proliferative and non-proliferative neural cells. The term includes both established lines of stem cells of various kinds, and cells obtained from primary tissue that are pluripotent in the manner described.

The term "embryonic stem cell" refers to pluripotent cells, preferably of primates, including humans, which are isolated from the blastocyst stage embryo.

The term "neural progenitor cell" refers to cells capable of dividing a limited number of times that have the capacity to differentiate into neuronal and glial cell types.

The terms "extracellular vesicle" and "EV" are used herein to refer to a vesicle of about 10nm to 10μm in size consisting of fluid, macro-molecules, solutes, and metabolites from a cell contained by a lipid bilayer or micelle. In some cases, the EV is a cell-derived EV. The term "EV" also includes lipid vesicle engineered to contain bioactive molecules found in a cell-derived EVs, such as a neural EVs. These terms encompass both exosomes and ectosomes. Exosomes are released on the exocytosis of multivesicular bodies (MVBs). Ectosomes are vesicles assembled at and released from the plasma membrane. In some cases, the EV is about 20nm to 10μm, 20nm to 1μm, 20

nm-500 nm, 30 nm-100nm, 30 nm-160nm, or 80-160 nm in size. In some embodiments, the EVs are exosomes that are about 20 to 150 nm in size.

The term "autologous EV" is used to describe a population of EVs which are obtained from cells from a subject or patient to whom the EVs are to be administered.

The term "neural EV" is used to refer to a cell-derived EV produced from neural progenitor cells derived *in vitro* from pluripotent stem cells or neural cells derived *in vitro* from said neural progenitor cells or from pluripotent stem cells. The term also refers to vesicles engineered to contain a sufficient number of the bioactive molecules found in the cell-derived neural EV to have substantially the same bioactivity.

Compositions

Disclosed herein are neural EVs (e.g. exosomes) and methods of using these EVs in the treatment of spinal cord injury, stroke, and traumatic brain injury and neurodegenerative diseases.

The disclosed EVs can be obtained in some embodiments, by culturing neural progenitor (NP) cells or mesenchymal stem cells (MSCs) that were produced *in vitro* from pluripotent stem cells (e.g. human embryonic stem cells (hESCs) or induced pluripotent stem cells (iPSCs)) in cell culture medium under conditions and for a time sufficient for the NP cells or MSCs to produce EVs.

Methods for the production of human neural progenitor (hNP) cells from human embryonic stem cells (ESCs) are described, for example, in U.S. patent no. 7,531,354, which is hereby incorporated by reference in its entirety for the teaching of these cells. Human neuroprogenitor cells (hNPs) are known to express markers associated with the earliest multipotent neural stem cells, including Nestin, Musashi-1, Soxl, Sox2 and Sox3. It is noted that although feeder cell free neural progenitor cells may be used to produce EVs, any neuroprogenitor cell as otherwise described herein may also be used. Preferred neuroprogenitor cells are produced according to the methods presented in U.S. patent no. 7,531,354, are adherent feeder cell free as well as free from embryoid bodies.

The disclosed EVs can be obtained in some embodiments by culturing differentiated neural cells, such as astrocytes, derived directly or indirectly from pluripotent stem cells in cell culture medium under conditions and for a time sufficient to produce EVs, and isolating said EVs from the culture medium. In some embodiments, the

differentiated neural cells are hN2™ neuronal cells (ArunA Biomedical), NeuroNet™ neurons, or AstroPro™ astrocytes (ArunA Biomedical Inc).

Pluripotent stem cells used to produce the EV-producing NP cells, neural cells, or MSCs include human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs).

Pluripotent stem cells may express one or more of the stage-specific embryonic antigens (SSEA) 3 and 4, and markers detectable using antibodies designated Tra-1-60 and Tra-1-81 (Thomson et al., Science 282:1145, 1998). Differentiation of pluripotent stem cells in vitro results in the loss of SSEA-4, Tra-1-60, and Tra-1-81 expression (if present) and increased expression of SSEA-1. Undifferentiated pluripotent stem cells typically have alkaline phosphatase activity, which can be detected by fixing the cells with 4% paraformaldehyde, and then developing with Vector Red as a substrate, as described by the manufacturer (Vector Laboratories, Burlingame Calif.) Undifferentiated pluripotent stem cells also typically express Oct-4 and TERT, as detected by RT-PCR.

The types of pluripotent stem cells that may be used include established lines of pluripotent cells derived from tissue formed after gestation, including pre-embryonic tissue (such as, for example, a blastocyst), embryonic tissue, or fetal tissue taken any time during gestation, typically but not necessarily before approximately 10-12 weeks gestation. Non-limiting examples are established ethical lines of human embryonic stem cells or human embryonic germ cells, such as, for example the human embryonic stem cell lines WA01, WA07, and WA099 (WiCell). Also contemplated is use of the compositions of this disclosure during the initial establishment or stabilization of such cells, in which case the source cells would be primary pluripotent cells taken directly from the source tissues. Also suitable are cells taken from a pluripotent stem cell population already cultured in the absence of feeder cells. Also suitable are mutant human embryonic stem cell lines, such as, for example, BG01v (BresaGen, Athens, Ga.), as well as normal human embryonic stem cell lines such as WA01, WA07, WA09 (WiCell) and BG01, BG02 (BresaGen, Athens, Ga.).

Human embryonic stem cells (hESCs) may be prepared by methods which are described in the in the art as described for example, by Thomson et al. (U.S. Pat. No.

5,843,780; *Science* 282:1145, 1998; *Curr. Top. Dev. Biol.* 38:133 ff., 1998; *Proc. Natl. Acad. Sci. U.S.A.* 92:7844, 1995). Alternatively, they may be obtained commercially.

Epiblast stem cells (EpiScs) and induced pluripotent stem cells (iPSCs) isolated from early post-implantation stage embryos. They express Oct4 and are pluripotent. iPSCs are made by dedifferentiating adult somatic cells back to a pluripotent state by retroviral transduction of four genes (c-myc, Klf4, Sox2, Oct4).

As described in U.S. Patent Application Document No. 20140356382, "[e]xosomes produced from cells can be collected from the culture medium and/or cell tissue by any suitable method. Typically a preparation of EVs can be prepared from cell culture or tissue supernatant by centrifugation, filtration or combinations of these methods. For example, EVs can be prepared by differential centrifugation, that is low speed (<2,0000 g) centrifugation to pellet larger particles followed by high speed (>100,000 g) centrifugation to pellet EVs, size filtration with appropriate filters (for example, 0.22 μm filter), gradient ultracentrifugation (for example, with sucrose gradient) or a combination of these methods." It is noted that the contents of EVs, i.e., EVs in which the lipid bilayer has been removed or eliminated and the contents obtained may also be used to engineer artificial EVs.

Further, as described in U.S. Patent Application Document No. 20140356382, exogenous protein and/or peptide and other cargo can be introduced into the EVs by a number of different techniques including electroporation or the use of a transfection reagent. Electroporation conditions may vary depending on the charge and size of the biotherapeutic cargo. Typical voltages are in the range of 20V/cm to 1,000V/cm, such as 20V/cm to 100V/cm with capacitance typically between 25 μF and 250 μF, such as between 25 μF and 125 μF. A voltage in the range of 150 mV to 250 mV, particularly a voltage of 200 mV is preferred for loading EVs with an antibody. Alternatively, the EVs may be loaded with exogenous protein and/or peptide using a transfection reagent. Despite the small size of the EVs, conventional transfection agents may be used for transfection of EVs with protein and/or peptide. EVs may also be loaded by transforming or transfecting a host cell with a nucleic acid construct which expresses therapeutic protein or peptide of interest, such that the therapeutic protein or peptide is taken up into the EVs as the EVs are produced from the cell.

In illustrative embodiments, the EV-producing NP cells and/or neural cells disclosed herein are cultured for about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days or for as long as about 1, 2, 3, 4, 5, 6, 7, 8 weeks or about 1, 2, 3, 4, 5, or 6 months, depending on the cell and its ability to produce EVs. The EV-producing cells may be cultured in suitable media and grown under conditions that are readily determined by one of ordinary skill in the art. Cell culture conditions may vary with cell type and the examples presented hereinafter illustrate suitable media and conditions. For example, CMRL 1066 medium (from Invitrogen) with fetal bovine serum (e.g., at 10%) and optionally supplemented with glutamine or glutamine-containing mixtures and antibiotics could be used. Cells can be grown on a surface (feeder cells) in some embodiments, e.g. they can be grown as a monolayer on the surface (feeder cell free) and may be grown until 30, 40, 50, 60, 70, 80, 90, 95 or 100% confluent.

Cell growth media are well known in the art and comprise at least a minimum essential medium plus one or more optional components such as growth factors, ascorbic acid, glucose, non-essential amino acids, salts (including trace elements), glutamine, insulin (where indicated and not excluded), Activin A, transferrin, beta mercaptoethanol, and other agents well known in the art and as otherwise described herein. A preferred media is a low protein, serum-free based growth medium that supports neural cells. The growth factor used can be fibroblast growth factor 2 (FGF2), alone or preferably in combination with leukemia inhibitor factor (LIF). Depending on the NP or neural cells to be grown in the growth media, the inclusion of LIF is preferred but may not be required. Additional media includes basal cell media which may contain serum, for example, between about 0.1% and 20% (preferably, about 2-10%) fetal calf serum, or for defined medium, an absence of fetal calf serum and KSR, and optionally including bovine serum albumin (about 1-5%, preferably about 2%). Preferred medium is defined and is serum-free and low protein. The components of the growth media depends on the type of neural cell to be grown, all of which are well known in the art. Particularly preferred media is media and supplement from ArunA. The AB2™ Neural Cell Culture Media Kit contains AB2™ Basal Neural Medium and ANS™ Neural Medium Supplement. The medium and supplement are specifically engineered for versatility to meet all neural cell culture needs. The AB2™ Basal Neural Medium and ANS™ Neural Medium Supplement can be used

as the base for specialized mediums to direct differentiation of the hNP1™ line toward various neural phenotypes. Each lot of medium and supplement is pre-qualified for use by testing for cell growth, sterility, pH, osmolarity, and endotoxins.

Formulations from ArunA allow neural cultures to maintain a stable karyotype over multiple passages without the need for feeder cells, making them an excellent choice for a wide variety of research applications including early stage drug discovery.

Other agents which optionally may be added to the medium include, depending on the cell type grown in the media, for example, any one or more of nicotinamide, members of TGF-β family, including TGF-β 1, 2, and 3, Activin A, nodal, Bone Morphogen Proteins (BMP 2 to 7) serum albumin, members of the fibroblast growth factor (FGF) family, platelet-derived growth factor-AA, and -BB, platelet rich plasma, insulin growth factor (IGF-I, II, LR-IGF), growth differentiation factor (GDF-5, -6, -8, -10, 11), glucagon like peptide-I and II (GLP-I and II), GLP-1 and GLP-2 mimetobody, Exendin-4, parathyroid hormone, insulin, progesterone, aprotinin, hydrocortisone, ethanolamine, epidermal growth factor (EGF), gastrin I and II, copper chelators such as, for example, triethylene pentamine, forskolin, Na-Butyrate, betacellulin, ITS, noggin, neurite growth factor, nodal, valporic acid, trichostatin A, sodium butyrate, hepatocyte growth factor (HGF), sphingosine-1, VEGF, MG132 (EMD, CA), N2 and B27 supplements (Gibco, CA), steroid alkaloid such as, for example, cyclopamine (EMD, CA), keratinocyte growth factor (KGF), Dickkopf protein family, bovine pituitary extract, islet neogenesis-associated protein (INGAP), Indian hedgehog, sonic hedgehog, proteasome inhibitors, notch pathway inhibitors, sonic hedgehog inhibitors, heregulin, or combinations thereof, among a number of other components. Each of these components, when included, are included in effective amounts.

By way of further example, suitable media may be made from the following components, such as, for example, Dulbecco's modified Eagle's medium (DMEM), Gibco #11965-092; Knockout Dulbecco's modified Eagle's medium (KO DMEM), Gibco # 10829-018; Ham's F12/50% DMEM basal medium; 200 mM L-glutamine, Gibco #15039-027; non-essential amino acid solution, Gibco 11140-050; β-mercaptoethanol, Sigma #M7522; human recombinant basic fibroblast growth factor (bFGF), Gibco #13256-029.

Cell media are commercially available and can be supplemented with commercially available components, including defined xeno-free components, such as those available from Invitrogen Corp. (GIBCO), Cell Applications, Inc., Biological Industries, Beth HaEmek, Israel, and Calbiochem. One of ordinary skill in the art will be able to readily modify the cell media to produce any one or more of the target cells pursuant to the present invention.

The disclosed EV-producing cells may be cultured on a layer of feeder cells that support the cells in various ways. Approaches for culturing cells on a layer of feeder cells are well known in the art. The cells may be grown on a cellular support or matrix, as adherent monolayers, rather than as embryoid bodies or in suspension. In certain embodiments, the use of a cellular support may be preferred, depending upon the cells used to produce the EVs. When used, cellular supports preferably comprise at least one substrate protein. Substrate proteins include, for example, an extracellular matrix protein, which is a protein found in the extracellular matrix, such as laminin, tenascin, thrombospondin, and mixtures thereof, which exhibit growth promoting and contain domains with homology to epidermal growth factor (EGF) and exhibit growth promoting activity. Other substrate proteins which may be used include for example, collagen, fibronectin, vibronectin, polylysine, polyornithine and mixtures thereof. In addition, gels and other materials such as methylcellulose of other gels which contain effective concentrations of one or more of these embryonic stem cell differentiation proteins may also be used. Exemplary differentiation proteins or materials which include these differentiation proteins include, for example, laminin, BD Cell-Tak™ Cell and Tissue Adhesive, BD™ FIBROGEN Human Recombinant Collagen I, BD™ FIBROGEN Human Recombinant Collagen III, BD Matrigel™ Basement Membrane Matrix, BD Matrigel™ Basement Membrane Matrix High Concentration (HC), BD™ PuraMatrix™ Peptide Hydrogel, Collagen I, Collagen I High Concentration (HC), Collagen II (Bovine), Collagen III, Collagen IV, Collagen V, and Collagen VI, among others.

Alternatively, these cells may be cultured in a culture system that is essentially free of feeder cells, but nonetheless supports proliferation of the cells to produce EVs. The growth of cells in feeder-free culture can be supported using a medium conditioned by culturing previously with another cell type. Alternatively, the growth of EV-

producing cells in feeder-free culture without differentiation can be supported using a chemically defined medium. These approaches are well known in the art. In certain embodiments of the present invention, the cells are grown in feeder cell free medium.

EVs can be harvested at various time intervals (e.g. at about 2, 4, 6, 8 or 3, 6, 9, 12 day or longer intervals, depending upon the rate of production of EVs). Exemplary yields of EVs can range from at least about 1 ng EVs/1 million cells, at least about 10 ng EVs/1 million cells, at least about 50 ng EVs/1 million cells, at least about 100 ng EVs/1 million cells, at least about 500 ng EVs/1 million cells, at least about 750 ng EVs/1 million cells, at least about 800 ng EVs/1 million cells, at least about 900 ng EVs/1 million cells, at least about 1.0 μg EVs/1 million cells, at least about 1.5 μg EVs/1 million cells, at least about 2.0 μg EVs/1 million cells, at least about 2.5 μg EVs/1 million cells, at least e.g. about 3.0 μg EVs/1 million cells, at least about 5.0 μg EVs/1 million cells, and at least about 10.0 μg EVs/1 million cells, during a time period of about 24 hours to seven days of culture of proliferative and non-proliferative neural cells as otherwise described herein.

In certain embodiments, EVs are harvested and collected by ultracentrifugation or differential centrifugation or any combination thereof, pelleted EVs are collected, and, optionally, collected pelleted EVs are washed with a suitable medium. For example, a preparation of EVs can be prepared from cell culture or tissue supernatant by centrifugation, filtration or combinations of these methods. In some embodiments, the EVs can be prepared by differential centrifugation, that is low speed (<2,0000 g) centrifugation to pellet larger particles followed by high speed (>100,000 g) centrifugation to pellet EVs, size filtration with appropriate filters (for example, 0.22 μm filter), gradient ultracentrifugation (for example, with sucrose gradient) or a combination of these methods. EVs may be purified by differential centrifugation, micro and ultra-filtration, polymeric precipitation, microfluidic separation, immunocapture and size-exclusion chromatography. These and/or related methods for isolating and purifying EVs are described by Théry, *et al.*, *Current Protocols in Cell Biology*, (2006) 3.221-3.22.29, copyright 2006 by John Wiley & Sons, Inc.; Sokolova, et al., *Colloids and Surfaces* B: Biointerfaces, 2011, 87, 146-150; Wiklander, et al., *Journal of Extracellular Vesicles*, 2015, 4, 26316, pp. 1-13; and Böing, et al., *Journal of Extracellular Vesicles*, 2014, 3,

23430, pp. 1-11. Other methods for isolation may be developed such as electrical field radiofrequency and acoustics.

Pharmaceutical compositions

Disclosed is a pharmaceutical compositions containing therapeutically effective amounts of one or more of the disclosed EVs and a pharmaceutically acceptable carrier. Formulations containing the disclosed EVs may take the form of liquid, solid, semi-solid or lyophilized powder forms, such as, for example, solutions, suspensions, emulsions, sustained-release formulations, tablets, capsules, powders, suppositories, creams, ointments, lotions, aerosols, patches or the like, preferably in unit dosage forms suitable for simple administration of precise dosages.

Pharmaceutical compositions typically include a conventional pharmaceutical carrier and/or excipient and may additionally include other medicinal agents, carriers, adjuvants, additives and the like. The weight percentage ratio of the EVs to the one or more excipients can be between about 20:1 to about 1:60, or between about 15:1 to about 1:45, or between about 10:1 to about 1:40, or between about 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1 or 1:1 to about 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, 1:15, 1:20, 1:25, 1:30, or 1:35, and preferably is about 20:1, 19:1, 18:1, 17:1, 16:1, 15:1, 14:1, 13:1, 12:1, 11:1, 10:1, 9:1, 8:1, 7:1, 6:1 or 5:1. In some embodiments, the disclosed composition comprises between about 1 μg to about 1 g or more of total EVs, about 500 μg about 500 mg, about 1 mg to about 500 mg of total EVs, about 5 to about 500 mg, about 10 to about 500 mg, about 25 to about 500 mg, about 50 mg to about 350 mg, about 75 mg to about 450 mg, about 50 mg to about 450 mg, or about 75 mg to about 325 mg or about 100 mg to about 650 mg of total EVs and may optionally contain one or more suitable pharmaceutical carriers, additives and/or excipients.

An injectable composition for parenteral administration (e.g. intravenous, intramuscular, intrathecal intracerebrospinal fluid, or intranasal), will typically contain the EVs and optionally additional components in a suitable i.v. solution, such as sterile physiological salt solution. The composition may also be formulated as a suspension in an aqueous emulsion.

Liquid compositions can be prepared by dissolving or dispersing the pharmaceutical composition comprising the EVs, and optional pharmaceutical adjuvants,

in a carrier, such as, for example, aqueous saline, aqueous dextrose, glycerol, or ethanol, to form a solution or suspension. For use in an oral liquid preparation, the composition may be prepared as a solution, suspension, emulsion, or syrup, being supplied either in liquid form or a dried form suitable for hydration in water or normal saline. In the case of intranasal, intratracheal or intrapulmonary administration, the compositions may be provided as liquid composition which can be sprayed into the nose, trachea and/or lungs.

For oral administration, such excipients include pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. If desired, the composition may also contain minor amounts of non-toxic auxiliary substances such as wetting agents, emulsifying agents, or buffers.

When the composition is employed in the form of solid preparations for oral administration, the preparations may be tablets, granules, powders, capsules or the like. In a tablet formulation, the composition is typically formulated with additives, e.g. an excipient such as a saccharide or cellulose preparation, a binder such as starch paste or methyl cellulose, a filler, a disintegrator, and other additives typically used in the manufacture of medical preparations.

Methods for preparing such dosage forms are known or are apparent to those skilled in the art; for example, see Remington's Pharmaceutical Sciences (17th Ed., Mack Pub. Co. 1985). The composition to be administered will contain a quantity of the selected compound in a pharmaceutically effective amount for therapeutic use in a biological system, including a patient or subject according to the present invention.

Intravenous formulations can comprise the EVs described herein, an isotonic medium and one or more substances preventing aggregation of the EVs. Example intravenous/ intrathecal/ intracerebrospinal fluid formulations may contain saline solutions (e.g. normal saline (NS); about 0.91% w/v of NaCl, about 300 mOsm/L) and/or dextrose 4% in 0.18% saline, and optionally 1%, 2% or 3% human serum albumin. In addition, the EVs may be disrupted to obtain the contents and the contents used in compositions according to the present invention.

In exemplary embodiments, formulations of the invention may comprise about 50 ng EVs/ml intravenous/intrathecal/intracerebrospinal fluid medium, including about 100

ng, 200 ng, 300 ng, 400 ng, 500 ng, 600 ng, 700 ng, 800 ng, 900 ng, 1.0 μg, 1.5 μg, 2.0 μg, 2.5 μg, 3.0 μg, 5.0 μg, 10.0, 15.0 μg, 20.0 μg, 100 μg, or more EVs/ml intravenous/intrathecal/intracerebrospinal fluid medium for use in treating spinal cord injury, stroke, traumatic brain injury and/or neurodegenerative diseases.

In some embodiments, intravenous formulations may comprise about 0.1 μg EVs/ml medium, about 0.2 μg EVs/ml intravenous medium, about 0.3 μg EVs/ml intravenous medium, about 0.4 μg EVs/ml intravenous medium, about 0.5 μg EVs/ml intravenous medium, about 0.6 μg EVs/ml intravenous medium, about 0.7 μg EVs/ml intravenous medium, about 0.8 μg EVs/ml intravenous medium, about 0.9 μg EVs/ml intravenous medium, about 1.0 μg EVs/ml intravenous medium, about 1.5 μg EVs/ml intravenous medium, about 2.0 μg EVs/ml intravenous medium, about 2.5 μg EVs/ml intravenous medium, such as at least e.g. about 3.0 μg EVs/ml intravenous medium, such as e.g. at least about 5.0 μg EVs/ml intravenous medium, about 10.0 μg EVs/ml intravenous medium, 15.0 μg EVs/ml intravenous medium or about 20.0 μg or more EVs/ml intravenous medium.

In some embodiments, the pharmaceutical composition is in a dosage form comprising at least 25 mg of EVs, at least 50 mg of EVs, at least 60 mg of EVs, at least 75 mg of EVs, at least 100 mg of EVs, at least 150 mg of EVs, at least 200 mg of EVs, at least 250 mg of EVs, at least 300 mg of EVs, about 350 mg of EVs, about 400 mg of EVs, about 500 mg of EVs, about 750 mg of EVs, about 1g (1,000mg) or more of EVs, alone or in combination with a therapeutically effective amount of at least one additional bioactive agent, which agent may be useful in the treatment of spinal cord injury, stroke, traumatic brain injury and/or neurodegenerative disease. In some embodiments, the pharmaceutical composition comprises between about 10 mg to about 750 mg, about 25 mg to about 650 mg, or between about 30 mg to about 500 mg, or about 35 mg to about 450 mg, most often about 50 to about 500 mg of EVs.

In some embodiments, an intravenous formulation comprises the EVs described herein, an isotonic medium, and one or more substances preventing aggregation of the EVs. Intravenous formulations may therefore contain saline solutions (e.g. normal saline (NS); about 0.91% w/v of NaCl, about 300 mOsm/L) and/or dextrose 4% in 0.18% saline, and optionally 1%, 2% or 3% human serum albumin.

In some embodiments, the composition comprising the disclosed EVs further comprises one more neurotrophic agents. The composition can further comprises one or more agents selected from the group consisting of leukemia inhibitory factor (LIF), brain-derived neurotrophic factor (BDNF), epidermal growth factor receptor (EGF), basic fibroblast growth factor (bFGF), FGF-6, glial-derived neurotrophic factor (GDNF), granulocyte colony-stimulating factor (GCSF), hepatocyte growth factor (HGF), IFN-γ, insulin-like growth factor binding protein (IGFBP-2), IGFBP-6, IL-1ra, IL-6, IL-8, monocyte chemotactic protein (MCP-1), mononuclear phagocyte colony-stimulating factor (M-CSF), neurotrophic factors (NT3), tissue inhibitor of metalloproteinases (TIMP-1), TIMP-2, tumor necrosis factor (TNF-β), vascular endothelial growth factor (VEGF), VEGF-D, urokinase plasminogen activator receptor (uPAR), bone morphogenetic protein 4 (BMP4), IL1-a, IL-3, leptin, stem cell factor (SCF), stromal cell-derived factor-1 (SDF-1), platelet derived growth factor-BB (PDGFBB), transforming growth factors beta (TGFβ-1) and TGFβ-3.

In some embodiments, the disclosed EVs are contained in or on a biocompatible scaffold, such as a hydrogel. Suitable hydrogels include temperature dependent hydrogels that solidify or set at body temperature, e.g., PLURONICS™; hydrogels crosslinked by ions, e.g., sodium alginate; hydrogels set by exposure to either visible or ultraviolet light, e.g., polyethylene glycol polylactic acid copolymers with acrylate end groups; and hydrogels that are set or solidified upon a change in pH, e.g., TETRONICS™. Examples of materials that can be used to form these different hydrogels include polysaccharides such as alginate, polyphosphazenes, and polyacrylates, which are cross-linked ionically, or block copolymers such as PLURONICS™ (also known as POLOXAMERS™), which are poly(oxyethylene)-poly(oxypropylene) block polymers solidified by changes in temperature, or TETRONICS™ (also known as POLOXAMINES™), which are poly(oxyethylene)-poly(oxypropylene) block polymers of ethylene diamine solidified by changes in pH.

Suitable hydrogels also include undefined extracellular matrix derived hydrogels that originated from tissues including but not limited to bladder intestine, blood and brain.

In some embodiments, the disclosed EVs are contained in or on a biocompatible scaffold comprising collagen, fibrin, silk, agarose, alginate, hyaluronan, chitosan, a biodegradable polyester such as polylactic-co-glycolic acid, polylacic acid, or polyglycolic acid, polyethylene glycol, polyvinylpyrrolidone, polyethersulfone, a peptide-based biomaterial, glycose amino glycan, fibronectin, laminin, or any combination thereof.

In some cases, the hydrogel is produced by cross-linking the anionic salt of alginic acid, a carbohydrate polymer isolated from seaweed, with ions, such as calcium cations. The strength of the hydrogel increases with either increasing concentrations of calcium ions or alginate. For example, U.S. Pat. No. 4,352,883 describes the ionic cross-linking of alginate with divalent cations, in water, at room temperature, to form a hydrogel matrix.

EVs are mixed with an alginate solution, the solution is delivered to an already implanted support structure and then solidifies in a short time due to the presence in vivo of physiological concentrations of calcium ions. Alternatively, the solution is delivered to the support structure prior to implantation and solidified in an external solution containing calcium ions.

In general, these polymers are at least partially soluble in aqueous solutions, e.g., water, or aqueous alcohol solutions that have charged side groups, or a monovalent ionic salt thereof. There are many examples of polymers with acidic side groups that can be reacted with cations, e.g., poly(phosphazenes), poly(acrylic acids), and poly(methacrylic acids). Examples of acidic groups include carboxylic acid groups, sulfonic acid groups, and halogenated (preferably fluorinated) alcohol groups. Examples of polymers with basic side groups that can react with anions are poly(vinyl amines), poly(vinyl pyridine), and poly(vinyl imidazole).

Polyphosphazenes are polymers with backbones consisting of nitrogen and phosphorous atoms separated by alternating single and double bonds. Each phosphorous atom is covalently bonded to two side chains. Polyphosphazenes that can be used have a majority of side chains that are acidic and capable of forming salt bridges with di- or trivalent cations. Examples of acidic side chains are carboxylic acid groups and sulfonic acid groups.

Bioerodible polyphosphazenes have at least two differing types of side chains, acidic side groups capable of forming salt bridges with multivalent cations, and side groups that hydrolyze under in vivo conditions, e.g., imidazole groups, amino acid esters, glycerol, and glucosyl. Bioerodible or biodegradable polymers, i.e., polymers that dissolve or degrade within a period that is acceptable in the desired application (usually in vivo therapy), will degrade in less than about five years and most preferably in less than about one year, once exposed to a physiological solution of pH 6-8 having a temperature of between about 25° C. and 38° C. Hydrolysis of the side chain results in erosion of the polymer. Examples of hydrolyzing side chains are unsubstituted and substituted imidizoles and amino acid esters in which the side chain is bonded to the phosphorous atom through an amino linkage.

Methods for synthesis and the analysis of various types of polyphosphazenes are described in U.S. Pat. Nos. 4,440,921, 4,495,174, and 4,880,622. Methods for the synthesis of the other polymers described above are known to those skilled in the art. See, for example Concise Encyclopedia of Polymer Science and Engineering, J. I. Kroschwitz, editor (John Wiley and Sons, New York, N.Y., 1990). Many polymers, such as poly(acrylic acid), alginates, and PLURONICS™, are commercially available.

Water soluble polymers with charged side groups are cross-linked by reacting the polymer with an aqueous solution containing multivalent ions of the opposite charge, either multivalent cations if the polymer has acidic side groups, or multivalent anions if the polymer has basic side groups. Cations for cross-linking the polymers with acidic side groups to form a hydrogel include divalent and trivalent cations such as copper, calcium, aluminum, magnesium, and strontium. Aqueous solutions of the salts of these cations are added to the polymers to form soft, highly swollen hydrogels.

Anions for cross-linking the polymers to form a hydrogel include divalent and trivalent anions such as low molecular weight dicarboxylate ions, terepthalate ions, sulfate ions, and carbonate ions. Aqueous solutions of the salts of these anions are added to the polymers to form soft, highly swollen hydrogels, as described with respect to cations.

For purposes of preventing the passage of antibodies into the hydrogel, but allowing the entry of nutrients, a useful polymer size in the hydrogel is in the range of between 10,000 D and 18,500 D.

Temperature-dependent, or thermosensitive, hydrogels have so-called "reverse gelation" properties, i.e., they are liquids at or below room temperature, and gel when warmed to higher temperatures, e.g., body temperature. Thus, these hydrogels can be easily applied at or below room temperature as a liquid and automatically form a semi-solid gel when warmed to body temperature. As a result, these gels are especially useful when the support structure is first implanted into a patient, and then filled with the hydrogel-EV composition. Examples of such temperature-dependent hydrogels are PLURONICS™ (BASF-Wyandotte), such as polyoxyethylene-polyoxypropylene F-108, F-68, and F-127, poly(N-isopropylacrylamide), and N-isopropylacrylamide copolymers.

