THE BACHMANN-STRAUSS
Dystonia & Parkinson Foundation, Inc.

2011 THINK TANK FOCUS

Connecting the Dots: How Can We Relate Circuit- and Systems-Level Mechanisms of Dystonia to the Genes and Proteins Which Trigger It?

The tenth annual Think Tank on dystonia and Parkinson's disease brought together an international group of neurologists, geneticists, and pharmacologists to share their knowledge and clinical expertise during an intensive day in New York. The December 2011 event focused on relating the circuits-and systems–level mechanisms in the brain to the genes and proteins that trigger dystonia.

Dystonia is a neurological muscle disorder that causes uncontrollable, painful spasms in one or more parts of the body. It affects an estimated 500,000 people in North America alone--more than Muscular Dystrophy, Huntington's Disease and Lou Gehrig's disease combined. Historically, dystonia has always been considered a disorder of the basal ganglia. But recent evidence has pointed towards cerebellar circuits as well. Many researchers now believe that dystonia is caused by a disruption of a motor network that involves both the basal ganglia and cerebellum, rather than an isolated dysfunction of only one motor system. But, how the motor network relates to the genes and proteins that are thought to be involved in the development of dystonia is a fertile area of research and debate.

The Bachmann-Strauss Foundation focuses on research projects that can help "connect the dots" in dystonia. Researchers and clinicians from varied disciplines are invited to participate in the Think Tank to share their research, discuss gaps in knowledge and share their ideas on where future research should be directed.

Co-chairs Henry Paulson, MD, PhD & David Standaert, MD, PhD

In his welcoming remarks, co-chairman Henry Paulson, MD, PhD, told the Think Tank participants that they were invited to compare notes, to discuss and learn. "There is a lot of excitement in the field of dystonia and many new voices, including those in attendance. Our goal is to integrate our knowledge about what is special about the mechanisms that underlie dystonia at the genetic, molecular, system and human levels."

In his welcoming remarks, co-chairman David Standaert, MD, PhD, said "although we might not connect all the dots today, our goal is to come into agreement as to what they are and begin to connect some of them."

The morning and afternoon sessions featured presentations on the circuits and systems in the brain that are thought to be involved in dystonia. The morning speakers focused on research involving circuits and systems and the basal ganglia. The afternoon session speakers focused on the newer research on the cerebellum.

Tom Wichmann, MD, set the tone for the day saying "We know a lot about the genetics of dystonia. We know a lot about the proteins involved. We are beginning to understand the circuits and systems involved. What we don't know is how to relate the two." Dr. Wichmann said that although the majority of his research has been in Parkinson's disease, the overall goal of his work is to gain a better understanding of the cascade of chemical and electrophysiologic changes that occur as

consequence of loss of striatal dopamine in parkinsonism that can then be translated into new and more effective therapies for both Parkinson's disease and dystonia.

Tom Wichmann, MD

One of the unique aspects of the Think Tank is that young researchers are given a chance to present their work to established researchers and clinicians. In her short career, researcher Aryn Gittis, PhD, has helped to elucidate how fast-spiking interneurons (FSIs) can exert powerful control over striatal output. "Deficits in this cell population have been observed in human patients with Tourette syndrome and in rodent models of dystonia." Her results not only provide direct evidence that when striatal FSIs functions improperly they can produce movement abnormalities. This suggests that FSIs are a novel therapeutic target for the treatment of hyperkinetic movement disorders.

The participants were in agreement that dystonia is difficult to treat because it manifests so differently than Parkinson's disease, whose symptoms are well known, gradually get worse and are apparent to clinicians, family members and

Aryn Gittis, PhD

friends. There are also decades of research on diagnosing Parkinson's disease as well as treating its symptoms.

Dystonia comes in many forms, is less known by the public and affects different areas of the body and different age groups. For example focal dystonias, like writer's cramp, affect just one part of the body, while generalized dystonias cause involuntary twisting movements and abnormal posture throughout the body. Symptom relief range from oral medications that have traditionally been used in Parkinson's disease as well as the injection of botulinum toxin into affected muscles, surgery and deep brain stimulation (DBS), which consist of implanting fine wires into the basal ganglia and delivering an electrical current to quiet the abnormal signals.

