Research Compass

a Families of Spinal Muscular Atrophy publication dedicated to Research News

Research Summary Update: 2006 Surfin' SMA Family and Professional Conference

Prepared by Jill Jarecki, Ph.D.
FSMA Research Director

Dr. Jarecki began the session by describing the FSMA-funded research activities in 2006, and by providing a global overview of the FSMA strategy to scientific funding (Please see her slide presentation for further details www.curesma.org/research.shtml). FSMA has three main components to its research program: 1. Funding research grants mostly in academic labs 2. Funding pre-clinical drug development in industry 3. Establishing and funding Project Cure SMA, a clinical trial network. FSMA believes that all three of these aspects of our research program are essential to finding a treatment for SMA.

First, the basic research grant program identifies the molecular targets that can be used to design the best and most effective drug discovery approaches. Thus, the academic research is a critical component in the path to finding SMA treatments because it clarifies the fundamental biology of SMA disease pathology, which in turn provides a framework for identifying the most rational and most successful drug identification schemes.

Next, using the knowledge gained from the basic research projects as a basis, the drug development programs generate potential drug candidates for SMA. Potential drug candidates discovered in the pre-clinical drug development programs must then be tested for safety and efficacy in humans. Project Cure SMA provides the infrastructure for such testing. Project Cure SMA, with its six clinical testing sites across North America, has developed and validated outcome measures to assess the clinical benefit of SMA drug candidates. These measures are now being used in the Project Cure SMA Phase II Carni-Val study for the efficacy of a combined regimen of Valproate and Carnitine in 90 children with SMA. Please see the www.projectcuresma.org for more details as well as the summary of Dr. Swoboda's presentation included in this addition of the Research Compass.

Next, Dr. Jarecki provided specific details about the exact nature of FSMA research funding in 2006. FSMA funded over $5 million in research in fiscal year 2006, which ended on June 30th, 2006. This currently includes 24 basic research grants, and twelve of these grants were newly funded in 2006. The newly funded research projects in 2006 are focused in two primary areas. The first is delineating the role of SMN in motor axons. The second is the identification of novel "druggable" molecular targets for SMA therapeutic intervention, which will lead to new, more focused drug development projects in the future. Each of these drug target identification projects using different experimental systems, for example model organisms such as mouse, fruit flies, the worm Caenorhabditis elegans or SMA cellular models, to identify genes that interact with SMN and/or regulate SMN function.

Next, Dr. Jarecki discussed FSMA funding of pre-clinical research. FSMA is funding two drug development programs – one at deCODE Chemistry and one at Paratek Pharmacueticals.

First she provided an overview of the project ongoing at deCODE. The FSMA/deCODE collaboration was initiated in 2003 as the continuation of a successful early phase drug discovery project at Vertex Pharmaceuticals.The deCODE chemistry-FSMA collaboration has focused on the optimization of a class of molecule called 2, 4-diaminoquinazolines that was discovered in the high-throughput, cell-based assay developed at Vertex. During the past three years, deCODE chemistry has developed optimized analogues that have the vast majority of characteristics needed for a potential SMA drug. These compounds are highly potent in the cell-based assay, have excellent metabolic stability, show very efficient penetration of the blood-brain barrier, possess an attractive pharmacokinetic profile, and demonstrate the desired activity in SMA cellular models, including increasing the numbers of SMN containing gems structures in cells derived from SMA Type I patients to levels found in carrier cells. This is a very substantial increase in SMN protein levels. As the lead optimization phase of the project comes to completion during the next 6 months and a final clinical candidate is selected, the focus of the collaboration will be to further assess the pharmaceutical properties of the clinical candidate in Investigational New Drug (IND) application-focused experiments. The IND package constitutes an extensive series of experiments required by the FDA to assess safety in animals before a drug can be tested in humans. With a novel compound like ours, human testing would commence in a Phase I trial, which is usually conducted in healthy volunteers. The goal of this first human study would be to assess drug safety and tolerability. If everything continues in a positive manner, the anticipated timeline for IND filing with the FDA is 2007 and Phase I testing can begin 30 days after that filing.

