From: [redacted]
To: Jeffrey Epstein <jeevacation@gmail.com>
Subject: What do you think?
Date: Sun, 10 Sep 2017 08:20:17 +0000

The Modern Neuron

I believe that mitochondrial organelle transplantation has the potential to change the way we manage acute and chronic disease of the nervous system and could also attenuate the effects of aging. In the same way blood transplantation can reverse deficits in oxygenation, immunity or hemostasis by replacing the cells responsible for those functions – we should be able to reverse energy deficits by replacing mitochondria.

- Mitochondrial pathology is the highest order issue in degenerative diseases (chronic) and stroke (acute). Both the function and concentration of mitochondria is decreased thereby reducing cellular function at every level. The same is true in cardiac conditions.

- Mitochondria are otherwise very motile and can be internalized via the synapse or from a glial donor. They are most concentrated in the synapses and travel via axonal transport to and from the cell body along the cytoskeletal conveyer belt powered by either dynein or kinesin (depending on whether retrograde or anterograde). These same conveyer belts bring materials to the cell body and also remove waste, including the damaged and dying mitochondria.

- Mitochondrial transplantation trials have worked well in heart and liver.

- Mitochondria can be transplanted from self, same species and even different species. They are easily internalized and not rejected.

Using either endovascular or intraneural delivery of fibroblast (self or donor) mitochondria to neurons, it should be possible to reverse the effects of acute and chronic pathology and rejuvenate brain tissue.

What makes this very appealing is that there are no known or effective treatments (with the exception of some for Parkinson's disease) for degenerative brain diseases, or the cognitive changes associated with aging. There are more than 75 million people with degenerative disease, 20 million strokes, and 8.5% of the world is over the age of 65. So, not a small audience.

There may be an opportunity to create a completely new type of neurotherapeutics company based on mitochondrial transplantation. I would like to call that company ***MODERN NEURON*** … My vision is that it would be more like a blood transfusion or skin-grafting approach – not one complicated by genetics. Not sure I want to run the company but I have been told being a scientific founder would be a very good thing - and I could run it or join in whatever capacity works.

The legal implications and regulatory path for transplantation are both very clear, especially if the tissue is derived from oneself. This is not genetic engineering and this not new science.

Below is a review of the relevant literature and existing intellectual property that I have been able to identify. There is work being done for heart disease and some for cancer, none for brain with the exception of early thinking at a hospital in Louisiana. I will send you a link to the googledrive file with all the papers. Let me know what you think.

Peer-Reviewed Literature

Fact	Delivery of mitochondria through the coronary arteries resulted in their rapid integration and widespread distribution throughout the heart and provided cardioprotection from ischemia-reperfusion injury
Implication	Arterial delivery of mitochondria to the region might also be possible.
Source	Intracoronary Delivery of Mitochondria to the Ischemic Heart for Cardioprotection
PMID	27500955
Abstract	We have previously shown that transplantation of autologously derived, respiration-competent mitochondria by direct injection into the heart following transient ischemia and reperfusion enhances cell viability and contractile function. To increase the therapeutic potential of this approach, we investigated whether exogenous mitochondria can be effectively delivered through the coronary vasculature to protect the ischemic myocardium and studied the fate of these transplanted organelles in the heart. Langendorff-perfused rabbit hearts were subjected to 30 minutes of ischemia and then reperfused for 10 minutes. Mitochondria were labeled with 18F-rhodamine 6G and iron oxide nanoparticles. The labeled mitochondria were either directly injected into the ischemic region or delivered by vascular perfusion through the coronary arteries at the onset of reperfusion. These hearts were used for positron emission tomography, microcomputed tomography, and magnetic resonance imaging with subsequent microscopic analyses of tissue sections to confirm the uptake and distribution of exogenous mitochondria. Injected mitochondria were localized near the site of delivery; while, vascular perfusion of mitochondria resulted in rapid and extensive dispersal throughout the heart. Both injected and perfused mitochondria were observed in interstitial spaces and were associated with blood vessels and cardiomyocytes. To determine the efficacy of vascular perfusion of mitochondria, an additional group of rabbit hearts were subjected to 30 minutes of

	regional ischemia and reperfused for 120 minutes. Immediately following regional ischemia, the hearts received unlabeled, autologous mitochondria delivered through the coronary arteries. Autologous mitochondria perfused through the coronary vasculature significantly decreased infarct size and significantly enhanced post-ischemic myocardial function. In conclusion, the delivery of mitochondria through the coronary arteries resulted in their rapid integration and widespread distribution throughout the heart and provided cardioprotection from ischemia-reperfusion injury.

Fact	Internalization of mitochondrial transplant in heart work.
Implication	Similar energetics and concentration of mitochondria in neurons as cardiomyoctyes
Source	Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury
PMID	23355340
Abstract	Electrocardiogram and optical mapping studies showed that no arrhythmia was associated with autologously derived mitochondrial transplantation. In vivo and in vitro studies show that the transplanted mitochondria are evident in the interstitial spaces and are internalized by cardiomyocytes 2–8 h after transplantation. The transplanted mitochondria enhanced oxygen consumption, high-energy phosphate synthesis, and the induction of cytokine mediators and proteomic pathways that are important in preserving myocardial energetics, cell viability, and enhanced post-infarct cardiac function. Transplantation of autologously derived mitochondria provides a novel technique to protect the heart from ischemia-reperfusion injury.

