

BIOMARKERS FOR ALZHEIMER'S DISEASE: A NEW FRONTIER

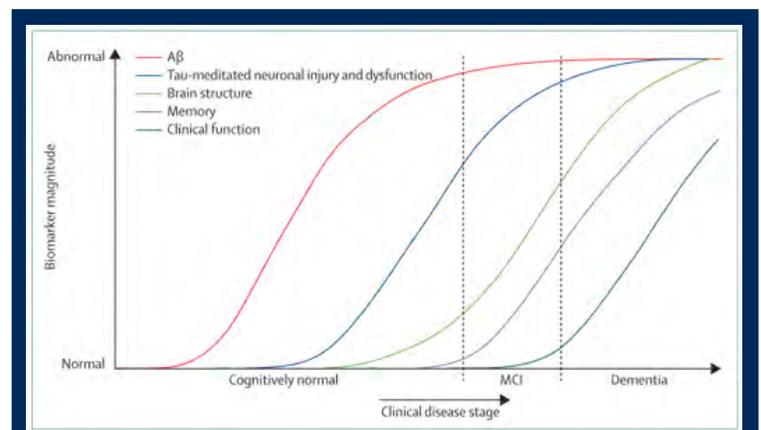
David Cribbs, Ph.D.

The National Institutes of Health defines a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” For purposes of this article, an Alzheimer’s disease biomarker is simply defined as an indicator of disease progression that may be altered by drug treatment, thereby demonstrating that the drug is hitting its disease target. Importantly, all clinical trials for Alzheimer’s disease utilize biomarkers of some form to assess whether the drug is actually affecting the disease pathway in the brain.

There is an enormous effort underway to identify and verify novel Alzheimer’s disease biomarkers, particularly early stage markers that reflect disease in the brain before there are any clinical symptoms. This is likely to be essential for effective drug development because so much damage has been done to the brain by the time clinical symptoms become evident. Over the past 15 years, cerebrospinal fluid biomarkers have been helpful diagnostically as well as for predicting who will eventually develop Alzheimer’s disease. For example, cerebrospinal fluid levels of amyloid- β 42 are a very good marker for the presence of amyloid deposition in the brain, regardless of clinical status. Likewise, total tau and phosphorylated forms of tau are useful in detection of neurodegeneration. When combined, these cerebrospinal fluid markers are useful not only in identifying people with Alzheimer’s disease, but also for predicting conversion from cognitive normalcy to very mild dementia, as well as monitoring rate of progression from Mild Cognitive Impairment or very mild dementia to more severe impairment.

Recently, the National Institute on Aging and the Alzheimer’s Association included biomarkers in new diagnostic criteria for Alzheimer’s disease because they are believed to result from specific pathological changes in the brain. For convenience, Alzheimer’s disease biomarkers can be divided into two

general classes: 1) imaging methods that can detect amyloid deposits in the brain, metabolic activity, or brain atrophy or shrinkage, and 2) biological samples, such as cerebrospinal fluid, where various forms of amyloid and tau can be measured. However, the order and magnitude of pathologic processes in Alzheimer’s disease are not well understood, partly because the disease develops over many years. Many diagnostic and therapeutic approaches to Alzheimer’s disease are currently changing due to the hypothesis that the underlying pathology starts 10 to 20 years before clinical signs of dementia appear (see figure below).



Dynamic biomarkers of the Alzheimer's pathological cascade

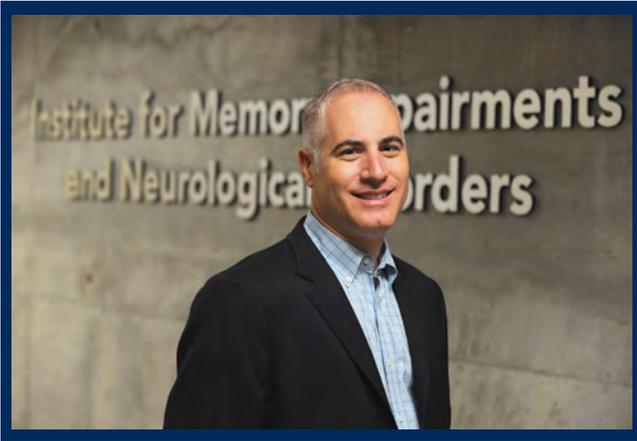
A β is identified by CSF A β 42 or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction are identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. A β = β -amyloid. MCI = Mild Cognitive Impairment. (With permission: Clifford R Jack Jr., et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurology*. 2010 Jan; 9 (1): 119-28)

Evidence for very early changes in brain pathology come from investigating individuals with autosomal dominant Alzheimer’s disease mutations as these individuals have a predictable age of onset and thus provide an opportunity to determine the sequence and magnitude of pathologic changes that occur before clinical symptoms can be detected.

