UCI MIND: From the Bench to the Bedside & Beyond

Annual Update • 2019
Dear Friend of UCI MIND,

It’s an exciting time at UCI MIND, with tremendous increases in laboratory discoveries, more participants enrolled in promising clinical trials than ever before, and continued emphasis on novel educational programs to share our expertise with the local community and beyond.

We’ve been working hard to translate more laboratory, or “bench,” discoveries into clinical trials and improved treatments deployed at the “bedside” with patients.

For example, the MODEL-AD team is diligently working to create the next generation of animal models for Alzheimer’s disease, making it possible to investigate new treatments more directly and efficiently (page 5). In another example, a philanthropically funded project in the laboratory of Mathew Blurton-Jones, PhD, aims to identify FDA-approved compounds that are suitable for testing in human clinical trials in Alzheimer’s disease (page 6). And two current UCI MIND clinical trials, the NEAT and EXERT studies, are built upon UCI MIND laboratory science to test interventions in patients (pages 10-11).

In addition, our outreach efforts have increased the number of people willing to be contacted about research participation by over 50% in the past year (page 17). We’ve also launched a Facebook version of our successful “Ask the Doc” series (page 18).

With the prevalence and cost of Alzheimer’s disease increasing dramatically, and in the wake of recent failed trials of candidate drugs, the need for more rapid translation of promising laboratory science has never been greater.

Through the work of our researchers and the support of the community, UCI MIND will continue to make discoveries that advance care and prevention of Alzheimer’s disease and other neurodegenerative conditions.

Thank you again.

Gratefully,

Joshua D. Grill, PhD, Director, UCI MIND
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### Thank You
At the Bench

Scientific discoveries originating from the laboratories at UCI MIND
Frank LaFerla, PhD, Andrea Tenner, PhD, Kim Green, PhD, Grant MacGregor, PhD, Ali Mortazavi, PhD, Marcelo Wood, PhD, and David Baglietto-Vargas, PhD are hard at work on an $11.35 million project from the National Institutes of Health to create the next generation of mouse models to study Alzheimer’s disease.

UCI MIND is home to the creation of the first-ever mouse model to develop both amyloid plaques and neurofibrillary tangles, the two hallmark pathologies of Alzheimer’s disease. Created by Dr. LaFerla’s laboratory, this model was based on genetic mutations that cause the rare early-onset inherited form of the disease and has been utilized by researchers worldwide.

The new funding enables UCI MIND investigators to incorporate genetic discoveries over recent years to create more accurate models of the common, older-onset “sporadic” form of Alzheimer’s disease. Such developments will be key to rapid testing of promising therapies and preventions, with improved translational potential for predicting outcomes in human testing. The new models developed through this grant will be shared broadly with the scientific community.
As we gain a deeper understanding of the mechanisms that drive the development of this disease, we will be able to utilize this information to develop safe and effective therapies to treat and, eventually, prevent this debilitating disease.
—Mathew Blurton-Jones, PhD

UCI MIND investigator Mathew Blurton-Jones, PhD was awarded a $500,000 grant from the Orange County Community Foundation’s S.L. Gimbel Foundation Fund. The funding will support the testing of more than 1,200 FDA-approved compounds to gauge their effectiveness in preventing microglia from destroying brain synapses in Alzheimer’s disease.

Such damage “is seen frequently in patients with Alzheimer’s disease,” said Dr. Blurton-Jones, who is also the leader of UCI MIND’s induced Pluripotent Stem Cell (iPSC) Core. Microglia are immune cells that function as gardeners of the brain. They help neurons grow and support healthy brain development, and they also weed out unwanted neuronal connections, or synapses. The “hijacking” of this process is thought to contribute to Alzheimer’s disease progression.

“The goal of this study is to identify the 20 leading genes and drugs that reduce microglial synaptic ‘overpruning’ without altering their other normal functions,” Blurton-Jones said. “We are grateful to be the recipients of this OCCF grant and remain confident that through our clinical trials and studies, we could be well on our way toward finding a cure for Alzheimer’s disease.”
We are working as quickly as possible to find answers to the mysteries of Alzheimer’s disease, particularly focusing on learning why women are so much more likely to be affected... Our partnership with UCI MIND, which is focused on Alzheimer’s research, is an important step in reaching our goal.

—Maria Shriver

UCI MIND-WAM Women’s Initiative

UCI MIND is in year two of an innovative and exciting collaboration with Maria Shriver’s Women’s Alzheimer’s Movement (WAM), called the UCI MIND-WAM Women’s Initiative.

WAM is committed to helping world-renowned researchers discover why two out of every three patients with Alzheimer’s disease are women. This new partnership funds UCI research projects aimed to improve understanding of sex disparities in Alzheimer’s disease.

