



Families of SMA *Research. Support. Hope.*

# COMPASS

A Publication Dedicated To Research Updates

## FSMA Hosted Annual Research Conference Brings Together Leading Scientists to Accelerate the Pace of SMA Research

### FSMA Goals for the SMA Research Group Meeting

An important way Families of SMA advances research is The Annual International SMA Research Group Meeting. This meeting is the largest SMA research conference in the world. For 17 years, FSMA has organized the conference, and has financially supported the meeting by covering hotel, travel, and registration for all research presenters for a total cost of about \$200,000 each year. The meeting this year was held at the Disneyland Hotel in Anaheim, California.

225 researchers attended the conference to learn about the latest developments in SMA research. The researchers attending represented over 60 academic organizations and 17 biotech and pharmaceutical companies, from 15 countries around the world. 110 research presentations were given at the conference this year, during 10 different scientific sessions.

Families of SMA has specific goals for the meeting to help benefit the entire SMA community:

- Enables open communication of early, unpublished scientific data among researchers to accelerate the pace of research.
- Creates a vital sense of community among SMA researchers to promote a collaborative spirit and produce research partnerships.



- Allows cross-disciplinary dialog among basic researchers, clinicians, and industry representatives, vital in creating effective therapies.
- Motivates SMA researchers by allowing for direct interaction with families and patients living with SMA.
- Provides a venue to integrate new researchers and drug companies into our community as efficiently as possible.
- Allows young researchers to interact with experienced leaders in the field to help build the future of the SMA research community.

Please see [www.curesma.org](http://www.curesma.org) for a detailed summary of the scientific findings from the 2013 SMA Research Group Meeting.

## What Do Researchers Say About The SMA Research Group Meeting?

“This meeting is immensely important. It grounds and motivates all the researchers to see the families and patients their work is meant to help. This is the single largest concentration of global SMA researchers and it provides great opportunities for networking, catching up and sharing new ideas. Seeing new data and ideas at this meeting really allows the research community to grow and collaborate.”

“Definitely is the yearly opportunity to network and forces us to reach out and talk about each others unpublished results, in the end fostering true, useful collaborations, resulting in more thorough and solid research and discoveries.”



# Summaries of Ongoing Drug Programs in SMA

The 2013 Annual SMA Conference brought together over 1,300 families and researchers from around the world. At the conclusion of the conference the families gathered for a special and unique opportunity to hear the very latest research announcements along with a Question & Answer session focused on the leading drug programs and human clinical research studies in SMA. Summaries of each of these programs are below.

  
  
Roche, in collaboration with PTC Therapeutics and the SMA Foundation, is developing small molecules that increase the production of SMN protein, which is deficient in patients with SMA. Pre-clinically, the compounds reach the central nervous system with oral administration. In various mouse models of SMA, these molecules have been observed to increase SMN levels, normalize the phenotype of neuromuscular junctions, improve motor function, increase body weight, and prolong survival. Current development efforts are focused on profiling the safety of such drugs in animals while exploring clinical biomarkers and defining the best measures for safe, rigorous and efficient clinical studies in SMA patients.

  
California Stem Cell, Inc is actively pursuing Phase I clinical trials for the lead therapeutic candidate MotorGraft in SMA Type I. MotorGraft is a high purity population of motor neuron progenitor cells from human embryonic stem cells that has been shown in vitro to be functionally active, secrete beneficial growth factors, and have the capability of innervating muscle. Animal studies have demonstrated that MotorGraft survives and integrates following transplantation. The functional benefits of MotorGraft observed in vivo include increased body weight, improved muscle EMG recordings, preservation of muscle function, and improved cardiorespiratory function. These benefits are supported by histological findings that reveal enhanced neurite branching, sparing of endogenous motor

neurons, preservation of proprioceptive input to the motor neurons, increased muscle fiber diameter, and increased neuromuscular junction innervation and maturation with transplantation of MotorGraft. Extensive preclinical safety testing demonstrates that MotorGraft does not form tumors, does not induce allodynia, does not biodistribute, and does not have toxic effects. California Stem Cell, Inc has submitted an application to the FDA to start a clinical trial, and is currently on clinical hold in the US. While the clinical hold issues are being addressed for the US clinical trial, California Stem Cell is also pursuing a Phase I clinical trial in the UK. California Stem Cell's program was presented at a recent Scientific Advice Meeting with the UK regulatory agency, the MHRA. A full clinical trial application will be submitted to the MHRA by the end of 2013.