Fact	There are methodologies for the isolation of mitochondria and methods that can be used for the uptake and internalization of mitochondria
Implication	Tried in rats for Parkinsons (only neuro application yet)
Source	Mitochondrial transplantation for therapeutic use
PMID	27130633
Abstract	Mitochondria play a key role in the homeostasis of the vast majority of the body's cells. In the myocardium where mitochondria constitute 30 % of the total myocardial cell volume, temporary attenuation or obstruction of blood flow and as a result oxygen delivery to myocardial cells (ischemia) severely alters mitochondrial structure and function. These alterations in mitochondrial structure and function occur during ischemia and continue after blood flow and oxygen delivery to the myocardium is restored, and significantly decrease myocardial contractile function and myocardial cell survival. We hypothesized that the augmentation or replacement of mitochondria damaged by

	ischemia would provide a mechanism to enhance cellular function and cellular rescue following the restoration of blood flow. To test this hypothesis we have used a model of myocardial ischemia and reperfusion. Our studies demonstrate that the transplantation of autologous mitochondria, isolated from the patient's own body, and then directly injected into the myocardial during early reperfusion augment the function of native mitochondria damaged during ischemia and enhances myocardial post-ischemic functional recovery and cellular viability. The transplanted mitochondria act both extracellularly and intracellularly. Extracellularly, the transplanted mitochondria enhance high energy synthesis and cellular adenosine triphosphate stores and alter the myocardial proteome. Once internalized the transplanted mitochondria rescue cellular function and replace damaged mitochondrial DNA. There is no immune or auto-immune reaction and there is no pro-arrhythmia as a result of the transplanted mitochondria. Our studies and those of others demonstrate that mitochondrial transplantation can be effective in a number of cell types and diseases. These include cardiac and skeletal muscle, pulmonary and hepatic tissue and cells and in neuronal tissue. In this review we discuss the mechanisms leading to mitochondrial dysfunction and the effects on cellular function. We provide a methodology for the isolation of mitochondria to allow for clinical relevance and we discuss the methods we and others have used for the uptake and internalization of mitochondria. We foresee that mitochondrial transplantation will be a valued treatment in the armamentarium of all clinicians and surgeons for the treatment of varied ischemic disorders, mitochondrial diseases and related disorders.

Fact	There has not yet been a failed transplantation trial.
Implication	Brain tissue should not behave differently.
Source	Mitochondrial transplantation: From animal models to clinical use in humans.
PMID	28342934
Abstract	Mitochondrial transplantation is a novel therapeutic intervention to treat ischemia/reperfusion related disorders. The method for mitochondrial transplantation is simple and rapid and can be delivered to the end organ either by direct injection or vascular infusion. In this review, we provide mechanistic and histological studies in large animal models and present data to show clinical efficacy in human patients.

Fact	Mitochondrial medicine emerging.
Implication	Need to get ahead.
Source	Prospects for therapeutic mitochondrial transplantation
PMID	28533168

Abstract	Mitochondrial dysfunction has been implicated in a multitude of diseases and pathological conditions- the organelles that are essential for life can also be major players in contributing to cell death and disease. Because mitochondria are so well established in our existence, being present in all cell types except for red blood cells and having the responsibility of providing most of our energy needs for survival, then dysfunctional mitochondria can elicit devastating cellular pathologies that can be widespread across the entire organism. As such, the field of "mitochondrial medicine" is emerging in which disease states are being targeted therapeutically at the level of the mitochondrion, including specific antioxidants, bioenergetic substrate additions, and membrane uncoupling agents. New and compelling research investigating novel techniques for mitochondrial transplantation to replace damaged or dysfunctional mitochondria with exogenous healthy mitochondria has shown promising results, including tissue sparing accompanied by increased energy production and decreased oxidative damage. Various experimental techniques have been attempted and each has been challenged to accomplish successful transplantation. The purpose of this review is to present the history of mitochondrial transplantation, the different techniques used for both in vitro and in vivo delivery, along with caveats and pitfalls that have been discovered along the way. Results from such pioneering studies are promising and could be the next big wave of "mitochondrial medicine" once technical hurdles are overcome.

Fact	All neurodegenerative disease have mitochondrial dysfunction at core.
Implication	Aging too.
Source	Brain mitochondrial dysfunction in aging, neurodegeneration, and Parkinson's disease.
PMID	20890446
Abstract	Brain senescence and neurodegeneration occur with a mitochondrial dysfunction characterized by impaired electron transfer and by oxidative damage. Brain mitochondria of old animals show decreased rates of electron transfer in complexes I and IV, decreased membrane potential, increased content of the oxidation products of phospholipids and proteins and increased size and fragility. This impairment, with complex I inactivation and oxidative damage, is named "complex I syndrome" and is recognized as characteristic of mammalian brain aging and of neurodegenerative diseases. Mitochondrial dysfunction is more marked in brain areas as rat hippocampus and frontal cortex, in human cortex in Parkinson's disease and dementia with Lewy bodies, and in substantia nigra in Parkinson's disease. The molecular mechanisms involved in complex I inactivation include the synergistic inactivations produced by ONOO- mediated reactions, by reactions with free radical intermediates of lipid

	peroxidation and by amine-aldehyde adduction reactions. The accumulation of oxidation products prompts the idea of antioxidant therapies. High doses of vitamin E produce a significant protection of complex I activity and mitochondrial function in rats and mice, and with improvement of neurological functions and increased median life span in mice. Mitochondria-targeted antioxidants, as the Skulachev cations covalently attached to vitamin E, ubiquinone and PBN and the SS tetrapeptides, are negatively charged and accumulate in mitochondria where they exert their antioxidant effects. Activation of the cellular mechanisms that regulate mitochondrial biogenesis is another potential therapeutic strategy, since the process generates organelles devoid of oxidation products and with full enzymatic activity and capacity for ATP production.

