

Recent Discoveries by DMRF-Funded Investigators

New discoveries about dystonia are published on a daily basis as investigators all over the world continue to work toward better therapies and a cure. These are just a handful of recent developments by DMRF-funded researchers.

- Crystallography techniques revealed the 3-D structure of TorsinA, a critical step for developing new treatment strategies.
- TorsinA has an unexpected role in lipid metabolism. Lipids are fat molecules that play a role in maintaining the structure and function neurons.
- In cell and animal models, a protein called TorsinB can rescue neurons from the dystonia-causing effects of mutated TorsinA.
- When TorsinA becomes abnormal, there is a disruption in calcium physiology at the cell level.
- A study that followed-up with deep brain stimulation patients for up to 10 years demonstrated the benefits for dystonia are long-term.
- Studies that failed to demonstrate the effectiveness of novel drugs in treating dystonia did reveal specific abnormalities in certain neurons that may help explain the origins of dystonia in the brain.



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globaldystoniaregistry.org

Big Lessons from the Littlest Patients Discoveries in Childhood Dystonia Reveal New Gene

Important new data on treating dystonia in children are being published by multiple research groups. For example, a team led by researchers from University College London published a seminal paper describing their discovery of mutations in a gene called KMT2B (DYT28) that cause progressive childhood dystonia. The investigators describe KMT2B dystonia as a dominantly inherited, complex dystonia with onset in infancy or early childhood. Most patients develop dystonia in the limbs as well as pronounced cervical, cranial, and laryngeal involvement. Some of the children presented with intellectual disability, psychiatric disorders, specific facial characteristics, and other non-motor symptoms.

In addition to identifying a novel genetic movement disorder, the team discovered a potentially pivotal new mechanism causing dystonia. Moreover, it has been observed that although this particular dystonia does not respond well to treatment with oral medications, response to deep brain stimulation (DBS) can be profound, in some cases restoring the ability to walk. This work reinforces that proper diagnosis, including comprehensive genetic testing, is necessary to achieve the most effective therapeutic treatment.



SCIENCE REPORT FROM DMRF CANADA 2017

Inspiring Discovery through Outreach & Inclusion DMRF Fuels Research Progress by Engaging Diverse Experts

Every year, the DMRF convenes a meeting of the Medical & Scientific Advisory Council (MSAC), the Foundation's science think tank, to discuss the latest dystonia research developments and strategize science activities for the year. A recurring theme throughout discussions at this year's MSAC meeting in Phoenix, February 16–17, was the importance of continuing to attract new investigators to work in dystonia. This was reflected in the guests invited to present their work.

The 2017 keynote speaker, Jesse Goldberg, MD, PhD of Cornell University, studies songbirds to understand brain mechanisms of motor learning. Songbirds have a basal ganglia pathway specialized for learning to sing, a pathway that is associated with dystonia and other movement disorders in humans. Dr. Goldberg's presentation prompted a riveting discussion on the somewhat unexpected relationship between the way songbirds master singing and the ability of the human nervous system to learn and control movements.

Mark Moehle, PhD, a postdoctoral research fellow at the Vanderbilt Center for Neuroscience Drug Discovery, earned the inaugural Mahlon DeLong Young Investigator Award just last year. After presenting his current research he was

Support from the DMRF saved the Dystonia Coalition \$1.5M in administrative costs, ensuring funds went directly to research.

commended for his "fantastic progress" in understanding how a mutation in the DYT25/GNAL gene leads to dystonia and testing the effectiveness of specific drugs that may counteract the negative effects of the mutation.

Look for interviews with Drs. Goldberg and Moehle to be posted on the DMRF's YouTube channel.

H. A. Jinnah, MD, PhD of Emory University and Principal Investigator of the Dystonia Coalition provided a summary of the Coalition's activities in the past few years. Beth-Anne Sieber, PhD, Program Director at the National Institute of Neurological Disorders & Stroke, provided an update on Institute activities related to dystonia.

