PMDF

THE PARKINSON'S AND MOVEMENT DISORDER FOUNDATION

Newsletter ☙ Spring 2019

The Parkinson's and Movement Disorder Foundation

14772 Moran Street
Westminster, CA 92683
(714) 369-7426
www.pmdf.org

MOVE4U 5k Walk/Run Fundraiser Event

by Tien Nguyen

The Parkinson's and Movement Disorder Foundation will be hosting our 9th MOVE4U 5K Walk/Run Fundraiser to raise funds and help spread awareness of Parkinson's and other movement disorders. The fundraising event will take place at Mile Square Park Group Shelter 17 in Fountain Valley, California, on Saturday, May 11, 2019. This is a great opportunity to get outdoors with family and friends, supporting the mission of our organization while raising awareness in our fight against movement disorders. This is a friendly family event that everyone can enjoy. We will have a children's booth with some giant games, including four in a row, tic tac toe, tumbling tower, corn hole, along with a coloring and drawing area. Kids under 12 do not need to pay the registration fee.

Prizes will be awarded to the first 3 runners to cross the finish line.

First Place - Helicopter Tour for 2 over Hollywood/ Downtown LA
Second Place - TBA
Third Place - TBA

All participants who paid the registration fee will automatically be entered in a raffle and have the opportunity to win gift card prizes ranging from $5 to $50. There are over twenty prizes being raffled off! In addition to a chance of winning one of our various prizes, registered participants will also receive lunch, popcorn chicken provided by Phở K-tea, a T-shirt, and beverages.

We would also like to give special thanks to the following companies for their generous sponsorships:

Gold Sponsor: US WorldMeds
Silver Sponsors: Adamas Pharmaceuticals, Amneal Pharmaceuticals, Avanir Pharmaceuticals, Neurocrine Biosciences, Teva Pharmaceuticals
Bronze Sponsor: Allergan

If you are in Orange County, Los Angeles County, or San Diego County, bring your family and friends and participate in the MOVE4U 5k event! Street parking is available around Mile Square Park, meter-free. If you park your car on the park grounds, parking is $5 per vehicle. You can register online by visiting http://www.pmdf.org/events.php or by mail using the form on the next page in the newsletter. If you are planning to bring a child (or children) under 12, please let us know so we can make sure our food arrangements can accommodate everyone attending. Due to park regulations, registration cannot be processed at the park.

If you are unable to attend the event, please consider helping us to promote the event by raising more awareness by promoting it on Facebook to your friends and family. Our Facebook page is http://www.facebook.com/thePMDF.

President's Letter

Dear friends of PMDF,

This year, PMDF received 33 proposals for research to be funded by our annual grant program. The proposals addressed therapies, new and repurposed drugs, new drug administration techniques, disease assessment, causes, interventions, models, and more, covering several different conditions. This newsletter features interviews with the two researchers receiving this year's grants. There is a lot to be done, and we're working to get it done.

Our spring fund-raiser, the MOVE4U 5K run/walk, will be happening very soon. Details are elsewhere in this newsletter. Sign up and come join us. I hope to see you there!

Sincerely,

Mark Wadsworth
PMDF President

Getting to Know Your 2019 PMDF Grant Winners

by April Ingram

Dr. Hardy Rideout

Running Gene Interference to Preserve Healthy Neurons

Principal Investigator - Hardy Rideout, PhD
Co- Principal Investigator - Alexia Polissidis, PhD

Research Title: Peptide inhibitors of mutant LRRK2-induced neurodegeneration: targeting the interaction between LRRK2 and FADD.

Since 2009, Dr. Hardy Rideout has been part of the Neurodegenerative Diseases Research Group at the Biomedical Research Foundation of the Academy of Athens in Greece. His work has focused on the links between altered LRRK2 (leucine-rich repeat kinase 2) gene localization and signaling, and the activation of neuronal death pathways.

Genes are short sections of our DNA, and each gene contains specific instructions that tell your cells how and when to make certain molecules, called proteins. Proteins perform various functions in your body to keep you healthy. A gene mutation can prevent one or more of these proteins from performing properly. Although PD is not typically thought of as a genetic disease, mutations in approximately 20 genes, including LRRK2, have been associated with genetic parkinsonism.

