

2021 Grants & Research Fellowships

The ultimate goal of the DMRF's science program is to support the discovery of improved dystonia therapies and a cure. The DMRF is dedicated to stimulating the field of dystonia research and supporting the collaborations and projects necessary to accelerate progress. Currently funded projects are furthering our fundamental understanding of what dystonia is, investigating shared mechanisms among dystonia types, exploring novel new therapeutic approaches, understanding how dystonia-causing mutations ultimately result in symptoms, and uncovering targets for new and improved therapeutics. The DMRF is committed to providing investigators with the grant funding and resources needed to address the most pressing unresolved questions in dystonia research and produce new discoveries.



Congratulations to the newest award recipients, and infinite thanks to DMRF supporters for making this research funding possible.

GRANTS & CONTRACTS

Research grants are available in support of hypothesis-driven research at the genetic, molecular, cellular, systems, or behavioral levels that may lead to a better understanding of the pathophysiology or to new therapies for any or all forms of dystonia. Contracts provide the opportunity to provide research support through the identification of specific, milestone-driven projects conducted by identified investigators.

Genetic Modifiers of Penetrance in DYT1 Dystonia – 2nd Year **David Arkadir, MD, PhD**

Hadassah Medical Center and Hebrew University of Jerusalem

Some types of dystonia are hereditary, for example, DYT1 dystonia caused by mutation in the TOR1A gene. It is not clear, however, why individuals with the same genetic mutation can develop different severities of symptoms. On the extremes, one individual may experience severe dystonia that starts in childhood and leads to significant motor disability while another individual may be totally asymptomatic and not even aware of having the genetic mutation. Dr. Arkadir and

his team believe that additional genes, yet to be discovered, determine whether an individual carrying a potentially dystonia-causing genetic mutation will develop this movement disorder or not. They attempt to find this gene(s) by comparing the genomes of individuals who have mutation in the TOR1A gene, with or without apparent dystonia symptoms. The goal is to find genes that protect some individuals from developing dystonia, even in the presence of the mutated gene.

Normalizing DYT1 Cholinergic Neurons by CRISPR **Disruption of Mutant TOR1A Allele**

Xandra Breakefield, PhD

Massachusetts General Hospital

Gene therapy is proving beneficial in an increasing number of neurological diseases. This proposal represents a step in evaluating whether gene therapy could be effective in DYT1 dystonia. Dr. Breakefield has shown that selective disruption of the mutant TOR1A/DYT1 gene can normalize biologic cell functions in patient skin cells. Since dystonia is a neurological disease, the next step is to evaluate whether this approach

can normalize function in TOR1A/DYT1 neurons (brain cells). Collaborating with Dr. D. Christopher Bragg and Dr. Nutan Sharma the investigators have access to stem cells from DYT1 patients, which can be turned into neurons. If successful in rescuing neurons, the lab will work with Dr. David Standaert to translate the technology into a mouse model which would provide some of the data needed for the Food & Drug Administration to allow a clinical trial. Ultimately, Dr. Breakefield envisions a clinical trial in which children carrying the mutant TOR1A/DYT1 gene and manifesting symptoms at an early age are administered gene therapy in a single dose. This could be done at the same time as deep brain stimulation (DBS), with the intent to eventually turn off the DBS device to assess if it remains needed. The ultimate goal of this effort is the development of better therapies for DYT1 dystonia.

A Next Generation Sensing Neural Interface Study for Adaptive DBS in Dystonia

Simon Little, MBBS, MRCP, PhD

University of California, San Francisco

In addition to being a treatment, deep brain stimulation (DBS) is helping researchers understand how dystonia affects the brain. Recent work has shown that brain signals in dystonia are different from individuals without dystonia or with other neurological disorders. This has revealed a pattern of activity in the deep parts of the brain that repeats around five times per second in people with dystonia and is linked to muscle activity. However, investigators don't yet know the significance of this signal and whether it causes muscles to contract or is simply a marker that they have done so. Also, if it is a cause of dystonia, it isn't yet known how this interferes with the healthy sensory messages that come into the brain or the movement signals that leave the brain. To answer these questions, Dr. Little and team will use new sensing-enabled DBS devices which can record brain signals as well as provide stimulation therapy. They have implanted this device in a small group of dystonia patients and found that the dystonia signals are present in all patients recorded so far. Next they plan to investigate how this signal relates to muscle activity and sensory processing. They will also test this new type of adaptive stimulation to see if it may be more effective and cause fewer side effects than standard continuous DBS. This study will further understanding of how brain signaling goes wrong in dystonia, knowledge which could potentially lead to the design of new and improved therapies.

