



Families of SMA *Research. Support. Hope.*

COMPASS

A Publication Dedicated To Research Updates

In this issue of “Compass” Families of SMA announces seven new basic research grant awards for 2011. These new awards encompass \$745,000 for the basic research portion of the \$3 Million in new research funding that FSMA announced earlier this year.

What is Our Research Goal at FSMA?

Our main goal 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.

Why is Basic Research Important to Our Overall Strategy?

Basic research is a critical component in 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, and what SMN protein does in different cell types. This knowledge provides seed ideas for new ways of making drugs.

The FSMA basic research program is governed by our Scientific Advisory Board (SAB). SAB bios can be found at <http://www.fsma.org/AboutFSMA/Board/ScientificAdvisoryBoard/>. The SAB carefully reviews all grant applications to ensure that we fund only the best quality research relevant to our mission.

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.

For example, Dr. Arthur Burghes, our longest standing SAB member and Professor at Ohio State University, stated, “**Basic research has made major strides in SMA, leading to promising potential therapies that work when given early in SMA mice. However, these treatments need to work in humans and we do not yet know that this is the case, or when they have to be given to be effective in humans. Basic research still has a major role to play and will impact SMA therapies, not**

just the ones we know today but new approaches that could for example influence later stages of the disease. Whether the therapy is a small molecule drug, gene therapy, an antisense oligonucleotide, a cellular therapy, or something yet unknown. An attack from multiple points is most likely to work and lead us to a treatment for SMA.”

What’s Exciting About Our New Research Grant Awards?

Three of the seven new grants for 2011 will help us to understand why motor neurons are selectively vulnerable to lowered SMN levels compared to other tissue types. These grants include projects led by **Dr. Henderson at Columbia University, Dr. Rossoll at Emory University, and Dr. Kothary at the University of Ottawa.**

The grant to **Dr. Ko at the University of Southern California** will help us understand exactly where defects in SMA occur and the reasons for observed selectivity at different muscles. The grant to **Dr. Monani at Columbia University** will help identify new genes that are protective against lowered SMN levels and will lead to new drug targets. Finally the funded projects led by **Dr. Kolb at The Ohio State University** and **Dr. Simard at the University of Manitoba** will validate molecular biomarkers that could make future clinical trials more efficient.

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

Jill Jarecki, Ph.D., FSMA Research Director

Basic Research Accomplishments

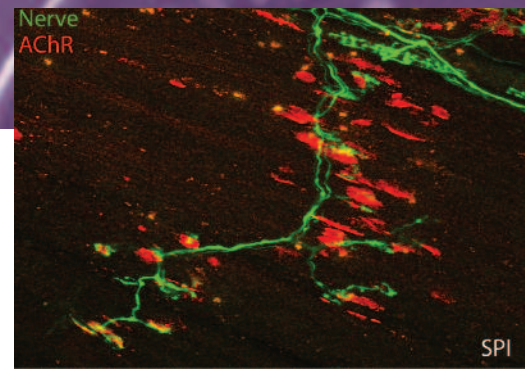
Over the last 25 years FSMA basic research funding has contributed to critical SMA breakthroughs, including:

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

FSMA has invested over \$26 million in basic research grants alone by funding over 145 projects at more than 70 institutions. For details please see our Funding Facts page at <http://www.fsma.org/Research/FSMAResearchFunding>



FSMA Awards 7 New Basic Research Grants



Neuromuscular junctions in SMA mice, kindly provided Dr. Ko.

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.

Identification and Characterization of Factors Critical in Regulating the Selective Vulnerability of Distinct Motor Neuron Pools in SMA Model Mice



Co-PIs: Rashmi Kothary, Ph.D.; Lyndsay 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.

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

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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.

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

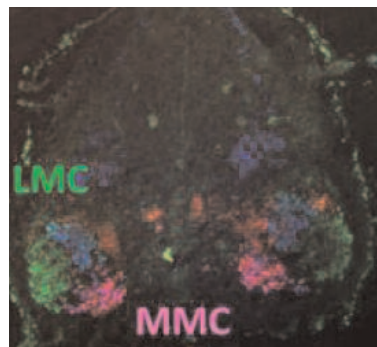


*Co-PIs: Wilfried Rossoll,
Ph.D., Claudia Fallini,
Ph.D., Emory University,
\$140,000 for 2 years.*

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.



Motor neuron subtypes.

Kindly provided by Chris Henderson, Gist Croft, and Mackenzie Amoroso.

continued from back page

selected from submitted abstracts and included the following topics: Human Clinical Research, SMA Models and Neuronal Phenotypes, SMN Molecular Functions & SMN Expression Regulation, and SMA Drug Development. Please see www.curesma.org for a summary of each session.

Highlighting the drug development session, platform presentations were given updating many of the ongoing drug programs in SMA, including talks on small molecules to enhance SMN levels, gene therapy to replace the SMN1 gene, cellular therapy to provide beneficial motor neuronal progenitors cells to the spinal cord, and antisense oligonucleotides (ASOs) to correct SMN2 splicing. Leading companies working on SMA drug development, including ISIS Pharmaceuticals, PTC Therapeutics, and California Stem Cell, Inc gave talks.

Many of the programs discussed in the drug session were represented during the final session at the SMA Families and Professionals Conference, which was held simultaneously. During that session, the leading experts in the SMA Research Community answered questions from SMA families. Three expert panels were held on: Basic Research, Therapy Development, and Clinical Research. Representatives of ISIS, Trophos, California Stem Cell, Repligen, Genzyme, and Ohio State University discussed their drug programs for SMA. In addition, talks were given by Dr. Jill Jarecki on FSMA Research Investments, by Dr. Charlotte Sumner on the Importance of Basic Research, by Dr. Douglas Kerr on the Drug Development Process, and by Dr. Elizabeth McNeil on the new NIH clinical trial network called NeuroNEXT.

Videos of this session can be found at SMA Community Connections at <http://www.smacommunity.org> under the Conference Tab.

Highlights from The 15th Annual SMA Research Group Meeting

An important way FSMA supports SMA research is the Annual SMA Research Group Meeting. The International SMA Research Group Meeting is the biggest SMA research conference in the world. FSMA organizes the conference, and financially underwrites the meeting by covering hotel, travel, registration for all research presenters. The 15th Annual International SMA Research Group Meeting was held June 23, 24, 25 at the Swan and Dolphin Resort in Disney World. 225 Researchers attended the conference, representing 70 total institutions, 14 biotech and pharmaceutical companies, and 11 countries worldwide.

The conference, the only open venue for annual communication between SMA researchers, has tangible benefits for the entire SMA community:

- Enables open communication of early, unpublished scientific data among researchers—a key component in accelerating the pace of research.
- Creates a vital sense of community among SMA researchers that generates a collaborative spirit, resulting in many productive research partnerships.
- Allows cross-disciplinary dialog among basic researchers, clinicians, and industry representatives, which is vital in creating effective therapies.
- Allows young researchers to interact with leaders in the field, which helps build the future of the SMA research community.
- Motivates SMA researchers by providing interaction with SMA families and patients.



The conference is organized into sessions focusing on major unanswered topics in the field. This year there were five distinct sessions with an expert moderator leading the discussion of each. Additionally, two poster sessions occurred, allowing for presentation of very current and still under investigation research. Over 100 presentations were given.

In addition, the conference started off with a Special Session organized by FSMA with invited speakers entitled, “Comparative SMA Pathology in Mice and Man with Therapeutic Implications”, designed to help inform therapy develop by highlighting the critical tissues and defects in SMA. All other podium talks were

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