*See our website for details about FSMA funding of the CSC project.*

  
**A SANOFI COMPANY**  
Genzyme (a Sanofi company) has an active program in SMA gene therapy, focused on AAV9-SMN gene delivery into the cerebrospinal fluid (CSF). In studies in mouse models of SMA, we have shown that delivery of AAV9-SMN1 into the CSF results in transfer of the gene to the spinal motor neurons, and expression of SMN protein. The treated mice show significant improvement in strength, motor function, and survival. We have determined the lowest percentage of motor neurons that must be modified by AAV9-SMN-1 in order to make significant improvement in SMA mice. We have also shown that this level of gene transfer can be achieved using CSF delivered gene therapy in large animals, such as juvenile pigs and non-human primates. These findings provide the foundation for continued development of this therapeutic concept for SMA.



Gene delivery using novel Adeno Associated Virus, such as AAV9 has demonstrated great promise for delivering genes to the brain and spinal cord. Two delivery routes have emerged as being effective for

targeting motor neurons. The first route is systemic delivered AAV9 through the bloodstream. Recently, we and others have demonstrated another route of delivery, injection into the cerebrospinal fluid (CSF) surrounding the brain and spinal cord that also effectively targets motor neurons. For the systemic route, we anticipate submitting an Investigation New Drug Application to the FDA over the coming months for approval of a Phase I trial entitled "Phase I Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1 Delivering the Survival Motor Neuron Gene by Self-Complementary AAV9". The trial is anticipated to enroll 9 infants with SMA Type I at Nationwide Children's Hospital in Columbus, Ohio. The study will enroll infants of six months of age and younger with type 1 SMA as defined by the following features: a) proven mutations of the SMN1 gene with two copies of SMN2, b) onset of disease at birth to 6 months of age, and c) hypotonia and muscle weakness demonstrated at time of enrollment. Additional exclusion criteria will also apply. The primary trial outcome will be safety, and the secondary outcomes are the CHOP INTEND functional motor scale and electrophysiological measures. The trial design will be an open-label, dose-escalation clinical trial of scAAV9.CB.SMN injected intravenously through a peripheral limb vein. The team will evaluate short-term safety over a two-year period. Patients will be tested at baseline, on days 7, 14, 30, and once every month for up to 2 years, with long term follow-up for at least 15 years. Trial launch is subject to FDA approval. The team also has excellent pre-clinical data on the finding that AAV9 can be delivered to motor neurons efficiently by placing the virus into the CSF and are advancing on this program too. CSF delivery permits the use of less virus, thereby potentially allowing treatment of older and bigger patients. Dr. Kaspar recently was awarded a \$3.8M cooperative award from NINDS to advance a CSF directed gene therapy for SMA.

*See our website for details about FSMA funding of the Dr. Kaspar's gene therapy project.*



Kolb Laboratory from the Wexner Medical Center at The Ohio State University is

conducting the SMA Biomarker in Infancy Study. This study will establish the natural history of putative SMA biomarkers during the first two years of life in SMA and healthy infants. Our results will aid in the rational design of future SMA interventional studies in infants and will serve as an important data set in the design of future clinical trials in additional diseases of infancy. The Biomarker Study is currently enrolling subjects and includes infants with genetically confirmed SMA and healthy infants without SMA. The Biomarker Study is being performed at 15 sites across the nation and is sponsored by the National Institutes of Health and FSMA. It is also the premier study for the NINDS Network of Excellence in Clinical Trials known as NeuroNEXT. For more information about the study, please type "SMA Biomarker Video" into your search engine and view our Informational YouTube™ Video and/or contact Amy Bartlett, CCRC at (614) 366-9050.

