

MIND Matters

WINTER 2023

SPECIAL FEATURE

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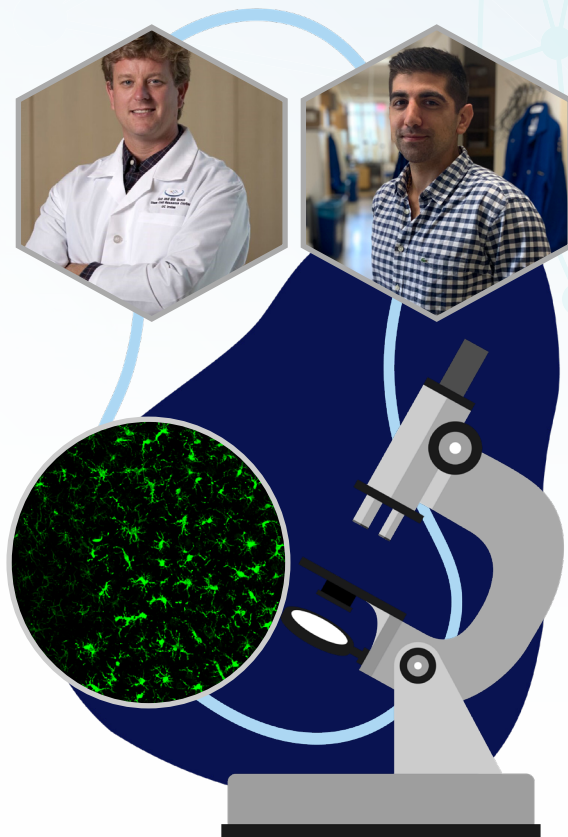
Research opportunity for adults with Down syndrome

Microglia replacement as a future treatment for neurodegenerative diseases?

The Blurton-Jones lab created new healthy microglia that carry a specific mutation to resist a drug called Plexxikon, a CSF1R inhibitor, to replace damaged microglial cells in the brain with healthy ones.

The term, “mutant microglia” might conjure images of destructive shapeless entities devouring entire city blocks, something like you might see in *The Blob*. But what if, instead of devouring city blocks, the blob was microscopic and it could be programmed to fight brain disease? Research from the Blurton-Jones lab, in collaboration with a team from the University of Pennsylvania, has shown that mutant microglia might actually one day play a therapeutic role in fighting neurodegenerative disorders like Alzheimer’s disease.

Microglia play a key role in brain health. They are the immune cells of the brain and emerging research, including work done at UCI MIND, has revealed that microglia are also implicated in the pathological progression of several neurological disorders, including Alzheimer’s disease. In a diseased state, microglia can become dysfunctional and may even contribute to further damage to brain tissue.



Mathew Blurton-Jones, PhD (top left) | Jean Paul Chadarevian PhD Student (top right)

Image of G795A microglia : Courtesy of Chadarevian et al., Journal of Experimental Medicine, 2022 (bottom)



Dear Friends of UCI MIND,

Advances in the field of Alzheimer's disease (AD) research and the contributions of UCI MIND investigators remain tremendously exciting. Two new drugs have been approved by the FDA (page 3). These approvals are believed by many to represent the dawn of a new age in AD research and treatment. Both drugs received accelerated approval and we await a decision from the FDA about "full approval" for lecanemab. If received, full approval could cause the Centers for Medicare and Medicaid Services to revisit their previous coverage decision about anti-amyloid antibody therapies. These events will be key to more fully understanding how these new drugs will change the care of people living with AD.

Even in the best case scenario of full approval and coverage, these drugs slow but do not stop disease progression and target only one of the signature brain changes that occur in AD. And for other brain diseases that cause dementia, such as Huntington's disease, even fewer options exist (page 4). Thus, exciting work like that happening in the laboratory

of Dr. Mathew Blurton-Jones (page 1) is urgently pursuing innovative treatment approaches that build on our growing understanding of disease pathophysiology.

