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# Neurodegeneration and Mitochondria Organelle Transplantation: "A Technology That Proof of Principle Suggest Is Ready for Prime Time"

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## Abstract

It is known that mitochondrial dysfunction is associated with neurodegenerative diseases including amyotrophic lateral sclerosis (ALS). Researchers have tested the therapeutic efficacy of many mitochondrial targeted agents; however, results have been disappointing without significant impact on disease survival. Several groups have demonstrated that mitochondrial transfer of isolated normal healthy mitochondria to defective calls can restore functional recovery. Our experience with mitochondria organelle transplantation (MOT) in cancer cells led to investigating the technology for neurodegenerative diseases (NDs), especially ALS. The rationale was that if the uptake of normal mitochondria into cancer cells inhibited proliferation and glycolysis; then MOT might be a cell-based therapy for NDs. In this communication, we will present background research on MOT *in vitro* and *in vivo* cell culture and animal models respectively. This research evidence showed proof of principle of the technology. This fact led us to try the procedure on a desperate human ALS patient.

## Keywords

Neurodegeneration, Mitochondrial Organelle Transplantation, Mitochondria, ALS

## 1. Introduction

ALS known as Lou Gehrig's disease involves both upper and lower motor neuron degeneration. It is sporadic and familial with the sporadic form more common. The familial form is due to mutations in Cu, Zn superoxide dismutase

(SOD1). The motor neuron degeneration leads to skeletal muscle atrophy, paralysis, and death. Mitochondrial dysfunction is involved in multiple NDs, such as, Parkinson's, Alzheimer's and Huntington's disease. It is also very prominent in genetic mitochondrial diseases and muscular dystrophy.

Mitochondria are dynamic vital intracellular organelles involved in many important essential cellular functions. They are involved in energy production, reactive oxygen species (ROS), metabolism, cell signaling, apoptosis, autophagy, and iron metabolism. A small defect in any of these functions might cause mitochondrial dysfunction. One major area is excessive ROS which causes free radicals that results in oxidative mitochondrial DNA (mtDNA) damage with disruption of membrane potential and a marked decrease in energy production [1]. This cascade leads to death of the motor neuron.

Mitochondrial dysfunction is associated with many other conditions and this has been discussed in detail by Nunnari and Suomalainen in a paper entitled "Mitochondria in Sickness and in Health". This article discusses all aspects of mitochondrial function in health and disease, and it is recommended for those interested in the complexity of the role of mitochondria in health and disease [1]. Many investigators have contributed to our knowledge of mitochondrial function in health and disease, and how mitochondria function in the mammalian species. Researchers learned that mitochondria are intimately networked with other cellular organelles. They undergo constant fission and fusion and are also involved in intercellular migration.

The goal of this communication is to explore the research done over several decades that has led us now to consider MOT to be a viable cellular biotherapy for disease. We will attempt to explain how we have reached this point and how much we owe other great investigators. It is impossible to recognize all that have made contributions to this endeavor. However, we will take you on a journey of early and later research that has produced evidence that there is now proof of principle that MOT is a viable therapy for NDs.

## 2. Early Research on Mitochondrial Transfer

Researchers have been involved in investigating injection techniques of mtDNA and mitochondria transfer to cells for many years. The transmission of a mtDNA dependent phenotype was obtained as early as 1965 by Diacumakos and group, while Knowles and team reported it in 1974. They injected mitochondria into large cells Neurospora hyphae and Knowles did in the Paramecium respectively [2] [3]. Before 1965, no injection of mitochondria into mammalian cells in culture had been attempted.

Later in 1982, Clark and Shay isolated mitochondria from cells with a mtDNA mutation providing resistance of the cells to chloramphenicol. They cocultured them with mammalian cells and transferred resistance of the antibiotic to these cells. The significance of their findings was not appreciated at that time [4].

In 1988, King and Attardi made a great contribution to this technology when

they published a paper entitled "Injection of Mitochondria into Human Cells Leads to a Rapid Replacement of the Endogenous Mitochondrial DNA". They injected viable genetically marked human mitochondria into the cytoplasm of human cells depleted partially of their mtDNA by incubation in ethidium bromide. They then carefully studied the fate of the exogenous mtDNA. They noticed an unexpected complete and rapid replacement of mtDNA in the recipient cells. These results contributed significant implications for mitochondrial genetics [5].

