Demystifying Dystonia with Inspired Science

Investigators Stretch Imagination & Invention to Push Research Forward

The Dystonia Medical Research Foundation (DMRF) benefits from the brilliant creativity of leading scientific investigators, and this was especially evident at the annual meeting of the Medical & Scientific Advisory Council (MSAC), February 15–16, in San Antonio, Texas led by Vice President of Science Richard Lewis, MD and Chief Scientific Officer Jan Teller, MA, PhD. The invited speakers presented some of today’s most original and cutting-edge work to better understand dystonia and ultimately devise improved treatments and a cure.

Keynote speaker Roy Sillitoe, PhD of Baylor University presented on the role of the cerebellum in dystonia and implications for treatment. Dr. Sillitoe has devised novel approaches to observe and control signals from the cerebellum in mice, and this is helping to clarify the role of this brain structure in relation to other brain areas involved in movement. This work may ultimately identify additional targets for dystonia therapies that directly act on the brain signals causing dystonia symptoms. Video of Dr. Sillitoe providing a summary of his presentation is available at youtube.com/FacesofDystonia

David Peterson, PhD of University of California, San Diego talked about the potentially groundbreaking use of face recognition technology to objectively measure symptom severity in cervical and facial dystonia. Read more about this work on page 2.

Speakers also included Mahlon DeLong Young Investigator Award recipient Aloysius Domingo, MD, PhD of Massachusetts General Hospital and newly appointed MSAC members: Jesse Goldberg, MD, PhD of Cornell University, Mark Hallett, MD of National Institutes of Health, and Christian Schlieker, PhD of Yale University.

H. A. Jinnah, MD, PhD of Emory University and Director of the Dystonia Coalition, and Beth-Anne Sieber, PhD, Program Director at the National Institute of Neurological Disorders & Stroke, also provided dystonia-relevant updates.

Drs. Christian Schlieker, David Peterson, and Roy Sillitoe were among the guest presenters at the 2018 MSAC meeting.

“Thank you for the opportunity to be part of such a wonderful foundation over the past three years. This has been a terrific experience for me both scientifically and personally. Having the chance to exchange with outstanding scientists in the field of dystonia and, most importantly, the opportunity to listen to the amazing stories of board members about themselves or their loved ones who struggle with dystonia, is something I will never forget.

“Being part of MSAC has enriched my knowledge about the disease and provided me the essential elements to develop a significant part of my research portfolio towards a deeper understanding of this intriguing disorder.

“Be assured that I will never forget my time with DMRF, and that I remain available to help you advance the Foundation agenda for years to come. You’re doing an amazing job that impacts the life of wonderful people. You should be very proud of yourselves.”

—Yoland Smith, PhD,
Emory University
DMRF Medical & Scientific Advisory Council (2014–2017)
Genome Editing
CRISPR (pronounced ‘crisper’) is a unique method that represents the latest in genome editing technology. CRISPR can be used to edit the genetic material of living organisms. What makes CRISPR extraordinary is that it makes it easier, faster, and more precise to edit DNA than any previous method. While reports in the news media focus on the potential use of CRISPR for genome editing in humans, the main application of this method has been in basic research using cell and animal models.

CRISPR removes segments of genetic material by harnessing a naturally-occurring process that bacteria use to defend against viruses. CRISPR can also replace the deleted genetic material with new DNA. How is genome editing useful to researchers? Investigators can learn a great deal about what a gene does by observing what happens when the gene is removed from the genome of a living organism. It is also possible for researchers to experiment with repairing damaged DNA, including the numerous genetic mutations known to cause dystonia.

Lilian Cruz, PhD of Massachusetts General Hospital recently earned a DMRF Research Fellowship for a project entitled “CRISPR/Cas9 system targeting specific DYT1 allele mutation in patient induced pluripotent stem cells (iPSCs): A strategy for phenotype reversion in iPSCs-derived neurons.” She is working under the mentorship of Xandra Breakefield, PhD and Cris Bragg, PhD. Dr. Cruz is applying CRISPR to repair neurons that are abnormal due to a dystonia-causing mutation in the DYT1 gene. Her work will also explore how the mutated torsinA protein encoded by the gene interferes with the function of neurons. This may lead to new strategies to treat the disorder.

Facial Recognition Software
Cervical dystonia, which affects the neck muscles, is among the most common forms of dystonia. Patients frequently experience disability, pain, depression, and anxiety disorders. At the moment there is no method to measure cervical dystonia symptoms objectively; diagnosis and evaluation depend on a doctor’s expert ability to observe the symptoms.

