

UC-DEPARTMENT OF PEDIATRICS
DIVISION OF HUMAN GENETICS, CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

SUMMER RESEARCH OPPORTUNITIES FOR UNDERGRADUATE students

FOR APPLICATION YEAR: 2024

PROJECT TITLE: Cracking pulmonary threats: Dissecting the complement 5a enigma in Parkinson's disease-associated lung inflammation

Manoj Pandey
Division of Human Genetics
Cincinnati Children's Hospital Medical
Center
College of Medicine, University of
Cincinnati
Location R1.019A,
3333 Burnet Avenue, MLC-7016
45229-3039 Cincinnati, OH USA.
Phone: 513-803-1694
Fax: 513-636-4373
Email: manoj.pandey@cchmc.org
Website: <https://www.cincinnatichildrens.org/bio/p/manoj-pandey>

Project Description

Mutations in the glucocerebrosidase (GBA) gene, linked to Gaucher's disease, are identified as a novel genetic risk factor for Parkinson's disease (PD), particularly in 5% of the overall PD population and a substantial 40% of cases with African ancestry. PD patients, regardless of African ancestry, also face a heightened risk of developing various lung abnormalities, including chronic obstructive pulmonary disease, asthma, and respiratory failure. Using GBA1 mouse models of Gaucher's disease and a hypoxia-induced mouse model, we have demonstrated the critical role of the C5a-C5aR1 axis in activating innate and adaptive immune responses, leading to lung damage in these diseases. Genetic deficiency or pharmaceutical blockade of the C5-C5aR1 axis has shown significant reduction in inflammation and protection from lung tissue damage in Gaucher's disease (Nature 2017: 543, 108-112 and Am J Respir Cell Mol Biol 2019, 60; 1: 106-116).

Therefore, this UC 2024 UPRISE Program- proposal seeks to investigate the role of Complement 5a (C5a) in orchestrating lung inflammation in Parkinson's Disease (PD). Our objectives encompass the analysis of C5a expression in lung tissues affected by PD, establishing correlations with the severity of inflammation, and elucidating the complex molecular pathways through which C5a contributes to pulmonary inflammation. Methodologically, we will examine lung tissues from the BLACK- GBA prone (GBA+/-) mouse model of PD and

background-matched C57BL/6 WT mice to assess C5a and C5aR1 receptor activation. The study will evaluate the impact on immune cell infiltration, activation (including macrophages, dendritic cells, and T cells), and the production of pro-inflammatory cytokines that lead to tissue damage in PD.

Anticipated outcomes include insights into the impact of the C5a-C5aR axis on altering innate and adaptive immune responses in PD-affected lungs, correlations with inflammation, and mechanistic insights. This research, slated for execution within the designated timeframe (May 6 - July 26), holds the promise of transcending current paradigms, providing crucial insights into the systemic dimensions of PD, and paving the way for innovative, targeted therapeutic interventions.