Kong and Xu contributed tremendously to the pathogenesis of familial ALS by studying mitochondrial degeneration in the motor neurons and onset of ALS in a mouse model expressing a mutant SOD1. At that time, they pointed out that despite pathological studies and a long history of clinical findings the pathological progression of ALS had not been clearly defined. This was probably because it was difficult to correlate clinical symptoms and motor neuron loss in human patients. They proposed two possible models to explain the progression of clinical symptoms.

The first one was that the patient had probably undergone a long period of motor neuron death at the time of muscle weakness. The second possibility was there is no motor neuron death; there is a decline of motor neuron function at the onset of clinical disease. They found that mitochondrial damage preceded the onset of the disease, and that progression of ALS in the mouse model was in four stages based on changes in muscle strength. Each stage showed specific pathological features. There were marked mitochondrial changes before the onset of muscle weakness. There was severe mitochondrial vacuolation at the time of muscle strength decline. Secondly, vacuolation is transient and decreases at end stage disease. The third stage signifies a degenerative process in the motor neuron that inhibits their function, but not death. The last stage is death of many neurons occurring at the paralysis and end stage of disease. In this fourth stage there is axonal atrophy, but during these stages, a majority of motor neurons have not died and could probably be rescued by effective therapy. This paper added much to our knowledge of progression of this disease [6].

Spees and Olson, *et al.* published a paper in 2006 showing that mitochondrial transfer between cells could rescue aerobic respiration [7]. Their goal was to see if stem-like progenitor cells or other somatic cells could repair cells with dysfunctional mitochondria by transfer of functional mitochondria or mtDNA. They used cells that were mutated or depleted of mtDNA by pretreatment with ethidium bromide. These cells were designated as (A549 $\rho^0$ cells). The A549 $\rho^0$ cells were then cocultured with adult non-hematopoietic stem/progenitor cells from human bone marrow (hMSCs) and with skin fibroblast. These cocultures yielded clones of rescued A549 $\rho^0$ cells with good functioning mitochondria. They did extensive testing to determine that the mitochondria were transferred from the fibroblast and hMSCs to the A549 $\rho^0$ cells without cell fusion. The observations confirmed that there was no evidence of cell fusion as a mechanism of mitochondrial transfer. The interactions between hMSCs and A549 $\rho^0$ cells were

done in an attempt to visually confirm the transfer of mitochondria. They transduced hMSCs with lentiviral vectors encoding hvGFP and red fluorescent protein DsRed2 fused to a mitochondrial localizing sequence. The cocultures were followed by time lapse microscopy. They noticed that mitochondrial segments were constantly pinching off from the larger mitochondrial network. Interestingly, mitochondria ran back and forth through cytoplasmic extensions of the cells, and at areas of cellular contact mitochondria reached toward the A549 $\rho^0$ cells. It would not be determined if mitochondria were transferred through direct cytoplasmic transfer or as formed vesicles. It appeared the transfer of mitochondria was not passive but appeared to involve an active cellular mechanism rather than passive uptake of cellular material or organelles [7].

## 3. Later and Recent Research on Proof of Principle for Mitochondria Organelle Transplantation

McCulley and his team have studied extensively the role of injected isolated mitochondria during early reperfusion for cardioprotection. McCulley, Cowan *et al.* published an incredibly detailed paper in 2009 about this subject. Their research was performed in New Zealand white rabbits. In the initial study the donor mitochondria were obtained from rabbit left ventricular tissue. The findings by confocal microscopy showed that injected mitochondria were distributed from the epicardium to the endocardium. The study revealed that isolated mitochondria, isolated from non-ischemic tissue and being respiration competent could protect the heart from reperfusion injury. Importantly, with their isolation technique taking less than 90 minutes; they observed the mitochondria to maintain membrane potential and respiratory competency. They also observed that the use of frozen mitochondria failed to provide cardioprotection [8].