The partnership has awarded a $100,000 grant to recipients, Sunil Gandhi, PhD and Mathew Blurton-Jones, PhD, in an inaugural grant competition. Drs. Gandhi and Blurton-Jones are both Associate Professors of Neurobiology and Behavior at UCI.

Gandhi and Blurton-Jones are performing an exciting set of experiments that utilize cutting-edge technology in human stem cells, cell labeling, and in vivo microscopic imaging, to study the role of one specialized brain cell, microglia, in Alzheimer’s disease.

2 out of every 3 people with Alzheimer’s disease are women
UCI MIND-WAM Women’s Initiative

This grant allows us to immediately begin research that may prove vital to furthering the field’s understanding of microglia and their role in Alzheimer’s disease. We are grateful to Maria Shriver’s WAM and to UCI MIND for this opportunity to potentially make major strides toward understanding the role of sex in this devastating disease.
—Sunil Gandhi, PhD

“Microglia are the brain’s primary immune cells and play important roles in the clearance of toxic proteins from the brain, including the protein beta-amyloid that accumulates in Alzheimer’s disease,” Blurton-Jones explains. “My team and I recently developed a technique to convert human stem cells into microglia. By combining this approach with stem cells derived from patient’s skin, we can now study the impact of sex and genetics on human microglia.”

Several of the recently identified genetic risk factors for Alzheimer’s disease point to microglia as primary culprits that contribute to Alzheimer’s disease risk. The funded project will use skin cells donated by male and female research participants at UCI MIND to investigate how male and female microglia may differ in their interactions in the Alzheimer’s brain. Specifically, the human microglia will be injected into male and female mouse models of Alzheimer’s disease, and visualized using state-of-the-art in vivo microscopy techniques pioneered in the Gandhi lab.

The $100,000 award is anticipated to make the investigators highly competitive for much larger grants on this topic from the National Institutes of Health. The initiative to fund research through a grant competition, which was the brainchild of Ms. Shriver and UCI MIND Director Dr. Joshua Grill, is meant to make UCI a major hub for research to understand sex and gender disparities in neurodegenerative disease. Funded through philanthropy, the goal is to offer more competitions like this one.

Sunil Gandhi, PhD is working with Mathew Blurton-Jones, PhD, both Associate Professors of Neurobiology and Behavior, to research sex and gender disparities in Alzheimer’s disease
At the Bedside

Translating laboratory discoveries into improved diagnosis, treatment, and prevention
Translational Research: NEAT Clinical Trial

Research performed by UCI MIND scientist, Kim Green, PhD, Associate Professor of Neurobiology and Behavior, helped pave the way for an exciting new clinical trial.

The NEAT (Nicotinamide as an Early Alzheimer’s Treatment) study is testing whether high doses of nicotinamide, a component of Vitamin B3, can reverse the neurofibrillary tangles of Alzheimer’s disease.

In experiments performed in the laboratories of Drs. Frank LaFerla and Kim Green, nicotinamide was shown to improve the memory performance of mice that get both plaques and tangles.

What was most intriguing about the results was that the benefit of nicotinamide, which was given at much higher doses than would be found in typical dietary supplements, was due to a specific effect on the neurofibrillary tangles.

Thus, UCI MIND investigators, led by Drs. Joshua Grill and Daniel Gillen (left), set out to design a clinical trial to test the impressive results from the animal studies. The team of investigators, which also includes Dr. Steven Tam and the UCI MIND clinical trials team, was awarded a $2 million grant from the University of California UC Cures Alzheimer’s Initiative to perform their study, which is well underway.

What was most intriguing about the results was that the benefit of nicotinamide was due to a specific effect on the neurofibrillary tangles.
Translational Research: EXERT Clinical Trial

Among his many seminal discoveries, Carl Cotman, PhD has characterized the positive impact of physical exercise on the brain. Dr. Cotman is now among an elite group of investigators who have translated their own laboratory discoveries into human clinical research.

Dr. Cotman is leading the EXERT (Exercise in Adults with Mild Memory Problems) study with Dr. Laura Baker of Wake Forest University. The EXERT study is a national, 18-month clinical trial to test whether physical exercise can slow the progression of mild memory loss and/or Mild Cognitive Impairment in older adults between the ages of 65-89.

The study got a major boost when Maria Shriver (left) took to the airwaves to make people aware of its importance and urge more people to participate (https://www.exertstudy.org).

UCI MIND Founding Director and Professor of Neurology and Neurobiology and Behavior, Carl Cotman, PhD, now leads a groundbreaking clinical trial of exercise.

