DEPARTMENT OF NEUROLOGY

Parkinson's Disease Research Progress Report

Thanks to generous support of visionary philanthropic partners like you, researchers at the University of Alabama at Birmingham (UAB) and the Center for Neurodegeneration and Experimental Therapeutics (CNET) are making tremendous progress in finding disease-modifying treatments for Parkinson's disease.

As a disease that affects more than 1 million Americans, Parkinson's impacts people of every socioeconomic background and ethnicity. This is expected to rise to 1.2 million by 2030. Around 60,000 Americans are diagnosed with Parkinson's disease each year, and more than 10 million people worldwide are living with it. Philanthropic support helps bring real breakthroughs closer to people living with Parkinson's disease and is critical to advancing the most promising research.

We leverage gifts to garner additional funding from other private donors, nonprofit organizations, and federal agencies like the National Institutes of Health (NIH). Your support enables us to provide unsurpassed care to the more than 7,000 patients each year at the UAB Movement Disorders Clinic. It has assisted us in becoming one of six NIH-funded Morris K. Udall Centers of Excellence in Parkinson's Disease Research in the U.S. Because of you, we're one step closer to finding disease-modifying treatments for Parkinson's disease.

For more than 10 years, UAB has been a national and international leader in Parkinson's disease research because we recruit and retain some of the best and brightest in the field. Here, we spotlight their research efforts aimed at new treatments in Parkinson's disease.

UAB HEERSINK SCHOOL OF MEDICINE

The University of Alabama at Birmingham

Parkinson's Disease Research Advances

DAVID G. STANDAERT, M.D., PH.D., PROFESSOR AND CHAIR

JOHN N. WHITAKER ENDOWED CHAIR IN NEUROLOGY

Dr. Standaert is studying the factors that cause Parkinson's disease and the effects of Parkinson's disease treatment on brain function. His research emphasizes that changes in the immune system may be critical to the progression of Parkinson's disease. Although there may be several upstream triggers for Parkinson's, this novel approach suggests that inflammation is responsible for progression after the degenerative process starts. We have important new evidence that indicates the significance of these mechanisms, and we are seeking a more powerful and targeted inhibitor of the Parkinson's disease-specific immune response to halt progression of the disease.

This work is the focus of our Morris K. Udall Center of Excellence in Parkinson's Disease Research, recently established at UAB by the National Institutes of Health. This Center, funded by an award of nearly $10 million and one of only six such centers in the United States, is leading the nation in exploring the role of the immune system in Parkinson's disease and the potential of immune-modulating therapies as treatments to slow the progression of the disease.

Dr. Standaert's lab is also studying the side effects of PD treatment, especially wearing off and dyskinesias seen when patients are treated with levodopa. Using advanced technologies, we are able to study changes in gene expression in individual neurons. This work is revealing new approaches to controlling these side effects and improving the outcomes of treatment.

BRIANA DE MIRANDA, PH.D., ASSISTANT PROFESSOR

Dr. De Miranda is a neurotoxicologist and studies the effects of environmental exposures on Parkinson's disease risk. Her lab investigates the mechanisms of toxicity to dopamine neurons from common environmental contaminants linked to Parkinson's disease, such as pesticides, metals, and organic solvents. The goal of this work is to prevent Parkinson's disease onset from occurring in individuals who are exposed to these ubiquitous chemicals. In addition, by understanding the mechanisms of neurotoxicity caused by exposure, therapeutic targets can be identified that may slow or stop Parkinson's progression. Dr. De Miranda's lab is funded by the National Institute for Environmental Health Sciences (NIEHS).

