Families of SMA
Research. Support. Hope.

COMPASS

A Publication Dedicated To Research Updates

Dear Families and Friends

In this issue of *"Compass"* Families of SMA announces 6 new basic research awards for 2009.

What is our Research Goal?

Our main goal is to accelerate the discovery of an effective therapy and cure for SMA, with this three-pronged approach:

1) Basic Research to reveal the best ways of making SMA drugs,
2) Drug Discovery to make new drugs, and
3) Clinical Trials to test these drugs.

Why is Basic Research Important?

The basic research portion of our strategy is critical to our overall success. Basic research provides fundamental information about what is going wrong in SMA at the cellular and molecular level. This information provides seed ideas for how to make the most effective SMA drugs. New ideas are then tested in cellular and animal models of SMA.

Our basic research program is governed by our Scientific Advisory Board (SAB). The SAB carefully reviews all grant applications and makes sure that we fund only the best research, based on quality and relevance to the FSMA mission.

Families of SMA issues an annual request for proposals in key unanswered areas of SMA basic research. This year we looked for research proposals on these topics:

- The role of SMN in motor axons and at motor terminals on muscle.
- New ways to make SMA drugs (often referred to as drug target identification).
- New therapeutic approaches in SMA cellular or animal models (small molecules, stem cell, gene therapy).
- Research and clinical trial tools and assays (new animal models, biomarkers, drug screening assays).

What's Exciting about our 2009 Research Awards?

- Three of the six new grants for 2009 will search for new ways to make SMA drugs or help us to better understand how current drug candidates work. These include projects lead by **Dr. Cote**
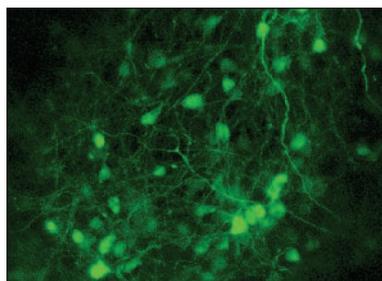
Stem cells differentiated into motor neurons in cell culture, kindly provided by Dr. Comi.
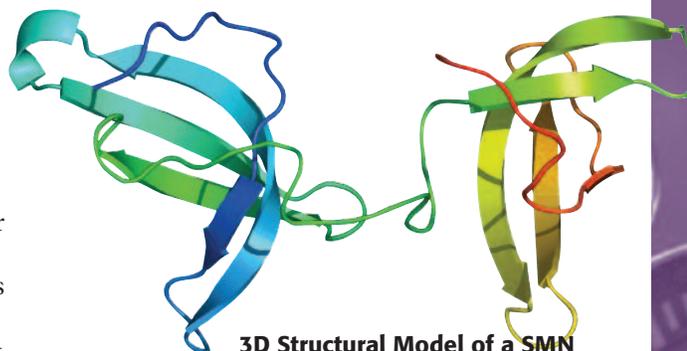
3D Structural Model of a SMN protein fragment, kindly provided by Dr. Allen.

of the University of Ottawa **(funded by Families of SMA Canada), Dr. Sen of Harvard University, and Dr. Kiledjian of Rutgers University.**

- Dr. Cote's grant will also help us understand the specific role of SMN protein in motor neurons.
- A grant to **Dr. Comi at the University of Milan, co-funded with SMA Europe,** will tell us more about the ability of neural stem cells to provide benefit in SMA mouse models.
- **Dr. Butchbach at Ohio State University** will lead an effort to build a new animal model for SMA that will allow us to measure SMN expression in living animals.
- A grant to **Dr. Allen at Arizona State University** will determine the 3-D structure of the SMN protein. This may lead to novel therapies for SMA through rational drug design.

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

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

FSMA Awards 6 New Basic Research Grants for 2009.

Quantitative Proteomic Study of the Motor Neuron SMN Complex.

Jocelyn Cote, Ph.D., University of Ottawa.

Background: Loss of a protein named SMN (for "Survival of Motor Neurons") causes SMA. SMA results in the loss of function of spinal cord motor neurons, which are the cells responsible for voluntary movements. Research in recent years has identified an essential function for the SMN protein, which should be equally important for all cells in the body.

Primary Research Question: How does the loss of SMN result in a motor neuron specific disease?

Research Plan: Our current research strategy will use novel, state-of-the-art approaches to identify the proteins that interact specifically with SMN in motor neurons.

Anticipated Results: Identification of new interactions with the SMN protein may provide crucial insights into the function of SMN important for motor neurons and to the etiology of SMA. Identifying SMN interactions will also help identify new targets for the development of novel approaches for therapeutic intervention.
Funded by FSMA Canada.

Mechanism of Drug Action in SMN2 Up-regulation.

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

Background: There are no current effective treatments for SMA although increased expression of the SMN2 gene is known to reduce the severity of SMA. Therefore, small molecule drugs that increase SMN2 expression should be beneficial for SMA patients. The recent optimization of a potential drug candidate in the Quinazoline family that can increase SMN2 expression holds great promise, as does the recent identification of the enzyme DcpS as the cellular target of the Quinazoline compounds.