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From the Director...

Frank LaFerla, Ph.D.

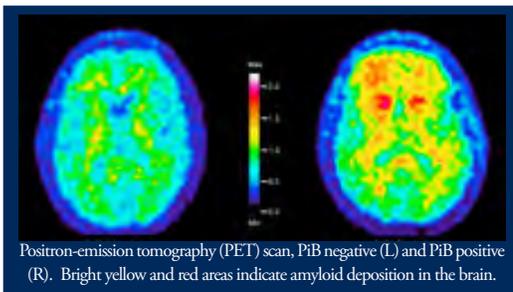


Despite the tremendous progress in Alzheimer's research, as of 2013, there are still no drugs or other therapies to definitively prevent, treat, or cure the disease. Now more than ever, it is time for us to marshal our resources to fight the war on this disease in much the same way that was done for cancer. The war on cancer began with the signing of the National Cancer Act of 1971 by President Nixon. I believe historians will eventually record that the war on Alzheimer's disease began with the signing of the National Alzheimer's Project Act by President Obama in January 2011. Now more than two years later, the first National Alzheimer's Plan has been released, and the President's fiscal year 2013 budget proposal includes \$100 million in additional funding for research, education and awareness, outreach, and caregiver support. This is certainly a step in the right direction, but still woefully inadequate.

With a new case of Alzheimer's disease developing every 68 seconds in the USA, the scale of the problem we are facing is simply colossal. As a result, UCI MIND seeks to establish strong partnerships with all interested stakeholders. Working together, we'll be able to harness our energies to maximize resources so that everyone with a vested interest understands the critical aspects of the disease course as well as how to best care for a loved one, and also to ensure that the pace of research continues, because the bottom line is that only research will identify an effective prevention, treatment or cure for this debilitating and awful disease.

We thank you for your support and urge you to engage your community of family, friends, and colleagues in this critical fight against a disease that will rob escalating numbers of Americans – at least 13.8 million by 2050 – of their most precious memories.

BIOMARKERS FOR ALZHEIMER'S DISEASE: A NEW FRONTIER (CONTINUED FROM PAGE 1)



The Dominantly Inherited Alzheimer Network (DIAN) is a collaborative effort of international Alzheimer disease centers that are conducting a multifaceted prospective biomarker study in individuals who are at risk for Autosomal Dominant Alzheimer's Disease (ADAD). These researchers found that ADAD was associated with a series of pathophysiological changes over decades in cerebrospinal fluid biochemical markers of Alzheimer's disease, brain amyloid deposition, and brain metabolism as well as progressive cognitive impairment. Concentrations of amyloid- β 42

in the cerebrospinal fluid appeared to decline 25 years before expected symptom onset. Amyloid- β deposition, as measured by positron-emission tomography with the use of Pittsburgh compound B (PiB), was detected 15 years before expected symptom onset. Increased concentrations of tau protein in the cerebrospinal fluid and an increase in brain atrophy were detected 15 years before expected symptom onset.

Rapid advances in the identification of Alzheimer's disease biomarkers now make it possible to detect Alzheimer's disease pathology in the preclinical stage of the disease in cognitively normal individuals. There currently is great optimism that improvements in Alzheimer's disease biomarkers will make it possible to select high-risk populations for clinical trials. In vivo visualization of Alzheimer's disease neuropathology and biological, biochemical or physiological confirmation of the effects of treatment likely will substantially improve development of new, more effective drugs.



UCI MIND AND ELITE OC PRODUCTIONS

Present

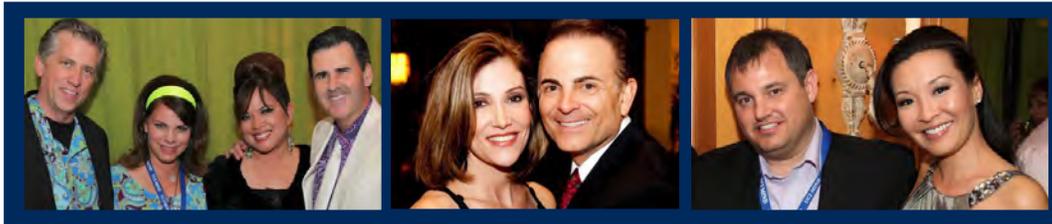
Time of Your Life

TOAST TO THE HOLIDAYS - THEN AND NOW



Time of Your Life, June 22, 2013 is the premiere event supporting Alzheimer's research at UCI MIND. Each year, guests enjoy a memorable evening that helps move us closer to a world without Alzheimer's. With support of our donors, UCI MIND is pursuing research to make memories last a lifetime. Proceeds from 2013 Time of Your Life will fund vital research directed at effectively treating and preventing this devastating disease.