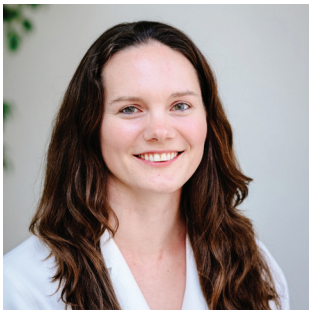
MATTHEW GOLDBERG, PH.D., ASSOCIATE PROFESSOR

CHARLES S. ACKERMAN ENDOWED PROFESSOR IN PARKINSON RESEARCH

Dr. Goldberg studies mutations in the Parkin gene and the PINK1 gene that cause early-onset Parkinson's disease. His lab uses cultured cells and animal models bearing these mutations to study disease mechanisms and to identify therapeutic targets. Grants from the Michael J. Fox Foundation for Parkinson's Research fund his ongoing projects to map the normal functions of Parkin and PINK1 that are vital to maintain healthy dopaminergic neurons and to develop strategies to enhance or restore the functions of PINK1 and Parkin that might prevent or slow Parkinson's disease progression.

ASHLEY HARMS, PH.D., ASSISTANT PROFESSOR

Dr. Harms has a background in studying both Parkinson's disease and immunology. She is studying the interaction of the peripheral immune system—including cells circulating in the blood—with the brain inflammation that develops in Parkinson's disease. She has found that brain injury in Parkinson's disease models signals immune cells, specifically T cells, to enter the brain, and these infiltrating "invaders" are a key to the injury to dopamine neurons. Blocking the entry of those T cells is an important new approach to prevent or slow Parkinson's disease in lab models. Due to her success in studying the role of immune cells in lab models, Dr. Harms was recently awarded two multi-million dollar Aligning Science Across Parkinson's awards to study the role of the immune system, specifically T cells, in Parkinson's disease progression. Her other work is funded by the National Institutes of Health and the Michael J. Fox Foundation.



KAREN JAUNARAJS, PH.D., ASSISTANT PROFESSOR

Dr. Jaunarajs uses animal models to study the mechanisms that underlie hyperkinetic movement disorders, including dystonia and a side effect of Parkinson disease medication termed L-DOPA-induced dyskinesia. Dr. Jaunarajs has found that several different genetic forms of dystonia share common dysfunction of a particular neuron subtype known as striatal cholinergic interneurons and current work is seeking to understand the repercussions of this dysfunction on brain circuits. Her work on L-DOPA-induced dyskinesia is seeking to discover the "program" of gene expression that leads to movement dysfunction and which particular cell subtypes are involved by using cutting-edge technology called single-nuclei RNA-sequencing. She has received funding from the Dystonia Medical Research Foundation and the American Parkinson Disease Association.

HAYDEH PAYAMI, PH.D., PROFESSOR

JOHN T. AND JUANELLE D. STRAIN ENDOWED CHAIR IN PARKINSON RESEARCH

A world-renowned geneticist and scientist in Parkinson's disease, Dr. Payami's goals are to prevent Parkinson's disease in individuals who are at risk and to stop its progression in individuals who have it. To those ends, Dr. Payami investigates the human genome and the gut microbiome. She observes how they interact with the environment to cause and drive the progression of Parkinson's disease. Her team also studies how each individual's unique genes, microbiomes, and environments influence the effectiveness of medications so that treatments can be customized for each individual's maximum benefit. Her work is supported by grants from the US Army, and the Michael J Fox Foundation ASAP Collaborative Research Network.

LAURA A. VOLPICELLI-DALEY, PH.D., ASSOCIATE PROFESSOR

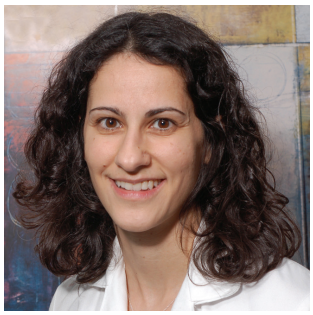
PARKINSON ASSOCIATION OF ALABAMA ENDOWED SCHOLAR IN PARKINSON'S RESEARCH

Clumps of a protein called α-synuclein found in the brain characterize Parkinson's disease. Dr. Laura Volpicelli-Daley's lab is interested in the impact of early formation of these aggregates on synaptic transmission. The goal is tointervene early in the disease process to halt the progression of the PD before neurons die. Her lab also studies how genes implicated in PD such as LRRK2 and GBA influence the formation of α-synuclein aggregates. Working with Merck Pharmaceuticals, Dr. Volpicelli-Daley's group found that mutations in the GBA gene, which increase PD risk, dramatically increase the abundance of α-synuclein aggregates in the brain, particularly in a brain region called the hippocampus which is important for memory. The lab also found that inhibitors of LRRK2 currently in pre-clinical trials for PD increase the normal form of α-synuclein and thus may prevent α-synuclein from taking on a form that leads to defective synaptic transmission.