These copolymers can be manipulated by standard techniques to affect their physical properties such as porosity, rate of degradation, transition temperature, and degree of rigidity. For example, the addition of low molecular weight saccharides in the presence and absence of salts affects the lower critical solution temperature (LCST) of typical thermosensitive polymers. In addition, when these gels are prepared at concentrations ranging between 5 and 25% (W/V) by dispersion at 4°C., the viscosity and the gel-sol transition temperature are affected, the gel-sol transition temperature being inversely related to the concentration.

U.S. Pat. No. 4,188,373 describes using PLURONIC™ polyols in aqueous compositions to provide thermal gelling aqueous systems. U.S. Pat. Nos. 4,474,751, '752, '753, and 4,478,822 describe drug delivery systems which utilize thermosetting polyoxyalkylene gels; with these systems, both the gel transition temperature and/or the rigidity of the gel can be modified by adjustment of the pH and/or the ionic strength, as well as by the concentration of the polymer.

pH-dependent hydrogels are liquids at, below, or above specific pH values, and gel when exposed to specific pHs, e.g., 7.35 to 7.45, the normal pH range of extracellular fluids within the human body. Thus, these hydrogels can be easily delivered to an implanted support structure as a liquid and automatically form a semi-solid gel when exposed to body pH. Examples of such pH-dependent hydrogels are TETRONICS™

(BASF-Wyandotte) polyoxyethylene-polyoxypropylene polymers of ethylene diamine, poly(diethyl aminoethyl methacrylate-g-ethylene glycol), and poly(2-hydroxymethyl methacrylate). These copolymers can be manipulated by standard techniques to affect their physical properties.

Hydrogels that are solidified by either visible or ultraviolet light can be made of macromers including a water soluble region, a biodegradable region, and at least two polymerizable regions as described in U.S. Pat. No. 5,410,016. For example, the hydrogel can begin with a biodegradable, polymerizable macromer including a core, an extension on each end of the core, and an end cap on each extension. The core is a hydrophilic polymer, the extensions are biodegradable polymers, and the end caps are oligomers capable of cross-linking the macromers upon exposure to visible or ultraviolet light, e.g., long wavelength ultraviolet light.

Examples of such light solidified hydrogels include polyethylene oxide block copolymers, polyethylene glycol polylactic acid copolymers with acrylate end groups, and 10K polyethylene glycol-glycolide copolymer capped by an acrylate at both ends. As with the PLURONIC™ hydrogels, the copolymers comprising these hydrogels can be manipulated by standard techniques to modify their physical properties such as rate of degradation, differences in crystallinity, and degree of rigidity.

Methods of Treatment

Also disclosed is a method of treating a subject with a with a spinal cord injury, stroke, traumatic brain injury or a neurodegenerative disease comprising administering to the subject an effective amount of a composition containing a population of neural EVs disclosed herein. In some embodiments, the neurodegenerative disease is Alzheimer's disease, Parkinson's disease, a Parkinson's-related disorder, Huntington's disease, prion disease, motor neuron disease (MND), spinocerebellar ataxia (SCA) or spinal muscular atrophy (SMA).

The term "spinal cord injury" is used to describe a spinal cord injury which results in a temporary or permanent change in the normal motor, autonomic or sensory function of the cord. The damage often results from physical trauma, such as sports injuries, slip and fall accidents or motor vehicular accidents but can also result from diseases such as spina bifida, Friedrich's ataxis and/or transverse myelitis. Injury to the spinal cord

resulting in a loss of function does not have to be the result of complete severing of the spinal cord. Depending on where the spinal cord and its nerve roots are damaged, the symptoms and degree of injury can vary widely, from pain to incontinence to paralysis. Spinal cord injuries are described at various levels of incomplete to complete injury, resulting in a total loss of function. The spinal cord injury can result in paraplegia or tetraplegia.

Traditional treatment of spinal cord injuries starts with stabilizing the spine and controlling inflammation associated with the spin cord damage to prevent further damage. Other interventions can vary widely depending on the location and extent of the injury. In many cases, using conventional therapy, spinal cord injuries require substantial, long-term physical therapy and rehabilitation, especially if the injury interferes with activities of daily life.

Spinal cord injury can be classified into three types based on its cause: mechanical forces, toxic, and ischemic, from lack of blood flow. Spinal cord damage can also be divided into primary and second injury. Primary injury is caused by the cell death that occurs immediately in the original injury (physical trauma, exposure to toxins, or ischemia), and secondary injury is caused by the resultant cascades that are caused by the original insult and cause further tissue damage. These secondary injury pathways include inflammation, swelling, neurotransmitter deficiencies/imbalances, the results of ischemia and cell suicide. The present invention may be used to treat all forms of spinal cord injury, including complete and incomplete injuries, ischemia, spinal cord injury without radiographic abnormality, central cord syndrome, anterior cord syndrome, Brown-Séquard syndrome, posterior cord syndrome, tabes dorsalis and conus medullaris, among others.

The term "stroke" is used to describe a cerebrovascular accident (CVA), cerebrovascular insult (CVI), or brain attack, occurs when poor blood flow to the brain results in cell death. There are two main types of stroke: ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding. Both of these types of stroke result in part of the brain not functioning properly. Signs and symptoms of a stroke may include an inability to move or feel on one side of the body, problems understanding or speaking, a sense of spinning, or loss of vision to one side, among others. Signs and symptoms often appear

soon after the stroke has occurred. If symptoms last less than one or two hours it is known as a transient ischemic attack. Hemorrhagic strokes may also be associated with a severe headache. The symptoms of a stroke can be permanent. Long term complications of stroke may include pneumonia or loss of bladder control The main risk factor for stroke is high blood pressure. Other risk factors include tobacco smoking, obesity, high blood cholesterol, diabetes mellitus, previous transient ischemic attack (TIA), and atrial fibrillation, among others. An ischemic stroke is typically caused by blockage of a blood vessel. A hemorrhagic stroke is caused by bleeding either directly into the brain or into the space surrounding the brain. Bleeding may occur due to a brain aneurysm. Both ischemic and hemorrhagic stroke are treated pursuant to the present invention.

The term "traumatic brain injury" (TBI) is used to describe an injury to the brain caused by movement of the brain within the skill or an injury to the brain caused by a foreign object. Causes of TBI may include falls, a motor vehicle crash or being struck by or with an object. TBI may also be caused by a penetrating object- an injury to the brain caused by a foreign object entering the skull. Causes may include firearm injuries or being struck with a sharp object. TBI may cause a concussion, a period of unconsciousness (coma) or amnesia. TBI may impair one or more of cognitive function (e.g., attention and memory), motor function (e.g., extremity weakness, impaired coordination and balance), sensation (e.g., hearing, vision, impaired perceptin and touch and emotion (e.g., depression, anxiety, aggression, impulse control, personality changes).

The term "neurodegenerative disease" is used throughout the specification to describe a disease which is caused by damage to the central nervous system and which damage can be reduced and/or alleviated through transplantation of neural cells according to the present invention to damaged areas of the brain and/or spinal cord of the patient. Exemplary neurodegenerative diseases which may be treated using the neural cells and methods according to the present invention include for example, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), Alzheimer's disease, lysosomal storage disease ("white matter disease" or glial/demyelination disease, as described, for example by Folkerth, *J. Neuropath. Exp. Neuro.*, 58, 9, Sep., 1999), Tay Sachs disease (beta hexosaminidase deficiency), other genetic diseases, multiple sclerosis, brain injury or trauma caused by ischemia, accidents, environmental insult, etc.,

spinal cord damage, ataxia and alcoholism. In addition, the present invention may be used to reduce and/or eliminate the effects on the central nervous system of a stroke or a heart attack in a patient, which is otherwise caused by lack of blood flow or ischemia to a site in the brain of said patient or which has occurred from physical injury to the brain and/or spinal cord. The term neurodegenerative diseases also includes neurodevelopmental disorders including for example, autism and related neurological diseases such as schizophrenia, among numerous others.

The herein disclosed compositions, including pharmaceutical composition, may be administered in a number of ways depending on whether local or systemic treatment is desired, and on the area to be treated.

Methods of treating subjects involve administration of a pharmaceutical composition comprising an effective amount of EVs described herein and optionally at least one additional bioactive (e.g. an agent which is useful in the treatment of a neurodegenerative disease, stroke and/or spinal cord injury) agent. For example, the compositions could be formulated so that a therapeutically effective dosage of between about 0.01, 0.1, 1, 5, 10, 15, 20, 25, 30 , 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90 or 100 mg/kg of patient/day or in some embodiments, greater than 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 200 mg/kg of the disclosed EVs can be administered to a patient receiving these compositions.

The dose of EVs administered to a subject can be less than 10 μg, less than 25 μg, less than 50 μg, less than 75 μg, less than 0.10 mg, less than 0.25 mg, less than 0.5 mg, less than 1 mg, less than 2.5 mg, less than 5 mg, less than 10 mg, less than 15 mg, less than 20 mg, less than 50 mg, less than 75 mg, less than 100 mg, less than 500 mg, less than 750 mg, less than 1 g or more than 1 g. Administration may be by numerous routes of administration, but intravenous, intrathecal, intranasal and/or intracerebrospinal fluid are often used as routes of administration.

In some embodiments, the disclosed EVs are administered within 24 after a stroke or trauma. However, in some embodiments, the EVs are administered at least 1, 2, 3, or 4 weeks after a stroke or trauma. In some embodiments, the disclosed EVs are administered in multiple doses 1, 2, 3, or more days apart. In some cases, such as cases of

neurodegenerative disease, the EVs are administered continuously (e.g., once every 1, 2, 3, or 4 weeks) over the course of the disease.

EVs may be loaded with small molecules, antisense oligonucleotides, siRNAs, peptides, proteins or antibodies that target, peptides or peptide translation products which are involved in neurodegenerative processes.

In certain embodiments, the disclosed EVs are loaded with additional bioactive agents or are co-administered with additional bioactive agents, especially agents which are useful in the treatment of neurodegenerative diseases.

The term "coadministered", "coadministration" or "combination therapy" is used to describe a therapy in which at least two active compounds/compositions in effective amounts are used to treat neural injury and/or a neurodegenerative disease. Although the term co-administration preferably includes the administration of EVs and at least one additional active compound to the subject at the same time, it is not necessary that the compounds/compositions be administered to the patient simultaneously, only that effective amounts of the individual compounds/compositions be present in the patient at the same time. Thus, the term co-administration includes an administration in which the EVs and the bioactive agent(s) are administered at approximately the same time (contemporaneously), or from about one to several minutes to about eight hours, about 30 minutes to about 6 hours, about an hour to about 4 hours, or even much earlier than the other compound/composition as otherwise described herein including up to a day or substantially more.

Agents which may be loaded or coadministered along with EVs may include, for example aricept, namenda, donepezil, excelon, razadyne, glantamine, rivastigmine, memantine, ergoloid, namzaric and mixtures thereof for Alzheimer's disease, biperiden, apomorphine, trihexyphenidyl, carbidopa/levodopa, rasagline, belladona, levodopa, benztropine, entacapone, selegiline, rivastigmine, pramipexole, rotigotine, bromocriptine, pergolide, ropinirole, carbidopa/entacapone/levodopa, amantadine, tolcopone, trihexiphenidyl and mixtures thereof, for Parkinson's disease, tetrabenazine, haloperidol, chlorpromazine, olanzapine, fluoxetine, sertraline, nortriptyline, benzodiazpines, paroxetine, venlafaxin, beta-blockers, lithium, valproate, carbamazepine, botulinum toxin and mixtures thereof for the treatment of Huntington's disease, anticholinergic drugs,

anticonvulsants, antidepressants, benzodiazepines, decongestants, muscle relaxants, pain medications, stimulants and mixtures thereof for the treatment of motor neuron disease, selective serotonin reuptake inhibitors (SSRI's), selective norepinephrine-serotoning reuptake inhibitors (SNRI's), acetazolamide, baclofen, clonazepam, flunarizine, gabapentin, meclizine, memantine, ondansetron, scopolamine, modafinil, armodafinil, amantadine, atomoxetine, buproprion, carnitine, creatine, modafinil, armodafinil, pyrudistigmine, selegiline, venlafaxine, desvenlafaxine, buspirone, riluzole, verenicline, memantine, baclofen, tizanidine, cymbalta, lyrica, acetazolamide, carbamazepine, clonazepam, isoniazid, droxidopa, ephedrine, fludrocortisones, midodrine, levodopa, pramipexole, fluoxetine, n-acetylcysteine, baclofen, dantrolene sodium, diazepam, ropinirole, tizanidine, trihexylphenidyl, clonazepine, flunarazine, levetiracetam, primidone, topiramate, valproic acid, phenytoin, 4-aminopyridine and mixtures thereof for the treatment of spinocerebellar ataxia and riluzole for the treatment of spinal muscular atrophy. Agents for the treatment of stroke include salicylates, such as aspirin, a thrombolytic agent (alteplase) and a platelet aggregation inhibitor (clopidogrel), among others.

More generally, non-steroidal anti-inflammatory drugs (NSAIDS) and other anti-inflammatory agents may be used in the treatment of neurodegenerative diseases as described herein.

The activities of EVs described herein can be evaluated by methods known in the art. The amount of EVs required for use in treatment can vary not only with the particular cell from which the EVs are prepared, but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and can be ultimately at the discretion of the attendant physician or clinician. In general, however, a dose can be in the range of from about 0.01 mg/kg to about 10 mg/kg of body weight per day.

Identifying EVs useful in the present methods for treating a spinal cord injury, stroke, traumatic brain injury and/or a neurodegenerative disease which occurs by modulating the activity and expression of a disease-related protein and biologically active fragments thereof can be made by screening EV activity in any of a variety of screening techniques. The screening can be made for whole EVs or their contents. Fragments

employed in such screening tests may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The blocking or reduction of biological activity or the formation of binding complexes between the disease-related protein, the EVs and/or one or more components of the EVs may be measured by methods available in the art.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

EXAMPLES

Studies were conducted to determine whether EVs confer paracrine benefits on neural stem cells and play a role in both optimal *in vitro* neural cultures conditions and in therapeutic outcomes of neural stem cell treatments. The objective of the study was to determine if it was possible to isolate EVs from human stem cells of a neural lineage, specifically neural progenitor cells and/or differentiated post-mitotic neuronal cells. EVs were purified from neural progenitor cells (SOX 1+and 2+, OCT4-; hNP1™ ArunA Biomedical), derived from human pluripotent stem cell lines or differentiated neuronal cells (β-III tubulin (Tuj1) +, MAP2+, Oct4-); hN2™ ArunA Biomedical).

Example 1:

Human pluripotent stem cells [see, Chambers, et al., Methods Mol Biol, 2016. 1307: p. 329-43] lines were cultured in media absent of serum such as MTeSR or E8 which is commercially available from vendors such Stem Cell Technology using feeder free conditions or media composed of knock-out serum replacement (KSR) media (DMEM=F12, 2mM L-glutamine, 0.1mM MEM nonessential amino acids, 50U/mL penicillin, 50 mg/mL streptomycin, and 20% KSR) (all from Gibco, Carlsbad, CA) and 4 ng/mL basic fibroblast growth factor bFGF; R&D Systems, Minneapolis, MN). Cells were cultured on Mitomycin-C (Sigma, St. Louis, MO) mitotically inactivated murine embryonic fibroblasts (MEF) or without feeders, manually or enzymatically dissociated, and passaged to new feeder layers every 2–5 days. For feeder-free culture of hPSC in

Conditioned media, cells grown on MEF were washed once with PBS (without Ca2+ and Mg2+), and then incubated with 0.25% trypsin (Gibco) until the MEF layer began to lift off the dish. The floating MEF layer was discarded after agitating it to release adherent stem cells that were collected, centrifuged, and resuspended in MEF-conditioned media (CM). CM was prepared by placing 20% KSR media on MEF for 24 h and then supplementing the collected media with an additional 4ng/mL of bFGF. Cells were plated on tissue culture dishes coated with laminin substrate (1 mg/cm2; Sigma) and grown to ~90% confluence. The cells were passaged at least three times to minimize MEF contamination [see, Boyd, et al., Tissue Eng Part A, 2009. 15(8): p. 1897-907, Mumaw, et al., Microsc Microanal, 2010. 16(1): p. 80-90 and Young, et al., Neuroscience, 2011. 192: p. 793-805,]. Regardless of the culture method all media is collected and EVs are collected from the media and used to treat patients

After manual passage onto fresh feeder cells, hESCs were allowed to proliferate in ES medium for 7 days (stage 1). Cell differentiation was then induced with either DN2, MEDII, or ES medium for another 7 days (stage 2). DN2 medium is DMEM/F12-based medium supplemented with N2 (Gibco), L-glutamine, penicillin/streptomycin (P/S), and 4 ng/ml bFGF. MEDII medium for this study is DN2 medium supplemented at 50% (unless otherwise noted) with conditioned medium. To understand and follow the differentiation steps applied here, phenotype marker expression was examined at various time intervals. At stages 1, 2, and 3, populations were harvested and the markers Musashi-1, Nestin, and Oct-4 were observed. Immunocytochemical analysis was also performed on the adherent cell population. The cells at both stages were double-stained with Nestin and Oct-4 and observed under the fluorescence microscope for immunocytochemical examination associated with morphology. Groups that displayed phenotypic difference were then subjected to quantitative analysis for these same markers using flow cytometry. All experiments were replicated three times unless otherwise noted. After manual passage onto fresh feeder cells, hESCs were allowed to proliferate in ES medium for 7 days (stage 1). Cell differentiation was then induced with either DN2, MEDII, or ES medium for another 7 days (stage 2). DN2 medium is DMEM/F12-based medium supplemented with N2 (Gibco), L-glutamine, penicillin/streptomycin (P/S), and 4 ng/ml bFGF. MEDII medium for this study is DN2 medium supplemented at

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hPSC were allowed to proliferate in hPSC medium (any of those described above) for approximately 5 to 10 days (stage 1) as a monolayer or as embryoid bodies. Cell differentiation was then induced with medium typically DMEM/F12-based medium supplemented with N2 (Gibco), L-glutamine, penicillin/streptomycin (P/S), and usually 4 ng/ml bFGF. Nestin, and Oct-4 were observed and neural rosettes form. Neural rosettes are isolated (manually or enzymatically and are immunocytochemical analysis was also performed on the adherent rosette population. The cells at both stages were double-stained and are Nestin+ and Oct-4 - and observed under the fluorescence microscope for immunocytochemical examination associated with morphology [Shin, et al., Stem Cells, 2006. 24(1): p. 125-38]. The rosettes when isolated from most of the contaminating cells

are considered human neural progenitor cells. Briefly, hNP cells were grown on poly-ornithine (20 mg/mL) /laminin (Sigma-Aldrich, Inc.) (5 mg/mL) coated plates or other ECM such as Matrigel, and maintained and expanded in media with 2 mM L-glutamine and 20 ng/mL b-FGF. hNP Cells were passaged approximately every 48 h and split 1:2 following manual dissociation [see, Mumaw, et al., Id., Young, et al. Id. and Dhara, et al., Methods Mol Biol, 2011. 767: p. 343-54].

Alternatively, neural induction may be stimulated by inhibition of SMAD signaling using inhibitors of Activin/Nodal pathway, and/or BMP signaling (examples of inhibitors might be Noggin, SB431542 [Chambers, et al. Nat Biotechnol, 2009. 27(3): p. 275-80], Compound C [Zhou, et al., Stem Cells, 2010. 28(10): p. 1741-508], or other strategies alone or in combination). Cells may be cultured on matrigel or other extracellular matrices, in AB2, Neurobasal, or other mediums listed above, in the presence of absence of Sonic Hedgehog [Chambers, et al., Id., and Zhou, et al., Id.].

hNP cells differentiated into neurons on poly-ornithine and laminin coated plates or other ECM such as Matrigel under maintenance media described above without bFGF and LIF. Alternatively LIF or EGF are added hNP cells were allowed to differentiate under these two conditions for 1 to 7 weeks [Mumaw, et al., Id., and Dodia, et al., PLoS One, 2011. 6(8): p. e232669].

After 1 to 4 weeks of neuronal differentiation such as hNP cells differentiated into neurons on poly-ornithine and laminin coated plates (under two conditions in maintenance media without bFGF or bFGF and LIF or EGF), astrocytic differentiation was induced by switching the neural to cells from hNSC Maintenance Medium to the basic medium (DMEM HAM's F12 medium, glutamine, Penicillin/Streptomycin) supplemented with 1% FCS (Gibco). See Mumaw, et al., Id. and Young, et al., Id. Finally, multilinear differentiation was achieved by replacing the maintenance medium by the basic medium containing 10% of FCS. After 45-50 days cultures were nearly 100% positive for glial markers S100β and vimentin [Palm, et al., Sci Rep, 2015. 5: p. 1632110].

Alternatively, hNP cells were propagated as adherent monolayer cultures in a proliferation media (such as AB2™ , ANS™ Neurobasal™, 1× B27, 1× Glutamax™, P/S, FGF2 (10 ng/mL) as described (Shin et al., Id.), and differentiated by removal of

FGF. For astrocytic differentiation of hNP cells, neuronal differentiation media were supplemented with recombinant proteins, such as BMP2 and combinations of chemicals such as Azacytidine, Trichostatin A, or similar molecules for 1-5 days, with complete media changes in between, followed by differentiation media supplemented with the molecules separately or in combination. Cells were harvested prior to analysis at 5, 15 or 30 days of treatment or for cryopreservation at d6 or d10 of differentiation. For cryopreservation, cells were dissociated with Accutase™ and frozen in differentiation media containing 10% DMSO [Majumder, et al., Stem Cell Res, 2013. 11(1): p. 574-86].

When hPSC cultured without feeders as described above reached approximately 90% confluence, the 100mm dishes were washed with PBS++ (with Ca2+ and Mg2+) and replaced with 10 mL of fresh endothelial growth media 2 microvascular (EGM2-MV) (Lonza; 5% FBS, proprietary endothelial basal media 2 (EBM2) basal media and concentrations of bFGF, VEGF, EGF, and R3-IGF-125). The media was changed every 2--3 days over a period of 20--30 days. After transition from hESC to epithelial sheet was completed, the cells were trypsin passaged to a T75 flask and grown to confluence. To expand the initial cell culture, cells were passaged and seeded at a target density of approximately 4 x 10^4 cells/cm_2 per flasks. For subsequent culture for experimentation, cells were subcultured at 10^6 cells=T75 flask (approximately 1.3 x 10^5 cells/cm_2) and grown to confluence over 5--7 days [Boyd, et al., Id].

Example 2:

Methods

Cell medium was collected from confluent cultures 24 hours post media change and frozen at -20°C. Medium was thawed at 4°C overnight and filtered through a 0.22 µm Steriflip unit prior to EV purification.

Extracellular vesicle purification by ultracentrifugation.

Isolation of extracellular vesicles from cell culture media was performed according to the protocols published by Théry, C., et al., Isolation and Characterization of EVs from Cell Culture Supernatants and Biological Fluids, in Current Protocols in Cell Biology. 2001, John Wiley & Sons, Inc. Briefly, filtered media was serially centrifuged at 300 x g for 10 minutes, and supernatant was transferred to a fresh tube for centrifugation

at 2,000 x g for 10 minutes. Collected supernatants were then centrifuged at 10,000 x g for 30 minutes, and resultant supernatant collected into a fresh tube. To label EVs, DiI was added to the purified supernatants at a final concentration of 10 μM and incubated at room temperature for 30 minutes. Supernatants were distributed into 11.5 ml Sorvall Ultracrimp tubes and sealed before transfer into a Sorvall T880 fixed angle rotor for centrifugation at 100,000 x g for 70 minutes at 4°C. Supernatant was carefully removed and pelleted material resuspended in PBS and transferred into another ultracrimp tube, and again centrifuged at 100,000 x g for 70 minutes at 4°C. The PBS was removed and pelleted material from each tube was resupended in 100 μl PBS. All purified EVs from the same cell type were pooled, triturated, and aliquoted into DNase/RNase free tubes (20-50 μl aliquots) for storage at -20°C.

Extracelluar vesicle purification by ultrafiltration

Ultrafiltration of extracellular vesicles was performed according to the procedure developed for purification of cardiomyocyte derived extracellular vesicles. Amicon Ultra-15 100 kDa molecular weight cutoff filters were wetted with 10 ml PBS and centrifuged in a swinging bucket rotor at 4,000 x g for 10 minutes. The PBS was discarded and the cell culture medium was added to the filter approximately 15 ml / tube and centrifuged at 4,000 x g for 10 minutes. Another 15 ml culture medium was added to the filter when filtering stem cell derived extracellular vesicles, because less media was retained in the filter from the first run through, so approximately 30 ml of medium total was filtered for the H9 derived NP, Astrocyte, and MSC lines, while only 15 ml of medium was filtered for SH SY5Y cells; the media in the filter was centrifuged at 4,000 x g in 5 minute increments to obtain approximately 1 ml of retentate. This was then either moved to a 1.5 ml tube for DiI labeling (at 10 μM for 30 minutes) or for unlabeled purification diluted to 15 ml with PBS and washed twice before repeating 5 minute centrifugation increments until a final volume of 1-1.5 ml was obtained. The purified extracellular vesicle preparation was then pooled from the same cell type and dispersed into approximately 100 μl aliquots (DNase/RNase free tubes) and stored at -20°C.

DiI-labeling vesicles

Labeled vesicles were generated by ultrafiltration. After the ultrafiltration was complete, the filter retentate was moved to a centrifuge tube, and 10 μM DiI was added to

the supernatant for 30 min. PBS was added to the filtration unit during this time to prevent the filter from drying out. After incubation with the labeling agent, supernatant was transferred back into the filtration device and washed three times with PBS (approximately 45 ml) to remove free label. After the final wash the retentate was concentrated to approximately 1 ml, which was aliquoted and stored at -20°C.

Electron Microscopy

Vesicle preparations were mixed 1:1 with 4 % paraformaldehyde (PFA) (to yield 2 % PFA final) and incubated for 15 minutes. 5 µl droplets of fixed vesicle suspensions were transferred to Formvar-coated grids for 20 min., and then washed by transferring to drops of PBS. Grids were transferred onto drops of 1 % glutaraldehyde for 5 min, and then moved over several drops of water to remove residual glutaraldehyde before transferring to uranyl-oxylate. Grids were imaged by electron microscopy at 80 kV.

Results

While initial reports indicate that neural progenitor cells secrete fewer EVs than other cell types, ultrastructural analysis of the cells revealed prominent vesicles of endocytic origin (Fig. 2A-2C), and many were in close proximity or associated with the outer limiting membrane of the cell (Fig. 2D, 2E). Cargoes within the multivesicular bodies (MVBs) vary in size (Fig. 2 B, 2C) and are occasionally visualized budding off into the vesicle (arrow). Smaller vesicles seem to coalesce into larger MVBs as they move to the periphery of the cell (Fig. 2F, 2G). It was possible to purify and visualize vesicles from the media of neural progenitor cells (Fig. 2H). These data suggest that neural progenitor cells do release extracellular vesicles into the cellular medium, and these vesicles can be purified using published EV purification protocols. All scale bars are 500 nm.

After realizing that neural progenitor cells have the capability of producing EVs that could be purified and visualized by electron microscopy, the process of characterizing the purified vesicles from multiple cell types began with protein profiling by Coomassie stain (Fig. 3A), and BCA Analysis of total protein content (Fig. 3B). The protein profiles were compared from neural progenitor cells, differentiated neural cells, and astrocytes, all derived from the same ES cell line, and SH SY5Y cells, a human neuroblastoma cell line used as a positive control. Early experiments indicate that the

protein profile overlaps, but there are distinct proteins in the neural progenitor and differentiated neural cells, even though the cells are of the same genetic origin. Similarly, comparing the size profiles of the vesicles from neural progenitors, and astrocyte cells from the same genetic origin indicates that the size of vesicles from the 2 cell types overlap (including a large percentage of 55 nm vesicles), but there are distinct subpopulations that vary between the two cell types, with astrocytes showing unique vesicle sizes including a 25 nm population, and slightly larger 135 nm population (Figs 3C, 3D). Taken together, these data indicate that cargoes are specifically targeted into MVBs, and these cargoes change in the differentiation process, supporting a role for EVs in cell to cell communication throughout the process of development.

In order to determine if it was possible to label EVs, and visualize their uptake by another cell, differentiated neural cells (6-8 weeks in differentiation medium without fibroblast growth factor (FGF) were treated with astrocyte derived vesicles at timepoints ranging from 30 seconds through 30 minutes, after which, cells were fixed, and stained for β-III tubulin. At the earliest time points, few vesicles were found in the cells, (Figs 4A-4C). By 5 minutes in the culture it was possible to find neural cells with prominent red fluorescence, indicating vesicle uptake in these cells (Figs. 4D-4F).

To determine if these vesicles could elicit an effect in recipient cells, differentiated neural cells were treated with serially diluted concentrations of vesicles derived from neural progenitors, astrocytes, or MSCs all derived from the same ES cell line, or SH SY5Y cells. These cells were then subjected to nutrient deprivation over 10 days and analyzed for neurite outgrowth. As expected, in wells that received only PBS the monolayer was disrupted and few cells were left (Fig 5. D). However, cells that received the highest concentrations of EVs from either neural progenitors or astrocytes were able to survive this nutrient deprivation, and the monolayer of cells with intact neurites were largely still intact (Fig 5. A, B). Wells treated with MSC derived EVs contained more cells than untreated wells, but the monolayer was no longer intact and neurites were largely lost (Fig 5. C). These data indicate that vesicle treatment protected the recipient cells from nutrient deprivation, and importantly, indicate that cells respond differently to vesicles that originate from different cell types, even if the vesicles are from an isogenic or autologous source.

Taken together, these data support the idea that the parental source of origin has an impact on the vesicles that result. This has huge implications for considering extracellular vesicles as a therapeutic source that can potentially be exploited for regenerative medicine, and highlights the need for vesicles derived from neural sources for the treatment of CNS injuries and / or disease. Importantly, these data also indicate that not only neuron derived vesicles, but also glial vesicles provide benefit *in vitro*.

Example 3:

Biodistribution Methods: Rodent biodistribution by single-photon emission spectroscopy. 1.5-2 mCi of Indium-111-oxine in PBS was added to 200 µl doses containing EVs (~2.7 x 10^{11} vesicles/kg) and incubated at 37°C for 20 minutes. Free indium was removed by three repeated PBS washes through an Amicon 100 kDa ultrafiltration device. Collected EVs were diluted to 200 µCi of radioactivity per dose, and injected intravenously into the mouse tail vein, either 1 hour or 24 hours post-stroke. Control animals received injection of free indium-111-oxine. Whole body and head single photon emission spectroscopy (SPECT) images were acquired by Mediso's nanoScan microSPECT/CT system 1 and 24 hours after injection, and projection images were reconstructed according to maximum intensity to determine radioactivity in the brain and throughout the body.

