Researchers' Conference

General Information

When: April 20-22, 2008
Where: L'Enfant Plaza Hotel
480 L'Enfant Plaza, SW
Washington, D.C.

Meeting Summary - By Dr. Chris Lorson, FightSMA's Science Director

Washington D.C was the host city once again for the annual FightSMA Research Conference, The Good Fight, was held April 21-22. Washington D.C. provides the ideal setting for this meeting as many of the SMA researchers are actively involved in pushing their local Representatives to support the SMA Treatment Acceleration Act, and the direct contact between SMA families and researchers provides a powerful one-two punch that truly delivers results on The Hill. 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clinical and research specialists from around the world were in attendance to present and discuss their most recent unpublished data and to address several important, but unanswered questions in the SMA field. The following is a summary of the Research Conference.

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.

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An 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 SMA, 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 remarkable 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 molucules specifically target SMN and are designed to increase SMN expression, including tricostatin-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. FightSMA appreciates the hard work and dedication that the researchers bring each year to this meeting. Without your tireless efforts, SMA would not be at the exciting stage at which we now stand.