



FAMILIES OF SPINAL MUSCULAR ATROPHY

COMPASS

A Publication Dedicated To Research Updates

Dear Families and Friends

In this "Compass" FSMA is announcing the award of nine new research grants in 2008 and four grants given in 2007 but not previously announced. These grants bestowed to research laboratories across the world constitute the basic research portion of the FSMA research agenda. The ultimate goal at FSMA is to accelerate the discovery of a treatment and cure for SMA. To reach this end, our research-funding program has three parts: basic research to unravel the biology of SMA, pre-clinical drug discovery to make SMA drugs, and human clinical trial initiatives to test these drugs.

All three of these research areas are equally critical and interdependent. Basic research in SMA biology tells us what causes SMA. Understanding what causes SMA reveals new and more effective ways of making SMA drugs. Finally, investment in clinical trial infrastructure provides the means to test these drugs in humans.

Without basic research our SMA drug pipeline would not grow and diversify. Basic research is our investment for the future!

Therefore every July FSMA issues a call for grant applications on specific research topics that address unanswered questions in SMA biology. This year it included areas below:

- Development of a large animal model of SMA

- Identification of new points of molecular intervention for SMA therapies
- Projects assessing candidate drug therapies and/or assessing their mechanism of action
- Development of biomarkers for SMA to enable clinical testing
- Projects testing whether neuromuscular dysfunction in SMA is due to nuclear, cytoplasmic, and/or axonal SMN functions.

In response to our 2007 call for grants, the FSMA Scientific Advisory Board considered 28 applications and selected meritorious grants for funding this past December at a meeting in Chicago. Due to the generous support of our donors, FSMA is pleased to fund eight new grants in 2008 selected by our Scientific Advisory Board, although not every meritorious application could be supported. We did fund grants in all but one of the project areas listed above. Details on all the awards can be found below:

Six of the eight new grants awarded in 2008 focus on ways to improve SMA drug development or to build the SMA drug pipeline. The two grants awarded to Dr. Cho at GNF and Dr. Androphy at the University of Massachusetts use cutting edge techniques to find new molecular points of intervention for SMA therapies. The project of Dr.



Burnett at the Scripps Institute aims to evaluate new more potent and selective class of HDAC inhibitors in SMA models.

The project in the laboratory of Dr. Kiledjian at Rutgers will investigate the mechanism of action of one class of SMN enhancing compounds, which will hopefully reveal a new directed way to make SMA drugs. Dr. Didonato's project at Northwestern University will result in two longer-lived animal models to be used for assessing SMA candidate drugs. The project being directed by Drs. Simard and Brahe will generate SMN biomarkers in order to more quickly determine whether SMN enhancing drugs are working in human clinical trials.

The grant award to Drs. Wirth and Hahnen at the University of Cologne will monitor non-genetic changes to DNA that might potentially make patients variably responsive to particular SMN enhancing drugs. Finally, Dr. Boon at The Ohio State University will be assessing the role of SMN directly in the motor neuron axon.

Jill Jarecki, Ph.D.
Research Director, Families of SMA



FSMA Awards 9 New Grants in 2008

Charles Y. Cho, Ph.D.,
Genomics Institute of the Novartis
Research Foundation (GNF)

Functional Genomic Screens for Novel Regulators of SMN2 Expression and Splicing

In SMA the discovery of new drugs often begins with large-scale high throughput screens to find compounds that increase SMN levels. An important complementary approach to SMA drug discovery would be to identify new protein targets than regulate SMN levels. To identify new protein targets for SMA drugs, we have begun functional genomic screens for genes whose inhibition increases SMN levels (in collaboration with Elliot Androphy's lab). We are using a technique, called RNAi, that can inactivate nearly all of the predicted 25,000 genes in the human genome. Genes found to regulate SMN expression, splicing, or stability will be further studied in SMA motor neuron models and ultimately help to find new protein targets for drugs.

Elliot J. Androphy, M.D.
University of Massachusetts Medical School

Identification of factors that control SMN protein levels

Current approaches to identify a medical treatment for SMA involve screening for chemicals that increase levels of the survival motorneuron (SMN) protein. Even after successful screens, we do not know how these candidate drugs act. Our project uses RNAi, a powerful genetic approach, to specifically reduce the amount of virtually every protein in the cell. In collaboration with the Genomics Institute of the Novartis Research Foundation, we will use an RNAi gene library to broadly query all cellular proteins that regulate SMN expression. The results from this project will 1) identify factors that control SMN expression, 2) identify candidate targets for therapeutic intervention, and 3) provide a method to assess how compounds currently in development work.

Christine DiDonato, Ph.D.,
Northwestern University

New Mouse Models for Pre-clinical Compound Testing

Mouse models of SMA are used to test the potential of therapeutic agents. Our project focuses on developing two new mouse models of SMA that present with symptoms at the 3-4 week age. These models are important because we currently lack a mouse model of SMA that has symptom onset at this intermediate age. One model contains SMN2, to allow testing of compounds that specifically act upon this target, while the other model will help identify compounds that bypass SMN function when SMN levels are low.