Maria Shriver, Founder of the Women’s Alzheimer’s Movement
Dementia in Down Syndrome

Down syndrome patients don’t always develop dementia, there’s an incremental increase of the risk with age, but the prevalence of dementia among this group is much higher than the typical population.

—Ira Lott, MD

Since its inception, UCI MIND has been a leading contributor to the study of the relationship between Down syndrome and Alzheimer’s disease. Director of the Down Syndrome Program, Ira Lott, MD, notes that the connection between the two diseases has been known since the 1940s. People with Down syndrome are born with an extra copy of chromosome 21, which carries the APP (Amyloid Precursor Protein) gene. This gene produces the amyloid precursor protein, which builds up in clumps called beta-amyloid plaques in Alzheimer’s disease. These plaques are fundamental to Alzheimer’s disease and are present in nearly all people with Down syndrome by age 40.

Dr. Lott, Professor and Emeritus Chair of Pediatrics at UCI’s School of Medicine, has led the Down syndrome research program for its entirety. UCI MIND recently recruited another prominent researcher in Alzheimer’s disease and Down syndrome, Elizabeth Head, PhD (right), who will co-lead the program. She has published over 150 peer reviewed papers, over 30 review papers and book chapters and serves as a grant reviewer for the National Institutes on Health. Dr. Head has dedicated over 20 years to the study of aging and Alzheimer’s disease with a focus on people with Down syndrome.
Brain Aging Across the Lifespan

The world famous 90+ Study continues to lead the field in understanding brain changes in the 9th, 10th, and 11th decades of life.

The productive research team, led by Claudia Kawas, MD, and Maria Corrada, ScD, successfully renewed the large National Institute on Aging grant that funds The 90+ Study and is recruiting new participants. The investigators have also launched critical collaborations with other institutions, such as a study with UC Davis to examine a diverse sample of people age 90 and older in Northern California.

The centerpiece of UCI MIND’s Alzheimer’s Disease Research Center is the Longitudinal Study, which follows more than 300 people annually. The goal is to understand changes over time, especially transitions across diagnostic categories.

All participants undergo a physical and neurological exam and a battery of cognitive tests. A large proportion also participate in additional tests, such as brain scans and lumbar punctures. The study includes people with normal cognitive function, Mild Cognitive Impairment, and Alzheimer’s disease. More than 20% of the study’s participants have been enrolled for a decade or longer, and most have agreed to donate their brain for autopsy research.
Making Strides for Huntington’s Disease

UCI MIND has a longstanding commitment to Huntington’s disease (HD) research in collaboration with our partner organization, HD-CARE.

UCI MIND scientist Leslie Thompson, PhD (above) and her team were recently awarded $6 million by the California Institute for Regenerative Medicine (CIRM) to perform continued testing of promising stem cell treatments for HD. This marks nearly $12 million in support from CIRM since 2008. The funding will allow the Thompson laboratory to conduct the late-stage testing needed to apply to the U.S. Food and Drug Administration for permission to start a clinical trial in people.

Dr. Thompson’s goal is to develop a therapy that slows down disease progression by transplanting stem cells shown to improve brain cell function in HD models.

HD is an inherited, fatal, neurodegenerative disorder that is currently incurable.

HD is an inherited, fatal, neurodegenerative disorder that is currently incurable.

Induced Pluripotent Stem Cell (iPSC) research at UCI MIND has the potential to lead to treatments and cures for neurodegenerative disorders, such as Huntington’s disease.
Beyond

Sharing knowledge gained through research with the community

Leadership Council

Gil Aranowitz       Diane Mondini
Sydney Balalis      Virginia Naeve
Judy Brower         Lorraine Navarro
Kim Butrum          Beverly Newton
Suzy Casey          Marla Noel
Susan Combs         Steve O’Leary
Barbara Demar       Ruth O’Leary
Carole Denham       Kathleen Olson
Jacqueline DuPont, Ph.D.  Karen Packard
William Edwards     Mark Phillips, Pharm.D.
Janet Gianulis      Randy Platt
Rick Godber         Jenn Quader
Joe Gonzalez        Susan Reese
Harriet Harris      Heather Sahargun
Lisa James          Wendy Salter
Karen Kamel         Jennifer Simpson
Sara Kelly          Keith Swayne
Katie Kirk          Jonathan Varenchik
Rosalyn Laudati, Ph.D.  Kitty Woodworth
Roger Lisabeth
The conference tackles an important theme each year with recent topics such as “Trials Today, Treatments Tomorrow” (2018) and “The Elephant in the Room: Sensitive Subjects in Dementia Care” (2017). The conference offers insight and access to cutting-edge scientific information for the entire Orange County community.

