

# Research Compass



*a Families of Spinal Muscular Atrophy publication dedicated to Research News*

## Research Director's Update

Dear Families,

When I last updated you about the research activities at Families of SMA, we were preparing for the upcoming grant review process by our Scientific Advisory Board (SAB). As many of you may recall from that edition of the Research Compass, FSMA received a substantial, 50% increase in the number of grant applications during this funding cycle, originating from both industrial and academic groups. I am very encouraged by this trend, and truly believe that it is an indication of increasing interest in SMA research from both of these sectors of the research community. The SAB was convened in December with great anticipation on my part, and they recommended eight new research grants be funded. FSMA is very proud to announce the award of these grants in this issue of the Research Compass. Descriptions of our newly funded research projects are found within. This brings the total number of research projects currently being funded by FSMA, outside of Project Cure and the deCODE drug discovery program, to twenty-one. Moreover, additional grant applications are currently under review, and FSMA anticipates announcing the award of several other grants in 2006.

In 2006, our newly funded research projects are focused in two primary areas. The first is delineating the role of SMN in motor axons. Examples of research projects concentrating on this question are those lead by Drs. Hynek Wichterle and Stephane Nedelec at Columbia University, Dr. Michelle McWhorter at Ohio State University, Dr. Jianhua Zhou at the University of Massachusetts Medical School, and



**Jill Jarecki, Ph.D.**

Dr. Wilfried Rossoll at Emory University. Each of these investigators bring different, but essential, research tools and areas of expertise to the table to address this important question. The second area of focus is the identification of novel "druggable" molecular targets for SMA therapeutic intervention, which will lead to new, more focused drug development projects in the future. The research projects designed to discover new

molecular targets for SMA therapeutic development are lead by Dr. Beth Westlund of Cambria Biosciences, Dr. Gregory Matera of Case Western Reserve University, Dr. Stefan Stamm of University of Erlangen, and Dr. Umrao Monani of Columbia University Medical Center. Each of these investigators are using different experimental systems, for example model organisms such as: mouse, fruit flies, and the worm *Caenorhabditis elegans* or SMA cellular models, to identify genes that interact with SMN and/or regulate SMN function.

I would like to highlight one research project of particular excitement to me. This is the project at Cambria Biosciences, which is intended to identify genes that interact with SMN using the tiny worm *Caenorhabditis elegans*. This is the first industrial grant awarded using our yearly grant application program for basic research. I am especially pleased that FSMA is promoting and encouraging companies to initiate projects in SMA

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## 2006 Grant Summaries

**Drs. Hynek Wichterle and Stephane Nedelec, Columbia University**

**The role of SMN protein in axonal mRNAs transport using Mouse Embryonic Stem cells derived motor neurons.**

SMA is characterized by the selective death of spinal motor neurons due to mutations in the gene coding for SMN protein. SMN protein is present in the cell body but also in axons and dendrites of motor neurons. Recent evidence suggests that SMN could regulate axonal transport of mRNAs, a mechanism essential for axon guidance and synapse formation. I would like to address this new role of SMN in the axonal transport of mRNAs to understand whether SMA pathogenesis might result from defects in axonal transport of mRNA molecules. The method developed by Dr. Wichterle to generate unlimited amounts of different motor neuron subtypes from mouse embryonic stem cells gives us for the first time the opportunity to address at the molecular and biochemical level, the axonal role of SMN in population of motor neurons differentially affected by the disease such as spinal motor neurons (affected) and cranial motor neurons (resistant to the disease). Understanding the molecular mechanisms underlying the difference in neuronal susceptibility to degeneration in SMA, might reveal new avenues for the development of effective therapies for this detrimental disease.

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## Summaries

*continued from front*

**Dr. Beth Westlund,  
Cambria Biosciences, LLC**

### **Identification of genetic suppressors of SMN mutations in *Caenorhabditis elegans***

The number of copies of the *SMN2* gene strongly influences the severity of disease in SMA patients, yet differences among some family members with the same number of *SMN2* genes suggest that other genes can play a modulatory role. A proven way to identify such modulatory genes is through genetics using relatively simple model animals, including the roundworm *Caenorhabditis elegans*. We will search for genetic mutations that can alleviate the problems associated with defects in *SMN1*, the *C. elegans* version of the human *SMN* genes. Identification of one or more genes bearing these mutations and their human counterparts may provide new targets for the development of novel therapeutics for SMA.