*See our website for details about FSMA funding of the NeuroNEXT SMA project.*



Trophos is conducting a Phase II study of Olesoxime (TRO19622) in 3-25

year old Spinal Muscular Atrophy (SMA) patients. Olesoxime prevents neuronal death and promotes neuroregeneration in multiple preclinical models of neurodegeneration. Olesoxime has been studied in several clinical trials showing that the compound is safe and well tolerated. Pharmacokinetics have been in healthy volunteers and both adults and children with spinal muscular atrophy. A phase II, multicentric, randomized, double-blind, placebo controlled study is ongoing to study the effects of olesoxime in the broadest range of SMA patients. Between November 2010 and September 2011, 165 non-ambulatory type 2 and 3 SMA patients ranging in age from 3-25 years, old were enrolled. Subjects were randomized 2:1 on olesoxime or placebo. The trial is conducted by experienced clinical child neurologists in 22 clinical centers in seven European countries. Patients receive

olesoxime or matching placebo in an oral liquid formulation once a day with a meal and are followed every three months for the 24 month study. Motor function assessed using MFM is the primary endpoint in the study. HMFS, respiratory function and EMG parameters (CMAP and MUNE) assessed at 6 month intervals are secondary endpoints, together with Pediatrics questionnaires (PedsQL). Interim efficacy and futility analyses were performed after all patients had been treated for one year. A data monitoring committee evaluated these interim data for safety and possible efficacy and recommended to continue the trial as planned. Final results of the trial should be available by the end of 2013. In parallel, blood samples are being collected at baseline during the screening visit, at one year and after completion of the trial for biomarkers analysis in collaboration with SMA Foundation. This clinical trial is funded by the AFM Telethon (French association against myopathies), which also supported the discovery and development of olesoxime specifically for SMA.



In January 2013, Repligen announced a licensing agreement with Pfizer to advance its spinal muscular atrophy (SMA) program, originally in-licensed from Families of SMA (FSMA). The program included RG3039, a small molecule therapy candidate in Phase 1 development, as well as backup compounds and enabling technologies. Pfizer is committed to advancing potential new treatment options for SMA, a rare disease with significant unmet need. At this time, RG3039 has completed two of four planned cohorts in the Phase 1 study initiated by Repligen. This initial study, in 16 healthy volunteers, provided a rich source of information about the profile of RG3039. Pfizer believes the Phase 1 data gathered to date is sufficient to achieve the research goals of this study at this stage. We have closed the Phase 1 trial to additional participants, and are working to generate a robust biomarker plan for RG3039 and to understand optimal dosing for this experimental molecule. We believe these steps will enable a better understanding of how to design future clinical studies. In parallel, we are

exploring earlier-stage experimental programs of research that may provide potential treatment options for SMA patients in the future.

*See our website for details about FSMA funding of the RG3039 (quinazoline) project.*



ISIS-SMNRx is an antisense drug Isis is developing to treat

SMA. SMA is caused by a loss of, or defect in, the SMN1 gene leading to a decrease in the amount of SMN protein. SMN protein is critical for the health and survival of nerve cells in the spinal cord that are responsible for neuromuscular growth and function. The severity of SMA correlates with the amount of SMN protein. Isis has designed ISIS-SMNRx to potentially treat all types of SMA by altering the splicing of a closely related gene, SMN2, which leads to the increased production of SMN protein. A Phase 1 clinical study evaluating the safety of single doses of ISIS-SMNRx in children with SMA has been completed. In this study, ISIS-SMNRx was well tolerated at all dose levels tested with no safety or tolerability concerns. The compound is delivered by an injection into the lower back (an 'intrathecal injection') into the space containing cerebral spinal fluid below the spinal cord in order to best distribute the drug to spinal cord motor neurons. The intrathecal injection procedure was also well tolerated in the children. ISIS-SMNRx is now being studied in Phase 2 clinical studies that are designed to examine the safety and tolerability of multiple doses of the drug given over a longer time period. These studies are being conducted in children with Spinal Muscular Atrophy aged 2 to 15 and in infants with SMA who are <7 months old and are expected to complete in 2013. Following on, larger controlled Phase 3 studies are planned to begin in early 2014. In January 2012, Isis and Biogen Idec entered into a preferred partner alliance that provides Biogen Idec an option to develop and commercialize ISIS-SMNRx. Isis also acknowledges support from the following organizations for this program: Muscular Dystrophy Association, SMA Foundation, and Families of Spinal Muscular Atrophy.

