

COMPASS

A Publication Dedicated To Research Updates



FSMA Awards New Research Grants

Yukio Sasaki, Ph.D., Emory University, Dysfunction of Axon Guidance in Spinal Muscular Atrophy

Recent studies suggest that SMA could be caused by developmental defects in neuromuscular interactions between motor neurons and muscle. Therefore, it is important to investigate the role of the survival motor neuron (SMN) pro-

tein, in several aspects of this process, including initial growth of the motor nerves to the muscle (called axon outgrowth and guidance) and in establishment of the subsequent interactions between the motor nerve and muscle in forming a functional neuromuscular synapse. This research project focuses on how SMN protein works at the distal tips of axons in response to axon guidance cues during axon outgrowth and will increase our understanding of the mechanisms of disease onset.

Douglas A. Kerr M.D. / Ph.D., Johns Hopkins University School of Medicine, Transplantation of Human Embryonic Stem Cell-Derived Motor Neurons in Large Mammals

In this project, we will transplant human embryonic stem cell derived motor neurons into a dog model of paralysis to extend our recent rat studies showing the formation of functional motor units using mouse embryonic stem cells and a sophisticated cocktail of factors. If we are to consider this as a possible human therapy, we need to establish both the safety and efficacy of human ES cells in a large animal model of lower motor neuron injury. Ultimately, we hope to use these studies as a springboard to clinical trials in humans with paralysis from a variety of causes including SMA, traumatic spinal cord injury, and ALS.

Charlotte J. Sumner, M.D., Johns Hopkins University, Targeting the muscle and the neuromuscular junction for SMA therapeutics

SMA is caused by deficiency of survival motor neuron (SMN) protein but it remains unclear whether primary

abnormalities in the muscle play an important role in the disease or whether motor neurons will degenerate regardless of the health of the muscle. In order to evaluate the role of muscle in this disease, we will perform a more comprehensive evaluation of the evolution of pathological changes in SMA and deliver therapy specifically to the muscle to evaluate whether this will improve the health of the motor nerve. These studies should provide important insights into whether therapy delivered to muscle alone could be of benefit in SMA patients.

Butchbach, Matthew E. R., Ph.D., Ohio State University, Mechanisms of Butyrate Neuroprotection in a Mouse Model of Spinal Muscular Atrophy

Butyrates and butyrate-like compounds, such as phenylbutyrate, have been suggested to be potential drug treatments for SMA. These compounds improve survival of a mouse model of SMA but do not increase SMN levels in the spinal cord of these mice. In this grant, we will examine potential mechanisms by which these drugs exert their protective effects in the spinal cord of SMA mice. This information will provide greater understanding about the effectiveness of these drugs in treating SMA and will lead to the design of newer drugs with better protective properties. The proposal will also generate a novel model to monitor SMN2 induction and splicing which can be used to identify new therapies for SMA.

Dear Supporters,

The new grant awards being announced in this issue of *Compass* focus on several of the open research questions in SMA. Dr. Sasaki's project at Emory University focuses on determining the critical function of SMN in causing SMA and in particular whether this function is specific to motor neurons. The new projects in the Kerr laboratory at Johns Hopkins and in the Keirstead laboratory at University of California assess the therapeutic possibilities of stem cell research for SMA.

The project being directed by Dr. Charlotte Sumner at Johns Hopkins covers several of these areas. Her work will look at the ability of HDAC inhibitors to provide therapeutic benefit in SMA animal models by investigating exactly how these drugs impact the neuromuscular synapse, both in the motor neuron and the muscle respectively. In the fifth grant we are awarding, Dr. Butchbach of Ohio State University will be assessing how HDAC inhibitors work at the molecular level in mice with SMA, as well as building a new SMA mouse model that will allow SMN levels to be measured directly from animals.

Kenneth Hobby
Executive Director, FSMA

continued on page 2



SMA Research in Print in 2006

FSMA is proud to have contributed funding to the research highlighted in the articles below.

Singh NN, Singh RN, Androphy EJ.

Modulating role of RNA structure in alternative splicing of a critical exon in the spinal muscular atrophy genes.

Nucleic Acids Research. December 14, 2006.

Butchbach ME, Edwards JD, Schussler KR, Burghes AH.