**Dr. Michelle McWhorter,  
Ohio State University**

### **The function of SMN in motor axons: snRNP assembly or motor-axon specific?**

To further understand the causes of SMA and to design optimal drug therapeutics, we have begun modeling SMA in zebra fish. We have found that during development of a SMA zebra fish embryo, the axons of the motoneurons do not travel to the correct places in the muscle. Additional studies in our zebra fish model of SMA suggest that motoneuron is the structure where SMN function is necessary for the axons to travel to the correct places in the muscle. To further understand the function of SMN that is responsible for SMA, we propose to examine what happens when SMN-interacting components are not present within the developing embryo. We also propose to examine what happens to the motoneurons when

we attempt to compensate for loss of SMN with other SMN-interacting components. Finally, we propose to examine where SMN and its interacting components localize within the motoneuron.

**Dr. Gregory Matera,  
Case Western Reserve University**  
**A *Drosophila* model for Spinal Muscular Atrophy**

The Survival of Motor Neurons (SMN) protein is mutated in the vast majority of SMA patients and is required for the biogenesis of small nuclear RNAs (snRNAs). In order to better understand how a defect in the metabolism of small RNAs relates to SMA, we need to know more about the pathway of snRNA biogenesis.

Any potential therapy for SMA will require detailed knowledge of metabolic pathway(s) involving the SMN protein. We have identified mutations in the fruit fly SMN gene that mimic the situation in humans and allow us to use the fly as a model system to study SMA. Flies have been used extensively by the genetics community to map out and connect different metabolic pathways, with a speed that cannot be matched by approaches using mammalian systems (e.g. the mouse). We plan to use the fly to help us find new genes that regulate SMN and the various pathways in which it participates.

**Dr. Stefan Stamm,  
University of Erlangen**  
**Regulation of SMN2 exon 7 through protein phosphatase**

Spinal muscular atrophy is caused by the loss of the *SMN1* gene. There is a second, almost identical gene (*SMN2*) in all patients. Before the information of the *SMN2* gene is made into protein, part of this information is lost in a process known as alternative splicing. We previously identified drugs that reverse this wrong alternative splicing patterns of *SMN2* by blocking a regulatory protein phosphatase. It is known what other drugs control this protein phosphatase. Our proposal aims to understand the

molecular mechanism of the regulatory protein phosphatase and will test whether existing drugs influencing the protein phosphatase can reverse the wrong splicing pattern of *SMN2*.

**Dr. Jianhua Zhou,  
University of Massachusetts Medical School**

### **Chaperone Activity of SMN against motor neuron cell death under stress conditions.**

We have found that SMN plays a role in response to stressors. We hypothesize that defects of SMN increase the threshold of cellular stress response, resulting in motor neuron death under stress in SMA patients. In this project, we will investigate whether SMN protects motor neurons against cell death under stress. We will examine if SMN regulates expression of stress response proteins and other chaperone proteins. In addition, we will test if over expression of these stress response proteins may compensate for the loss of SMN to protect motor neurons.

**Dr. Umrao Monani,  
Columbia University Medical Center**  
**Does the Slow Wallerian Degeneration (*Wld<sup>s</sup>*) mutation and compounds that mimic its activity rescue the SMA phenotype in a mouse model of the disease?**

Spinal Muscular Atrophy (SMA) is a debilitating motor neuron disease for which there is no effective treatment or cure. It is equally prevalent among the different peoples of the world and the leading genetic cause of infant mortality. Emerging evidence suggests that SMA begins by destroying the processes, i.e., the axons, which project from the motor neurons and normally make contact with the muscles whose contractions these cells control. The *Wld<sup>s</sup>* mutation has a remarkable protective effect on axons injured due to physical damage or motor neuron disease. In this project, we wish to test whether the *Wld<sup>s</sup>* mutation has a similar protective effect on diseased motor neurons and their axons in SMA by introducing the mutation into a mouse model of

the disease. Our results could lead to a novel therapeutic strategy in the treatment of Spinal Muscular Atrophy.

**Dr. Wilfried Rossoll, Emory University**  
**The role of SMN in the axonal compartments of motor neurons**

Spinal Muscular Atrophy (SMA) is caused by a deficiency of Survival Motor Neuron (SMN) protein, which leads to the degeneration of "motor neuron" nerve cells in the spinal cord. It is a very important question to understand why these cells are so specifically vulnerable to low levels of SMN. SMN is part of a complex that is important for certain types of RNA molecules in all cell types and in all tissues. In motor neurons, SMN is found in complexes in both the cell body and additionally also in the long processes which extend to the muscle cells ("axons"). Presently it not known which complexes are critical for the development of SMA. Our aim is to answer the questions "what is the role of SMN in the axon?", "how does it contribute to SMA?" and "how can this

## FSMA Helps to Fund Two SMA Breakthroughs Published in Major Scientific Journals

*The following summaries are from two research projects. FSMA is proud to be a co-funder of these important breakthroughs.*

### New Role Discovered for SMN in SMA

A new paper published in **Experimental Cell Research**, by the FSMA-funded Morris group in Wales discusses a possible role of SMN in Spinal Muscular Atrophy. Spinal Muscular Atrophy (SMA) is caused by reduced levels of SMN (survival of motor neuron protein) and the subsequent loss of motor neurons. It is well established that SMN plays a role in assembling the RNA splicing machinery for transport into the cell nucleus in all cell types. In addition, several previous research studies during the last few years have shown that SMN has some role in the axons of neurons, and the paper written by Dr. Sharma and colleagues further defines the function of SMN in axons.

