**Promise & Progress**

A Science Report from the Dystonia Medical Research Foundation (DMRF) 2014

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**Asking the Tough Questions**

**DMRF Invites Experts to Explore Research Challenges**

At the DMRF’s recent Medical & Scientific Advisory Council (MSAC) meeting on February 20–21, 2014 the title assigned to the discussion was “Dystonia: Controversies, Questions, Dilemmas.” Scientific Director Mahlon R. DeLong, MD and Chief Scientific Officer Jan Teller, MA, PhD invited MSAC members to present and debate the unresolved issues facing the dystonia field today. Every panel discussion encouraged a critical examination of select topics: *How can we identify environmental (non-genetic) causes that contribute to dystonia? Why is deep brain stimulation only effective for some forms of dystonia? Are we looking closely enough at “unorthodox” treatment approaches?* These are just a few of the questions raised over a day and a half of debate. The DMRF is already acting upon some of the directions stemming from the discussions.

Ultimately, the DMRF is interested in answering one question above all others: *How do we find a cure?* This issue of *Promise & Progress* provides an update on just some of the ways the Foundation is pursuing every opportunity to better understand dystonia and generate progress for affected individuals and families.

**Scientific Workshops as Engines for Progress**

For decades the DMRF has brought experts together from around the world at scientific workshops to assess a specific aspect of dystonia research, discuss, brainstorm, and develop a strategy to advance understanding in that area. Since 1976, the DMRF has organized nearly 30 scientific meetings and workshops that have proven to be critical to scientific progress. Important—often unexpected—new directions and collaborations result from every meeting.

Beginning in 2014, the DMRF will continue to host scientific workshops on the most pressing topics in the field, and one of the outcomes from each workshop will be a request for relevant research proposals. Kicking off this new approach to identifying and supporting key research projects was a workshop entitled, *Receptor Neuropharmacology in Dystonia*, February 27–28, 2014 in Miami. Neuropharmacology is the study of neurons and their neurochemical interactions for the purpose of developing medications that benefit the brain and nervous system. Chaired by Jonathan Brotchie, PhD of Toronto Western Research Institute and P. Jeffrey Conn, PhD of the Vanderbilt Center for Neuroscience Drug Discovery, the meeting brought together leaders from academia, industry, and the National Institutes of Health to discuss current trends in receptor neuropharmacology in dystonia and related movement disorders. In the wake of the meeting, the DMRF is developing a request for proposals to be released in the coming weeks. Funding will begin later this year.

Receptors are a hot topic in dystonia research because they are convenient targets for drug development. Receptors are the gatekeeper proteins that control how neurons receive signals from one another. The recent workshop was part of the DMRF’s efforts toward drug discovery and development, as well as finding existing therapies that are relevant to dystonia.
Clinical Fellowship Award Recipients Share Program Experience

As part of a commitment to nurturing the next generation of dystonia experts, the DMRF sponsors one-year clinical fellowships to train exceptional neurologists in the diagnosis and treatment of movement disorders with concentration in dystonia. Here is what several recent participants had to say about the training they received from this program.

“This was an exceptional educational opportunity… I hope to build a career focused on treating those with dystonia and studying underlying pathophysiology in an effort to improve future therapy.”

“My experience has been incredible. I feel I have had enough exposure to be able to run a dystonia-focused movement disorder practice comfortably.”

“The heavy clinical exposure to different forms of dystonia was the greatest benefit of the program. I don’t believe I would have had the opportunity to grow as much in the management of these conditions had I not been an award recipient.”

The 2014 clinical fellowships will begin in July. More information about this program can be found at www.dystonia-foundation.org

DMRF Partners with Expert Clinicians to Publish Updated Dystonia Definition and Classification

Dystonia is a complex disorder, and in 1984 the DMRF assembled a committee of movement disorder experts to define what dystonia is and the many forms it can take. Thirty years later, the field of dystonia had progressed to the extent that it outgrew even the language used to discuss it. Spearheaded by movement disorder specialist Alberto Albanese, MD of the National Neurological Institute, Carlo Besta (Italy), the DMRF collaborated with an international committee of experts and partners to revise the clinical definition and classification of dystonia. After nearly two years, a consensus paper was published in Movement Disorders. The authors offer a simplified, more accurate system for doctors to diagnose and treat dystonia, and for investigators to guide further research. The DMRF is proud to have played a role in this important research milestone.

For an in-depth description of the new clinical definition and classification published in the Winter 2013 issue of the Dystonia Dialogue, the DMRF’s newsletter, visit www.dystonia-foundation.org/archive
Research Highlights
Below are examples of the discoveries dystonia researchers are making around the world.

- Researchers are trying to find relationships among TOR1 (DYT1), THAP1 (DYT6), and GNAL (DYT25). Mutations in these genes can all cause primary torsion dystonia but the clinical symptoms may be quite different.

