Basic Research Grants Funded for 2011

Stem Cell Models of SMA: Molecular and Cellular Mechanisms. Christopher Henderson, Ph.D., Columbia University, $160,000 for 2 years.

Objective: One of the main challenges in understanding SMA is determining how the lack of a precise protein, SMN, found in all the cells of the body primarily affects motor neurons. The objective of this project is to establish and characterize human cellular models of the disease "in a dish" and to use these models to determine the molecular pathways affected.
Research Strategy: This team will develop unique new tools, using human stem cells carrying the genetic mutation responsible for SMA, which can be differentiated in vitro into any kind of specific cell type of the human organism. In this case, they will be turned into motor neurons. They will be used to generate a series of SMA motor neurons with differing levels of SMN protein and then characterized both at the morphological and molecular level, in order to better understand the pathological of the disease. Thus the project will generate a highly valuable set of tools for studies of SMA pathology in a dish. The project will be impact multiple points of SMA translational research, for instance modeling SMA path to determine the molecular cellular changes in SMA motor neurons and for cell based drug screening.
Significance of Project: Even though the biological cause of SMA in humans has been identified and animal models of the disease have been developed, remarkably little is known about the cellular and molecular mechanisms that lead to the specific loss of motor neurons in the human patients. The use of this unique set of tools will help us to answer these questions and to lead to new targets for therapeutic strategies for SMA.

New Neuromuscular Preparations for In Vivo Evaluations of Drug Efficacy in SMA. Chien-Ping Ko, Ph.D., University of Southern California, $70,000 for 1 year.

Objective: The project will use a mouse model of SMA to test the hypothesis of whether defects in neuromuscular synapses play a key role in the pathogenesis of SMA, and also to establish novel neuromuscular preparations for in vivo evaluation of drug efficacy in SMA.
Research Strategy: The project will characterize how certain muscles are highly vulnerable to loss of synaptic connections between motor nerves and muscle fibers. In addition, these vulnerable muscles will be used to test for drug efficacy in SMA. The proposed study is expected to establish a group of vulnerable muscles that can be used for future in vivo drug testing in SMA animal models.
Significance of Project: The proposed studies will provide new understanding of the basic biology of synapse maintenance and disruption, which would in turn lead to novel insights into the pathogenesis of SMA and its apparently selectivity. Furthermore, this research can help lead to new therapies that promote synapse maintenance and prevent synapse disruption in SMA.

Validation of Spinal Muscular Atrophy Biomarkers in VALIANT Subjects
Co-PI: Stephen Kolb, M.D., Ph.D., The Ohio State University, $70,000 for 1 year.
Co-PI: Louise Simard, Ph.D., University of Manitoba, $25,000 for 1 year.

Objective: In 2007, this team initiated a Phase II Placebo Controlled Trial of Valproic Acid in Ambulant Adults with Spinal Muscular Atrophy (VALIANT; ClinicalTrials.gov identifier NCT00481013). The trial is now completed and the analysis of clinical outcomes is currently in progress. During the course of the trial, a large number of blood samples were obtained so that a systematic analysis of molecular SMA biomarkers could be achieved.
Research Strategy: The team plans to measure SMN mRNA in the Simard lab and SMN protein in the Kolb lab using well-characterized, validated assays in SMA patient blood samples. They will also assess a more novel assay of SMN functionality in human samples for SMN functional activity. In addition, they will assess HDAC activity in these samples, as this is the proposed mechanism for Valproic acid. It is anticipated that they will detect any biochemical changes in SMA patient blood samples that are the result of VPA administration.
Significance of Project: The design of therapeutic clinical trials for SMA patients hinges upon the expectation that survival or objective improvement in phenotype will be achieved. However, this is greatly aided at early stages by molecular biomarkers. At the completion of this project, it is expected that this project will be able to provide clearer recommendations for the design of biological measures in SMA trials.
Co-Funded with FSMA Canada.

Basic Research Grants Funded for 2011

Identification and Characterization of Factors Critical in Regulating the Selective Vulnerability of Distinct Motor Neuron Pools in SMA Model Mice. Rashmi Kothary, Ph.D.; Lindsay Murray, Ph.D., University of Ottawa, $120,000 for 2 years.

Objective: In SMA, motor neurons connect the spinal cord to skeletal muscle degenerate. However not all motor neurons are affected equally, with those targeting muscles for control of posture and respiration being the most vulnerable. The project objective is to determine the underlying differences in gene expression between motor neurons that are vulnerable in SMA and those that are less vulnerable.
Research Strategy: This team proposes to use mouse models of SMA to dissect out individual motor neurons from the spinal cord and use novel technology to compare the expression profile of genes that are turned on and off between motor neurons which are vulnerable and non-vulnerable to degeneration in SMA. This work will help identify genes that make motor neurons more vulnerable to degeneration in SMA.
Significance of the Project: This work will help uncover the fundamental mechanisms that make motor neurons vulnerable in SMA and will generate new avenues to develop therapeutic strategies by identifying new drug targets.
Funded by FSMA Canada.

Exploring novel genetic determinants of disease severity in spinal muscular atrophy model mice. Umrao Monani, Ph.D., Columbia University, $160,000 for 2 years.

Objective: SMA is caused by mutations in the SMN1 gene that lead to reduced SMN protein. The project stems from observations that members of the same family sometimes exhibit different SMA severities, even though they have same genotype (the same SMN1 mutation and same number of SMN2 gene copies). The researchers aim to better understand the genetic and biochemical pathways that lead from reduced SMN protein to the neuromuscular phenotype characteristic of SMA.
Research Strategy: Mouse models of the disease will be used to probe the existence of genetic factors that alter the course and severity of SMA. This project expects to successfully identify one or more factors that modify disease symptoms in SMA mice.
Significance of Project: The identification of factors that alter the disease in SMA mice will shed light on novel pathways that lead from SMN protein deficiency to neurodegeneration. Additionally, they could lead to the design of novel and more effective therapies for SMA by identifying new drug targets.

Effects of SMN on mRNA transport and local protein synthesis in motor axons. Wilfried Rossoll, Ph.D., Claudia Fallini, Ph.D., Emory University, $140,000 for 2 years.

Objective: SMN carries out an essential function in all cell types, though it still remains unclear why only the highly specialized and polarized motor neurons degenerate in the disease. This research group hypothesize that defects in the transport of messenger RNAs (mRNAs) along the axon and the synthesis of new proteins at the neuromuscular junction itself may be responsible for this selectivity.
Research Strategy: In this study, the researchers propose to investigate defects in mRNA transport and protein synthesis in motor neurons derived from the SMA mouse model. The team plans to identify specific defects in the regulation of mRNA metabolism that may contribute to the selective susceptibility of motor neurons to low levels of SMN.
Significance of Project: The proposed project will help gain insight into the mechanisms leading to specific motor neuron degeneration in SMA, paving the way to the development of new therapeutic strategies.
With Support from Stop SMA.