Piglet biodistribution: EVs were concentrated by ultrafiltration using Centricon units as previously described and then moved to 50 ml falcon tubes for DiR labeling (5 µM) in the dark for 30 minutes. Labeled EVs were collected by ultracentrifugation at 100,000 x g for 4 hours. Pelleted EVs were washed with PBS and again collected by ultracentrifugation. EVs were resuspended in PBS and diluted into 2.7 x 10^{10} vesicle/kg body weight (in 200 ul PBS) doses for individual piglets based on NanoSightNS 300 nanoparticle tracking analysis. Piglets were anesthetized with isoflourane for intravenous injection (tail vein), intranasal delivery, cerebrospinal fluid EV injection into the subarachnoid cistern, or injection directly into the brain parenchyma. For intraparenchymal injection EVs were delivered at a flow rate of 5 µl per minute. Animals were euthanized by isoflourane followed by CO_2 asphyxiation 30 minutes after

completion of EV delivery. Brain, heart, liver, kidneys, lungs, and spleen were removed and imaged using Lumina IVIS (model) to detect DiR fluorescence.

Mouse: EV biodistribution was evaluated after either free indium-111 or indium-111 labeled EVs were injected into the mouse tail vein either immediately (Fig. 6B), or 24 hours post-stroke (Fig. 6C). SPECT scans were performed 1 hour after injection (Fig. 6A, 6B, 6C, left panels), and again 24 hours after injection (Fig. 6A, 6B, 6C, right panels). Images reconstructed by maximum intensity indicate that indium-111 labeled EVs are distributed throughout the bodies filtration organs in lungs, liver, spleen, and kidneys at both the initial timepoint, and 24 hours later (Fig. 6B, 6C; whole body scans) while free indium-111 is initially localized mostly to the lungs before disbursing into the liver, spleen, and kidneys 24 hours later (Fig. 6A; whole body scans) likely indicating clearance through the renal system. Uniquely, labeled EVs were present in the brain in proximity of the stroke within 1 hour of injection when injected either immediately or 24 hours after stroke (Fig. 6B, 6C; circles), indicating either access from the circulation due to disruption of the blood brain barrier, homing to the damaged tissue, or some combination of the two. Free indium did not localize to the stroked tissue at either time point assessed (Fig. 6A, circles).

Uniqueness: This is the first time that anyone has shown that IV injection of EVs are actually distributed in and around the infarcted brain following stroke. The majority of the EVs were distributed in other organs such as heart, liver, lung, and kidney, and we have data to suggest that the EVs for the first time have a systemic effect on the immune response post stroke (data in other sections). Thus it is likely that systemic effects of peripheral EVs have a positive effect on molecular and phenotypic benefits following stroke. Thus the EVs may have a direct effect at the site of injury, could be via local immune cells or via direct effect on the neurons, as well as a system effect on the immune system. This is the first data showing biodistribution in a large animal brain.

Piglet: In order to optimize EV delivery to the brain following stroke, biodistribution of fluorescently labeled (DiR, 5 μM) was evaluated in uninjured piglets. Labeled EVs were detected in the brain after injection directly into the parenchyma (Fig. 7, top panels), or into the CSF of the subarachnoid cistern at the base of the skull (Fig. 7,

lower panels). This is the first demonstration of EV biodistribution in a large animal study.

Example 4:

Methods

Mouse model

Middle-aged C57/B6 male mice (retired breeders of 9 – 11 months) were pre-trained for adhesive tape test (ATT) for 3 days prior to the stroke surgery (3 trials/ day). Mice were marked for identity, numbered, and randomized for therapy after stroke in a block size of 4 (4 animals from the same cage) to different treatment groups following induction of embolic stroke. The surgeon performing the stroke surgery and cerebral blood flow (CBF), and the investigator performing neurobehavior and neurologic deficit scoring remained blinded to the identity of the groups. All four therapies received were thawed and injected intravenously at 2, 14 and 38 hrs post stroke with doses 1, 2 and 3, respectively. Relative cerebral blood flow (CBF) was measured at 6 and 48 hrs post stroke. Neurologic deficit score (NDS) was assessed at 48 hrs post stroke; the ATT that reflects the somatosensory function was performed at 96 hrs post stroke just prior to euthanasia. Mortality was monitored daily and recorded until day 4 and prior to euthanasia.

Embolic stroke

Mice were sedated with Buprenorphine (0.05 mg/ kg SC) 20 min prior to stroke surgery, and anesthetized with 3.5% isofluorane. Surgical plain of anesthesia was maintained with 1.5 – 2.0% during the surgery. Body temperature was maintained at 37 °C by a thermo-regulated surgery pad. By a midline incision on the ventral side of the neck, the right common carotid artery (CCA), external carotid artery (ECA), and the internal carotid artery (ICA) were assessed. A temporary atraumatic clip was placed on the CCA to prevent loss of blood during catheter insertion. A modified PE-10 catheter containing a single fibrin rich clot (9 ±0.5mm length) was introduced into the ECA and advanced into the ICA. The clot was gently injected with 100 µL of PBS, the catheter was removed immediately after embolization, and the arterial wound was secured to prevent blood loss. Induction of stroke was confirmed using on-site portable single point

cortical laser Doppler flowmetry (PeriMed Inc.). Finally, the temporary clip was removed and the blood flow in the CCA was reinstated. The site of surgery was closed using #6 sterile monofilament nylon suture, and Buprenorphine (0.05 mg/ kg SC) was again injected. Mice were transferred to clean recovery cages and animal temperature was maintained. Conscious mice were transferred to clean regular cages with free access to food and water. NAPA gel and lactated ringers solution were provided as needed, in case of any sign of dehydration; otherwise 1 ml of regular sterile saline pre-warmed at 37 °C was injected SC every 12 hours.

Laser Speckle Contrast Imaging:

Briefly, 6 hrs after stroke, mice were anesthetized using isofluorane, while body temperature was maintained at 37 ±0.5 °C. The skull was shaved and a midline skin incision was made to expose the middle cerebral region. Perfusion images were acquired using PeriCam high resolution Laser Speckle Contrast Imager (LSCI; PSI system, Perimed) with a 70 mW built-in laser diode for illumination and 1388 x 1038 pixels CCD camera installed 10 cm above the skull (speed 19 Hz, and exposure time 6 mSec, 1.3 x 1.3 cm). Acquired video and images were analyzed for dynamic changes in CBF. Overall perfusion of the ischemic region will be compared to an equally sized region of interest from the uninjured contralateral hemisphere to estimate relative CBF. The skin wound was closed using tissue glue. At 48 hrs post-stroke, the skin wound was again opened, cleaned, and the middle cerebral artery region was exposed to repeat the LSCI procedure as previously described.

Neurologic Deficit Score (NDS):

Neurologic deficits in mice were assessed by investigators blinded to the therapeutic group at 48 hr post stroke on a 5-point scale with the highest number indicating the worst outcomes and lower number indicating better neurological outcomes according to the following criteria: 0, no deficit (normal mice); 1, forelimb flexion deficit on contralateral side; 2, flexion deficit along with decreased resistance to lateral push and torso turning to the ipsilateral side when held by tail; 3, All deficits as in Score 2, including very significant circling to the affected side during the move inside the cage, and reduced capability to bear weight on the affected side; 4, All deficits as above but

rarely willing to move spontaneously, and prefer to stay in rest; 5, considered terminal and euthanized in accordance with animal care requirements.

ATT for Somatosensory Test:

Adhesive tape test (ATT) was used as a test of somatosensory motor function, and was performed at 96 hrs post-stroke immediately prior to euthanasia. Briefly, naïve mice were acclimatized to the procedure of the test for 3 days prior to surgery by placing them in a transparent acrylic box (15 cm x 25 cm). Two pieces of adhesive tape (0.3 cm x 0.4 cm) were used as bilateral tactile stimuli after they were attached at the distal-radial region on each forelimb such that it covered the hairless part (3 pads, thenar and hypothenar). Within 180 seconds, the tape removal time was recorded as the sensorimotor function. If a mouse failed to remove the tape within 180 seconds, it was given a score of 180 seconds. Therefore, a shorter time score indicates a better outcome while longer time indicates an outcome with higher deficit.

Euthanasia and 2,3,5-Triphenyltetrazolium Chloride (TTC) -staining:

TTC-stain differentiates between metabolically active (live or penumbra) and inactive (dead or core) tissues after stroke. TTC is a colorless solution, which is reduced to red 1,3,5-triphenylformazan (TPF) by the enzymatic action of various dehydrogenases primarily mitochondrial dehydrogenase from the living tissues, while the core (dead tissue) remains white. Therefore, larger white area indicates higher injury and infarction volume. At 96 hrs post stroke and after performing ATT, mice were deeply anesthetized with isofluorane (5%). Blood was collected via direct cardiac puncture to isolate and obtain serum later. Brains were very quickly perfused with 25 mls of cold 0.01 M phosphate-buffered saline (PBS), harvested fresh, and immediately transferred to a metallic mouse brain matrix. Looking at the infarcted area, 5-blades were placed in alternate gaps to obtain 2-mm coronal slices (4 sections per brain). Sections were individually placed in a 35-mm dish containing pre-warmed (37 °C) 3 ml of 5% TTC in PBS (Sigma) for 20 - 30 minutes at 37 °C, followed by 2x washing with cold PBS and fixation with 10% formalin. In order to image, fixed sections were taken out of the dish and placed in order on a high-resolution Cannon Scanner. Images were cropped and saved for analysis. Corrected infarct volume was estimated using gray scale image and Scion Image software, and presented as the % volume of the uninjured side.

Blood sample flow cytometry (Th17, Treg, M2)

Prior to euthanasia blood was collected and purified cells were subjected to fluorescence activated cell sorting to identify populations of immune cells present systemically including T-helper (CD4+/FOX3P+) populations, regulatory T-cells (CD4+/IL17+), and M2 macrophage (IL10+/CD206+) populations.

Results

EVs were purified from isogenically derived astrocyte progenitors (APEX), MSCs (MSCEX), and neural progenitor (NPEX) cells using standard methods (see manufacturing section), evaluated by nanoparticle tracking analysis (NanoSight-NS300) and stored in individual dose aliquots at -20°C until they were thawed at room temperature immediately prior to tail vein injection following embolic stroke. The 3 EV types and PBS were administered by blinded investigators following embolic stroke, in 3 doses of approximately 2.7 x 10^{11} vesicles/kg (or vehicle) at 2, 14, and 28 hours post-stroke. In all parameters evaluated both APEX and NPEX outperformed the vehicle treated controls as well as the MSCEX treatment group. Immediately after euthanasia, 2,3,5-Triphenyltetrazolium Chloride (TTC) was used to differentiate metabolically active (live, red) and inactive (dead, colorless) tissues. Importantly, TTC indicates decreased injury and infarction volume following APEX or NPEX ™ treatment (Fig 8 A), while MSCEX treatment was comparable to control. Within the 96 hrs following stroke APEX and NPEX treatments decreased mortality by 20 and 17% respectively (Fig. 8B). Neurologic deficits evaluated 48 hrs post stroke (on a 5-point scale from no deficit [0] with increasing severity through terminal deficits [5]) indicated significantly better behavioral outcomes for mice that received APEX or NPEX (Fig. 8D). Ability to remove adhesive tape used as bilateral tactile stimuli attached at the distal-radial region of each forelimb indicated improved sensorimotor function as well (Fig. 8E). Taken together, these data indicate improved survival, molecular, and functional outcomes in NPEX treated thromboembolic stroke rodent models compared to contemporary vehicle controls.

Flow cytometric analysis of blood cells at the 96 hour time point just prior to euthanasia indicates that neural cell type derived EVs, APEX and NPEX treatment resulted in an increase in the presence of protective regulatory T cells in circulation (Fig.

9A), while MSCEX were indistinguishable from controls. Pro-inflammatory T-helper cells were reduced in the APEX and NPEX groups (Fig. 9B), while anti-inflammatory M2 macrophages were increased in these groups (Fig. 9C). Taken together, these data indicate that neural cell type derived EVs exert part or all of their effects by modulating the immune response following stroke.

The production and quality control methods used to produce isogenically (genetically identical) derived neural progenitor, astrocyte progenitor, and MSC cells from the same ES cell line produce a unique opportunity to compare the EVs from these 3 cell types without the confounding variable of genetic variation due to source of the donor material. The vast majority of stem cell derived EV literature centers on use of MSC derived EVs. Here, for the first time neural cell derived EVs (APEX and NPEX) were evaluated and compared directly with MSC-derived EVs. There is a substantial improvement in molecular benefit (infarct volume), also increased survival and improved functional outcomes of neural derived EVs (APEX and NPEX) over the MSCEX. These improvements were immediate in older animals which is more prone to death. Thus no other group has shown that any EV (MSC or neural) therapy has such stark and immediate improvements in a mouse model that replicates the human stroke condition (embolic stroke) and factors in co-morbidly factors such as age (middle age mice). It appears that these early strong effects can only be obtained with a neural EV as disclosed herein.

These studies suggest that the mechanism of action in part may be through immune modulation suppressing the inflammatory M1 response including but not limited to suppressing IL17 cytokine while enhancing the M2 response perhaps through IL10 or other cytokines.

Example 5:

Pig Model, ischemic injury induced by middle cerebral artery (MCA) occlusion.

Landrace barrows (5-6 months, 150-170 lbs) were subjected to injury as previously described using the only fully developed porcine stroke model [1]. Briefly, a portion of the zygomatic arch was resected and the underlying muscle was elevated dorsally revealing the parietal bone. A window was generated in the bone surface

exposing the dura mater. The proximal MCA was permanently occluded resulting in infarction spanning the most caudal aspect of the frontal lobe as well as significant portions of the temporal, parietal, and occipital lobes.

Magnetic Resonance Spectroscopy

Magnetic resonance imaging (MRI) was performed 24 hours and 90 days post-MCAO surgery on a GE 16- channel fixed-site Twin gradient Signa HDx 3.0 Tesla MRI system. Under anesthesia, MRI of the neurocranium was performed using a multichannel phase array spine coil, with the patient in dorsal recumbency. Standard multiplanar MR brain imaging series were acquired. These included T2-weighted (T2w), T2-weighted fluid attenuated inversion recovery (FLAIR), and T1-weighted (T1w) FLAIR, as well as diffusion-weighted imaging (DWI) series. DWI was acquired with b = 0 and b = 1000. DWI, apparent diffusion coefficient (ADC) maps and T1w-FLAIR images were evaluated using Osirix® software for presence of cerebral infarction and changes in cerebral hemisphere volume. Specifically, the volume of the ischemic area was manually derived from the ADC maps generated from DWI sequences. The ischemic area was defined by two levels of ADC number reduction, with the ADC number from the contralateral cerebral hemisphere providing normal ADC values. Ischemic areas, defined by those with 80% and 40% ADC values of normal, were manually traced on the sequential ADC images. Each area was multiplied by slice thickness to produce a volume of ischemic tissue. This method was chosen because it has been demonstrated to strongly correlate with histologically defined areas. The cerebral hemisphere volume was determined through a similar process, whereby the cerebral hemisphere volume was quantified (excluding sulci and the lateral ventricular spaces) on T1w FLAIR images. The T2w FLAIR images were used for reference to differentiate areas filled with CSF and parenchymal areas of hyperintensity (Platt, S.R., et al., Experimental & Translational Stroke Medicine, 2014, 6:5).

EV dosage and administration

NPEX EVs containing ~2.7 x 10^{10} vesicles/kg in 50-60 ml PBS were thawed at 4°C and transferred into a 60 cc syringe using aseptic technique while in a biological safety cabinet. Samples were inverted a minimum of 25 times immediately prior to

intravenous injection via an ear vein catheter. Pigs received either 3 doses (50-60 ml) of NPEX or PBS (vehicle) at 2, 14, and 24 hours post-MCAO.

Animal evaluation and recovery

Following surgery, animals were moved to a clean recovery pen and monitored continuously until extubation. Rectal temperature, heart rate, and respiration rate (TPR) were recorded every 15 minutes until the pig was awake and vital signs were stable within normal limits. Thereafter, TPR measurements were initially reduced to 1-2 hour intervals unless vital signs deviated from normal (for example, a fever), then to longer intervals over the next 48 hours as the pig recovered. During the first 36 hours, pigs were never left for more than 4 hours without observation, and generally for no more than 2 hours. In addition to TPR, other observations recorded included time from arrival in recovery until the animal first stood up on its own, time to drink and eat with assistance, and time to eat and drink unassisted. Events such as fevers (rectal temperature 103°F or greater), circling behavior, and seizures were also monitored and documented.

As seen in Table 1, routine evaluation indicates improved survival and functional outcomes in immediate recovery post-stroke with NPEX treatment. Survival was substantially better in the NPEX treatment group, with 7/7 pigs surviving more than 72 hours post-stroke, while only 5/8 survived in the control group. Time until the animals could stand unassisted was reduced by about 2 hours with NPEX treatment. Fevers, which are very common within 72 hours post-stroke, were reduced in the NPEX treatment group where 4/7 animals had one or more fever episodes as compared to control group where 6/8 animals had at least one fever. Time to eat and drink unassisted, number of animals exhibiting circling behavior, and number of animals with documented seizure activity were similar between groups.

Table 1

	Percent Survival (72 hrs	Time to stand (hrs)	Fevers (%)	Time to eat (days)	Assisted drinking (days)	Unassisted Drinking (days)
Treated	100	4.21	57.14	1.24	1.56	3.13
Control	62.5	6.28	75.00	1.36	0.96	3.12

As seen in Table 2, gait analysis indicates improved motor function in NPEX treated pigs compared to controls. At 7 days post-stroke, NPEX treated pigs move faster and with more cadence (rhythmicity) as they move throughout their stride. Due to stroke in the right hemisphere, the left side specific deficits were more pronounced. Left side specific measurements indicate greater step length, shorter cycle time, greater stride length, and swing percent of cycle time. Treated animals placed more pressure on each foot as they moved through their stride and displayed more pronounced movement of the hind limbs past the front limb evidenced by the reach, indicating a more natural movement compared to controls.

Table 2

	Velocity	Cadence	Step Length (cm)	Cycle Time (sec)	Stride Length (cm)	Swing % of Cycle	Foot Pressure	Hind Reach
NPEX	131.45	91.99	41.43	0.79	80.89	41.06	62.87	-12.34
Control	106.63	79.99	38.60	0.83	77.14	38.28	57.18	-9.55

Results

Initial MRI analysis at 28 ± 4 hours indicated a smaller lesion volume in NPEX treated pigs compared to controls (Fig. 10A-10C). Volume measurements of the ipsilateral and contralateral hemispheres indicate less change in volume after stroke with NPEX treatment (Fig. 10D), indicating less swelling in the ipsilateral hemisphere in the first 24 hours after stroke, consistent with the rodent data indicating an early modulation of the immune response and indicative of a neuroprotective effect in the porcine model as well. Physiological parameters, most notably survival, was also increased in the 72 hours following induction of stroke. Treated animals were also able to stand unassisted ~2 hours faster than controls. Gait analysis at 7 days post-stroke indicated improved motor function as detected by increased velocity and cadence (rhythmicity), more pressure being applied to each foot throughout the motion, as well as increased step and stride length, an increased percentage of time in swing stance (foot off of ground) per cycle, and a more pronounced reach with the rear limb extending past the fore-limb, as is expected in quadrupeds.

NPEX treatment also had a profound effect on molecular benefit in the animals 12 weeks post-stroke as detected by MRI T2 and T2 FLAIR images (Fig. 11). Dead/dying tissue was reduced by treatment and damaged tissue (green traces) were far reduced, involving mainly cortical tissue while largely preserving integrity of the ventricle compared to the control. Animals that received NPEX were able to survive larger infarct sizes (as much as 3.8 cm3 larger at 24 hours post-stroke) over the 12 week study than those that received control treatment. This is probably due to the anti-inflammatory properties of NPEX leading to decreased stroke severity and promoting better long-term outcomes including integrity of brain tissue, as well as behavioral and motor function.

Never before have EVs of any kind improved the outcome of stroke or for that matter any neural deficit in a large animal. Consistent with the small animal we show that NPEX effects the brain immediately, thus NPEX is fast acting in the pig and the mouse. We do not know of any other study that has suggested such and immediate effect of EVs on a stroked animal. Immediately NPEX improved survival and motor function (speed in which animals recover, time to stand, balance, etc). Molecular and phenotypic outcomes in a large animal species expand upon previously described rodent data, indicating that EVs exert a likely neuroprotective effect that is longer lasting. This effect is likely due in part to modulation of the secondary injury cascade by muting the immune response that occurs following stroke, as molecular and phenotypic differences are detectable as early as 24 hours post-stroke and a later effect on the enhanced M2 response, which is neuro-reparative. The longer lasting effects are observed throughout, with improved gait of the NPEX treated animals.

In summary, this is the first stroke study to suggest to mechanisms of action are consistent across animals and includes a study in a more complex brain with a structure that is similar to humans. Our in vitro human cell studies suggest neuroprotective action directly on the damaged neural cells, and the mouse and pig studies suggest protection through the immune system. The longer acting effects on neuro-reparative mechanisms in both species were observed and could be in part due to up regulation of Treg cells (mouse only to date). Importantly, the porcine brain unlike the mouse shares many homologies with the human brain including white matter ratio, presence of gyrencephalic cortex, cytoarchitecture, and size. Due to these similarities, the pig is considered a

superior model system compared to rodents, and is likely more representative of anticipated benefits in human treatment of ischemic stroke with therapeutically produced neural progenitor derived EVs.

This is possible due to an ability to produce a large quantity of EVs from neural progenitor cultures, approximately 5 times greater than yields obtained from MSCs. The ability to generate EVs on a commercial scale consistently from cultures will require that EV-producing cells be dependent on a rigorous quality control process for handling the cells and purifying the resultant EVs.

Example 6:

Primary Filtration (Step 1, used for all purification methods)

Media is harvested from plates or flasks containing cultured cells. The harvested media was frozen at -20°C before or after the primary filtration and thawed at 4°C. Filtration is completed in a sterile laminar flow hood to minimize contamination. The harvested media was filtered via dead end filtration through a 0.22μm filter (EMD Millipore Stericup). This primary filtration removes any cellular debris and/or dead cells from the harvested media. This allows for the EVs and microvescicles to pass through to the filtrate for further purification.

Centricon Ultrafiltration

Having undergone primary filtration, the media is ready for secondary filtration. This step utilizes a system including Centricon centrifuge units, which can process up to 70 ml culture medium per spin. This filtration process uses a 100 kDa filter to collect enriched EVs. During this process the media is forced through the filter discs via centrifugation at 4,000 x g. Once the retentate reaches approximately 250μL to 5mL per unit, a buffer exchange is then performed using approximately 90% of the starting media volume of PBS+/+. The PBS+/+ is passed through the Centricon filters by centrifugation at 2,000 x g until the retentate reaches 250μL to 1mL of volume per filter unit. At this point the retentate is collected for EV analysis. A sample is taken for immediate nanoparticle tracking analysis, and purified EVs from the same cell type were pooled, triturated, and aliquoted into DNase/RNase free tubes for storage at -20°C.

Amicon Stirred-Cell Ultrafiltration

For larger volume ultrafiltrations, Amicon stirred-cell ultrafiltration units were used, connected 3 units in tandem. Each base unit held 400 ml medium, which was further expanded using a reservoir to increase throughput. This step utilizes a system including a pressure vessel, and three EMD Millipore Stirred Cell Units (Fisher Scientific, USA) working in sequence. This step utilizes dead end filtration as well with media passing through a 100kDa filter disc (Fisher Scientific, USA). During this process the media is forced through the filter discs using 25 psi of positive pressure supplied by compressed nitrogen gas. Once the retentate reaches 50 ml / stirred cell unit the system is de-pressurized. A buffer exchange is then performed using 50% of the starting media volume of PBS+/+. The PBS+/+ is passed through the stirred cell filters until the retentate reaches 50mL of volume per filter unit. At this point the retentate is collected for EV analysis. A sample is taken for immediate nanoparticle tracking analysis, and purified EVs from the same cell type were pooled, triturated, and aliquoted into DNase/RNase free tubes for storage at -20°C.

Fibroblast Growth Factor ELISA

To determine hFGF2 content, cryopreserved samples of NPEX™, APEX, and MSCEX EVs were thawed at 4°C and lysed with an equal volume of EV lysis buffer to release exosomal content. The lysate was analyzed for human FGF2 using a commercially available human FGF2 ELISA assay kit (Thermo Scientific – Catalog number KHG0021) following manufacturers protocol. FGF2 standards provided with the kit were used to generate a standard curve and quantitated FGF2 in the test sample. FGF2 was detected in NPEX™ sample at 490 pG / mL. No FGF2 could be detected either in APEX™ or in MSCEX™ samples.

Mass spectroscopy

To compare proteins unique to neural EVs versus MSC derived EVs, purified EV proteins were subjected to mass spectroscopy by Bioproximity, LLC.

Results

Ultracentrifugation and ultrafiltration methods were used as previously described. Large volume purifications utilized the Amicon stirred-cell system to purify over 24 liters of cell culture medium in a single work week.

Fibroblast Growth Factor ELISA results

The protein human Fibroblast Growth Factor 2 (hFGF2) is added to hNP1™ culture media to maintain the proliferative state of hNP1™ cells. EVs produced by hNP1™ cells (NPEX) cultured in hFGF2 supplemented media may accumulate/contain any of this hFGF2 protein as part of the exosomal protein content. NPEX EVs, harvested from hNP1™ culture media collected from live hNP1™ cell cultures were tested for the presence of hFGF2. These purified and cryopreserved NPEX™ EVs contained detectable levels of hFGF2 after thaw. On the other hand, EVs from hAstroPro™ human astrocytes (APEX), and from mesenchymal stem cells (MSCEX), where the cell culture media is not supplemented with hFGF2, did not contain any detectable hFGF2. Taken together, these data indicate that proteins supplemented in the medium are taken up by the cells and are present in the enriched EV sample even in the absence of transfection or other techniques to overexpress proteins in the cells.

Mass spectroscopy

Figure 12 is a Venn diagram showing the number of proteins unique to, and shared by NPEX, APEX, and MSCEX vesicles. A total of 2727 proteins were shared by all of these vesicles (Table 3). APEX and MSCEX shared 2786 proteins that were not in NPEX vesicles (Table 4). NPEX shared 467 proteins only with MSCEX (Table 5) and 426 proteins only with APEX vesicles (Table 6). MSCEX had 536 unique proteins that were not identified in APEX or NPEX vesicles (Table 7). APEX had 596 proteins that were not identified in NPEX or MSCEX vesicles (Table 8). NPEX had 1653 proteins that were not identified in APEX or MSCEX vesicles (Table 9).

