From: [redacted] <[redacted]>
To: Jeffrey Epstein <jeevacation@gmail.com>
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here is the concept i am discussing w arch capital today and then w third rock and voyager on thursday and friday. i will also go visit the scientists that harvest and inject mitochondria at harvard (hearts only).

oxygen and energy are the two highest order system issues - nonspecific to just add oxygen or energy but it works for everything. doesn't fix underlying problem but does buy time, improve function and prevent greater damage from certain injuries if caught quickly. i think it can change the game big time in the neuro space.

Mitochondrial transplantation in the human brain

Idea

Mitochondrial transplantation is based on the delivery of isolated, viable mitochondria to the target organ to restore bioenergetic function.

I believe we can augment or replace mitochondria in the brain damaged by ischemia/aging/disease as a mechanism to enhance cellular function and cellular rescue.

Feasibility

- **Human trials underway elsewhere.** 2016 heart trials effective - cardiac, skeletal muscle, pulmonary & hepatic tissue + neuronal
- **Augments a natural process.** Glial/neuronal bidirectional organelle transfer, retrograde axonal recycling
- **Known delivery mechanisms.** Accessible directly or via arterial endovascular
- **Known outcomes in other organs with similar bioenergetic demands.** Cardiac trial results show that 10 min following mitochondrial transplantation myocardial function is significantly enhanced as compared to hearts receiving injection of respiration media (vehicle) alone and that this function remains enhanced for at least 28 days – the end point of current studies.

Safety

- **Seems to mimic and turbocharge a natural process.** Direct injection and vascular - rescues and restores function without immune, autoimmune activation or arrhythmia, etc
- **No systemic effects or side effects.** In all studies of animal or humans, the distribution of mitochondria following delivery by direct injection or by vascular infusion remains within the end organ and is not detectable in other organs. This finding is important as the delivery of mitochondria by vascular infusion provides for localized therapy without cross-contamination to other end-organs.
- **Easy harvest.** All cells in the human body contain mitochondria, except erythrocytes. Unless there is an underlying mitochondrial genetic disease, brain mitochondria in degenerative disease and aging are uniquely affected in function or reduced in amount.

Efficacy

- **Compared to...** Data indicates that autologous mitochondrial transplantation is efficacious as a cardioprotective therapy whether these organelles are delivered by directly injection or delivered by vascular infusion through the coronary arteries.
- **Mitochondrial isolation.** Mitochondrial transplantation is based on the delivery of isolated, viable mitochondria to the target organ. The isolation of mitochondria can be performed using a variety of techniques and methodologies currently takes 90-120 minutes to complete.
- **Lifespan.** Isolated mitochondria can be stored on ice for approximately 1 h but storage beyond this time point greatly reduces efficacy. Previous reports that have shown that mitochondrial bioenergetic function is decreased to bw 10–15% of normal after the mitochondria were frozen, even when preservatives are used.
- **Organelle dynamics.** Total mitochondria must be used for mitochondrial transplantation. The bioenergetic function of this population includes that of sub-sarcolemmal and intra-fibrillar mitochondria. Previous studies have shown that mitochondrial sub-populations have differing but suboptimal effects. In most studies the number of mitochondria used for direct injection is 1–3 × 107 mitochondria. The mitochondria are suspended in buffer and injected directly or via the vascular tree.
- **Lifespan of transplant.** Fluorescence microscopy has demonstrated that transplanted mitochondria delivered by direct injection are present and viable for at least 28 days following injection into the myocardium in animals. In the human heart: The transplanted mitochondria are widely distributed from the epicardium to the subendocardium. The majority of injected mitochondria are found initially within the interstitial spaces between cardiomyocytes.
- **Time to effect.** In the human heart: within 1 hour post-directly injected delivery, the transplanted mitochondria are detectable within cardiomyocytes residing near the sarcolemma between Z lines of the sarcomeres and in clusters around endogenous damaged mitochondria as well as near the nucleus. Vascular delivery of mitochondria through the coronary arteries results in the rapid and widespread distribution of exogenous mitochondria throughout the heart, within 10 min and provides for cardioprotection. Also delivered mitochondria to the lung by vascular infusion through the pulmonary artery. In these studies, the mitochondria were

labeled with 18F-rhodamine 6G. Positron emission tomography and computed tomography showed that the mitochondria were localized in the lung and were not detectable in any other areas of the body.

- **Dose calculation.** Enumeration of injected mitochondria has shown that 43% of the injected mitochondria are attached to or found within cardiomyocytes.
- **Mechanism.** At present, no known mechanism for this "end-organ homing", where the transplanted mitochondria are retained by the immediate down-stream organ, but suggest that this observation may play an important therapeutic role in future studies and applications using mitochondrial transplantation.