



Families of SMA *Research. Support. Hope.*

COMPASS

A Publication Dedicated To Research Updates

Families of SMA Awards Six New Basic Research Grants for \$710,000.

In this issue of "Compass" Families of SMA announces six new basic research grant awards for 2012. These new awards total \$710,000. Additional funding for both clinical research and drug discovery projects will be announced soon.

Importance of Our Six New Basic Research Grants:

Two of the six new basic research grants in 2012 will help us to understand the functional role of SMN in motor axons. They look to understand whether the SMN protein has a novel function in motor axons and to determine exactly what this function might be. These grants include projects led by **Drs. Custer and Androphy at the Indiana University** and **Dr. Cote at the University of Ottawa**.

The grants to **Dr. Ko at the University of Southern California** and **Dr. Sumner at Johns Hopkins University** will help understand the exact nature of the defects in the both the spinal cord and in the periphery in SMA. They will be studying the role of two different types of glia or support cells that interact with motor neurons, namely Astrocytes in the Central Nervous System (CNS) and Schwann cells in the Peripheral Nervous System (PNS) respectively.

Dr. Ma is a Assistant Professor at Northwestern University. His work focuses on understanding the molecular pathways causing motor neuron degeneration in SMA. He will be exploring ways to exploit the information about these new molecular pathways for therapeutic benefit, by attempting to identify and validate new drug targets.

Finally, Dr. Christine DiDonato also of Northwestern University is working on a new mild mouse model of SMA, which has the potential to more accurately reflect human SMA. She plans to use this model to assess when and where SMN is needed in more mild forms of the disease.

FSMA Research Mission:

Our main research goal at FSMA is to accelerate the discovery of an effective therapy and cure for SMA by funding and advancing a comprehensive research program, using a three-pronged approach:

- 1) Basic Research to reveal the best ways of making SMA drugs,

- 2) Drug Discovery to make new drugs, and
- 3) Developing Clinical Trial infrastructure to help test new drugs.

Basic Research Is Critical to Finding Effective SMA Treatments:

Basic research is a key aspect to finding a treatment for SMA. It provides fundamental information about what is going wrong in SMA by telling us when and where SMN protein is needed. It also tells us how the SMN protein is working in different cell types. Having this kind of information in hand provides seed ideas for new ways and better ways of making drugs.

We strongly believe at FSMA that continued investment in basic research, leading to a greater understanding of the exact nature, causes, and consequences of SMA, is key to ensuring the most effective SMA treatments can be identified and developed as quickly as possible.

FSMA Research Projects Are Selected by Our Scientific Advisory Board:

In order to fund the most critical research possible, the FSMA basic research program is governed by our Scientific Advisory Board (SAB). The SAB is comprised of nine leading SMA researchers with expertise in basic biology, clinical research, and drug development. SAB bios can be found at www.fsma.org/AboutFSMA/Board/ScientificAdvisoryBoard/.

The SAB carefully reviews all grant applications so that FSMA awards funding to projects that are the most critical to achieving a better understanding of SMA pathology.

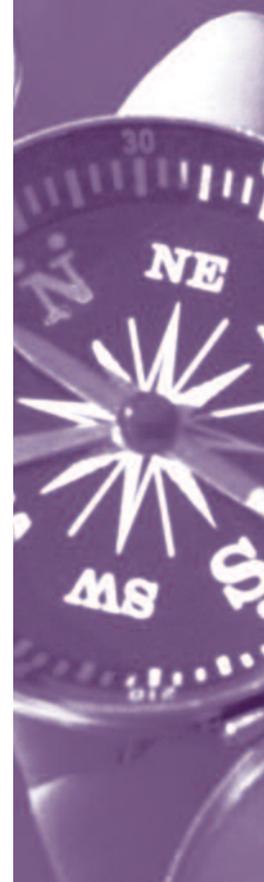
Thank you for your continued support of these important basic research projects.

Jill Jarecki, Ph.D.,
FSMA Research
Director

Ongoing Basic Research Projects Being Funded by FSMA:

- Christopher Henderson, Ph.D., Columbia University, \$160,000 for 2 years.
- Rashmi Kothary, Ph.D. and Lindsay Murray, Ph.D., University of Ottawa, \$120,000 for 2 years. (Funded by FSMA Canada)
- Wilfried Rossoll, Ph.D. and Claudia Fallini, Ph.D., Emory University, \$140,000 for 2 years. (Funded with Stop SMA)
- Umrao Monani, Ph.D., Columbia University, \$160,000 for 2 years.

See previous issues of *Compass* for more details on these projects.



Descriptions of Newly Funded Research Grants

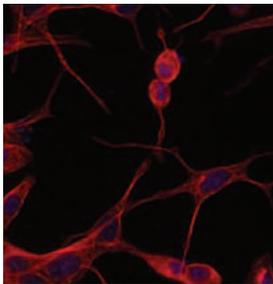


The role of vehicle coat protein alpha-COP in new models of SMA.

