RUSH

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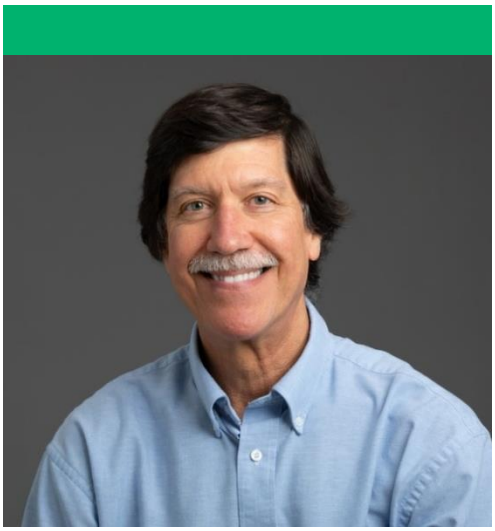

Advancement of Medicine

Over the past three decades, we have systematically built a platform to identify risk factors and novel drug discovery for neurologic conditions of the central nervous system. We 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 cognitive and motor function loss. Over the past 15 years, we have generated an unprecedented multi-omic, multi-brain region and blood database to drive drug discovery in the cognition space. It also drives discovery in the motor function space, as it generates omic data for spinal cord and muscle conditions and multiple sclerosis. Finally, we generated induced pluripotent stem cells on 110 autopsied participants, with another 70 under construction and funding for an additional 30. Rush Alzheimer's Disease Center, or RADC, resources are distributed globally via our Resource Sharing Hub.

Research

The current National Institutes of Health salary cap cannot entirely cover the salary of senior investigators who receive full project funding from federal sources. Thus, the proceeds from the chair were used to supplement two full professors with a long track record of bringing millions in external funding to Rush.

Grants

In May 2024, **Jinying Zhao, MD, PhD**, director of the Center for Genetic Epidemiology and Bioinformatics at the University of Florida, and I, along with colleagues, received a multimillion-dollar grant to characterize the N-glycome in relation to aging and Alzheimer's disease.

In September 2024, **Francine Grodstein, ScD**, epidemiologist at the RADC, colleagues and I received a multimillion-dollar grant to do cognitive testing and genetic sequencing of 18,000 people across 11

Mexican states to identify genomic variants for cognition in persons of Native Mexican, European and African ancestries.

In December 2024, I received a multimillion-dollar grant from the Paul M. Angell Family Foundation to identify brain molecular pathways to Alzheimer's disease, build predictive models from clinical data and perform drug screens in brain organoids, all from the same participants.

Publication Highlights – Abbreviated

- Oveisgharan S, et al. Association of age-related neuropathological findings at autopsy with a claims-based epilepsy diagnosis in older adults. *Neurology*. 2024 Apr 9;102(7):e209172.
    - Here, we leverage our unique resource of clinical data linked to Medicare claims data with brain pathology to identify brain pathologies associated with epilepsy in later life.
- Trumpff C, et al. Psychosocial experiences are associated with human brain mitochondrial biology. *Proc Natl Acad Sci USA*. 2024 Jul 2;121(27):e2317673121.
    - Here, we leverage our unique resource of clinical data, including a wide range of psychological factors with brain pathology and molecular omics, and find differences in mitochondrial biology related to psychosocial traits.
- Mathys H, et al. Single-cell multiregion dissection of Alzheimer's disease. *Nature*. 2024;632(8026):858-868.
    - Here, we leverage our unique resource of clinical data with brain pathology, molecular omics and brain tissue to generate the first single-cell RNAseq multi-region dataset from the human brain and identify cell-specific pathways associated with resilience to common brain pathologies.
- Li J, et al. The MIND diet, brain transcriptomic alterations, and dementia. *Alzheimers Dement*. 2024 Sep;20(9):5996-6007.
    - Here, we leverage our unique resource of clinical data, including a detailed food frequency questionnaire from which we developed the MIND diet, with brain pathology and molecular omics to identify a transcriptomic signature of the MIND diet and show that it can predict cognitive decline.

- Green GS, et al. Cellular communities reveal trajectories of brain ageing and Alzheimer's disease. *Nature*. 2024 Sep;633(8030):634-645.
    - Here, we leverage our unique resource of clinical data with brain pathology and deep sequencing to identify novel brain pathways that underlie aging and Alzheimer's disease.

Invited Presentations – Abbreviated

- Embracing Complexity. Dementia Platform United Kingdom Translation 2024. London, England. April 19, 2024
- Multi-omic approaches to defining disease heterogeneity, subtypes, and progression. The Accelerating Medicines Partnership Alzheimer's Disease (AMP-AD) at 10: Progress toward a precision medicine approach for AD. Bethesda, MD. July 29, 2024
- Collecting [Brains &] Neuroimaging Data in Diverse Cohort Studies in the USA and Brazil. NIA-NIMHD Workshop on Enhancing Diversity in Healthy Aging Cohorts for Improved Research on Longevity and Health Span. NIH, Bethesda, MD. August 6, 2024
- Deconstructing the Complexity of AD/ADRD: From Translational Epidemiology to Precision Medicine. Building a Precision Medicine Research Enterprise. Keynote address 2024 NIH Alzheimer's Research Summit. NIH, Bethesda, MD. September 23, 2024
- Epidemiology of Dementia. 10th International Course of Epidemiology: Methods and Clinical Applications. Erice, Italy. November 23, 2024

The Year Ahead: 2025 and Beyond

After generating an unprecedented multi-omic brain platform for novel drug target discovery in human brains from non-Latino white people, we are now generating multi-omic data from blood from the same persons to predict the brain omics. Second, we are embarking on an ambitious study in Brazil with thousands of diverse brains to generate a similar platform. Third, we recently launched a study in Mexico to identify genomic variants for cognition of Native Mexican ancestry. Fourth, 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. Finally, we believe in open science and will continue to share our findings across the field.

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With Gratitude

As always, thank you for your generous support of our work. These funds are instrumental in ensuring Rush and the RADC continue to conduct excellent aging and Alzheimer's disease research.