Finally, an update was given on the newly funded drug development program at Paratek Pharmaceuticals. Funding was initiated in March 2006. This new drug development collaboration focuses on optimizing and advancing into the clinic a novel small molecule within Paratek's library derived from the tetracycline class of compounds. This molecule directly influences SMN2 splicing, resulting in the production of more SMN protein. The Krainer laboratory at Cold Spring Harbor will be assessing additional compounds from Paratek's collection for effects on SMN2 splicing. In parallel, Paratek will be developing new proprietary compounds based on this initial lead.

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Research News from the 10th International SMA Research Group Meeting in Montreal by Dr. Arthur Burghes

Dr. Burghes provided an update from the Montreal meeting. He discussed that is essential to understand the function of SMN in motor neurons in order to gain a better understanding of SMN disease pathology. Motor neurons are very special cells. They have cell bodies located in the spinal cord, but also must send out very long extensions called axons. These axons must grow all the way to the muscles to in order to control muscle movement. Therefore, axons often need to extend very long distances, for example several feet in length from the spine all the way to the foot. SMN is known to have a very particular function in the cell body of every single cell type in the human body (specifically in snRNP assembly). However, it is not fully understood why just one cell type, motor neurons, die in patients having SMA. One proposal is that SMN has a specialized function needed in motor axons. Another idea is because motor neurons are very specialized cells they could be more sensitive to the loss of the SMN in the cell body (snRNP assembly) than all the other cells types. While researchers are divided about this, it has been known for several years that SMN is found in both the cell body and the axons of motor neurons, suggesting a specialized axonal function is feasible.

Some of the most exciting new data in Montreal focused on this controversy. Several presentations were given showing that SMN likely has a distinct function in the axons than its role in the cell body and it forms a distinct complex in motor neurons than in the cell body. Representatives of the Beattie lab, the Sendtner lab, the Morris lab, the Cote lab, the Acsadi lab, the Kothary lab, the Burghes lab, the Androphy lab, the Bassell lab, the Claus lab, and the Battaglia labs gave these presentations.

Dr. Burghes also discussed that animal models of Type 0, I, II, and III SMA have been developed (many of these in his lab). These models are currently being used to test drug candidates in his lab and in other laboratories. In his lab they have identified several drug candidates in the butyrate family, for example PBA that can extend life in the mouse model of type I SMA. Related to this, a number of talks focusing on drug discovery efforts to find novel small molecule therapies for SMA were presented in Montreal. Talks on this topic were given by representatives of the labs of deCODE Chemistry, Elliot Androphy, Christina Brahe, Brunhilde Wirth, Brent Stockwell, the NINDS SMA project, and Trophos.

Potential of RNA-mediated therapies for SMN by Dr. Klemens Hertel

Dr. Hertel described that very low levels of SMN protein are made from the SMN2 gene, and therefore the amount of SMN protein produced from the SMN2 gene is too low to compensate for the loss of the SMN1 gene in SMA. SMN2 makes low levels of SMN protein due to a processing defect when producing its mRNA transcript. This process is called pre-mRNA splicing. During SMN2 splicing, a small segment of required RNA, called exon 7, is left out of the final mRNA transcript. This results in very little functional SMN protein being made from SMN2.

Because all individuals with SMA possess a copy of the SMN2 gene, increasing the amount of SMN protein being produced from SMN2 is an obvious therapeutic avenue. One way to accomplish this is to correct the SMN splicing defect by promoting exon 7 inclusion into the final SMN2 mRNA transcript. Several labs, including those of Dr. Hertel, Dr. Ravindra Singh, and Dr. Krainer, have developed a molecular approach to correct SMN2 splicing, resulting in the production of more functional SMN protein. To increase exon 7 inclusion, these labs have designed short RNA pieces call "anti-sense oligoneucleotides". These anti-sense RNAs can interact with the SMN2 pre-mRNA. Through this interaction they mask portions of the SMN2 mRNA that work to inhibit the inclusion of exon 7. By masking these elements, their inhibitory influence on splicing can be suppressed, resulting in a correction of the SMN2 splicing defect. This allows for the inclusion of exon 7 into the SMN2 final mRNA transcript and functional protein to be produced from the SMN2 genes. Experiments of this type result in a several fold increase in SMN proteins levels in cells derived from Type I SMA patients. Ongoing studies will focus on developing gene therapy approaches using viral gene delivery systems to deliver anti-sense oligonucleotides to motor neurons in living organisms. These systems will then be used to test the efficacy of this approach in SMA animal models.