Fact	Existing therapies for mitochondrial diseases have not been successful.
Implication	Transplantation has not been broadly tried for the many mitochondrial conditions.
Source	Mitochondrial diseases: therapeutic approaches.
PMID	17486439
Abstract	Therapy of mitochondrial encephalomyopathies (defined restrictively as defects of the mitochondrial respiratory chain) is woefully inadequate, despite great progress in our understanding of the molecular bases of these disorders. In this review, we consider sequentially several different therapeutic approaches. Palliative therapy is dictated by good medical practice and includes anticonvulsant medication, control of endocrine dysfunction, and surgical procedures. Removal of noxious metabolites is centered on combating lactic acidosis, but extends to other metabolites. Attempts to bypass blocks in the respiratory chain by administration of electron acceptors have not been successful, but this may be amenable to genetic engineering. Administration of metabolites and cofactors is the mainstay of real-life therapy and is especially important in disorders due to primary deficiencies of specific compounds, such as carnitine or coenzyme Q10. There is increasing interest in the administration of reactive oxygen species scavengers both in primary mitochondrial diseases and in neurodegenerative diseases directly or indirectly related to mitochondrial dysfunction. Aerobic exercise and physical therapy prevent or correct deconditioning and improve exercise tolerance in patients with mitochondrial myopathies due to mitochondrial DNA (mtDNA) mutations. Gene therapy is a challenge because of polyplasmy and heteroplasmy, but interesting experimental approaches are being pursued and include, for example, decreasing the ratio of mutant to wild-type mitochondrial genomes (gene shifting), converting mutated mtDNA genes into normal nuclear DNA genes (allotopic expression), importing cognate genes from other species, or

	correcting mtDNA mutations with specific restriction endonucleases. Germline therapy raises ethical problems but is being considered for prevention of maternal transmission of mtDNA mutations. Preventive therapy through genetic counseling and prenatal diagnosis is becoming increasingly important for nuclear DNA-related disorders. Progress in each of these approaches provides some glimmer of hope for the future, although much work remains to be done.

Fact	Mitochondrial transplants to the heart are protective, safe and successful in animals.
Implication	Human trials are underway.
Source	Transplantation of autologously derived mitochondria protects the heart from ischemia-reperfusion injury
PMID	23355340
Abstract	Mitochondrial damage and dysfunction occur during ischemia and modulate cardiac function and cell survival significantly during reperfusion. We hypothesized that transplantation of autologously derived mitochondria immediately prior to reperfusion would ameliorate these effects. New Zealand White rabbits were used for regional ischemia (RI), which was achieved by temporarily snaring the left anterior descending artery for 30 min. Following 29 min of RI, autologously derived mitochondria (RI-mitochondria; $9.7 \pm 1.7 \times 10^6$/ml) or vehicle alone (RI-vehicle) were injected directly into the RI zone, and the hearts were allowed to recover for 4 wk. Mitochondrial transplantation decreased ($P < 0.05$) creatine kinase MB, cardiac troponin-I, and apoptosis significantly in the RI zone. Infarct size following 4 wk of recovery was decreased significantly in RI-mitochondria (7.9 ± 2.9%) compared with RI-vehicle (34.2 ± 3.3%, $P < 0.05$). Serial echocardiograms showed that RI-mitochondria hearts returned to normal contraction within 10 min after reperfusion was started; however, RI-vehicle hearts showed persistent hypokinesia in the RI zone at 4 wk of recovery. Electrocardiogram and optical mapping studies showed that no arrhythmia was associated with autologously derived mitochondrial transplantation. In vivo and in vitro studies show that the transplanted mitochondria are evident in the interstitial spaces and are internalized by cardiomyocytes 2–8 h after transplantation. The transplanted mitochondria enhanced oxygen consumption, high-energy phosphate synthesis, and the induction of cytokine mediators and proteomic pathways that are important in preserving myocardial energetics, cell viability, and enhanced post-infarct cardiac function. Transplantation of autologously derived mitochondria provides a novel technique to protect the heart from ischemia-reperfusion injury.

Fact	Glial cells are a more specific indicator of brain aging than neurons.
Implication	Both neurons and glia are rich in mitochondria.
Source	Major Shifts in Glial Regional Identity Are a Transcriptional Hallmark of Human Brain Aging
PMID	28076797
Abstract	Gene expression studies suggest that aging of the human brain is determined by a complex interplay of molecular events, although both its region- and cell-type-specific consequences remain poorly understood. Here, we extensively characterized aging-altered gene expression changes across ten human brain regions from 480 individuals ranging in age from 16 to 106 years. We show that astrocyte- and oligodendrocyte-specific genes, but not neuron-specific genes, shift their regional expression patterns upon aging, particularly in the hippocampus and substantia nigra, while the expression of microglia- and endothelial-specific genes increase in all brain regions. In line with these changes, high-resolution immunohistochemistry demonstrated decreased numbers of oligodendrocytes and of neuronal subpopulations in the aging brain cortex. Finally, glial-specific genes predict age with greater precision than neuron-specific genes, thus highlighting the need for greater mechanistic understanding of neuron-glia interactions in aging and late-life diseases.