This research is arduous and expensive. "Breakthroughs" come after years of deliberate efforts in the lab and the clinic. In addition to performing cutting edge research, we are committed to giving a next generation of scientists and clinicians the tools to carry on this important work. That is why we are so grateful to Joan and Don Beall for their support in UCI MIND's training mission (page 6). Indeed, support from philanthropists like the Beall's and Carla and Arthur Liggett, MD (page 5) propel us forward faster in training and research, toward eventual solutions for brain disease.



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Director, UCI MIND

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Lecanemab and Donanemab: A Tale of Two Drugs

In January, the US Food and Drug Administration (FDA) granted accelerated approval to lecanemab, a monoclonal antibody against the beta amyloid protein that accumulates in the brain of people with Alzheimer's disease (AD). Lecanemab was approved on the basis of the treatment's demonstrated effect of lowering levels of brain amyloid, as measured by a type of brain scan known as positron emission tomography (PET) imaging. Lecanemab is now approved for the treatment of patients with mild cognitive impairment or mild dementia and should be used in patients in whom that same amyloid PET brain scan (or measures of amyloid in the cerebrospinal fluid) suggests that AD is the most probable cause of the person's cognitive impairment. The treatment is not approved for people with moderate or severe dementia, or as a prevention for cognitive impairment.

Lecanemab joins the drug aducanumab as the second treatment that directly targets the biology of AD to receive accelerated approval. Neither drugs have received full approval, which relies on demonstration of clinical benefit, rather than sole demonstration of biological effect. Lecanemab, which will also be known by the brand name Leqembi, remains under consideration for full approval by the FDA.

More is anticipated in the coming months on how the FDA will approach this decision. CLARITY, the phase 3 trial of lecanemab, showed a statistically significant slowing of cognitive decline in people treated with the active drug, compared to people treated with placebo. The results of the trial were viewed by many in the field to be compelling, though debate about the meaningfulness of lecanemab's clinical benefit will be a central feature of discussion as a full approval decision looms.

In related but somewhat surprising news, the FDA, less than a month after approving lecanemab, declined to grant accelerated approval to Eli Lilly's donanemab. Like aducanumab and lecanemab, donanemab is a monoclonal antibody treatment against beta amyloid. Eli Lilly published very prom-

ising results for donanemab in 2021, which included demonstration that donanemab could lower amyloid levels (the basis for accelerated approval) in the brain of people with mild cognitive impairment and mild dementia. But the number of participants in the study, particularly the number with at least 12 months of treatment data, was apparently not sufficient for the FDA to grant accelerated approval. A Phase 3 clinical trial of donanemab that is intended to test whether the drug is clinically beneficial is under way and could render the FDA decision moot—if donanemab demonstrates efficacy it could be in line for full approval. The results of that trial are expected later this year.

What is clear from the recent FDA decisions is that, while the field is making long anticipated progress towards disease modifying treatments for AD, there is still more work to be done. Therefore, research participation is key. In fact, prevention trials of lecanemab are currently underway to test if the drug is safe and can delay or stop the onset of symptoms in people at risk for developing dementia due to AD.

To learn more about the prevention trial at UCI MIND, visit the AHEAD study at <https://www.aheadstudy.org>





HD-CARE celebrates 10 years

HD-CARE, the non-profit organization that supports Huntington's disease (HD) patient care, advocacy, education and research in Orange County, has turned 10 years old. In 2012, the new organization launched by Frances Saldana and Linda Pimental, two remarkable leaders and advocates whose families were tragically struck by the disease, was recognized by the campus as a UCI Support Group. Since inception, the mission of HD-CARE has been to advance HD research and clinical care at UC Irvine, and it has raised \$377,000 towards that mission.

Today, HD-CARE is stronger than ever, and its contributions have, in part, supported the groundbreaking work of UCI MIND faculty members, including Leslie Thompson, PhD, and Joan Steffan, PhD. Their research has been pivotal to better understanding how mutations in the huntingtin gene, lead to the pathology and clinical symptoms associated with HD as well as efforts to develop therapies for this fatal disease. "HD-CARE has dramatically helped our group carry out key research to identify potential therapeutic strategies and to enable care for those who would not otherwise have access," says Dr. Leslie Thompson.

