

Influence of ovarian hormones on the expression of parkinsonism and LIDs

Ellen J. Hess, PhD., Principal Investigator

Biological sex is a risk factor in Parkinson's disease (PD). Males are more likely to develop PD and have an earlier age of onset than females. Disease presentation also differs with males exhibiting more bradykinesia and rigidity than females whereas females tend to have tremor-predominant PD. In later stages, females exhibit more severe L-DOPA-induced dyskinesias (LIDs) than males. Although small clinical studies implicate estrogens in the sex-biased features of PD and LIDs, the findings are inconsistent. Because systematic clinical studies are lacking and little basic research has focused on the question, the mechanisms underlying sex differences in PD and LIDs are not understood. To begin to address this gap in knowledge, we will test the hypothesis that *estradiol mediates parkinsonism and the pathogenesis and severity of LIDs* in a mouse model of parkinsonism and LIDs by experimentally manipulating ovarian hormones. To accomplish this, 6OHDA-treated mice will be ovariectomized and challenged with estrogen or progesterone or vehicle before, during and after the induction of LIDs to identify the effect of each hormone on the severity parkinsonism and the severity and time course of the development of LIDs. Based on the very limited information available, we expect estrogen to reduce the severity of LIDs while progesterone may have little effect or exacerbate LIDs. Regardless of the results, the proposed work has immediate implications because it is not known if hormone replacement therapy in postmenopausal women is therapeutic or contraindicated for PD, particularly for the development of LIDs. Further, it is also critical to identify the role of both estrogen and progesterone since anecdotal evidence suggests that estrogen and progesterone may have opposing effects, which has implications for the specific formulation of hormone replacement therapy appropriate for females with PD.

Translation of LRRK2-specific PET radiopharmaceuticals in humans

Steven Liang, PhD, Principal Investigator; David Schuster, MD, Co-investigator

Mutations in LRRK2 are the most common cause of familial Parkinson's disease (PD). The most common LRRK2 variant, G2019S, is present in more than 85% of PD patients carrying LRRK2 mutations. This mutation, which occurs within the LRRK2 kinase activation loop, leads to increased LRRK2 activity and expression. As a non-invasive imaging technology, PET is capable of quantifying biochemical processes *in vivo*, and a suitable PET ligand would substantially improve our understanding of LRRK2 signaling under disease conditions otherwise inaccessible by *ex vivo* (destructive) analysis. Furthermore, quantification of LRRK2 in living brain by PET would provide the assessment of distribution, target engagement and dose occupancy of novel LRRK2-targeted neurotherapeutics.

In 2022, the PI developed the first and only validated LRRK2 PET ligand, namely [18F]PF-943, in cross-species studies (transgenic LRRK2-G2019S mutant mouse models and nonhuman primates). The ligand is highly potent and selective among all the LRRK2 inhibitors reported to date. Preliminary PET imaging in NHPs confirmed that we have overcome the two major obstacles for LRRK2 ligand development by achieving high brain uptake and high target specificity. However, LRRK2-targeted PET imaging has not yet been conducted in humans (PD patients and age-matched healthy controls) and *in vivo* evidence in living Parkinson's brain is still deficient in demonstrating the underlying mechanism between LRRK2 dysfunction and PD. The availability of [18F]PF-943 now provides a unique opportunity to address this unmet clinical need. Therefore, we will take advantage of Udall pilot grant support to complete key regulatory components, including radiation dosimetry, toxicological study and CMC production validation. The successful completion of this work will enable us to file an FDA IND Application under PET drug 21CFR212 and obtain IRB approval for first-in-human study, which ultimately serves as a molecular imaging tool for industry-sponsored trials and/or strong preliminary data for NIH applications.

Novel lipid transfer pathway between erythrocytes and plasma Provides a Parkinson's diagnostic strategy

Fathima Shaima Muhammed Nazaar, PhD, Principal Investigator; Blaine R. Roberts, PhD, Co-Investigator

Diagnosis of idiopathic Parkinson's disease (PD) is a major challenge, and unlike Alzheimer's disease, the field is still without accurate molecular diagnostic tools (e.g., blood tests and imaging). To address this gap, we recently completed a Michael J. Fox foundation-funded project to conduct lipidomic analysis on paired red blood cells and plasma from a cohort of PD and control cases (n=284). We discovered over 150 differentially expressed lipids, with approximately 10 that have the potential to serve as a lipid biomarker panel for PD. During this project, we made the surprising discovery that many of the lipids in red blood cells that accumulate in PD are depleted in plasma. This was contrary to the hypothesis that lipid signatures in the RBCs would be reflected in plasma. The discordance in the changes in lipid abundance between RBC and plasma suggests a novel active lipid transport or metabolic process. The purpose of this study is to determine if the proteins involved in lipid metabolism and transport are also differentially regulated in RBC. The results from this study, combined with data collected in our MJFOX grant, will be used to submit an RO1 application in 2023.