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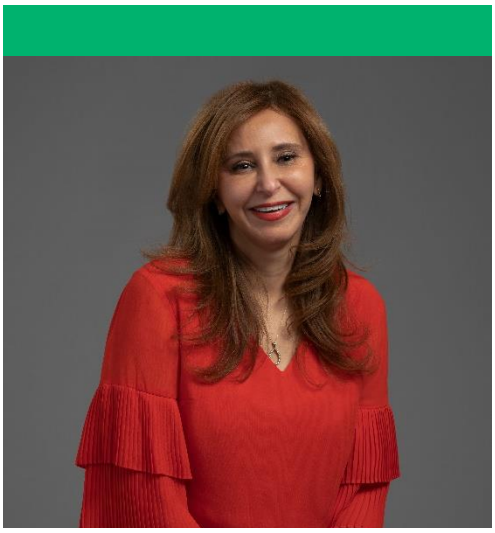

Advancement of Medicine

In 2025, my research program continued to focus on understanding the biological mechanisms that drive complex diseases, with the goal of translating these discoveries into improved approaches for diagnosis, prevention and treatment. Across multiple projects, our work addresses conditions that pose significant and growing challenges to public health, including long COVID, neurodegenerative disease, HIV and chronic inflammatory disorders.

Research

The funds associated with my endowed faculty position play a critical role in sustaining and expanding research and educational activities that are not yet supported by federal grants but are essential for advancing medicine. While portions of my research program receive external funding, many high-impact projects require early-stage exploration and data generation before they are competitive for national support. The endowment has allowed us to pursue these important but unfunded areas.

One major area of focus has been **long COVID**, also known as post-acute sequelae of SARS-CoV-2 infection, or PASC. Many individuals experience persistent symptoms long after the virus has been cleared, including problems with memory, concentration and cognition. Importantly, these symptoms often cannot be explained by direct viral infection of the brain. In 2025, we advanced studies testing whether long COVID may, in part, reflect an abnormal immune response. Through new collaborations, we identified inflammatory antibodies in individuals with neurologic long COVID and began defining the specific brain-related proteins these antibodies target. This work is important because identifying these targets may open the door to therapies that block harmful immune

responses and reduce long-term neurologic symptoms. It may also inform how certain individuals are monitored or treated in the context of COVID-19 infection or vaccination.

A second major research area examined **environmental contributors to neurodegenerative disease**, particularly Alzheimer's disease. While a minority of Alzheimer's cases are explained by inherited genetic mutations, most cases are thought to arise from poorly understood environmental and biological factors. Using advanced three-dimensional human brain cell models, known as organoids, we studied the effects of metals such as cobalt and titanium, which are commonly used in dental and orthopedic implants. We found that exposure to these metals can trigger inflammation and Alzheimer's-related protein changes in brain support cells without causing outright cell death. These findings suggest a potential mechanism by which environmental exposures may contribute to early disease processes and provide a new direction for understanding preventable risk factors in neurodegeneration.

Finally, we expanded our longstanding work on **gut inflammation and barrier dysfunction**, which is increasingly recognized as a driver of systemic and brain inflammation. In people living with HIV, current antiviral therapies cannot fully restore damage to the gut barrier, often referred to as "gut leakiness." In 2025, we demonstrated that activating a specific cellular signaling pathway can reverse this gut barrier dysfunction in experimental models. Building on this success, we are extending these studies beyond HIV to explore whether similar approaches could benefit individuals with Crohn's disease and related conditions. Portions of this work are currently unfunded, making endowment support essential for pursuing these high-risk, high-impact research directions.

Collectively, these efforts advance our understanding of how immune dysfunction, environmental exposures and chronic inflammation contribute to disease, and they lay the foundation for new strategies to improve long-term health outcomes. Our work has continued to attract national and international attention through collaborations, invited discussions and progress toward competitive external funding, reflecting its relevance to advancing modern medicine and patient care. These exploratory studies would not be possible without flexible funding and are essential for developing new, competitive grant applications.

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Outreach and Education

Endowment funds were used to provide effort support for research personnel, ensuring continuity, rigor, and progress in these projects. This included support for scientific staff and trainees who conducted experiments, analyzed data and helped drive these investigations forward. In addition, the endowment covered laboratory supplies and research reagents, which are necessary to perform these studies but are often difficult to fund through traditional grant mechanisms.

Importantly, the endowment has also directly supported student training and mentorship, allowing undergraduate, graduate and early-career trainees to engage in meaningful research experiences. These opportunities are critical for preparing the next generation of scientists, clinicians and health professionals. By supporting both personnel and supplies, the endowment has strengthened our research infrastructure while simultaneously advancing education and workforce development.

Overall, this flexible support has allowed us to pursue innovative, high-risk, high-reward research; generate preliminary data for future funding; and provide hands-on research training, thereby amplifying the impact of our work on both mentorship and scientific discovery.

Grants

Research activities supported by my endowed faculty position directly contributed to securing external national funding and recognition in 2025.