A novel method for oral delivery of drug compounds to the neonatal SMN Δ 7 mouse model of spinal muscular atrophy.

Journal of Neuroscience Methods. December 8, 2006.

Carrel TL, McWhorter ML, Workman E, Zhang H, Wolstencroft EC, Lorson C, Bassell GJ, Burghes AH, Beattie CE.

Survival motor neuron function in motor axons is independent of functions required for small nuclear ribonucleoprotein biogenesis.

Journal of Neuroscience. October 25, 2006.

Singh RN.

Association of severity of spinal muscular atrophy with the loss of NAIP gene.

Neurology India. September 2006.

Zhang H, Xing L, Rossoll W, Wichterle H, Singer RH, Bassell GJ.

Multiprotein complexes of the survival of motor neuron protein SMN with Gemins traffic to neuronal processes and growth cones of motor neurons.

Journal of Neuroscience. August 16, 2006.

Salah-Mohellibi N, Millet G, Andre-Schmutz I, Desforges B, Olaso R, Roblot N, Courageot S, Bensimon G, Cavazzana-Calvo M, Melki J.

Bone marrow transplantation attenuates the myopathic phenotype of a muscular mouse model of spinal muscular atrophy.

Stem Cells. December 2006.

Hahnen E, Eyupoglu IY, Brichta L, Haastert K, Trankle C, Siebzehnrubl FA, Riessland M, Holker I, Claus P, Romstock J, Buslei R, Wirth B, Blumcke I.

In vitro and ex vivo evaluation of second-generation histone deacetylase inhibitors for the treatment of spinal muscular atrophy.

Journal of Neurochemistry. July 2006.

Krosschell KJ, Maczulski JA, Crawford TO, Scott C, Swoboda KJ.

A modified Hammersmith functional motor scale for use in multi-center research on spinal muscular atrophy.

Neuromuscular Disorders. July 2006.

Riessland M, Brichta L, Hahnen E, Wirth B.

The benzamide M344, a novel histone deacetylase inhibitor, significantly increases SMN2 RNA/protein levels in spinal muscular atrophy cells.

Human Genetics. August 2006.

Doran B, Gherbesi N, Hendricks G, Flavell RA, Davis RJ, Gangwani L.

Deficiency of the zinc finger protein ZPR1 causes neurodegeneration.

Proceedings of the National Academy of Science U S A. May 2006.

Brichta L, Holker I, Haug K, Klockgether T, Wirth B.

In vivo activation of SMN in spinal muscular atrophy carriers and patients treated with valproate.

Annals of Neurology June 2006.

Baughan T, Shababi M, Coady TH, Dickson AM, Tullis GE, Lorson CL.

Stimulating full-length SMN2 expression by delivering bifunctional RNAs via a viral vector.

Molecular Therapeutics. July 2006.

Singh NK, Singh NN, Androphy EJ, Singh RN.

Splicing of a critical exon of human Survival Motor Neuron is regulated by a unique silencer element located in the last intron.

Molecular and Cellular Biology. February 2006.

Deshpande DM, Kim YS, Martinez T, Carmen J, Dike S, Shats I, Rubin LL, Drummond J, Krishnan C, Hoke A, Maragakis N, Shefner J, Rothstein JD, Kerr DA.

Recovery from paralysis in adult rats using embryonic stem cells.

Annals of Neurology. July 2006.

Gangwani L.

Deficiency of the zinc finger protein ZPR1 causes defects in transcription and cell cycle progression.

Journal of Biological Chemistry. December 29, 2006.

Markus, M. A., Heinrich, B., Raitskin, O., Adams, D. J., Mangs, H., Goy, C., Lodomery, M., Sperling, R., Stamm, S., and Morris, B. J.

WT1 interacts with the splicing protein RBM4 and regulates its ability to modulate alternative splicing in vivo.

Experimental Cell Research. 2006.

Wirth B, Brichta L, Schrank B, Lochmuller H, Blick S, Baasner A, Heller R.

Mildly affected patients with spinal muscular atrophy are partially protected by an increased SMN2 copy number.

