PROJECT TITLE: **Alpha-synuclein-specific autoantibodies fuel neurodegeneration in Parkinson’s disease**

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**Project Description**

1. **Area of the Research** - Neuro-immunology
2. **Research tasks that student will perform.** The overarching goal of this research mission is to investigate the mechanism by which aggregated-alpha synuclein (Agg-Î±syn) triggers brain inflammation and neurodegeneration in Parkinson’s disease (PD). These studies will more precisely investigate the impact of targeting Fc gamma receptors for IgG (FcγR), leading to a reduction of brain inflammation and neurodegeneration in PD. In preliminary data, we have identified high brain levels of pro-inflammatory cytokines and immunoglobulin G2a/c (IgG2a/c) antibodies specific to Agg-Î±syn in two murine models of synucleinopathies, i.e., (1) GbaD409/D409 and a (2) chemically (conduritol B epoxide; CBE) induced glucocerebrosidase (GCase)-targeted mouse model. Ouchterlony double immunodiffusion performed between the sera (prepared from the GbaD409/D409 and CBE-induced GCase-targeted mouse models) and aggregated Î±-syn showed a strong precipitin line between the sera and aggregated Î±-syn. These findings suggested the development of Agg-Î±syn-specific immune complexes (Agg-Î±syn-ICs) in PD. Brain reactive antigens, autoantibodies and their link to FcγR effector function cause loss of blood-brain barrier integrity and neurodegeneration in aging and several neurodegenerative diseases. We will therefore test the central hypothesis that activating FcγR-Agg-Î±syn-ICs interactions lead to the generation of pro-inflammatory cytokines, eventually leading to brain inflammation and neurodegeneration in models related to PD and that pharmacological blockade of activating FcγR-mediated signaling could be a potential alternative therapy for PD and other synucleinopathies. Targeting FcγR-Agg-Î±syn-ICs pathways will help to understand disease mechanisms and development of
alternative therapy for PD.

3. Training that the mentor will provide to the WISE student. Student will learn and perform following procedures.
   a. Mice genotyping. This study will use (1) Gba D409+/- (i.e., that reduce GCase activity by ~25-50%, analogous to what is observed in PD with GBA) and their background-matched wildtype (both are available to PI lab) mice.
   b. Human iPSCs. This proposal will involve use of normal human iPSCs-differentiated dopaminergic neurons and/or microglia (growing in PI lab).
   c. Pharmaceutical blockade of activating FcγR-down stream signaling, with use of Syk kinase inhibitors in mouse and in vitro-human models of PD.
   d. Mouse and human microglial cells and neurons identification by FACS.
   e. Gene and protein expression of pro-inflammatory cytokines specific to autoimmunity with uses of ELISA, westernblotting, and PCR approaches.

4. Specific requirements, if any, that the mentor expects the student to meet. Interested student should be from one of the indicated field, (e.g., molecular biology/cell biology/ neuroscience/biochemistry/immunology/system-biology/biotechnology/medicine). Ideal students should be quick learners, hard working, and have good written and verbal communication skills.