This year’s conference, scheduled for October 25, 2019, will focus on “30 Years of Discovery: Hope on the Horizon.” How close are we to solving Alzheimer’s disease? What have we learned so far? Where do we go from here? In its Pearl Anniversary, national experts will explore what we have discovered and charge forward with hope for solutions!
Research Participation

Simply put, across all areas of medicine, the single greatest deterrent to improving treatment and care is low levels of participation in research. Studies have shown the single most common reason clinical trials fail is they fail to accrue an appropriate number of patient participants.

—Joshua Grill, PhD

The UCI C2C Registry is a free, online tool to help inform the community about research opportunities at UCI that may be right for them

Seventy percent of people say their doctor has never talked to them about research. In an effort to increase awareness and encourage participation in medical research studies, UCI MIND designed and launched the UCI Consent-to-Contact (C2C) Registry. The C2C aims to improve the rate at which willing participants are enrolled in important medical research studies.

The registry, which was created with a $300,000 philanthropic gift from HCP, Inc. and launched in 2016, has enrolled more than 4,000 community members, well on its way to the goal of 10,000 volunteers. Signing up for the registry is simple and involves a short health information survey that takes about 20 minutes to complete. The registry is confidential and safe, free of charge, and enrollees are given the option to receive UCI MIND newsletters and social media posts. To date, more than 1,000 C2C registrants have been referred to important studies at UCI (https://c2c.uci.edu).
Ask Our Docs

UCI MIND’s Ruth Benca, MD, PhD, Professor and Chair of Psychiatry and Human Behavior, moderates a community Q&A panel with expert clinicians and scientists.

Ask the Doc: UCI MIND’s quarterly “Ask the Doc” program connects researchers with community members to answer questions about brain health, Alzheimer’s disease, and related topics. The series brings a medical doctor, psychologist, and neuroscientist to the community for short presentations and long Q&A sessions. We also offer an Ask the Doc translated in Mandarin, a Down syndrome-focused Ask the Doc, and plans are underway to hold our first “Pregúntele al Doctor,” in Spanish.

Facebook LIVE: In an effort to provide even more people access to this unique opportunity, UCI MIND recently launched its first-ever Facebook LIVE series, “Ask the Doc: Alzheimer’s Research Today!” The series features a new topic with a research expert the first Friday of every month at 9AM PST on UCI MIND’s Facebook page. Live viewers can type their questions into the comments box and receive an immediate answer from a UCI MIND researcher. So far, topics have included the connection between sleep and brain health, the causes of memory problems as we age, the role of inflammation and immunity in AD, and vaccines as a potential treatment for AD. Together, the first four episodes have been viewed over 4,000 times, and we hope to connect with many more people over the course of the series. Past episodes are posted on UCI MIND’s Blog and YouTube channel for those who do not use Facebook.

The series brings a medical doctor, psychologist, and neuroscientist to the community for short presentations and long Q&A sessions.
UCI MIND excelled at one of its major goals, namely, to attract talented investigators to the campus who offer creative and out-of-the-box ideas that advance Alzheimer’s disease research.

Elizabeth Head, PhD is an expert on Down syndrome and now directs the Alzheimer’s Disease Research Center Tissue Repository.

Ruth Benca, MD, PhD is a Professor and Chair of Psychiatry and Human Behavior who studies sleep and brain disease.

Bryce Mander, PhD is an Assistant Professor of Psychiatry and Human Behavior who investigates sleep disorders and cognitive aging.

Daniel Nation, PhD is a neuropsychologist who studies vascular contributions to cognitive impairment. He is an Associate Professor of Psychological Science.

Bin Nan, PhD has a history of working in Alzheimer’s disease, brain imaging, and high dimensional data. He is a Professor of Statistics.

Mari Perez-Rosendahl, MD is a fellowship-trained neuropathologist who is an investigator in our Neuropathology Core.

S. Ahmad Sajjadi, MD, PhD, MRCP is a behavioral neurologist who studies aphasia and hippocampal sclerosis and is an investigator in our Clinical and 90+ Cores.

David Sultzer, MD is a prominent geriatric psychiatrist who will lead the Alzheimer’s Disease Research Center Clinical Core and the UCI MIND Clinical Trials Program.

Vivek Swarup, PhD is an Assistant Professor of Neurobiology and Behavior who uses systems biology methods in human tissue to identify new treatment targets.
Thank You

On behalf of the entire UCI MIND team, thank you for this opportunity to share our work with you.

For questions or more information, please contact:

Joshua D. Grill, PhD
Director, UCI MIND
Associate Professor, Psychiatry and Human Behavior and Neurobiology and Behavior

Danny Harper
Senior Director of Development, UCI MIND
2656 Biological Sciences III
Irvine, CA 92697-4545
949.824.3793 office
714.369.7283 cell
ddharper@uci.edu
mind.uci.edu