

## Basic Research Grants Funded for 2012

### **Motor axon development in SMA: Charlotte Sumner, M.D., Johns Hopkins University School of Medicine for \$140,000 for two years.**

**Objective:** We have observed abnormalities of motor axon growth and myelination in SMA patient autopsy tissue and SMA mice. Our primary research question is what is the basis of this abnormal axonal development in SMA? We hypothesize that impaired axonal development is due to SMN deficiency both in motor neurons and Schwann cells. The objective of our project is to establish whether SMN deficiency in Schwann cells is an important contributor to SMA disease manifestations. Schwann cells are the principle [glia](#) or support cells of motor neurons in the [peripheral nervous system](#) (PNS).

**Research Strategy:** We plan to analyze the morphology and gene expression profiles of axons, Schwann cells, and myelin in severe SMA mice and in SMA mice where SMN expression has been selectively increased in motor neurons. We will then generate and analyze novel SMA mice in which SMN has been selectively restored to Schwann cells. Finally, we will evaluate the combination of SMN expression in both motor neuron and Schwann cells to see if this fully restores the abnormalities of axonal development

**Significance:** The results of this project could reveal a previously unrecognized role for Schwann cells in SMA pathogenesis, which will increase our understanding of how SMN deficiency leads to disease manifestations. It will also provide important information regarding which cell and tissue types need to be targeted during the delivery of novel SMA treatments.

### **Regulation of HDAC5 phosphorylation by Cdk5 in SMA: Yong-Chao Ma, Ph.D., Northwestern University for \$75,000 for one year.**

**Objective:** Our goal is to study a novel biological pathway that may be impaired in SMA. Understanding the involvement of this pathway in SMA pathology could lead to a greater understanding of the mechanisms of the disease. It could also have potential therapeutic implications later by identifying new drug targets.

**Research Strategy:** We plan to use SMA mouse and zebrafish models, as well as human SMA and mouse motor neurons to further investigate a novel mechanism that leads to motor neuron degeneration in SMA. This mechanism involves cellular regulation of two proteins called HDAC5 and Cdk5, when SMN is lowered.

**Significance:** The proposed study will provide insights into our understanding of motor neuron degeneration in SMA, and facilitate the development of new therapeutic approaches for SMA by identifying possible new drug targets in the HDAC5 and Cdk5 cellular pathways.

### **The role of glia cells in SMA: Chien-Ping Ko, Ph.D., University of Southern California for \$75,000 for one year.**

**Objective:** The present proposal will investigate the involvement of a type of glial cells called astrocytes in SMA pathogenesis. Astrocytes are star-shaped glia located in the central nervous system (CNS) that hold neurons in place, get nutrients to them, and digest parts of dead neurons. It has been discovered that astrocytes can communicate with neurons and modify the signals they send or receive. This means astrocytes have the potential to be involved in the processing of information and signaling that occurs at the synapse.

**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 in SMA.

**Significance:** The results of the proposed studies will help elucidate new roles of astrocytes in SMA pathogenesis, which in turn would lead to new therapeutic approaches.

### **Arginine Methylation as a Regulator of SMN Activities in Motoneurons: Jocelyn Côté, Ph.D., University of Ottawa for \$140,000 for two years.**

**Objective:** We will study and obtain more information about the role of a novel protein, called PRMT8, which is present at the surface of the cells that are most affected in SMA, the motor neurons in the lower spinal cord.

**Research Strategy:** We will test the possibility that PRMT8 may be able to make the SMN protein that is still present in small amounts in SMA patient cells, more active. Preliminary results suggest that PRMT8 can regulate the binding of specific proteins to a region of the SMN protein called the Tudor domain in motor neurons. We hypothesize that PRMT8 regulates SMN function in motor neurons, and it may be

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possible to stimulate SMN function in SMA cells through modulation of PRMT8 levels and/or activity.

**Significance:** Stimulating the activity of the protein, PRMT8, could potentially have beneficial influence on the activity of SMN that is still present inside SMA cells. Thus our work has the potential to lead to completely new strategies for SMA therapies as well as a greater understanding of how SMN functions specifically in motor neurons.

### **The role of vehicle coat protein alpha-COP in new models of SMA: Sara Custer, Ph.D., Indiana University for \$140,000 for two years.**

**Objective:** This award supports Dr. Sara Custer's postdoctoral training in the lab of Dr. Elliot Androphy at the Indiana University School of Medicine. The main focus of the project is to understand how low levels of the SMN protein leads to dysfunction of motor neurons. To achieve this goal, the group will generate new cell culture and animal models of SMA to gain a better understanding of the basic functions of SMN protein and with novel cellular binding partners in motor axons.

**Research Strategy:** We have identified a protein called alpha-COP that interacts with SMN and will investigate whether this interaction is necessary for normal maturation and function of motor neurons. First, we have generated a cell culture model of SMN depletion, which can be used as a biological assay of SMN functions, such as those important for growth and maintenance of neurons. The cells will be used to determine which aspect of SMN and its various interacting partners are important for neurite outgrowth and normal cellular function. Second, we have used a novel viral-mediated transgenic approach to produce two new mouse lines that will help elucidate the importance of alpha-COP function to SMA pathology.

**Significance:** Our cell culture model provides a rapid, reproducible assay of meaningful SMN function. These cells will be useful in exploring many aspects of SMA pathology. Our novel transgenic system allows for rapid delivery of transgenes into SMA model mice, expediting the study of SMN interacting proteins. Finally, we are characterizing the SMN binding protein alpha-COP, which may be a viable therapeutic target in the future.

### **The when and where requirements of SMN in mild SMA: Christine DiDonato, Ph.D., Northwestern University for \$140,000 for two years.**

**Objective:** The objective of this work is to determine if re-introducing SMN after disease onset and once functional loss has already occurred in milder forms of SMA can be of benefit. Additionally we will also determine whether increasing SMN only in the spinal cord of adult mice will be useful, using the same mild mouse model.

**Research Strategy:** We are using a mild SMA mouse that carries the human SMN2 gene and is also inducible. This means we can increase Smn levels in the animal in different tissues and at different times. In the first set of experiments, we will increase SMN everywhere in the body but at different times. This will allow us to bypass potential problems that might exist in one organ system or another. In the second set of experiments we will only increase SMN in the spinal cord. This experiment will determine whether high levels of SMN are only required within the CNS.

**Significance:** We know from all of the research that has been performed to date that in severe SMA mice there is a limited time window of opportunity in which increases in SMN can be of benefit. We do not know if this is also true for milder forms of SMA, because we have previously lacked the appropriate models. In this project, we will assess this by increasing SMN in adult mice that mimics mild SMA, after measurable functional loss has occurred and during the slow-declining phase of disease.



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