Time of Your Life 2013 is being spearheaded by four couples committed to ending Alzheimer's disease, **Dr. Jacqueline DuPont and Marc Carlson, Linda and Burton Young, Rosemary and Rand Sperry, and Alice and Sean Cowell.**



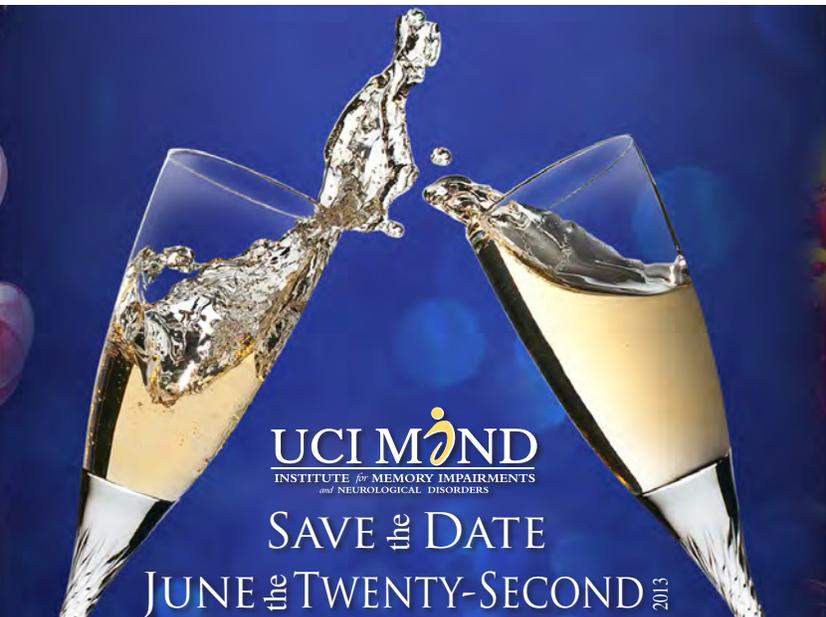
Our passionate Co-Chairs have planned something new and exciting for you! This year's event will take us back to cherished memories of holidays past, even as we make new memories today. Time of Your Life guests will celebrate the holidays – then and now – **on a new date, Saturday, June 22, 2013, in the new Hangar at the Orange County Fairgrounds.** Come celebrate with us!

- Valentine's Day
- Halloween and Thanksgiving
- Holidays at the Lodge
- A Happy New Year's Eve Countdown in the Big Apple

All funds raised by Time of Your Life will be used to enable our team of world-renowned scientists to pursue innovative, cutting edge research into the cellular, molecular and clinical risk factors for Alzheimer's disease and other neurodegenerative disorders. Notable projects underway today include development of a new mouse model which mimics the sporadic and most common form of Alzheimer's disease, immunization techniques, and creation of induced pluripotent stem cells (iPS) from one's own skin for investigation as a potential treatment modality.

Hundreds of volunteers have made a lifetime commitment to participating in the Institute's long-term study on memory and aging, including brain donation upon death. As the only NIH-designated Alzheimer's disease center in Orange County, and one of 29 in the nation, UCI MIND is at the forefront of scientific breakthroughs, from the bench to the bedside.

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RESEARCH TODAY. HOPE TOMORROW

The impact of Alzheimer's on families, the healthcare system, and our society as a whole is staggering today and will grow exponentially over the next 20 years as our population ages. Each day, over 10,000 Boomers are turning 65 – the age at which risk for Alzheimer's disease begins to increase dramatically. Costs associated with caring for people with Alzheimer's disease are expected to escalate to \$1.1 trillion dollars by 2030. Our nation has adopted the first national plan to address Alzheimer's Disease, the National Alzheimer's Project Act (NAPA), which sets forth the goal of effectively preventing and treating Alzheimer's disease by 2025. We are in a countdown to 2025. Only twelve years away! Please join us today!

We ask you to consider sponsoring Time of Your Life at one of the following levels. Each sponsorship level has multiple benefits in addition to those noted below.

\$25,000 Exclusive Platinum Sponsor – New Year's Eve Celebration

- All guests will enjoy a 90-minute exclusive virtual video-image production of our New Year's Eve Celebration incorporating your logo and name
- Premium table seating for 10 guests

\$10,000 Exclusive Gold Sponsors – Choice of one of Three Holiday Celebrations

- Three Gold sponsors will each benefit from all guests enjoying a 60-minute virtual-image production with your logo and name during the holiday production of your choice – Valentine's Day, Fall Halloween & Thanksgiving or Holidays at the Lodge
- Tickets for 8 guests

\$5,000 Silver Sponsor

- All guests will enjoy a 30-minute virtual-image production incorporating your logo and name
- Tickets for 8 guests

\$2,500 Bronze Sponsor

- Tickets for 2 guests; Name on Invitation and Program

Time of Your Life Ticket Information

Invitations coming soon; you will also be able to register online via our website: www.mind.uci.edu

Ultimate Premiere Reserved Tables \$3,000

Limited number of tables of ten. You and your guests will have your own table where you can celebrate the featured holidays and the "New Year's Eve Countdown to Midnight."