Primary Research Question: Our objective is to determine the exact way that inhibiting DcpS leads to increases in SMN2 expression.

Research Plan: We will test to see if the Quinazoline compounds lead to increased amounts of SMN protein by: regulating promoter activity (driving the gene engine); increasing mRNA stability (maintaining the presence of the protein template for longer periods); or by enhancing protein translation in cells (directly increasing the amount of protein being made).

Anticipated Results: Knowing how the Quinazolines work will provide further insights and may lead to greater optimization of the efficacy of this drug class. This knowledge may lead us to more effective second generation therapeutic interventions that target DcpS in SMA patients

Development of a Model to Monitor SMN Expression In Living Mice: Applicability to Drug Discovery.

Matthew Butchbach, Ph.D., The Ohio State University.

Background: Butyrates and butyrate-like compounds, such as phenylbutyrate, have been suggested to be potential drug compounds for treating SMA patients. These compounds improve survival of a mouse model of SMA but do not increase SMN in the spinal cord. It is possible that they may induce SMN expression in vivo at levels which are below the detection limit of currently available assays.

Primary Research Question: In this grant, we will try to develop a more sensitive tool for testing SMN enhancing drugs.

Research Plan: We will generate a novel mouse model to monitor SMN2 induction and splicing in the spinal cord of living SMA mice.

Anticipated Results: This information will be extremely useful in understanding the effectiveness of SMN-inducing drugs in treating SMA and will lead to the design of newer drugs with better protective properties.

## A Molecular Understanding of Why Alterations of SMN Give Rise to SMA.

James Allen, Ph.D., Arizona State University.

Background: Spinal Muscular Atrophy is a neurodegenerative disorder due to the loss of motor neurons with three clinical forms that arise from changes in a gene identified as SMN1. The gene encodes the survival of motor neurons protein, or SMN protein.

Primary Research Question: Why the observed changes in this gene give rise to the observed clinical characteristics remains unknown. A critical reason for our limited understanding of why SMA arises from these changes is the lack of understanding at the molecular level of how SMN functions in cells.

Research Plan: To overcome this limitation, we propose to determine the three-dimensional structure of SMN, including both the form found in healthy individuals as well as the predominant form found in SMA patients.

Anticipated Results: Once these studies are completed, we anticipate that the resulting molecular structures will lead to an improved understanding of SMN and insight into novel protein-based therapies for the treatment of SMA.
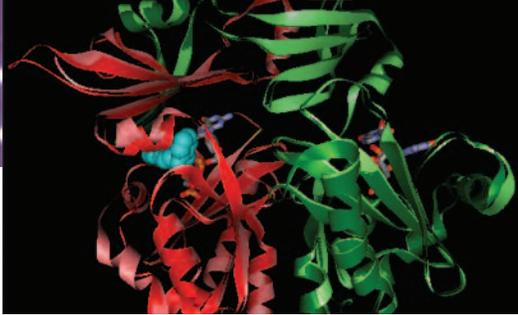
3D Structural Model of a Quninazoline Compound Bound to the Human Enzyme DcpS, from Singh et al 2008.

Modifiers of SMN Using Transgenic Drosophila as a Model System.

Anindya Sen, Ph.D.,
Harvard Medical School.

Background: Spinal Muscular Atrophy is an autosomal recessive neurodegenerative disease that is the leading cause of genetically-linked infant mortality. The observation of fundamental importance with respect to developing treatments for SMA is that the severity of the disease relies critically on the amount of Survival Motor Neuron (SMN) protein present in the affected individual.

Primary Research Question: Are there genes which can regulate the amount of SMN protein made?

Research Plan: We will use a model genetic system that easily allows identification of genes that interact with and regulate SMN activity.

Anticipated Results: We will identify different factors that regulate SMN with an aim to find new therapeutic strategies for SMA by identifying novel drug targets.

Development of Therapeutic Strategies Based on Stem Cell Transplantation for SMA.

Giacomo Comi, M.D., University of Milan.

Background: The objective of this project is to contribute to the development of a stem cell therapy for Spinal Muscular Atrophy, which is caused by mutations in the Survival Motor Neuron gene.

Primary Research Question: We will investigate the therapeutic potential of transplanted Neural Stem Cells (NSCs).

Research Plan: We will evaluate whether NSC engraftment into the spinal cord modifies disease progression in a transgenic mouse model of SMA. We will investigate strategies that can be combined with cell transplantation to promote motor axon growth toward muscles. Furthermore, we will evaluate the molecular mechanisms responsible for the therapeutic effect of NSCs.

Anticipated Results: This study is anticipated to contribute to, and assess the feasibility of, the development of a cell-based therapy for SMA.
Co-funded with SMA Europe.

Major SMA Research Results of 2008.

