Families of SMA is pleased to announce the award of up to $750,000 for an important new grant to Dr. Brian Kaspar at Nationwide Children’s Hospital. This award will support pre-clinical development of a CNS-delivered Gene Therapy for Spinal Muscular Atrophy. With funding from FSMA, Dr. Kaspar’s team will initiate the studies needed for an Investigational New Drug (IND) application for this therapy to the Food and Drug Administration (FDA).

“This is extremely important funding from FSMA to allow us to collect additional pre-clinical data for a CNS delivered AAV gene delivery into the cerebrospinal fluid, which will be important information to present to the FDA. It also jump starts research prior to obtaining government and commercial involvement which we are actively pursuing. We are quite hopeful for a positive funding decision on a recent NIH proposal for co-funding of this project with FSMA.”

Brian Kaspar, PhD, Associate Professor, Principal Investigator The Research Institute at Nationwide Children’s Hospital, The Ohio State University.

The overall project goals are:

1) to optimize the dosing regimen for CNS-delivered SMA gene therapy;
2) to conduct the GLP toxicology, immune response, and bio-distribution experiments required by the FDA;
3) to prepare and hold a pre-IND meeting with the FDA;
4) to submit an IND to the FDA to begin human clinical trials; and
5) to produce clinical grade material for human studies.

The overall timeline for this work is expected to be three years.

This Program was chosen for funding by the FSMA Translational Advisory Committee (TAC), after reviewing multiple potential new drug programs. Please see the following webpage for short biographies of the TAC members: http://www.fsma.org/AboutFSMA/Board/TranslationalAdvisoryCouncil/
Ever drug program carries risk of encountering hurdles at each of the stages described above. Therefore, a project-specific Steering Committee has been put in place, which is comprised of experts in both gene therapy and in SMA biology, with representatives from academia and industry. This committee will help manage the project, ensuring it progresses in an efficient and well-run manner. In addition, project funding will be awarded upon meeting pre-determined milestones, decided on by the Steering Committee.

Steering Committee members include:

Jerry R. Mendell, MD.  
Professor of Pediatrics and Neurology  
Director, Center for Gene Therapy  
The Research Institute at Nationwide Children’s Hospital

Katherine Klinger, PhD.  
Sr. Vice President, Genetics and Genomics  
Genzyme Corporation

James M. Wilson, MD. PhD.  
Professor of Pathology and Laboratory Medicine  
University of Pennsylvania

Richard S. Finkel, M.D.  
Professor, Division of Neurology  
The Children’s Hospital of Philadelphia

Susan T. Iannaccone, MD, FAAN  
Jimmy Elizabeth Westcott Distinguished Chair in Pediatric Neurology  
UT Southwestern Medical Center

Timothy P. Reilly, PhD, DABT  
Director, Drug Safety Evaluation Research & Development  
Bristol-Myers Squibb

Ex-officio member

Barbara C Engel, M.D., Ph.D.  
Vice Chair, Committees for the Protection of Human Subjects Chair, Institutional Review Board B  
The Children’s Hospital of Philadelphia,

“I am incredibly excited by FSMA’s decision to support Dr. Kaspar and his team in this very important project. As a pharmaceutical scientist who works every day in drug discovery and development, I am encouraged by the quality of the science and the fact that it aims to address SMA treatment from a different vantage point from other programs in the SMA drug pipeline. This is only the first step, but it’s a critically important step toward assessing whether gene therapy is a viable approach in SMA. Time will tell but I, for one, am incredibly hopeful and look forward to working with FSMA to facilitate the efforts of Dr. Kaspar and his team. I should add that as a parent of an SMA child, I am always looking for a medical breakthrough that could transform the lives of SMA patients.”

Timothy P. Reilly, PhD, DABT  
Director, Drug Safety Evaluation, Bristol-Myers Squibb. TAC Member.

A major goal at FSMA has been to build the SMA drug pipeline, and we have been investing in drug research since 2000 towards this goal. Even with our community’s current progress in adding programs to the SMA drug pipeline and advancing programs to start clinical trials, FSMA believes it is critical to do more. Statistics show that only 10% of all drugs initiating human clinical trials ultimately receive FDA approval. The new funding announced here by FSMA for this preclinical drug program will help achieve this goal. FSMA has been involved in funding half of all the ongoing novel drug programs for SMA. See figure 1 for the SMA drug pipeline.
Why Fund Direct CNS Delivery versus Systemic Delivery for Gene Therapy.

The previously published work described earlier using systemic gene therapy delivery, by injection into a vein, sets the stage to advance to human clinical trials. Systemic or intravenous gene delivery may have certain advantages for the youngest SMA patients, such as the ability to correct possible non-CNS manifestations. However, the systemic approach has limitations for bigger and older Type 1, 2, and 3 SMA patients. Direct CNS delivery may overcome many of these limitations. Advantages of CNS delivery may include:

1. Systemic gene delivery requires large amounts of virus, and production may be technically and economically challenging in order to treat bigger and older patients, possibly those over one year of age.
2. CNS gene delivery will only target certain limited organs, which may help reduce possible safety issues.
3. Direct CNS delivery may circumvent immune responses from previous exposure. Older patients are more likely to have been exposed to AAV infection resulting in neutralizing antibodies against AAV9, which would cause the therapy to be less effective if delivered systemically.