Megerditch Kiledjian, Ph.D.,
Rutgers, The State University of New Jersey

Mechanism of Action for a Drug-Mediated up-Regulation of SMN2

Unfortunately there are no effective treatments for Spinal Muscular Atrophy, although increased expression of the SMN2 gene can reduce the severity of SMA. Therefore therapeutic approaches to increase SMN2 expression would be beneficial in SMA patients. The identification in a FSMA funded collaboration of a potential quinazoline drug that can increase SMN2 expression holds great promise. Our objective is to decipher the molecular mechanism of drug action in order to understand how it increases SMN2 expression and gain insights into further optimization of its efficacy for therapeutic intervention in SMA patients, which could lead to new improved drugs.

Ryan Burnett, Ph.D.,
The Scripps Research Institute

Novel Histone Deacetylase Inhibitors as Therapeutics for Spinal Muscular Atrophy

This project is aimed at the development of therapeutic candidates to treat the inherited neurodegenerative disease

Spinal Muscular Atrophy (SMA). SMA is a genetic disease that results in under-expression of a key protein, SMN, in neurons. Classes of small molecules known as histone deacetylase inhibitors (HDACi) have been shown to increase the amount of SMN present in established cells derived from SMA patients as well as in mouse models of the disease. Our lab has developed a new generation of HDAC inhibitors that retain the ability to increase SMN expression in SMA cell lines while being much less toxic.

Kum- Loong Boon, Ph.D.,
The Ohio State University

Analysis of motoneuron specific expression of SMN in promoting normal motor axon outgrowth and β -actin mRNA transport

To further understand the cause of SMA and to design optimal drug therapeutics, we need to understand how SMN functions in motoneurons. Decreasing SMN during early development causes the motor axons to grow out improperly in zebra fish. In this proposal, I will test whether increased SMN protein expressed in only motoneurons can rescue this defect. If it can, I will also test different mutant forms of SMN in motoneurons for their ability to rescue. This experiment will help find the region of SMN protein responsible for normal motor axon outgrowth. In addition, I will study the role of SMN in transporting axonal factors required for axonal growth (such as β -actin mRNA) into the motor axons. Results of these experiments will further our understanding of how decreases in SMN in motoneurons cause SMA.

Brunhilde Wirth, Ph.D., Eric Hahnen, Ph.D., MBA, University of Cologne

Analysis of natural and drug-induced epigenetic changes in SMN2

SMA is caused by absence of the SMN1 gene, and the SMN2 copy number strongly influences the severity of the

FSMA Awarded 4 Additional Grants in 2007

Sibylle Jablonka, Ph.D., University of Wuerzburg

Analysis of cAMP Effects in a Cell Culture Model of SMA

Co-funded with Initiative "Forschung und Therapie für SMA"

This project will use motorneuron screening assays developed in the lab to help identify substances, initially cyclic AMP analogues, able to compensate for the morphological and functional defects of SMN-deficient motorneurons.

Brunhilde Wirth, Ph.D., Eric Hahnen, Ph.D., MBA, University of Cologne

Characterization of new drugs for SMA therapy

Co-funded with Initiative "Forschung und Therapie für SMA"

This project will assess the potential efficacy of a highly potent second-generation histone deacetylases inhibitor (SAHA) in SMA animal models.

Alex E. MacKenzie, M.D., Ph.D., Children's Hospital of Eastern Ontario

SMA cellular assay optimization and SMN2 inducing small molecule assessment.

Funded by Families of SMA Canada.

This project will assess the potential efficacy of a new drug candidate found in the lab in a panel of SMA cellular assays.

Jean-Yves Masson, Ph.D., Laval University

DNA damage signaling and repair in Spinal Muscular Atrophy

Funded by Families of SMA Canada.

This project aims to understand how DNA damage can affect SMA pathology because proteins involved in DNA repair are sometimes physically linked to the SMN protein, and neurons in general suffer naturally from a high level of DNA damage.

Funding for the project was also approved for extension through 2008.

disease. Nevertheless, identical SMN2 copy number can correlate with all three types of SMA, which raises the possibility that non-inherited changes in DNA called epigenetic can influence the SMN2 expression level. We will search and characterize these epigenetic differences in the SMN genes. Furthermore various drugs, such as histone deacetylase inhibitors, act through epigenetic modifications of SMN. This will be analyzed at a comprehensive level. Additionally, because various patients react very differently to HDAC inhibitors, we will search for pathways responsible for variable responses, including epigenetic ones. Finally by treating SMA mice with various drugs we will analyze in vivo the epigenetic changes that occur in the target tissues (spinal cord and muscles).

Christina, B. Brahe, Ph.D., Istituto di Genetica Medica, Rome, ITALY; Louise R. Simard, Ph.D., University of Manitoba, Winnipeg, Manitoba CANADA

Co-funded by Famiglie SMA in Italy and Families of SMA Canada.
SMN Biomarker: Towards a validated international Standard operating procedure.

