

# fight<sup>s</sup>ma

June 16, 2008

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Dear Dr. Gwinn,

Andrew's Buddies (also known as FightSMA) is grateful to NINDS and ORD for their generous support of the 2008 FightSMA Annual Conference, *The Good Fight*. Please find attached our final report for this conference.

This year's conference was held in Washington, DC and included over 25 researchers and healthcare professionals and more than 70 family members and friends. Andrew's Buddies/FightSMA bore the cost of all food and lodging for conference attendees as well as transportation for presenters. This translated to over \$85,000 in expenses this year. Many researchers commented on the productive sessions and intimate atmosphere that encouraged the sharing of ideas. 100% of conference survey respondents said they would participate in future FightSMA conferences and would recommend them to other professionals in their field.

Andrew's Buddies/FightSMA will return to Washington, DC in April 2009 for our seventh Annual Conference. This conference includes international leaders in SMA research who will discuss their work and decide our next steps in finding a cure for this horrible disease. Now that the stage has been set for translational research we hope to expand on this topic and emphasize drug development as part of next year's meeting. In addition to scientific meetings and discussions, researchers will be given the opportunity to meet with SMA families and put a face with the research. Results from the scientific portion of the event will be shared with over 100 attendees, including the parents of children with SMA, during the last two days of the Conference.

FightSMA is grateful for the support NINDS/ORD provided us in 2008 and hope that continued funding will allow Andrew's Buddies/FightSMA to offer this valuable resource to SMA research specialists and families with SMA. FightSMA has accomplished so much, but there is still much to be done. Thank you for your encouraging words and for all of your time and support. Of course, please contact me if we can provide any further information or answer any additional questions.

Very Best Regards,



Martha Slay  
President, Andrew's Buddies/FightSMA

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*Spinal Muscular Atrophy (SMA) kills more babies than any other genetic disease.*

ANDREW'S BUDDIES CORPORATION  
DBA FIGHTSMA

## FINAL REPORT – R13 CONFERENCE FUNDING

JUNE 16, 2008

**GRANT NUMBER:** 1-R13-NS-062648-01

**AWARD:** \$5K/NIH, NINDS; \$25K ORD

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### INTRODUCTION

Washington D.C was the host city once again for the annual FightSMA Research Conference, *The Good Fight*, which was held April 21-22, 2008.

Invited clinical and research specialists from around the world were in attendance to present and discuss their most recent unpublished data and to address several important, but unanswered, questions in the SMA field.

### RESEARCH CONFERENCE SUMMARY

Tremendous strides have been made since the identification of the SMA-determining gene regarding SMN function, however, it is still unclear why a defect in SMN results in the motor neuron disease. There are two primary concepts that have been proposed to explain the motor neuron-specific loss associated with SMN deficiencies. In the first scenario, SMN is involved in the generation of RNA/protein complexes required for proper gene expression, called snRNP (small nuclear ribonucleoproteins). Motor neurons have been proposed to have a uniquely high requirement for snRNPs that makes them especially sensitive to SMN levels. Additionally, analysis of the SMA mouse models has identified that a subset of snRNPs (referred to as the 'minor' pathway) are more perturbed in the SMA context than the snRNPs that are more likely to be involved in more general 'housekeeping' gene expression. For example, a computer-based analysis of the genes that are regulated by the 'minor' snRNP pathway are not randomly scattered throughout the genome, rather, a significantly large percentage of these genes encode factors that are likely involved in neuronal function, such as calcium channels. In the second scenario designed to explain the loss of motor neurons in SMA, SMN is predicted to be involved in the transport of RNA/protein complexes along the length of the axon toward the growth cone and the

neuromuscular junction. SMN is associated with non-snRNP components, such as hnRNP proteins and beta-actin mRNA. To date, the primary focus has been upon snRNP biogenesis, however, this is an intriguing component of SMN function that still needs more attention. The recent discovery of plastin-3 as a potent SMA modifying gene by the Wirth laboratory indicates that axonogenesis is likely an important component of SMA development.