The DMRF plans to announce a new research fellowship for young investigators later this year. Recipients of the 2017 clinical fellowships to help train up-and-coming movement disorders specialists were announced in March.



L to R: MSAC meeting keynote speaker Dr. Jesse Goldberg, DMRF Scientific Director Dr. Mahlon DeLong, DMRF Chief Scientific Officer Dr. Jan Teller, & DMRF MSAC member and grant awardee Dr. Rose Goodchild.



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Dr. Dauer's work in dystonia represents some of the most groundbreaking discoveries in the field.

Movement, Models, Momentum

Interview with William Dauer, MD

As one example of how investment in junior scientists leads to exponential research progress, Dr. William Dauer is a movement disorder specialist and basic scientist at University of Michigan who received his first DMRF grant in 1998.

DMRF: How did you get involved in dystonia research?

WD: I became aware and interested in dystonia research as a neurology resident at Columbia where I had contact with Stan Fahn and Susan Bressman primarily, and Paul Greene, all of who were actively involved in pursuing research on dystonia, supported by the DMRF. I had a background in basic research, and I was contemplating what project I would pursue during a combined clinical and research movement disorders fellowship. It was during that time that the DYT1 gene was discovered. That was extremely exciting and led me to want to devote my studies at that time to developing a model of that disease and understanding the pathogenesis of DYT1 dystonia, hopefully with the outcome down the road of leading to better treatments.

A moment that was and remains very exciting was getting that first DMRF grant. When you're a young researcher and a little unsure of how people will take to your work, getting that first grant is big. Having the trust of the Foundation to go forward with a project was the start of a really wonderful relationship. Without repeated funding and support, and symposia provided by the DMRF, there is a very good chance I wouldn't be doing the work I am doing. That also means that the people who have come through my lab wouldn't have necessarily worked on DYT1—most notably Rose Goodchild who joined my lab early on and who is now an independent dystonia researcher. None of that might have happened were it not for that first DMRF grant.

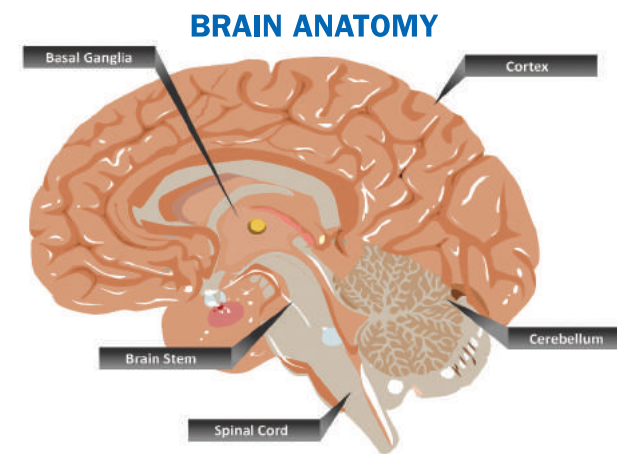
DMRF: What progress in either basic or clinical research, contributed by you or others, stands out for you?

WD: In clinical treatment, the most exciting research advancement since I began has been deep brain stimulation [DBS]. This has without question transformed the lives of many patients. But there remain patients who continue to have symptoms and just don't get that much benefit from deep brain stimulation.

There's a lot of work in the DBS field generally, and in dystonia brain imaging and circuit work more specifically, that is trying to understand how we can do better because obviously we want to treat all patients with dystonia effectively. That includes understanding what circuit changes are happening in the brain, looking for new targets, and there's technical work being done on the DBS machines themselves.

That clinical work on circuits is synergistic with basic research that's going on to understand what groups of brain cells are doing abnormally to cause dystonic movements and how different groups of brain cells might be communicating with each other in an abnormal way, which may be really important to understanding the disease. In relation to our work, what we've been particularly excited about in recent years has been the first development of mouse models of the disease that actually show the sort of overt abnormal movements that people with dystonia have. This allows us, for the first time, to begin to ask some of those questions about brain circuits—different brain regions—and try to figure out which of them might be critical for the movements and how we might manipulate them in new ways. Our hope would ultimately be finding drugs that would be able to accomplish this.