The combined efforts of active clinical research worldwide have facilitated the development of reliable and reproducible clinical tools, including assays to monitor potential biomarkers to monitor drug response. This project aims to develop an international standard operating procedure to determine whether SMN RNA levels are altered in SMA patients participating in clinical drug trials. In addition, these procedures will be very useful for testing the effects of drugs in SMA cell lines and SMA mice.

What basic research is left to do and why? *continued from page 4*

3. Is SMN important for the ability of the axon to communicate with muscle?
4. Can an improved basic understanding of SMN function in axons lead to the development of a more restorative therapy for SMA?

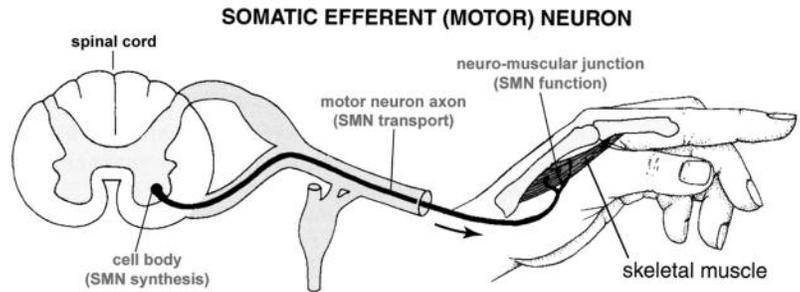
From the diagram above, one can see that a motorneuron (nerve cell) is extremely long. One end of the motorneuron (left), termed the *cell* body, is located within the spinal cord. This neuron sends a very long extension, called the *axon*, from the spinal cord to the muscle. The distal site at which the motorneuron's axon makes a contact with a skeletal muscle is called the *neuro-muscular junction* (right). The total length of a single motorneuron (from spinal cord to muscle) can be on the order of 1-3 feet (entire path of the axon is shown in black). Note that many axons (black) are bundled together to form a nerve (yellow).

Research by Zhang and colleagues in Dr. Bassell's laboratory at Emory University (funded in part by FSMA) has used cultured nerve cells to discover that SMN is actively transported down the axon. Using sophisticated imaging methods, they have been able to see SMN run down the axon, much like a marathon runner! However, SMN does not take the journey alone, and appears to move in a particle with other protein molecules that are known to promote axon growth. One hypothesis is that SMN may be essential for axon function by virtue of its ability to direct the transport other critical molecules. Several laboratories, in addition to Drs. Bassell and Zhang, are actively pursuing this line of basic science and have also made important contributions. Collectively, it is our hope that these basic science studies on SMN will lead to a more clear picture of what nerve functions are lost in SMA. We anticipate, for example, that these studies will lead to development of new drugs that facilitate the transport of deficient molecules in axons of SMA patients. Our goal is to identify new drugs that possess the unique ability to directly treat the underlying defect leading to SMA.

What basic research is left to do and why?

FSMA is proud to have contributed funding to the research presented in 25 published journal articles in 2007. The summary of one such journal publication, written by Dr. Garry Bassell at Emory University, is below (Zhang H, Xing L, Singer RH, Bassell GJ. QNQKE targeting motif for the SMN-Gemin multiprotein complex in neurons. *Journal of Neuroscience Research*, September 2007). (See our web site for details on more publications that FSMA helped fund.)

We choose to highlight this particular publication in this issue of *Compass* because it focuses on a major unanswered question in SMA biology: the role of the SMN protein in motor axons. Dr. Bassell's lab has been at the forefront of investigating the role of SMN in the motor axon, and FSMA has provided funding to help his lab do this. In addition to past funding for Dr. Zhang that helped result in the *Journal of Neuroscience Research* publication summarized here, FSMA is currently funding two researchers in the Bassell lab -- Dr. Wilfried Rossoll and Dr. Yuko Sasaki. Both continue the type of studies described below to determine the exact role of SMN in motor axons. As announced in this issue of *Compass*, FSMA also recently awarded a grant to Dr. Boon in Dr. Beattie's lab at Ohio State University that focuses on the role of SMN in motor axons in zebra fish. Understanding the specific function of SMN in SMA will allow us to develop more directed and effective therapies.



Spinal Muscular Atrophy (SMA) is a progressive neurodegenerative disease caused by an inherited (genetic) defect in a single gene (SMN1) that normally codes for the synthesis of the Survival of Motor Neuron (SMN) protein. While it has long been appreciated that SMN plays an essential role in all body tissues, it has been unclear why and how SMN deficiency leads to the degeneration and death of nerve cells. Moreover, a specific type of nerve cell, the motorneuron, is most affected in SMA. A major challenge of ongoing basic research is to answer these questions:

1. What are the normal functions of the SMN protein in motorneurons?
2. Does SMN play a direct role in the development and/or maintenance of the motorneuron's axon?

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FAMILIES OF SMA FUNDS NEW BASIC RESEARCH

- FSMA funds nine new research grants in 2008.
- Basic research is an investment in future drug discovery programs.

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