MODEL-AD: CREATING BETTER MOUSE MODELS FOR THE ALZHEIMER’S FIELD

Contributed by Claire Butler, PhD

The growing societal and economic impact of Alzheimer’s disease (AD) illustrates the urgent need to develop effective therapies. Mice have long been used as scientific models to advance our knowledge of disease because of their relatively homologous biology and accelerated lifespan. Unlike humans, aging mice do not naturally develop AD; scientists have had to use genetic mutations to create mouse models that mimic components of the disease. These mouse models have enabled important discoveries but they have not wholly recapitulated this complex disease.

To address these challenges, the National Institute of Aging (NIA), through a multimillion dollar initiative, established the Model Organism Development and Evaluation for Late-onset Alzheimer's Disease (MODEL-AD) consortium in 2017 (renewed in 2022) at UCI, University of Pittsburgh, Indiana University and Jackson Laboratory. Led at UCI by Frank LaFerla, PhD, Andrea Tenner, PhD, and Kim Green, PhD, MODEL-AD aims to design, produce, and evaluate the next generation of genetically modified mouse models, utilizing and integrating important information gleaned from human data to better reflect the

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Dear Friends of UCI MIND,

Please enjoy the latest issue of MIND Matters from UCI MIND. In this Spring issue, we highlight a number of exciting updates about the impact UCI MIND investigators are having in the field. On the cover, post-doctoral fellow Dr. Claire Butler highlights progress made by the collaborative MODEL-AD group, including a publication she led. Another post-doctoral fellow, Dr. Jessica Noche, highlights an exciting collaboration in which UCI MIND investigators are playing a leading role on the Ann S. Bowers Women’s Brain Health Initiative (page 4).

We also highlight several awards in this issue. Numerous faculty have recently been bestowed prestigious honors, including three – Drs. Elizabeth Head, Michael Yassa, and Frank LaFerla – who received awards from the campus. Dr. Daniel Gillen was selected as a Fellow of the American Association for the Advancement of Science (AAAS), a tremendous national honor (page 5). Post-doctoral fellow Dr. Tiffany Petrisko was granted a $200,000 award from the Alzheimer’s Association (page 5). And we selected trainees within UCI MIND for honors at our annual Emerging Scientists Day (page 7).

This issue also introduces you to some new members of our UCI MIND team and asks you to put on your calendar our fall conference and winter gala (page 8).

We hope to see you soon.

Joshua D. Grill, PhD
Director, UCI MIND

MESSAGE FROM THE DIRECTOR
A 5xFAD mouse brain with extensive Aβ pathology represented by the bright green dots.

A 5xFAD + ABCA7 variant mouse with significantly less Aβ pathology.

complexity of late onset AD seen in humans. Once created, and tested, these mice will be freely distributed to researchers world-wide.

The UCI MODEL-AD team recently generated two new mouse models, called MAD1 and MAD2, which combine several important human aspects of the disease. Unlike past transgenic mouse models, these new models synthesize physiological levels of both human amyloid beta (Aβ) and tau protein in the mouse brain, and carry the genetic risk allele, APOE4. The integration of these three new components into MAD1 and MAD2 will allow scientists from around the world to do more comprehensive AD research.

Experiments are already underway to incorporate other known genetic risk variants into these new mouse strains.

To date, researchers have identified over 100 gene variants that could affect a person’s risk of developing AD. One of the most important of these variants is in a gene called ABCA7, which plays critical roles in lipid metabolism and immune response. To investigate the role of ABCA7 in AD susceptibility, I led a study, recently published in *Alzheimer’s & Dementia*, that introduced an amino acid variant in ABCA7 called V1599M into a well-known Aβ overexpressing mouse model, 5xFAD. Human genetic studies suggest the V1599M variant was predicted to be deleterious to ABCA7 function, which in turn could lead to increased risk of developing AD. Strikingly, our experiments demonstrated that in mice, this variant instead conferred protection against many Aβ-related pathologies, including lowering the production of Aβ and reducing the accumulation of Aβ into plaques. It also enhanced normal ABCA7 functions. These exciting results suggest that increasing the normal function of ABCA7, potentially by using small molecule drugs, could demonstrate a novel therapeutic intervention for AD.