David Peterson, PhD of University of California, San Diego is developing a novel, computerized method to measure cervical dystonia symptoms in a truly objective fashion. The method is based on advanced software called the Computer Expression Recognition Toolbox (CERT). Using patient videos recorded with a standard video camera, CERT automatically measures the position of the head in each frame—as well as facial expressions associated with pain—so that complex movements that vary from one person to the next can be...
precisely detected and quantified without requiring human judgment. CERT will provide a powerful objective complement to the existing clinical evaluation, helping doctors to assess cervical dystonia accurately, treat it effectively, and help develop new treatments. CERT may also be applied for facial dystonias such as blepharospasm and oromandibular dystonia.

Dr. Peterson’s project received funding through the Department of Defense (DOD) Congressionally Directed, Peer-Reviewed Medical Research Program thanks to the hard work of Dystonia Advocacy Network volunteers who push every year to ensure dystonia research continues to be funded through the DOD. Video of Dr. Peterson speaking about this work with clinical collaborator Cynthia Comella, MD of Rush University Medical Center is available at youtube.com/FacesofDystonia

Myoclonus-Dystonia Research Update

The Myoclonus-Dystonia Research Program is a partnership between the DMRF and the Brown Family Foundation focused on advancing knowledge of this little-known movement disorder. Although myoclonus-dystonia (M-D) is considered a rare disease, research on M-D is making progress in areas relevant to other dystonias: molecular biology, genetic risk and inheritance patterns, non-motor symptoms, and quality of life.

Below are just a few recent advancements, many of which were supported by the Brown Family Foundation.

- New gene mutations. The first gene associated with M-D was DYT11/SGCE. Close to 80 different pathogenic gene variants or deletions in the gene have been reported.
- Other genes have been associated with M-D: DYT1/TOR1A, DYT15, DYT26/KCTD17, RELN, and possibly CACNA1B.
- Dysfunction of the cerebellum contributes to the pathophysiology of M-D as well as other types of dystonia including focal and DYT1/TOR1A dystonias.
- A recent clinical trial demonstrated that zonisamide improves myoclonus in individuals with M-D.
- Deep brain stimulation (DBS) is being applied with success in increasing numbers of M-D patients.

James C. Kilik Memorial Research Awards Fund Groundbreaking Science

The DMRF is funding two grants in memory of clarinetist Jim Kilik to investigate innovative treatment strategies for dystonia:

“Modulating the Functional Connectivity of the Cerebellum in Musician’s Dystonia”
Robert Chen, MA, MSc, MB BCh, MB BChir, University of Toronto

“A Study to Identify Kinematic and Force Measures Capturing Impairment in Musician’s Dystonia among String Players and Improvement with Retraining Therapy”
Christine Kim, MD, Columbia University

Details about these and additional funding awards are available in the Spring 2018 issue of the Dystonia Dialogue.
Technology Advancements in Deep Brain Stimulation

Neuromodulation is the process of altering brain activity to study and treat disease, often by the use of electrical stimulation or chemical agents. This field combines biomedical research with cutting-edge engineering design, often inspiring collaboration among academic researchers and private companies. Deep brain stimulation (DBS) is a neuromodulation technique used to treat dystonia and other disorders. DBS therapy continues to evolve and improve, in large part due to advancements in medical devices engineering.

The basic concept of DBS is to use electrical stimulation to interrupt abnormal brain activity that causes dystonia symptoms. A typical DBS system consists of an electrode placed deep into the brain, an implanted pulse generator (IPG), and wires that connect the electrode to the IPG. The IPG contains a battery and electronic circuitry that generates the signals delivered to the brain. Once the system is surgically implanted, the electrical stimulation is manually adjusted by remote device.

Multiple efforts are underway to make DBS systems more personalized and more effective. Emerging DBS technologies include:

- Creating DBS systems that automatically make stimulation adjustments by sensing and responding to brain activity. This involves improved sensors and increased device memory.
- Rechargeable IPG batteries to increase the duration in between battery replacements.
- Smaller and upgradeable devices. Ultimately, IPGs may be small enough to implant under the scalp rather than the chest or abdominal wall.
- Increasing the number of electrode contacts in each lead for more selective targeting of brain pathways—and the ability to avoid stimulating brain pathways associated with unwanted side effects.
- Greater flexibility of stimulation options, including the ability to have different settings for specific brain targets.

In addition to being a powerful therapy, DBS is a research tool that allows for direct recording of brain activity. Researchers know DBS can have a dramatic positive effect on treating dystonia but how and why it works—or fails to work in some people—remain poorly understood. By continuing to better understanding DBS, researchers will better understand dystonia.

The Global Dystonia Registry

Share your dystonia history with researchers searching for a cure.
globaldystoniaregistry.org