Fact	Peptide-mediated mitochondrial delivery (PMD) occurs easily between cells and also promotes mitochondrial biogenesis.
Implication	Peptide-mediated delivery is one way to deliver mitochondria that are easily internalized.
Source	Functional Recovery of Human Cells Harbouring the Mitochondrial DNA Mutation MERRF *A8344G* via Peptide-Mediated Mitochondrial Delivery
PMID	23006856
Abstract	We explored the feasibility of mitochondrial therapy using the cell-penetrating peptide Pep-1 to transfer mitochondrial DNA (mtDNA) between cells and rescue a cybrid cell model of the mitochondrial disease myoclonic epilepsy with ragged-red fibres (MERRF) syndrome. Pep-1-conjugated wild-type mitochondria isolated from parent cybrid cells incorporating a mitochondria-specific tag were used as donors for mitochondrial delivery into MERRF cybrid cells (MitoB2) and mtDNA-depleted Rho-zero cells (Mitoρ°). Forty-eight hours later, translocation of Pep-1-labelled mitochondria into the mitochondrial regions of MitoB2 and Mitoρ° host cells was observed (delivery efficiencies of 77.48 and 82.96%, respectively). These internalized mitochondria were maintained for at least 15 days in both cell types and were accompanied by mitochondrial function recovery and cell survival by preventing mitochondria-dependent cell death. Mitochondrial homeostasis analyses showed that peptide-mediated mitochondrial delivery (PMD) also increased mitochondrial

	biogenesis in both cell types, but through distinct regulatory pathways involving mitochondrial dynamics. Dramatic decreases in mitofusin-2 (MFN2) and dynamin-related protein 1/fission 1 were observed in MitoB2 cells, while Mitoρ° cells showed a significant increase in optic atrophy 1 and MFN2. These findings suggest that PMD can be used as a potential therapeutic intervention for mitochondrial disorders.
Fact	Strong correlation between mitochondrial function and brain function.
Implication	Duh.
Source	Brain mitochondrial dysfunction in aging.
PMID	18421773
Abstract	Aging of mammalian brain is associated with a continuous decrease of the capacity to produce ATP by oxidative phosphorylation. The impairment of mitochondrial function is mainly due to diminished electron transfer by complexes I and IV, whereas inner membrane H+ impermeability and F1-ATP synthase activity are only slightly affected. Dysfunctional mitochondria in aged rodents show decreased rates of respiration and of electron transfer, decreased membrane potential, increased content of the oxidation products of phospholipids and proteins, and increased size and fragility. In aging mice, the activities of brain mitochondrial enzymes (complexes I and IV and mtNOS) are linearly correlated with neurological performance (tightrope and T-maze tests) and with median life span and negatively correlated with the mitochondrial content of lipid and protein oxidation products. Conditions that increased mice median life span, such as moderate exercise, vitamin E supplementation, caloric restriction, and high spontaneous neurological activity; also improved neurological performance and mitochondrial function in aged brain. The diffusion of mitochondrial NO and H2O2 to the cytosol is decreased in the aged brain and may be a factor for reduced mitochondrial biogenesis.

Fact	Mitochondria are transferred from glia to neurons after acute stroke.
Implication	Unclear signalizing mechanism and if it also happens during chronic states.
Source	Transfer of mitochondria from astrocytes to neurons after stroke
PMID	27466127
Abstract	Neurons can release damaged mitochondria and transfer them to astrocytes for disposal and recycling1. This ability to exchange mitochondria may represent a potential mode of cell-to-cell signalling in the central nervous system. Here we show that astrocytes in mice can also release functional mitochondria that enter neurons. Astrocytic release of extracellular mitochondrial particles was mediated by a calcium-dependent mechanism involving CD38 and cyclic ADP ribose signalling. Transient focal

	cerebral ischaemia in mice induced entry of astrocytic mitochondria into adjacent neurons, and this entry amplified cell survival signals. Suppression of CD38 signalling by short interfering RNA reduced extracellular mitochondria transfer and worsened neurological outcomes. These findings suggest a new mitochondrial mechanism of neuroglial crosstalk that may contribute to endogenous neuroprotective and neurorecovery mechanisms after stroke.

Fact	Mitochrondria are extremely motile and concentrated in synapses.
Implication	Not unusual for mitochondria to travel retro and anterograde = go where needed.
Source	The axonal transport of mitochondria
PMID	16306220
Abstract	Organelle transport is vital for the development and maintenance of axons, in which the distances between sites of organelle biogenesis, function, and recycling or degradation can be vast. Movement of mitochondria in axons can serve as a general model for how all organelles move: mitochondria are easy to identify, they move along both microtubule and actin tracks, they pause and change direction, and their transport is modulated in response to physiological signals. However, they can be distinguished from other axonal organelles by the complexity of their movement and their unique functions in aerobic metabolism, calcium homeostasis and cell death. Mitochondria are thus of special interest in relating defects in axonal transport to neuropathies and degenerative diseases of the nervous system. Studies of mitochondrial transport in axons are beginning to illuminate fundamental aspects of the distribution mechanism. They use motors of one or more kinesin families, along with cytoplasmic dynein, to translocate along microtubules, and bidirectional movement may be coordinated through interaction between dynein and kinesin-1. Translocation along actin filaments is probably driven by myosin V, but the protein(s) that mediate docking with actin filaments remain unknown. Signaling through the PI 3-kinase pathway has been implicated in regulation of mitochondrial movement and docking in the axon, and additional mitochondrial linker and regulatory proteins, such as Milton and Miro, have recently been described.