Table 3. Protein codes found in NPEX, APEX, and MSCEX

1	A0A023UFG1	12	A0A024R663	23	A0A024RBR1
2	A0A024QZ30	13	A0A024R6C6	24	A0A024RC42
3	A0A024R0R4	14	A0A024R7F1	25	A0A024RD01
4	A0A024R1Q5	15	A0A024R816	26	A0A024RDU6
5	A0A024R269	16	A0A024R900	27	A0A087WTT9
6	A0A024R294	17	A0A024R972	28	A0A087WTY7
7	A0A024R2A8	18	A0A024R9G7	29	A0A087WU72
8	A0A024R3H6	19	A0A024RA85	30	A0A087WUP3
9	A0A024R3W5	20	A0A024RAB6	31	A0A087WUR9
10	A0A024R473	21	A0A024RB27	32	A0A087WUZ8
11	A0A024R4U7	22	A0A024RB49	33	A0A087WV01

34	A0A087WV58	75	A0A0K2FPC8	116	A2RTY3
35	A0A087WVQ9	76	A0A0R4J2G5	117	A3KMF7
36	A0A087WVY5	77	A0A0S2Z3C0	118	A3KMG4
37	A0A087WX41	78	A0A0S2Z3H6	119	A4D0R5
38	A0A087X1N7	79	A0A0S2Z3N2	120	A4D1F6
39	A0A087X208	80	A0A0S2Z4F6	121	A4D263
40	A0A087X270	81	A0A0S2Z4K6	122	A4D2F6
41	A0A088AWP7	82	A0A0S2Z4S4	123	A4FU99
42	A0A090N7U3	83	A0A0U1RQF0	124	A5XEJ8
43	A0A090N8G0	84	A0A0U1RQK4	125	A6NCJ1
44	A0A090N8I2	85	A0A0U1RR05	126	A6NDG6
45	A0A090N8Z3	86	A0A0U1RRH6	127	A6NHK2
46	A0A096LNH2	87	A0A0U4BW16	128	A6NMH8
47	A0A096LP10	88	A0A0U4DR30	129	A8K1Z4
48	A0A096LPK6	89	A0A0U5Q0I5	130	A8K2Q7
49	A0A0A0MQZ3	90	A0A0X7YLB8	131	A8K2X9
50	A0A0A0MR11	91	A0A0X9T0I7	132	A8K4L4
51	A0A0A0MRA3	92	A0A0X9TDD0	133	A8K580
52	A0A0A0MRA8	93	A0A0X9UWM4	134	A8K5W7
53	A0A0A0MT16	94	A0A109PSY4	135	A8K646
54	A0A0A7NZX2	95	A0A126GVT4	136	A8K674
55	A0A0B4J262	96	A0A126GVV9	137	A8K6Q8
56	A0A0C4DG44	97	A0A126GVY4	138	A8K6R3
57	A0A0C4DGP4	98	A0A126GW97	139	A8K889
58	A0A0C4DGQ0	99	A0A126LAV0	140	A8K941
59	A0A0C4DGR9	100	A0A126LAW8	141	A8K948
60	A0A0C4DGV7	101	A0A140VJG3	142	A8KA19
61	A0A0C4DH10	102	A0A140VJM5	143	A8KAM8
62	A0A0C4DH26	103	A0A140VJZ1	144	A8KAQ0
63	A0A0C4DH32	104	A0A140VJZ4	145	A8MQ14
64	A0A0C4DH71	105	A0A140VK24	146	A8MSG4
65	A0A0D9SF05	106	A0A142K0N8	147	A8MUM1
66	A0A0D9SF53	107	A0N7J6	148	A8MYJ1
67	A0A0D9SFF0	108	A1A5C4	149	B0AZV0
68	A0A0E3SU01	109	A1L0U7	150	B0I1R4
69	A0A0F7TC28	110	A1YZK0	151	B0I1R7
70	A0A0G2JQ57	111	A2IPH5	152	B0I1R8
71	A0A0J9YWL9	112	A2J1M8	153	B0I1S0
72	A0A0J9YY17	113	A2MYD2	154	B1AH62
73	A0A0J9YY65	114	A2N0U1	155	B2R604
74	A0A0K0K1J1	115	A2RRE5	156	B2R6E3

157	B2R8C2	198	B4DKL5	239	B4DZ96
158	B2R8R5	199	B4DL04	240	B4DZD8
159	B2RAG9	200	B4DL67	241	B4DZK5
160	B2RAK1	201	B4DLV7	242	B4DZL0
161	B2RD27	202	B4DM31	243	B4DZX5
162	B2RDG9	203	B4DMC6	244	B4DZY9
163	B2RDV2	204	B4DMD7	245	B4E0C3
164	B2RP65	205	B4DMI9	246	B4E116
165	B2ZZ86	206	B4DMK9	247	B4E1Z8
166	B3KMD3	207	B4DMS8	248	B4E2C9
167	B3KMX8	208	B4DMY4	249	B4E310
168	B3KNH6	209	B4DN39	250	B4E358
169	B3KNH8	210	B4DN66	251	B4E396
170	B3KNJ3	211	B4DN96	252	B4E3S1
171	B3KR88	212	B4DNS4	253	B5BUB5
172	B3KS22	213	B4DPB7	254	B5MC96
173	B3KS78	214	B4DPF0	255	B7SXT3
174	B3KT94	215	B4DPS3	256	B7WPN9
175	B3KUL2	216	B4DQF8	257	B7Z1C7
176	B3KV04	217	B4DQJ9	258	B7Z1Y1
177	B3KVE3	218	B4DRF2	259	B7Z208
178	B3KVJ2	219	B4DRV4	260	B7Z225
179	B3KW39	220	B4DRZ1	261	B7Z2P6
180	B3KX05	221	B4DRZ5	262	B7Z395
181	B3KXG9	222	B4DSD8	263	B7Z3F9
182	B4DE59	223	B4DSI2	264	B7Z3I3
183	B4DEA8	224	B4DSK2	265	B7Z425
184	B4DEN3	225	B4DTD5	266	B7Z4S3
185	B4DGW2	226	B4DTF5	267	B7Z5R5
186	B4DGX3	227	B4DTI4	268	B7Z5U1
187	B4DH09	228	B4DTV0	269	B7Z6G1
188	B4DHQ3	229	B4DUV1	270	B7Z6T9
189	B4DHR1	230	B4DVQ8	271	B7Z865
190	B4DHV2	231	B4DVY2	272	B7ZAS5
191	B4DI57	232	B4DXJ3	273	B7ZKX2
192	B4DJ98	233	B4DXW6	274	B7ZKY2
193	B4DJM8	234	B4DXX8	275	B7ZL41
194	B4DK16	235	B4DYE2	276	B7ZL68
195	B4DK41	236	B4DYM1	277	B7ZMC8
196	B4DKE0	237	B4DYQ3	278	B7ZVX0
197	B4DKG5	238	B4DYV9	279	C0JYZ2

280	C4P0A0	321	E9PB28	362	H0YJI8
281	C8CHS3	322	E9PDD2	363	H0YM90
282	C9IYI4	323	E9PFQ4	364	H3BM60
283	C9IZK7	324	E9PJ15	365	H3BMQ8
284	C9J0E9	325	E9PJG1	366	H3BPI1
285	C9J6F5	326	E9PKH2	367	H3BPK7
286	C9J8V2	327	E9PKQ0	368	H3BPS8
287	C9J9C4	328	E9PS68	369	H3BQK9
288	C9JBI4	329	F1LLU8	370	H3BQQ2
289	C9JG87	330	F5GZB4	371	H3BQT0
290	C9JKM5	331	F5H7Y6	372	H3BRQ0
291	C9JKM9	332	F6X3N5	373	H3BS19
292	C9JSJ3	333	F8VBW7	374	H3BS34
293	C9JX31	334	F8VPD4	375	H3BT13
294	D3DPG0	335	F8VQY3	376	H3BV16
295	D3DQH8	336	F8VY01	377	H7BYH4
296	D3DTX7	337	F8VYK9	378	H7BZ70
297	D3DUZ3	338	F8W6H2	379	H7BZ95
298	D3DV53	339	F8W883	380	H7BZL8
299	D3DWL0	340	F8WEI7	381	H7BZY4
300	D3DX49	341	G3V1C3	382	H7C013
301	D3VVE1	342	G3V1Y7	383	H7C0I1
302	D3VVP9	343	G3V2J9	384	H7C0Q9
303	D4YW75	344	H0Y390	385	H7C132
304	D6RCE4	345	H0Y3V5	386	H7C1F8
305	D6RCP5	346	H0Y5A2	387	H7C1W1
306	D6RCQ3	347	H0Y720	388	H7C3P6
307	D6RGX4	348	H0Y8I2	389	H7C446
308	D6RHD5	349	H0Y935	390	H7C4N3
309	D6RHJ5	350	H0Y991	391	H7C4W1
310	D6W573	351	H0Y9B6	392	H7C557
311	D9ZGF2	352	H0Y9P3	393	H7C5G5
312	E2QRN8	353	H0Y9Z7	394	H9E7H3
313	E5RFF8	354	H0YA40	395	I3L174
314	E5RG49	355	H0YAA7	396	I3L1P4
315	E7EMW7	356	H0YDK7	397	I3L3B3
316	E7EQW5	357	H0YDZ4	398	I3L3U6
317	E7ESB3	358	H0YF10	399	I6L965
318	E7ETY2	359	H0YFH1	400	J3KNJ2
319	E7EUH7	360	H0YHN7	401	J3KP25
320	E7EX80	361	H0YJ21	402	J3KQ96

403	J3KRF1	444	O15327	485	P35527
404	J3KTA9	445	O43149	486	P43251
405	J3KTL8	446	O43697	487	P46531
406	J3QQK7	447	O60248	488	P53621
407	J3QQP2	448	O60284	489	P55291
408	J3QR51	449	O60568	490	P56589
409	J3QRM5	450	O75095	491	P59510
410	J3QS68	451	O75197	492	P59923
411	J3QS89	452	O75874	493	P60602
412	J3QS93	453	O94804	494	P61160
413	J3QSE7	454	O94905	495	P78407
414	K7EIX3	455	O95185	496	P86434
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416	K7EMJ3	457	P02769	498	P98168
417	K7ENJ9	458	P04040	499	Q02952
418	K7EPV5	459	P04206	500	Q03188
419	K7EQA8	460	P04207	501	Q04741
420	K7EQP5	461	P04434	502	Q05CY8
421	K7EQQ3	462	P05543	503	Q0ZCI6
422	K7EQV0	463	P06312	504	Q10471
423	K7ERC0	464	P08779	505	Q12789
424	K7ERL1	465	P09382	506	Q13707
425	K7ERP4	466	P0C1S8	507	Q14402
426	K7ES39	467	P0C7M3	508	Q14517
427	K7N7B3	468	P10909	509	Q14789
428	K9JJH7	469	P11055	510	Q15050
429	L0R6L1	470	P14543	511	Q15198
430	L8E9M8	471	P16152	512	Q15293
431	L8E9T4	472	P16930	513	Q15645
432	L8EA98	473	P17039	514	Q15917
433	M0QYS6	474	P17301	515	Q16696
434	M0R0R9	475	P19838	516	Q16706
435	M0R0Z7	476	P21359	517	Q17R55
436	M0R248	477	P22059	518	Q2NNQ8
437	M1VKI3	478	P22314	519	Q2TAC2
438	M4N8S7	479	P22680	520	Q2TAC6
439	O00629	480	P25054	521	Q2VWP7
440	O00716	481	P25398	522	Q32MA5
441	O15034	482	P26641	523	Q3B776
442	O15049	483	P28325	524	Q3B836
443	O15230	484	P31689	525	Q3MJ16

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530	Q4R9M8	571	Q5PT55	612	A0A087WUL2
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536	Q53FV4	577	Q5TBG1	618	A0A024R4E9
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540	Q53H80	581	Q5VSQ6	622	A0A087WW06
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559	Q5H9P2	600	Q6FH59	641	A0A142CHG9
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651	A5XEH9	692	B4DM56	733	D6NKH9
652	A6NFK2	693	B4DMC3	734	D6RA67
653	A6NMD2	694	B4DMR0	735	D6RDA2
654	A6NNH2	695	B4DN86	736	D6RF03
655	A7MBM2	696	B4DP97	737	D6RIA3
656	A8K243	697	B4DQG2	738	D6W5C0
657	A8K3A8	698	B4DRY1	739	E2PU09
658	A8K491	699	B4DS24	740	E5KBQ3
659	A8K6K2	700	B4DS65	741	E5RFG5
660	A8K7J3	701	B4DSN3	742	E5RHT6
661	A8K7K7	702	B4DTV8	743	E7EPA6
662	A8K8Q0	703	B4DTZ8	744	E7ET48
663	A8MQ27	704	B4DUN3	745	E7EU81
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666	B1AMG5	707	B4DXZ7	748	E9PEZ1
667	B2R742	708	B4DZE2	749	E9PGT3
668	B2R9V7	709	B4DZL4	750	E9PIK2
669	B2RCE6	710	B4E216	751	E9PK47
670	B3KNP2	711	B4E2V9	752	E9PNH1
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672	B3KQ86	713	B5BU24	754	E9PP73
673	B3KRC4	714	B7Z1V9	755	E9PR23
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675	B3KSP5	716	B7Z5V6	757	F2YYR6
676	B3KT66	717	B7Z7Y3	758	F5GWJ4
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678	B3KUG8	719	B7ZW01	760	F5H1Y4
679	B3KWB1	720	B9A6J8	761	F5H2D5
680	B3KWZ6	721	C0IMJ3	762	F5H793
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683	B4DEJ9	724	C9J5G4	765	F6WFU6
684	B4DFW5	725	C9J634	766	F8VPW2
685	B4DGL0	726	C9J9K3	767	F8VPW9
686	B4DI08	727	C9JDQ2	768	F8VRS4
687	B4DIS3	728	C9JEJ9	769	F8VWZ8
688	B4DJI1	729	C9JKR2	770	F8VXB0
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775	F8WBZ7	816	H7C5N9	857	P16234
776	F8WCD0	817	H9ZYJ2	858	P20248
777	F8WD89	818	I3L2W4	859	P27987
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780	F8WER7	821	J3KQF5	862	P78509
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905	Q58FF7	946	Q6P2Q9	987	Q7Z6J9
906	Q59EM6	947	Q6P2S7	988	Q7Z6M2
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1283	B7Z829	1324	I3L4N8	1365	Q6YN16
1284	B7Z983	1325	J3KRN5	1366	Q7Z7J9
1285	B7ZA86	1326	J3QR93	1367	Q8IZJ3
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1303	E9PSE1	1344	Q2NKN3	1385	Q9UM07
1304	F5H077	1345	Q2Q1W2	1386	Q9UM47

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1390	V9GY66	1431	H0Y3Q4	1472	Q8TE47
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1396	B2R870	1437	I3L188	1478	Q9P1C0
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1765	C9JPF8	1806	E9PLK6	1847	H0YCP4
1766	C9JQ82	1807	E9PM30	1848	H0YEX9
1767	C9JQI7	1808	E9PMQ3	1849	H0YFA9
1768	C9JSP6	1809	E9PMV1	1850	H0YFT1
1769	C9JTC5	1810	E9PNF1	1851	H0Y1A0
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1771	C9JY46	1812	E9PPM7	1853	H0YJP0
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1775	D3DR43	1816	F4ZW64	1857	H0YNY7
1776	D3DU04	1817	F5GXA0	1858	H3BM10
1777	D3DVC4	1818	F5GY56	1859	H3BNR2
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1779	D3DX93	1820	F5H7E5	1861	H3BTE9
1780	D3VVD3	1821	F5H8I3	1862	H6VRF9
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1786	D6W5C2	1827	F8WBI5	1868	H7C0Y8
1787	D7RTA7	1828	F8WBJ2	1869	H7C0Z9
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1789	E5RHN3	1830	F8WD09	1871	H7C435
1790	E5RIY1	1831	F8WDF1	1872	H7C4A7
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1881	I3L202	1922	O00186	1963	P0C091
1882	I3L2B0	1923	O00228	1964	P0C671
1883	I3L454	1924	O00231	1965	P0C7M7
1884	I6U4P1	1925	O00300	1966	P0C7V6
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1886	J3KRI7	1927	O00602	1968	P0DKB5
1887	J3KRQ5	1928	O15031	1969	P10745
1888	J3KRS3	1929	O15061	1970	P12109
1889	J3KRZ0	1930	O15379	1971	P12268
1890	J3KSI7	1931	O15389	1972	P13196
1891	J3QKM3	1932	O15400	1973	P15531
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1897	K7ES57	1938	O60869	1979	P25786
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1907	L8ECD0	1948	O95396	1989	P35908
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1910	L8ECM9	1951	O95760	1992	P38606
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1915	M0R0B6	1956	P01782	1997	P49454
1916	M0R0I5	1957	P04264	1998	P49588
1917	M0R1Y0	1958	P05388	1999	P49788
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1919	M0R2B8	1960	P08572	2001	P50570

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2006	P56537	2047	Q2I009	2088	Q5JY65
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2008	P62318	2049	Q2M2I5	2090	Q5K684
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2011	P82987	2052	Q2WEN9	2093	Q5SQS7
2012	P98160	2053	Q2WGN9	2094	Q5SR54
2013	Q01959	2054	Q3T906	2095	Q5T6X5
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2153	Q8IYV9	2194	Q96FN9	2235	Q9H7U1
2154	Q8IYX0	2195	Q96HJ3	2236	Q9H814
2155	Q8IZ13	2196	Q96IT5	2237	Q9H863
2156	Q8N0Y7	2197	Q96JQ0	2238	Q9H993
2157	Q8N2E1	2198	Q96KQ4	2239	Q9H996
2158	Q8N3G4	2199	Q96L96	2240	Q9HAR7
2159	Q8N5C1	2200	Q96LM5	2241	Q9HBV4
2160	Q8N609	2201	Q96LQ0	2242	Q9HBW1
2161	Q8N7E2	2202	Q96MK8	2243	Q9HC10
2162	Q8N7U5	2203	Q96MX6	2244	Q9HD43
2163	Q8N944	2204	Q96N75	2245	Q9NQL0
2164	Q8N9V7	2205	Q96PD2	2246	Q9NQX0
2165	Q8NB66	2206	Q96PD5	2247	Q9NRN1

2248	Q9NS98	2289	Q9UPY3	2330	X6RE28
2249	Q9NSF5	2290	Q9UPZ3	2331	A0A024R3N3
2250	Q9NT48	2291	Q9UQR0	2332	A0A024R456
2251	Q9NU22	2292	Q9Y277	2333	A0A024R462
2252	Q9NUL7	2293	Q9Y2K3	2334	A0A024R6P6
2253	Q9NVD3	2294	Q9Y3A2	2335	A0A024R7W9
2254	Q9NXD9	2295	Q9Y3D6	2336	A0A024R893
2255	Q9NYQ8	2296	Q9Y3I0	2337	A0A024R9I0
2256	Q9NYU2	2297	Q9Y4K0	2338	A0A024R9Q1
2257	Q9NZ56	2298	Q9Y574	2339	A0A024RAA7
2258	Q9NZI8	2299	Q9Y5G4	2340	A0A024RC00
2259	Q9NZJ4	2300	Q9Y5Q9	2341	A0A087WTA8
2260	Q9NZQ3	2301	Q9Y680	2342	A0A087WUA7
2261	Q9P0K0	2302	Q9Y6C2	2343	A0A087WVP1
2262	Q9P0Z3	2303	R4GMQ5	2344	A0A087WYF9
2263	Q9P104	2304	R4GN15	2345	A0A087X163
2264	Q9P186	2305	S4R3C7	2346	A0A087X1V8
2265	Q9P1F0	2306	S4R3Q3	2347	A0A0A0MRD2
2266	Q9P266	2307	U3KQG5	2348	A0A0A0MRS2
2267	Q9P2C8	2308	U5IRJ4	2349	A0A0A0MSD0
2268	Q9P2R9	2309	V9GY54	2350	A0A0C4DFM7
2269	Q9UBK8	2310	V9GZ55	2351	A0A0C4DG73
2270	Q9UBW8	2311	V9GZG2	2352	A0A0D9SFA9
2271	Q9UCR1	2312	V9H0A6	2353	A0A0E3DCV7
2272	Q9UE50	2313	V9H102	2354	A0A0J9YVW2
2273	Q9UF29	2314	V9HW11	2355	A0A0J9YVW5
2274	Q9UGK2	2315	V9HW34	2356	A0A0J9YX90
2275	Q9UIY3	2316	V9HW62	2357	A0A0S2Z4B5
2276	Q9UJX5	2317	V9HW88	2358	A0A0X9UWJ6
2277	Q9UKE0	2318	V9HWB4	2359	A0A126GVE6
2278	Q9UKX2	2319	V9HWB5	2360	A0A126LB13
2279	Q9UL97	2320	V9HWE1	2361	A1L4H1
2280	Q9ULH4	2321	V9HWF2	2362	A6NEQ2
2281	Q9ULI3	2322	V9HWI6	2363	A6PVK5
2282	Q9ULL8	2323	V9TNI8	2364	A8K0K1
2283	Q9UMG4	2324	W8YM35	2365	A8K0P8
2284	Q9UMJ0	2325	X5DNI9	2366	A8K0R7
2285	Q9UML5	2326	X5DP31	2367	A8K2P0
2286	Q9UMR3	2327	X5DPA6	2368	A8K7T4
2287	Q9UN70	2328	X5DR62	2369	A8K874
2288	Q9UPX8	2329	X6R647	2370	A8K8X0

2371	A8K964	2412	E1A689	2453	P05109
2372	A8MTJ3	2413	E5RJI5	2454	P0C869
2373	B0AZS6	2414	E9PAV3	2455	P0CB47
2374	B3KM36	2415	E9PL83	2456	P0CG39
2375	B3KNK5	2416	E9PPG5	2457	P0DKL9
2376	B3KPZ8	2417	F1T0E5	2458	P12757
2377	B3KQU2	2418	F2Z2U4	2459	P26022
2378	B3KWQ8	2419	F6QYI9	2460	P28070
2379	B3KX74	2420	F8W0W6	2461	P35442
2380	B4DEB0	2421	F8W8H5	2462	P35558
2381	B4DEG1	2422	G3V471	2463	P43652
2382	B4DFY0	2423	H0Y645	2464	P54753
2383	B4DGQ7	2424	H0YAB8	2465	P55089
2384	B4DGQ8	2425	H0YB13	2466	Q05CW1
2385	B4DIP4	2426	H0YJ11	2467	Q09028
2386	B4DJ30	2427	H3BRX4	2468	Q0VAS5
2387	B4DL30	2428	H3BT74	2469	Q14455
2388	B4DM84	2429	H3BUH4	2470	Q16281
2389	B4DMV8	2430	H7BZH1	2471	Q32MQ0
2390	B4DP50	2431	H7C149	2472	Q53HB3
2391	B4DPV2	2432	H7C2W8	2473	Q53TR0
2392	B4DPY2	2433	I6L894	2474	Q59EG0
2393	B4DRQ4	2434	I6L957	2475	Q59F22
2394	B4DU77	2435	J3KQU2	2476	Q59FG6
2395	B4DW52	2436	J3QLS9	2477	Q59H91
2396	B4E0D8	2437	K0P793	2478	Q5BKT1
2397	B4E2L2	2438	K4DIA0	2479	Q5FBY7
2398	B4E2M7	2439	K4K7V6	2480	Q5T1R4
2399	B4E2Y4	2440	K7EQ63	2481	Q5TBK7
2400	B7Z1H7	2441	L0CQ38	2482	Q5TH58
2401	B7Z2V6	2442	M0QZR9	2483	Q658L2
2402	B7Z4C0	2443	M0R261	2484	Q658N2
2403	B7Z6W4	2444	M0R315	2485	Q684P5
2404	B7ZLW8	2445	O00420	2486	Q69YM0
2405	B7ZMN7	2446	O14980	2487	Q6IC83
2406	C6GLW5	2447	O15240	2488	Q6L9N1
2407	C9JH44	2448	O43854	2489	Q6N097
2408	C9JR58	2449	O75691	2490	Q6NUJ9
2409	C9JW04	2450	O95243	2491	Q6NUN2
2410	D6R9I8	2451	P00800	2492	Q6NUP7
2411	D6REZ4	2452	P01833	2493	Q6NXR7

2494	Q6P0Q1	2535	D7RF68	2576	Q53S27
2495	Q6P2I0	2536	E0CX09	2577	Q53T09
2496	Q6P5R7	2537	E1U340	2578	Q5BN46
2497	Q6PJ72	2538	E5RH59	2579	Q5RHP9
2498	Q6PK65	2539	E5RJV2	2580	Q5T6X2
2499	Q6QE20	2540	E7EPF0	2581	Q5TCI4
2500	Q6TCJ2	2541	E7ESP4	2582	Q5VX52
2501	Q6TFL3	2542	E7EW93	2583	Q6AHZ7
2502	A0A075B6H0	2543	E9PQ73	2584	Q6IBJ0
2503	A0A0A0MSY2	2544	F5GX09	2585	Q6NWP9
2504	A0A0B4J1Z7	2545	F5GYN0	2586	Q6P5T1
2505	A0A0B4J2E5	2546	F5H4E5	2587	Q6PIP7
2506	A0A0J9YXN7	2547	F5H6Q4	2588	Q6U2F8
2507	A0A0S2Z4J7	2548	F8VWA3	2589	Q6UXN8
2508	A4D2H0	2549	F8W1K8	2590	Q6UXQ0
2509	A5PLN9	2550	G3V599	2591	Q6Y288
2510	A8K2M0	2551	H0UI12	2592	Q6ZMS2
2511	A8K7H1	2552	H0Y853	2593	Q6ZMU0
2512	A8K9P0	2553	H0YAH0	2594	Q6ZMY6
2513	B2R769	2554	H0YFK0	2595	Q6ZNI2
2514	B2RA94	2555	H3BPJ7	2596	Q6ZNS1
2515	B3KMG3	2556	H3BPS9	2597	Q6ZQQ2
2516	B3KNF6	2557	H3BTH8	2598	Q6ZQY1
2517	B3KSB9	2558	H7C0I7	2599	Q6ZRK5
2518	B3KSG0	2559	H7C4L7	2600	Q6ZRK6
2519	B3KSJ0	2560	J3KS13	2601	Q6ZRM8
2520	B3KU66	2561	J3QS03	2602	Q6ZU10
2521	B4DJB9	2562	L0R5C4	2603	Q6ZV46
2522	B4DN12	2563	O75603	2604	Q6ZWC0
2523	B4DNP9	2564	P08588	2605	Q6ZWE2
2524	B4DPX6	2565	P0CE72	2606	Q6ZWG9
2525	B4DQ18	2566	P20742	2607	Q70JA7
2526	B4DQL5	2567	P21453	2608	Q71F56
2527	B4DTK1	2568	P35251	2609	Q71U70
2528	B7Z1Z9	2569	P49720	2610	Q75RY1
2529	B7Z5P0	2570	Q14766	2611	Q765P7
2530	C7TPG7	2571	Q15333	2612	Q7LGC8
2531	C9J5J4	2572	Q15389	2613	Q7Z418
2532	C9JYJ6	2573	Q15631	2614	Q7Z527
2533	D3DPB7	2574	Q17RW2	2615	Q7Z528
2534	D6RHV3	2575	Q53RS3	2616	Q7Z5A3

2617	Q7Z5L7	2655	Q8N8V4	2693	Q9C005
2618	Q7Z5P4	2656	Q8N904	2694	Q9H1K6
2619	Q7Z5W6	2657	Q8N987	2695	Q9H212
2620	Q7Z5Y7	2658	Q8N9V6	2696	Q9H382
2621	Q7Z7L8	2659	Q8NA33	2697	Q9H3R1
2622	Q7Z7M0	2660	Q8NAV8	2698	Q9H4L7
2623	Q7Z7M9	2661	Q8NAY8	2699	Q9HBR0
2624	Q86SQ6	2662	Q8NB82	2700	Q9HBU3
2625	Q86SV6	2663	Q8NCD8	2701	Q9HD29
2626	Q86TJ9	2664	Q8ND61	2702	Q9NQ33
2627	Q86UD1	2665	Q8NE22	2703	Q9NQW1
2628	Q86V85	2666	Q8NEZ4	2704	Q9NR48
2629	Q86VD1	2667	Q8TA93	2705	Q9NTB9
2630	Q86VY4	2668	Q8TAS6	2706	Q9NZ53
2631	Q86W11	2669	Q8TB82	2707	Q9P2B2
2632	Q86XP0	2670	Q8TD20	2708	Q9UC91
2633	Q86YP6	2671	Q8TDY8	2709	Q9UDL0
2634	Q8IUZ8	2672	Q8TE73	2710	Q9UHK0
2635	Q8IV28	2673	Q8WUV3	2711	Q9UL81
2636	Q8IV92	2674	Q8WXC6	2712	Q9ULI1
2637	Q8IVE3	2675	Q8WXE0	2713	Q9ULL0
2638	Q8IWD5	2676	Q92861	2714	Q9ULL1
2639	Q8IXM7	2677	Q969F2	2715	Q9ULM8
2640	Q8IY33	2678	Q96AA8	2716	Q9UPU5
2641	Q8IYA7	2679	Q96BY7	2717	Q9UPU9
2642	Q8IYF3	2680	Q96JF0	2718	Q9Y3Q7
2643	Q8IYP2	2681	Q96KN7	2719	S4R3E2
2644	Q8IZ52	2682	Q96KP6	2720	U5XN63
2645	Q8IZD9	2683	Q96M27	2721	U6FSN9
2646	Q8IZK6	2684	Q96M95	2722	V9GYK6
2647	Q8IZQ8	2685	Q96N28	2723	V9H019
2648	Q8N1G2	2686	Q96QE3	2724	V9HW33
2649	Q8N2C7	2687	Q96QZ0	2725	V9HW38
2650	Q8N397	2688	Q96S01	2726	V9HW43
2651	Q8N4T4	2689	Q96T80	2727	X2L7S8
2652	Q8N715	2690	Q96TB4		
2653	Q8N7P7	2691	Q99715		
2654	Q8N7S3	2692	Q9BWG1		

Table 4. Proteins in both MSCEX and APEX					
1	A0A024R0P8	2	A0A024R3G0	3	A0A087WVV2

4	A0A087WXZ2	45	B1AKQ8	86	A0A0S2Z430
5	A0A0A0MR07	46	B2R780	87	A8K2T9
6	A0A0A0MSZ4	47	B2RAQ9	88	B4DE36
7	A0A0G2JIC2	48	B3KNK9	89	B4DMR3
8	A0A0K0K1H9	49	B3KVV5	90	B4E2A1
9	A0A0S2Z4G9	50	B3KXA5	91	B4E3S2
10	A0A140VK05	51	B4DH55	92	B9EK61
11	A0A140VK46	52	B4DKZ3	93	C9JEL4
12	A2RU30	53	B4DL46	94	C9JXX4
13	A2VCQ4	54	B4DNX1	95	A0A087X0T3
14	A4PB67	55	B4DQF6	96	A0A0S2Z3J5
15	A8K3Y6	56	B4DQQ9	97	B3KUJ8
16	A8KAQ8	57	B4DRV9	98	B4DM82
17	A8MXT8	58	B4DS32	99	B4DP93
18	B1AKG0	59	B4DUQ1	100	B4DS46
19	B2R7P8	60	B4DUY7	101	B4DY39
20	B2R8Z8	61	B4DVU1	102	B7Z2Y4
21	B2RBJ8	62	B4DWG4	103	C9J673
22	B3KMD9	63	B4DWH5	104	A0A024R8L6
23	B3KQF9	64	B4DZN3	105	A0A024RBZ8
24	B3KQX9	65	B4E047	106	A0A087WUI7
25	B3KVF9	66	B4E3M5	107	A0A0B4J1Z4
26	B4DDT3	67	B7Z1I2	108	A0A0S2Z3L7
27	B4DE33	68	B7Z2W3	109	A0A0S2Z4I7
28	B4DFP1	69	B7Z2Z8	110	A0A0U1RQJ2
29	B4DHX7	70	B7Z6U7	111	A0A0U1RQK7
30	A0A024RA75	71	B7ZMB3	112	A2A352
31	A0A024RDS3	72	B8Y0L3	113	A0A024R1N1
32	A0A087WV40	73	B8ZZ80	114	A0A024R8F1
33	A0A087WYY5	74	B9ZVT1	115	A0A087WVD1
34	A0A0C4DFX3	75	C5HTY9	116	A0A0C4DGF5
35	A0A0J9YX34	76	C9J406	117	A0A0C4DGS5
36	A1JUI8	77	C9J7H8	118	A0A0S2Z542
37	A1L4G8	78	C9J9E8	119	A0A140TA45
38	A6NHB5	79	C9JJV6	120	A0A140VJW5
39	A7J1R1	80	C9JNG9	121	A4FVC0
40	A8K2H9	81	C9JPM3	122	A4QPE1
41	A8K3B0	82	D3DS95	123	A5PKV2
42	A8K4S1	83	A0A087X1Q2	124	A6NEM2
43	A8K5U9	84	A0A087X225	125	A8K5S1
44	A8K7A4	85	A0A0A0MTC7	126	A8K651

127	A8K9T9	168	C9JJP8	209	D6R972
128	B1AMW7	169	C9JUM1	210	A0A024R0G0
129	B1Q3B3	170	C9JZG1	211	A0A024R4C5
130	B2R577	171	C9JZW3	212	A0A024R7Z5
131	B2R7F8	172	C9K028	213	A0A024RC72
132	B2R7M3	173	D3DQB3	214	A0A087WUW5
133	B2R7T2	174	D3DQI7	215	A0A087WVV1
134	B2R8H4	175	D3DWY7	216	A0A087X1N8
135	B3KN59	176	D3DX70	217	A0A087X232
136	B3KQT9	177	D3K0R1	218	A0A0A0MT20
137	B3KS79	178	D6RAL9	219	A0A0N7A6P0
138	B3KSG1	179	A0A024R0G8	220	A0A0U1RQV3
139	B3KSR8	180	A0A024R1Y8	221	A0A140TA54
140	B3KTM9	181	A0A024RCZ4	222	A0AV88
141	B3KTP2	182	A0A087WTQ6	223	A3KC71
142	B3KTP9	183	A0A087X2E9	224	A4QPB0
143	B3KW21	184	A0A140VK29	225	A7E2Y1
144	B3KWF2	185	B1ALD0	226	A7LFP5
145	B3KXY6	186	B2RBA0	227	A8K6I4
146	B4DE00	187	B3KWJ0	228	B1ALC0
147	B4DF60	188	B4DGD7	229	B2R514
148	B4DGH6	189	B4DKI0	230	B2R6L0
149	B4DH24	190	B4DM67	231	B2R7J8
150	B4DI69	191	A6NE76	232	B2RCM3
151	B4DID5	192	A6NJA2	233	B2ZZ90
152	B4DK14	193	A9LSU1	234	B3KM30
153	B4DL98	194	B4DDL1	235	B3KMW3
154	B4DLA1	195	B4DIV8	236	B3KP89
155	B4DLA3	196	B4DNH8	237	B3KR36
156	B4DNR7	197	B4DP22	238	B3KUS2
157	B4DPJ4	198	B4DR58	239	B3KW84
158	B4DRT0	199	B4DTN6	240	B4DFR3
159	B4DTX0	200	B4DX99	241	B4DG30
160	B4E368	201	B4DYQ7	242	A0A024R879
161	B7Z1D9	202	B4E0S6	243	A0A087WYV9
162	B7Z992	203	B4E2M0	244	A0A087X054
163	B8ZZF3	204	B7Z2S7	245	A0A087X0S5
164	C9J4J8	205	B7Z2V8	246	A0A0D9SG88
165	C9J4Z7	206	B7Z864	247	A0A0E3JSF5
166	C9JBE1	207	C9JPU9	248	A0A0S2Z3W2
167	C9JDW2	208	C9JZ53	249	A0A0S2Z6B4

