Leading the Global Effort to Find a Cure

The Dystonia Medical Research Foundation (DMRF) is a leader in dystonia research, collaborating with partners around the world toward improved therapeutics and a cure. The DMRF seeks to support not just individual projects, but to stimulate the entire field. For 37 years the DMRF has expanded science's understanding of this disorder by inviting the most knowledgeable and talented researchers to the table regardless of geography. These decades of effort have provided a solid foundation for advancements that were previously impossible—for example the expanding possibilities emerging with drug discovery. The DMRF leaves no stone unturned, in any corner of the world, that may accelerate our efforts to provide relief for individuals and families living with dystonia. This issue of Promise & Progress offers an update on recent activities and highlights some of our collaborations.

The Reward of Good Research is More Research

Antonio Pisani, MD of University of Rome Tor Vergata, Italy was awarded his first DMRF grant in 2005 and has since become thoroughly engaged in the field. As a clinician and researcher, he has been exploring how to enhance and improve drug treatment benefits for dystonia patients by understanding how specific brain circuits and receptors interact with each other.

Most recently, Dr. Pisani earned the DMRF's prestigious Stanley Fahn Award for an ongoing investigation entitled “D2 Dopamine Receptor Signaling Alteration in a Mouse Model of DYT1 Dystonia: A Novel Rescue Approach,” which explores a possible strategy to alleviate or eliminate the effects of the DYT1 gene mutation in mice. “Primary forms of dystonia lack clear evidence for neurodegeneration,” Dr. Pisani explains. “This has led to the assumption that dystonia may be a circuit disorder. Such evidence represents the basis for my profound interest in dystonia research, both as a neurologist and as neurophysiologist involved in basic science research. By means of electrophysiological techniques, we managed to characterize the circuit alterations in rodent models of DYT1 dystonia.”

Dr. Pisani has organized a series of biennial international dystonia meetings that the DMRF has been pleased to co-sponsor: “Update on Dystonia: From Basic Science to Therapeutic Strategies” in 2007, “Neuronal Plasticity in Dystonia” in 2009, “Dystonia and Parkinson's Disease: The Dopamine Connection” in 2011, and the upcoming “Circuits and Pathways in Dystonia and Parkinsonism” later this year. Dr. Pisani was also a Session Chair at the 5th International Dystonia Symposium in 2011 in Barcelona, Spain and serves on the DMRF’s Medical & Scientific Advisory Council.

“Our accomplishments would have never been possible without the generous support of DMRF,” says Dr. Pisani. “Since 2005, DMRF funded my research projects and this made possible our deep involvement and commitment in this field of research. Moreover, DMRF has contributed substantially to the biennial workshop on dystonia I have been organizing in Rome. The fourth meeting will be held in 2013, and DMRF will again be there to help and encourage my initiative.”
Forging Ahead: Research Contracts

The DMRF does not only fund research proposals submitted by investigators. Through research contracts, the DMRF enlists partners to work on a specific project or address a knowledge gap in the field. This would not be possible without the DMRF’s years of investment in basic science.

Likewise, one of the most important outcomes from the last decade of dystonia research is that the data has advanced to the point where drug discovery efforts are now possible, as indicated by the DMRF’s drug target discovery contract project with a Dutch company called BioFocus, DPI. The DMRF is pleased to partner with Tyler’s Hope for a Dystonia Cure in supporting this project.

The major objective of this partnership, which began in 2010, is to identify genes and proteins that modify the effects of the DYT1 dystonia mutation on torsinA, the protein coded by the DYT1 gene. Several hundred hits have been identified from a library of more than 4,500 candidates. These hits represent proteins and genes that potentially can rescue cells from lost torsinA function, which is believed to be the primary cause of DYT1 dystonia. The next step of the project is to identify a small number of the most promising targets to be used in drug discovery efforts.

The identified targets are also important clues in understanding the DYT1 dystonia mechanism. Many are potentially druggable, meaning that they are capable of being altered or manipulated by small molecules. For some there are already drug candidates available for testing in appropriate cell models or other systems to monitor torsinA-related effects.

