American Parkinson Disease Association, Inc.

2015-2016 Proposal Form

Instructions for Proposal Form:

* Provide a brief bio and picture for use on the APDA website and APDA publications

* Provide a description in donor terms of the aims of the grant/fellowship for the 12 month period

* Submit this form electronically, no later than July 1, 2015, to hgray@apdaparkinson.org

USE YOUR INDIVIDUAL FORM, FOLLOWING THE OUTLINE BELOW:

Name of Institution:

Mayo Clinic Jacksonville, Department of Neuroscience

Project Title:

Pathophysiological relevance of phospho-ubiquitin to genetic and environmental Parkinsonism

Investigators/Authors Bio/Pictures:

Fabienne Fiesel, PhD, is an Instructor for Neuroscience in the Department of Neuroscience at Mayo Clinic in Florida. She received her MSc in Biology from the University of Stuttgart in 2005 and earned a PhD in 2010 from the Eberhard-Karls-University in Tuebingen, Germany. She then continued her training as a post-doctoral fellow in the laboratory of Dr. Philipp Kahle at the Hertie-Institute for Clinical Brain Research, Germany before joining the lab of Dr. Wolfdieter Springer at Mayo Clinic, Jacksonville in late 2011. She is interested in the molecular and cellular mechanisms contributing to Parkinson's disease (PD) and has developed screening assays for the detection of Parkin activation by automated High Content imaging. These have been used to identify Parkin's coenzymes in a functional genetics approach and to determine defects of Parkin mutations that have been genetically associated to PD.

Objective:

To determine the amount and location of phospho-ubiquitin in human fibroblasts from PINK1 and Parkin mutation carriers upon stress and to quantify phospho-ubiquitin in human sporadic PD brain samples.

Background:

Phosphorylation of ubiquitin has been just recently discovered. It occurs upon mitochondrial stress and is mediated by the mitochondrial kinase PINK1 and amplified by the E3 ubiquitin ligase Parkin. Notably, PINK1 and Parkin are mutated in forms of early-onset familial recessive PD and are critically involved in a mitochondrial quality control pathway. Parkinsonism-inducing toxins have been shown to damage mitochondria either directly or indirectly and mitochondrial dysfunction is observed early during pathogenesis of familial and sporadic disease. The goal of this study is to elucidate the presence of mitochondrial stress upon treatment of cells with PD toxins and in human brain samples from patients

with sporadic PD.

Methods/Design:

High content imaging of skin fibroblasts from PINK1 and Parkin patients and controls will be performed to assess the localization and amount of phospho-ubiquitin upon treatment of cells with PD toxins. Human brain samples will be used to study the amount of phospho-ubiquitin in sporadic PD patients versus controls.

Relevance to Diagnosis/Treatment of Parkinson's disease:

Mitochondrial dysfunction is increasingly appreciated as a key determinant of dopaminergic neuronal susceptibility in PD and is a feature of both familial and sporadic disease, as well as in toxin-induced Parkinsonism. This study will help to better determine the role of mitochondrial dysfunction for disease pathogenesis and will help to establish mitochondrial quality control as a potential therapeutic target.