

Executive Summary  
**Spinal Muscular Atrophy: What is the molecular basis of neuron loss?**  
The Banbury Conference Center  
Cold Spring Harbor Laboratory, Cold Spring Harbor, NY  
March 7-10, 2004

This conference was organized to provide a multidisciplinary forum for discussions on neuronal development and pathophysiology in spinal muscular atrophy (SMA), at the molecular, cellular and animal levels. Experts in motor neuron development, neuromuscular junction formation and in other neurodegenerative diseases were invited to share their research and ideas with leaders in SMA research. The goal of the participants was “to develop a clearer understanding of the site and nature of SMN conferred motor neuron injury and the subsequent implications for therapeutics development.” The list of attendees is attached.

The conference was organized by Alexander MacKenzie, MD, PhD, Children’s Hospital of Eastern Ontario, Kenneth Fischbeck, MD of the NINDS, and Adrian Krainer, PhD, Cold Spring Harbor Laboratory and was supported by a grant from the SMA Foundation. The Banbury Center is located on the Cold Spring Harbor Laboratory campus. It is an internationally recognized venue for small, closed meetings where emerging scientific developments can be shared and discussed in confidence. To foster open and frank discussion, no meeting publications or reports are allowed.

The limitations of the meeting are fairly clear: the closed format, the multidisciplinary approach and the constraints of the meeting space all conspired to restrict the number of participants that could be invited to attend. To that end, the meeting organizers have reviewed and approved the release of this Executive Summary for the benefit of the SMA community.

SMA Biology/Pathology

There is a growing body of evidence that the motor neuron loss in SMA is a cell autonomous process, unique to motor neurons, and possibly modulated by target muscle groups. Evidence for changes in axonal pathfinding and branching defects has been observed in at least one animal model of SMA. Cycles of denervation and reinnervation of the target tissue have also been reported. A pathologic process appears to precede motor neuron cell death. Full length SMN protein may play a direct role in these events and/or may influence other factors downstream of its known functions in RNA processing.

Questions to be asked of the research community include:

- What are the functions of SMN in the axon? How do they correlate with SMN functions in the nucleus? How do these functions result in the SMA phenotype?
- How do less than physiologic concentrations of SMN affect axonal pathfinding and synapse formation? Are these the anomalies that cause motor neuron loss?
- What role do trophic factors play in the disease process?
- Do muscle targets influence motor neuron responses in SMA? If so, how?

- What is the electrophysiology of SMN-deprived motor neurons at the cellular level?
- Can the timecourse of axonal degeneration and neuron cell death be described? How does it correlate with SMN concentrations?
- Can motor neuron defects be rescued or reversed by SMN? If so, how? What is the timecourse of treatment?

It was clearly recognized by all the disciplines in the room that an understanding of the answers to these questions is key to advancing new treatments for SMA. This information will support more effective assessment and optimization of the treatments currently under consideration and will guide the development of even more novel and effective interventions in the future.

#### Implications for Therapeutics Development

The need for standardized assays, outcome measures and clinical trial methodologies became a consistent theme of the meeting. Attendees emphasized their interest and desire to pursue research progress on multiple fronts, particularly since the drugs under investigation appear to have only a modest effect on SMN protein levels in the assays studied thus far. At the same time, the group supported the need for standardization because of the efficiency and cost-effectiveness it will bring to the research effort.

The NINDS pilot project in SMA therapeutics development is well-positioned to act as a resource for centralizing and standardizing methodologies. The contracting process is designed to identify and support key functions in preclinical therapeutics development as a service to the community. These functions include the development of motor neuron cell cultures for in vitro screening, SMN RNA and protein level assays, medicinal chemistry evaluations, toxicity screens and other studies required by the Food and Drug Administration (FDA). In addition, NINDS will host a meeting on clinical trial design and implementation in September 2004 that will assist SMA investigators in addressing standardization issues in the clinical phases of drug development.

Key questions that emerged from discussion included:

- Can we generate a better profile of HDAC inhibitor activity in SMA? How can we optimize the HDAC inhibitors for efficacy, safety and tolerability?
- Do we need more high through-put screens? If so, how can we conduct them more efficiently and effectively? How do we avoid duplication of effort?
- Will new in vitro models for SMA suggest other treatment approaches? New treatment combinations? How do trophic factors influence HDAC treatment?
- What is the treatment window for different therapy options in SMA?
- Should gene therapy be pursued more aggressively?
- How do currently used outcome measures correlate with our understanding of the disease process? Are they appropriate measures now? What needs to be done to improve or standardize these measures?
- What new outcome measures can be developed for clinical trials? Is neuroimaging an option?
- Does the community have adequate intellectual property resources?

- How can the community balance the need for urgency with the need for order and process in therapeutics development?
- How do we do a better job of incorporating parent and family input in the therapeutics development process? Can we adopt existing mechanisms or do we need new ones?
- How can the community work together to manage our finite money, investigator and patient resources?

There was a strong plea that the rapid and careful assessment of these questions be completed in parallel with drug discovery efforts so that no time or effort is lost in the transition from preclinical to clinical phases of drug development. Both efforts are of equal importance to the community and the hope is that continuing discussion will help ensure that this goal is met.

The SMA community can expect new research projects and research collaborations to emerge from the Banbury meeting. The attendees agreed that multidisciplinary discussions during the meeting were particularly valuable in thinking about their own research. The organizers were urged to follow a similar path in future events.

#### 2004 Banbury Conference Attendees

Gary Bassell, PhD	Albert Einstein College
Christine Beattie, PhD	The Ohio State University
Arthur Burghes, PhD	The Ohio State University
Gregory Cox, PhD	The Jackson Laboratory
Thomas Crawford, MD	The Johns Hopkins Hospital
Tony Dajer, MD	New York University Downtown Hospital
Darryl DeVivo, MD	Columbia University
Christine DiDonato, PhD	Northwestern University
Gideon Dreyfuss, PhD	University of Pennsylvania
Loren Eng	Spinal Muscular Atrophy Foundation
Gerald Fischbach, MD	Columbia University
Kenneth Fischbeck, MD	NINDS, NIH
Utz Fischer, PhD	University of Wuerzburg
Mark Gurney, PhD	deCODE Genetics, Inc.
Jill Heemsker, PhD	NINDS, NIH
Erika Holzbaur, PhD	University of Pennsylvania
Thomas Jessell, PhD	Columbia University
Cynthia Joyce	Spinal Muscular Atrophy Foundation
Douglas Kerr, MD, PhD	The Johns Hopkins Hospital
Haig Keshishian, PhD	Yale University
Adrian Krainer, PhD	Cold Spring Harbor Laboratory
Story Landis, PhD	NINDS, NIH
Alexander MacKenzie, MD, PhD	Children's Hospital of Eastern Ontario
Judith Melki, MD, PhD	INSERM
Umrao Monani, PhD	Columbia University

Luis Parada, PhD  
Samuel Pfaff, PhD  
Michael Sendtner, PhD  
Anneliese Schaefer, PhD  
Dinakar Singh  
Charlotte Sumner, MD  
Brent Stockwell, PhD  
Kathryn Swoboda, MD  
Brunhilde Wirth, PhD  
Kai Zinn, PhD

University of Texas Southwestern Medical Center  
Salk Institute for Biological Studies  
University of Wuerzburg  
Washington University  
Spinal Muscular Atrophy Foundation  
NINDS, NIH  
Whitehead Institute for Biomedical Research  
The University of Utah  
Institute for Human Genetics  
California Institute of Technology