While the vast majority of PD does not have a known cause (referred to as idiopathic), about 10% may be linked to some genetic cause. In 2004 the LRRK2 gene was discovered and researchers have found that mutations to this gene may be responsible for 1□2% of all PD. This proportion can be much higher for people in some ethnic groups; more specifically, mutations in the LRRK2 gene can account for up to 20% of PD in Ashkenazi Jews and as many as 40% of PD in North African Arab Berbers.

Dr. Rideout has studied how the mutations of LRRK2 are linked to the death of dopaminergic neurons, which lead to the motor symptoms associated with PD. Once he and his team determined the location of the interaction between mutant LRRK2 and the death signaling protein FADD in dopamine neurons, they hypothesized that blocking the mechanism that activates the neuron death pathways may be key to developing treatment interventions.

To test this hypothesis, they are taking a three step approach. First, they will design peptides (small proteins) specifically made to interfere with the interaction between the gene LRRK2 and the FADD protein. Second, they will assess how well these peptides interrupt the process of cell death *in vitro* (in test tubes*)*. Finally, they will confirm that the peptides consistently perform their specific intended action. Dr. Rideout explains, "Our proposed novel strategy to disrupt neuronal death induced by mutant forms of LRRK2 may prove promising in the future of disease-modifying neuroprotective therapeutic interventions for PD."

Dr. Rideout and his co-investigators feel that this is a very exciting time for Parkinson's research, and movement disorders, in general. He shares, "It is particularly inspiring to work with foundations such as the PMDF, who not only support research but also play an important role in public awareness and education; as well as with patient groups who are so eager to become active participants in the research process, at many different levels."

Dr. Rideout's interest in movement disorder research, and PD research in particular, stemmed from his early training in neuronal cell death pathways, and the approaches aimed at blocking this cell death. He explains, "At the time, it was believed that the predominant site of dysfunction in PD was the loss of dopamine neurons in the substantia nigra; however, as we now know it is a considerably more complex disease affecting other systems and, as some researchers believe, originating at other sites before eventually spreading to the substantia nigra. Thus, while the goal of protecting dopamine neuron survival remains, our understanding of the pathogenic mechanisms preceding their demise continues to evolve."

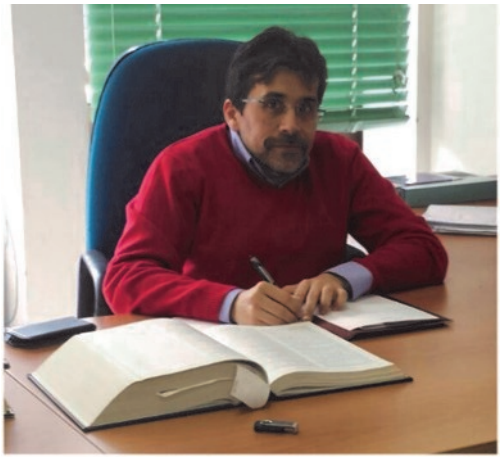
When asked which aspects of his research Dr. Rideout is most excited about, he explains, "It has been fascinating to watch the progress of research in the LRRK2 field since its initial identification in 2004 as pathogenetically linked to Parkinson's disease; to reach the point now where inhibitors of LRRK2 activity have entered early clinical trials. Now, the goals are to continue this momentum forward with our multidisciplinary team, identifying novel targets for therapeutic development, and sensitive biomarkers that can be deployed in the clinic." He adds, "Additionally, as more substrates of LRRK2 are identified, we have the opportunity to not only understand its role under physiological conditions, but also potentially target specific activities, perhaps in specific cell types, to more potently disrupt its ability to trigger neurodegeneration, not only in PD associated with mutations in LRRK2, but also in the much more common idiopathic forms."

Although excited about recent advancements, Dr. Rideout explains that there are several challenges that still need to be tackled in movement disorder research. "First, finding an appropriate model for the disease in question represents a significant challenge in that it is rare to have a model that faithfully recapitulates multiple aspects of such a complicated family of diseases, as movement disorders. This is true for cellular as well as *in vivo* models [studies performed on living organisms].

Continued on Page 4

Secondly, and this is particularly true in the case of LRRK2, some proteins will have multiple activities and sites of action, all contributing to the pathogenesis of the disease. Thus, with a protein such as LRRK2 as a potential therapeutic target, we have to consider its normal and pathological function not only in neurons, but also in other cell types as well (e.g. immune cells), where it is also known to play a critical role."

