EASTON LABS FOR NEURODEGENERATION

Mary S. Easton Center for Alzheimer's Research and Care at UCLA

The Easton Labs for Neurodegeneration fund continues to accelerate innovations in Alzheimer's disease (AD) research and improve patient care at the Mary S. Easton Center for Alzheimer's Research and Care at UCLA. These efforts are led by S. Thomas Carmichael, MD, PhD, holder of the Frances Stark Chair in Neurology and chair of the UCLA Department of Neurology. Jason Hinman, MD, PhD, and Jeffrey Saver, MD, continue to serve as interim co-directors of the center. With AD affecting a rapidly growing senior population—projected to increase exponentially to 13 million in the United States by 2050—the center is expanding its footprint in the medical community.

Capital Projects Summary

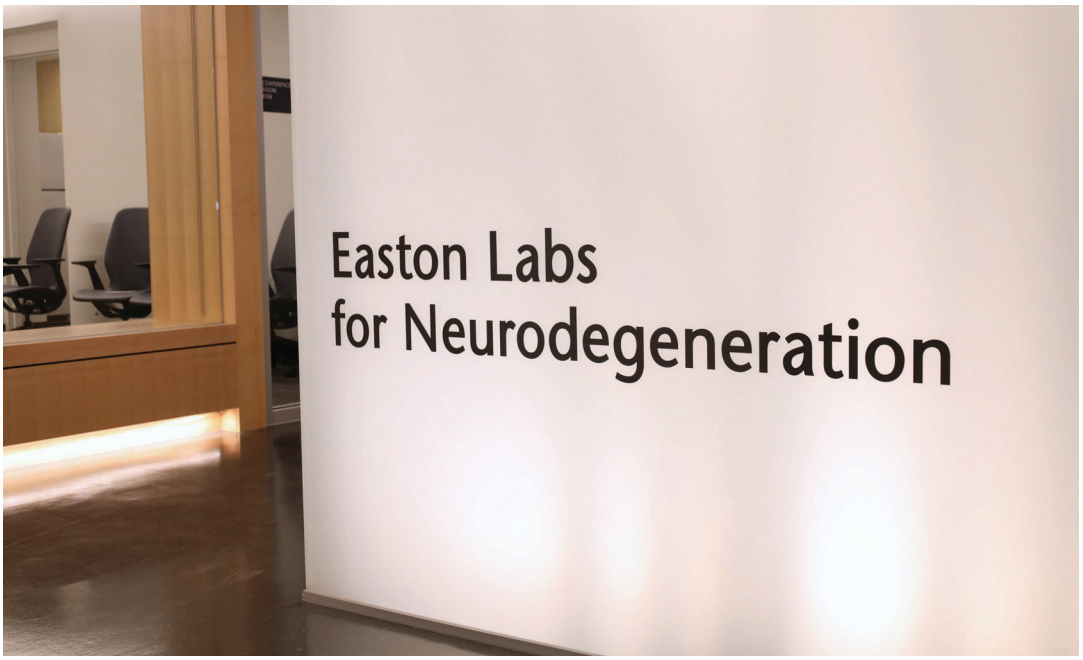
This past year, the lab on the B floor of the Reed Neurological Research Center was renovated at a cost of more than $1 million. Plans for the lab shifted throughout the COVID-19 pandemic, and restrictions on interpersonal interactions significantly delayed the process. Faculty and staff are expected to begin moving into the revamped space in late 2025. The conference room that serves the Easton Labs for Neurodegeneration has been extensively remodeled as part of this process and will now serve the full Mary S. Easton Center for Alzheimer's Research and Care.

This state-of-the-art, collaborative lab space will enable the Easton Center to use leading-edge technology and tools—such as blood-based biomarkers for early disease detection and basic research on mechanisms that cross neurodegenerative diseases—to enhance the scientific community's understanding of AD and related conditions. It contains areas designated for conferences, dry lab computational analysis, cell culture, confocal microscopy, biospecimen storage, scientific model surgery, biochemical assays, and other experimental work. These facilities will also be used for undergraduate, graduate, and postdoctoral fellowship training. Offices for the center director and four faculty members are located on the B floor as well.

