



FA Research Flash Talk Series

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Need a break from COVID-19 news?
Join Us for the FA Research Flash Talk Mini-Series!

In honor of FA Awareness Month, FARA is excited to launch our FA Research Flash Talk series- featuring Young Investigators from FARA funded laboratories around the world. This five-part series will cover key aspects of FARA funded research from gene and protein function to clinical outcomes and insights. Each session will include Flash Talks from three to four Young Investigators (ie postdocs and graduate students). A Flash Talk is limited to a maximum of five minutes and a single PowerPoint slide, and will be suitable for a lay audience. We have also allotted time for a brief Q&A following the talks. If you'd like to attend a session, email info@curefa.org to request registration information.

Understanding FXN Gene and Protein Function

May 4, 2020 - 12pm EST

FXN Gene Performance

Layne Rodden, University of Oklahoma

We are focused on determining if DNA hypermethylation in a potential enhancer element in intron 1 of the FXN gene contributes to FXN silencing in Friedreich's ataxia.

Targeting to the Human Frataxin: Quaternary Addition of Small Trojan Tutors

Florencia Pignataro, University of Buenos Aires

In mitochondria, Iron-Sulfur cluster are assembled by the Iron Sulfur Cluster assembly machinery which is formed by several proteins and where frataxin plays a key role. Frataxin accelerates the Iron-Sulfur cluster formation and this process turns out to be impaired in frataxin deficiency. In this work, we studied the modulation of Fe-S clusters formation by quaternary addition of small specific protein tutors against FXN and some of its unstable variants.

On the Structure of the Human ACP-ISD11 Complex

Georgina Herrera, University of Buenos Aires

Iron-Sulfur clusters are assembled in mitochondria by a complex of proteins, including the Desulfurase NFS1 which is stabilized by the ISD11 protein. This protein has recently been shown to interact with the mitochondrial acyl carrier protein. Here, we will present insights on the biophysical properties and structure of the ACP-ISD11 complex.

Role of Mutations in FRDA

Leah Gottlieb, University of Pennsylvania

The presentation will briefly discuss the difference between mature mitochondrial frataxin and isoform E, mutations in frataxin that arise in some cases of Friedreich's ataxia and survey how they impact both mature and isoform E frataxin levels.

Understanding FRDA with Disease Models

May 7, 2020 - 7pm EST

Generation of Proprioceptor Neurons from hPSC Using Genetic Engineering

Amy Hulme, University of Wollongong

This talk will focus on the generation of proprioceptor neurons from hPSC using genetic engineering, which will be used to develop therapies for FRDA.

Investigation of the Mechanism of Neuronal Preservation after Hematopoietic Stem Cell Transplantation using Mini-Brain Model

Priyanka Mishra, Univeristy of California- San Diego

Our group previously showed that wild-type hematopoietic stem and progenitor cell (HSPC) transplantation prevents development of the disease phenotype in a mouse model of FA, providing an evidenced-based approach for treatment of FA patients. We also observed transfer of frataxin from HSPC-derived microglia to diseased neurons in brain, spinal cord and dorsal root ganglia. However, the mechanism of frataxin transfer and their functional implications are still unknown. Thus, the aim of our study is to explore the transfer mechanisms of FXN from microglia cells to neurons by utilizing the induced pluripotent stem cell (iPSC)-based mini-brain model. Our results suggest that iPSC derived microglia cells carrying frataxin could be transferred through long membranous extensions called tunneling nanotubes (TNTs) to the diseased neurons.

Cerebellar Degeneration in an Inducible Frataxin Knockdown Mouse Model of FRDA

Elizabeth Mercado Ayon, Children's Hospital of Philadelphia

I will present data showing how knockdown of frataxin leads to degeneration of VGLUT1- and VGLUT2- containing glutamatergic and GAD65-positive GABAergic synapses in FRDAkd mouse cerebellum.

Disrupted proteostasis in skeletal muscle of mice with Frataxin depletion

Cesar Vasquez, Thomas Jefferson University

Maintenance of skeletal muscle mass is controlled by two processes, protein synthesis/translation (anabolic state) and protein breakdown/degradation (catabolic state). Muscle protein balance together with energy metabolism control muscle function. Here, we evaluated mass and function under Frataxin (Fxn) depletion in mice. We studied skeletal muscle mitochondrial metabolism and stress response, as well as specific pathways controlling protein translation (mTOR/eIF2a) and degradation (ubiquitin-proteasome system). In Fxn-depleted skeletal muscles, alongside metabolic alterations, we detected a smaller muscle mass, accompanied by decreased grip strength. Biochemical analysis of muscle indicated a proteostasis imbalance, with evidence for enhanced protein degradation and suppressed protein translation. Both of these changes would strongly favor decreased muscle mass, which, in turn, would decrease absolute force generation by muscle.