The DMRF is also using research contracts to create resources for dystonia researchers. In a project entitled, “Patient-specific Induced Pluripotent Stem Cells as a Model for DYT1 Dystonia,” Nutan Sharma, MD, PhD and Christopher Bragg, PhD of Massachusetts General Hospital/Harvard University are establishing a collection of cell models that will serve as a public resource for dystonia investigators pursuing the development of potential therapies. These models will enable dystonia researchers to study changes in neurons caused by the DYT1 mutation in cells obtained from patients.

Steps toward Drug Target Discovery for Dystonia: BioFocus

**Step 1: Identify Goal**
To interrupt or prevent the negative effects of DYT1 dystonia gene mutation. **Completed.**

**Step 2: Assay Development**
Create a tool to measure interaction between a library of molecules and cells impacted by the DYT1 mutation. **Completed.**

**Step 3: Screen**
Identify genes and proteins that show interaction in the assay. **Completed.**

**Step 4: Rescreen & Validate**
Select most promising targets and confirm results. **Ongoing.**

Innovative Techniques Reveal New Connections

Pedro Gonzalez-Alegre, MD of the University of Iowa is a pioneer in the use of RNA interference techniques to turn off mutated genes that cause dystonia, first in cells and now in animal models. Dr. Gonzalez-Alegre was awarded the DMRF Stanley Fahn Award to support his latest investigation entitled “Regulatory RNA Networks in Inherited Dystonia.”

This project is advancing our understanding of the dystonia mechanism by closely examining neurons for the consequences of mutations in the DYT1 and DYT6 genes. TorsinA, the protein associated with the DYT1 gene for childhood onset dystonia, is believed to have a role in monitoring other proteins in cells. THAP1, the protein associated with the DYT6 gene for childhood and adult onset primary dystonias, is believed to influence how torsinA functions. One of the aims of Dr. Gonzalez-Alegre’s work is therefore to characterize the precise disruptions in neurons linked to both mutated torsinA and THAP1. This study represents a meaningful milestone in that researchers are beginning to uncover exciting connections among some of the genes and proteins associated with different forms of dystonia.
Recent Highlights in Research

Below are just some of the advancements that dystonia investigators are making around the world.

- Primary dystonia (a.k.a. primary torsion dystonia) represents a broad category of patients whose dystonia is the only present neurological disorder. This includes childhood as well as adult onset dystonia. Symptoms may be focal, multifocal, segmental, or generalized. The DYT1 gene was the first gene identified for primary dystonia, and additional genes have since been discovered: THAP1, CIZ1, GNAL, ANO3, and TUBB4A.

- Mutations in the PRRT2 gene cause paroxysmal kinesigenic dyskinesias and other paroxysmal disorders. Each gene discovery provides a protein that is a potential therapeutic target; every therapeutic target is one step closer to a brand new approach to treatment.

- Researchers are also discovering different dystonia mutations within a single gene. The DMRF helped fund an investigation that recently identified a previously unknown mutation in the GNAL gene stemming from a first-of-its-kind genetics study in a large African American family.

- The THAP1 gene is emerging as a critical piece to the dystonia puzzle—it may have great significance for several forms of dystonia. An assortment of mutations in this gene may account for one in four cases of childhood onset primary dystonia. The symptoms associated with these mutations typically include less lower-body involvement, more upper limb involvement, and prominent dystonia of the facial muscles and vocal cords.

- Investigators at University of Luebeck, Germany and The Institute of Neurology Queen Square, London identified the DYT4 gene associated with a dominantly inherited form of spasmodic dysphonia—called whispering dysphonia. DYT4 is an inherited form of dystonia, causing muscles to contract uncontrollably in the voice and the neck muscles.

- Advancements in MRI technology have led to preliminary studies on high-intensity focused ultrasound as a potential non-invasive neurostimulation treatment for dystonia and new methods to implant electrodes in deep brain stimulation surgery.

- It is essential to have an infrastructure and strategy for testing promising new dystonia therapies in human volunteers. Recommendations from last year’s DMRF Clinical Trials for Dystonia meeting address the current status of clinical trials for dystonia, identify obstacles to clinical trials in dystonia, and suggest designs that would optimize future trials. These recommendations have been submitted for publication.