The renovation has created additional capacity for six faculty members, and the team is focused on recruiting exceptional candidates.

Ongoing Research

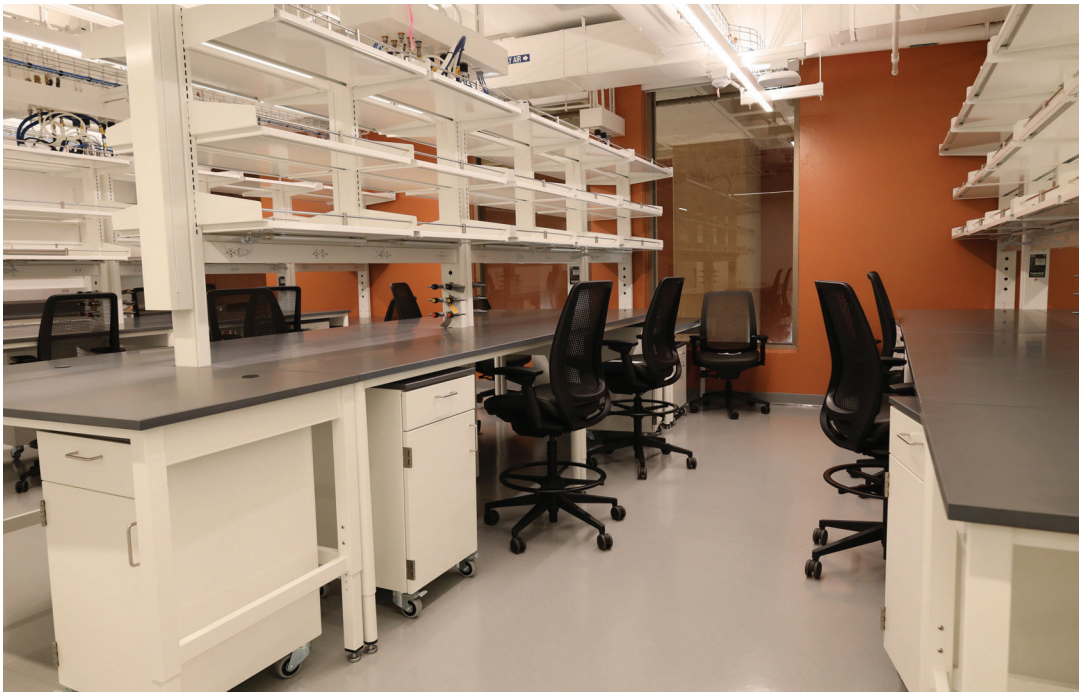
Devoted to both high-quality care and groundbreaking investigations, the Easton Center serves a unique patient population whose data informs research that translates into life-changing treatments. Clinical research at the center involves a wide variety of observational and interventional studies to better understand AD. These trials provide patients with access to the latest experimental therapies related to memory and dementia.



The newly renovated Easton Labs for Neurodegeneration are ready to welcome faculty.

In highlights from select scientific studies at the center, researchers Varghese John, PhD; Istvan Mody, PhD; and their colleagues have developed a new therapy for AD. Drugs recently approved by the FDA, including lecanemab and aducanumab, remove harmful plaque from the brain. While these drugs slow the rate of cognitive decline, they do not restore memory or reverse cognitive impairments. Dr. John and Dr. Mody sought a compound that would target fast-firing neurons known as parvalbumin interneurons. These neurons are crucial in generating gamma oscillations, which integrate brain activity by linking regions during tasks like memory formation, allowing them to function as a cohesive network. Gamma oscillations are lost in AD. This newly developed drug is a first-in-class compound that promotes these brain waves through natural stimulation of the circuits affected in AD. Dr. John and Dr. Mody found that