250	A0A0U1RRC9	291	C9J315	332	A0A0J9YVZ6
251	A0PJC9	292	C9J9C1	333	A0A0J9YWZ2
252	A1KY36	293	C9JKA9	334	A0A0S2Z3K0
253	A4UCT2	294	C9JN98	335	A0A0U1RRA4
254	A8K0G3	295	D3DPK5	336	A0A140VJF9
255	A8K709	296	D3DPU8	337	A4UCT0
256	A8K8Z1	297	D3DUK1	338	A8K7E0
257	A8KAY3	298	A0A024R1A3	339	A8KA38
258	B2R8G9	299	A0A024RC58	340	A8KA74
259	B2RBF8	300	A0A0S2Z5A5	341	B1AH99
260	B3KWG6	301	A8K2R3	342	B2RCA1
261	B3KY55	302	A8K482	343	B2RCJ7
262	B4DHT1	303	A8K6V0	344	B2RDI7
263	B4DI54	304	B1ALD9	345	B3KN37
264	B4DKW1	305	B1B5R8	346	B3KNG6
265	B4DL92	306	B2RDG0	347	B3KNX0
266	B4DLZ2	307	B3KU23	348	B3KPI8
267	B4DMF7	308	B3KUI4	349	B3KQH1
268	B4DPQ6	309	B4DGN8	350	B3KRC6
269	B4DPS0	310	B4DIW7	351	B3KRN4
270	B4DPU0	311	B4E3I6	352	B3KS36
271	B4DPU6	312	C9J539	353	B3KS49
272	B4DQ56	313	A0A087WX80	354	B3KSB2
273	B4E0N9	314	A0A140VK07	355	B3KT90
274	B4E261	315	B3KUJ2	356	B3KTR9
275	B4E302	316	B3KXN4	357	B3KUP0
276	B7Z273	317	B4DJF2	358	B3KY30
277	B7Z2M1	318	B4DM34	359	B4DDH3
278	B7Z4F6	319	A0A087WZ85	360	B4DFM1
279	B7Z4W2	320	B2RCP7	361	B4DL06
280	B7Z856	321	B3KNZ4	362	B4DM22
281	B7Z9M4	322	A0A024R127	363	B4DM79
282	B7ZAJ4	323	A0A024R755	364	B4DQH6
283	B7ZB44	324	A0A024RDT5	365	B4DUI5
284	B7ZLI7	325	A0A087WUV5	366	B4E0H8
285	B7ZM04	326	A0A087WUZ3	367	B7Z1H4
286	B9DI82	327	A0A0A0MSX9	368	B7Z213
287	B9EGI2	328	A0A0A7C7U2	369	B7Z2N5
288	C0JYZ1	329	A0A0C4DG95	370	B7Z5S9
289	C1PHA2	330	A0A0C4DH07	371	B7Z658
290	C4P0D4	331	A0A0D9SG74	372	B7Z7E5

373	B9EIS5	414	E9PKP4	455	H0Y9Q9
374	C9J1P7	415	E9PKW6	456	H0YAY4
375	C9JC48	416	E9PMR6	457	H0YCE1
376	C9JUP7	417	E9PNW4	458	H0YCX6
377	C9K031	418	E9PQ82	459	H0YCY8
378	D6R9L2	419	E9PRM1	460	H0YD73
379	D6RAF4	420	E9PS23	461	H0YEL2
380	D6RAX7	421	E9PS78	462	H0YGK8
381	D6RB21	422	F5GX11	463	H0YH82
382	D6RBE9	423	F5GXD8	464	H0YI09
383	D6RBJ7	424	F5GZN3	465	H0YI26
384	D6RCL6	425	F5H520	466	H0YJP3
385	D6RDP1	426	F6MF51	467	H0YM36
386	D6RF19	427	F8VUF6	468	H0YMB1
387	D6RF62	428	F8VYY9	469	H0YMP8
388	D6RF77	429	F8VZY9	470	H3BPX2
389	D6RF86	430	F8W7P5	471	H3BQU9
390	D6RGK8	431	F8W943	472	H6UK83
391	D6RGV2	432	F8WBV3	473	H6VRG2
392	D6RJ91	433	F8WCH0	474	H7BXY6
393	D6RJ96	434	F8WD56	475	H7BZL4
394	D6RJA4	435	F8WDR7	476	H7C063
395	D6RJI3	436	F8WEQ7	477	H7C064
396	D9ZGF4	437	G3CIH8	478	H7C0U5
397	E2DRY6	438	G3V1B5	479	H7C1H6
398	E5RGB0	439	G3V1S6	480	H7C1U0
399	E5RGR6	440	G3V210	481	H7C2H5
400	E5RGU3	441	G3V281	482	H7C410
401	E5RH00	442	G3V4S5	483	H7C5K4
402	E5RIV9	443	G3V5Z7	484	H7C5L4
403	E6Y3G0	444	G3XAM7	485	H7C5N8
404	E7ERL0	445	G5E9W1	486	H7C5W6
405	E7ETE2	446	H0Y409	487	H7C5W8
406	E7ETF9	447	H0Y430	488	I1YAQ5
407	E7EX41	448	H0Y465	489	I3L1Y9
408	E9PCM2	449	H0Y4A0	490	I3L392
409	E9PD92	450	H0Y5U1	491	I3L3P5
410	E9PFL9	451	H0Y7G9	492	I3L425
411	E9PGT6	452	H0Y7R7	493	I3VM54
412	E9PJF7	453	H0Y8M8	494	J3KND3
413	E9PKD5	454	H0Y9N2	495	J3KNE3

496	J3KPM9	537	O00267	578	G8I2S9
497	J3KRB5	538	O00549	579	H0Y326
498	J3KRT5	539	O14562	580	H0YAP6
499	J3KRT8	540	A0A0A0MSA0	581	H0YDN1
500	J3KSV6	541	A0A0R4J2F3	582	H0YHV6
501	J3KTQ0	542	B4DHB6	583	H0YLD0
502	J3QKR0	543	B4DHD2	584	H0YN28
503	J3QL20	544	B7Z2F4	585	H3BQZ7
504	J3QQT0	545	A0A0S2Z4D6	586	H3BU13
505	J3QQX2	546	B4DXI1	587	H3BUW1
506	J3QR48	547	B4E1U3	588	H7BZU1
507	J3QRS3	548	B7Z2B3	589	H7C1C2
508	J3QS32	549	B0YJC5	590	H7C1J5
509	J3QS41	550	B2R4D5	591	H7C248
510	J3QTA5	551	A0A024R0E5	592	H7C3I4
511	J7HH10	552	A0A024R151	593	H7C5S0
512	J7M3T8	553	A0A087WZ38	594	I3L155
513	K7EJ01	554	B2R7B5	595	I3L1F7
514	K7EJH8	555	B2RDZ9	596	J9ZVQ3
515	K7EKM4	556	B3KN51	597	K7EL90
516	K7EKW4	557	B4DIJ6	598	K7EMN4
517	K7EL50	558	B4DNJ0	599	M0QZ24
518	K7ELI6	559	B7Z4P8	600	M0R081
519	K7EM20	560	B7Z5V2	601	O14660
520	K7EP19	561	B7Z5Z3	602	A0A024R0J4
521	K7EPB9	562	C9IZA5	603	A0A024RDG1
522	K7ER62	563	C9J8I8	604	A0A024RDW7
523	K7ERC6	564	D6RCL1	605	A0A075B730
524	K7ESB6	565	E1P506	606	A0A087WTJ7
525	K7ESE8	566	E5RJR0	607	A0A087WU44
526	K7ESG6	567	E7EN95	608	A0A087WUE6
527	K7N7D6	568	E9PI65	609	A0A087WZP6
528	L7QJ95	569	E9PKA3	610	A0A0A0MSB2
529	L8EAR0	570	E9PLE9	611	A0A0C4DFM8
530	M0QZ17	571	E9PQ67	612	A0A0D9SFN7
531	M0QZC5	572	F5H7C6	613	A0A0S2Z457
532	M0R0N8	573	F5H7T4	614	A0A0S2Z486
533	M0R0Q9	574	F5H815	615	A0A0S2Z4C3
534	M0R1H5	575	G3CC15	616	A0A0S2Z5H3
535	M1TIV1	576	G3V4X5	617	A0A0U1RQR6
536	M1VPF9	577	G5E9R9	618	A0A0U1RRA7

619	A0A140T9K1	660	B5BU28	701	B3KXB6
620	A0A140VJS6	661	B5MCV4	702	B4DDN8
621	A0A158SIU0	662	B5MDV5	703	B4DE23
622	A0AVI4	663	B6VEX3	704	B4DE69
623	A2RQD9	664	B7Z2K1	705	B4DKE2
624	A6XMH5	665	B7Z3E7	706	B4DM63
625	A7MBN2	666	B7Z4A9	707	B4DN01
626	A8K224	667	B7Z4X6	708	B4DNL4
627	A8K3T5	668	B7Z523	709	B4DRE8
628	A8K668	669	B7Z553	710	B4DRR8
629	A8K6A5	670	B7Z5F6	711	B4DRY5
630	B1AHN3	671	B7Z5K4	712	B4E0Q9
631	B1AKN5	672	B7Z7N3	713	B7Z2S5
632	B2CNW3	673	B7ZKX1	714	B7Z8A8
633	B2RCQ9	674	B7ZLW3	715	B7Z8C6
634	B2RDL6	675	B7ZW00	716	B7Z994
635	B3KMC9	676	C9J941	717	C9J5M1
636	B3KPL5	677	A0A024R9L9	718	C9JE56
637	B3KQF4	678	A0A024R9X5	719	C9JF79
638	B4DDN4	679	A0A087WV29	720	C9JFC0
639	B4DE01	680	A0A087WYS1	721	D3TTY5
640	B4DEL3	681	A0A087X243	722	D6R9X8
641	B4DH41	682	A0A0C4DGA1	723	D6RBL6
642	B4DHK9	683	A0A0E3MS57	724	D6RBS1
643	B4DJA4	684	A0A0U1RR26	725	D6RBX4
644	B4DJB3	685	A0A140T998	726	E5RFY0
645	B4DJJ5	686	A4QPE4	727	E7ERF2
646	B4DJK3	687	A6NG45	728	E7ERK4
647	B4DKC9	688	A6NLJ7	729	E7ES21
648	B4DNG6	689	A6QRH1	730	E7ESA7
649	B4DVI2	690	A6YID4	731	E7ET40
650	B4DW26	691	A8K2U2	732	E9PBS1
651	B4DWB5	692	A8MXP8	733	E9PC84
652	B4DX85	693	B2R8Y6	734	E9PG15
653	B4DYN5	694	B2RA03	735	E9PKF6
654	B4DZN4	695	B2RMN7	736	E9PKY7
655	B4E1H7	696	B3KNN9	737	E9PNR9
656	B4E201	697	B3KQE1	738	E9PP27
657	B4E2A3	698	B3KT37	739	E9PSF4
658	B4E2J2	699	B3KUI1	740	F1T0J8
659	B4E394	700	B3KVX6	741	F1T0K3

742	F8W079	783	A0A141PNN3	824	D6RD63
743	F8W4S1	784	A0PK02	825	D6W5E6
744	F8W810	785	A1A4Z1	826	F5GX75
745	F8WDG7	786	A5GZ70	827	H0Y5N9
746	G3V154	787	A7E293	828	H0YDZ9
747	G3V3Y5	788	A8K479	829	H0YEA0
748	H0YB88	789	A8K9B9	830	K4DI93
749	H0YCC6	790	A8K9V7	831	A0A024R7E0
750	H0YD69	791	A8KAY2	832	A0A024R7P5
751	H0YI18	792	A8MZG1	833	A0A0E3DC72
752	H0YK69	793	B3KM68	834	A0A0U1RQT3
753	H3BMF9	794	B3KQF5	835	B2RBR9
754	H3BUC1	795	B3KSL2	836	B3KU41
755	H3BVA8	796	B4DEB4	837	B4DL19
756	H7C0C4	797	B4DJ78	838	B4DNL9
757	H7C298	798	B4E3G9	839	B4DPQ4
758	H7C2K7	799	B7Z8F6	840	B4DPU3
759	H7C300	800	B7ZC06	841	B4DSX0
760	H7C4L5	801	C9J6N7	842	B4DT47
761	I3L2G5	802	E7EQL5	843	B4DTC0
762	I3L3H7	803	E9PLY3	844	B4DTI0
763	I3L504	804	H0Y5K2	845	B4DYN7
764	I6XKI8	805	H0YI02	846	B4DZ41
765	J3KN16	806	H7C4W4	847	B7Z4E6
766	J3KPY5	807	J3QLH6	848	A0A024R224
767	J3QKW7	808	B2RBH2	849	A0A024R319
768	J3QRG4	809	A0A024R238	850	A0A024R4H0
769	K7EIE7	810	A0A024R433	851	A0A024R5Q7
770	K7EIT4	811	A8K3W7	852	A0A024R771
771	K7EJ44	812	B1Q3B4	853	A0A024R872
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773	K7EKQ5	814	H0YKN4	855	A0A024R9V5
774	K7EPW7	815	H0YL43	856	A0A024RDD7
775	K7ERZ3	816	H7C341	857	A0A075BW43
776	M0QXZ3	817	H7C3S9	858	A0A087WY35
777	M0QY43	818	I3NI29	859	A0A087WZI0
778	M0R061	819	B4DM40	860	A0A090N8P3
779	A0A024RE10	820	B4DWQ3	861	A0A096LNH1
780	A0A0A0MTC8	821	B4DWR3	862	A0A0A0MSA3
781	A0A0C4DGP0	822	C9JSM2	863	A0A0B4J1Y2
782	A0A0J9YXZ5	823	D6RAM7	864	A0A0G2JP44

865	A0A0U1RRC3	906	B4DTX6	947	H0UI27
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867	A0A140VKF3	908	B4DWI2	949	H0Y9D7
868	A2VDJ4	909	B4DYC8	950	H0YAR1
869	A8K4A5	910	B4DYZ8	951	H0YB80
870	A8K4C2	911	B4DZ90	952	H0YF44
871	A8MTM1	912	B4DZW8	953	H0YJC4
872	B0AZU6	913	B4E0C7	954	H0YNJ8
873	B1AHM6	914	B4E104	955	H3BM42
874	B2R4P2	915	B4E1T8	956	H3BPE1
875	B2R853	916	B4E2N1	957	H7BY98
876	B2RAX5	917	B4E2P8	958	H7BZ76
877	B2RC37	918	B4E2S7	959	H7C0S0
878	B2RCU2	919	B4E2Z6	960	H7C0V2
879	B3KN94	920	B4E385	961	H7C3T4
880	B4DDN7	921	B5A943	962	H7C4H6
881	B4DDQ2	922	B5MCJ9	963	H7C4N2
882	B4DDU2	923	B7Z1C9	964	H9XGZ7
883	B4DEU0	924	B7Z1U8	965	I1Y8W7
884	B4DFN9	925	B7Z2Y7	966	I3V9R4
885	B4DFW2	926	B7Z3Y2	967	I6TRR8
886	B4DGV4	927	B7Z475	968	J3KR84
887	B4DIL5	928	B7Z5A2	969	J3QRU8
888	B4DKP9	929	B7Z602	970	J3QT73
889	B4DMS0	930	B7Z7K9	971	J7FK29
890	B4DNE1	931	B7ZLY3	972	K7EMQ1
891	B4DNV4	932	C9J4D3	973	O14956
892	B4DPA0	933	C9JBB3	974	O15050
893	B4DPA3	934	C9JRL6	975	O15063
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895	B4DQV1	936	D3DWB6	977	A4D2Q0
896	B4DR76	937	D6RBZ4	978	H3BQ34
897	B4DRB7	938	D6RFM2	979	B7Z7M2
898	B4DST8	939	D6RGI3	980	G3V4U2
899	B4DSV2	940	E1B4S5	981	H0YDG0
900	B4DT29	941	E7ESF4	982	H0YDG7
901	B4DTA7	942	E7ESK7	983	B3KXY4
902	B4DTG8	943	F5GXT7	984	B4DNP4
903	B4DTK3	944	F5GZI0	985	B7Z230
904	B4DTK7	945	F5GZK1	986	A0A024QZL1
905	B4DTS5	946	G8FSY7	987	A0A024R6E0

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993	A0A140VJI7	1034	H1AE11	1075	Q14400
994	A0A163HNC8	1035	H3BR66	1076	Q14730
995	A0A173GMX0	1036	H3BTF6	1077	Q147W7
996	A8K455	1037	H3BUK7	1078	Q15036
997	B3KUR6	1038	I3L4X5	1079	Q15483
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999	B4DI30	1040	J3KSD8	1081	Q17RA0
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1001	B4DKX5	1042	K7ENJ2	1083	Q1P9K4
1002	B4DNG0	1043	M0R1X9	1084	Q1XBU6
1003	B4DNH2	1044	O15376	1085	Q2F839
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1005	B4DTM7	1046	O60400	1087	Q2MCL6
1006	B4DVB9	1047	O76081	1088	Q2TA90
1007	B4DVJ0	1048	O95101	1089	Q2VJ45
1008	B4DY23	1049	O95425	1090	Q3L3Q5
1009	B4DYY1	1050	O95654	1091	Q3SY86
1010	B4E2Y9	1051	P01591	1092	Q45KI0
1011	B7Z2M8	1052	P05452	1093	Q495U0
1012	B7Z9U8	1053	P08754	1094	Q49A78
1013	C9J0J7	1054	P0CG43	1095	Q49AI3
1014	C9JC03	1055	P11277	1096	Q49IK8
1015	D6RAX0	1056	P25105	1097	Q4G7P9
1016	D6REJ2	1057	P30086	1098	Q4KMR2
1017	D6RGZ6	1058	P42356	1099	Q4LE36
1018	D6RH21	1059	P49746	1100	Q4LE49
1019	E5RGY4	1060	P61578	1101	Q52NV4
1020	E5RIA2	1061	P83369	1102	Q53ET2
1021	E5RJL2	1062	Q05BT9	1103	Q53EX3
1022	E7EPG1	1063	Q05D06	1104	Q53EZ0
1023	E9PKD3	1064	Q05DE9	1105	Q53FB0
1024	F5GWX5	1065	Q05DS6	1106	Q53G95
1025	F5GXS2	1066	Q0PHS6	1107	Q53GB6
1026	F5H198	1067	Q0QEN7	1108	Q53GG0
1027	F5H2I0	1068	Q0VGA5	1109	Q53GQ8
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1115	Q53HT9	1156	Q5HYD8	1197	Q6LAF9
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1129	Q59F63	1170	Q5STK2	1211	Q6P468
1130	Q59FE0	1171	Q5SX87	1212	Q6PJ56
1131	Q59FG9	1172	Q5T0I0	1213	Q6PJK6
1132	Q59FI0	1173	Q5T244	1214	Q6PK82
1133	Q59FQ4	1174	Q5T670	1215	O19760
1134	Q59FZ7	1175	Q5U8W9	1216	P28072
1135	Q59G81	1176	Q5VSR5	1217	P35556
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1137	Q59GD4	1178	Q5VXX4	1219	Q05D76
1138	Q59GQ7	1179	Q5XG79	1220	Q13041
1139	Q59GR8	1180	Q5ZEY3	1221	Q13509
1140	Q59GT9	1181	Q63HQ4	1222	Q14006
1141	Q59GX5	1182	Q658U4	1223	Q1M0P4
1142	Q59GX9	1183	Q67AI3	1224	Q2F831
1143	Q59H49	1184	Q68D25	1225	Q2KQ74
1144	Q59H77	1185	Q68DU0	1226	Q2TAB6
1145	Q59H95	1186	Q68DU4	1227	Q3MIM8
1146	Q59HE5	1187	Q69YV6	1228	Q3T7C5
1147	Q5BJH1	1188	Q6FGE5	1229	Q4G0E1
1148	Q5BKV1	1189	Q6FHE1	1230	Q4ZG85
1149	Q5CAQ5	1190	Q6FHK8	1231	Q53F60
1150	Q5D044	1191	Q6FHL8	1232	Q53FC3
1151	Q5EC54	1192	Q6FHW5	1233	Q53GC9

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1237	Q59EE6	1278	B3KS53	1319	B4DF27
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1243	Q5T5N3	1284	A5PLK9	1325	A4UCS6
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1245	Q5YLW1	1286	B2RBM1	1327	B2RD89
1246	Q6DHW5	1287	B3KTS7	1328	B3KTX0
1247	Q6FHN3	1288	B4DHC4	1329	B3KTX3
1248	Q6IE36	1289	B4DHL6	1330	B4DME4
1249	Q6IPN6	1290	B4DYW5	1331	B4DQX3
1250	Q6MZG6	1291	B4E0I7	1332	B7Z431
1251	Q6MZT2	1292	D6R917	1333	B7ZLP8
1252	Q6PJJ3	1293	A0A0D9SFK2	1334	C9JKG1
1253	Q6PRD1	1294	B2R951	1335	C9JN42
1254	A0A024RAY2	1295	B4DI06	1336	E7ENL6
1255	A0A087WXW9	1296	B4DLF7	1337	E7EP32
1256	A0A087WYG4	1297	B4E1W8	1338	E7EQR6
1257	A0A087WZ47	1298	B4E3A7	1339	F5GY03
1258	A0A0A0MSA8	1299	B4E3Q3	1340	G3V3A5
1259	A0A0S2Z5C0	1300	A0A024R7D5	1341	G3V3F4
1260	A0A0U1RQJ8	1301	A1YZ08	1342	G3V5M2
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1262	A8K5A7	1303	B3KQJ7	1344	H0Y7F7
1263	B2RBV7	1304	B3KSZ4	1345	H0Y827
1264	B3KV72	1305	B3KTR3	1346	H0Y8V7
1265	B4DDH0	1306	B3KXU8	1347	H0YH27
1266	B4DDR8	1307	B4DFG4	1348	H3BRL3
1267	B4DEF7	1308	A0A024R6R3	1349	H3BU53
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1270	B4DS98	1311	A5Z217	1352	H9C5C5
1271	B4DTB1	1312	A8KA64	1353	I3NI03
1272	B7Z752	1313	B2R6U9	1354	J3KNQ1
1273	B7Z7T1	1314	B4DI81	1355	J3KRF8
1274	C9J8I6	1315	B4DZ47	1356	K7ELN9

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1358	B4E205	1399	E9PQ34	1440	A0A087WSW9
1359	B7Z5D9	1400	H0Y3V4	1441	B3KQQ3
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1361	B1AK85	1402	H7C5L0	1443	H0YAS8
1362	B4DP54	1403	I3L1H5	1444	H3BR68
1363	B7Z4B2	1404	J3KRF5	1445	Q0Z8D6
1364	E9PIA2	1405	J3KSI6	1446	Q10567
1365	F8VQ14	1406	J3KSQ2	1447	Q53HA4
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1378	B3KMI7	1419	B2R5H0	1460	Q6MZZ3
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1382	B4DTH9	1423	B4DHT9	1464	Q6PJ44
1383	B4DYS5	1424	B4DN99	1465	Q12986
1384	B4E1E0	1425	B4DQ93	1466	Q562S2
1385	B7Z2B6	1426	B4DRN5	1467	Q59GK6
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1387	B7Z6T6	1428	B4DXF3	1469	Q6T4R5
1388	B7Z998	1429	B4E027	1470	A0A024RAV2
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1394	B0I1S1	1435	H7C381	1476	B3KSS4
1395	B3KN63	1436	H7C5R6	1477	B3KY38
1396	B3KQQ9	1437	M0R2L7	1478	B4DDM1
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1482	B4DX81	1523	A6YID5	1564	H0Y5J5
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1504	B4DT32	1545	B4E320	1586	B7Z582
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1506	B4DX93	1547	D3DSM7	1588	F8VZH8
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1514	A8K270	1555	F6XY72	1596	A8K8D9
1515	B2RE43	1556	F8VX58	1597	A8K8S6
1516	B3KRA9	1557	F8W1K6	1598	B3KWT5
1517	B4DDL4	1558	F8W6C1	1599	B4E0H6
1518	B4DFW6	1559	F8WD80	1600	H7BXV5
1519	B4DHN1	1560	F8WDD7	1601	I3L3X7
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1607	H0YI37	1648	E9PJ32	1689	Q6PJT4
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1610	B4DH11	1651	F8VZB4	1692	A0A024R599
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1613	A0A024R6D1	1654	G3V3U4	1695	A0A024R9Y3
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1620	A8K9E1	1661	H7C144	1702	A0A087X080
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1625	B3KSM5	1666	P29279	1707	A0A0B4J1R7
1626	B3KXY0	1667	Q0P5U8	1708	A0A0B6XK25
1627	B4DJS0	1668	Q14215	1709	A0A0C4DFW8
1628	B4DM61	1669	Q14DR2	1710	A0A0D9SET8
1629	B4DMH3	1670	Q1RMC8	1711	A0A0D9SG79
1630	B4DPS8	1671	Q2TU64	1712	A0A0G2JPA8
1631	B4DPX8	1672	Q2VIM7	1713	A0A0J9YWE8
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1633	B4DTH4	1674	Q504U3	1715	A0A0K0Q0G7
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1635	B4DXW2	1676	Q53GR3	1717	A0A0S2Z3X3
1636	B4DYM0	1677	Q53H39	1718	A0A0S2Z3X8
1637	B4DZB4	1678	Q56CY1	1719	A0A0U1RR07
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1639	B4E0L1	1680	Q59H37	1721	A0A140T936
1640	B4E1R7	1681	Q5JVS8	1722	A0A140VJT0
1641	B7Z1F8	1682	Q5SX86	1723	A0A140VK45
1642	B7Z4V4	1683	Q5SXM2	1724	A0A173GMX4
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1726	A4QPA1	1767	B4DID6	1808	D3DT96
1727	A4UCT1	1768	B4DIW2	1809	D3DUT5
1728	A4UCT9	1769	B4DJ06	1810	D6R904
1729	A5YM53	1770	B4DJ44	1811	D6RJI2
1730	A6NDY9	1771	B4DMJ0	1812	E0Z3H2
1731	A8K1S0	1772	B4DN77	1813	E2QRI1
1732	A8K2I0	1773	B4DND6	1814	E5RG57
1733	A8K477	1774	B4DQQ2	1815	E5RGA2
1734	A8K4G9	1775	B4DQX0	1816	E7EPM4
1735	A8K590	1776	B4DQZ0	1817	E7EU13
1736	A8K5T0	1777	B4DSF8	1818	E7EUI6
1737	A8K690	1778	B4DT18	1819	E9PCC8
1738	A8K6S3	1779	B4DW31	1820	E9PF58
1739	A8K7F7	1780	B4DX43	1821	E9PL37
1740	A8K7Q1	1781	B4DYA7	1822	E9PLD0
1741	A8K7T8	1782	B4DZX4	1823	E9PLK3
1742	A8K8A4	1783	B4E392	1824	E9PLY5
1743	A8K900	1784	B4E3Q9	1825	E9PMN5
1744	A8K979	1785	B5MDS3	1826	E9PPQ4
1745	A8MXT2	1786	B7Z5H9	1827	E9PQK6
1746	B0YJC4	1787	B7Z6E5	1828	E9PRR2
1747	B2R932	1788	B7Z6L5	1829	F1BXA6
1748	B2RBP3	1789	B7Z7W6	1830	F1D8R6
1749	B3KMH6	1790	B7Z822	1831	F5H6W8
1750	B3KMM7	1791	B7Z842	1832	F8VP67
1751	B3KNB9	1792	B7Z8E7	1833	F8VWV4
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1754	B3KRK8	1795	B7ZAX6	1836	G3V2W4
1755	B3KT98	1796	B7ZKR5	1837	G3V380
1756	B3KTM1	1797	C6GLZ1	1838	G3V393
1757	B3KU27	1798	C9J7B7	1839	G3V511
1758	B3KU60	1799	C9JBU9	1840	G3XL79
1759	B3KUY5	1800	C9JIF9	1841	G5E9Z2
1760	B3KX16	1801	C9JMZ3	1842	H0Y400
1761	B3W6H4	1802	C9JQJ4	1843	H0Y897
1762	B4DG55	1803	C9JSL4	1844	H0YAB0
1763	B4DG73	1804	C9JT74	1845	H0YAH8
1764	B4DGT1	1805	C9JU11	1846	H0YBW3
1765	B4DGX9	1806	C9K0H9	1847	H0YCK7
1766	B4DI19	1807	D0V481	1848	H0YEG8