- Working in partnership with an international panel of expert dystonia clinicians, the DMRF has led the effort to improve the current definition and classification of dystonia. A modern classification intended to set new standards of diagnosis is scheduled to be published in the medical literature this year.

For more information about the DMRF’s science activities visit http://www.dystonia-foundation.org/research

The Next Generation: Clinical Fellowship Training Program

The DMRF is partnering with Ipsen Biopharmaceuticals, Inc. and Merz Pharmaceuticals to help train aspiring neurologists in the evaluation and treatment of dystonia through one-year fellowship grants. Now in its second year, the Clinical Fellowship Training Program focuses on diagnosis and evaluation, ongoing patient care and management, pharmacotherapy with emphasis on neurotoxin therapy, and neurosurgical interventions. Training is patient-oriented and includes hands-on experience in movement disorders clinics.

One of the first DMRF Clinical Fellows, Andres Deik, MD, who completed his fellowship at Beth Israel Medical Center in New York under the mentorship of Susan Bressman, MD and Rachel Saunders-Pullman, MD, MPH, recently accepted a position at the University of Pennsylvania to help develop their movement disorder center. Dr. Deik explains: “Thanks to the DMRF’s clinical fellowship program, I have far expanded my expertise in the nature and treatment of the different dystonias. It’s also provided me with insight on the existing gaps in the management of these conditions, giving me new focus for future research.”
The DMRF continues to support the work of the Dystonia Coalition by providing staff and organizational support for the Coalition’s main clinical projects, Pilot Projects, Career Development Awards, and the annual meeting. Clinical centers represent multiple communities across the United States and Canada as well as throughout Europe and in India. There are 22 sites enrolling patients across three main clinical projects:

- **Project 1**: Biorepository & Natural History Study
- **Project 2**: Revision of TWSTRS Rating Scale for Cervical Dystonia
- **Project 3**: Diagnostic Tool for Spasmotic Dysphonia

Each of these projects is focused on improving the lives of patients. For example, an improved rating scale for cervical dystonia and the creation of a rating scale for spasmotic dysphonia will make it easier for people to demonstrate their eligibility for Social Security disability benefits which is often the biggest hurdle during the application process. Rating scales are also important for clinical trials to accurately measure benefit to new therapies.

Fifteen additional sites are finalizing preparations to begin recruiting for Project 1. Recruitment for Project 2 was completed in January of 2013, and plans are underway to start recruiting video raters for the second phase of that project. The Dystonia Coalition is currently in the fourth of its five years of funding, and preliminary discussions are underway regarding a renewal application.

### Cheat Sheet: Genes & Mutations

Mutations in specific genes cause certain types of dystonia. Every gene is linked to a protein. Here is a chart of genes mentioned in this report, the proteins with which they are associated, and forms of dystonia.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1</td>
<td>torsinA</td>
<td>Childhood onset primary dystonia</td>
</tr>
<tr>
<td>DYT4</td>
<td>β-tubulin 4a</td>
<td>Whispersing dysphonia with prominent symptoms in neck muscles</td>
</tr>
<tr>
<td>DYT6</td>
<td>THAP1</td>
<td>Primary dystonia with prominent symptoms in face and upper body</td>
</tr>
<tr>
<td>DYT10</td>
<td>PRRT2</td>
<td>Paroxysmal kinesigenic dyskinesias</td>
</tr>
<tr>
<td>DYT23</td>
<td>CI21</td>
<td>Primary cervical dystonia</td>
</tr>
<tr>
<td>DYT24</td>
<td>anoctamin 3</td>
<td>Primary cranial and cervical dystonia</td>
</tr>
<tr>
<td>DYT25</td>
<td>GNAL</td>
<td>Primary dystonia of varied anatomical symptoms and age of onset</td>
</tr>
</tbody>
</table>

A complete list of genes associated with dystonia is available at [http://www.dystonia-foundation.org](http://www.dystonia-foundation.org)