Cure SMA Brings Together Leading Scientists at the Largest SMA Research Conference in the World

Over the last decade, we've seen many advances in SMA research, from new techniques in gene therapy to drugs that show promise in slowing or stopping the progress of the disease. With such great promise in the research landscape, we know that no single group can develop a treatment for SMA alone—it requires collaboration between academics, industry, government, and families.

From the start, Cure SMA has been working to bring all of those groups together, and the researcher meeting is one of the primary ways we accomplish this goal. The research meeting is held each year as part of our Annual SMA Conference.

This year's 18th Annual SMA Research Group Meeting was held in Washington, D.C. in June. In addition to sessions in which researchers shared the latest breakthroughs in SMA science, we also hosted a Continuing Medical Education (CME) meeting to help educate local clinicians on the best care practices for SMA patients.

“An important aspect of moving basic findings towards therapies is the collaborative efforts between academics and biotechnology/pharmaceutical companies. The research meeting has been critical in fostering these interactions, and [through the meeting] my laboratory has developed collaborative efforts [with industry partners].”

Christine DiDonato, PhD
Associate Professor, Northwestern University

Over 350 researchers and clinicians attended both events, representing 15 different countries, 80 different academic and government organizations, and 19 biotech and pharmaceutical companies.

Goals of the Meeting
For the SMA research community, the research meeting is an anticipated event because of its tangible impact on our mission of a world without SMA.

The meeting gives researchers a chance to share unpublished scientific data, accelerating the pace of research. It also creates a sense of community among SMA researchers, encouraging collaboration and long-standing research partnerships. And it allows young researchers to meet and learn from leaders in the field, helping to build the next generation of the SMA research community.

“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 questions, get advice and help with proposals, and obtain reagents or suggestions on how to perform a technique. The junior investigators have the chance—in either poster sessions or talks—to present their work and obtain feedback from senior investigators. And young investigators are exposed to the leaders in the SMA field,” said Arthur Burghes, PhD, a member of the Cure SMA Scientific Advisory Board.
The meeting also allows for cross-disciplinary dialog among basic researchers, clinicians, and industry representatives, which is vital to developing effective therapies.

The meeting is also the main forum in the SMA scientific community for integrating new researchers and drug companies as efficiently as possible.

**Importance of Researcher and Patient Interaction**

Most importantly, the conference motivates SMA researchers by allowing direct interaction with families and patients living with SMA. “This meeting is the best of its kind,” said one researcher. “The value of meeting with researchers, physicians and parents all in one place is immeasurable. Parents see how much we care, physicians see how much work is required for drug development, and researchers see how much their hard work is appreciated.”

These combined researcher and patient events are unique and special opportunities to both form relationships and share new information on current research. The first event was the Meet and Greet, the fun-filled opening of the family conference. During the Meet and Greet, researchers and families can become better acquainted through events like the “researcher relay race.”

Research-related sessions included the Family Friendly Research Poster Session. At the poster session, 31 research groups—including 10 different SMA drug programs—presented their findings, sharing the newest scientific information one-on-one with families.

At the conclusion of the conference, families gathered to hear from leading experts in the field about new advances, strategies, and challenges in SMA drug development. These experts also answered questions about their drug programs through two panel discussions. The first panel, “The Government Panel on SMA Research and Drug Development,” featured two NIH officials and two FDA officials. The second panel, “The Panel on SMA Drugs in Development,” included representatives from all the major companies working on SMA drug development: Isis Pharmaceuticals, AveXis, Biogen Idec, PTC Therapeutics, Genzyme Corporation, Pfizer, Trophos, and Novartis.

A full summary of the research meeting findings can be found on our website, www.cureSMA.org.

“I first attended the 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.”

*Kathie Bishop, PhD*

*Vice President of Clinical Development, Isis Pharmaceuticals*
Moving beyond SMN?
Strategies to Identify Non-SMN Drug Targets for SMA

Written and moderated by Professor Arthur Burghes, PhD, The Ohio State University.

Each year, the Cure SMA Scientific Advisory Board plans a special session focusing on timely topics to open the SMA Research Group Meeting. This year’s session was called, “Moving beyond SMN? Strategies to Identify Non-SMN Drug Targets for SMA.”

SMA is caused by a mutation in the survival motor neuron gene 1 (SMN1). In a healthy person, this gene produces a protein—called survival motor neuron protein or SMN protein—that is critical to the function of the nerves that control our muscles. Individuals with SMA do not produce this protein at high enough levels.

Scientists are pursuing many treatment strategies that address the loss of SMN protein. But other treatment strategies may also be effective. This special session addressed questions such as:

- What genes can alter the severity of SMA symptoms besides SMN?
- Can these genes, called modifiers, be used as therapeutic targets in drug development for SMA?
- What are the critical downstream genetic pathways that are affected by the loss of SMN?
- Once identified, how can these pathways be used for drug development?
- What lessons can SMA researchers learn from the study of genetic pathways and modifiers in other disorders?

Dr. Kurt Fischbeck from the National Institutes of Health (NIH) opened with an overview of the treatment options in development for SMA today, including SMN and non-SMN based therapies.