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1851	H0YGZ3	1892	A0A096LPA6	1933	B4DSQ5
1852	H0YI33	1893	A0A0A1HAN9	1934	B4DUK1
1853	H0YKU5	1894	A0A0C4DGH2	1935	B4DUM2
1854	H0YLD1	1895	A0A0G2JP90	1936	B4DVL8
1855	H0YLJ1	1896	A0A0S2Z3H5	1937	B4DWA8
1856	H0YLM2	1897	A0A0S2Z476	1938	B4DXJ6
1857	H3BN34	1898	A0A0U1RRI8	1939	B4DYU2
1858	H3BN75	1899	A0A0U5BLD0	1940	B4E163
1859	H3BNR4	1900	A0A0U5EM55	1941	B4E190
1860	H3BNT7	1901	A0A140VK69	1942	B4E1H9
1861	H3BPG7	1902	A0A140VK70	1943	B4E2V8
1862	H3BQA8	1903	A8K309	1944	B4E356
1863	H3BRL2	1904	A8K3Q7	1945	B5A941
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1865	H3BU24	1906	A8K8U1	1947	B7Z6I3
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1867	H3BUV8	1908	A8MVZ9	1949	B7Z9C4
1868	H3BV30	1909	A8YQF3	1950	B7ZAB0
1869	H7BZE9	1910	B2RD14	1951	C6ZGX2
1870	H7C0M5	1911	B2RDI5	1952	C9JAM8
1871	H7C0V9	1912	B3KQM1	1953	C9JEG3
1872	H7C278	1913	B3KRK1	1954	C9K0C5
1873	H7C531	1914	B3KXF2	1955	D3DPU0
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1875	H7C5J5	1916	B4DFG7	1957	D6RFX4
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1877	I3L3Q7	1918	B4DHQ7	1959	E5KRG5
1878	I3L3Z3	1919	B4DJQ5	1960	E5RFS1
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1880	J3QS16	1921	B4DMT4	1962	E9PKK9
1881	J3QTJ6	1922	B4DN21	1963	E9PMR4
1882	K4RH61	1923	B4DN30	1964	E9PNW5
1883	K7ENH5	1924	B4DN32	1965	E9PQH6
1884	K7EPG3	1925	B4DN78	1966	F5GYU2
1885	K7ERA3	1926	B4DNM8	1967	F8VP03
1886	K7ERX2	1927	B4DPP0	1968	G1UD79
1887	L8E758	1928	B4DQK5	1969	H0YA83
1888	A0A087WT80	1929	B4DR44	1970	H0YBG6
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1974	H3BLS7	2015	Q4LE33	2056	Q5T3N0
1975	H7C183	2016	Q4LE71	2057	Q5TA01
1976	I3L0S0	2017	Q4V347	2058	Q5TBG5
1977	I3L3P9	2018	Q4W5E0	2059	Q5TEK2
1978	I3L3W3	2019	Q53F79	2060	Q5TZP0
1979	I4AY87	2020	Q53FX5	2061	Q68D23
1980	J3KQ66	2021	Q53G35	2062	Q69YT6
1981	J3KTI8	2022	Q53G83	2063	Q6DHY5
1982	J3QKQ5	2023	Q53GG3	2064	Q6FGL0
1983	J3QT34	2024	Q53GZ2	2065	Q6FHZ0
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1985	K7EP68	2026	Q53RS1	2067	Q6I7N8
1986	L7RSL3	2027	Q53SM6	2068	Q6IB71
1987	M0R0W6	2028	Q53TA7	2069	Q6IC76
1988	M0R2Z9	2029	Q53TY1	2070	Q6IPN0
1989	O14549	2030	Q53X91	2071	Q6LCH2
1990	O15018	2031	Q562U1	2072	Q6MZF4
1991	O15289	2032	Q562X2	2073	A0A024R411
1992	P07195	2033	Q56VW8	2074	A0A024R3H2
1993	P0C221	2034	Q58I23	2075	A0A024R3V8
1994	P11217	2035	Q59E90	2076	A0A024R5L0
1995	P17032	2036	Q59EB3	2077	A0A024RAM4
1996	P18669	2037	Q59EL5	2078	A0A087WYF2
1997	P21912	2038	Q59F04	2079	A0A097EV82
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1999	P48741	2040	Q59FD0	2081	A0A125S6H6
2000	P53675	2041	Q59FF0	2082	A0A140VK56
2001	P61201	2042	Q59FJ0	2083	A0PJ81
2002	Q0PNF2	2043	Q59FK6	2084	A8K8B0
2003	Q14329	2044	Q59GI7	2085	A8KAK1
2004	Q14769	2045	Q59GI8	2086	A8MXH5
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2006	Q1LZN2	2047	Q59GS3	2088	B2R921
2007	Q2I0A6	2048	Q59H74	2089	B4DE40
2008	Q2PUK1	2049	Q59HA6	2090	B4DIX1
2009	Q2V4X9	2050	Q5CZ99	2091	B4DSW9
2010	Q2VPA1	2051	Q5JPB8	2092	B4DX08
2011	Q3B787	2052	Q5JPE4	2093	B4E0B4
2012	Q3MIC3	2053	Q5JTH9	2094	B4E0X6

2095	B5MD23	2136	A0A0U1RR39	2177	A0A140VJX3
2096	B7Z2Z0	2137	A0A140VJR3	2178	A2VCK8
2097	B7Z3Z2	2138	A7MBM6	2179	A7E2S2
2098	B7Z4G0	2139	A8K1Y7	2180	B2R708
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2101	C9JK86	2142	B3KVI8	2183	B3KTJ9
2102	C9JKQ7	2143	B4DQH3	2184	B3KWY2
2103	C9JPC3	2144	B4DRT3	2185	B4DDG4
2104	D6RIA0	2145	B4DWQ5	2186	B4DMK2
2105	E5RJ43	2146	B4DY05	2187	B4DP06
2106	E9PRU1	2147	B4DY98	2188	B4DT73
2107	F5GXU1	2148	F5H2L3	2189	B4DU71
2108	F8WAA0	2149	F8W787	2190	B7Z4C7
2109	H0Y5C6	2150	H0YMC2	2191	B9VPB4
2110	H0Y875	2151	H7C2S8	2192	C9JPC0
2111	H0Y9P0	2152	Q14918	2193	C9JUU5
2112	H0YAF9	2153	Q49A43	2194	C9K055
2113	H0YIB2	2154	Q4W5D3	2195	D3DSM4
2114	H0YN01	2155	Q53FG3	2196	E7ER45
2115	H7C3F9	2156	Q53H18	2197	E9PCH4
2116	H7C4Y7	2157	Q53HJ0	2198	E9PN91
2117	J3QRA5	2158	Q59ET0	2199	E9PNX1
2118	J3QS88	2159	F6S8N6	2200	F6XZQ7
2119	P19022	2160	F6X2W2	2201	F8WC37
2120	Q05BR9	2161	H0Y8I3	2202	G3V295
2121	Q14568	2162	H0YCR7	2203	H0UI49
2122	Q53SM9	2163	H0YMM1	2204	H0Y4E8
2123	Q59F65	2164	J3KQ42	2205	H0Y789
2124	Q5FWG8	2165	M1LAK4	2206	H0Y8F1
2125	Q6FH10	2166	O43532	2207	H0YMJ5
2126	Q6M1B8	2167	Q0P682	2208	H3BV48
2127	Q6MZT4	2168	Q59FU7	2209	H7C3T2
2128	Q6NZ44	2169	Q59GT2	2210	A0A024QYX7
2129	A0A024R084	2170	Q5T4U8	2211	A0A024R017
2130	A0A024R5W3	2171	Q5T9S5	2212	A0A024R1D0
2131	A0A024R6B5	2172	Q5TCI8	2213	A0A024R2W4
2132	A0A024RDG6	2173	A0A024R7C7	2214	A0A024R321
2133	A0A024RDY3	2174	A0A087WWU3	2215	A0A024R4K5
2134	A0A087X0M6	2175	A0A0A0MSV3	2216	A0A024R7J0
2135	A0A0A0MRQ5	2176	A0A140GPP7	2217	A0A024R8K6

2218	A0A024R8Q1	2259	B3KT70	2300	E9PD53
2219	A0A024R8U1	2260	B3KU58	2301	E9PIA9
2220	A0A024RAB2	2261	B4DDF3	2302	E9PJF9
2221	A0A024RAJ6	2262	B4DE78	2303	E9PKH0
2222	A0A024RCA7	2263	B4DF49	2304	E9PM19
2223	A0A024RDW8	2264	B4DG47	2305	E9PM22
2224	A0A075EKM8	2265	B4DHV7	2306	E9PMC9
2225	A0A087WT21	2266	B4DJJ9	2307	E9PNQ9
2226	A0A087WU05	2267	B4DMB5	2308	E9PPD2
2227	A0A087WW79	2268	B4DNH1	2309	E9PPK9
2228	A0A087WWP7	2269	B4DP69	2310	E9PPR9
2229	A0A087WWY3	2270	B4DPW9	2311	E9PQ70
2230	A0A087WY61	2271	B4DTA8	2312	E9PR84
2231	A0A087WZM5	2272	B4DTH2	2313	E9PRJ8
2232	A0A087WZN9	2273	B4DYM7	2314	F2Z3H1
2233	A0A087X1J2	2274	B4E1B0	2315	F4ZW63
2234	A0A0A0MQX7	2275	B4E284	2316	F5GWI0
2235	A0A0A0MRF9	2276	B7Z2F0	2317	F5H3N3
2236	A0A0A0MRH2	2277	B7Z2I6	2318	F5H4N4
2237	A0A0A0MTC1	2278	B7Z597	2319	F5H4Z8
2238	A0A0A7M1X5	2279	B7Z754	2320	F8VR50
2239	A0A0B6XK12	2280	B7Z924	2321	F8VRX1
2240	A0A0C4DFS1	2281	B7Z9B8	2322	F8VXW2
2241	A0A0G2JJ52	2282	B7ZA28	2323	F8W1A0
2242	A0A0G2JN90	2283	B7ZAG1	2324	F8W1H8
2243	A0A0G2JNE7	2284	B7ZAY4	2325	F8W1K5
2244	A0A0G2JQ91	2285	B7ZML4	2326	F8W9J4
2245	A0A0S2Z487	2286	C9IY79	2327	F8WAE6
2246	A0A0S2Z4T2	2287	C9JKZ2	2328	F8WD26
2247	A2RUE7	2288	D6RHZ5	2329	F8WDY7
2248	A6XMV8	2289	D9ZGF8	2330	G1EPL1
2249	A6YID7	2290	E2ITE0	2331	G3V1E2
2250	A8K0T9	2291	E5RGZ4	2332	G3V2H3
2251	A8K126	2292	E5RH50	2333	G3V2X9
2252	A8K168	2293	E5RII0	2334	G3V4U0
2253	A8K335	2294	E5RJ14	2335	G3V5X8
2254	A8K6D3	2295	E5RK62	2336	G5EA44
2255	A8K849	2296	E5RK63	2337	G8XWS8
2256	B0I1S3	2297	E7EMB3	2338	H0UI76
2257	B3KS68	2298	E7EMF1	2339	H0Y351
2258	B3KS71	2299	E9KL30	2340	H0Y3A8

2341	H0Y4K8	2382	K7EKL3	2423	Q59GH5
2342	H0Y4R1	2383	K7EKS1	2424	Q59GK2
2343	H0Y554	2384	K7EM90	2425	Q59GZ8
2344	H0Y586	2385	K7EMN2	2426	Q59HA3
2345	H0Y5C0	2386	K7EPL0	2427	Q59HB3
2346	H0Y5F3	2387	K7ERF7	2428	Q59HB5
2347	H0Y5U0	2388	M0R0U4	2429	Q5FC05
2348	H0Y8S0	2389	M1VKI9	2430	Q5HYA2
2349	H0Y987	2390	O94985	2431	Q5JPH6
2350	H0Y998	2391	O95617	2432	Q5JQ13
2351	H0Y9C2	2392	P30419	2433	Q5QNY5
2352	H0YAM7	2393	P98174	2434	Q5T0F3
2353	H0YAP9	2394	Q00839	2435	Q5TA02
2354	H0YC35	2395	Q05BW8	2436	Q5TFM2
2355	H0YC94	2396	Q05DA4	2437	Q60FE5
2356	H0YCR9	2397	Q05DS5	2438	Q658J0
2357	H0YEM3	2398	Q14650	2439	Q68CW0
2358	H0YET2	2399	Q1RMZ5	2440	Q68CX6
2359	H0YIH3	2400	Q2EF79	2441	Q6AI13
2360	H0YJ03	2401	Q2VP91	2442	Q6EHZ3
2361	H0YJD3	2402	Q2YD88	2443	Q6PEG1
2362	H0YKB3	2403	Q3B7A7	2444	Q6PK56
2363	H0YKS8	2404	Q4G0Q4	2445	Q6PKD2
2364	H0YL50	2405	Q4LE57	2446	Q6PQ81
2365	H0YM03	2406	Q4VC00	2447	Q6S4P3
2366	H0YM92	2407	Q504V9	2448	Q6U2L6
2367	H3BPF6	2408	Q508I7	2449	Q6U8A4
2368	H3BTD4	2409	Q53F09	2450	Q6UQL6
2369	H3BTN5	2410	Q53FI4	2451	Q6UUU9
2370	H3BU78	2411	Q53FK2	2452	Q6W6M8
2371	H3BUH7	2412	Q53FU5	2453	Q6XYD2
2372	H7BY82	2413	Q53GU8	2454	Q6ZMY0
2373	H7C1M6	2414	Q53GW3	2455	Q6ZMY3
2374	H7C2H7	2415	Q53HE2	2456	Q6ZN49
2375	H7C2Q8	2416	Q53HU7	2457	Q6ZNB8
2376	H7C2U0	2417	Q53S41	2458	Q6ZNL4
2377	H7C2Y0	2418	Q58FF2	2459	Q6ZNU3
2378	H7C4X4	2419	Q59EG5	2460	Q6ZP35
2379	I3L4F9	2420	Q59EZ1	2461	Q6ZP53
2380	I3L4N7	2421	Q59F71	2462	Q6ZR44
2381	J3K000	2422	Q59FD9	2463	Q6ZRZ8

2464	Q6ZS01	2505	Q86U75	2546	Q8NG20
2465	Q6ZS03	2506	Q86U79	2547	Q8NH73
2466	Q6ZS14	2507	Q86UP3	2548	Q8NI27
2467	Q6ZSD7	2508	Q86V48	2549	Q8TAS1
2468	Q6ZSL4	2509	Q86W61	2550	Q8TAT5
2469	Q6ZT31	2510	Q86WD0	2551	Q8TB01
2470	Q6ZT94	2511	Q86XU5	2552	Q8TB95
2471	Q6ZTY7	2512	Q86YN0	2553	Q8TBN2
2472	Q6ZVC6	2513	Q8IVF4	2554	Q8TDG6
2473	Q71RC2	2514	Q8IWC8	2555	Q8TDS4
2474	Q71S06	2515	Q8IWL5	2556	Q8TEP3
2475	Q71SW6	2516	Q8IXX0	2557	Q8TES4
2476	Q71UD4	2517	Q8IY44	2558	Q8WTY5
2477	Q71UM7	2518	Q8IY97	2559	Q8WU03
2478	Q75MN1	2519	Q8IY98	2560	Q8WUI6
2479	Q75MY0	2520	Q8IYQ9	2561	Q8WVX2
2480	Q75N18	2521	Q8IZD4	2562	Q8WW96
2481	Q75N89	2522	Q8N1I1	2563	Q8WWB2
2482	Q7KZ71	2523	Q8N1I8	2564	Q8WX69
2483	Q7L4M3	2524	Q8N274	2565	Q8WZ56
2484	Q7L4N0	2525	Q8N294	2566	Q92468
2485	Q7L8K0	2526	Q8N4Z1	2567	Q92547
2486	Q7RTQ9	2527	Q8N505	2568	Q92681
2487	Q7RU04	2528	Q8N5L9	2569	Q92945
2488	Q7Z2F6	2529	Q8N6N5	2570	Q93063
2489	Q7Z2X7	2530	Q8N6P3	2571	Q93093
2490	Q7Z355	2531	Q8N7Y3	2572	Q969I5
2491	Q7Z3G7	2532	Q8N7Z5	2573	Q96AA2
2492	Q7Z3T9	2533	Q8N9C4	2574	Q96AQ0
2493	Q7Z427	2534	Q8N9F8	2575	Q96AR9
2494	Q7Z487	2535	Q8N9K4	2576	Q96AX1
2495	Q7Z497	2536	Q8N9Q8	2577	Q96B07
2496	Q7Z4Z1	2537	Q8NA68	2578	Q96B60
2497	Q7Z6M3	2538	Q8NB89	2579	Q96BA4
2498	Q7Z738	2539	Q8NBH6	2580	Q96BG6
2499	Q7Z757	2540	Q8NCJ3	2581	Q96C61
2500	Q7Z7K9	2541	Q8NE02	2582	Q96CD8
2501	Q7Z7R0	2542	Q8NF03	2583	Q96CV8
2502	Q86TQ3	2543	Q8NF19	2584	Q96D30
2503	Q86TX4	2544	Q8NF24	2585	Q96DQ5
2504	Q86U12	2545	Q8NF60	2586	Q96DZ4

2587	Q96EB3	2628	Q9BW34	2669	Q9NVY6
2588	Q96G38	2629	Q9BXG2	2670	Q9NW05
2589	Q96GF5	2630	Q9BXV5	2671	Q9NW43
2590	Q96GW1	2631	Q9BZ93	2672	Q9NWD6
2591	Q96HC2	2632	Q9BZQ0	2673	Q9NWP5
2592	Q96HF4	2633	Q9H049	2674	Q9NWW3
2593	Q96HI1	2634	Q9H0M4	2675	Q9P0V0
2594	Q96HN5	2635	Q9H2E0	2676	Q9P1C5
2595	Q96IE3	2636	Q9H2E1	2677	Q9P1G4
2596	Q96JJ7	2637	Q9H369	2678	Q9P1N9
2597	Q96K48	2638	Q9H3B0	2679	Q9P1Y0
2598	Q96K89	2639	Q9H3R3	2680	Q9P262
2599	Q96KC0	2640	Q9H3U3	2681	Q9P2G7
2600	Q96LJ7	2641	Q9H511	2682	Q9UBC7
2601	Q96LN7	2642	Q9H5S1	2683	Q9UD42
2602	Q96LR2	2643	Q9H5T0	2684	Q9UD69
2603	Q96MN8	2644	Q9H717	2685	Q9UDE8
2604	Q96N76	2645	Q9H7J0	2686	Q9UDY3
2605	Q96NB3	2646	Q9H8J8	2687	Q9UDZ8
2606	Q96NX2	2647	Q9HAP0	2688	Q9UE33
2607	Q96PA3	2648	Q9HAP1	2689	Q9UE89
2608	Q96PJ0	2649	Q9HB74	2690	Q9UES0
2609	Q96PV0	2650	Q9HBB2	2691	Q9UFZ4
2610	Q96Q06	2651	Q9HBP0	2692	Q9UG85
2611	Q96QU5	2652	Q9HC77	2693	Q9UGU0
2612	Q96RL8	2653	Q9HCI6	2694	Q9UIU0
2613	Q96RP4	2654	Q9NP01	2695	Q9UJ56
2614	Q96RS2	2655	Q9NPA9	2696	Q9UJM0
2615	Q96RZ7	2656	Q9NPM2	2697	Q9UJM1
2616	Q96SE4	2657	Q9NQG5	2698	Q9UJN9
2617	Q99435	2658	Q9NRE2	2699	Q9UJZ2
2618	Q99529	2659	Q9NRY4	2700	Q9UJZ7
2619	Q99538	2660	Q9NS89	2701	Q9UM89
2620	Q99666	2661	Q9NSH2	2702	Q9UMB3
2621	Q9BR56	2662	Q9NSK3	2703	Q9UMN4
2622	Q9BR60	2663	Q9NSM5	2704	Q9UNF3
2623	Q9BS14	2664	Q9NT11	2705	Q9UNU2
2624	Q9BS75	2665	Q9NTC4	2706	Q9UPH5
2625	Q9BSD0	2666	Q9NTU6	2707	Q9UQC1
2626	Q9BTL0	2667	Q9NV59	2708	Q9UQS6
2627	Q9BVS9	2668	Q9NVF8	2709	Q9Y267

2710	Q9Y2Q2	2736	V5QSK8	2762	V9HWC6
2711	Q9Y4R1	2737	V9GYK3	2763	V9HWC7
2712	Q9Y546	2738	V9GYL0	2764	V9HWE9
2713	Q9Y5E1	2739	V9GYV7	2765	V9HWF4
2714	Q9Y623	2740	V9GZ17	2766	V9HWF5
2715	Q9Y6D3	2741	V9GZ54	2767	V9HWG9
2716	Q9Y6N6	2742	V9GZ76	2768	V9HWH6
2717	Q9Y6U3	2743	V9GZR9	2769	V9HWH9
2718	R4GMY1	2744	V9H0H3	2770	W5X314
2719	R4GNC2	2745	V9H1C1	2771	W6I206
2720	R4GNC7	2746	V9H1D9	2772	W6MEN4
2721	R4RWV3	2747	V9HVZ6	2773	W8QEH3
2722	S4R328	2748	V9HVZ7	2774	W8QRJ0
2723	S4R3E9	2749	V9HW24	2775	X5D2F4
2724	S4R3G7	2750	V9HW31	2776	X5D2Z4
2725	S4R451	2751	V9HW35	2777	X5D784
2726	S5FMV1	2752	V9HW55	2778	X5D7K9
2727	U3KPX5	2753	V9HW63	2779	X5D7R7
2728	U3KQA9	2754	V9HW80	2780	X5DQS5
2729	U3KQE2	2755	V9HW89	2781	X5DQV1
2730	U3KQI3	2756	V9HW90	2782	X5DR74
2731	U3KQK2	2757	V9HW95	2783	X6R3R3
2732	U3KQK8	2758	V9HWA6	2784	X6R6Z1
2733	U3KQP1	2759	V9HWA9	2785	X6RJP6
2734	U3PXP0	2760	V9HWC0	2786	X6RLX0
2735	U3REJ1	2761	V9HWC1		

Table 5. Proteins in both NPEX and MSCEX					
1	A0A024RBF5	11	B3KM34	21	B2RWN8
2	A0A087WTU5	12	B3KS32	22	B3KQE6
3	A0A087WTY5	13	B4DK21	23	B4DIY9
4	A0A087WZY3	14	B4DLA8	24	F2Z2Y4
5	A0A0A0MSD7	15	B4DM04	25	I7GY12
6	A0A0U1RQQ9	16	B4DYP3	26	K7EIZ7
7	A8K457	17	B7Z220	27	A1DRY3
8	B0YIW5	18	B7Z3F8	28	A8K2S5
9	B2R6M6	19	A0A0A0MRE5	29	B4DJ85
10	B2RWN5	20	A8K5A6	30	D3DSZ2

31	D6RHJ6	72	K7ENM8	113	B2RN10
32	E5RK22	73	A0A024R2Q7	114	B4DX19
33	A0A090N7W7	74	A0A024RAC9	115	A0A087WTM7
34	A0A024R9U8	75	A0A087X043	116	A0A087WVZ9
35	A0A087WTQ1	76	A1L497	117	A0A087WZI7
36	A0A0A0MTS5	77	A8K5C2	118	A0A0C4DGZ0
37	A0A0J9YWF7	78	B2R7A1	119	A0A0F7T737
38	A0A0S2Z5A6	79	B3KML1	120	A0A126GW30
39	A0A140G945	80	B4DPN0	121	A8K5R3
40	A0PJA6	81	B4DPP6	122	B1AA16
41	A8MYA2	82	B4DSG6	123	B2RD71
42	B3KY01	83	B4DW61	124	B4DQ03
43	B4DDZ2	84	B4DY21	125	B4DRU3
44	B4DJ87	85	B4E1C1	126	B4E1H3
45	B4DN40	86	B7Z3E5	127	B4E3L4
46	B4DPI7	87	B7Z8R2	128	B5A930
47	B4DQJ6	88	B7ZM83	129	G1UI21
48	B7WNR7	89	C9JUF9	130	H7C5E8
49	B7ZAV4	90	A0A0S2SW46	131	I3L0S6
50	C9J4J0	91	A0A140G961	132	K7ELE6
51	D1CS68	92	A5YM44	133	K7ERU1
52	E9PR32	93	A8K3I0	134	O00303
53	H0Y4V9	94	B2RCM2	135	O15232
54	H0YE86	95	B2RD90	136	O75144
55	H3BM13	96	B2RDH6	137	O75643
56	H7C124	97	B2RUU6	138	O95757
57	J3KNF5	98	B3KPC9	139	O95816
58	J3KTE8	99	B4DKV6	140	P00390
59	J3QQZ1	100	C7FEB0	141	P04406
60	K7EMU5	101	E7EUN2	142	P05455
61	A0A087X1K6	102	F2Z2C0	143	P06576
62	B9EK65	103	G3F4G3	144	P11908
63	D2CPJ9	104	H3BUZ9	145	P12277
64	A8K9G8	105	I3L2G4	146	P13010
65	E9PDY4	106	J3KST4	147	P13797
66	E9PKB7	107	L0R875	148	P13798
67	F5GWB9	108	M0QY24	149	P14625
68	H0Y5A3	109	M0QY93	150	P17787
69	H0YDX7	110	M0R167	151	P18206
70	H0YGC5	111	A0A140T9N1	152	P20592
71	I3L2H2	112	B3KV66	153	P20618

154	P21399	195	Q6P668	236	P20700
155	P23381	196	B4DVZ8	237	P23528
156	P24534	197	E9PN76	238	P28066
157	P25787	198	A0A0A0MS56	239	P43686
158	P30520	199	A8K228	240	P51665
159	P30566	200	B4DHL3	241	P63241
160	P35052	201	A0A024R0V9	242	Q12765
161	P37837	202	A0A024R2F7	243	Q14666
162	P40925	203	B2RB99	244	Q5T9B7
163	P43490	204	B3KVJ8	245	A0A024R0F1
164	P43699	205	B4DL71	246	A6NNK5
165	P48723	206	B7Z5Q5	247	A7Y9J9
166	P49721	207	F8WCB0	248	B2RCN5
167	P49916	208	G3V470	249	B3KNG8
168	P50991	209	H0YGP2	250	B3KW67
169	P55290	210	H7BXX0	251	B4DJ43
170	P60842	211	P11310	252	B7ZBJ6
171	P61158	212	P13639	253	E5RGB1
172	P61970	213	P22234	254	E9PNV8
173	P78357	214	P41250	255	G5E9C5
174	P78371	215	P52209	256	H0YD68
175	Q02809	216	P98095	257	O15020
176	Q04446	217	Q00610	258	A0A024R3W8
177	Q05BW9	218	Q04760	259	A0A024R4E7
178	Q05CU5	219	Q1JQ81	260	A0A024R7L2
179	Q05DQ6	220	Q4LE34	261	A0A024R8K8
180	Q08431	221	Q4ZG60	262	A0A024R8L5
181	Q13191	222	Q562P0	263	A0A024R8U4
182	Q14397	223	Q5SZP4	264	A0A024R9F1
183	Q14974	224	Q5T7Q5	265	A0A087WVC6
184	Q16555	225	Q6NR85	266	A0A087WW67
185	Q4G0U7	226	Q6PKB2	267	A0A087WYA1
186	Q4LE70	227	A0A024RDI0	268	A0A0C4DFY7
187	Q4QQP8	228	B3KVT0	269	A0A0G2JNI0
188	Q56A80	229	B3KW08	270	A0A0J9YY10
189	Q58F05	230	B5BU64	271	A0A126GVS6
190	Q59GL5	231	F8VTS6	272	A2RTX5
191	Q59H14	232	Q17RV3	273	A6NF36
192	Q5SRE5	233	Q4LE35	274	A8K324
193	Q5VTG7	234	Q53ZD9	275	A8K4N3
194	Q6P1A2	235	H7BZ78	276	A8K8J5

277	A8K8R2	318	H0YF13	359	Q5XUU0
278	B3KQ44	319	H0YGG5	360	Q6FH47
279	B3KWP3	320	H0YL42	361	Q6IFB0
280	B3KXW2	321	H3BRY5	362	Q6LAP8
281	B4DEL6	322	H7C463	363	Q6W4X9
282	B4DH82	323	I6NLS4	364	Q6XYC2
283	B4DJT2	324	J3QKX5	365	Q6ZMN7
284	B4DLC6	325	O00410	366	Q6ZS81
285	B4DNG2	326	O14943	367	Q6ZTQ4
286	B4DS99	327	O15067	368	Q6ZWK7
287	B4DWK2	328	O95996	369	Q7L2H7
288	B4DYK9	329	O96005	370	Q7Z3Y4
289	B4DYX8	330	P05386	371	Q7Z3Z0
290	B4E303	331	P06744	372	Q7Z442
291	B4E367	332	P08069	373	Q7Z4C2
292	B7Z1P9	333	P12956	374	Q7Z534
293	B7Z671	334	P22102	375	Q7Z5C1
294	C9JDR5	335	P29401	376	Q7Z6C1
295	C9JVG0	336	P30153	377	Q86T01
296	D3DTQ7	337	P32119	378	Q86T64
297	D3DXG8	338	P42785	379	Q86VU1
298	D4PHA4	339	P50747	380	Q86X45
299	E3W983	340	P53396	381	Q86XV5
300	E5G743	341	P62314	382	Q86YS3
301	E5RG96	342	Q06323	383	Q8IVC0
302	E5RGT3	343	Q06AH7	384	Q8IVV2
303	E7EVQ3	344	Q08629	385	Q8IWJ2
304	E9JVC4	345	Q13393	386	Q8IXV0
305	E9PH60	346	Q13616	387	Q8IYT4
306	E9PK12	347	Q14563	388	Q8IZ41
307	F5GXY0	348	Q15828	389	Q8IZC6
308	F5GY37	349	Q1KLZ0	390	Q8N303
309	F5H2D1	350	Q29RF7	391	Q8N3N3
310	F5H8J8	351	Q2I0A9	392	Q8N3T6
311	F8UU18	352	Q32Q12	393	Q8N696
312	F8VWL0	353	Q495G0	394	Q8N8W4
313	F8W7F7	354	Q53R19	395	Q8NAD5
314	G3V5M4	355	Q59EI5	396	Q8NBX0
315	H0Y3H6	356	Q59ET3	397	Q8NFN8
316	H0Y6A5	357	Q59GA8	398	Q8NG11
317	H0YBF7	358	Q5SYQ9	399	Q8TA92

400	Q8TAK2	423	Q99436	446	Q9UCS3
401	Q8TCE1	424	Q99598	447	Q9UE54
402	Q8TDJ6	425	Q99707	448	Q9UF55
403	Q8TDW7	426	Q99832	449	Q9UGA0
404	Q8TEU7	427	Q9BT36	450	Q9UHV7
405	Q8WUM4	428	Q9BT78	451	Q9UIW2
406	Q8WVV7	429	Q9BTY9	452	Q9UKP4
407	Q8WVW5	430	Q9BWV3	453	Q9UKU9
408	Q8WY27	431	Q9BX63	454	Q9ULC4
409	Q92484	432	Q9BXS5	455	Q9ULJ3
410	Q92820	433	Q9BXT5	456	Q9UNA2
411	Q92863	434	Q9C0C2	457	Q9UNM6
412	Q92905	435	Q9H0G2	458	Q9UPV8
413	Q92973	436	Q9H1W6	459	Q9Y266
414	Q96AA1	437	Q9H3E1	460	S4R3N1
415	Q96HI4	438	Q9H3Q7	461	S4R3S7
416	Q96I12	439	Q9HC03	462	S4R400
417	Q96KR9	440	Q9NR71	463	T1S9D5
418	Q96LC1	441	Q9NU86	464	V9HWF8
419	Q96P44	442	Q9NWN9	465	W4VSQ3
420	Q96RY7	443	Q9NYC9	466	W8SJH0
421	Q96SM3	444	Q9P0S0	467	X6R6S3
422	Q96ST3	445	Q9UCB0		