The PMDF grant award will provide critical funding to advancing this important work. Dr. Rideout explains, "We are incredibly grateful for the grant money awarded by the PMDF; this will allow us to perform critical experiments in cellular models of mutant LRRK2 PD, testing various strategies to boost neuronal survival in neurons expressing mutant forms of the protein. These studies will form the basis of subsequent projects applying these approaches in different animal models of PD."



Dr. Guiseppe Esposito and colleagues at his laboratory in the Department of Physiology and Pharmacology 'Vittorio Erspamer' at the University SAPIENZA in Rome Italy, are focused on new ways to reduce the neuroinflammation that can be an underlying cause of neurodegeneration in disorders like Parkinsons' Disease (PD).

Repositioning a Traditional Therapy - Taking Aim at a New Target

Principal Investigator - Giuseppe Esposito, PhD
Collaborators: Maria Carafa, PhD, Dr. Carlotta Marianecci, PhD, Stefano Gigli and Luisa Seguella

Research Title: Innovative Parkinson's disease modifying strategy: preclinical evaluation of intranasal delivery of pentamidine (IN-pentasome) in MPTP-intoxicated mice.

The term neuroinflammation is used to describe an inflammatory response within the brain or spinal cord. This inflammatory process is controlled by the production of cytokines, a large group of proteins and other neurochemicals that are secreted by specific cells of immune system. These cytokines are powerful regulators of glial cells—the cells responsible for supporting neurons in the brain. When glial cells are not performing normally, they can become activated in a process called gliosis, and produce inflammatory and toxic chemicals that can damage or kill neurons. Gliosis is a key step in the progression of PD, so it would make sense that blocking gliosis from occurring might delay or stop PD from progressing.

A protein called S100B is produced by normally reacting glial cells and it regulates normal neuron development, but there can be too much of a good thing. Secretion of too much S100B can be toxic and cause destruction of dopamine-producing neurons in areas of the brain responsible for movement control.

Dr. Esposito is excited to share an important part of his research, linked to the possibility of targeting the glial cells to act on gliosis and protect the dopaminergic neurons indirectly. It is important to protect the dopaminergic neurons because they are the main source of dopamine in the central nervous system and their loss underlies the motor symptoms of PD. Dr. Esposito explains that there are nine glia for every neuron, so glia are not bystanders in neurodegeneration, but actively participate in cell death.

Animal research has shown that when too much S100B is expressed, animals are predisposed to develop severe PD. Dr. Esposito shares the potential in this research, "The possibility of pharmacologically blocking the S100B protein can represent an interesting strategy in limiting the progression of Parkinson's

disease and favoring a sensible improvement, which is key. Our research project is based on the study of an antiprotozoal drug, pentamidine, which has shown the ability to block the activity of S100B in different pathological conditions in which this protein is overexpressed, such as in cancer, colitis and experimental Alzheimer's disease." Studies have shown that pentamidine, historically used to prevent the growth of harmful or infectious microorganisms, effectively blocks S100B, so it has been repositioned as anti-tumor treatment and is in phase III studies on melanoma. Research is being conducted to determine if it can be successfully repurposed to treat other conditions.

Pentamidine is usually administered by aerosol or intravenously, and Dr. Esposito is looking to produce a form that can be administered as a nasal spray. This is a novel way to deliver the drug, allowing for microscopic particles of pentamidine to be easily absorbed. The Esposito lab will conduct a study of the new pentamidine formulation, niosome (IN-pentasome), in Parkinsonian mice and verify improvements in movement and neuropathology (study of the actions of the drug on the nervous system) in the animals. Dr. Esposito explains, "This work will lead to more in-depth studies in the future to determine if repositioning pentamidine treatment in Parkinson's disease may represent an important innovation to improve the conditions of people living with PD."

Dr. Esposito recognizes the challenges of conducting movement disorder research. He explains, "I believe that one of the most important challenges in the field of movement disorder research, particularly in PD, is early diagnosis and the possibility to optimize the individual therapeutic approach for the patient. Early diagnosis implies a wide range of therapeutic options for the subjects, minimization of side-effects and huge achievement of therapeutic success. Today we are experiencing a total renewal of anti-PD drugs, beyond Levodopa, there is a new exciting world of molecules to be tested, that can be developed in the attempt to delay the disease progression and, at the same time, obtain a significant reduction of on-off phases that strongly limit in the time the patient's life quality. Pentamidine is one of them. It has the advantage to be quickly repositioned from laboratory research to being used in the clinics since it has been largely known as an antiprotozoal drug. We already know its potential toxic profile, and that it can be strongly limited by its intranasal administration."