This research suggests that in addition to playing a role in the nucleus of cells, SMN may be involved in the mechanism by which axons find their way to muscle to form neuromuscular junctions. More specifically, the data in the Sharma paper shows that SMN is part of a larger protein complex in axons that may be involved in transporting the mRNAs of proteins crucial for axon formation and pathfinding into the axons of neurons as they are growing towards the muscles to form neuromuscular junctions. In particular, the research team headed by Sharma indicates that the axonal SMN complex likely does this for the molecule actin, a protein whose activity is absolutely crucial to these processes. Therefore, the axonal function of SMN seems to closely parallel its well-documented function in the cell body of assembling and transporting the splicing machinery into the nucleus. In addition, this paper also indicates that SMN may have a second axonal function related to actin. SMN may be directly involved in regulating the way the actin protein actually does its job during pathfinding and axon formation, in addition to transporting it into the axon. Axonal SMN functions could explain why reduced SMN levels in SMA specifically affect motor neurons and why reduced levels of SMN make motor neurons less able to form neuromuscular junction.

### Possible New Drug Target for SMA Discovered

In the February issue of **Molecular and Cellular Biology**, Dr. Ravinda Singh and his colleagues report the discovery of a novel SMA drug target for the correction of the defective second copy of the SMN gene, SMN2. They have named this target as Intronic Splicing Silencer-N1 or ISS-N1. The ISS-N1 sequence is found in intron 7 of the SMN2 gene and contributes to exon 7 exclusion from the SMN2 transcript. The authors show that using antisense oligonucleotide technology to target ISS-N1, preventing it from exerting its inhibitory effect on SMN2 splicing, results in increased SMN protein in cells derived from SMA patients. This suggests targeting ISS-N1 with antisense oligonucleotides could be a possible therapeutic strategy for SMA.

The antisense effect was very specific against the target sequence, was observed at extremely low concentrations, and could be achieved with short oligonucleotides, allowing for their cheap production and greater ability to cross the blood brain barrier. All of these properties are highly desirable features for an antisense mediated therapy. This is the first report in which blocking an intronic target was able to fully correct the aberrant SMA gene. To a broader significance, discovery of ISS-N1 is a major development that expands the possibilities of finding novel targets within the hitherto uncharacterized large intronic sequences of the defective SMA gene.

# FSMA

was founded in 1984 for the purpose of raising funds to promote research to find a cure for Spinal Muscular Atrophy, and to support families affected by SMA. FSMA is the largest private funder of SMA research and is leading the way to find a cure.



*Balancing Life's Tough Times™*

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For more information contact the FSMA office **800-886-1762** or visit the website **www.curesma.org**.

**Director's Update**, continued from front

research, as these have the potential to develop directly into full drug discovery programs. I anticipate this funding trend will continue with future grant cycles.

Finally, I want to give you a brief report on the FSMA/deCODE drug discovery collaboration. In early January, deCODE chemistry and FSMA announced the renewal of our current collaboration to develop a small molecule therapeutic for spinal muscular atrophy. As most of you are aware, the FSMA/deCODE collaboration was initiated in 2003 as the continuation of a successful early phase drug discovery project at Vertex Pharmaceuticals (a paper describing the research undertaken at Vertex was published in the second half of 2005 in **Human Molecular Genetics**, July 2005, 14:2003-18). The deCODE chemistry-FSMA collaboration has focused on the optimization of a class of molecule called 2,4-diaminoquinazolines that was discovered in the high-throughput, cell-based assay developed at Vertex. During the past three years, deCODE chemistry has developed optimized analogues that have high potency in the assay, excellent metabolic stability, efficient penetration of the blood-brain barrier, an attractive pharmacokinetic profile, and the desired activity in SMA cellular models, which are many of the features required in a beneficial SMA drug. As the lead optimization phase of the projects comes to an end, the focus of the collaboration in the coming year will be to further assess the pharmaceutical properties of lead candidates and select a small number of analogues for investigational new drug (IND) application-directed, pre-clinical development. In light of this goal, we anticipate entering a new collaboration agreement with deCODE during 2006 to begin the IND enabling phase of the project (which constitutes an extensive series of experiments required by the FDA before a drug can enter Phase I trials in humans), and I will keep you apprised about these developments in future installments of the research compass.

Thank you very much for your continued support. Together we can find a cure.

Sincerely,  
Jill Jarecki, Ph.D.

If you have a question, please email it to: **info@fsma.org**.



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