targeting parvalbumin interneurons can revitalize cognitive deficits in an amyloid-based scientific model of AD. They deployed the molecule DDL-920 to activate these neurons, allowing them to sustain more powerful gamma oscillations. They synthesized DDL-920 and demonstrated that it can restore cognitive functions in scientific models genetically modified to express symptoms of AD by effectively jump-starting the brain's memory circuitry. If proven to produce similar results in humans, the candidate compound would be a novel AD treatment because of its ability to revitalize memory and cognition. More work is needed to determine if the treatment would be safe and effective in humans. Since gamma oscillations are lost or abnormal in many neurologic diseases, this approach could potentially be applied widely in neurology to treat other conditions in addition to AD.



State-of-the-art labs will facilitate translational research.

Last year, the center applied for a large Centers Without Walls (CWOW) grant from the National Institutes of Health (NIH) to study vascular contributions to cognitive impairment and dementia, based on Dr. Hinman's robust body of work on this disease. Damage to blood vessels impairs blood flow to the brain, leading to vascular dementia, and is the second most common cause of dementia. This impairment can also co-occur with AD, the most common contributor to dementia, to produce mixed dementia. The team received a grant for its project seeking to create a framework for understanding

cerebral small vessel disease phenotypes and molecular targets. The CWOW program encourages sharing prepublication data, methods, and results to promote collaboration, accelerate research progress, and develop viable treatments. The UCLA CWOW site is part of a small and select national network that integrates techniques and ideas toward new therapy development.

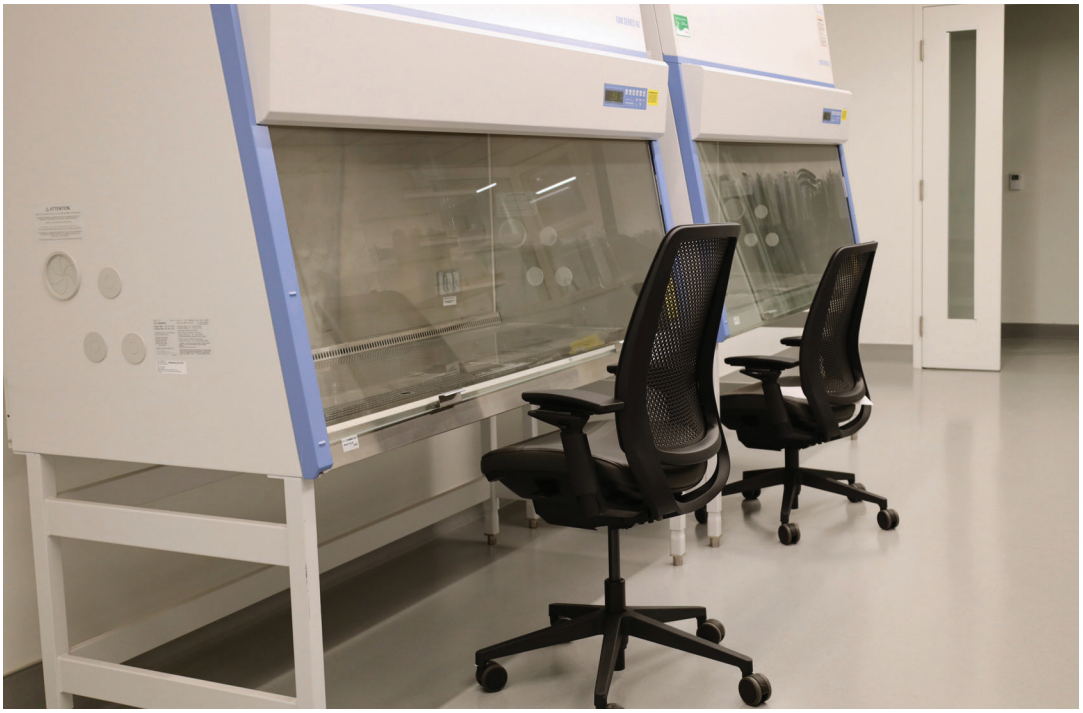
Faculty will have everything they need in reach from their new offices.