Update on the Hydroxyurea Clinical Trial at Stanford University by Dr. Ching Wang

Dr. Wang reported on two clinical trials he is leading at Stanford University to test the safety and efficacy of Hydroxyurea in patients living with SMA. Both of these trials are double blind randomized placebo trials with a ratio of 2 to 1 patients receiving drug versus placebo. The first study is being conducted in Type I SMA patients. Dr. Wang currently has 14 patients enrolled in this study and needs 4 more to complete enrollment. The second study involves Type II and severe Type III patients. Enrollment is complete for the Type II/III trial with 24 patients enrolled at this point in time. The outcome measures being assessed in the study are Gross Motor Function Measurement, Time Test, and MUNE. This study is currently ongoing, and full analysis is not yet available. In addition, the study has not yet been unblinded (i.e. the patient receiving hydroxyurea versus placebo remains unknown). However, the data suggest that the safety profile is reasonable. In a few patients a drop in the white blood cell count was noted, but was temporary. In the interim analysis, SMN transcript and protein levels were also assessed. A responder group with increased SMN levels was reported, although it unclear at this point whether these patients have received drug as the study is still blinded. This study is continuing over the next several months and final results regarding efficacy in the functional motor tests will be presented upon completion.

Stem Cell Therapy in SMA by Dr. Hans Keirstead

Dr. Keirstead explained his work regarding the development of human motor neurons from human embryonic stem cells, which are obtained from in vitro fertilization procedures. He has developed a protocol to generate a very pure population of motor neurons (about 95%) from stem cells. His procedure has

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Update from the FSMA Research Director

Jill Jarecki, Ph.D.

Dear Families,

In June the 10th Annual Spinal Muscular Atrophy Research Group Meeting was held in Montreal Canada. Over 160 researchers and clinicians attended. Scientific sessions were held on the following topics: Clinical Trials, Outcome Measures, Stem Cell Therapies, SMN Function, and Drug Discovery Initiatives. Over 80 presentations were given, and a detailed summary of each session can be found on our website (www.curesma.com).

The Research Group Meeting was held in Montreal this year to coincide with the 10th World Congress of the International Child Neurology Association (www.ICNC2006.com), where over 1500 pediatric neurologists from 80 countries were in attendance. FSMA sponsored a number of events at this meeting to raise awareness about SMA within the child neurology community.

On Monday June 11th, FSMA sponsored and organized a very well attended panel discussion on the clinical management of SMA. Presentations focused in four areas: Respiratory Management by Dr. Mary Schroth, Orthopedic and Functional Disabilities by Dr. Julie Dube, Metabolic Dysfunction and Nutritional Management by Dr. Kathryn Swoboda, and Therapeutic Directions by Dr. Enrico Bertini. The session was standing room only in a room with seating for 250 people. Our goal for this event was to provide the most advanced practices in the clinical management of SMA to the general pediatric neurology community in order to improve the clinical care of all children living with this disease.

On Wednesday, June 13th FSMA also sponsored a plenary session entitled **"Therapeutic Innovations In The Neuromuscular Disorders"**, which was given by Dr. Victor Dubowitz of Imperial College London, Hammersmith Hospital. This session was also well attended and well received.

I would also like to take this opportunity to highlight several particularly relevant developments from the Research Meeting in Montreal. First, several novel clinical trial outcome measures for both Type I and ambulatory Type III patients were discussed, which will allow clinical trials to enroll more diverse SMA patient types in the future. Also presented were updates regarding several ongoing clinical trials, and the summaries of these talks can be found within this issue of the Compass.

On the basic research front, one of the most interesting developments was the presentation of new data from multiple labs indicating that SMN forms a distinct protein complex in motor axons and that it has specific functions in axons, which are different than those in the cell body. This is an important issue because delineating and understanding the importance of the specific role of SMN in SMA will facilitate more strategic design of drug discovery screens.

Drs. Hans Keirstead and Doug Kerr gave exciting talks on stem cell therapies for SMA. Dr. Kerr showed that mice motor neurons derived from mouse stem cells send axons out of the spinal column and into the periphery when injected into the spinal cord. These motor axons can form functional connections on muscles, which provided clinical improvement in mice with motor neuron disease. Moreover, Dr. Keirstead reported good progress on developing stem cell-derived motor neurons for eventual motor neuron replacement trials in SMA.