In his presentation, John Rothwell, PhD said that the control of plasticity may be abnormal in people with dystonia and the reduced inhibition could account for the excess muscle activity. He believes plasticity may help to explain why it takes weeks for DBS to work in patients with dystonia. "The memories of abnormal movement in the cells persist and take time to normalize. This suggests that plasticity may be a driver of long-term therapeutic effects of deep brain stimulation in dystonia."

Kamran Khodakhah, PhD, said "I cannot imagine future discussions of dystonia not involving discussions of the cerebellum in the pathophysiology of dystonia." He discussed the paper he published in

Kamran Khodakhah, PhD

The Bachmann-Strauss Foundation's Scientific Advisory Board discuss related topics at the annual Think Tank.

Nature Neuroscience on how dysfunctional interactions between the cerebellum and the basal ganglia are a key factor in the underlying pathophysiology of rapid-onset dystonia–parkinsonism.

His lab developed a mouse model for a rare disorder called rapid-onset dystonia-parkinsonism (RDP). Using these mice, the researchers were able to separately test the role of the basal ganglia and the cerebellum in RDP. They found that the mice developed dystonia only if the cerebellum was dysfunctional, clearly implicating the cerebellum. "The results are going to motivate the research community to look at the cerebellum as a factor in other dystonias." His research also suggested that deep brain stimulation of the cerebellum could hold promise for treating dystonia.

Ted Dawson, MD, PhD, Chair of The Bachmann-Strauss Foundation's Scientific Advisory Board is excited on how quickly the cerebellum theory has caught on with researchers. He said, "understanding the communication pathways between structures like the basal ganglia and cerebellum is enormously important. Moreover targeting the cerebellum in future therapies has particular promise for treating patients and making them better."

After the presentations, Dr. Paulson asked the attendees to use the remaining time to discuss what they had learned today and what future research is needed. Although there was some disagreement over the speed that the cerebellum theory is being advanced, there was wide agreement that there was a need for a non-human primate model of dystonia. Use of a primate model could be instrumental in increasing the understanding of neuronal connections that play important roles in the dystonia – ultimately leading to better molecular targets and pharmacological treatments for dystonia.

Ted Dawson, MD, PhD

2011 THINK TANK PARTICIPANTS

CO-CHAIRS

Henry Paulson, MD, PhD
Lucile Groff Professor, Department of Neurology, University of Michigan Ann Arbor, MI

David Standaert, MD, PhD
Professor and Chair of Neurology
John N. Whitaker Endowed Chair
Director, Center of Neurodegeneration and Experimental Therapeutics
University of Alabama at Birmingham, Birmingham, AL

Charles H. Adler, MD, PhD
Professor of Neurology,
Mayo Clinic College of Medicine
Scottsdale, AZ

Joshua Berke, PhD
Associate Professor,
Department of Psychology and Neuroscience Program,
University of Michigan,
Ann Arbor, MI

David R. Borchelt, PhD
Professor, Department of Neuroscience/CTRND
Director, SanteFe HealthCare Alzheimer's Disease Research Center, University of Florida, Gainesville, FL

Xandra Breakefield, PhD
Geneticist, Neurology and Radiology, Massachusetts General Hospital, Charlestown, MA;
Professor of Neurology, Harvard Medical School, Boston, MA

Susan Bressman, MD
Chair, Mirken Department of Neurology, Beth Israel Medical Center, Professor of Neurology, Albert Einstein College of Medicine, New York, NY

Mitchell Brin, MD
Senior VP Global Development, Chief Scientific Officer, BOTOX®, Allergan, Irvine, CA
Professor of Neurology, University, California, Irvine, CA

Sandra F. Cahn
Executive Director,
The Bachmann-Strauss Dystonia & Parkinson Foundation,
New York, NY

Nicole Calakos, MD, PhD
Assistant Professor, Neurology and Neurobiology, Center for Translational Neuroscience, Duke University Medical Center,
Durham, NC

William Dauer, MD
Elinor Levine Professor of Neurology, Associate Professor of Cell and Developmental Biology, University of Michigan Medical School, Ann Arbor, MI

Ted M. Dawson, MD, PhD
Leonard and Madlyn Abramson Professor in Neurodegenerative Diseases, Scientific Director, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD

