Getting to Know Your 2019 PMDF 2nd Grant Winners

By April Ingram, Apr, 2019

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 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 (ie, 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]. 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."