The Role of Cholinergic Neurons in Isolated Focal Cervical Dystonia – 2nd Year

Scott Norris, MD

Washington University School of Medicine

Cervical dystonia produces excessive involuntary muscle contractions in the neck. These muscle contractions result in uncomfortable, awkward, and sometimes painful positions of the head, neck, and shoulders. This research project focuses on improving understanding of the brain's role in cervical dystonia, specifically directed toward improved treatment. The investigators use state-of-the-art brain imaging techniques, positron emission tomography (PET) and magnetic resonance imaging (MRI), to observe the working brain. PET allows researchers to observe chemical messengers (neurotransmitters) in the brain—in this case, acetylcholine. MRI allows researchers to observe how one region of the brain communicates with other brain regions. Combining PET and MRI techniques provides a powerful opportunity to determine how altered chemical messenger levels may influence the way brain regions communicate in cervical dystonia by comparing brain activity of patients with cervical dystonia and control volunteers without cervical dystonia. Acetylcholine is a neurotransmitter of interest because some dystonia patients improve when taking medications that alter levels of acetylcholine. The researchers suspect that brain regions that use acetylcholine are damaged in patients with cervical dystonia and therefore the communication between brain regions that rely on acetylcholine is disrupted. If they find that acetylcholine affects how brain regions communicate in cervical dystonia, future research can attempt to correct the communication problem with new medication or brain stimulation therapies.

Role of Cerebellar Network Excitability and Plasticity in the Pathophysiology of Dystonia

Antonio Pisani, MD

University of Pavia

Dr. Pisani and his team are studying brain circuits in two types of genetic dystonia: DYT1 dystonia, which is the most common inherited form, and DYT25 dystonia which is rarer. They are testing the idea that loss of these genes leads to changes in brain plasticity, which is how the brain learns motor tasks and adapts to new environments. They believe that abnormal plasticity is a shared factor responsible for abnormal movements observed in patients. They study two animal models, one with the DYT1/TOR1A gene mutation and

the other with loss of DYT25/GNAO1. By conducting studies on brain circuits in these models, they hope to learn about the effects of the loss of these genes on brain plasticity. One of the features of abnormal movements in dystonia is that once the symptoms develop, they can be difficult to treat and may become permanent. This is a kind of dysfunctional plasticity. Therefore, if investigators can understand the mechanisms and control the abnormal plasticity, they might be able to 'undo' the changes in the brain that cause these movements, leading to better treatments.

Targeting the cAMP Pathway in the Striatum to Treat Dystonia

Emmanuel Roze, MD

Paris Brain Institute

The striatum is a deep structure in the brain that plays a critical role in the control of movements. cAMP is a molecule that regulates many cell functions, including those in neurons (brain cells). The cAMP signaling pathway controls processes important for the function of neurons in the striatum and the control of movements. (A signaling pathway is the string of communication among a group of molecules to complete a specific task in the cell.) Various genes that encode proteins involved in this cAMP pathway can cause dystonia when mutated, particularly GNAL and ADCY5. Mutations of GNAL lead to *reduced* cAMP production while mutations of ADCY5 lead to *increased* cAMP production. To better understand how disruptions in the cAMP pathway produce dystonia, the investigators will attempt to characterize movement dysfunction and striatal biochemical abnormalities of genetic mouse models. To investigate the cAMP pathway as a target to treat dystonia, they will 'correct' the abnormal cAMP pathway in the mouse models using drugs and investigate whether treatment improves the biochemical abnormalities and movement dysfunction. Finally, they will evaluate the effect of caffeine in ADCY5-related dystonia patients which is suspected to reduce excess of cAMP production and has been found to be helpful in some patients. To this end, they will use questionnaires and a randomized, controlled clinical trial with a single dose of caffeine.

Connie and Jim Brown Early Stage Investigator Award Cerebellar Repetitive Transcranial Magnetic Stimulation in Monogenic Myoclonus-Dystonia

Anne Weissbach, MD

University of Lübeck

Myoclonus-dystonia (M-D) is a neurological movement disorder often characterized by a combination of generalized

myoclonic jerks, dystonia, and psychiatric disorders. Mutations in the SGCE and VPS16 genes have been identified as genetic causes of the disease. Both genes are important for the function of an area of the brain called the cerebellum. These investigators and others have demonstrated that individuals with M-D have deficits of cerebellar mediated learning. How cerebellar malfunction in these patients affects the cortex of the brain, particularly regions important for motor control is of particular interest. Dr. Weissbach is leading the first study to investigate potential symptom reduction and neurophysiological changes in M-D patients before and after repetitive non-invasive transcranial magnetic stimulation (rTMS). The study aims to identify the clinical cerebellar deficit, identify abnormalities of cerebellar function and its interaction with the cortex of the brain as well as examine the reversibility of these abnormalities through the application of cerebellar rTMS. These findings will foster development of new treatment strategies.