Masuzawo, Black and Pacak *et al.*, all part of the McCulley team reported that transplantation of autologously derived mitochondria can protect the heart from ischemia reperfusion injury. This study was also very extensive checking multiple parameters proving transplantation of autologously derived mitochondria as a unique technique to protect the heart from ischemia-reperfusion damage. The study used New Zealand whited rabbits, and the mitochondria were obtained from small biopsies from the pectoralis major muscle. The isolated autologous mitochondria injected into the hearts were in the interstitial spaces surrounding cardiomyocytes at 0, 2, 4, 8, and 24 hours after injection. There was an extensive subendocardial distribution and labeled mitochondria were localized within cardiomyocytes at 2 hours after injection. These mitochondria appeared to be localized near the sarcolemma between Z lines of the sarcomeres. These internalized mitochondria maintained viability and function producing adequate ATP levels. Importantly, the transplanted mitochondria decreased inflammatory markers and did not promote autoimmunity or arrhythmia [9].

Chuang, Lui and Li *et al.*, from Taiwan have investigated a Pep-1 conjugated wild-type mitochondria isolated from parent cybrid cells incorporating a mitochondria—specific to deliver into MERRF cells (Mito B2) and mtDNA-depleted

Rho-zero cells (Mito $\rho^0$). The peptide medicated mitochondrial delivery (PMD) entered the cells easily, lasted for at least 15 days in both cells and rescued mitochondrial function and prevented mitochondria dependent cell death. These early results suggested that PMD could possibly be used as a potential therapy for mitochondrial dysfunction and diseases. This observation was very encouraging as though cell penetrating peptides like Pep-1 had been shown to deliver other agents to cells *in vitro* and in vivo, their delivery of organelles and mitochondria were unknown.

These researchers studied extensively the recovery functions, cell viability, and mitochondrial biogenesis in the rescued cells. There was improvement in the membrane potential with significant induction of ATP synthesis and reduction in lactate production. The important result was that PMD restores mitochondrial function and also reduces the tendency of cell death caused by mitochondrial dysfunction. Mitochondrial biogenesis genes were also upregulated by (PMD) for several days, and this confirms that PMD restores mitochondrial function by stimulating mitochondrial biogenesis [10]. This is an extremely important observation especially if we are going to bring MOT to the clinical arena for human mitochondrial disorders.

Kitani, Kami, Matoba and Gojo have reported on the internalization of isolated functional mitochondria and the involvement of macropinocytosis. They studied the mechanism of mitochondrial uptake in their model by using ethyl isopropyl amiloride (EIPA), a specific inhibitor of micropinocytosis. Coincubation of DsRed2 labeled mitochondria with the cell model was done in the presence of EIPA. After 2 hours, fluorescent microscopy showed suppression of mitochondrial transfer in the EIPA group vs the non-EIPA group confirming EIPA treatment eliminated the therapeutic effect of mitochondrial transfer. After a detailed study, their findings suggested that mitochondrial transfer with its beneficial effects is probably a prominent biological process in mammalian cells. Their data demonstrated the potential of MOT for mitochondrial diseases, such as, myocardial infarction and stroke [11].

In 2015, some of the Taiwan group with others presented an in vivo study that has contributed very much to the proof of principle that MOT is a viable biotherapy for mitochondrial disorders. In their previous *in vitro* study (10), they demonstrated an effective technique for treating mitochondrial diseases with mitochondrial transfer enhanced by conjugating mitochondria to Pep-1, a cell penetrating peptide [10]. In this study, they looked at the efficacy of MOT for Parkinson's disease (PD) *in vitro* and in a Spraque-Dawley rat model. They compared the transfer of allogeneic and xenogeneic mitochondria with and without Pep-1 conjugation. The *in vitro* cell line was (PC 12) and the rats were a 6 hydroxydopamine (6OHDA) lesion model. Isolated mitochondria were injected into the medial forebrain bundle (MFB) in the nigrostriatal loop and not in the soma of the dopamine neuron of the substantia nigra (SN). This was done to investigate MOT and the dynamics of the transfer in neuron axon transport in PD pathology.