Along with raising funds to support research, HD-CARE holds an annual symposium in the fall to disseminate the latest advances in clinical therapies and research. The organization also supports the UCI HD-CARE Clinic at Gottschalk Medical Plaza, and helps families affected by Huntington's to identify resources.

In addition, HD-CARE promotes patient advocacy and public education about HD. HD-CARE sponsors fundraising events like the Orange County (OC) Marathon and communicates the latest HD news on its website. "HD-CARE is an extraordinary warrior in the fight against HD" says Dr. Joan Steffan.

The work of HD-CARE is appreciated greatly by the HD community at large in Orange County, the HDSA Center of Excellence at UCI, and the UCI HD scientists and clinicians, all with the common goal of finding therapeutics to slow HD progression and improving patient quality of life.



Drs. Leslie Thompson and Joan Steffan participate in HD-CARE event (left)

Team poses for the HD-CARE sponsored event, December Run for a Claus (right)



HD-CARE Research Symposium audience (left)

Some of the members from the HD-CARE Board and Scientific Advisory Board (right)



2022 Gala and the Establishment of Endowed Chair

The 2022 December to Remember Gala, our first in person gala since the COVID pandemic, raised more than \$500,000 for Alzheimer's disease and related dementias (ADRD) research, making this the most successful gala in our 12-year history. Three hundred guests and UCI leadership celebrated at the Balboa Bay Resort with signature cocktails, appetizers, live music from Maximo Marcuso and an Italian-themed dinner. Zack Krone once again emceed the historic event, which culminated with the annual UCI MIND Award, presented to our esteemed colleague and friend Dean Frank M. LaFerla, PhD, for his tremendous contributions to the field of AD and to UCI MIND.

It was at this year's gala that UCI MIND announced the establishment of the Carla Liggett & Arthur S. Liggett, MD, Endowed Chair in Honor of Dean Frank M. LaFerla. This is the second endowed chair for UCI MIND. Such an accomplishment would not have been possible without this generous legacy gift from a remarkable and consistent supporter, Ms. Liggett.

Philanthropy plays a vital role in the success of UCI MIND and we are honored to have the legacy of Carla & Arthur Liggett, MD live on with us. The awarded funds will support an outstanding faculty member who has made significant contributions to UCI MIND and research in Alzheimer's disease and related disorders. The inaugural recipient of the endowment will be announced by June 2023.



Dean Frank LaFerla, PhD



Guests dine at the 2022 Gala

Thank you to our donors



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or visit www.mind.uci.edu/donate

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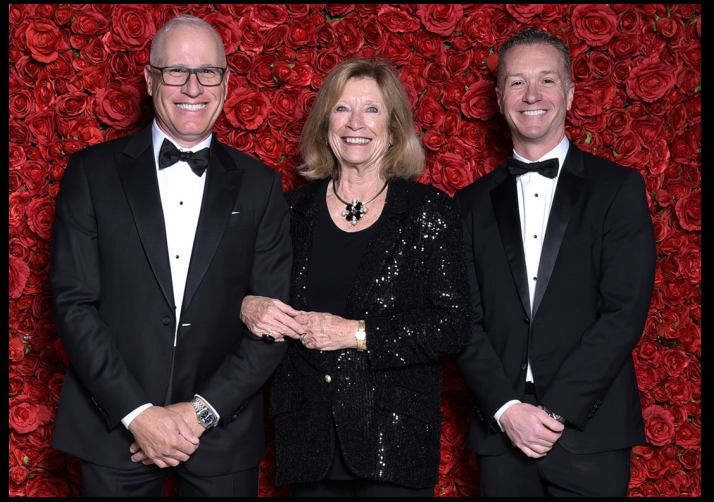
UCI M^{IND} Presents



*A December to
Remember
2022
Gala Recap*









SAVE THE DATE

*A December to Remember
2023 Gala*

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09





Funding to Support the Next Generation of Scientists

Increased annual support from Joan and Don Beall will fund two important education and training programs at UCI MIND. The Beall Scholar Program is a free summer neuroscience course for diverse 11th graders from Orange County that was launched in 2021. The program exposes students to research in brain science and covers transportation, materials and food and provides students with a \$500 stipend. The program is run by the trainee led Research and Education for Memory Impairments and Neurological Disorders (REMIND).