Fact	Mitochondria go where they are needed.
Implication	When they are injured = they aren't as helpful or when they can't reach target = bad
Source	Transporting mitochondria in neurons
PMID	27508065
Abstract	Neurons demand vast and vacillating supplies of energy. As the key contributors of this energy, as well as primary pools of

	calcium and signaling molecules, mitochondria must be where the neuron needs them, when the neuron needs them. The unique architecture and length of neurons, however, make them a complex system for mitochondria to navigate. To add to this difficulty, mitochondria are synthesized mainly in the soma, but must be transported as far as the distant terminals of the neuron. Similarly, damaged mitochondria—which can cause oxidative stress to the neuron—must fuse with healthy mitochondria to repair the damage, return all the way back to the soma for disposal, or be eliminated at the terminals. Increasing evidence suggests that the improper distribution of mitochondria in neurons can lead to neurodegenerative and neuropsychiatric disorders. Here, we will discuss the machinery and regulatory systems used to properly distribute mitochondria in neurons, and how this knowledge has been leveraged to better understand neurological dysfunction.

Fact	Nonsymbiotic extracellular mitochondria can provide an effective cell defense against acute injurious ischemic stress
Implication	Xenogenic transplants work too
Source	Transferring Xenogenic Mitochondria Provides Neural Protection Against Ischemic Stress in Ischemic Rat Brains.
PMID	26555763
Abstract	Transferring exogenous mitochondria has therapeutic effects on damaged heart, liver, and lung tissues. Whether this protective effect requires the symbiosis of exogenous mitochondria in host cells remains unknown. Here xenogenic mitochondria derived from a hamster cell line were applied to ischemic rat brains and rat primary cortical neurons. Isolated hamster mitochondria, either through local intracerebral or systemic intra-arterial injection, significantly restored the motor performance of brain-ischemic rats. The brain infarct area and neuronal cell death were both attenuated by the exogenous mitochondria. Although internalized mitochondria could be observed in neurons and astrocytes, the low efficacy of mitochondrial internalization could not completely account for the high rate of rescue of the treated neural cells. We further illustrated that disrupting electron transport or ATPase synthase in mitochondria significantly attenuated the protective effect, suggesting that intact respiratory activity is essential for the mitochondrial potency on neural protection. These results emphasize that nonsymbiotic extracellular mitochondria can provide an effective cell defense against acute injurious ischemic stress in the central nervous system.

Fact	Mitochondrial transplant works in cancer.
Implication	Could work in neuro.

Source	Mitochondria and Neurodegeneration "Could Mitochondrial Organelle Transfer be a Cellular Biotherapy for Neurodegenerative Diseases?"
PMID	N/A
Abstract	It has been known for some time the abnormal function of mitochondria is associated with neurodegenerative diseases. Mitochondrial dysfunction has been implicated in the pathogenesis of Parkinson', Alzheimer's, amyotrophic lateral sclerosis, and Huntington's diseases. Researchers have postulated the therapeutic efficacy of mitochondrially targeted antioxidants, and some have shown encouraging results. We have demonstrated that mitochondrial organelle transplantation of isolated normal mitochondria into cancer cells decreased proliferation, lactate production and increased drug sensitivity of the cancer cells. Studies have shown that cellular uptake of exogenous mitochondria has restored functional recovery of defective recipient cells. Based on our experience with Mitochondrial Organelle Transfer (MOT) in cancer, we present this review commentary evidence that (MOT) might be a cell-based therapy for neurodegenerative diseases.

Fact	Healthy mitochondria replace damaged ones and restore function.
Implication	Likely also rejuvenating.
Source	Actin-dependent mitochondrial internalization in cardiomyocytes: evidence for rescue of mitochondrial function
PMID	25862247
Abstract	Previously, we have demonstrated that the transplantation of viable, structurally intact, respiration competent mitochondria into the ischemic myocardium during early reperfusion significantly enhanced cardioprotection by decreasing myocellular damage and enhancing functional recovery. Our *in vitro* and *in vivo* studies established that autologous mitochondria are internalized into cardiomyocytes following transplantation; however, the mechanism(s) modulating internalization of these organelles were unknown. Here, we show that internalization of mitochondria occurs through actin-dependent endocytosis and rescues cell function by increasing ATP content and oxygen consumption rates. We also show that internalized mitochondria replace depleted mitochondrial (mt)DNA. These results describe the mechanism for internalization of mitochondria within host cells and provide a basis for novel therapeutic interventions allowing for the rescue and replacement of damaged or impaired mitochondria.