*See our website for details about FSMA funding of the Isis project.*

# Mentorship, Collaboration, and Integration

For 17 years, the SMA Research Group Meeting has brought together the leading researchers from around the world to share ideas and the latest scientific breakthroughs about SMA. Doing so has helped new researchers enter into the SMA field, promote collaborations among established research groups, and allowed pharmaceutical companies interested in SMA to quickly integrate into our community. Please read several real world examples from the SMA research community about how the SMA Research Group Meeting has impacted their organization.



**Arthur Burghes,  
Ph.D., Professor,  
The Ohio State  
University**

“I have attended the Annual International SMA Research Group Meeting hosted by

FSMA from the very start 17 years ago. The meeting was first started after the identification of the SMN gene to give a forum for all researchers from many different scientific areas to attend, but with all focused on the common theme of SMA. Prior to that point there had been some research meetings, but these were specifically concerned with exchange of genetic data to find the SMA gene. The subsequent meetings, which developed into the Annual SMA Research Group Meeting, became much broader in topic areas and have expanded from a few people around a table to many people in a conference setting. The conference serves many important roles, and one of these is mentorship. At the SMA Research Group Meeting, there is the opportunity for one-on-one interactions with those at all levels of scientific training from junior to senior investigators. Here researchers are free to ask multiple question, get advice and help with proposals, and obtain reagents or suggestions on how to perform a technique. Second the junior investigators have the chance in either poster sessions or talks to present their work and obtain feedback from senior investigators. Lastly there is exposure of the young investigator to the leaders in the SMA field. In summary at the FSMA meeting, there has been exchange of reagents, ideas, and the formation of collaborations between many groups. The meeting has also encouraged spirited debate, and the presentation of new ideas. This is helpful for junior researchers to see, as it defines the scientific problems more clearly. This fosters the design of experiments, typically completed by the junior investigators, to be more directed and thus resolve the scientific issues surrounding SMA more clearly.”



**Christine DiDonato,  
Ph.D., Associate  
Professor,  
Northwestern  
University**

“The FSMA International meeting has been instrumental in

moving basic science forward toward our understanding of why low SMN levels affect the nerves that control our muscles and the development of a number of different therapeutic strategies aimed at increasing SMN levels or treating other symptoms of disease. An important aspect of moving basic findings towards therapies is the collaborative efforts between academics and biotechnology/pharmaceutical companies. FSMA and the yearly international research meeting has been critical in fostering these interactions, and my laboratory has developed collaborative efforts with Repligen, Inc through the conference. Our collaborative work with Repligen and now Pfizer has focused on performing pre-clinical efficacy studies in mice using RG3039, the novel quinazoline compound, which has recently completed a Phase I clinical trial. In fact, Pfizer hosted one of their first in-face meetings with Key Opinion Leaders at the 2013 conference. Our pre-clinical work helped lay the foundation for filing an Investigational New Drug (IND) application with the FDA. Our current research correlates survival and functional benefits and drug exposure in mice and has helped in guiding dose levels in the first in human studies. This work has been a long-term labor intensive endeavor to reach this point, but personally very rewarding for my academic group to know that we are helping to bring a drug forward to the clinic for our patients.”



**Kathie Bishop,  
Ph.D., Director  
of Clinical Development,  
Isis  
Pharmaceuticals**

“I first attended the Families of SMA Annual

Research/Families Meeting in 2010, shortly after joining Isis Pharmaceutical and starting to work on their ISIS SMN-Rx drug development program. That meeting was invaluable for myself and the other Isis attendees, as it was where we held our first advisory meeting for the program and made initial connections with advisors, collaborators, foundation members, and potential clinical investigators, which has set the stage for many of our activities since then. I also attended in 2011, 2012, and 2013, again finding the experience invaluable for learning about the latest research and clinical advancements in SMA, but also for the opportunity to network and meet with existing and new collaborators and advisors to our program. In 2011, we also held an advisory meeting, this one to seek advice and input on the initial Phase 1 clinical study of ISIS SMN-Rx. In 2013, Isis held at training meeting at the conference for our clinical trial evaluators. In 2011 2012, and 2013, I was also honored to participate in the Families Meeting Drug Development panel, an experience that I think is very important for connecting with SMA families and learning about what their questions and concerns about the drug development process are, and hopefully answering those questions. In addition, for all of us here at Isis who have attended the meeting, the unique experience of the side-by-side meetings with researchers and the SMA families is extremely motivating, as is meeting and talking with the families and children with SMA.”

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