Grant funding is essential to new discoveries and advancements. Dr. Esposito is grateful for the support of the PMDF and shares how this grant is fundamental to move their work toward future treatments. "This grant will help my group to determine if IN-pentasome works the way we expect it to, leading to clinical improvements in experimental PD in mice. We will also be able to determine if administering it as a nasal spray is as safe as we expect it will be."

Dr. Esposito strongly believes that new therapies for PD are right around the corner, "A more detailed understanding of neurological triggering factors, and early diagnosis are fundamental to achieve a new perspective of care. New approaches have to be developed, but also need to be looked at in a 360 degree view. Drugs capable of acting earlier, more effectively, and most importantly with fewer side effects, require a better knowledge of the mechanisms that predispose someone to PD."

Move4U 5K Walk/Run Fundraiser

Family Friendly Event

Mile Square Park
Group Shelter 17
Fountain Valley, CA

Saturday, May 11, 2019
8:30 am: Sign-In
10:00 am: Race Start Time
11:00 am: Lunch Available

First Place Prize–Helicopter Tour for 2 over Hollywood/ Downtown LA
Second Place Prize – To Be Announced
Third Place Prize - To Be Announced

Chance to win a prize in raffle drawing. Raffle prizes include: Target Gift Card, Starbucks Gift Card & More

$20 Entry Fee Per Person
Children ages 12 and under are free to attend

Free Street Parking

Lunch, T-shirt, Popcorn Chicken, and Beverages are provided for participants

Kid's Corner Featuring Fun Games Including Giant Four In a Row, Tumbling Tower, Corn Hole, & Tic Tac Toe!

Register online at: http://www.pmdf.org/events.php

Sponsors

US WorldMeds™ · Neurocrine Biosciences · Teva Pharmaceutical Industries Ltd. · Avanir Pharmaceuticals · Amneal · Allergan · Adamas™ · Mission Home Health · Home Care · Hospice · Whole Health Pharmacy · Alzheimer's Orange County · Phở K-tea · One Pharmacy

5K Run/Walk
Saturday
May 11, 2019
8:30 a.m.

Movement Disorders

Move4U 5k

Registration Form

Due to Park Regulations, Registration cannot take place at the park

NAME: _____

ADDRESS: _____

CITY: _____STATE:_____ZIP:_____

EMAIL: _____PHONE: _____

5K T-SHIRT SIZE (Circle One) Adult: S M L XL Minimum age of entry 13

How many child/children you will be bringing under 13: _____ (free)

IN CASE OF RAIN: The race will proceed as planned. We reserve the right to change the date under extreme circumstances.

ADDITIONAL DONATIONS

Donations are tax-deductible and an acknowledgement letter will be sent to the donor for tax purposes

Contributor Information			
First Name	Last Name	Mailing Address	Amount

ENTRY FEE(S) OR DONATION

Entry Fee: $_____ ($20)

Donation: $_____

Total: $_____

My Employer has a Matching Gift Program: $_____

Please make check payable to PMDF

Visa ( ) MasterCard ( )

_____
Credit Card No.

_____
Expiration Date

_____
CVV Code (last 3 digit on the back of your card)

Mail Entry Form & Payment to:
PMDF
14772 Moran St.
Westminster, CA 92683

For more information call: 714-369-7426

RELEASE FORM (all registrations must be signed)

I hereby waive any and all claims against PMDF, event sponsors, personnel, and all other persons, firms, corporations and/or entities or anyone associated with this event, their respective or successors, for any injury or claims for damages that I may suffer from participation in this event. I grant full permission for organizers to use photographs, videotapes, recordings or any other record for this event.

_____
Signature

_____
Date

_____
Signature of parent or guardian (if under 18 years old)

_____
Date

THE PARKINSON'S AND MOVEMENT DISORDER FOUNDATION
14772 Moran Street
Westminster, CA 92683
PMDF
www.pmdf.org

OUR MISSION

To support basic and clinical research into the causes, treatments and cures for Parkinson's disease and other movement disorders such as dystonia, myoclonus, spasticity, and tremor.

The Parkinson's and Movement Disorder Foundation is committed to working with other organizations that have similar philosophies in an effort to bring together expertise from both basic and clinical science perspectives.

We are dedicated to enhancing the quality of life for those who suffer from movement disorders and their families, through research, education, and community outreach.