Fact	Mitochondrial transplants inhibit cell proliferation and increase sensitivity to chemo in breast cancer.
Implication	Why not brain

Source	Mitochondria organelle transplantation: introduction of normal epithelial mitochondria into human cancer cells inhibits proliferation and increases drug sensitivity.
PMID	23080556
Abstract	Mitochondrial dysfunction of cancer cells includes increased aerobic glycolysis, elevated levels of ROS, decreased apoptosis, and resistance to chemotherapeutic agents. We hypothesized that the introduction of normal mitochondria into cancer cells might restore mitochondrial function and inhibit cancer cell growth, and reverse chemoresistance. First, in the present study, we tested if mitochondria of immortalized, untransformed mammary epithelial MCF-12A cells could enter into human cancer cell lines. Second, if introducing normal mitochondria into cancer cells would inhibit proliferation. And third, would the addition of normal mitochondria increase the sensitivity of human breast cancer MCF-7 cells to chemotherapy. We found that JC-1-stained mitochondria of immortalized, untransformed mammary epithelial MCF-12A cells can enter into the cancer cell lines MCF-7, MDA-MB-231, and NCI/ADR-Res, but cannot enter immortalized, untransformed MCF-12A cells. The normal mitochondria from immortalized, untransformed MCF-12A cells suppressed the proliferation of MCF-7 and NCI/ADR-Res cells in a dose-dependent pattern, but did not affect the proliferation of immortalized, untransformed MCF-12A cells. The normal mitochondria from immortalized, untransformed MCF-12A cells increased the sensitivity of human breast cancer MCF-7 cells to doxorubicin, Abraxane, and carboplatin. In conclusion, the introduction of normal mammary mitochondria into human breast cancer cells inhibits cancer cell proliferation and increases the sensitivity of the MCF-7 human breast cancer cell line to doxorubicin, Abraxane, and carboplatin. These results support the role of mitochondrial dysfunction in cancer and suggest the possible use of targeted mitochondria for cancer therapeutics.

Fact	Unpackaged vs. packaged mitochondrial transplants work well.
Implication	Likely different for different locations.
Source	Alternative Methods for Mitochondrial Transplantation: Efficiency of Unpackaged and Lipid-Packaged Preparations
PMID	N/A
Abstract	Mitochondrial transplantation is currently being explored as a means to repair and restore proper organelle function in a variety of inherited and acquired disorders of energy metabolism. The optimal preparation and application of donor mitochondria is unknown, but most studies in vivo have used injection techniques or, for tissue studies, unpackaged mitochondria (organelles isolated and suspended in buffer) in transplant experiments. Packaging in lipid rafts can increase recipient cell uptake of some compounds and objects. We present the first data comparing recipient cell uptake of unpackaged mitochondria to recipient cell

	uptake of mitochondria packaged in cell membrane lipids. Mitochondria and membranes were prepared from autologous cells and applied to cells (fibroblasts) in culture. Both unpackaged and lipid-packaged mitochondria were taken into recipient cells and the donor mitochondria showed evidence, in each case, of retained functionality and the ability to merge with the recipient mitochondrial matrix. However, lipid packaging appeared to enhance the uptake of functional mitochondria. Current studies of mitochondrial transplantation in animal models might fruitfully explore the utility and efficacy of lipid-packaged mitochondria in transplant experiments.

Fact	Hypothetical.
Implication	Why synthetic when there are plentiful organic mitochondria
Source	Synthetic mitochondria as therapeutics against systemic aging: a hypothesis.
PMID	25182226
Abstract	We hypothesize herein that synthetic mitochondria, engineered, or reprogrammed to be more energetically efficient and to have mildly elevated levels of reactive oxygen species (ROS) production, would be an effective form of therapeutics against systemic aging. The free radical and mitochondria theories of aging hold that mitochondria-generated ROS underlies chronic organelle, cell and tissues damages that contribute to systemic aging. More recent findings, however, collectively suggest that while acute and massive ROS generation during events such as tissue injury is indeed detrimental, subacute stresses, and chronic elevation in ROS production may instead induce a state of mitochondrial hormesis (or "mitohormesis") that could extend lifespan. Mitohormesis appears to be a convergent mechanism for several known anti-aging signaling pathways. Importantly, mitohormetic signaling could also occur in a non-cell autonomous manner, with its induction in neurons affecting gut cells, for example. Technologies are outlined that could lead towards testing of the hypothesis, which include genetic and epigenetic engineering of the mitochondria, as well as intercellular transfer of mitochondria from transplanted helper cells to target tissues.

Fact	Interesting glial – neuronal relationship
Implication	More on the reasons how/why mitochondrial transfer between happens
Source	Learn to Forget: Regulation of Age-Related Memory Impairment by Neuronal-Glial Crosstalk
PMID	25459404
Abstract	Dementia is among the most feared complications of aging in the U.S. In this issue of Neuron, Yamazaki et al. (2014) present a tour de force mechanistic analysis of a "hit" from a proteomic

	screen carried out using a Drosophila mutation that affects memory.