Some other exciting things we have been a part of include asking why does a specific group of cells function abnormally when someone has a dystonia mutation. In DYT1, there's been a lot of exciting things that have happened since the discovery of the gene in terms of how that protein works inside a neuron—a nerve cell. Just to highlight work we've been focused on, we initially discovered that the TorsinA protein works at the membrane that surrounds the cell nucleus, the nuclear envelope. Increasingly, we and others are identifying the different consequences for nuclear envelope functions when TorsinA is deficient. If you think of the nucleus as the control center of the cell, there is something called the nuclear pore which is the gateway that allows information into and



out of that control center. It looks like TorsinA may have a role in how those control centers are formed and the kind of information they allow back and forth. That's ongoing work and what's exciting about it, as well as for the circuit work, is that people who are not "dystonia researchers" but who are interested in these basic processes like brain circuits or nuclear trafficking are becoming interested in the disease.

The more that we learn and map out basic areas that are involved in primary dystonia, and let the research world know about it, we'll then be able to draw in other researchers who right now don't have dystonia on their radar. That process will hopefully speed progress by bringing new, smart people into the field who can challenge existing ideas. That is what makes great science. It's an exciting time where many things are coming together. We feel like the coming years are going to produce faster discoveries and hopefully ones that will make a difference to patients.

DMRF: Can you tell us more about your most recent mouse models, and what these models are teaching us?

WD: We've published a couple of papers recently describing a variety of mouse models, all of which show abnormal twisting movements that look similar to human dystonia. For many years we had great difficulty in making models that had what I would call "overt" twisting movements. It is important to develop such models since, if the animals have those symptoms, we can try to figure out the cause and what interventions might make them better. The clinical features of DYT1 dystonia, especially its onset during childhood, suggest that important steps in the disease process occur during brain maturation. Based on this, we designed our new models to have markedly impaired TorsinA function during that period of "juvenile" development, but not so severe as to be lethal, allowing the animals to live long enough for the abnormal movements to occur. Previous models may not have had severe enough TorsinA problems or died prematurely.

FYI

- Neurons are cells in the brain and spinal cord. Neurons communicate with each other by transmitting signals along brain circuits (also called brain networks or pathways).
- TorsinA is a protein found in neurons that causes dystonia when it fails to function normally. The DYT1 gene, discovered by DMRF-funded investigators, is responsible for encoding TorsinA.

Once we developed these models, we focused on asking what is it about the developing nervous system that makes it vulnerable to the failure of TorsinA. We found that certain cells in the movement areas of the brain are uniquely vulnerable to getting sick and potentially dying from the lack of TorsinA function. A particularly interesting and potentially important group of these vulnerable cells are located in the basal ganglia, and are called cholinergic interneurons. Among the millions of cells in the basal ganglia, only this tiny population of cells shows clear defects (many even die). Now we're asking why are these cells vulnerable, what makes them special? If we learn that hopefully we can figure out a way to block it from happening or, if it does happen, to reverse or suppress it. We feel like we have the tools in hand in order to do that.

We're currently putting a grant into the NIH [National Institutes of Health], and based on the power of these models we've been able to attract outstanding collaborators to help us with this work. Just to give you a little preview, there are several technologies now that allow you to turn on or turn off the activity of certain types of brain cells out of the billions that are there. So in one of our models we are planning to excite or suppress these cholinergic interneurons to see if that by itself will suppress symptoms or exacerbate symptoms—that has never been done before. So that is very exciting because it has the opportunity to really pinpoint at a certain group of cells that are important to focus on. Other research groups have produced interesting findings to implicate these cells, but they've never been looked at in an overtly symptomatic model. This is very exciting for us, and we are really looking forward to that.

For the full interview with Dr. Dauer and additional information about his discoveries and ongoing work, visit dystoniacanada.org/dauer_interview