Molecular Pathways in FRDA

May 15, 2020 - 12pm EST

Thermogenesis Dysfunction in a Mouse Model of Frataxin Deficiency: Brown Adipose Tissue as a Possible Therapeutic Target to Prevent Type 2 Diabetes Development in Friedreich's Ataxia Patients

Riccardo Turchi, University of Rome

Several studies have recognized brown adipose tissue (BAT) as anti-diabetic tissue. By using the FXN knock-in/knock-out (KIKO) mouse model, we performed a multi-layered analysis of BAT morphology and function. As expected, we found a significant raise of serum triglycerides and cholesterol levels that was accompanied by the increase in the concentration of circulating leptin (an adipose tissue-secreted hormone), hinting a type 2 diabetes-like profile in KIKO mice. We observed that BAT of KIKO mice shows accumulation of intracellular lipids and impaired lipid degradation and we found an altered number and morphology of mitochondria. Finally, by comparing the BAT transcriptome of KIKO with respect to WT mice following cold exposure, we found a blunted up-regulation of genes orchestrating the thermogenic program. Overall these data indicate that BAT could be dysfunctional in FA patients and give effort to the idea that this tissue represents a valuable druggable target to treat metabolic complications in FA.

Investigating the Role of Bioactive Sphingolipids in Friedreich's Ataxia (FRDA)

Ester Kalef-Ezra, Brunel University

Sphingolipid is a group of lipids important for the activity of the brain and therefore, disturbances in their metabolism can have a huge impact on brain function. We have recently found that the sphingolipid levels and their related genes are altered in FRDA mouse and human samples, which may play a critical role in the disease progression. We aim to have a clear picture of the sphingolipid changes in FRDA and to identify potential and novel targets for the development of therapeutic strategies in the disease. While we are assessing the safely and effectively use of gene therapy to 'cure' the root cause of FRDA, there is an urgent, unmet need to alleviate the suffering and prolong the lives of individuals with FRDA by other, scientifically reasoned, approaches. We seek to directly target the molecules that cause extensive cell damage and drive disease progression, using a compound that is readily available, inexpensive and already clinically tested in humans for other diseases.

Nrf2 and Frataxin in FRDA

Nicolas Eskenazi , University of Pennsylvania

This talk will be focused on the link between frataxin and the antioxidant-response protein Nrf2 in Friedreich's ataxia, and how Nrf2 could be a promising target and drug biomarker for FRDA treatment.

Therapeutic Approaches

May 21, 2020 - 12pm EST

How does Omapalaterone Affect Your Cells

Joseph Johnson, Children's Hospital of Philadelphia

Omapalaterone performed well in its clinical trials, but we need more a more thorough understanding on how it affects Friedreich ataxia patients' cells. I will be speaking about how this drug affects mitochondrial morphology and function in FA.

CRISPR/Cas9 Gene Editing of Friedreich's Ataxia Patients' Blood Stem Cells

Joseph Rainaldi, University of California- San Diego

Since publishing in 2017 on the treatment of FA in a mouse model through the transplantation of blood stem cells (hematopoietic stem cells), the Cherqui lab at UCSD has worked to translate this method into a therapeutic capable of autologously treating humans with FA. Through utilization of the CRISPR/Cas9 system, the lab group has been able to gene edit the blood stem cells of FA patients, generating cells capable of producing healthy levels of frataxin protein without any observable toxicity. The corrected cells will be further evaluated before selection as a clinical trial candidate.

Safe Delivery of Frataxin Gene to Mouse Brain and Body Using Engineered AAVs

Acacia Hori, Cal Tech

We use engineered viruses to direct the delivery of the frataxin gene to the cells and organs that need it most in mouse models of FA, while avoiding off-targets such as the liver in order to decrease potential side effects of this type of therapy.

Clinical Outcomes & Insights

May 28, 2020 - 7pm EST

Heart Proteins in Friedreich Ataxia

Chukwunonso Okoli, VA Medical Center- Albany

I will be discussing heart proteins that are significantly different in individuals with FA, specifically two that are related to diabetes mellitus which is also prevalent in persons with FA. I also plan on discussing the significance and possible implications of the changes in these proteins.

SpeechATAX - a Multi-Language Biofeedback Speech Treatment for Ataxia

Hannah Reece, University of Melbourne

SpeechATAX is an intensive home-based speech rehabilitation program developed by the Centre for Neuroscience of Speech at the University of Melbourne. SpeechATAX is based on principles of motor learning and neuroplasticity and is designed specifically for people with hereditary ataxia to improve overall intelligibility of speech.

Survey on Bone Health in Friedreich's Ataxia

Jaclyn Tamaroff, Children's Hospital of Philadelphia

I will review the potential risks related to poor bone health in FA. I will then describe a survey that will be distributed to better understand the burden of fractures and bone health concerns.