For more information on MODEL-AD and to keep up to date with news/publications please visit https://www.model-ad.org
Nearly two-thirds of Americans with Alzheimer’s disease are women, but the underlying cause of this sex disparity is still poorly understood. For decades, research focusing on women’s health has been inadequate, for example, with a mere 0.5% of all neuroimaging studies conducted over the past 25 years focusing on women’s health. The potential to reach new heights in our understanding of the brain, especially today in the era of “big data” and artificial intelligence, is promising, but requires the right combination of expertise on women’s health and large-scale coordinated efforts to take meaningful steps forward.

The Ann S. Bowers Women’s Brain Health Initiative (WBHI), a new brain imaging consortium officially launched in November, represents a first-of-its-kind effort spanning multiple UC institutions specifically aimed at accelerating transformative discoveries in women’s health through deeply collaborative science. The namesake of the WBHI honors the legacy of the late Ann S. Bowers, a trailblazer known for her leading roles in Intel, Apple, and the Noyce Foundation who dedicated much of her life to philanthropy and advancing efforts in technology and innovation.

“Often in the neuroimaging community, we collect small amounts of data, and we do that repetitively. We have a siloed science model of how neuroimaging research is done. It overlooks one of the core features of the UC — we are one university system with campuses spread out across a geographically and demographically diverse state,” says the Director of the WBHI, Emily Jacobs, PhD, a cognitive neuroscientist from UC Santa Barbara (UCSB). Dr. Jacobs has spent her career conducting cutting-edge neuroimaging research for understanding the role of hormone action on the human brain. Her visionary work led to Dr. Jacobs being invited to the White House in March, where she represented the Ann S. Bowers WBHI at the signing of the historic executive order calling for $12B in funding for women’s health research.

UCI MIND faculty member and Professor of Neurobiology and Behavior, Craig Stark, PhD, is a founding member of the WBHI and leads a team of researchers who are spearheading data sharing efforts that will support the WBHI vision of generating the most diverse and comprehensive collection of data ever acquired for women’s brain health. Furthermore, UCI Associate Professor of Neurobiology and Behavior, Elizabeth Chrastil, PhD, is co-leading one of the WBHI’s inaugural studies, the Maternal Brain Project along with Dr. Jacobs, where their labs are using precision imaging to map the maternal brain starting pre-conception through one year postpartum. Enrollment for this study at each site is currently ongoing.

Together, UCSB, UCI, along with Stanford and Cornell as well as four other UCs, will harness the collective expertise and resources of the world-class imaging and computational science centers to collect, house, analyze and share WBHI neuroimaging data to drive discovery for women’s brain health.

To stay updated on WBHI’s latest news and research, visit the Ann S. Bowers WBHI website where you can find information about participating in research studies and registering for their monthly webinar series.
UCI MIND FACULTY RECEIVE HONORS

Four members of UCI MIND recently honored with prestigious awards.

Daniel Gillen, PhD, Chancellor’s Professor and Chair of Statistics and the leader of the Alzheimer’s Disease Research Center (ADRC) Data Management and Statistical Core was recently named a fellow of the American Association for the Advancement of Science (AAAS). AAAS Fellows are a distinguished cadre of scientists, who have been recognized for their achievements across disciplines, from research, teaching, and technology to administration in academia, industry and government, to excellence in communicating and interpreting science to the public. Dr. Gillen will be honored in September in Washington D.C. for this rare achievement.

Elizabeth Head, PhD, Professor and Vice Chair of Research in the Department of Pathology and Laboratory Medicine was awarded the Basic Science Faculty Mentor of the Year in the UCI School of Medicine. Dr. Head leads the Research Education Component (REC) of the UCI MIND ADRC and co-leads the TITAN T32 training grant, the SMAART T35 training grant, and the RAMP program for UCI medical students.

Michael A. Yassa, PhD, Professor of Neurobiology and Behavior in the School of Biological Sciences, James L. McGaugh Endowed Chair in the Neurobiology of Learning and Memory, Director of the Center for the Neurobiology of Learning and Memory and Associate Dean of Diversity, Equity and Inclusion has been awarded the Distinguished Faculty Award for Mentorship.

Frank M. LaFerla, PhD, Distinguished Professor and Dr. Lionel and Fay Ng Dean of the School of Biological Sciences, was honored with the 2024 Academic Senate – Better World Award. The award recognizes the exceptional efforts of faculty who have made extraordinary contributions to an area of importance to the core values of the University of California, Irvine.

We congratulate Professors Gillen, Head, Yassa, and Dean LaFerla for their immeasurable contributions to UCI MIND, the campus, and the world.