RESEARCH FELLOWSHIPS

Over the years, DMRF has created funding awards to support young investigators at different stages in their scientific training. Postdoctoral fellowship awards support outstanding young scientists who have earned a doctoral degree and have embarked on a period of mentored research. DMRF is supporting postdoctoral fellows who are working to fundamentally improve our understanding of brain dysfunction and molecular mechanisms underlying dystonia.

Investigating Abnormal Neurodevelopment in a Novel in vivo Model of Inherited Dystonia

Simon Lowe, PhD

University College London Institute of Neurology

While researchers have uncovered a number of genetic mutations that cause dystonia, and it is well-known that dystonia affects certain areas of the brain, not enough is known about the mechanisms that ultimately cause the movement dysfunction. Some disease-causing mutations act *acutely*, which means they cause a disorder by directly altering the function of the brain, affecting its ability to perform tasks. Other mutations act *developmentally*, which means they alter the way the brain develops, causing lasting alterations in the way the brain works. Knowing which is happening is key to understanding and treating a disorder. Dr. Lowe is investigating a form of dystonia caused by a single mutation in the gene KCNMA1, which has a number of important roles in neurons (brain cells). Dr. Lowe and his team developed the first

animal model of this disorder in the fruit fly. Using advanced genetic techniques he is able to turn the mutation 'on' and 'off' at different stages of the flies' lifecycle. Preliminary data show that turning the mutation on in the adult fly has no effect, but turning the mutation on and then back off again during its development causes severe, lasting movement defects in the adult fly. These defects very much resemble the movement dysfunction seen in humans. This is a clear demonstration that the mutation causes movement dysfunction in the fly by altering nervous system development. Dr. Lowe aims to confirm this and delineate the key developmental stage with additional experiments, and then ask the question *how* this mutation affects development. The investigation intends to provide mechanistic insights into a specific form of inherited dystonia and answer key questions about *when* and *how* dystonia occurs that may be the same in other forms of dystonia.

Neural Signals in the Cerebellar Nuclei Gate the Manifestation of Dystonia-like Symptoms

Meike van der Heijden, PhD
Baylor College of Medicine

The wide range of underlying causes for dystonia has made it difficult to develop one-size-fits-all treatment. Development of a treatment that would be broadly effective across the dystonias would be highly beneficial. Recent studies have suggested that the cerebellum may be a central node in a brain network that triggers dystonia in humans and mouse models. One specific area of the cerebellum, the cerebellar nuclei, sends neural signals to other regions of the brain and spinal cord that are involved in motor control. Imaging studies in dystonia patients and electrical recordings in dystonia mouse models have shown that these neuronal signals are different from people without symptoms and control mice, respectively. Interestingly, therapeutic stimulation of the cerebellar nuclei using deep brain stimulation (DBS) alleviates symptoms in some people with acquired dystonia and in a mouse model with severe dystonia. Dr. van der Heijden hypothesizes that the cerebellar nuclei act as a fulcrum in the

expression of dystonia symptoms. On the one hand, abnormal neuronal signals in the cerebellar nuclei can cause dystonia-associated symptoms. On the other hand, stimulating these nuclei with DBS can alleviate dystonia-associated symptoms. However, to fully understand how to best optimize DBS treatment, it is necessary know precisely what the balanced state neuronal signaling is in the cerebellar nuclei, and in what direction these communication signals are skewed in mouse models of dystonia. To answer this question, the investigators are recording brain activity profiles in multiple mouse models of dystonia with different severities of dystonia-associated symptoms. They use mathematical computations to determine what aspect of the neural signals are abnormal and cause dystonia-associated movement impairments. They hope to find precisely how cerebellar signals contribute to dystonias with different causes. This knowledge will be an important step for optimizing cerebellar DBS to become a first-line treatment for patients with dystonia.

DYSTONIA COALITION CAREER DEVELOPMENT AWARDS

The DMRF is proud to support two Dystonia Coalition Career Development Awards. The goal of the Career Development Program is to facilitate career development for junior investigators interested in clinical and translational research relating to dystonia, or to provide a mechanism for more senior investigators from other fields to get involved in dystonia research. More information about the Dystonia Coalition is available at: rarediseasesnetwork.org/cms/dystonia

Non-invasive Neuromodulation to Study Long-term Plasticity Mechanisms in Task-specific Dystonia

Noreen Bukhari-Parlakturk, MD, PhD
Duke University School of Medicine

Immune Mechanisms in Cervical Dystonia

Laura Scorr, MD
Emory University School of Medicine

DMRF Merchandise to Promote Awareness

Have you checked out the DMRF online store lately? You'll find many practical items to promote dystonia awareness: face masks, tote bags, pop sockets, pins, key chains, and more. For details and to order visit: dystonia-foundation.org/merch

