



Families of SMA *Research. Support. Hope.*

BASIC RESEARCH

WINTER 2014

COMPASS

A Publication Dedicated To Research Updates

Families of SMA Awards Seven New Basic Research Grants for \$600,000.

In this issue of *Compass* Families of SMA announces seven new basic research grant awards for a total of \$600,000. They were selected from applications received in response to our Fall 2013 Request for Proposals (RFP).

Basic Research Leads to Effective SMA Treatments:

Basic research is a key component in finding a treatment for SMA. Basic research into SMA biology tells us what causes the disease. Understanding what causes SMA reveals new and better ways of making new drugs. Therefore, at Families of SMA, we strongly believe in the importance of continued investment into basic research. It will lead to a more precise understanding of the causes and consequences of SMA, allowing for the most effective SMA treatments for each type and stage of SMA to be identified.

Our RFP Solicited Projects on Important Unanswered Questions in SMA Biology:

In order to fund the most critical research, our 2013 Request for Proposals solicited studies in important research to enable SMA drug development. These included:

- Studies to discover genes switching SMN on/off or genes mediating SMN function, which could lead to new drug targets and critical SMN protein functions.
- Studies to gain understanding of what is going wrong in SMA, including the exact timing of when defects appear, and in what tissues or cell types.
- Early assessment of new therapeutic approaches in animal or cellular models of SMA.
- Development of SMA research tools, like animal models, cellular assays, and biomarkers / outcome measures for clinical trials.

Importance of Our New Basic Research Grants:

The first new project led by **Dr. Burnett at Uniformed Services University of the Health Sciences** will help define the functional role of SMN in muscle and determine the extent to which muscle defects contribute to SMA pathology. Two projects from the laboratories of **Dr. Ko at the University of Southern California** and **Dr. Ebert at the Medical College of Wisconsin** will study the role of a specific type of cells called astrocytes in SMA pathology, which support and interact with motor neurons in the central nervous system. These two projects will also help determine the exact cells that influence SMA. **Dr. Kothary from the Ottawa Hospital Research Institute** will investigate non-SMN mediated mechanisms that provide therapeutic benefit in mouse models of SMA. This work could lead to new ways to make SMA drugs beyond those enhancing SMN levels. **Dr. Murray from the University of Edinburgh** will undertake a project to identify molecular pathways causing motor neuron degeneration in SMA. If strategies are found to prevent or delay motor neuron death, they could also lead to new therapeutic avenues for SMA. **Dr. Han from the University of Colorado, a newcomer to SMA research**, will investigate what controls the correct distribution of SMN protein in neuronal cells, providing a greater understanding of SMN function. Finally, **Drs. Lutz and Bogdanik from Jackson Laboratory** will lead a multi-center team investigating electrophysiological endpoints in drug testing in mice. This work could help move drugs more efficiently from preclinical research to human trials.

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



Descriptions of Newly Funded Research Grants



To Characterize the Role of SMN Protein in Myoblast Fusion.

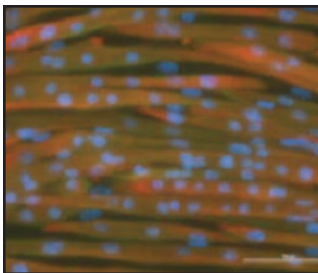
Barrington G. Burnett, PhD
at Uniformed Services
University of the Health

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.



Developing Myotubes.
Courtesy of Dr. Burnett.



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.

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.



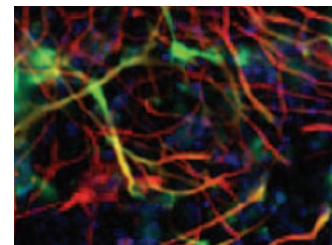
Astrocytes and Oxidative Stress in SMA.

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 induced-pluripotent 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.



Astrocytes with Reduced SMN Protein. Courtesy of Dr. Ebert.

Basic Research Accomplishments

FSMA invests in four areas of research: Basic Research, Drug Discovery, Clinical Research, and Care Research. FSMA has invested over \$55 Million in SMA research since our inception in 1984, with \$35 Million in funding in the past decade alone.

In Basic Research, the FSMA Scientific Advisory Board has awarded 79 basic research grants to 53 different principal investigators at 38 different institutions for almost \$10 Million in funding in the past 10 years alone. FSMA basic research funding has contributed to many critical SMA breakthroughs, including:

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

Please see our Funding Facts page at <http://www.fsma.org/Research/> for details.

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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.



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

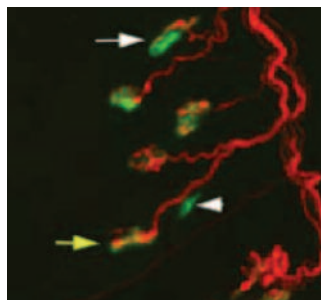
The Ottawa Hospital Research Institute for \$100,00 for two years.

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 SMN-independent 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.



Neuromuscular Junctions in SMA Mice. Courtesy of Dr. Kothary.



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.

Ongoing Basic Research Projects Being Funded by FSMA

- The when and where requirements of SMN in mild SMA: Christine DiDonato, Ph.D., Northwestern University for \$140,000 for two years.
- 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.
- Arginine Methylation as a Regulator of SMN Activities in Motoneurons: Jocelyn Côté, Ph.D., University of Ottawa for \$140,000 for two years.
- Motor axon development in SMA: Charlotte Sumner, M.D., Johns Hopkins University School of Medicine for \$140,000 for two years.
- Regulation of HDAC5 phosphorylation by Cdk5 in SMA: Yong-Chao Ma, Ph.D., Northwestern University for \$75,000 for one year.

2014 Families of SMA Research Mission and Funding

The overall mission at Families of SMA is a world without SMA. Making this happen requires scientific research investments. Thus, our main research goal at FSMA is to accelerate the discovery of an effective treatment and cure for SMA by funding and advancing a comprehensive research program, including:

- 1) Basic Research to reveal the best ways of making SMA drugs,
- 2) Drug Discovery to make new drugs,
- 3) Developing Clinical Trial infrastructure to help test new drugs, and
- 4) Clinical Care Research to improve the quality of life in SMA patients.

New 2014 Funding:

In addition to the funding announced in this edition of Compass, Families of SMA will invest in more research in 2014 to advance our vision of a world without SMA. Please be on the lookout for two upcoming Requests for Proposals (RFPs) for additional research funding from FSMA in 2014 in the following research areas:

- 1) **Drug Discovery** – Overseen by the Translational Advisory Council
- 2) **Clinical Care** – Overseen by the Medical Advisory Council

FSMA Research Projects Are Selected by Our Scientific Advisory Board:

In order to fund the most critical research, the FSMA basic research program is overseen 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.

The SAB carefully reviews all grant applications to ensure FSMA funds projects that are the most critical for enabling future SMA drug discovery. Projects are considered on both research quality and relevance to the FSMA mission.



The Families of SMA Scientific Advisory Board Discussing Basic Research Grants.

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