Mahlon DeLong, MD,
Professor of Neurology, Emory University School of Medicine, Atlanta, GA

Audrey Dufour, PhD
Associate Director Research Programs, The Michael J. Fox Foundation for Parkinson's Research, New York, NY

Michelle E. Ehrlich, MD
Professor, Departments of Pediatrics and Neurology, Mount Sinai School of Medicine,
New York, NY

David Eidelberg, MD
Susan and Leonard Feinstein Professor of Neurology, New York University School of Medicine;
Director, Center for Neuroscience, Feinstein Institute for Medical Research, North Shore - LIJ Health System, Manhasset, NY

Aryn Gittis, PhD
Postdoctoral Fellow, Gladstone Institute of Neurological Disease
San Francisco, CA

Ann M. Graybriel, PhD
Institute Professor, Massachusetts Institute of Technology
Investigator, McGovern Institute for Brain Research, Cambridge, MA

Phyllis Hanson, MD, PhD
Professor, Department of Cell Biology & Physiology Washington University School of Medicine, Saint Louis, MO

Ellen Hess, PhD
Professor, Departments of Pharmacology and Neurology
Emory University School of Medicine, Atlanta, GA

Naoto Ito, PhD
Research Associate, Instructor in Neurology, Harvard Medical School
Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA

Karen Jaunarajs
Post-Doctoral Fellow, University of Alabama at Birmingham
Birmingham, AL

Kamran Khodakhah, PhD
Professor, Albert Einstein College of Medicine, Dominick P. Purpura Department of Neuroscience
Bronx, NY

Christine Klein, MD
Schilling Professor of Neurogenetics, Head of the Section of Clinical and Molecular Neurogenetics at the Department of Neurology, University of Luebeck, Luebeck, Germany

Tom Loeb
Member, Board of Directors, The Bachmann-Strauss Dystonia & Parkinson Foundation
New York, NY

Tom Otis, PhD
Professor and Vice-Chair of Neurobiology, Gefffen School of Medicine at UCLA, Los Angeles, CA

John Rothwell, PhD
Professor of Human Neurophysiology, Institute of Neurology, University College London, United Kingdom

Giuseppe Sciamanna
Lab Neurophysiology and Plasticity, Santa Lucia Foundation
Rome, Italy

Vikram Shakkottai, MD, PhD
Assistant Professor, Department of Neurology, University of Michigan, Ann Arbor, MI

Bonnie Strauss
Founder and President
The Bachmann-Strauss Dystonia & Parkinson Foundation,
New York, NY

Tom Strauss
Treasurer and Vice President, The Bachmann-Strauss Dystonia & Parkinson Foundation,
New York, NY

Peter L. Strick, PhD
VA Senior Research Center Career Scientist, Director Neurosciences Institute, Co-Director, Center for the Neural Basis of Cognition
Distinguished Professor of Neurobiology, University of Pittsburgh, Pittsburgh, PA

James Surmeir, PhD
Nathan Smith Davis Professor of Physiology and Chair, Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, IL

Jan-Willem Taanman, PhD
Reader in Clinical Neurosciences
University Department in Clinical Sciences Institute of Neurology, University College, London, United Kingdom

Jan Teller, MA, PhD
Science Officer, Dystonia Medical Research Foundation
Chicago, IL

Aziz M. Ulug, PhD
Director, MRI Core, Associate Investigator, Center for Neuroscience, Feinstein Institute for Medical Research,
North Shore – LIJ Health System, Manhasset, NY

Thomas Wichmann, MD
Professor, Department of Neurology , Emory University, Atlanta, GA

THE BACHMANN-STRAUSS
Dystonia & Parkinson Foundation, Inc.
551 Fifth Avenue, Suite 520, New York, NY 10176
Phone: 212.682.9900 Fax: 212.682.6156
www.dystonia-parkinson.org

Follow us on:

The Bachmann-Strauss Dystonia & Parkinson Foundation was established in 1995 to find better treatments and cures for the movement disorders dystonia and Parkinson's disease, and to provide medical and patient information. An independent, nonprofit, 501(c)3 organization, its funding is made possible through the generosity of individual and corporate contributors.