

Potential Role of Cardiolipin in Improving U M Neuron Health
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Dr. Gautam began by thanking The Spastic Paraplegia Foundation for the opportunity to make this presentation. This is his first time to attend a Spastic Paraplegia Foundation Annual Conference. He also thanked the Spastic Paraplegia Foundation for the honor of having his grant proposal rewarded for this coming two years. He hopes to bring more cellular understanding about PLS. His lab is very involved with upper motor neuron research.

He will be talking about TDP-43 pathology and how it has been detected with HSP and PLS. Degenerating Upper Motor Neurons with TDP-43 pathology have mitochondrial problems especially within the inner mitochondrial membrane (IMM). Targeting the integrity and function of mitochondria could be an effective treatment strategy for both HSP and PLS.

A diagram of the upper motor neuron was put up on the screen that showed how it starts in the upper brain and continues down through the spinal cord to the lower muscles. The diagram demonstrated how the degenerating upper motor neurons of people with PLS and HSP have Cytosolic TDP-43 inclusions, an Autophagy deficit, Proteasome deficit and Mitochondrial CA2 dyshomeostasis.

TDP-43 research began with ALS research and now they know that it exists for PLS & HSP patients as well. TDP-43 usually lives in the nucleus of a cell but in the diseased condition will migrate into the cytoplasm and aggregate. It predominantly affects the RNA Metabolism. It causes Nonsense mediated decay, altered auto regulation, non-coding RNAs dysfunction and Altered

epigenetics. Most importantly, TDP-43 affects many different parts of the mitochondria function.

He showed a very enlarged cellular photo of mitochondria that demonstrated how the outer mitochondrial membrane is OK but TDP-43 causes the inner membrane to be totally lost and so the mitochondrial function is completely lost.

He showed another photo comparing the upper motor neurons in mice with the upper motor neurons in people and how they showed exactly the same diseased pathology. They know, therefore, that any treatment they can use to improve the upper motor neuron pathology in these mice will also, almost certainly, improve the same function in humans.

The diseased mice were 60 days old and so adults. They wanted to see how early these malfunctions appeared so they looked at a 15 day old mouse (a child), and the malfunctions were just barely beginning to show.

Cardiolipin is a protein that is very important to the structure of the membranes of mitochondria. Because of its unique structure, it allows the membrane to fold. When the membrane folds, cardiolipin is sitting at the fold. Without cardiolipin, the membrane cannot fold and so is very vital for the mitochondria function. Cardiolipin is very important for both the function and structure of the inner mitochondrial membrane. Targeting the integrity and function of mitochondria could be an effective treatment strategy for HSP and PLS.

They are studying treatment strategies for improving the inner mitochondrial membrane with the help of a company called Stealth Biotherapeutics. Stealth Biotherapeutics has a compound called SBT-272. Their initial experiments show that it binds to cardiolipids and stabilizes this molecule.

They strongly suspect that SBT-272 will be a good treatment for people with HSP and PLS and this has been demonstrated with HSP mice of various ages. This is true both for the structure and function of their mitochondrial cells. He showed several photos showing how this drug improves the function and motility of the mitochondrial cells. They have done experiments to determine the best concentration of SBT-272 and have shown that it is more effective with ALS cells than the other known ALS drugs.

In summary:

SBT-272 improves:

1. Mitochondrial membrane structure
2. Mitochondrial function
3. Mitochondrial motility
4. Overall UMN health
5. Provide neuroprotection
6. Reduce astrogliosis and microgliosis

He is also working on High Density Lipid (HDL) nanoparticles to bind to scavenger receptor B1 (SR-B1) expressing cells in another way to improve the health of Cardiolipin and improve mitochondrial health and function. They have also done experiments to show what the proper dosage should be for HDL nanoparticles. They tested HDL nanoparticles on HSP mice over a long time span and it showed continued improvement in the function of these mice.

Summary:

Upper Motor Neurons with TDP-43 pathology display prominent mitochondrial defects.

Translation is at the cellular level: focused on diseased neurons (construct. Validity.

Improving the integrity of the inner mitochondrial membrane is important. Improved inner mitochondrial membrane integrity results in:

1. Enhanced UMN health in vitro,.

2. Retention of UMNs in vivo,
3. Reduction of astrogliosis and microgliosis.

Dr. Gautam closed by answering a few questions.