Transfer of allogenic and xenogeneic Pep-1 labeled mitochondria greatly sustained mitochondrial function, survival, and neurite outgrowth in PC12 cells in the *in vitro* model. They were able to identify the translocation graft of the allogeneic mitochondria from the MFB to the calbintin-positive SN neuron even after a 3-month period from treatment. They found that tyrosine hydroxylase was restored in the dopaminergic neurons in the substantia nigra pars compacta and striatum. Mitochondrial complex I expression was rescued. This confirmed a serious possible proof of principle for MOT. The fact that the Pep-1 medicated mitochondrial transplantation improved motor movements and improved the deterioration of dopaminergic neurons in the rat models lasting for 3 months before investigating the rat brain. It is important to mention that the xenogeneic transplantation was beneficial for the PD therapy but was less effective than the allogeneic transplant at 3 months [12].

Another significant contribution to proof of principle for MOT for mitochondrial disorders was published in 2016 by again the Taiwan group. In this study, they wanted to explore if after internalization of exogenous mitochondria was there symbiosis with the host cells that was essential for the therapeutic effect. They investigated this in a rat brain stroke model induced by middle central artery occlusion (MCAO). They also did *in vitro* studies in rat primary cortical neurons subjected to a nutrient depleted environment. They used xenogeneic mitochondrial obtained from hamster cells to test their therapeutic efficacy for eliminating ischemia and stroke related stress. The study was thorough and extensive, reviewing histologic features of protection, neural protection, mitochondrial uptake in host cells, ratio of mitochondrial uptake and the exact mechanism of mitochondrial therapy. The animal model was a Spraque-Dawley rat.

The motor function of the MCAO treated rats was severely impaired but the ones that had direct injection of xenogeneic mitochondria 24 hours after surgery had marked recovery of motor function at 7 days post operation. The rats that had arterial infusion of mitochondria did not at 7 days but had a similar level of motor activity recovery at 14 days as the direct injection group at 7 days. Their results confirmed that hamster mitochondria transfer protects neural function and promotes functional recovery in brain ischemic rats. They noticed a low percentage of fusion between internalized and the host mitochondria. This suggests the recovery may not depend on fusion between host and engrafted mitochondria necessary for xenogeneic mitochondrial-mediated neural protection. The exogenous mitochondria may just be a source of ATP and or a ROS scavenger to protect cells from damage by free radicals [13].

A recent review by Gallihue, Patel and Rabchevsky discussed mitochondrial transplantation strategies as potential therapeutics for central nervous system trauma [14]. They discussed all the methods of mitochondrial transfer or transplantation. This paper is great for those interested in some of the more possible mechanisms of transfer. Shi, Zhao, Fu and Fu have reposted results of the intravenous administration of mitochondria for treating experimental Parkinson's disease. The mitochondria increased the behavioral recovery close to the control

levels. The labeled mitochondria were found in multiple different organs and tissue types. The intravenous systemic injection demonstrated that the mitochondria reached targeted and untargeted tissues. They postulated that the mechanism of uptake was endocytosis because they were not seen in red blood cells, which lacks the ability for endocytosis [15].

## 4. Discussion, Conclusion, and Future Direction

The observations and data presented in this review, in our opinion, have presented strong evidence that MOT is probably a viable cellular biotherapy for neurodegenerative disease and other mitochondrial disorders. We will present our experience with MOT, how it can be improved and developed and expanded into a viable clinical cellular biotherapy. Stem cell therapy has received a great deal of attention and regenerative clinics are popping up all over the country. I can assure you that stem cells are ineffective unless they have abundant healthy mitochondria that are involved in much cross talk with the stem cell nucleus [16].

We have most of our experience with MOT in *in vitro* cancer cell lines [17] [18]. However, working in this endeavor made it very hard to ignore the role of mitochondrial dysfunction in neuro-degenerative disease. Therefore, we depleted mtDNA in a mouse neuronal NSC-34 cell line by incubating them in ethidium bromide for 3 months. We then isolated mitochondria from the mtDNA nondepleted cell line and transplanted them into the depleted cells; and MOT immediately rescued these cells and restored total normal function for many generations (data not shown or yet published). These results prompted us to publish a paper on mitochondria and neurodegeneration and the possibility of MOT being a probable cellular biotherapy for neurodegenerative diseases [19].