Table 6. Proteins in NPEX and APEX					
1	A0A024R3G7	17	B4DXB2	33	E9PFH7
2	A0A024R8E2	18	B7Z7R2	34	E9PKG1
3	A0A087WTU9	19	B7Z8P5	35	G1UI17
4	A0A087X191	20	B3KSE9	36	H0Y871
5	A0A0A0MSS2	21	B4DIA1	37	H0YME5
6	A0A0A0MTL9	22	B4DMS3	38	H3BMM5
7	A0A0A6YYJ5	23	B4E2P9	39	H9KV48
8	A0A0J9YY72	24	B4E3I5	40	J3QS51
9	A4FTX9	25	B7Z380	41	K7EIJ8
10	A5D906	26	B7Z403	42	K7ELF8
11	A5HML1	27	B7Z625	43	K7ELK0
12	B4DDH4	28	B7Z8W6	44	A0A140CTX8
13	B4DDI8	29	B7ZLP5	45	A8K3Y5
14	B4DFH6	30	C9J2C0	46	B4DFM5
15	B4DJQ7	31	C9JER5	47	B4DGH0
16	B4DV85	32	E7EUT5	48	B4DWX3

49	B4DXM1	90	H3BT58	131	A6NHN2
50	B7Z780	91	A0A024RAM0	132	A8K291
51	C9JMY1	92	A0A0G2JS52	133	B2R4S5
52	A0A024R9W5	93	A0A0U1ZI18	134	B4DDN3
53	A0A068F7M9	94	A8K972	135	B4DDS9
54	A0A0A0MQZ2	95	A8K9U4	136	B4DFK1
55	A0A0K0Q2Z1	96	A8KA50	137	B4DM68
56	A8K719	97	B2R6U8	138	B4DNJ2
57	A8KAC4	98	B3KMK2	139	B4DRC6
58	B2R6V9	99	B4DV51	140	B4DZV8
59	B3KW36	100	B4DVV1	141	B4DZW2
60	B4DEN5	101	B4DYQ4	142	B5A928
61	B4DJX6	102	B4DZP8	143	D3DWL9
62	B4DMD5	103	B5BUC0	144	E5RFX4
63	B4DMN1	104	B7Z1E1	145	E7ENU7
64	B4DPD5	105	B7Z7U9	146	F8WBE0
65	B4DUJ5	106	A0A024RA21	147	H0YCC0
66	B4DZR3	107	A0A087X201	148	H7BYM0
67	B7ZLC9	108	A2MYD1	149	I3NI20
68	B7ZLX9	109	A8K6R5	150	J3KP74
69	F5H6J0	110	A8K9I9	151	J3KRC3
70	F8VV04	111	B2R7E8	152	O60391
71	H0YEZ5	112	B3KXS5	153	O60486
72	H7C1I7	113	B4DIX9	154	O60760
73	J3KS22	114	C5J0G2	155	O75322
74	K7ESP4	115	C9J5X1	156	O76061
75	A0A126GW47	116	E9PGN7	157	P02549
76	B3KVV6	117	F5H7S7	158	P11216
77	B4DEQ2	118	H7BY57	159	P20908
78	B4DL70	119	I3L2J8	160	P27105
79	B4E3H4	120	J3KR44	161	P42694
80	B9EK46	121	A0A140VK43	162	P42702
81	C9JJE5	122	A8K2P6	163	P48426
82	C9K0S6	123	B7Z6W9	164	P54578
83	A8K7H3	124	A0A087WXD4	165	P59998
84	A9UEZ6	125	B3KT18	166	P60660
85	B3KNM0	126	A0A024R333	167	P61812
86	D4YW74	127	A0A024R637	168	Q01995
87	F8W888	128	A0A059U7G5	169	Q0VAP0
88	G3V200	129	A0A0C4DGM5	170	Q14571
89	G3V3A7	130	A0A0S2Z4F3	171	Q15181

172	Q15670	213	Q12771	254	B3KM58
173	Q1WWK5	214	Q2QD09	255	B3KXP1
174	Q1WWK6	215	Q2VPJ6	256	B4DFC4
175	Q4LE40	216	Q59HC8	257	B4DS57
176	Q53EU0	217	Q5R210	258	B4DVN5
177	Q53GP3	218	Q5VZB5	259	B7Z670
178	Q53HI6	219	Q68D26	260	J3QSF4
179	Q562U0	220	A0A024R566	261	O43242
180	Q580X3	221	A0A024R899	262	O75554
181	Q59EA4	222	A0A087WTK0	263	P02771
182	Q59ES1	223	A0A087WWY8	264	P07476
183	Q59EY7	224	A0A0K0K1L8	265	P13521
184	Q59G44	225	A0A0U1RRM0	266	P52951
185	Q59G78	226	A0JLR0	267	Q53FB6
186	Q59GJ6	227	A4F4K4	268	Q53G25
187	Q5GIA7	228	A4FVC3	269	Q53GZ5
188	Q5H9N4	229	A6NLU0	270	Q53H60
189	Q5T765	230	A8K1G1	271	Q53HR1
190	Q5TDF0	231	B4DEX9	272	Q53SW3
191	Q5VT06	232	B4DF07	273	Q59FX3
192	Q5W0B7	233	B4DHL2	274	Q59GW6
193	Q5XJ04	234	B4DJ31	275	Q59H85
194	Q6IN74	235	B4DRK5	276	Q5GJ68
195	Q6NSB2	236	B7Z6W5	277	Q5U0Q1
196	F8W9Z1	237	B7ZAG8	278	Q5VWT9
197	H0YHD9	238	C9JCJ5	279	Q68DF0
198	F6TR53	239	C9JQU8	280	Q6ICB4
199	H0Y796	240	E5RIA9	281	A0A0S2Z455
200	A7E2C0	241	E9PI86	282	B4DHJ3
201	B0I1R1	242	F5H5K0	283	B4E354
202	A0A0G2JNC5	243	F8W1A4	284	B5BTY4
203	B3KNW3	244	H0Y831	285	O75952
204	B4DGV1	245	H0YF06	286	A0A024R5W0
205	D6RJD3	246	H0YLN7	287	A8K607
206	E9PMI5	247	H3BRP2	288	B3KTA8
207	H0YD65	248	H7BYJ9	289	Q16798
208	O43491	249	J3KR05	290	B7Z7A4
209	O95782	250	J3KTP9	291	G3V504
210	P16035	251	K7EJ78	292	H0YCA1
211	P19320	252	A6MW40	293	B3KS69
212	Q05D08	253	A6NIW5	294	F8W062

295	A0A024QZ45	336	P29317	377	Q96DF0
296	A0A0A0MTE8	337	B4DHN0	378	Q96M29
297	A0A0A1TTP8	338	A0A024QZL4	379	Q9BZ26
298	A4FU65	339	A0A024R235	380	Q9H197
299	A8K8J2	340	A0A024R8H6	381	Q9H3W5
300	A8K9A5	341	A0A087WZX0	382	Q9H4B7
301	B3KQQ7	342	A0A0G2JNJ8	383	Q9H5H4
302	B4DI59	343	B4DFL3	384	Q9H7K8
303	B4DNH7	344	B4DVM7	385	Q9H853
304	B4DVM1	345	I6L9I5	386	Q9NQY1
305	B4E2K5	346	P84243	387	Q9NS29
306	B4E3M8	347	Q0EFC9	388	Q9P019
307	B7Z6H0	348	Q13787	389	Q9P2Y4
308	B8XXQ3	349	Q15102	390	Q9UBV4
309	D6RBD3	350	Q6PK50	391	Q9UEH4
310	D6W632	351	Q6PKT5	392	Q9UHV4
311	E5RI06	352	Q6UVJ0	393	Q9UKN7
312	E7EPB6	353	Q6ZP82	394	Q9UKV8
313	E7ERH2	354	Q7Z3P6	395	Q9UKX3
314	E7ERU0	355	Q7Z5Q5	396	Q9UNP4
315	E7ETU9	356	Q7Z5V0	397	Q9UQH3
316	E9PMI6	357	Q7Z5V6	398	Q9UQM3
317	F5GX94	358	Q86UF4	399	Q9Y2D4
318	F5GYF1	359	Q86Y65	400	Q9Y2I4
319	F8VRQ0	360	Q8IY52	401	Q9Y2J7
320	F8VRZ4	361	Q8IYA8	402	Q9Y5T6
321	G3V2J8	362	Q8IZ02	403	Q9Y617
322	G3V595	363	Q8N754	404	S4R2Z6
323	H0YAN8	364	Q8N948	405	S4R3K3
324	H0YCE8	365	Q8N959	406	S4R457
325	H0YJK0	366	Q8N995	407	V5N4G2
326	M0QXS6	367	Q8NEZ3	408	V9HW13
327	P08697	368	Q8NHP6	409	V9HW39
328	P61604	369	Q8NI77	410	V9HW77
329	Q13415	370	Q8TA90	411	V9HWD6
330	Q1L857	371	Q8TCL2	412	X5D2V8
331	Q4FEB4	372	Q8TE54	413	Q7Z407
332	Q53FV3	373	Q8WU08	414	Q86UP2
333	Q53G79	374	Q8WXI3	415	Q8N3Y0
334	Q5SPU2	375	Q8WY81	416	Q8TB46
335	Q6IS14	376	Q96AP5	417	Q8TBN9

418	Q92736	421	Q9H281	424	Q9UML6
419	Q96QD5	422	Q9HCU0	425	X5D9D6
420	Q99698	423	Q9UC36	426	X6R3L3

Table 7. Proteins unique to MSCEX					
1	A0A024QYT5	37	A0A0A0MTE1	73	A8MYV6
2	A0A024QZN8	38	A0A0A1TE42	74	A9YTQ3
3	A0A024R059	39	A0A0A6YY96	75	B0QYK4
4	A0A024R1C3	40	A0A0B4J1S7	76	B1AHR3
5	A0A024R241	41	A0A0C4DFX6	77	B1AJW0
6	A0A024R2M8	42	A0A0C4ZN31	78	B1AUU8
7	A0A024R407	43	A0A0G2JMD2	79	B2R6H3
8	A0A024R4B7	44	A0A0G2JNH7	80	B2R6X6
9	A0A024R4W0	45	A0A0G2JNU3	81	B2R6Y1
10	A0A024R5D9	46	A0A0G2JQU7	82	B2R702
11	A0A024R5G9	47	A0A0J9YY34	83	B2R928
12	A0A024R5Z8	48	A0A0K0KS85	84	B2R969
13	A0A024R6C0	49	A0A0S2Z3G9	85	B2RB72
14	A0A024R6F8	50	A0A0S2Z645	86	B2RC85
15	A0A024R6I1	51	A0A0U1RQC7	87	B2RE36
16	A0A024R6L8	52	A0A0U1RRH9	88	B2RWN6
17	A0A024R6X4	53	A0A140F1N4	89	B3KQ04
18	A0A024R8B3	54	A0A140T9S2	90	B3KR61
19	A0A024R8V7	55	A0A140VK13	91	B3KRU1
20	A0A024R930	56	A0AVL2	92	B3KS75
21	A0A024R9X6	57	A0PJ76	93	B3KSD8
22	A0A024RB85	58	A0PJM7	94	B3KTT6
23	A0A024RCP3	59	A1KZ92	95	B3KU51
24	A0A068B0Y9	60	A1L3V6	96	B3KUR8
25	A0A068BI38	61	A2I2N5	97	B3KV69
26	A0A087WSZ1	62	A2RRC9	98	B3KW35
27	A0A087WTU7	63	A2VDK1	99	B3KW47
28	A0A087WW54	64	A6NFQ2	100	B3KXX8
29	A0A087WXB0	65	A6NFU0	101	B4DDE5
30	A0A087WY10	66	A7MAY2	102	B4DE87
31	A0A087WZV0	67	A8K0Z6	103	B4DER4
32	A0A087X0V8	68	A8K2M5	104	B4DEV8
33	A0A088QF11	69	A8K454	105	B4DFA5
34	A0A0A0MRF6	70	A8K5X8	106	B4DFX9
35	A0A0A0MRS7	71	A8K6R9	107	B4DHR9
36	A0A0A0MRZ9	72	A8K9U6	108	B4DIA7

109	B4DIH7	150	B8ZZH7	191	F5H4B6
110	B4DNL5	151	C4B4C6	192	F6TLX2
111	B4DNW7	152	C9J4M6	193	F8VU88
112	B4DPQ0	153	C9J613	194	F8VXG7
113	B4DQI9	154	C9JGT3	195	F8VXL3
114	B4DQQ0	155	C9JGV6	196	F8VY04
115	B4DR29	156	C9JLB7	197	F8W0U9
116	B4DSP1	157	C9JQI2	198	F8W9U4
117	B4DST5	158	C9JSI2	199	F8W9W0
118	B4DTZ9	159	C9JT28	200	F8WCF6
119	B4DU14	160	C9JYI9	201	G1UI33
120	B4DWE2	161	D2KTB5	202	G5E971
121	B4DWG5	162	D2XBF0	203	G5ELZ6
122	B4DWQ4	163	D3DV75	204	H0Y468
123	B4DXC4	164	D3DVD8	205	H0Y5R6
124	B4DYB8	165	D6R9U7	206	H0Y6I0
125	B4DYX7	166	D6RA00	207	H0Y8G5
126	B4DZK1	167	D6RF53	208	H0YAN3
127	B4DZP2	168	D6RGY2	209	H0YBI2
128	B4E0I8	169	D6W633	210	H0YC83
129	B4E164	170	E3W994	211	H0YCJ2
130	B4E1Z4	171	E5KMI6	212	H0YEL4
131	B4E295	172	E5KR05	213	H0YH65
132	B4E3R6	173	E5KRK5	214	H0YL91
133	B4E3S9	174	E5KTI5	215	H0YM70
134	B5MCN7	175	E5RGN8	216	H3BP20
135	B7Z2D6	176	E5RHI0	217	H3BSC0
136	B7Z2E6	177	E7ENN3	218	H3BSE1
137	B7Z3I0	178	E7EUY3	219	H3BSM2
138	B7Z3K9	179	E7EWC2	220	H3BTW3
139	B7Z427	180	E7EX20	221	H3BV41
140	B7Z4H0	181	E9PKT1	222	H7BYJ1
141	B7Z549	182	E9PQI5	223	H7BYX7
142	B7Z5X3	183	E9PR16	224	H7C074
143	B7Z8B9	184	F2Z2C8	225	H7C1W8
144	B7Z9H7	185	F2Z2K5	226	I3L3E8
145	B7Z9J0	186	F5GX59	227	I3L3P7
146	B7ZAB8	187	F5GYJ8	228	J3KN38
147	B7ZAL5	188	F5H065	229	J3KNC6
148	B7ZL25	189	F5H226	230	J3KPK1
149	B7ZMF3	190	F5H432	231	J3KQ09

232	J3KTB8	273	O95165	314	P61978
233	J3QL70	274	O95177	315	P62701
234	K0I859	275	O95361	316	P63208
235	K7EIS7	276	P00450	317	P68104
236	K7EKQ3	277	P00488	318	P78477
237	K7EL65	278	P00519	319	Q10570
238	K7ELC2	279	P02538	320	Q10713
239	K7ELW0	280	P02786	321	Q12770
240	K7EMJ5	281	P04054	322	Q12905
241	K7EMR1	282	P04075	323	Q12913
242	K7EPJ9	283	P04818	324	Q13241
243	K7ESE0	284	P05091	325	Q13315
244	L0R6V3	285	P05231	326	Q13765
245	L8E853	286	P05937	327	Q13885
246	M0R1K3	287	P06493	328	Q14019
247	M0R361	288	P09622	329	Q14112
248	O00469	289	P09960	330	Q14584
249	O00562	290	P0DMV8	331	Q14678
250	O00592	291	P10398	332	Q14691
251	O14530	292	P13667	333	Q14980
252	O14879	293	P13807	334	Q149N5
253	O15013	294	P15311	335	Q14CN4
254	O15042	295	P18065	336	Q15274
255	O15131	296	P22670	337	Q15431
256	O43505	297	P23109	338	Q15751
257	O43820	298	P28065	339	Q15878
258	O60245	299	P28482	340	Q1L838
259	O60266	300	P29074	341	Q1RMC9
260	O60294	301	P30532	342	Q1W6H9
261	O60296	302	P31327	343	Q20BJ8
262	O60343	303	P34932	344	Q2I096
263	O60522	304	P35916	345	Q2TA76
264	O60543	305	P40189	346	Q38SD2
265	O60603	306	P42898	347	Q3KP44
266	O75161	307	P46782	348	Q3KRB0
267	O75339	308	P47755	349	Q3ZCN5
268	O75390	309	P48058	350	Q3ZCT4
269	O75578	310	P48643	351	Q495V9
270	O94844	311	P49863	352	Q4G0L2
271	O94854	312	P50748	353	Q4G192
272	O94925	313	P51828	354	Q4QRK8

355	Q4VNC1	396	Q6P4R9	437	Q8WYG9
356	Q4W5F5	397	Q6P6D5	438	Q8WYJ0
357	Q53GQ2	398	Q6PD62	439	Q92530
358	Q53HH4	399	Q6UWZ7	440	Q92539
359	Q53QE9	400	Q6UXN9	441	Q92823
360	Q53Y51	401	Q70IA8	442	Q969U7
361	Q58P21	402	Q71U36	443	Q96A69
362	Q59E87	403	Q75MN6	444	Q96B09
363	Q59G22	404	Q7L6B3	445	Q96B65
364	Q59G34	405	Q7Z3Z1	446	Q96CU9
365	Q59GT7	406	Q7Z4W1	447	Q96CZ8
366	Q59GW5	407	Q7Z6M0	448	Q96F45
367	Q59GX6	408	Q86T35	449	Q96FJ0
368	Q59HG1	409	Q86U18	450	Q96GE4
369	Q5CCK6	410	Q86UU0	451	Q96HY6
370	Q5EBN2	411	Q86UW9	452	Q96JB2
371	Q5F0I5	412	Q86V60	453	Q96JM4
372	Q5I0G3	413	Q86XL3	454	Q96MM8
373	Q5J9B1	414	Q86YL5	455	Q96N57
374	Q5NV87	415	Q8IVH2	456	Q96PX1
375	Q5STU8	416	Q8IWP9	457	Q96QF4
376	Q5SVJ3	417	Q8IYA6	458	Q96QI5
377	Q5T764	418	Q8N304	459	Q96S69
378	Q5TEJ7	419	Q8N3P5	460	Q99539
379	Q5U608	420	Q8N4P6	461	Q99574
380	Q5VU34	421	Q8N5U0	462	Q9BPU6
381	Q5VUJ6	422	Q8N7F5	463	Q9BQN1
382	Q5VYI1	423	Q8NBB8	464	Q9BQS2
383	Q5VYS4	424	Q8NE35	465	Q9BS61
384	Q5VZ00	425	Q8NES3	466	Q9BSD7
385	Q5VZB4	426	Q8NFP9	467	Q9BW71
386	Q5VZL5	427	Q8NFQ8	468	Q9BWD1
387	Q68CZ1	428	Q8NGS8	469	Q9BWT3
388	Q68DA4	429	Q8TAA3	470	Q9BXB5
389	Q68DB7	430	Q8TC08	471	Q9BXT8
390	Q6EKJ0	431	Q8TEQ6	472	Q9BYF1
391	Q6FI27	432	Q8WVC6	473	Q9C091
392	Q6NT96	433	Q8WVJ9	474	Q9H0Q0
393	Q6P0N9	434	Q8WWJ6	475	Q9H2E5
394	Q6P1K8	435	Q8WWL7	476	Q9H2I8
395	Q6P2S1	436	Q8WXI9	477	Q9H2Z3

478	Q9H7U7	498	Q9P2N1	518	Q9Y613
479	Q9H7W5	499	Q9UBG9	519	Q9Y696
480	Q9H8N6	500	Q9UBL0	520	Q9Y6K1
481	Q9H8Q1	501	Q9UC78	521	Q9Y6S7
482	Q9HA17	502	Q9UEH6	522	Q9Y6U9
483	Q9HAR0	503	Q9UF08	523	R4GMT0
484	Q9HD74	504	Q9UFA7	524	S4R2X0
485	Q9NP17	505	Q9UIA9	525	S4R314
486	Q9NPU7	506	Q9UJD0	526	S4R3C8
487	Q9NR45	507	Q9UJT0	527	U3KQK0
488	Q9NRD1	508	Q9UL70	528	U5YBI9
489	Q9NT26	509	Q9ULJ7	529	V9GY77
490	Q9NTG1	510	Q9ULW6	530	V9GYE3
491	Q9NW02	511	Q9UME3	531	V9HW26
492	Q9NX58	512	Q9UNM1	532	V9HWC4
493	Q9NX91	513	Q9UNS1	533	V9HWH0
494	Q9NZF5	514	Q9UPN4	534	X5D7Q2
495	Q9P283	515	Q9UPV0	535	X5D9D2
496	Q9P291	516	Q9Y216	536	X6RL08
497	Q9P2M7	517	Q9Y4L1		

Table 8. Proteins unique to APEX					
1	A0A087WXN9	20	A0A024RCS3	39	A0A0U1WUY1
2	A0A0A0MTD1	21	A0A0G2JPN1	40	A1L196
3	A0A0C4DFS8	22	A0A140VJP0	41	A9CQZ2
4	A0A0J9YX41	23	B3KR94	42	B3KX52
5	A0A140VJI6	24	B3KSB6	43	A0A087X0D8
6	A2VED2	25	B4DET1	44	B2RCJ5
7	B0YJ74	26	B4DG15	45	B4DN90
8	A0A0B4J1X7	27	B4DJI2	46	B4DNZ9
9	A0A5A9	28	B7Z919	47	B4DZG1
10	A8K1P5	29	C9J3L8	48	B7Z6I1
11	B3KMN2	30	A0A087X298	49	C9J1D9
12	B5A934	31	B4DG65	50	C9J1K7
13	B7Z9C0	32	A0A0C4DH13	51	A0AV47
14	A0A087X1U1	33	B4DSP4	52	B3KNC3
15	A8K0G7	34	B4DSR4	53	A0A024R120
16	B7ZLC4	35	C9J826	54	A0A087WUL9
17	A0A140VKF7	36	A0A024RBC0	55	B3KMX4
18	B4DY95	37	A0A087X120	56	B3KNL6
19	A0A024R1K7	38	A0A0C4DGC5	57	B3KPZ7

58	B3KWB6	99	B2RA91	140	B4DNX8
59	B3KWC4	100	B3KNB4	141	B4DQY2
60	D1CS35	101	B4DMA2	142	B4DR52
61	D2CPK5	102	B4DTA5	143	B4DR67
62	D3DUJ0	103	B4DUF8	144	B4DTA9
63	D6REL5	104	A0A0C4DGH5	145	B4E058
64	E5RHP0	105	A6NEP9	146	B7ZAW7
65	E9PCP0	106	A8K0K0	147	B7ZLB7
66	E9PJL7	107	B3KMS6	148	E9PNS9
67	E9PNX2	108	B3KY88	149	H7BXG6
68	F5H0Y9	109	B7Z4X0	150	H7C520
69	F6QTA4	110	E7ETB4	151	I3L466
70	F8W026	111	E9PGC0	152	A0A0A0MRM2
71	G3V5R6	112	F5H0M4	153	A4FU77
72	G5E9J0	113	F5H5D3	154	A0A024QZ75
73	H0Y757	114	H0Y463	155	A0A024R674
74	H0Y9N5	115	H7C080	156	A0A0A0MRH0
75	H0YDE4	116	I3L0G6	157	A8K4M1
76	H0YGV8	117	I3L1K1	158	B3KTQ2
77	H3BTQ9	118	K7EJX8	159	B4DJ21
78	H7BZZ8	119	K7EK57	160	B4DMJ5
79	H7C0D9	120	A0A024R283	161	B4DV55
80	J3KPD9	121	A0A0C4DGB8	162	D3DSV6
81	J3KTL9	122	A0A140VK27	163	D6R9D5
82	K7EL58	123	B4DY04	164	E9PP50
83	K7EMM9	124	B7ZM05	165	H0Y2M6
84	K7EQR9	125	K7ENN8	166	H0YCV9
85	A2RRR7	126	B2R8P5	167	H0YJ91
86	B4DFQ9	127	H0Y873	168	H7C5H1
87	B4DWW6	128	A0A024R542	169	J3QRV6
88	A8MT18	129	A0A024R7E1	170	L8E9P0
89	A0A024R461	130	A0A0M4FNU3	171	M0R120
90	B4DZ23	131	B4DUC5	172	O00512
91	B7ZMJ6	132	B4DZ03	173	O00763
92	E5RJD0	133	A0A024R957	174	O14524
93	I7HAS0	134	A0A0A0MRY9	175	O15078
94	A0A075B6I0	135	A0A140VK76	176	O15090
95	A0A087WU14	136	B0YJ32	177	O15244
96	A0A0U1ZBR1	137	B3KPK8	178	O43570
97	A0A140TA43	138	B4DEY4	179	O60291
98	A0A140VK41	139	B4DMJ7	180	O75094

181	O75600	222	Q5TEU4	263	I0CMK4
182	P00352	223	Q68DP4	264	K7ENA0
183	P02749	224	Q69YH5	265	B3KNV9
184	P05546	225	Q6FHK0	266	B4DUK7
185	P08910	226	Q6FHK9	267	K7EPF6
186	P10916	227	Q6FHU3	268	A0A024QZF7
187	P17927	228	Q6FI03	269	A0A024R5V2
188	P27169	229	Q6IFE0	270	M0QY71
189	P29400	230	Q6JH03	271	O75843
190	P35499	231	Q6NUI8	272	O95905
191	P35749	232	O15123	273	O96011
192	P39023	233	O43301	274	P07585
193	P40939	234	O43424	275	Q0VD99
194	P46059	235	O95239	276	Q15374
195	P50225	236	P02533	277	Q5VX85
196	P54756	237	P55283	278	Q6IC98
197	P61964	238	Q15142	279	P30405
198	P84085	239	Q1HP67	280	Q5VIR6
199	Q003V9	240	Q562N6	281	A0A0C4DFQ8
200	Q01831	241	Q5H9B5	282	B1AMW3
201	Q0VAI6	242	Q5HY54	283	A0A087WUF5
202	Q12873	243	Q5HYL7	284	A0A024R6K8
203	Q12980	244	Q5VUA0	285	B2R9P0
204	Q13349	245	Q6IAX6	286	A0A087WSV7
205	Q14145	246	Q6P1L4	287	A0A0K0KR34
206	Q14469	247	Q6P5Q4	288	A6NFY4
207	Q15238	248	B3KXC1	289	A0A024RD47
208	Q15697	249	B3KP29	290	B2RTX2
209	Q15762	250	B7Z7C2	291	E9PFF2
210	Q16820	251	A0A024RDT3	292	F2Z2G2
211	Q2TSD0	252	A8K990	293	F5GWA7
212	Q32Q67	253	E5RGT9	294	F5GXC7
213	Q3SY52	254	E9PMW9	295	F5GYF8
214	Q53G92	255	G3V174	296	F5H3Q5
215	Q53GF5	256	H7BXS7	297	H9C875
216	Q53HR5	257	H7C402	298	B7Z2E2
217	Q53SE2	258	H9A532	299	J3KQ72
218	Q58DX5	259	H3BP35	300	A0A024R909
219	Q59EF3	260	A0A024RDR3	301	F5GXR6
220	Q59HA9	261	B4DEW9	302	J3KS93
221	Q5GJ67	262	C9J3M5	303	A0A126GVW7

304	B4E266	345	F5H032	386	D6RHE5
305	A0A024R2H7	346	G3V454	387	O14777
306	A0A097CK88	347	H0YF19	388	Q6IBD2
307	A0A140T999	348	H0YGH1	389	A0A024R684
308	A8K8H7	349	H3BRL9	390	A8K5F3
309	B4DND2	350	K0A7K7	391	B3KU50
310	B4DQM1	351	A0A0G2JN61	392	B4DUZ8
311	B4DZ35	352	A0A0M4FEM1	393	K7EQ48
312	E7ERI8	353	A0A0U1RQL8	394	O75665
313	F5GZQ4	354	A8K6X5	395	Q59EK9
314	F8WFC4	355	B3KW51	396	A0A024R7D2
315	H0Y9E9	356	B4DQG4	397	A3KFK1
316	H7C1T2	357	B4DW50	398	G3V0E6
317	K7EPY4	358	B4DZY4	399	A0A024QYZ8
318	M0R2D3	359	B4E1S5	400	A0A024RAM1
319	O76074	360	B4E1T9	401	A0A087WWI0
320	P15085	361	B4E3A4	402	A0A0A0MQR2
321	Q3YA63	362	B7Z1Y2	403	A4D0S8
322	Q5MNZ6	363	C9JUE0	404	A4FU51
323	Q6IPX8	364	D6RDI0	405	A4QMW8
324	A0A087X2E5	365	F8VUX9	406	A8K4Q4
325	A0A0A0MQR7	366	J9UPX7	407	C9JVG3
326	A0A0C4DGY8	367	K7ENE1	408	D6RC52
327	A0A0D9SF28	368	P13637	409	E7ENJ7
328	A0A0S2Z333	369	P28827	410	E9PHK0
329	A0A0S2Z366	370	P31150	411	E9PQV8
330	A4D202	371	P31946	412	F5GZI5
331	A8K731	372	Q12769	413	F5GZK2
332	B3KX01	373	Q13841	414	F5H2D0
333	B3KX41	374	Q20BG7	415	F5H6I7
334	B4DEM5	375	Q2F838	416	F6U236
335	B4DK22	376	Q58FF6	417	F8WAS2
336	B4E337	377	Q658X2	418	F8WAX8
337	B7Z4N1	378	Q659A9	419	F8WCJ1
338	C9J8U1	379	Q6FGX9	420	H3BTW5
339	D6R9E4	380	A0A024R3D4	421	H3BUA3
340	E7EP61	381	A0A024RAM6	422	K7EJH1
341	E7EWZ1	382	A0A0G2JP38	423	M5EDK8
342	E9KL23	383	A0A140VJV9	424	O00160
343	E9PJK2	384	A0A140VKF6	425	O15054
344	F5GXY2	385	B4DLH5	426	P48444