Dr. Volpicelli-Daley is also Director of the Animal Models Core of the Morris K. Udall Center of Excellence in Parkinson's Disease Research. The model she helped developed, the fibril model, is one of the most used rodent models in the PD field. The Core assists research projects determining the impact of the immune system in progression of PD and ensures projects are reproducible. The lab is also funded by R56 and R01 awards from the NIH. Dr. Volpicelli-Daley. She is also a collaborator for projects at the University of Washington, Massachusetts General Hospital, Yale University, and the Van Andel Institute.

HARRISON WALKER III, M.D., PROFESSOR

Dr. Walker is a physician scientist with expertise on deep brain stimulation (DBS) and neuromodulation. DBS is more effective than medications and other conventional therapies for motor symptoms of Parkinson's disease, dystonia, and essential tremor. Emerging DBS technologies have substantial potential to improve a variety of patient outcomes. However, these devices are increasingly adaptable and complex, and we lack robust tools to fully realize their clinical potential. Dr. Walker's lab investigates how deep brain stimulation works with electroencephalography, cortical and subcortical field potentials, single unit recordings, and behavioral assessment in patients with movement disorders. His goal is to obtain new knowledge about the therapeutic mechanism of DBS and apply these findings to guide technological innovation, both for established indications and for emerging indications in neurology and psychiatry. Currently his research is supported by grants from the NIH BRAIN Initiative and the Michael J. Fox Foundation. Dr. Walker also serves as chair of the NIH BRAIN Initiative study section (NSD-C) that evaluates first-in-human neuromodulation studies in patients with Parkinson disease and other complex neuropsychiatric disorders.



TALENE YACOUBIAN, M.D., PH.D., PROFESSOR

JOHN A. AND RUTH R. JURENKO ENDOWED PROFESSOR IN NEUROLOGY

Dr. Yacoubian is a physician scientist pursuing translational research in Parkinson's disease. Her research laboratory is focused on understanding the mechanisms underlying neurodegeneration in Parkinson's disease and related neurodegenerative diseases. She and her team have discovered that changes in the 14-3-3 chaperone proteins have significant implications for the development and progression of Parkinson's disease and Lewy body dementia. Her group recently discovered that boosting 14-3-3 protein levels can slow the misfolding and spread of alpha-synuclein, a key protein implicated in Parkinson's disease and Lewy body dementia. Her group is now focused on understanding how the function of these proteins are disrupted in disease.
Additionally, she has identified a novel trafficking protein, Rab27, that dramatically regulates the spread of alpha-synuclein in PD models. She leads the Udall Clinical Research Core, which is responsible for the longitudinal clinical and immunological assessment of subjects with newly diagnosed Parkinson's disease. Her work is funded by the NIH and the American Parkinson Disease Association.

Therapeutic Discovery

The primary focus of our work is the discovery and development of new treatments, and ultimately, a cure for Parkinson's. We have well-established drug discovery programs around several targets including the enzyme LRRK2, which is over-active in PD, and the protein 14-3-3, which seems key in managing misfolded alpha-synuclein. We have been awarded a patent for a highly specific LRRK2 inhibitor and are pursuing licensing to pharma companies for further development. We have several promising drugs in development based on actions at 14-3-3. We are also developing new approaches based on modulation of inflammation, PINK1 and Parkin, and approaches to changing the aggregation of alpha-synuclein.

I WANT TO THANK OUR PHILANTHROPIC PARTNERS. YOUR SUPPORT IS VITAL TO PROGRESSING ADVANCES IN PARKINSON'S DISEASE RESEARCH. WITHOUT YOU, THIS WOULD NOT BE POSSIBLE.

RAY L. WATTS, M.D., UAB PRESIDENT, PROFESSOR, DEPARTMENT OF NEUROLOGY

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