Clinical and basic research in AD progresses through the center's engagement with its Los Angeles neighbors and patients. Community engagement initiatives allow for healthy clinical trial recruitment, public education on modifiable AD risk factors, and dissemination of the center's scientific findings. Conversely, communication from the community's patients and their caregivers enriches the center's knowledge, leading the way toward greater health in aging and dementia prevention. A recent $1 million donation will help Easton Center researchers work with some of these communities to identify ways in which genetic risk may affect AD's progression.

Timothy Chang, MD, PhD, holder of the Augustus S. Rose Chair in Neurology and assistant professor in the Department of Neurology; Mirella Diaz-Santos, PhD, assistant professor-in-residence in the Department of Neurology; and the UCLA Department

of Family Medicine continue to develop a dementia screening toolkit to use at primary care facilities in predominantly Latino communities, which have a substantially higher risk of AD. Such tools will then be available for use by primary care providers throughout UCLA Health.

The center is initiating the fifth wave of a North American multicenter observational study launched in 2004. Sponsored by the NIH and the National Institute on Aging, the goal of this ongoing study is to discover, optimize, standardize, and validate clinical biomarkers used in AD research and clinical trials.



Leading-edge equipment enables tissue assays.

Jessica Rexach, MD, PhD, spearheaded an investigation that identified 32 shared, disease-associated cell types. The study was published in the high-impact journal *Cell*. Fourteen of these cell types were specific to dementias from three brain regions varying in vulnerability and pathological burden for the condition. Dr. Rexach's team identified specific pathways in these diseased cells that regulate how a cell succumbs to dementia or how it might be resilient to the disease. Uncovering which cell types are associated with the development of dementia reveals potential therapeutic targets. Such advancements in the understanding of shared and distinct molecular features in the human brain can lead to effective treatments for dementia.

The Mary S. Easton Center for Alzheimer's Research and Care at UCLA has made meaningful progress across both research and patient care. With the completion of a major lab renovation, the recruitment of new faculty, and the advancement of key research initiatives—including a novel drug candidate and a new NIH CWOW award—the center is well positioned to continue advancing researchers' understanding of AD and related conditions.

In the year ahead, the center will expand its community partnerships, train emerging scientists, and pursue studies that connect basic discoveries to real-world impact. These efforts reflect a steady commitment to improving care, expanding access to new treatments, and addressing the complexity of aging and dementia through interdisciplinary research. With continued support from the Easton Family as well as the broader UCLA community, the Easton Center remains focused on the work ahead—grounded in science, informed by patients, and driven by the potential for progress.

EASTON BRAIN HEALTH INITIATIVES

Easton Brain Health Initiatives funding is essential to the work of the Easton Labs for Brain Health Research. The labs are overseen by Christopher Giza, MD, professor of pediatric neurology and neurosurgery at the David Geffen School of Medicine at UCLA and UCLA Mattel Children's Hospital, and director of the UCLA Steve Tisch BrainSPORT Program. The labs conduct leading-edge translational research, enhance patient care, and launch the careers of outstanding young investigators. Dr. Giza also serves on the Major League Soccer Concussion Program committee and the National Basketball Association Concussion committee; advises the United States Soccer Federation; and directs the National Football League Neurological Care Program at UCLA. One year ago, Dr. Giza and his neurology colleagues became team physicians for the Los Angeles Chargers.

In the decade since the Easton Brain Health Initiatives were established, the clinical staff have treated more than 10,000 patients. Of those, more than 1,000 are veteran or active-duty military service members.

Approximately 100 of the military patients receive care through UCLA Health Operation Mend. Operation Mend patients undergo either a one-week treatment protocol or an intensive two-week outpatient treatment program targeting post-traumatic stress or traumatic brain injury (TBI). Patients stay at a nearby hotel and receive multiple consultations and comprehensive testing.