Patents

Title	Methods and compositions for transfer of mitochondria into mammalian cells
Abstract	Disclosed are compositions comprising a lipid carrier and a mitochondria. Also disclosed are methods of delivering exogenous mitochondria to a cell and methods of treating or reversing progression of a disorder associated mitochondrial dysfunction in a mammalian subject in need thereof
Publication number	US 20130022666 A1
Year	2013

Title	Method for introducing exogenous mitochondria into mammalian cells
Abstract	Disclosed are synthetic mitochondria obtained by introducing exogenous DNA into mitochondria or mitochondrial shells. Cells containing exogenous mitochondria are then obtained by introducing the synthetic mitochondria into mammalian cells via endocytosis, thereby allowing the exogenous mitochondria to perform effectively within the cells. After being introduced, synthetic mitochondrial DNA genes can be expressed stably, and passaged effectively. The method for introducing exogenous mitochondria into cells can serve as a new mitochondrial molecular cloning method, performing gene knockout, gene knock-in, gene rearrangement etc. within mitochondria, thereby enabling any molecular cloning of mammalian mitochondrial DNA to be engineered, which has significant implications for the treatment of diseases caused by mitochondrial DNA mutations.
Publication number	WO 2015067089 A1
Year	2015

Title	Method For Introducing Exogenous Mitochondria Into A Mammalian Cell
Abstract	The present disclosure provides a method for producing a cell with exogenous mitochondria by obtaining synthetic mitochondria via introduction of exogenous mitochondrial DNA into mitochondria or empty mitochondrial shells, and incorporating the same into mammalian cells via endocytosis. As such, effective functionality of exogenous mitochondria in cells is realized. The synthetic mitochondrial DNA genes introduced according to the present disclosure can be stably expressed and effectively passaged. The method for introducing exogenous mitochondrial DNA into mammalian cells as disclosed herein may be used as a whole new mitochondrial molecular cloning means to perform site-directed mutagenesis, gene insertion, gene knockout, gene rearrangement, and the like in mitochondria. Therefore, any molecular cloning modification can be performed on a mammalian mitochondrial DNA, which is of great importance to therapeutic schemes of diseases derived from mitochondrial DNA mutations.
Publication number	US 20170159017 A1
Year	2017

Title	Method for introducing exogenous mitochondria into mammalian cells
Abstract	The present disclosure provides a method for producing a cell with exogenous mitochondria by obtaining synthetic mitochondria via introduction of exogenous mitochondrial DNA into mitochondria or empty mitochondrial shells, and incorporating the same into mammalian cells via endocytosis. As such, effective functionality of exogenous mitochondria in cells is realized. The synthetic mitochondrial

	DNA genes introduced according to the present disclosure can be stably expressed and effectively passaged. The method for introducing exogenous mitochondrial DNA into mammalian cells as disclosed herein may be used as a whole new mitochondrial molecular cloning means to perform site-directed mutagenesis, gene insertion, gene knockout, gene rearrangement, and the like in mitochondria. Therefore, any molecular cloning modification can be performed on a mammalian mitochondrial DNA, which is of great importance to therapeutic schemes of diseases derived from mitochondrial DNA mutations.
Publication number	EP 3067416 A1
Year	2016

Title	Targeted retrograde gene delivery for neuronal protection
Abstract	Methods are disclosed for transducing neurons with heterologous genes using retrograde viral transport. The methods disclosed employ substantially non-toxic vectors, such as adeno-associated virus vectors, that are capable of retrograde axonal transport to introduce and express genes in the neurons. This method has applications in the mapping of neural pathways, in stimulating or inhibiting the growth of neurons, and in the treatment of various neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.
Publication number	US 6998118 B2
Year	2001

Title	Method for administering neurologic agents to the brain
Abstract	Disclosed is a method for transporting neurologic therapeutic agents to the

	brain by means of the olfactory neural pathway and a pharmaceutical composition useful in the treatment of brain disorders.
Publication number	US 5624898 A
Year	1997

Title	Method for administering insulin to the brain
Abstract	Disclosed is a method for transporting neurologic therapeutic agents to the brain by means of the olfactory neural pathway and a pharmaceutical composition useful in the treatment of brain disorders.
Publication number	US 6313093 B1
Year	2001

Title	Methods and compositions for enhancing intranasal delivery of therapeutic agents
Abstract	A method for treating a patient suffering from a condition with an active compound comprising the steps of (a) treating the patient intranasally with an effective amount of MMP-9 or a functionally equivalent fragment, wherein the tight junctions of the patient's nasal epithelial cells are modulated or wherein the basal lamina of the patient is partially digested and type IV collagen of the patient is degraded or wherein access to the patient's perineural, perivascular, or lymphatic compartment spaces is facilitated and (b) treating the patient intranasally with an active compound is disclosed.
Publication number	US 9320800 B2
Year	2016

Title	Indirect delivery of growth factors into the central nervous system
Abstract	A method of delivering a therapeutic to the central nervous system comprising

	admininistering a therapeutic intramuscularly in to muscle innervated by cranial and/or spinal nerves,and transporting the therapeutic peripherally through the nerves into the CNS.
Publication number	WO 2005021065 A3
Year	2005

Title	Use of particulate agents
Abstract	A novel means of pharmaceutical delivery for therapy or prophylaxis or to assist surgical or diagnostic operations on the living body is provided by neuronal endocytosis and axonal transport following pharmaceutical administration into vascularized, peripherally innervated tissue, e.g. intramuscular injections of a nerve adhesion molecule in coupled particle comprising a physiologically active substance or a diagnostic marker.
Publication number	EP 0548157 B1
Year	1998