In addition to asking “what is the function of SMN,” this meeting was designed to ask the question: what tissues require SMN expression? SMN expression was experimentally driven by relatively restrictive promoters, designed to express SMN exclusively in muscle or exclusively in neurons. Expression of SMN in neurons dramatically increased the life span of the severe SMA mice. In the severe SMA model, mice live ~3-5 days, whereas neuronal SMN expression extended the average life span to greater than 200 days. High levels of SMN expression in muscle did not significantly extend survival. These results are not to suggest that SMN does not perform an important function in muscle, but rather that SMN function in muscle is likely not directly linked to SMA development.

Building upon the molecular biology and biochemistry, several labs presented translational research programs designed to develop potential therapeutics for SMA. SMN protein is a very stable protein, however, the exon-skipped isoform is remarkably unstable and is rapidly degraded. Current work is being performed to better understand the regulation of SMN degradation as a means of increasing the intracellular pool of SMN.

Currently, a number of compounds are being examined in the SMA mouse model. Importantly, a detailed analysis of this mouse model has recently been published that identifies the most sensitive phenotypic traits that can be followed during drug testing. Several small molecules specifically target SMN and are designed to increase SMN expression, including trichostatin-A (TSA) and synthetic antisense oligonucleotides (AONs). Similar AONs have made tremendous strides in other genetic diseases, such as Duchenne muscular dystrophy. In the SMA context, AONs are used to increase full-length SMN expression from the SMN2 gene by modulating the pre-mRNA splicing regulatory factors. Modulating SMN2 gene expression at the RNA level through a variety of platforms is still extremely intriguing, however, the issue of delivery is a hurdle that faces SMA and other central nervous system disorders. Additional small molecule screens are being performed with optimized SMN reporters that are designed to identify the most robust SMN inducers. This novel platform has the potential to identify compounds that function through pathways such as transcriptional activation or SMN2 exon 7 splicing, but also through mechanisms that are more ambiguous, such as RNA stability or through minor contributions of multiple pathways.

Gene therapy strategies were presented that included the development of vectors through a novel platform referred to as ‘bio-panning’ or in vitro evolution. In essence, a randomized pool of novel viral vectors can be generated and then through a series of enrichment steps using a mouse as ‘bio-panning’ tool, novel vectors can be identified that are ideally suited for specific gene expression in specific cellular lineages.

Collectively, this was an excellent forum to openly discuss cutting-edge research that continues to build the critical base of knowledge regarding SMN function, as well as the translational studies that are bringing novel compounds and molecules closer to clinical trial.

## PARTICIPANTS

Attendees included Elliot Androphy, M.D., University of Massachusetts Medical School; Gary Bassell, Ph.D., Emory University School of Medicine; Nicholas Boulis, M.D., Emory University School of Medicine; Arthur Burghes, Ph.D., Ohio State University; Barrington Burnett, Ph.D., National Institutes of Health; Matthew Butchbach, Ph.D., Ohio State University; Kenneth Fischbeck, M.D., National Institute of Neurological Disorders and Stroke; Katrina Gwinn-Hardy, M.D., National Institutes of Health; Brian K. Kaspar, Ph.D., The Research Institute at Nationwide Children's Hospital; Rashmi Kothary, Ph. D., Ottawa Health Research Institute; Adrian Krainer, Ph.D., Cold Spring Harbor Laboratory; Robert Leshner, M.D., Children's National Medical Center; Chris Lorson, Ph.D., University of Missouri-Columbia; Alex MacKenzie, M.D., Ph.D., Children's Hospital of Eastern Ontario Research Institute; Eric Munoz, medical student, National Institutes of Health; Marco Passini, Ph.D., Genzyme Corporation; Livio Pellizzoni, Ph.D., Columbia University Center for Motor Neuron Biology and Disease; Michael Sendtner, M.D., University of Wurzburg; Charlotte Sumner, M.D., Johns Hopkins University School of Medicine; Kathy Swoboda, M.D., University of Utah; and Meg Winberg, Ph.D., Spinal Muscular Atrophy Foundation.

FightSMA requested that all participants complete an on-line survey at the end of the conference. The purpose of this survey is to help better serve the attendees and determine the most efficient means for planning and administering the 2009 conference. A summary of this survey is below.