After a discussion about our results and the possibility of the technology with some research colleagues, we were contacted by a desperate female ALS patient that wanted a chance to try this technology. She was 52 years old. Her ALS was diagnosed 2 years ago. She had tried two clinical trials but her disease continuously deteriorated. We reluctantly met with her and her husband and had several long consultations about the technology and present literature. We advised we could make no promises and that there could be a serious adverse reaction and even death. She decided she had nothing to lose and signed a release to attempt the procedure as a right to try. Her leg muscle strength was tested before the procedure, and she has now had 4 transplant procedures 6 weeks apart. Allogeneic healthy and viable mitochondria were isolated from a human fibroblast cell line and within 30 minutes were injected into her quadriceps and hamstring muscles on both legs. She has had no adverse reaction or complications but has had significant improvement in leg muscle strength by testing and clinical function. She has regained all sensory sensations. This therapy is still a work in progress with so far incredibly positive results.

A detailed case report will be presented in the near future. We are convinced

that based on our research experience, evidence presented in this communication and this patient's results; that MOT will be a beneficial cellular biotherapy for ALS, other neurodegenerative diseases, and possibly cancer. Regarding ALS, if not curative, it will be palliative improving muscle function, mobility, quality of life, possibly longevity and hope. Any patient with any of these diseases would be happy to reach these goals.

Although, results and evidence of MOT in this communication are great and impressive, we believe that changing a major step will improve the technology tremendously. That step is eliminating antibiotics in the cell culture media that donor cells are incubated in before isolating mitochondria for transplantation. We have shown that antibiotics cause tremendous damage to mitochondria inducing severe mitochondrial dysfunction [20] [21] [22]. This is because mitochondria are evolutionary bacteria and share similar ribosomes and protein synthesis machinery as their ancient relative. Most of the investigators in this presentation harvested mitochondria from cells that had been incubated with antibiotic containing culture media to prevent contamination. I predict had they harvested mitochondria from cells not exposed to antibiotic cell culture media, results would have been even better. The damage to mitochondria caused by antibiotics and how the effect of antibiotics skews cell culture data has recently been published by us in PLOS one [23]. Therefore, for accurate cell culture data and healthier mitochondria for MOT antibiotics should be avoided.

We believe we have presented research and early clinical evidence that MOT can be developed into a viable cellular biotherapy for ALS and other neurodegenerative diseases. We are in the embryonic stage of this technology, but we believe with the proper funding and more clinical and research data it can be introduced to the clinical arena. We are convinced it will and can palliate and improve the ALS patient. In order for MOT to be introduced to the clinic many obstacles have to be overcome. It also needs to be practical and easily available. To reach that goal it should be done in a specialized center that is properly funded. We need to be able to isolate healthy mitochondria, possibly culture, expand and bank them for when needed. In our lab mitochondria have been cultured (proprietary) for over 3 weeks. Their viability was confirmed by a vital fluorescent stain, JC-1, indicating a good membrane potential. The cultured mitochondria still entered cancer cells and inhibited proliferation. Cultured mitochondria were also frozen for several weeks, thawed and were still viable, however, they were less in number and JC-1 staining was less intense. This endeavor will be a difficult, expensive and complicated task, but if we can impact the treatment of neurodegenerative diseases, possibly cancer and alleviate suffering and death from these diseases, it is worth it.

There is another important message in this communication and an extremely important observation from our experience with MOT in this ALS patient. That message and observation are that allogeneic and xenogeneic mitochondria show efficacy in animals without serious complications. There were no adverse events in the ALS patient with definite improvement in mobility and muscle strength.

These findings are huge and support proof of principle of this technology and emphasize the need for more research and patient clinical trials. This will, in our opinion, mean establishing a comprehensive MOT center with proper equipment, supplies, and personnel. This will be an expensive project that could yield tremendous results in treatment for all neurodegenerative diseases like Parkinson's, Alzheimer's, ALS, possibly cancer, and other mitochondrial disorders. This would impact the lives of millions of people, and there is now enough proof of principle to give this project a super chance. Stem cell therapy and organ transplantation have proved their place in medicine, and now it is time to give birth to Mitochondrial Organelle Transplantation as a cellular biotherapy for these diseases. The time is NOW!!

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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