Most notably, this work led to the award of a National Institutes of Health, or NIH, R56 grant focused on autoimmune mechanisms underlying the neurologic complications of long COVID. This project grew out of exploratory studies supported by flexible endowment funding, which allowed us to generate the preliminary data needed to pursue competitive federal funding. **The resulting application was identified by the NIH as especially innovative and impactful, qualifying it for conversion to the R56 mechanism,** an award reserved for highly meritorious projects.

This R56 award was formally announced by the NIH Office of Autoimmune Disease Research, in collaboration with multiple NIH institutes. The announcement highlighted our work for addressing a critical unmet need: understanding how abnormal immune responses may drive long-term neurologic symptoms in individuals recovering from COVID-19, with the ultimate goal of informing future therapeutic strategies.

In addition, endowment-supported research efforts have positioned another project for external funding consideration. Applications related to metal and Alzheimer's disease received competitive reviews and are currently under evaluation for funding, with outcomes pending further NIH guidance. In these cases, endowment support has been instrumental in sustaining momentum and avoiding interruptions in promising lines of research while federal decisions are underway.

Overall, the endowed faculty position has served as a catalyst, enabling innovative, early-stage work to mature into nationally recognized research efforts that attract competitive external funding and advance progress in areas of significant public health relevance.

Publication Highlights

- Narasipura SD, Zayas JP, Ash MK, Reyes AF, Shull T, Gambut S, Szczerkowski JLA, McKee C, Schneider JR, Lorenzo-Redondo R, **Al-Harthi L**, Mamede JI. Inflammatory responses revealed through HIV infection of microglia-containing cerebral organoids. *Journal of Neuroinflammation*. 2025 Feb 10;22(1):36. doi:10.1186/s12974-025-03353-2.
- Chen L, Kreko-Pierce T, Cassoday SL, **Al-Harthi L**, Hu XT. Methamphetamine self-administration causes neuronal dysfunction in rat medial prefrontal cortex in a sex-specific and withdrawal time-dependent manner. *Frontiers in Pharmacology*. 2025 Feb 14;16:1527795. doi:10.3389/fphar.2025.1527795.
- Shull T, Bhimalli P, Welninski S, Cho BK, Mattamana B, Arivalagan J, Tarhoni I, Goo YA, Schneider JA, Agrawal S, Bennett DA, Leurgans S, Patel MB, Ely EW, Kelleher NL, Borgia JA, Schneider JR, **Al-Harthi L**. Elevated neuroinflammation, autoimmunity, and altered IgG glycosylation profile in the cerebrospinal fluid of severe COVID-19 patients. *Brain, Behavior, and Immunity*. 2025 Aug;128:289-302. doi:10.1016/j.bbi.2025.03.031.
- Chen L, Cassoday SL, Mamede JI, **Al-Harthi L**, Hu XT. Methamphetamine and neuroHIV suppress astrocytic potassium channel function in the medial prefrontal cortex via different mechanisms. *Frontiers in Pharmacology*. 2025 Nov 24;16:1691165. doi:10.3389/fphar.2025.1691165.

Invited Presentations

- March 18, 2025. George Mason University. Mechanisms at the Interface of HIV Neuropathogenesis and Viral Latency
- October 14, 2025. Icahn School of Medicine at Mount Sinai. HIV, the Brain, and the Gut: Wnt You Like to Know?

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The Year Ahead: 2026 and Beyond

In the year ahead, I will prioritize advancing research projects that address urgent and emerging health challenges, particularly those that require continued data generation to move toward broader clinical impact. A central focus will be expanding studies on the neurologic consequences of long COVID, with the goal of further clarifying disease mechanisms and identifying pathways that may be targeted to reduce long-term cognitive and neurologic symptoms.

I will also continue to develop research exploring the intersection of metal exposure and Alzheimer's disease, an area of growing importance in assessing the impact of environmental factors on disease. These studies aim to deepen our understanding of modifiable risk factors and identify early biological changes that may inform prevention or intervention strategies.

Equally important is my commitment to training and workforce development. I will continue to provide structured research opportunities for students, postdoctoral trainees and early-career investigators, allowing them to engage directly in meaningful scientific discovery. These experiences are essential for preparing the next generation of scientists and clinician-investigators and for sustaining a strong, innovative research environment.

Finally, I will continue to build mentorship pathways that support junior faculty and instructors in developing independent research programs while contributing to collaborative, multidisciplinary efforts. Together, these priorities reflect a commitment to advancing scientific knowledge, strengthening research training, and translating discovery into long-term benefits for health and medicine.

With Gratitude

I am deeply grateful for the continued support of the donors who invest in this endowed position and in Rush's mission. Your generosity provides the flexibility needed to pursue important lines of inquiry, support trainees and sustain progress during critical phases of research. This support has a meaningful impact, not only on the work itself, but on the people involved and the patients we ultimately hope to serve. Thank you for your confidence in our efforts and for your ongoing commitment to advancing science and health care at Rush.