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 new 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 1.5 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 (including more than 10,000 in Alabama). Philanthropic support helps bring real breakthroughs closer to people living with Parkinson's disease and is critical to advancing the most promising research.

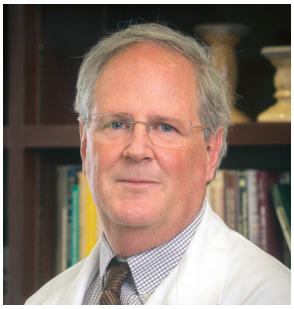
We leverage gifts to garner additional funding from other private donors, nonprofit organizations, and federal agencies like the National Institutes of Health (NIH). Your support enables us to provide unsurpassed care to the more than 8,000 patients each year at the UAB Movement Disorders Clinic. It has assisted us in becoming one of five 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, established at UAB by the National Institutes of Health. This Center, funded by an award of nearly $10 million and one of only five 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
PATSY W. AND CHARLES COLLAT SCHOLAR IN NEUROSCIENCE

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, heavy metals, and organic solvents. One goal of this work is to prevent Parkinson's disease onset from occurring in individuals who are exposed to these ubiquitous environmental pollutants. Another key goal of her research is to uncover mechanisms of neurotoxicity that can be targeted for therapeutic development to slow or stop Parkinson's progression. Her lab is also currently investigating how environmental exposures may accelerate brain aging as a mechanism of neurodegeneration, and working to identify ways to intervene in this process. Dr. De Miranda's lab is funded by the National Institute for Environmental Health Sciences (NIEHS), the Parkinson's Foundation, the US Department of Defense, and the American Parkinson's Disease Association.

MATTHEW GOLDBERG, PH.D., ASSOCIATE PROFESSOR
CHARLES S. ACKERMAN ENDOWED PROFESSORSHIP IN NEUROLOGY

Dr. Goldberg is an expert on inherited forms of Parkinson's disease caused by mutations in the Parkin gene and the PINK1 gene. Dr. Goldberg also studies the interface between aging, inflammation and Parkinson's disease. His laboratory uses cultured cells and animal models bearing Parkin and PINK1 mutations to better understand what causes Parkinson's disease and to identify novel targets for therapeutic development. The Goldberg laboratory is testing the ability of Parkin to protect against loss of neurons in the substantia nigra and thereby protect against the development or progression of Parkinson's disease motor symptoms.

ASHLEY HARMS, PH.D., ASSOCIATE PROFESSOR
WILLIAM A. MAJOR ENDOWED FACULTY SCHOLAR IN PARKINSON'S DISEASE

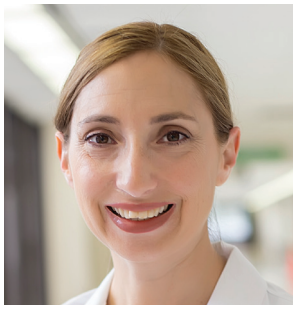
Dr. Harms has a background in studying both Parkinson's disease and immunology. She is studying the interaction of the peripheral immune system—including cells circulating in the blood—with the brain in the context of inflammation that develops in Parkinson's disease. She has found that brain injury 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 promotion and tenure in the department of neurology. Her work is funded by the National Institutes of Health, the Michael J. Fox Foundation, and Aligning Science Across Parkinson's (ASAP).

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, the American Parkinson Disease Association, and the Department of Defense.

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 and how they interact with the environment, diet and exposures 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. The U.S. Army awarded Dr. Payami a 2.5 million dollar grant to study the interactive effects of genes, environment, and the gut microbiome on Parkinson's disease, and the findings were so promising that she was awarded a 1.6 million dollar grant by Aligning Science for Parkinson Disease / Michael J Fox Foundation to continue the work as part of an international Collaborative Research Network committed to open science. In a ground-breaking paper in Nature Communication (4th on Top 25 Life and Biological Sciences Articles of 2022), the team led by Dr. Payami revealed ways in which gut microbes contributes to mechanisms that drive Parkinson's disease, opening new critical areas for research, as well as microbiome-based therapeutics to slow disease progression.



LAURA A. VOLPICELLI-DALEY, PH.D., ASSOCIATE PROFESSOR
PARKINSON ASSOCIATION OF ALABAMA ENDOWED PROFESSORSHIP IN NEUROLOGY

One of the primary hallmarks of Parkinson's disease (PD) is the aggregation of a protein called α-synuclein. Increasing evidence suggests that abnormal α-synuclein contributes to symptoms of PD such as cognitive changes, anxiety, depression, and sleep abnormalities. The goal of Dr. Laura Volpicelli-Daley's lab is to prevent α-synuclein aggregation to prevent development of these symptoms. Laura's lab recently discovered that α-synuclein aggregates in brain regions such as the amygdala and prefrontal cortex cause behavior phenotypes in mice that are related to anxiety and cognitive changes. Thus, this model can help us discover therapeutic strategies to prevent α-synuclein pathology in these brain areas. Working with Merck Pharmaceuticals, Laura's lab has also found that mutations in the GBA1 gene which increase PD risk and risk of cognitive decline, dramatically increase the abundance of α-synuclein aggregates in the hippocampus, a brain area important for memory. We also found that mutations in this gene increase levels of a lipid, glucosylsphingosine. These findings were recently accepted as a manuscript in the Journal of Neuroscience. We were awarded an NIH R01 grant to study the role of glucosylsphingosine in cognitive decline in PD. We will be collaborating with the Italian Institute of Technology who developed a compound that reduces glucosylsphingosine levels. We are also collaborating with Columbia University to test glucosylsphingosine levels in the brains of individuals with GBA1 mutations. We hope our findings will lead to development of a treatment to prevent cognitive symptoms in PD.

HARRISON WALKER III, M.D., PROFESSOR

Dr. Walker is an expert on deep brain stimulation (DBS) for movement disorders. 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, electrocorticography, single unit recordings, neuroimaging, 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 NIH.

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 Dementia with Lewy bodies. 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, and is now trying to understand the mechanisms that cause the disruption of 14-3-3 function in human disease. Additionally, she has identified a novel trafficking protein, Rab27, that dramatically regulates the spread of alpha-synuclein in Parkinson's disease models. She also leads the Alabama Udall Clinical Research Core, which is responsible for the longitudinal clinical and immunological assessment of subjects with newly diagnosed Parkinson's disease. Through this work, her group has found increased brain and systemic inflammation in early Parkinson's disease. Her work is funded by the NIH, the Michael J Fox Foundation, 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.

"THANK YOU FOR THE TREMENDOUS IMPACT YOU ARE MAKING ON PARKINSON'S DISEASE RESEARCH AT UAB. YOUR PARTNERSHIP IS A DRIVING FORCE BEHIND OUR PROGRESS TO DATE AND AN ONGOING INSPIRATION TO OUR PHYSICIANS AND SCIENTISTS AS THEY PURSE NEW TREATMENTS THAT WILL ULTIMATELY BENEFIT THE PATIENTS WE SERVE."

RAY L. WATTS, UAB PRESIDENT AND CHARLES S. ACKERMAN ENDOWED PROFESSOR OF NEUROLOGY

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