Other patients also benefit from the interdisciplinary care of the Easton Brain Health Initiatives. Rather than coordinating appointments at different specialty clinics, patients can see various clinicians during the same office visit. The Easton clinical staff offer services spanning adult and pediatric neurology, neuropsychology, occupational therapy, nutrition, and psychotherapy, as well as consultations in other areas. The team meets once a week to review the most challenging cases and gain insight from other physicians.

Easton Labs for Brain Health Research

The Easton Labs for Brain Health Research are dedicated to the multidisciplinary and cross-institutional collaboration required to investigate TBIs.

The labs' research program is exceptionally strong. Since their inception, the labs have been awarded more than $25 million in grant funding. The team has also published more than 330 papers in prominent peer-reviewed journals.

Mayumi Prins, PhD, professor and vice chair of the UCLA Department of Neurosurgery and director of the UCLA Health Brain Injury Research Center's education program, has started an exciting new project focused on brain metabolism. Using a cytometer to analyze the physical and chemical properties of cell populations, Dr. Prins is analyzing the metabolism of different types of cells and how they react to brain injury. Using this knowledge, she is examining methods to alter brain cell metabolism through the gut microbiome. Dr. Prins plans to submit the study for grant consideration soon.

Building on previous investigations of the glymphatic system—which clears waste from the brain and is most active during slow-wave sleep—Dr. Prins has teamed up with Anthony Wang, MD, associate professor-in-residence of neurosurgery and radiation oncology at UCLA; and Zoe Teton, MD, a fifth-year neurosurgery resident at UCLA. They are studying the glymphatic system in scientific models. By injecting dye into post-traumatized models, the investigators were able to see activity in the brain. This enabled them to image the activity of the glymphatic system, which was markedly impaired after trauma. This is especially significant because when the glymphatic system doesn't work properly, proteins such as amyloid-beta and tau aggregate, contributing to Alzheimer's disease.

Dr. Teton also investigated the effects of craniectomy on the glymphatic system. To relieve pressure from bleeding or blood clots, a piece of skull is removed during craniectomy. Dr. Teton studied whether that piece should be replaced—and, if so, how quickly. She found that although a craniectomy may be necessary to save a patient's life, the glymphatic flow reduces to almost nothing while the piece is out. Potential solutions to improve long-term results include replacing the piece swiftly or introducing an artificial flap until the swelling in the brain has gone down.

Sam Vander Dussen, the current Easton Brain Health Fellow, is using MRI and focused ultrasound for functional imaging in a preclinical model. These images provide insight into more complex human behaviors and effects of TBI, such as changes in brain connections.

The multicenter CARE4KIDS study, funded by the National Institutes of Health (NIH), is now in its fourth and penultimate year. The $10 million study aims to identify biomarkers that can predict which children ages 11 to 17 will not recover from concussion within three months.

Last October, the Brain Injury Research Center hosted the 23rd annual University of California and Western Neurotrauma Symposium, organized by Dr. Prins.

Easton Brain Health Fellows

Many recipients of the Easton Brain Health Fellowship go on to achieve success in their field. They have led groundbreaking translational research that improves the lives of patients and contributes to the scientific community's increasing knowledge of the brain. Seven scholars have participated in the program. After securing some of the most coveted grants available for their pioneering investigations, they now teach at UCLA and other prestigious schools where they helm their own research labs. Their accomplishments have enriched the program and allowed the fellowship to continue. The Easton Brain Health Fellows benefit from a culture of discovery at UCLA that transcends basic training in laboratory or clinical science.

Vander Dussen is a PhD student in the UCLA Department of Bioengineering. He received his MS degree from UCLA in bioengineering with a specialization in neuroengineering in 2023. His current research with the Brain Injury Research Center focuses on the system design of a synchronous behavioral and functional ultrasound imaging platform to acquire information about functional network connectivity changes after TBI. Vander Dussen's investigative interests include using computational neuroscience, machine learning, and graph theory to understand plasticity and working memory in the brain. His mentor is Paul Mathews, PhD, an associate professor-in-residence of neurology in UCLA's Graduate Programs in Bioscience.