427	Q14258	468	Q7Z668	509	Q99973
428	Q14434	469	Q7Z7H5	510	Q99989
429	Q14690	470	Q7Z7P9	511	Q9BT21
430	Q549N0	471	Q86SG7	512	Q9BT27
431	Q6FH62	472	Q86TE2	513	Q9BVJ8
432	A0A024RB92	473	Q86TI0	514	Q9BWT2
433	A0A087WW76	474	Q86UE3	515	Q9BZF9
434	B4DI80	475	Q86X82	516	Q9C0A1
435	B4DTQ1	476	Q86XM6	517	Q9H295
436	B4E0B2	477	Q86XQ3	518	Q9H2M9
437	D6RE83	478	Q86YC4	519	Q9H4N8
438	D9HTE9	479	Q8IUN7	520	Q9H6A9
439	E9PMM8	480	Q8IUQ0	521	Q9H6L3
440	E9PNE6	481	Q8IV08	522	Q9H6Z9
441	F2Z393	482	Q8IWJ6	523	Q9H769
442	F5H0P4	483	Q8IXA4	524	Q9H995
443	H0Y476	484	Q8IYT1	525	Q9HBM3
444	H0YCK3	485	Q8N1M4	526	Q9NPL4
445	J3KRJ6	486	Q8N1Y9	527	Q9NS28
446	J3QS44	487	Q8N4M9	528	Q9NUJ7
447	O75077	488	Q8NC18	529	Q9NWV8
448	P06727	489	Q8NCS7	530	Q9NX81
449	P20062	490	Q8NGA0	531	Q9NX98
450	Q09472	491	Q8TBG4	532	Q9NXP1
451	Q14643	492	Q8TCC9	533	Q9NYK1
452	Q6PKD3	493	Q8WLP1	534	Q9NZ52
453	Q6QWC0	494	Q8WV67	535	Q9P0C1
454	Q6RBX8	495	Q8WVV4	536	Q9P0P1
455	Q6UW88	496	Q8WYB5	537	Q9P2H3
456	Q6UX71	497	Q92574	538	Q9UBK7
457	Q6ZMU5	498	Q92615	539	Q9UDV6
458	Q6ZP56	499	Q92932	540	Q9UDX4
459	Q6ZPD6	500	Q92990	541	Q9UFP2
460	Q6ZR36	501	Q969V5	542	Q9UFU2
461	Q6ZU35	502	Q96FW1	543	Q9UG36
462	Q6ZVM7	503	Q96G03	544	Q9UG64
463	Q709C8	504	Q96HX7	545	Q9UGU8
464	Q7M4R4	505	Q96KR4	546	Q9UH61
465	Q7Z2V5	506	Q96MY1	547	Q9UHC1
466	Q7Z606	507	Q99062	548	Q9UHC9
467	Q7Z612	508	Q99440	549	Q9ULH1

550	Q9UNX4	566	Q6ZP01	582	Q9BTS8
551	Q9UPS8	567	Q7Z5U6	583	Q9C0K3
552	Q9Y287	568	Q86TA0	584	Q9H583
553	Q9Y4G6	569	Q86VI3	585	Q9HBG7
554	S4R3L5	570	Q86WN1	586	Q9P2H0
555	T1WFC1	571	Q86YG0	587	Q9UF83
556	U3KPS2	572	Q8IWK6	588	Q9UHP3
557	U5YEI7	573	Q8IXR5	589	Q9UIT6
558	V9GYM3	574	Q8N111	590	Q9UJ65
559	V9HW42	575	Q8N976	591	Q9UN47
560	V9HWC2	576	Q8NG48	592	Q9UNY4
561	V9HWC3	577	Q8TCU4	593	U3KQU8
562	V9HWG1	578	Q8WYK0	594	X5D5A9
563	W6JLH6	579	Q99994	595	X5D7Z6
564	W8SBA0	580	Q9BRL4	596	X5DNR2
565	Q6ZNY8	581	Q9BS12		

Table 9. Proteins unique to NPEX					
1	A0A024DAK3	24	A0A024R7B6	47	A0A075B6S4
2	A0A024QYX2	25	A0A024R7L5	48	A0A075B734
3	A0A024QZJ1	26	A0A024R7T7	49	A0A087WSW7
4	A0A024QZM2	27	A0A024R884	50	A0A087WT58
5	A0A024QZW5	28	A0A024R8F4	51	A0A087WTH0
6	A0A024QZX5	29	A0A024R8I4	52	A0A087WTK9
7	A0A024R095	30	A0A024R936	53	A0A087WU78
8	A0A024R0A0	31	A0A024R944	54	A0A087WUK8
9	A0A024R233	32	A0A024RAF7	55	A0A087WUM0
10	A0A024R2G9	33	A0A024RAS2	56	A0A087WVI0
11	A0A024R2K1	34	A0A024RB01	57	A0A087WW59
12	A0A024R301	35	A0A024RBE5	58	A0A087WWE7
13	A0A024R4A0	36	A0A024RBT9	59	A0A087WXK5
14	A0A024R4D1	37	A0A024RCB7	60	A0A087WXM9
15	A0A024R4F1	38	A0A024RCE1	61	A0A087WXX8
16	A0A024R4Z0	39	A0A024RCI0	62	A0A087WYC6
17	A0A024R4Z5	40	A0A024RD04	63	A0A087WYK9
18	A0A024R5M9	41	A0A024RD09	64	A0A087WYW3
19	A0A024R5U3	42	A0A024RD36	65	A0A087WZ40
20	A0A024R5V6	43	A0A024RD77	66	A0A087WZC4
21	A0A024R5Y2	44	A0A024RDM3	67	A0A087WZR8
22	A0A024R6G3	45	A0A024RDV8	68	A0A087WZZ7
23	A0A024R701	46	A0A024RDW5	69	A0A087X052

70	A0A087X0D6	111	A0A0G2JI86	152	A0A140VJL3
71	A0A087X176	112	A0A0G2JM47	153	A0A140VJN8
72	A0A087X1Z6	113	A0A0G2JNH0	154	A0A140VJP5
73	A0A087X250	114	A0A0G2JP14	155	A0A140VJU3
74	A0A087X2B0	115	A0A0G2JP37	156	A0A140VK35
75	A0A090N8H8	116	A0A0G2JRM9	157	A0A141PNN4
76	A0A097IQZ3	117	A0A0G2JRN3	158	A0A146IHP0
77	A0A0A0MQS0	118	A0A0J9YVY3	159	A0A158T700
78	A0A0A0MRP0	119	A0A0J9YVZ3	160	A0JLR2
79	A0A0A0MRT2	120	A0A0J9YWL0	161	A0PJY9
80	A0A0A0MRV0	121	A0A0J9YWY2	162	A1A512
81	A0A0A0MRX4	122	A0A0K1JS24	163	A1L3A3
82	A0A0A0MS45	123	A0A0K2GMW5	164	A2A2M0
83	A0A0A0MS53	124	A0A0S2Z3P7	165	A2A368
84	A0A0A0MS59	125	A0A0S2Z451	166	A2ADX3
85	A0A0A0MS84	126	A0A0S2Z489	167	A2NX49
86	A0A0A0MSA7	127	A0A0S2Z4F1	168	A2PYH4
87	A0A0A0MSU4	128	A0A0S2Z4H6	169	A2RUH7
88	A0A0A0MT74	129	A0A0S2Z4I9	170	A2VCK2
89	A0A0A0MTC4	130	A0A0S2Z4R1	171	A4D126
90	A0A0A0MTD9	131	A0A0S2Z4Y4	172	A4D1B7
91	A0A0A0MTQ1	132	A0A0S2Z4Y6	173	A4D1P7
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106	A0A0D9SF54	147	A0A140T9Y3	188	A6NN40
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108	A0A0D9SG17	149	A0A140TA77	190	A6QRJ1
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195	A8E631	236	B2R7Z4	277	B3KSZ3
196	A8K0E1	237	B2R892	278	B3KTD8
197	A8K146	238	B2R9P8	279	B3KTM6
198	A8K1W3	239	B2R9S6	280	B3KTR4
199	A8K3A3	240	B2RA29	281	B3KU97
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204	A8K525	245	B2RCD2	286	B3KUU1
205	A8K594	246	B2RCG9	287	B3KV11
206	A8K5E6	247	B2RD40	288	B3KVH9
207	A8K5H7	248	B2RDD7	289	B3KVJ1
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212	A8K855	253	B3FR89	294	B3KW31
213	A8K8K1	254	B3KM41	295	B3KW52
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222	B1AKN6	263	B3KPA6	304	B4DE48
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224	B1ALU6	265	B3KPK9	306	B4DEI6
225	B1B5Q8	266	B3KPM6	307	B4DEX7
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227	B2R694	268	B3KQZ8	309	B4DFB6
228	B2R6V2	269	B3KR52	310	B4DFF1
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231	B2R736	272	B3KS20	313	B4DGF4
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320	B4DKC2	361	B4DZD2	402	B7ZAV2
321	B4DKX2	362	B4DZS8	403	B7ZB07
322	B4DL63	363	B4E0B7	404	B7ZB16
323	B4DLP0	364	B4E0E1	405	B7ZBD5
324	B4DM77	365	B4E0J9	406	B7ZBH1
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326	B4DND4	367	B4E143	408	B7ZLC8
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328	B4DP52	369	B4E282	410	B7ZMM1
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335	B4DS66	376	B5A954	417	C6ZGQ9
336	B4DSA0	377	B5BU72	418	C7S316
337	B4DSC7	378	B5MBY4	419	C9J0Q5
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442	D5KMU6	483	E9PB90	524	F5H6T1
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444	D6R936	485	E9PDF5	526	F6SS63
445	D6R938	486	E9PEW0	527	F8LFZ0
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447	D6R9E3	488	E9PG59	529	F8VS27
448	D6R9V7	489	E9PGK7	530	F8VXU5
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452	D6RD46	493	E9PL71	534	F8W1Y6
453	D6RD74	494	E9PLE2	535	F8W6X9
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473	E7ERS3	514	F5H081	555	H0Y2R3
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475	E7ET15	516	F5H1B0	557	H0Y5G0
476	E7ETR9	517	F5H248	558	H0Y626
477	E7EU35	518	F5H269	559	H0Y6T7
478	E7EUC7	519	F5H2B9	560	H0Y7U8
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1086	Q3LIF6	1127	Q59FI9	1168	Q5VYK3
1087	Q3SXZ7	1128	Q59FL3	1169	Q5VZK9
1088	Q3ZCM1	1129	Q59GL0	1170	Q5VZV1
1089	Q3ZLR7	1130	Q5BJE1	1171	Q63HP0
1090	Q3ZTS5	1131	Q5CZ70	1172	Q643R0
1091	Q461N2	1132	Q5CZA0	1173	Q658R0
1092	Q494Z1	1133	Q5CZC0	1174	Q659E8
1093	Q495C1	1134	Q5EBM7	1175	Q659F6
1094	Q495F8	1135	Q5HYB0	1176	Q659F8

1177	Q68D86	1218	Q6WCQ1	1259	Q7Z4L4
1178	Q68DA7	1219	Q6WRI0	1260	Q7Z4X1
1179	Q68DM7	1220	Q6XZE5	1261	Q7Z583
1180	Q68DN3	1221	Q6YNQ1	1262	Q7Z5L2
1181	Q68DS2	1222	Q6ZMW9	1263	Q7Z5M5
1182	Q68DS3	1223	Q6ZN06	1264	Q7Z5X8
1183	Q6AZY7	1224	Q6ZN13	1265	Q7Z679
1184	Q6FGL8	1225	Q6ZNK6	1266	Q7Z7G0
1185	Q6FI91	1226	Q6ZNS6	1267	Q85ZX8
1186	Q6IAT7	1227	Q6ZPB4	1268	Q86SG6
1187	Q6IAX5	1228	Q6ZR08	1269	Q86SJ2
1188	Q6IB29	1229	Q6ZR62	1270	Q86T20
1189	Q6IBR6	1230	Q6ZR81	1271	Q86TS1
1190	Q6ICD2	1231	Q6ZRR7	1272	Q86U45
1191	Q6IE37	1232	Q6ZRR9	1273	Q86U53
1192	Q6IPS9	1233	Q6ZS30	1274	Q86UB2
1193	Q6K0P9	1234	Q6ZSA3	1275	Q86UE9
1194	Q6MZF2	1235	Q6ZUX3	1276	Q86VS8
1195	Q6MZM3	1236	Q6ZVH7	1277	Q86W50
1196	Q6NSC9	1237	Q6ZVJ0	1278	Q86W67
1197	Q6NTE8	1238	Q6ZWD7	1279	Q86WT6
1198	Q6NV74	1239	Q70Q86	1280	Q86XA9
1199	Q6NX68	1240	Q76KX8	1281	Q86YW9
1200	Q6NZ83	1241	Q76M96	1282	Q8IU62
1201	Q6P0Q8	1242	Q76NI1	1283	Q8IUU5
1202	Q6P2D0	1243	Q7KZF4	1284	Q8IUX7
1203	Q6P3W7	1244	Q7L1I2	1285	Q8IVB1
1204	Q6P528	1245	Q7L2K0	1286	Q8IVL5
1205	Q6P5Z4	1246	Q7L5A8	1287	Q8IW47
1206	Q6PCE3	1247	Q7L5N1	1288	Q8IWB6
1207	Q6PEW0	1248	Q7LBC6	1289	Q8IWE2
1208	Q6PIK3	1249	Q7LBX6	1290	Q8IYT3
1209	Q6PIW4	1250	Q7LFX5	1291	Q8IZF3
1210	Q6PJ36	1251	Q7RTM4	1292	Q8IZG2
1211	Q6PKF2	1252	Q7RTU9	1293	Q8IZP2
1212	Q6Q4G3	1253	Q7RTV5	1294	Q8IZZ8
1213	Q6Q759	1254	Q7Z304	1295	Q8N137
1214	Q6UWP2	1255	Q7Z3G2	1296	Q8N248
1215	Q6UWW8	1256	Q7Z3L3	1297	Q8N2I2
1216	Q6UXE8	1257	Q7Z410	1298	Q8N2S1
1217	Q6UXH8	1258	Q7Z4H8	1299	Q8N412

1300	Q8N414	1341	Q8TF27	1382	Q96B70
1301	Q8N427	1342	Q8TF62	1383	Q96C11
1302	Q8N474	1343	Q8WUQ3	1384	Q96C57
1303	Q8N4E4	1344	Q8WUS6	1385	Q96CP2
1304	Q8N508	1345	Q8WV16	1386	Q96CW1
1305	Q8N6J3	1346	Q8WW02	1387	Q96DX8
1306	Q8N7D9	1347	Q8WWH5	1388	Q96EB6
1307	Q8N7X0	1348	Q8WWI5	1389	Q96ES0
1308	Q8N822	1349	Q8WWN8	1390	Q96HK3
1309	Q8N8F1	1350	Q8WWV3	1391	Q96I86
1310	Q8N961	1351	Q8WXA3	1392	Q96IC2
1311	Q8N9D1	1352	Q8WXG9	1393	Q96II9
1312	Q8NA02	1353	Q8WXJ2	1394	Q96J40
1313	Q8NA54	1354	Q8WY19	1395	Q96J66
1314	Q8NBJ4	1355	Q8WZ74	1396	Q96J72
1315	Q8NBS9	1356	Q8WZ99	1397	Q96JC1
1316	Q8NCC3	1357	Q8WZA0	1398	Q96JH7
1317	Q8NDD5	1358	Q92545	1399	Q96JM2
1318	Q8NDM7	1359	Q92598	1400	Q96JP2
1319	Q8NE71	1360	Q92614	1401	Q96L42
1320	Q8NEL0	1361	Q92621	1402	Q96M20
1321	Q8NEN0	1362	Q92667	1403	Q96M97
1322	Q8NEP9	1363	Q92673	1404	Q96MC4
1323	Q8NEZ5	1364	Q92777	1405	Q96MY7
1324	Q8NFF3	1365	Q92791	1406	Q96N32
1325	Q8NFW1	1366	Q92794	1407	Q96N83
1326	Q8NFZ4	1367	Q92878	1408	Q96NX8
1327	Q8NHX6	1368	Q92896	1409	Q96Q42
1328	Q8TB37	1369	Q92913	1410	Q96QB0
1329	Q8TB73	1370	Q93008	1411	Q96QF1
1330	Q8TBC4	1371	Q93009	1412	Q96RE7
1331	Q8TBW1	1372	Q969J2	1413	Q96RT7
1332	Q8TCE6	1373	Q969P5	1414	Q96RZ6
1333	Q8TCU5	1374	Q969X0	1415	Q96T23
1334	Q8TCY9	1375	Q96AB3	1416	Q96T70
1335	Q8TD47	1376	Q96AC1	1417	Q96TA1
1336	Q8TDD1	1377	Q96AG3	1418	Q96TC7
1337	Q8TDD2	1378	Q96AL5	1419	Q96TG0
1338	Q8TDR4	1379	Q96AW4	1420	Q99422
1339	Q8TEC9	1380	Q96AY3	1421	Q99471
1340	Q8TEF5	1381	Q96B45	1422	Q99497

1423	Q99525	1464	Q9H0P5	1505	Q9HCG1
1424	Q99608	1465	Q9H106	1506	Q9HCM1
1425	Q99613	1466	Q9H128	1507	Q9HCN6
1426	Q99623	1467	Q9H156	1508	Q9HD26
1427	Q99626	1468	Q9H173	1509	Q9NNZ5
1428	Q99712	1469	Q9H1J1	1510	Q9NPK3
1429	Q99767	1470	Q9H1J7	1511	Q9NPW9
1430	Q99868	1471	Q9H1Z3	1512	Q9NQW6
1431	Q99874	1472	Q9H1Z5	1513	Q9NR18
1432	Q9BR76	1473	Q9H299	1514	Q9NRA1
1433	Q9BRM9	1474	Q9H2J7	1515	Q9NRN5
1434	Q9BSH8	1475	Q9H2K3	1516	Q9NRY6
1435	Q9BSJ5	1476	Q9H2P8	1517	Q9NS13
1436	Q9BSK1	1477	Q9H3P9	1518	Q9NS15
1437	Q9BT66	1478	Q9H3S7	1519	Q9NS87
1438	Q9BTF5	1479	Q9H4A4	1520	Q9NSJ3
1439	Q9BTG3	1480	Q9H4D0	1521	Q9NTH6
1440	Q9BTN2	1481	Q9H4F8	1522	Q9NUY8
1441	Q9BTZ8	1482	Q9H4M9	1523	Q9NVA2
1442	Q9BU99	1483	Q9H515	1524	Q9NVE4
1443	Q9BUB5	1484	Q9H5L6	1525	Q9NVE5
1444	Q9BV90	1485	Q9H5R6	1526	Q9NVR2
1445	Q9BW52	1486	Q9H6D4	1527	Q9NWL6
1446	Q9BW58	1487	Q9H7D0	1528	Q9NXA5
1447	Q9BWZ5	1488	Q9H7H0	1529	Q9NXC3
1448	Q9BXF1	1489	Q9H7H5	1530	Q9NXZ1
1449	Q9BXF3	1490	Q9H7P3	1531	Q9NY33
1450	Q9BXL5	1491	Q9H8E8	1532	Q9NYM2
1451	Q9BYT8	1492	Q9H8G5	1533	Q9NYQ7
1452	Q9BZ74	1493	Q9H8H3	1534	Q9NZ08
1453	Q9BZE3	1494	Q9H8S9	1535	Q9NZN4
1454	Q9BZQ4	1495	Q9H8V8	1536	Q9NZP2
1455	Q9C040	1496	Q9H903	1537	Q9NZQ9
1456	Q9GZP4	1497	Q9H9Q2	1538	Q9NZU1
1457	Q9GZT8	1498	Q9HA51	1539	Q9NZV1
1458	Q9GZV3	1499	Q9HB40	1540	Q9P0K1
1459	Q9H0A0	1500	Q9HBH9	1541	Q9P1S5
1460	Q9H0B8	1501	Q9HC39	1542	Q9P1W9
1461	Q9H0E2	1502	Q9HC87	1543	Q9P246
1462	Q9H0H0	1503	Q9HCC0	1544	Q9P2L0
1463	Q9H0I3	1504	Q9HCF4	1545	Q9P2W4

1546	Q9P2X3	1583	Q9ULT8	1620	Q9Y4G2
1547	Q9TQL1	1584	Q9ULU8	1621	Q9Y4G8
1548	Q9UBC0	1585	Q9ULY4	1622	Q9Y4M4
1549	Q9UBF2	1586	Q9UM21	1623	Q9Y5E6
1550	Q9UBP4	1587	Q9UMG6	1624	Q9Y5S2
1551	Q9UBQ5	1588	Q9UMG7	1625	Q9Y5V3
1552	Q9UBU7	1589	Q9UMN6	1626	Q9Y5Z7
1553	Q9UC56	1590	Q9UMV8	1627	Q9Y687
1554	Q9UCV3	1591	Q9UN71	1628	Q9Y6B7
1555	Q9UDG3	1592	Q9UNN5	1629	Q9Y6D5
1556	Q9UDL5	1593	Q9UNP5	1630	Q9Y6N7
1557	Q9UEB7	1594	Q9UNS2	1631	Q9Y6V7
1558	Q9UF52	1595	Q9UP50	1632	R4GNE8
1559	Q9UF61	1596	Q9UPJ7	1633	R4GNI9
1560	Q9UFC6	1597	Q9UQP3	1634	S4R2Z0
1561	Q9UFT4	1598	Q9UQR1	1635	S4R354
1562	Q9UFW3	1599	Q9UQR9	1636	S4R3N6
1563	Q9UGJ1	1600	Q9Y224	1637	S4R3P9
1564	Q9UHY1	1601	Q9Y234	1638	T2FFJ4
1565	Q9UI42	1602	Q9Y240	1639	U3KQ69
1566	Q9UIF8	1603	Q9Y264	1640	U3KQL2
1567	Q9UIY4	1604	Q9Y2B0	1641	U5TP13
1568	Q9UJ70	1605	Q9Y2E5	1642	V9GYP9
1569	Q9UJ71	1606	Q9Y2G5	1643	V9HVU7
1570	Q9UJC6	1607	Q9Y2H8	1644	V9HW54
1571	Q9UJF2	1608	Q9Y2M5	1645	V9HWB9
1572	Q9UJJ2	1609	Q9Y2S0	1646	W8JD10
1573	Q9UJJ9	1610	Q9Y2T6	1647	X5D2S9
1574	Q9UJU4	1611	Q9Y2X7	1648	X5DNF2
1575	Q9UKA4	1612	Q9Y3I1	1649	X6R3I0
1576	Q9UKJ8	1613	Q9Y3R5	1650	X6R772
1577	Q9UL63	1614	Q9Y3X0	1651	X6R8W7
1578	Q9UL95	1615	Q9Y423	1652	X6R922
1579	Q9ULA0	1616	Q9Y450	1653	X6RLN4
1580	Q9ULD6	1617	Q9Y467		
1581	Q9ULG3	1618	Q9Y4C4		
1582	Q9ULJ9	1619	Q9Y4E8		

Therefore, the disclosed EVs are unique based on the source of cells from which they are derived. Moreover, these proteins can be used as a signature to identify the EVs.

Discussion

This is the first documentation that we are aware of on a scale that requires the Amicon stirred-cell ultrafiltration units, allowing filtration and EV enrichment from 24 liters of media within one week, an amount of media that could not logistically be purified by ultracentrifuge, and would require intense manpower and multiple centrifuges using the smaller Centricon/Amicon centrifugal filter units.

The inclusion of hFGF2 from cell culture media in NPEX™, combined with the ability of NPEX EVs to distribute to targets within the CNS (as demonstrated in biodistribution section), suggests that these EVs can potentially deliver hFGF2 across the blood brain barrier to target CNS tissue. These results suggest that a potential method for delivering large molecules including proteins (hFGF2 in the example above) to targets in vivo, including the CNS, using extracellular vesicles (NPEX™ by supplementing the EV source cell (hNP1™ in example above) culture media with the molecule of interest.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Publications cited herein and the materials for which they are cited are specifically incorporated by reference.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising an isolated population of extracellular vesicles (EVs) derived from non-transformed neural progenitor (NP) cells, and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim 1, wherein the NP cells are human cells.

3. The pharmaceutical composition of claim 1, wherein the NP cells are derived from human pluripotent stem cells.

4. The pharmaceutical composition of claim 1, wherein the NP cells are derived from human induced pluripotent stem cells.

5. The pharmaceutical composition of claim 1, wherein the NP cells are derived from human embryonic stem cells.

6. The pharmaceutical composition of claim 1, wherein the NP cells are SOX 1+, SOX 2+ and OCT4-.

7. The pharmaceutical composition of any one of claims 1-6, wherein the EVs comprise one or more protein biomarkers set forth in Table 9.

8. A composition comprising extracellular vesicles (EVs) obtained by culturing non-transformed neural progenitor (NP) cells derived from human pluripotent stem cells in cell culture medium under conditions and for a time sufficient to produce EVs, and isolating said EVs from the culture medium.

9. The composition of claim 8, wherein the human pluripotent stem cells are embryonic stem cells.

10. The composition of claim 8, wherein the human pluripotent stem cells are induced pluripotent stem cells.

11. The composition of claim 8, wherein the neural progenitor cells are SOX 1+, SOX 2+ and OCT4-.

12. The composition of any one of claims 8 to 11, wherein the EVs comprise one or more protein biomarkers set forth in Table 9.

13. The composition of any one of claims 1 to 12, further comprising one or more neurotrophic factors.

14. The composition of claim 13, wherein the one or more neurotrophic factors are selected from the group consisting of leukemia inhibitory factor (LIF), brainderived neurotrophic factor (BDNF), ciliary neurotrophic factor (CTNF), epidermal growth factor receptor (EGF), basic fibroblast growth factor (bFGF), FGF-6, glialderived neurotrophic factor (GDNF), ciliary neurotrophic factor (CTNF), granulocyte colony-stimulating factor (GCSF), hepatocyte growth factor (HGF), IFN-γ, insulin-like growth factor binding protein (IGFBP-2), IGFBP-6, IL-1ra, IL-6, IL-8, monocyte chemotactic protein (MCP-1), mononuclear phagocyte colony-stimulating factor (MCSF), neurotrophic factors (NT3), tissue inhibitor of metalloproteinases (TIMP-1), TIMP-2, tumor necrosis factor (TNF-β), vascular endothelial growth factor (VEGF), VEGF-D, urokinase plasminogen activator receptor (uPAR), bone morphogenetic protein 4 (BMP4), IL1-a, IL-3, leptin, stem cell factor (SCF), stromal cell-derived factor-1 (SDF-1), platelet derived growth factor-BB (PDGFBB), transforming growth factors beta (TGFβ-1) and TGFβ-3.

15. The composition of any one of claims 1 to 14, wherein the EVs are suspended in a hydrogel scaffold.

16. The composition of any one of claims 1 to 15, further comprising a protease inhibitor, a RNAse inhibitor, or combination thereof.

17. The composition of any one of claims 1 to 16, wherein the composition comprises about 1 mg to about 750 mg of EVs.

18. The composition of any one of claims 1 to 17, wherein the EVs further comprise a small molecule.

19. The composition of any one of claims 1 to 17, wherein the EVs further comprise an antisense oligonucleotide or a siRNA.

20. The composition of any one of claims 1 to 17, wherein the EVs further comprise an exogenous peptide or an exogenous protein.

21. The composition of any one of claims 1 to 17, wherein the EVs further comprise an antibody.

22. The composition of any one of claims 1 to 21, wherein the EVs comprise exosomes.

23. The composition of any one of claims 1 to 22, wherein the EVs are about 20 nm to 10 μm in size.

24. The composition of any one of claims 1 to 23, wherein the EVs are about 20 nm to about 150 nm in size.

25. Use of a pharmaceutical composition comprising extracellular vesicles (EVs) derived from non-transformed neural progenitor (NP) cells in the manufacture of a medicament for treating a subject who has suffered a stroke.

26. Use of a pharmaceutical composition comprising extracellular vesicles (EVs) derived from non-transformed neural progenitor (NP) cells in the manufacture of a medicament for treating a subject who has suffered a spinal cord injury, a traumatic brain injury, or a neurodegenerative disease.

27. The use of claim 26, wherein the neurodegenerative disease is Alzheimer's disease, Parkinson's disease, a Parkinson's-related disorder, Huntington's disease, amyotrophic lateral sclerosis, prion disease, motor neuron disease (MND), spinocerebellar ataxia (SCA) or spinal muscular atrophy (SMA).

28. The use of any one of claims 25 to 27, wherein the NP cells are human cells.

29. The use of claim 28, wherein the NP cells are derived from human pluripotent stem cells.

30. The use of claim 28, wherein the NP cells are derived from human induced pluripotent stem cells.

31. The use of claim 28, wherein the NP cells are derived from human embryonic stem cells.

32. The use of any one of claims 25 to 31, wherein the NP cells express one or more markers selected from the group consisting of nestin, SOX1, and SOX2, and do not express OCT4.

33. The use of any one of claims 25 to 32, wherein the medicament comprises about 1 mg to about 750 mg of EVs.

34. The use of any one of claims 25 to 33, wherein the EVs comprise exosomes.

35. The use of any one of claims 25 to 34, wherein the EVs are about 20 nm to 10 μm in size.

36. The use of any one of claims 25 to 35, wherein the EVs are about 20 nm to about 150 nm in size.

37. The use of any one of claims 25 to 36, wherein the EVs further comprise an agent selected from the group consisting of a small molecule, an antisense oligonucleotide, a siRNA, an exogenous peptide, an exogenous protein, or an antibody.

38. The use of any one of claims 25 and 28 to 37, wherein the subject has suffered an ischemic stroke.

39. The use of any one of claims 25 and 28 to 37, wherein the subject has suffered a hemorrhagic stroke.

40. The use of any one of claims 25 to 39, wherein the medicament is formatted for intravenous administration.

41. The use of any one of claims 25 to 39, wherein the medicament is formatted for administration via a route of delivery selected from intrathecal, intraperitoneal (IP), oral, intranasal, or direct delivery into the brain.

42. The use of any one of claims 25 and 28 to 41, wherein the medicament is to be initially administered to the subject within 24 hours following a stroke.

43. The use of any one of claims 25 and 28 to 41, wherein the medicament is to be administered to the subject 1-4 weeks following a stroke.

44. The use of any one of claims 25 to 43, wherein the medicament reduces swelling in the brain of the subject and/or reduces inflammation in the subject.

45. The use of any one of claims 25 to 44, wherein the medicament improves sensorimotor function in the subject and/or improves behavioral function in the subject.

46. The use of any one of claims 25 to 45, wherein the medicament improves the likelihood of survival of the subject.

47. The use of any one of claims 25 to 46, wherein the medicament reduces lesion volume in the subject.

48. The use of any one of claims 25 and 28 to 47, wherein the medicament is to be administered to the subject in conjunction with an additional bioactive agent useful in the treatment of stroke.

49. The use of claim 48, wherein the additional bioactive agent is selected from the group consisting of a salicylate, a thrombolytic agent, and a platelet aggregation inhibitor.

50. The use of claim 49, wherein the additional bioactive agent is selected from the group consisting of aspirin, alteplase, and clopidogrel.