Basic Research Grants Funded for 2013

To Characterize the Role of SMN Protein in Myoblast Fusion. Barrington G. Burnett, PhD at Uniformed Services University of the Health Sciences for $95,000 for two years.
Objective: Our preliminary results indicate that SMN-deficient muscle cells have reduced capacity to fuse into myotubes to form muscles. Our goal is to characterize the role of SMN in myotube formation using SMN-deficient muscle precursor cells.
Research Strategy: Using muscle cell lines we will compare the gene expression changes, structural dynamics, and membrane fusion events of wild type and SMN-deficient cells during myotube formation.
Significance: While motor neuron degeneration is critical to the pathogenesis of SMA, it is becoming clear that SMN protein deficiency in peripheral tissues might also contribute to the disease. In particular, there is evidence from human tissue and SMA model organisms that SMN deficiency may lead to intrinsic muscle defects. We hypothesize that SMN is involved in myotube formation. Greater understanding of SMN function will allow us to determine how and why deficiency of SMN leads to SMA pathology in muscles and nerves.

A Multi-Center Electrophysiological Evaluation of Clinically Relevant Phenotypes in SMA Mouse Models. Laurent Bogdanik, PhD & Cathleen Lutz, PhD at The Jackson Laboratory for $90,000 for one year.
Objective: Electrophysiology measures the activity of the motor nerves controlling the muscles by non-invasive methods like skin-adhesive electrodes. We will show that these techniques, frequently used on patients, can also reliably identify the disease progression in SMA mouse models.
Research Strategy: Our multicenter collaboration will consist of providing three research centers with groups of virtually identical mice, all modeling SMA. The three centers will measure in parallel the electrophysiological signals on these mice and compare data. These three centers include: 1) Laurent Bogdanik at The Jackson Laboratory, 2) W. David Arnold, MD at The Ohio State University, and 3) Seward Rutkove, MD at Beth Israel Deaconess Medical Center / Harvard Medical School**.**
Significance: Standard research procedures will be provided to the research community to allow for the comparison of different therapeutic strategies in SMA mouse models, across different institutes. Current mouse models lack symptoms that can be easily measured and resemble patient symptoms. By establishing a procedure to measure neuronal activity, this project will offer a powerful and clinically relevant way to follow symptoms in mice.

Astrocytes and Oxidative Stress in SMA. Allison Ebert, PhD at the Medical College of Wisconsin for $95,000 for one year.
Objective: We aim to determine if astrocytes directly contribute to oxidative stress and motor neuron death in an in vitro model of SMA. Astrocytes are a type of support cell for motor neurons in the central nervous system.
Research Strategy: We propose to use astrocytes and motor neurons derived from SMA patient and control inducedpluripotent stem cells to study mitochondrial function and markers of oxidative stress to assess cell health, as well as measure cell death.
Significance: These studies will provide additional mechanistic insight into the contribution of astrocytes to disease pathology in SMA, which could have important implications for therapeutic development.

Investigate Ubiquitination- Dependent SMN Transport. Ke-Jun Han, PhD at the University of Colorado for $95,000 for two years.
Objective: The project goal is to determine how SMN protein is localized and transported to axons. The project will assess whether modification of SMN with a tag called ubiquitin regulates this process.
Research Strategy: The team will use biochemical and cell biological techniques to determine 1) how SMN is recruited into a subcellular compartment called the trans Golgi network, where proteins are sorted for transport to different parts of the cell; and 2) whether modification of SMN with the tag ubiquitin inside the golgi network regulates whether SMN protein and SMN mRNA is transported to the motor neuron axons.
Significance: These findings could unravel a novel role for the ubiquitin modification of SMN in regulating SMN function and localization, which has potential implications in the understanding of SMA pathogenesis and points of intervention for possible treatments.

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The Role of Glia Cells in SMA. Chien-Ping Ko, PhD at University of the Southern California for $75,000 for a second year of funding.
Objective: The present proposal will investigate the involvement of two types of glial cells (supporting cells for neurons), called astrocytes and microglia, in SMA pathogenesis.
Research Strategy: We will use genetically engineered mice to restore or reduce SMN expression selectively in astrocytes. We will also use cell-based assays to study the mechanisms of neuron-astrocyte interactions and neuron-microglia interactions in SMA.
Significance: The results of the proposed studies would provide a novel concept that, in addition to motor neurons, glial cells may also play a key role in SMA pathogenesis. The elucidation of new roles of astrocytes and microglia in SMA would in turn lead to new therapeutic approaches by targeting these glial cells.
Funding Made Possible by a Generous Donation to FSMA from The Dhont Family Foundation.

The Non-SMN Mediated Benefits of The HDAC Inhibitor Trichostatin A. Rashmi Kothary, PhD at The Ottawa Hospital Research Institute for $100,00 for two years.
Objective: Our goal is to better understand how a small molecule (TSA) that is a global gene regulator ameliorates the disease symptoms and pathology in a mouse model of SMA.
Research Strategy: We will study what aspects of muscle growth and maintenance are targeted by TSA, both at the biological and molecular levels. **Significance:** These studies are directed towards gaining a better understanding of the mechanism of action behind the beneficial effects of TSA on our intermediate mouse model of SMA. Our data currently points to a SMNindependent mechanism for the drug. Therefore, this work has the potential to find novel therapeutic strategies for SMA by generating additional pathways to target for drug discovery beyond SMN enhancement.
Funded by Families of SMA Canada.

Investigating The P53 Signaling Pathway in Pathogenesis of Mouse Models of SMA. Lyndsay Murray, PhD of the University of Edinburgh for $50,000 for one year.
Objective: In this study we aim to ask two main questions. Firstly, how early does motor neuron cell death occur? Secondly, we want to investigate whether delaying cell death while administering other therapies, can increase the beneficial effects.
Research Strategy: We will use mouse models of SMA to investigate when motor neurons actually start to die in SMA. We will also use transgenic mice to restore SMN protein at symptomatic phases while simultaneously inhibiting cell death.
Significance: This work has important implications both for understanding the basic process of disease in SMA and for developing a new therapeutic approach, which could help patients who are treated after their symptoms begin. It will also begin to assess combination therapeutic approaches for SMA.