- Mutations in the ANO3 (DYT24) gene are associated with primary cervical and cranial dystonia, and a spectrum of additional clinical manifestations including tremor and myoclonus.

- Mutations in ATP1A3 (DYT12) have been demonstrated to cause rapid-onset dystonia-parkinsonism and now are associated with additional rare disorders including alternating hemiplegia of childhood and CAPOS syndrome.

- Individuals with cervical dystonia may have persistent trouble sleeping, even if symptoms improve significantly with treatment. Little is known about sleep disturbance in dystonia and this may be relevant to the overall treatment strategy.

- Researchers continue to study sensory tricks, in which certain gestures or positioning can temporarily lessen dystonia symptoms. Evidence suggests that these gestures work at the central nervous system level by actually changing the balance of activity in the brain.

Moving toward the Cure
The DMRF believes the best service it can provide the dystonia community is to work every day toward improved therapies and a cure. How will we get there? Here are some of our key approaches:

1. **Work with the best people.** The Medical & Scientific Advisory Council is made up of dystonia clinicians and scientists whose work is shaping neurology, neuroscience, neurosurgery, and related fields.

2. **Fill in the gaps.** The DMRF partners with investigators to answer specific questions about dystonia by working on specific problems.

3. **Uncover targets for new drugs.** The DMRF is partnering with biotech/pharmaceutical companies to identify and study new drug targets, which is a first step toward new medications.

4. **Expedite a pipeline for diverse dystonia therapeutics.** The DMRF has formed alliances with industry partners intended to speed-up the development of brand new therapies. This effort also includes putting measures in place to support clinical trials when new approaches need to be tested.

5. **Provide researchers with the tools they need.** The DMRF has funded cell and animal models that allow multiple research teams to pursue specific studies and helps oversee a collection of brain tissue samples through the Dystonia Brain Collective.

6. **Get the community involved.** The DMRF regularly announces dystonia studies in need of volunteers.

7. **Attract young investigators and clinicians.** The DMRF helps the next generation of dystonia experts establish careers in research and patient care.

8. **Connect the research community.** Scientific workshops and meetings stimulate the exchange of ideas, lead to collaborations, and attract new specialists to the field.

9. **Partner with other dystonia organizations.** The patient community wins when like-minded organizations work together to connect investigators and support a worldwide cooperative effort.

10. **Collaborate.** The DMRF serves as an administrative center for several dystonia community projects including the Global Dystonia Registry, Dystonia Advocacy Network, and Dystonia Brain Collective.

11. **Protect federal research funding.** As member of the Dystonia Advocacy Network, the DMRF actively supports the funding of dystonia research at the federal level at the National Institutes of Health and more recently through the Department of Defense.

12. **Don’t stop.** Because every member of the DMRF Board of Directors is personally affected by dystonia, there is no other option but to keep working toward a cure. The work will be complete when no other person or family is ever again burdened by dystonia.
UPDATE: Dystonia Coalition

The Dystonia Coalition is in the final year of its inaugural grant from the Office of Rare Diseases Research and the National Institute of Neurological Disorders & Stroke. The work over the past five years has been productive, promoting collaboration among investigators while developing new tools for researchers and clinicians. There have been 25 primary peer-review publications, 17 published reviews/commentaries, and 33 abstracts/poster presentations made at scientific meetings. At the time of this report, the application to renew funding for an additional five years was submitted. Notifications will be made in September 2014.

Projects 1, 2 & 3
The three main studies of the Dystonia Coalition are actively enrolling patient volunteers at 35 sites. Over 2,000 volunteers have enrolled across all three projects, and Project 2 exceeded its enrollment goal:

Project 1: Natural History Study with Linked Biorepository
Project Leader: Joel Perlmutter, MD, Washington University

Project 2: Revise and Improve the TWSTRS Rating Scale for Cervical Dystonia
Project Leader: Cynthia Comella, MD, Rush University

Project 3: Test and Refine a New Diagnostic Tool for Spasmodic Dysphonia
Project Leader: Christy Ludlow, PhD, James Madison University

For information on volunteering for a Dystonia Coalition study, contact the DMRF at dystonia@dystonia-foundation.org or visit www.dystoniacoalition.org

Pilot Projects
Funding has been awarded for 13 clinical and translational studies relevant to primary dystonia. Topics include new rating scales for focal dystonias, genetic studies, imaging studies, building a stem cell resource, and neuropathology studies.

Career Development Awards
The DMRF has co-funded five of 12 Career Development Awards to support junior investigators interested in clinical and translational research relating to dystonia. Recipients represent the USA, Italy, Israel, and Canada. Areas of research include imaging, deep brain stimulation targeting, rating scales for focal and childhood-onset dystonias, learning studies related to brain plasticity, testing new technology to diagnose and assess severity of dystonia, and sensorimotor retraining in focal hand dystonia.