90% of participants rated the overall conference as "excellent." 90% of participants rated the ease of traveling to Washington, DC as "very easy" and 100% rated the ease of traveling around the City as "average" or better. 100% of participants rated the choice of topics as above average to excellent. 89% said that the choice of speakers was excellent. The majority of participants felt that the number of people attending the conference was the right amount for sharing ideas and discussing current topics. 100% of participants said they would participate in another FightSMA Research Conference and would recommend the Conference to others. 20% of the participants were new attendees and 90% had attended some form of SMA conference prior to this event.

Comments regarding the participants' reasons for attending the conference were:

- Small group
- People attending and the small forum with open forum to talk
- The round table atmosphere
- Interdisciplinary
- Fight SMA has been a leader in SMA research, the group of participants are true experts in their field
- The leaders in the SMA field are present

Some general comments from participants were:

- I would maintain the balance among the different topics relevant to SMA research presented at this year's FightSMA conference.
- I consider the strategy to bring together basic scientists and clinical experts as perfect, this should not be changed
- This was an excellent selection of speakers from drug trials, basic biology, gene therapy and clinical studies. Overall, I thought the conference led to new understanding for all the covered topics and all attendees would walk away with excellent new information. I truly wouldn't change one thing. These are all experts in the field and all have strong interests.
- (A suggestion for next year's speakers would be an) MD with experience injecting into human spinal cord or into the human intrathecal space.
- This is one of the better scientific conferences I attend all year long. It would be helpful for a clinician to start the program off, to expand where the field stands with therapies or lack thereof, challenges for patients, and even the small steps in research that will benefit patients. Overall, the organization is superb, and many applauds for the organization, and smooth movements from the chairs of the scientific meeting to Heather and staff at Fight SMA. Finally, Martha and the chairs (Chris and Alex) pull together an amazing event, and I know families as well as scientists all benefit from the efforts of Fight SMA. I am honored to attend the meetings and know that with the knowledge the field is gaining, (and) that truly some major changes in SMA will be seen in the near future. We will certainly keep up our studies to the highest degree of science.

## DECISIONS AND RECOMMENDATIONS

Based upon the presentations, there are several important take-home points:

1. The role of SMN in muscle is likely not central to SMA development.
2. Muscle, however, may prove to be an intriguing target for therapeutics in SMA (in a non-SMN dependant manner).
3. SMN has (at least) two critical cellular functions that may both contribute to SMA development: snRNP biogenesis and axonal transport. To date, neither pathway excludes the other from contributing to the phenotype, or from being the primary defect in SMA.
4. Therapeutic development, specifically with small molecules and modified oligos, represent an excellent platform for SMA-specific drug development. SMN-induction and life span are increased in the SMA mice following repeat administration with a variety of compounds, holding promise for clinical trials.

## ACTION TAKEN

- Although tremendous progress has been made in the area of understanding SMN function, it will be critical to further delineate the exact cellular pathway(s) that lead to SMA development. For example, it will be important to create transgenic mice that express mutant SMN proteins that separate SMN's roles in snRNP biogenesis and axonal trafficking.
- Delivery strategies and delivery paradigms need to be established for the large number of oligo-based therapeutics. Clearly many of these compounds do change SMN splicing and increase SMN levels. The central problem of delivery still remains. Insight, however, into intraventricular injections is likely to shed light into this area, however, experiments are still pending.
- Related to #2, it is still unclear when a therapeutic needs to be administered to elicit a protective affect. A window of approximately PND 4-10 has been identified that is important for extending life span. However, is this the best possible extension of survival that can be achieved in this mouse model? Current studies are underway through the construction of mouse models that will express SMN at various stages of development. This will be critical to understanding the potential therapeutic window that is available in SMA.
- This year, the 2008 annual FightSMA Research Conference, *The Good Fight*, focused more on basic and translational research. This was designed to answer fundamental questions in the field and introduce promising new translational work currently being examined in the mouse model. An emphasis on drug development will be an important focus for the 2009 meeting.

## FOLLOW UP

Planning for the 2009 FightSMA Researcher's Conference *The Good Fight* has already begun. The meeting is scheduled to take place April 19-21, 2009 in Washington, DC.