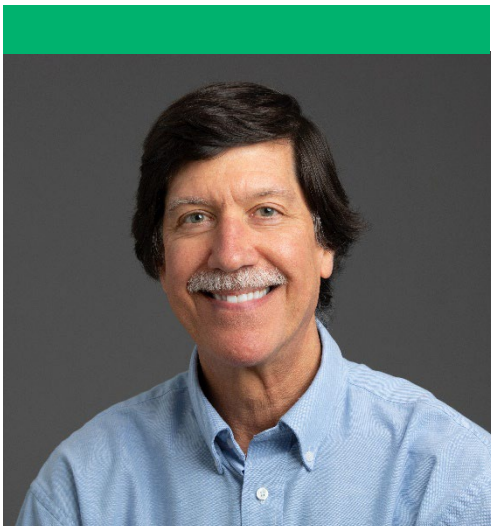
RUSH

David A. Bennett, MD

The Robert C. Borwell Professor of Neurology



Advancement of Medicine

In 2023, we continued efforts that began more than 25 years ago when we started to systematically build a platform for novel drug discovery for neurologic conditions of the central nervous system.

Over time, we have identified numerous risk factors for loss of cognitive and motor function, numerous pathologies and numerous resilience factors. We are now discovering new potential therapeutic targets to treat and prevent loss of cognitive and motor function.

Over the past 10-plus years, we have generated an unprecedented multi-omic multi-brain region database to drive drug discovery in the cognition space as well as motor function, complementing it with omic data generation in spinal cord and muscle and in multiple sclerosis.

Research

- Your support enabled us to complete one study illustrating cell type differences in non-lesional white and gray matter tissue in individuals with multiple sclerosis.
- Another investigated the biology of function MRI, which has long been an enigma. We are the only group with autopsies on persons with functional MRI proximate to death. We identified hundreds of proteins that explain between-individual differences in functional connectivity.
- We have the only study in the world with autopsies on persons with dietary interview data. The MIND and Mediterranean diets, especially green leafy vegetable intake, was associated with less Alzheimer's disease pathology.
- Finally, taking advantage of more than three decades of autopsies, we showed that Alzheimer's disease pathology has been stable, but brain vascular disease has come down steadily, contributing to a reduction in age-specific prevalence of dementia.
- Your generosity enabled us to supplement two full professors, each of whom have secured millions of dollars in external funding for Rush.

RUSH

Publication Highlights – Abbreviated

- "Human disease-specific cell signatures in non-lesional tissue in multiple sclerosis detected by single-cell and spatial transcriptomics," *bioRxiv Journal*. December 2023.
- "A molecular basis of human brain connectivity," *bioRxiv Journal* [Preprint]. July 2023.
- "Association of Mediterranean-DASH intervention for neurodegenerative delay and Mediterranean diets with Alzheimer disease pathology," *Neurology*. May 2023.
- "Trends in postmortem neurodegenerative and cerebrovascular neuropathologies over 25 years," *JAMA Neurology*. April 2023.

Grants

In August 2023, Dr. Bennett received "Whole Genome Sequencing and Admixture Analyses of Neuropathologic Traits in Diverse Cohorts in USA and Brazil," a multimillion-dollar grant to conduct genetic sequencing for the remaining Rush Alzheimer's Disease Center participants and a large study in Brazil with a focus on African ancestry.

In April 2023, Dr. Bennett received a multimillion-dollar grant to identify and quantify the demand for and access barriers to potential dementia treatments from non-Hispanic Black stakeholders' perspectives.

Other grants and subcontracts include:

- "Defining the effect of Alzheimer pathologies on the aged brain in 3 dimensions," co-investigator.
- "Child and adult metal exposures, gene expression and neuropathologically confirmed Alzheimer's disease," co-investigator.
- "Brain glycosphingolipids and Alzheimer's disease," co-investigator.

The Year Ahead: 2024 and Beyond

After generating an unprecedented multi-omic brain platform for novel drug target discovery in the human brain from non-Latino whites, we are now generating multi-omic data from blood from the same individuals to predict the brain omics. Second, we are embarking on an ambitions study in Brazil with thousands of diverse brains to generate a similar platform. Finally, we are generating brain

cell lines from our autopsied participants so we can do experiments that get us closer to precision medicine for brain diseases.

With Gratitude

Thanks, as always, Herb, for generously supporting our work.