Several lines of evidence suggest that direct CNS delivery of AAV-SMN gene therapy will be effective in SMA.

- The Kaspar lab has shown that delivery of AAV9 to the cerebrospinal fluid (CSF) in pigs results in substantial motor neuron targeting using just a fraction of the virus utilized in systemic gene delivery studies. This work was partially published in Molecular Therapy in 2011.
- Recent work by Dr. Nick Boulis at Emory University published in Molecular Therapy has also shown that CSF delivered AAV9 targets motor neurons efficiently in large animals too.
- When AAV-SMN is delivered to the CSF, via intraventricular injections, the Kaspar lab has demonstrated that SMA mice survive significantly longer, greater than 100 days of age with a single administration of drug (unpublished data).
- Dr. Chris Lorson’s lab recently published that CNS delivery of SMA gene therapy using a method called ICV provides greater protection over systemic delivery in mice. While both types of delivery resulted in a subpopulation of mice surviving more than 200 days, the ICV injected mice gained more weight, displayed fewer early deaths, and resulted in higher levels of SMN induction in the central nervous system.

After assessing all of these considerations, the FSMA TAC and the FSMA Gene Therapy Steering Committee have elected to focus our funding on direct-CNS delivery of the AAV-SMN gene therapy.

AAV9-SMN gene therapy has been tested in mouse models of SMA. In mouse models of SMA, mice are born with normal motor neuron numbers. Within weeks after birth, motor neurons begin to be lost, with corresponding synaptic failure and denervation at the neuromuscular junction. This also results in muscle atrophy. These SMA mice die at about two weeks of age. Injection of AAV9-SMN into veins of 1 day-old SMA mice resulted in increased SMN protein levels in motor neurons, correction of synaptic function, and an extension of life span to >250 days. These results were published by the Kaspar lab at Nationwide Children’s Hospital in 2010 in Nature Biotechnology. The result has been replicated by multiple labs worldwide, including at Genzyme Corporation, the lab of Dr. Martine Barkats, and the lab of Dr. Mimoun Azzouz.

Treatment in mice at older ages was less effective. Earlier work by the Kaspar lab, funded by Families of SMA, has shown that AAV9 delivery to motor neurons is not age dependent in primates. However, studies have shown the effectiveness of SMN itself is age-dependent in severe mouse models. It remains to be determined whether this will translate to humans or not. The mouse data clearly suggests the earlier SMN is increased, whether by gene therapy, antisense oligos, or small molecule drugs, the larger the benefit will likely be.

Figure 2: Genetics of SMA.

SMA is caused by reduced levels of SMN protein

SMA is caused by mutation of the SMN1 gene and reduced expression of SMN protein. 95% of patients are missing the SMN1 gene. All patients retain one or more copies of the SMN2 gene. However, it is unable to fully compensate for loss of SMN1. SMN2 contains a small mutation in its DNA, which leads to the production of a shortened RNA called SMN*.7. This results in the production of mostly unstable protein product that is rapidly degraded. A small amount of RN2 RNA contains exon 7 and makes normal, full-length SMN protein. Some therapeutic strategies work by modulating or correcting SMN2 production. Gene Therapy works by directly replacing the SMN1 gene itself.
Gene therapy is an approach to treating diseases by either replacing faulty genes, modifying the expression of an individual's normal genes, or correcting abnormal genes. Gene therapy basically works by administration of DNA rather than a drug to a patient.

In the case of SMA, the most direct approach for a gene therapy is to replace the lost SMN1 gene in cells. See figure 2. In SMA, the SMN1 gene is missing in about 95% of patients, and the aim of gene therapy is to deliver the missing gene using a viral vector. This then allows SMN protein to be made in the cells where it is needed. In the case of SMA, these cells would include motor neurons and perhaps other currently undefined cell types.

In the past the challenge with gene therapy for SMA has been to find a way to deliver the genetic material to the central nervous system (CNS), where motor neurons are located. A number of viruses have been studied for their ability to safely and effectively carry the genetic material across the blood brain barrier and to “infect” motor neurons. In the past few years, a new virus called Adeno-Associated Virus 9 (AAV9) has been made that reaches motor neurons very effectively.

AAV is a small virus that infects primate species and is not known to cause disease. This makes AAV ideal to be used as a viral vector to carry DNA for gene therapy. See figure 3.

Figure 3: A new gene is injected into an adeno-virus vector, which is used to introduce the modified DNA into a human cell. If the treatment is successful, the new gene will make a functional protein. A gene that is inserted directly into a cell usually does not function. Instead, a carrier called a vector is genetically engineered to deliver the gene. Certain viruses are often used as vectors because they can deliver the new gene by infecting the cell. The viruses are modified so they can’t cause disease when used in people. Viruses, such as adeno-viruses, introduce their DNA into the nucleus of the cell, but the DNA is not integrated into a chromosome. The vector can be given systemically by IV or injected directly into a specific tissue in the body, where it is taken up by individual cells. The latter is the strategy being used in this approach.

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