Easton Brain Health Fellows Making a Lasting Impact

The six previous fellows are accomplished translational scientists who continue to contribute to brain health research and patient care.

Ann Hoffman, PhD, the 2022-24 fellow, has remained at the center. She is also an assistant researcher for the Fanselow lab in the UCLA Department of Psychology. Dr. Hoffman is interested in the mechanisms of environmental challenges, such as concussive TBI and traumatic stress, on fear learning and psychological health. She is exploring acute and chronic changes in sensory and emotional network systems that

are impacted by TBI, post-traumatic stress disorder, and anxiety in male and female patients across the lifespan.

Kevin Bickart, MD, PhD, a 2021-22 fellow, is now an assistant professor of neurology at the David Geffen School of Medicine and a care provider at Operation Mend and the UCLA Health Neurology Clinic in Westwood. Dr. Bickart's research focuses on the brain networks that underlie affective and social behavior, both in typical development and in the context of brain injury and neurodegenerative conditions. He is also investigating the role of exercise and sports in maintaining brain health. Dr. Bickart's work contains multiple layers of analysis, from genetics and brain imaging to affective behavior and real-world social networks. His future work will combine his expertise in brain mapping with noninvasive neuromodulation to develop individualized treatments for chronic affective and social symptoms related to TBI and frontal lobe dementias.

Aliyah Snyder, PhD, the other 2021-22 fellow, is an assistant professor of clinical health and psychology at the University of Florida. She also serves as director of the Holistic Interventions for Brain Health and Recovery Clinic, which provides brief therapeutic interventions for brain injury and postviral neurological conditions. Dr. Snyder's clinical work at the University of Florida Health's Norman Fixel Institute for Neurological Diseases focuses on neuropsychological assessment and interdisciplinary management of concussion and brain injury. She is also interested in the treatment and development of biobehavioral therapy, including mindfulness-based biofeedback, for postviral neurological conditions, as well as the role of autonomic dysregulation in persistent symptoms after brain injury. Despite living far from UCLA, Dr. Snyder is a contributing investigator in the Autonomic Biomarker Core of the CARE4Kids study.

Sinifunanya Nwaobi, MD, PhD, the 2020-21 fellow, is a pediatric neurologist specializing in headache and pain medicine in the UCLA Goldberg Migraine Program. She is also a clinical instructor in the Department of Neurology. Dr. Nwaobi is continuing to work on her study, "Adenosine Modulation of the Bi-Directional Relationship between Sleep and Migraine," supported by the Faculty Development Award to Promote Diversity in Neuroscience Research from the National Institute of Neurological Disorders and Stroke (NINDS). With a focus on astrocytes—a type of glial cell that can affect brain health—Dr. Nwaobi seeks to elucidate the bi-directional relationship between sleep and migraine by examining the specific mechanisms by which sleep modulates migraine pathophysiology.

Lindsay Ferguson, PhD, the 2018-19 fellow, remained for a time at UCLA as a project scientist. Her research focused on overall brain health and the consequences of mild brain injuries, as well as the effects of exercise, stress, and injury on neurophysiology, inflammation, and gut microbes. She now works in the private sector.

Tiffany Greco, PhD, the inaugural Easton Fellow, is now an assistant professor of neurosurgery at the David Geffen School of Medicine. She is on track to complete her NIH/NINDS-funded study, "Cerebral Mechanisms of Vulnerability Following Female Traumatic Brain Injury," this year. Dr. Greco also collaborates with Dr. Prins and Dr. Giza. Her research focuses on sex hormones, brain energy metabolism, and concussions. Although one-third of athletes are women, the vast majority of concussion studies are conducted on male athletes. However, there is strong evidence suggesting that men and women experience physiological differences while sustaining and healing from head injuries. Dr. Greco's research offers insights into how head trauma affects people differently and how brain health differs in women and men.