The funding will also establish the Joan and Don Beall Scholar Award, a funding opportunity for early career investigators at UCI studying ADRD. The award was announced this year and will provide \$50,000 per year for 5 years to support the research endeavors of an outstanding assistant or associate professor at UCI. The award funds will help early career researchers establish an ADRD research program.



A Beall Scholar examining a human brain. (left)

continued from page 1: Microglia replacement as a future treatment for neurodegenerative diseases?

With this in mind, the Blurton-Jones lab explored ways to replace damaged microglial cells in the brain with healthy ones. Using CRISPR technology in human-derived induced pluripotent stem cells (iPS), they created new healthy microglia that carry a specific mutation to resist a drug called Plexxikon, a CSF1R inhibitor. These new cells were transplanted into the brains of young mice that were later treated with this drug, so that the native microglia died off and were readily replaced by the new resistant microglia. These new microglia can perform normal functions in the brain and persist for months, offering a possible new approach to not only replace diseased



To learn more about research, visit mind.uci.edu or call 949.824.0008

microglia but also engineer microglia to deliver therapeutics in the brain. The research is being lauded by many in the field as a breakthrough discovery in cell replacement therapy, which will no doubt open the door for future research, including understanding how these mutated microglia respond in AD.

To learn more about this research, read the full article in the December 2022 issue of the Journal of Experimental Medicine or watch the recent MINDcast episode of Accelerating Discovery, with lead author and graduate student, Jean Paul Chadarevian.

Putting your cells to work:

Skin specimens taken from participants enrolled in our ADRC longitudinal study are collected and turned into induced pluripotent stem cells and used in studies like this one. Dr. Mathew Blurton-Jones and his team maintain a repository of stem cell lines that are shared broadly for research studies.

STAFF SPOTLIGHT

Meet Milagros Rangel and Malia Tano:



Milagros Rangel:

Milagros will serve as the Alzheimer's disease research center (ADRC) and clinical trial recruitment coordinator. She has a bachelor's degree in Community Health from Cal State Dominguez Hills and was previously employed as a population health coordinator. She is a native Spanish speaker and looks forward to learning more about clinical research, cognitive impairment, and providing health education to all including to the Spanish speaking communities of OC.

Malia Tano:

Malia joined UCI MIND as an administrative specialist. She will manage administrative duties for the Institute. Malia holds a bachelor's degree in business, hotel and restaurant management from Northern Arizona University and has extensive experience working in the hotel industry. She looks forward to assisting the staff and faculty as well as learning more about the research being done in UCI MIND.



STUDY SPOTLIGHT

Research Opportunity for Adults with Down Syndrome

Lifespan Approach to Alzheimer's Disease in Down Syndrome

Researchers at UC Irvine, under the direction of Dr. Ira T. Lott, are seeking volunteers for a research study. The purpose of this research project is to gather information across several age periods that will provide information regarding risk and prevention factors, early detection, and potential therapeutic pathways.

Participation in this study requires annual visits and consists of:

- Medical evaluations including medical history, neurologic and physical exams
- Cognitive testing to measure memory, thinking and functional skills
- Questionnaires to assess abilities, characteristics and habits
- A blood draw
- An optional brain MRI (If willing and qualified)

To be eligible, study volunteers with Down syndrome must be:

- 18 years or above and
- Have a study partner who knows them well



To learn more about research,
email: downsyndrome@uci.edu or
call 714.456.8443



Individuals with Down syndrome are at high risk of developing Alzheimer's-type dementia over age 40 years.



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and Neurological Disorders
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