**Pushing the Boundaries**

**DMRF Accelerates Research Progress**

2015 marks the 40th anniversary of the first International Dystonia Symposium, the groundbreaking medical and scientific meeting that preceded the formal establishment of the DMRF in 1976. A number of newly published discoveries demonstrate how far our understanding of dystonia has expanded since that time. This issue of Promise & Progress shares the results of some of these studies. From the very beginning, the DMRF strategically and methodically pushed the boundaries of what was known about dystonia. Nearly 40 years of supporting research has shown us this is a proven formula for making and accelerating progress.

**BiP is First Identified TorsinA Chaperone Protein**

Since 1997, scientists have known that a mutated protein called TorsinA causes one of the most severe childhood onset torsion dystonias, but the function of the protein remains unknown. Jeffrey Brodsky, PhD and Michal Zolkiewski, PhD co-led a DMRF-supported study that used a sophisticated yeast cell model to investigate several proteins that interact with normal TorsinA and its dystonia-causing mutant. The cell proteins belong to a family of chaperones, which are molecules that help other proteins take shape and function properly or, in case of faulty proteins, disassemble and deactivate them. BiP stabilizes normal and mutated TorsinA structures when they are exposed to stress. When TorsinA is mutated, it becomes a target for chaperones—and especially for BiP which also appears to have an essential role in degrading mutant TorsinA when it ceases to function properly. It is the first identified chaperone to act on TorsinA. The function of BiP is well-understood, and development of potential treatments based on its interaction with TorsinA may now be possible.

The next step is to identify other cellular helpers that impact TorsinA. This work is being conducted by DMRF Research Fellow Lucia Zacchi, PhD at Fundacion Instituto Leloir in Argentina, formerly a post-doctoral researcher in the Brodsky lab.

**Possible Genetic Risk Factor for Dystonia Discovered**

A team of researchers led by DMRF grant recipient and past DMRF Medical & Scientific Advisory Council (MSAC) member Mark LeDoux, MD, PhD has identified a variant of the THAP gene as a possible risk factor for adult-onset primary dystonia. Volunteers participating in this study represented cervical dystonia, spasmodic dysphonia/laryngeal dystonia, oromandibular dystonia, blepharospasm, and other adult onset dystonias. THAP1, also referred to as DYT6, is a gene associated with torsion dystonia of mixed age type and variable age of onset. Further investigations may clarify the role of this new THAP variant in dystonia.

Among others, Dr. LeDoux collaborated with current MSAC member Joel Perlmutter, MD and Zbigniew Wszolek, MD (a former grantee, in a joint project with Dr. LeDoux), and MSAC member and Director of the Dystonia Coalition H.A. Jinnah, MD, PhD.

New research funding announcements will be made in the coming weeks at www.dystonia-foundation.org
New Insights into Interaction between Cerebellum and Basal Ganglia Critical to Dystonia

Dystonia has long been linked to abnormalities in the basal ganglia, clusters of neurons deep in the brain known to be involved in normal voluntary movement. Recent studies show that origins of dystonia in the brain appear to reside in the complex interactions of the basal ganglia and cerebellum in conjunction with the cortex—not in a single structure in the brain but brain pathways.

A team of investigators led by Kamran Kho-dakah, PhD, a member of the DMRF’s Medical & Scientific Advisory Council (MSAC), published a paper of fundamental importance to dystonia in the prestigious journal Nature Neuroscience. The study describes how the cerebellum affects function of the basal ganglia. This may have direct implications for advances in deep brain stimulation and other clinical applications.

The human body’s ability to move smoothly and purposefully is an incredibly complicated task. Much of the information needed for complex movements is generated by the cerebellum and basal ganglia in conjunction with the cortex. However, there has been little functional evidence to explain how the cerebellum and the basal ganglia can directly exchange information with the timing necessary to support normal, fluid motion. Investigators have found there is a pathway from the cerebellum to the basal ganglia. This pathway allows for rapid communication between the cerebellum and the basal ganglia and permits cerebellar regulation of corticostriatal plasticity. (Plasticity is the ability of the brain to adapt and learn.) Under dysfunctional conditions, the pathway enables the transfer of abnormal cerebellar activity to the basal ganglia, causing movement disorders such as dyskinesia and dystonia.

In separate studies, investigators have described a reverse pathway from the basal ganglia to the cerebellum. This provides the opportunity to explore whether rapid transfer of information by this route in both directions serves as a fundamental means of movement control. If dystonia is caused by subtle disturbances in these pathways, the entire network is a target for therapeutic intervention.