Next, Dr. Jeehye Park from Baylor College of Medicine spoke on the identification of genetic pathways in spinocerebellar ataxia type 1 (SCA1). Dr. Park’s lab has used special assays, called RNAi screens, to identify genetic pathways that influence SCA1 severity. Dr. Park and her team have identified a particular protein, called a suppressor, that removes the toxicity of the SCA1 protein. Identification of suppressors is a powerful way to find new drug targets, including in SMA. We don’t yet know whether modifiers of SMN protein activity exist, so it is critical to explore this further.

Dr. Charles Thornton of the University of Rochester then spoke about myotonic dystrophy (MD1). This disease results in muscle weakness and is caused by mutations in a protein called muscle blind.

Genes are encoded by mRNA, a blueprint that tells the cell how a protein should be made. In MD1, the mutated muscle blind protein causes mRNAs of other genes to be put together incorrectly, meaning proteins will also be produced incorrectly. This is known as gene mis-splicing.

When a disease causes genes to mis-splice, researchers want to know how many genes are affected, and which gene changes are critical to causing disease symptoms. In MD1, there is clear involvement of a large number of tissues, each with specific gene splicing defects contributing to symptoms.

Will this also be true in SMA? The loss of SMN also causes genes to mis-splice. In SMA, however, symptoms are much more restricted to the motor system, perhaps indicating fewer downstream splicing targets. Recent studies seem to indicate that the majority of genes splice correctly in SMA, with only a small number of changes detected.

Determining the extent of mis-splicing in SMA is important. Is it thousands of splicing changes that contribute to SMA or a few key changes? Finding the exact downstream gene(s) that contribute to the symptoms of SMA is a very important basic research goal.

Dr. Livio Pellizzoni of the Motor Neuron Center at Columbia University presented data on one downstream splicing target of SMN deficiency. Using animal models of SMA, Dr. Pellizzoni identified a gene called stasimon, which is mis-spliced in SMA.

The Pellizzoni laboratory is using AAV9 gene therapy vectors to restore stasimon to the neurons in the spinal cord. A vector is a virus that “infects” a cell with new DNA to correct mis-splicing. Dr. Pellizzoni and his team want to see if this can rescue the SMA symptoms in mouse models. Understanding this will be crucial in determining whether stasimon can be useful as a drug target in SMA.

One of the best examples of genetic modifiers in human disease is from the globin disorders, like sickle cell anemia. Dr. Martin Steinberg from Boston University presented data from the globin disorders at the meeting. One of the key modifiers in sickle cell anemia is the expression of fetal globin, which is normally expressed only before birth. Turning fetal hemoglobin back on later in life can replace the muted adult globin genes. Similarly, SMA has a “back-up gene,” survival motor neuron gene 2 (SMN2), that might be able to completely or partially replace the mutated SMN1 gene.

Next, Dr. Kevin Flanagan of Nationwide Children’s Hospital presented on the LTB4 gene, a recently identified modifier in Duchenne muscular dystrophy (DMD). It has been shown to be a good predictor of the age when boys with DMD lose the ability to walk. This shows that genetic modifiers can have significant influence on the severity of symptoms, indicating the importance of identifying them in SMA too.

To close the special session, Dr. Brunhilde Wirth of the University of Cologne also presented on potential modifiers in SMA, including the gene plastin, which has been reported to modify SMA symptoms in female patients, but not male patients. Dr. Wirth also presented a scenario in which both the SMN2 gene and a modifier gene could be used together to increase in SMN protein and boost therapy effectiveness, particularly in SMA type I.

After the presentations, a panel discussed the downstream pathways that cause the symptoms of SMA, and possible modifiers of SMA severity. The SMA research community considered how to apply the lessons from these other diseases to SMA, in order to advance future drug development through the identification of genetic modifiers and downstream targets.
Update from the Continuing Medical Education (CME) Conference

Cure SMA’s commitment to the entire SMA community extends to those with providing care—including physicians, specialists, nurses or nurse practitioners, genetic counselors, physical or occupational therapists, nutritionists, social workers and more. Our CME Conference provides these healthcare professionals with a comprehensive curriculum on the diagnosis and care of SMA.

This year’s CME Conference, *Interdisciplinary Perspectives on Spinal Muscular Atrophy*, was held on Friday, June 13, in Washington D.C., in partnership with the University of Wisconsin School of Medicine and Public Health. Over 100 medical professionals attended the conference, representing over 30 states and provinces.

The course focused on the diagnosis of infants and children with neuromuscular weakness, how care standards should be applied to individuals with SMA, and possible strategies for intervention. Both regional and national expert faculty made presentations and hosted panel discussions.

This year’s conference was organized into seven distinct general sessions in the morning, with speakers presenting on a variety of topics.

An addition to this year’s meeting was a joint poster session/luncheon with the Research Group Meeting. This allowed CME attendees the opportunity to review the latest clinical research, and engage with the researchers.

In the afternoon, there were four alternating breakout sessions: cardiopulmonary care, orthopedic care, breathing, and rehab therapy recommendations. Attendees chose the breakout sessions that best fit their specialty.

The breathing breakout was a highlight of the afternoon sessions. In this interactive session, family members and presenters gave hands-on demonstrations of breathing equipment that children and families with SMA often use in their daily lives.

Demonstrations were provided by Justin Kuester and his daughter, Addison, from Wisconsin; Kate Sohl and her son, MacArthur, from Massachusetts; and Drs. Mary Schroth, Rob Graham, and Oscar Hank Mayer.