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



SMN knockdown reduces neurite length in a cell culture model of SMA, kindly provided by Drs. Custer and Androphy.

produce two new mouse lines that will help elucidate the importance of alpha-COP function to SMA pathology.

Project 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.

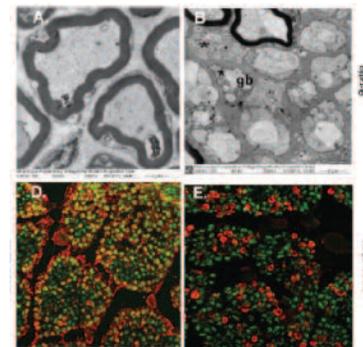


Motor axon development in SMA.

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 in 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



Ventral root axons from human tissues, kindly provided by Dr. Sumner.

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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.



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. That 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.



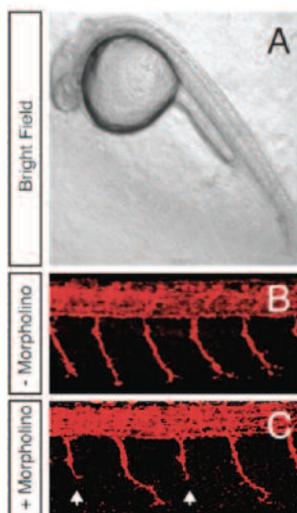
Regulation of HDAC5 phosphorylation by Cdk5 in SMA.

*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.



A zebrafish model of SMA, kindly provided by Dr. Ma.



Arginine methylation as a regulator of SMN activities in motoneurons.

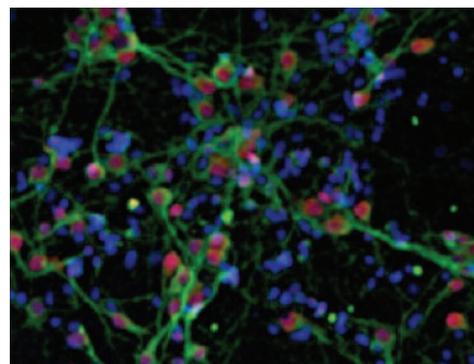
*Jocelyn Côté, Ph.D.,
University of Ottawa for
\$140,000 for two years.*

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

Significance of the Project: 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.

Funded by Families of SMA Canada.



PRMT8 is expressed in primary motor neurons, kindly provided by Dr. Cote.

Basic Research Accomplishments

Over the last 28 years FSMA basic research funding has contributed to critical SMA breakthroughs, including:

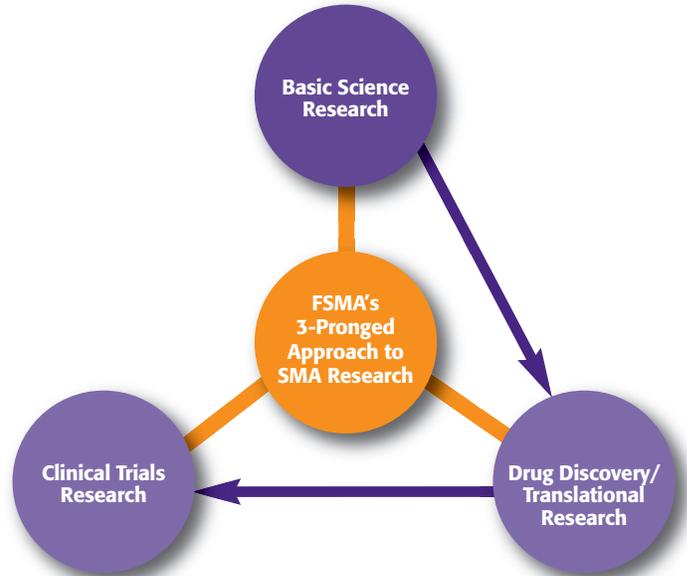
- Mapping and cloning of the SMA gene, SMN1.
- Discovery of the back-up SMA gene, SMN2.
- Development of animal models for SMA.
- Identification of the nucleic acid sequence used in the ISIS ASO drug.

Important questions in Basic Research remain today, including:

- What function does SMN protein perform in motor neurons?
- What tissues are affected by reduced SMN protein?
- Are there SMA drug targets, in addition to SMN itself?
- When can SMN be provided back and still provide benefit in SMA?

Overall, FSMA has invested \$27 million in basic research grants alone by funding 155 projects at more than 70 institutions worldwide. For details please see our Funding Facts page at <http://www.fsma.org/Research/>

Investing in basic research leads to the most effective ways of making drugs for all stages and types of SMA.



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