Title	Intranasal administration of pharmaceutical agents for treatment of neurological diseases
Abstract	Pharmaceutical formulations for treating neurological diseases are described, wherein the formulations comprise a pharmaceutically active agent-transport moiety complex. The formulations are suitable for administration via an intranasal route. Neurological diseases and conditions are associated with reduced brain insulin signaling (i.e., CNS insulin insensitivity), reduced dopaminergic signaling, reduced serotonergic signaling, reduced cholinergic signaling, or reduced GABAergic signaling, and include Alzheimer's disease, Parkinson's disease, epilepsy, neuropathic pain, fibromyalgia, post-herpetic neuralgia, insomnia, or

	anxiety. Neurological diseases also include cancers of the central nervous system (CNS).
Publication number	US 20140100282 A1
Year	2014

Title	Method and applications of peptide-mediated mitochondrial delivery system
Abstract	The present invention relates to a method using a cell penetrating peptide (Pep-1) for labeling and delivering mitochondria separated from healthy cells to replace damaged mitochondria. At present, microinjection of mitochondria into cells can only process one cell at a time, and therefore, this technique is limited to embryo related research and relevant applications. The advantages of the said peptide-mediated mitochondrial delivery system (PMD) include less steps with more efficiency, where a number of cells can be treated following one labeling process; the delivery process can be easily controlled, there is no cell toxicity after delivery under appropriate conditions, and delivery efficiency is over 80% depending on different cell types. Mitochondria delivered by the PMD system will move to the original mitochondrial location in the cells and will not be catalyzed in lysosomes; thus, the therapeutic effects can last at least one week.
Publication number	US 8648034 B2
Year	2014

Title	Method and applications of peptide-mediated mitochondrial delivery system
Abstract	The present invention relates to a method using a cell penetrating peptide (Pep-1) for labeling and delivering mitochondria separated from healthy cells to replace damaged

	mitochondria. At present, microinjection of mitochondria into cells can only process one cell at a time, and therefore, this technique is limited to embryo related research and relevant applications. The advantages of the said peptide-mediated mitochondrial delivery system (PMD) include less steps with more efficiency, where a number of cells can be treated following one labeling process; the delivery process can be easily controlled, there is no cell toxicity after delivery under appropriate conditions, and delivery efficiency is over 80% depending on different cell types. Mitochondria delivered by the PMD system will move to the original mitochondrial location in the cells and will not be catalyzed in lysosomes; thus, the therapeutic effects can last at least one week.
Publication number	US 20140178993 A1
Year	2014

Title	Therapeutic use of mitochondria and combined mitochondrial agents
Abstract	The disclosure relates to compositions comprising isolated mitochondria or combined mitochondrial agents, and methods of treating disorders using such compositions.
Publication number	WO 2017124037 A1
Year	2017

Title	Methods and compositions for mitochondrial replacement therapy
Abstract	The invention features methods, kits, and compositions for mitochondrial replacement in the treatment of disorders arising from mitochondrial dysfunction. The invention also features methods of diagnosing neuropsychiatric (e.g., bipolar disorder) and neurodegenerative disorders based on mitochondrial structural abnormalities.

Publication number	US 20170065635 A1
Year	2017

Title	Methods and compositions for mitochondrial replacement therapy
Abstract	The invention features methods, kits, and compositions for mitochondrial replacement in the treatment of disorders arising from mitochondrial dysfunction. The invention also features methods of diagnosing neuropsychiatric (e.g., bipolar disorder) and neurodegenerative disorders based on mitochondrial structural abnormalities.
Publication number	EP 2641617 A1
Year	2013

Title	Methods and compositions for mitochondrial replacement therapy
Abstract	The invention features methods, kits, and compositions for mitochondrial replacement in the treatment of disorders arising from mitochondrial dysfunction. The invention also features methods of diagnosing neuropsychiatric (e.g., bipolar disorder) and neurodegenerative disorders based on mitochondrial structural abnormalities.
Publication number	US 20110008310 A1
Year	2011

Title	Method for promoting survival of injured neurons by virtue of mitochondria transplantation
Abstract	The invention provides a method for promoting the survival of injured neurons by virtue of mitochondria transplantation. The method comprises the following steps: (1) carrying out trypsinization centrifuge on P1-P3-generation mesenchymal stem cells, and counting the number of the cells; (2) separating by virtue of a

	mitochondria separation agent to obtain mitochondria, and carrying out protein quantification and ATP content determination; and (3) preparing suspension from the mitochondria obtained in the step (2), and transplanting the suspension to a neuron injury region to contact with the neuron injury region. Compared with the transplantation of mesenchymal stem cells, the method has the advantages that the allogeneic immunogenicity problem is avoided, the implantation problem of chromosomes of allosome-derived stem cell nucleuses is avoided, and the regeneration of neuronal cells is promoted.
Publication number	CN 106190963 A
Year	2016

Title	Method and applications of peptide-mediated mitochondrial delivery system
Abstract	The present invention relates to a method using a cell penetrating peptide (Pep-1) for labeling and delivering mitochondria separated from healthy cells to replace damaged mitochondria. At present, microinjection of mitochondria into cells can only process one cell at a time, and therefore, this technique is limited to embryo related research and relevant applications. The advantages of the said peptide-mediated mitochondrial delivery system (PMD) include less steps with more efficiency, where a number of cells can be treated following one labeling process; the delivery process can be easily controlled, there is no cell toxicity after delivery under appropriate conditions, and delivery efficiency is over 80% depending on different cell types. Mitochondria delivered by the PMD system will move to the original mitochondrial location in the cells and will not be catalyzed in lysosomes;

	thus, the therapeutic effects can last at least one week
Publication number	US 8648034 B2
Year	2014