Here are some important highlights of SMA research that were published in important scientific journals in 2008:

- **Development of a novel clinical drug candidate for SMA and the identification of the molecular manner in which it works.** This work is a step forward towards an effective treatment for SMA. The work was done by the **deCODE team and their collaborators at Rutgers, Invitrogen, and Ohio State University**. It can be read in *Thurmond et al, Journal of Medicinal Chemistry and Singh et al., ACS Chemical Biology*. **FSMA funding was critical to these studies.**

- **Neural stem cell transplantation benefits mice with SMA.** Mice transplanted with the neural stem cells showed improved muscular function and increased lifespan when compared with untreated mice. The work was done by the group of **Dr. Comi at the University of Milan** and published in the *Journal of Clinical Investigation*. **FSMA will be co-funding an extension of this work in 2009.**

- **Induced pluripotent stem cells from SMA patients.** This is the first study to show that human induced pluripotent stem cells from an adult patient's skin cells can be used to model the specific pathology seen in a genetically inherited disease. It represents a promising resource to study disease mechanisms, screen new drug compounds and develop new therapies in the future. The work was led by the **Thomson and Svendsen laboratories at the University of Wisconsin**. It was published in the prestigious journal *Nature*.

- **A possible non-SMN modifier of SMA disease severity called Plastin 3.** This discovery would represent the first report ever of a strong protective modifier for a Mendelian disorder in humans. In addition, the discovery of the Plastin 3 protein as a protector against SMA could help generate new drug therapies for SMA. This work was done in the laboratory of **Dr. Brunhilde Wirth** and published in the prestigious journal *Science*. **FSMA funding contributed to these results.**

- **Delivery of recombinant follistatin lessens disease severity in SMA mice.** This suggests that increasing muscle strength could be a therapeutic target for SMA, particularly in concert with drugs that induce SMN levels in motor neurons. This work was done by the group of **Dr. Chris Lorson at the University of Missouri** and published in *Human Molecular Genetics*.

- **Co-administration of the research drug TSA with supplemental nutrition resulted in sustained survival in SMA mice, which was substantially longer than that observed with TSA alone.** Nutritional supplementation itself did not impact lifespan. **Dr. Charlotte Sumner's group at Johns Hopkins University** carried the work. It was published in the *Annals of Neurology*. **FSMA funding helped this work.**

- **Replacing SMN protein in motor neurons alone significantly impacted survival of SMA mice, while muscle-specific replacement had no effect.** This suggests that motoneurons are likely to be the major tissue impacted by SMA. This work was done in the laboratory of **Dr. Arthur Burghes at Ohio State University** and published in *Human Molecular Genetics*. **FSMA funding helped this work.**

- **Antisense therapy approach to treat SMA. Dr. Krainer's group at Cold Spring Harbor Laboratory**, and colleagues at **Isis Pharmaceuticals**, sought to correct SMN2 RNA splicing by introducing synthetic molecules, called Antisense Oligonucleotides (ASOs), that precisely match various sections of the RNA. The researchers injected promising ASOs into SMA mice and were able to correct SMN2 RNA splicing. Their results highlight the therapeutic potential of ASOs for SMA and were published in *The American Journal of Human Genetics*.

Meet the FSMA Scientific Advisory Board

Jill Jarecki, Ph.D., FSMA Research Director.

Arthur H. Burghes, Ph.D. Professor of Molecular and Cellular Biochemistry at The Ohio State University

Thomas Crawford, M.D. Associate Professor of Neurology and Pediatrics at the Johns Hopkins School of Medicine.

Mark Gurney, Ph.D., M.B.A. Senior Vice President, Drug Discovery and Development at deCODE genetics, Inc.

Douglas Kerr, M.D., Ph.D. Associate Professor at Johns Hopkins Medical School in the Department of Neurology.

Adrian Krainer, Ph.D. Professor at the Cold Spring Harbor Laboratory.

Brian Pollok, Ph.D. Chief Scientific Officer and Head of Global R&D for Invitrogen Corporation.

Louise Simard, Ph.D. Professor and Head of the Department of Biochemistry & Medical Genetics at the University of Manitoba in Winnipeg, Canada.
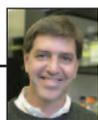
Christopher Spancake, Ph.D. Director in Pharmaceutical Development at GlaxoSmithKline.

Stephen Strittmatter, M.D., Ph.D. Vincent Coates Professor of Neurology and Neurobiology at Yale University School of Medicine.

Kathryn Swoboda, M.D. Associate Professor of Neurology and Pediatrics at the University of Utah School of Medicine.

17 Journal Articles Published On FSMA Funded Research In 2008.

Publication of peer-reviewed articles in scientific journals means we're funding the right research. This means our investments are leading to new and important discoveries in SMA.

Basic research helps us answer critical questions on SMA biology. The answers reveal new and more effective ways of making SMA drugs. Important results from our basic research funding over the past 25 years include:

1. 1996 - Mapping and cloning of the SMA gene.
2. 1996 and ongoing - Identification of the SMN protein and its roles in the cell.
3. 1999 - Discovery of the back-up SMA gene, called SMN2 that provides a unique and straightforward approach to develop a treatment for the disease.
4. 2000 and ongoing - Development of animal models for SMA to test new and existing drugs.
5. 2002 and ongoing - Identification of existing drugs, such as VPA, PBA, HU and others, as potential drug candidates for SMA.

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Basic research is an investment for future drug discovery programs. It provides the building blocks upon which other types of research are based.