Human Genetics. 2006 May

To date, FSMA funding of fundamental research has helped lead to the following discoveries:

- Mapping and cloning of the SMA gene
- Identification of the SMN protein and its roles in the cell
- Identification of the SMN2 gene as a therapeutic target
- Development of carrier testing for SMA
- Creation of multiple mouse models for SMA
- Identification of VPA, and other HDAC inhibitors, as a drug candidates for SMA

Meet the FSMA Scientific Advisory Board



Christopher Spancake



Douglas A. Kerr



Adrian R. Krainer



Arthur Burghes



Mark Gurney



Stephen M. Strittmatter



Thomas Crawford



Kathryn J. Swoboda



Louise Simard

Christopher Spancake, Ph.D. Dr. Spancake is currently a Director in Pharmaceutical Development at GlaxoSmithKline and he has 18 years of pharmaceutical development experience. Having a child with SMA, Dr. Spancake became interested in SMA research and served as FSMA's Research Director from 1998 to 2005.

Douglas A. Kerr, M.D., Ph.D., Dr. Kerr is an Associate Professor of Neurology with a joint appointment in the Department of Molecular Microbiology and Immunology; and Cellular and Molecular Medicine at Johns Hopkins University. He is also the Director of the Johns Hopkins Transverse Myelitis Center. Dr. Kerr investigates neural stem cells as a potential tool for functional recovery in patients with motor neuron disease.

Adrian R. Krainer, Ph.D. Dr. Krainer is a Professor at Cold Spring Harbor Laboratory. His research interests include unraveling the mechanisms controlling pre-mRNA splicing, including in genetic diseases such as SMA. He is a leading expert in this area with over 100 research articles published to date.

Arthur Burghes, Ph.D., Dr. Burghes is a Professor of Molecular and Cellular Biochemistry at the Ohio State University and an expert in the field of SMA biology. His laboratory focuses on the molecular understanding of genetic neuromuscular disorders, in particular SMA. He has developed several critical animal model of SMA as well as identified a class of small molecule compounds that can correct SMN2 splicing.

Mark Gurney, Ph.D., M.B.A. Dr. Gurney is the Senior Vice President of Drug Discovery and Development at deCODE Genetics. Dr. Gurney brings extensive drug development experience to the FSMA science advisory board. In addition, Dr. Gurney held academic appointments at the University of Chicago and at the Northwestern University. He has a long-standing interest in neuromuscular disease and helped develop one of the first transgenic animal models for human neurodegenerative diseases while in academia.

Stephen M. Strittmatter, M.D., Ph.D. Dr. Strittmatter currently holds the Vincent Coates Professorship of Neurology at Yale University School of Medicine and co-founded the Yale Program in Cellular Neuroscience, Neurodegeneration and Repair. His research focuses on axonal growth during development and regeneration. He has been recognized by honors from the Ameritec Foundation, the John Merck Fund, the Donaghue Foundation, the McKnight Foundation, the Jacob Javits Award of the NINDS and the American Academy of Neurology.

Thomas Crawford, M.D., Dr. Crawford is an Associate Professor of Neurology and Pediatrics at the Johns Hopkins School of Medicine. He is co-director of the MDA clinic for Neuromuscular Disorders. His practice involves general child neurology with a principal interest in caring for children with neuromuscular, neuromotor, and ataxic disorders. His primary research interests involve the basic science and clinical characterization of two important neurologic disorders that affect children: Spinal Muscular Atrophy and Ataxia Telangiectasia.

Kathryn J. Swoboda, M.D., Dr. Swoboda is an Associate Professor of Neurology and Pediatrics at the University of Utah School of Medicine, and Director of the Pediatric Motor Disorders Clinic at Primary Children's Medical Center in Salt Lake City, Utah. The primary focus of her work is to better understand the pathophysiology contributing to muscle weakness in children with spinal muscular atrophy, and to help facilitate the rapid translation of new therapies for treatment trials.

Louise Simard, Ph.D. Dr. Simard has recently taken the position of Professor and Head of the Dept. Biochemistry & Medical Genetics at the University of Manitoba in Winnipeg, Canada. Dr. Simard's group demonstrated that SMN protein is abundant in neuronal growth cones and, most recently, they have published their work on the use of SMNmRNA as a biomarker in SMA clinical trials.

Did you know: Over 200 SMA researchers and clinicians are expected at the 11th Annual SMA International Research Group Meeting being held in conjunction with the FSMA Family Conference June 21st-23rd, 2007 in Schaumburg, Illinois.

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