Chipping Away at the Mystery of TorsinA

When DMRF-funded investigators discovered the DYT1 gene responsible for childhood onset torsion dystonia in 1997 it began one of the biggest mysteries in the field. The DYT1 gene encodes the protein TorsinA, which had never been seen before. It was an unusual protein and no one knew the function it served. Since that time, researchers have begun putting the pieces together. Although questions remain as to its exact function, several recent discoveries have shed important light on this important protein:

Researchers Reveal Details of TorsinA Structure and Function:
A study led by DMRF grant recipient Thomas Schwartz, PhD is providing insights into the function of TorsinA by using specialized techniques to analyze its structure and relationships with other proteins. TorsinA belongs to a family of ATPase proteins, which help cells generate the energy needed to accomplish all of the many processes and activities within the cell. Previous studies have shown that TorsinA has a relationship with two proteins, LAP1 and LULL1, but the nature of their interactions required clarification. Researchers at Massachusetts Institute of Technology have revealed that LAP1 and LULL1 activate TorsinA. The data show that a mutation in LAP1 reduces its ability to interact with TorsinA. This work will help uncover how TorsinA causes dystonia.

A separate team of investigators led by Christian Schlieker, PhD (whose work has also clarified the relationship between TorsinA, LAP1, and LULL1) corroborates and extends Schwartz’s work by clarifying the role of TorsinA in generating the energy cells need to function. Torsin proteins do not fulfill this function unless they encounter their binding partners LAP1 or LULL1. Researchers revealed surprising structural details about LAP1 and LULL1 that clarify interactions with TorsinA. This suggests that LAP1 and LULL1 are integral parts of Torsin machinery, creating important ramifications for how Torsins function. Further exploration may ultimately lead to targeting TorsinA activation as a novel therapeutic approach.

TorsinA Variants Play a Role in Dystonia Development:
An international team of researchers has revealed that variants of the human protein TorsinA may be implicated in the development of dystonia. Childhood onset torsion dystonia occurs when a mutation in the DYT1 gene makes TorsinA shorter by one amino acid. As a result, the mutated TorsinA functions abnormally. While the causative role of this particular mutation has been well established, human variants of TorsinA have been discovered and it was initially unclear whether these variants contribute to disease.

DMRF-funded researchers led by Flávia Nery, PhD revealed that these new variants are strikingly similar in their properties to the previously known TorsinA mutant. These findings provide functional evidence that these rare mutations in the DYT1 gene may directly contribute to the development of dystonia. The approach developed in this study provides new methods to assess the role of rare TorsinA variants and may lead to validation of novel therapies.
RESEARCH INSIGHTS
from Dystonia Coalition
Co-Director Joel Perlmutter

The Dystonia Coalition is a collaboration of medical researchers and patient advocacy groups funded through the National Institutes of Health to accelerate clinical research on dystonia. Movement disorder expert Dr. Joel Perlmutter is the Dystonia Coalition Co-Director and shares his thoughts on developments in dystonia.

PP: What recent advancements have impressed you the most in dystonia research?

JP: There are several areas of exciting new research in dystonia. Major advances in understanding the role of TorsinA, the abnormal protein made by the defective gene in DYT1 dystonia may yield insights important for many forms of dystonia. Another area of research is the new findings about changes in specific brain networks that may underlie the manifestations of dystonia. These two types of findings are quite complementary. The more specific findings may open the avenue for new targeted treatment for DYT1 dystonia and may down the road help other forms. The network abnormalities may be more likely to identify targets for therapy that could be important for multiple different forms of dystonia.

PP: What impact have you seen the DMRF have in research?

JP: DMRF has driven dystonia research in several ways. First, new areas of investigation including the original genetic advances have been initiated and then supported by DMRF. DMRF has provided funding for fellowships and junior investigators permitting us to capture new research scientists to focus on dystonia. This is the type of support that continues to give for many years. Finally, research support by the DMRF for the Dystonia Coalition has made possible the first of its kind large, multicenter studies of dystonia.

This has catalyzed research, inspired young investigators, and generated greater education of clinicians and the dystonia community.

PP: How did you get interested in dystonia and what has kept you in the field?

JP: I was fascinated by a patient that I saw as a resident with post traumatic paroxysmal hemidystonia—and I subsequently wrote a neuroimaging paper about this patient. That really started the ball rolling. I went on to do a large number of neuroimaging studies to identify brain changes that underlie this mysterious disease. I was particularly fascinated since in the early 1980s many docs thought dystonia was a psychiatric disorder and this did not seem right to me. I wanted to prove it, learn more, and find new ways to treat it. Support by the DMRF permitted me to attend the 2nd International Dystonia Symposium and by then I was clearly hooked.