POST-DOCTORAL SCHOLAR AWARDED ALZHEIMER’S ASSOCIATION GRANT

Tiffany Petrisko, PhD, a postdoctoral scholar in Dr. Andrea Tenner’s lab was recently awarded a grant by the Alzheimer’s Association for her work examining the role of C1q, a component of the immune system hypothesized to have both beneficial and detrimental effects against Alzheimer’s disease. We sat down with Dr. Petrisko to ask her about her research and the award that will help propel her career.

What is the grant that you were awarded?

Petrisko: I was awarded the Alzheimer’s Association Research Fellowship, which is a 3-year, $200,000 award for postdoctoral fellows to pursue diverse research interests like mine.

What is C1q and how is it related to Alzheimer’s disease?

Petrisko: Loss of connections between neurons or synaptic loss is known to occur with cognitive decline in AD. This detrimental loss has recently been shown to be the result of activation of the complement cascade, a powerful component of the immune system that normally fights pathogens as well as disposes of dead cells and cellular debris including that in the brain. However, recent studies indicate that one component of that cascade, C1q, may have a neuroprotective role in the early stages of AD, where it can help the brain and synapses defend against the amyloid pathology.

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Will you tell us about your project?

Petrisko: We propose that C1q functions as a response to amyloid-associated injury early in AD to help clear amyloid and/or cellular debris to avoid neurotoxicity as well as directly trigger neuronal protective pathways in response to amyloid. As the disease progresses, activation of more detrimental components of the complement cascade can occur thereby contributing to the loss of synapses and the development of memory impairment. To test these hypotheses, C1q will be deleted from the brains of normal mice and genetically modified AD mice at two different periods: 1) at an early age prior to amyloid deposition and 2) just after significant amyloid plaque deposition. We will then profile the brain cells at each stage to examine differences in gene expression in the absence of C1q. Amyloid pathology and the number of synapses will also be assessed using high and super resolution microscopy.

Finally, we will test memory in these mice at both timepoints to examine how the absence of C1q affects cognition. If our hypothesis is correct and removing C1q early in AD worsens memory, but is beneficial later in disease, anti-C1q therapies now in clinical trials should be reevaluated to assure that treatment is delivered at the stage of the disease where it will provide benefit and not accelerate decline.

How do you hope this grant will help your career?

Petrisko: This grant will help lay the foundation for my own independent laboratory, in which I will continue to focus on the role of C1q on the progression of Alzheimer’s.
Every year the trainee led group, Research and Education in Memory Impairments and Neurological Disorders (REMIND) hosts a research symposium to highlight the work of trainees and early career scientists at UCI studying neurogenerative diseases.

The 15th Annual Emerging Scientists Symposium was held this year on March 13th, 2024. More than 125 people were in attendance to hear Elizabeth Head, PhD, Professor and Vice Chair of Research for the department of Pathology and Laboratory Medicine, give the keynote presentation on Alzheimer’s disease in people with Down syndrome. Her presentation highlighted the important research being done in her lab in this high-risk population and the significant contribution to research made by people with Down syndrome. The symposium also included six selected talks by graduate students and post-doctoral scholars on topics ranging from sleep alterations and COVID-19 to Alzheimer’s disease genetic mutations and microglial responses to amyloid pathology.

One of the highlights of the event is a poster competition where trainees present their work to a panel of judges. This year the judges awarded the post-doctoral scholar award to Poortata Lalwani, PhD in Dr. Craig Stark’s lab for her presentation titled, “Aquaporin-4: Unraveling reactive astrogliosis in Down syndrome with Alzheimer disease.”

Every year at the symposium, UCI MIND recognizes by committee decision, two scholars who have shown exemplary conduct in neurodegenerative research. The Carl W. Cotman Award, named after UCI MIND’s founder director, was awarded to Jean Paul Chadarevian, PhD, from the Blurton-Jones lab and Marina Ritchie from the Grill lab.

Jessica Noche, PhD, presenting her poster to the judges

Poortata Lalwani, PhD

Jean Paul Chadarevian, PhD

Cherie Stringer

Marina Ritchie
35th Annual Southern California Alzheimer's Disease Research Conference

Advances in Dementia Care
September 6, 2024
8:00 am - 3:15 pm | Hilton Irvine
conference.mind.uci.edu

The UCI MIND AD Research Center is supported by the National Institute on Aging (NIA) of the National Institutes of Health (NIH) under award number P30 AG066519.

This newsletter is supported in part by the California Department of Public Health, AD Program. Funding is pursuant to California Health and Safety Code Section 125275 – 125285.

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