Finally, there were a number of talks focusing on drug discovery efforts to find novel small molecule therapies for SMA. Talks on this topic were given by representatives of the labs of deCODE Chemistry, Elliot Androphy, Christina Brahe, Brunhilde Wirth, Brent Stockwell, the NINDS SMA project, and Trophos. FSMA-funded deCODE Chemistry presented the drug initiative that is closest to the clinic, focused on up-regulating SMN levels for SMA.

Several weeks later, SMA researchers provided research updates, highlighting the most important developments from Montreal, at the Family and Professional Conference in San Diego this July. Talks were given on FSMA-funded Research Activities, Dr. Hans Keirstead on Stem Cell Therapies for SMA, Dr. Klemens Hertel on RNA-Mediated Therapies for SMA, Dr. Arthur Burghes on Basic Research News form Montreal, Dr. Ching Wang on the Hydroxyurea Clinical Trial, and Kathy Swoboda on Project Cure SMA and the Carni-Val Clinical Trial. A summary of this session is found within this issue of the Research Compass.

Together we will find a cure!

Jill Jarecki, Ph.D.

been developed and tested under strict government controls in compliance with the quality requirements of the FDA. This will allow human testing to advance at a much faster pace. In addition, Dr. Keirstead demonstrated during his talk that his lab has generated motor neurons that both look and behave like normal motor neurons. For example, they express genes known to be found only in motor neuron cells opposed to any other cell type. More importantly, he demonstrated that these motor neurons function like normal motor neurons. For example, Dr. Keirstead played a movie showing the motor neurons causing muscles to actively twitch when co-cultured together in a Petri dish. Dr. Keirstad's ultimate goal is to produce clinically relevant cell populations for therapeutic development in SMA, which can be used for motor neuron replacement. For further details regarding this project, please see the article written by Dr. Keirstead describing his FSMA-funded research on our website (http://www.curesma.com/keirstead06.shtml).

Project Cure SMA Update by Dr. Kathryn Swoboda

Dr. Swoboda reported on two Project Cure SMA trials assessing sodium valproate in SMA patients greater than 2 years of age. In an open label study (n=40 patients), Project Cure SMA assessed tolerability and toxicity of sodium valproate. It was shown that valproate was well tolerated in these children, when given in combination with Carnitine. Only four children dropped out of the study: two due to excessive weight gain and two due to lack of perceived benefit after 6 months. The modified Hammersmith scale was used to assess efficacy. An average increase of 6 points was observed after 12 months, and a 3-point increase is viewed as a clinically relevant change. This data was further assessed by dividing children into two groups: children over 5 years of age and children under 5 years of age. Overall, both groups considered together improved on the modified Hammersmith Score in motor function as discussed above. However, the most notable improvement was seen in children less than 5 years of age. 93% of children under 5 showed a significant improvement in Hammersmith score, while only 37% of children over the age of 5 showed a significant improvement.

While the open label nature of this study does not allow definitive conclusions to be drawn, the encouraging results suggested that a randomized placebo controlled study was warranted. Currently, Project Cure SMA is conducting a randomized placebo controlled study to test a combined regimen of Valproate and Carnitine. This is a multi-center study with testing sites in Utah lead by Dr. Swoboda, Ohio lead by Dr. Kissel, Wisconsin by Dr. Schroth, in Maryland by Dr. Crawford, Michigan by Dr. Acsadi, and Montreal by Dr. D'Anjou. This study consists of two distinct cohorts. The first is for children ages 2 to 8 years with non-ambulatory Type II SMA, who can site independently for 3 seconds. This portion of the study is randomized double blind and placebo controlled. The study duration is for 12 months. For the first 6 months children will be divided into placebo and drug treatment groups. For the second 6 months, all children will receive drug. Sixty children are needed in this cohort. The second cohort is for children ages 3 to 17 years with SMA Type III who can stand independently without braces or other support for 2 second. All patients in cohort 2 receive drug, and 30 children are needed for this cohort. The target date for the completion of the study is October of 2007.

Please see www.projectcuresma.org.

If you have a question, please email it to: **sma@fsma.org.**

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Families of Spinal Muscular Atrophy
P. O. Box 196
Libertyville, IL 60048-0196