Joel Perlmutter, MD is Head of the Movement Disorders Section, Elliot Stein Family Professor of Neurology at Washington University in St. Louis. He is Leader of the Dystonia Coalition Natural History and Biorepository Studies. Dr. Perlmutter is a member of the DMRF Medical & Scientific Advisory Council and is among the expert clinicians who have mentored up-and-coming movement disorder specialists through the DMRF Clinical Fellowship Training Program.

Novel DYT1 Dystonia Animal Model Mimics Human Disorder

A team of researchers at the University of Michigan led by William Dauer, MD published a comprehensive study linking abnormal TorsinA to loss of cells in specific brain structures responsible for movement and overt dystonia symptoms in mice. Dauer focused on developmental aspects of DYT1 childhood onset dystonia, which typically starts between the ages of 8 and 11 years. However, even if a child has the DYT1 gene mutation, if he/she reaches adulthood without symptoms the likelihood of ever developing dystonia is reduced to nearly nothing. This suggests that specific changes in the early stage of brain development make the nervous system vulnerable to the effects of the genetic mutation.

Dauer and team have developed a genetic mouse model of DYT1 dystonia that mimics the human disorder. These genetically engineered mice demonstrate overt movement symptoms of dystonia, marked by patterned twisting and fixed postures in the limbs. The mouse model reveals a period of subtle neurodegeneration in specific brain structures involved in movement control that lasts only for the period of time that coincides with the onset of dystonia symptoms. The study makes a critical, experimentally testable connection between impaired TorsinA function, neural circuits, and dystonia symptoms—a tour de force of experimental neuroscience that opens up countless opportunities for future studies. The mouse model will be available to other researchers to help accelerate understanding of all forms of dystonia and the search for treatments. In 2006, Dauer was the very first recipient of the DMRF’s Stanley Fahn Award. Co-author Lauren Tanabe, PhD, was awarded a two-year DMRF research fellowship in 2011.
UPDATE: Drug Discovery & Development

Several collaborative projects represent the DMRF’s commitment to discovering and developing new dystonia drugs.

The DMRF and Cure Dystonia Now are co-supporting a research investigation that may lead to a new dystonia drug.

A team of American and European investigators is exploring whether a novel nicotinic agonist called AZD1446 could potentially provide relief for dystonia patients without the unintended effects frequently caused by existing pharmacological therapies. The investigation is led by David Standaert, MD, PhD and includes Antonio Pisani, MD, PhD. The investigators responded to a request for applications following the DMRF workshop, Receptor Neuropharmacology in Dystonia.

Addex Therapeutics and the DMRF have announced a collaborative effort to explore the use of dipraglurant to treat dystonia.

Dipraglurant is one of Addex’s lead products, a novel small molecule that inhibits the metabotropic glutamate receptor 5 and has shown promise in the treatment of levodopa-induced dyskinesia and dystonia in Parkinson’s disease. The drug normalizes the effects of the DYT1 dystonia mutation in the brains of mice. DMRF and Addex are teaming up to identify opportunities to further develop this drug.

Through a multi-year collaboration with BioFocus, the DMRF has identified a number of potential dystonia drug targets. These leads continue to be explored by partnering with expert investigators and the DMRF will report on further developments later this year.

UPDATE: Myoclonus Dystonia Research Program

Myoclonus dystonia (M-D) is a movement disorder characterized by a combination of myoclonus (rapid, brief muscle contractions) and/or dystonia (sustained twisting and repetitive movements that result in abnormal postures). A significant percentage of cases of M-D are caused by mutations in the SGCE gene, and researchers are attempting to identify other disease causing genes in affected families without mutations in SGCE. Two collaborative studies funded by the DMRF Myoclonus Dystonia Research Program supported by the Brown Family Foundation are focusing on genetics:

“A New Gene and A Novel Pathway Leading to Myoclonus Dystonia”

Dennis Bulman, PhD, Children’s Hospital of Eastern Ontario Research Institution

“Whole Exome Sequencing in Families with Myoclonus-Dystonia Syndrome without SGCE Mutations from Turkey and Germany”

Thomas Gasser, MD, University of Tübingen, Germany

For more information on the DMRF’s research activities, visit www.dystonia-foundation.org/research