Individual Ticket Prices \$200/\$250

Early Bird Special – Tickets \$200 per person until **May 5, 2013**; \$250 thereafter.



Dr. Frank LaFerla arrives at Time of Your Life 2012

For additional information about this event, sponsorships, ticket purchases or donations, or to volunteer, please contact Linda Scheck, Director of Development and Donor Stewardship, at UCI MIND, 949-824-3251 or lscheck@uci.edu.

UCI MIND 501(c)3 Non-Profit Tax ID # 95-2226406



Highlights of the IRA Charitable Rollover

- Effective through December 31, 2013
- You must be 70½ or older on the date of the distribution in order to participate
- IRA Rollover Gifts count towards your required minimum distribution for an IRA
- Disbursements must be made directly to a qualified public charity, such as the UC Irvine Foundation
- You may rollover up to \$100,000 per person
- IRA charitable rollover gifts are not deductible

To learn more, contact Roland Ho at 949.824.6454 or e-mail roland.ho@uci.edu



PEOPLE IN THE NEWS

Highlighting Achievements at UCI MIND

UCI MIND RESEARCHER HELPS ORGANIZE ONLY DOWN SYNDROME CONFERENCE



Dr. Jorge Busciglio
Associate Professor

Jorge Busciglio, Ph.D., Associate Professor in the Department of Neurobiology and Behavior, is helping to organize the nation's only conference exclusively devoted to Down syndrome (DS) – Workshop on Down Syndrome: Molecular, Cellular and Behavioral Features and the Promise of Pharmacotherapies – to be held in Washington, D.C. this April. Dr. Busciglio will be presenting his team's latest findings on the role of energy deficits and oxidative stress in DS phenotypes at this conference, which provides a forum for scientists to share new discoveries, develop collaborations, and expand research related to cognition and pharmacotherapies in DS.

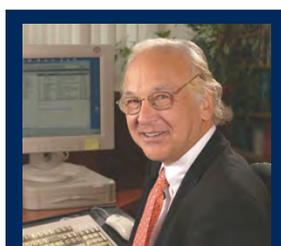
TWO RESEARCHERS HONORED WITH CARL W. COTMAN SCHOLAR AWARD

Szofia Bullain, M.D., a fellow in Geriatric Neurology and clinical instructor in the Department of Neurology, and Emily Mitchell Sontag, Ph.D., post-doctoral scholar with the Department of Psychiatry and Human Behavior, were recognized with 2012 Carl W. Cotman Scholar Awards at the annual UCI MIND Holiday Reception this past December. Working with UCI MIND's Claudia Kawas, M.D., Dr. Bullain has been investigating cognitive impairment in the oldest old and recently published an article in the *Archives of Neurology* showing that difficulty performing activities like walking at age 90 and older greatly increases the odds of having dementia. A recipient of many honors, Dr. Sontag has focused on Huntington's disease (HD), specifically helping to develop new, promising targets for drug development. Notably, Dr. Sontag's work investigating the structure and formation of toxic fibrillar oligomers and their modulation by small molecules with protective potential in HD models was published in the recently released inaugural edition of the *Journal of Huntington's Disease*.



(L to R) Dr. Frank LaFerla, Dr. Emily Sontag, Dr. Szofia Bullain, and Dr. Carl Cotman

DR. CARL COTMAN AWARDED NIH FUNDING TO STUDY BENEFITS OF EXERCISE IN MCI

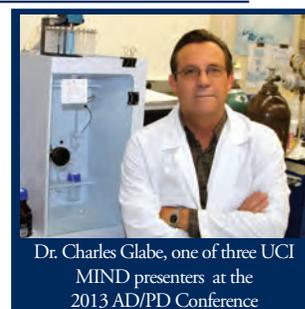


Dr. Carl Cotman
UCI MIND's Founding Director

In January 2013, Carl Cotman, Ph.D., founding director of UCI MIND, and Laura Baker, Ph.D., of the Wake Forest School of Medicine, received NIH funding to undertake the first clinical trial of exercise as an intervention in Mild Cognitive Impairment (MCI) as part of the Alzheimer's Disease Cooperative Study, a national consortium focused on developing treatments and diagnostic tools. The newly funded randomized, controlled trial is designed to investigate if supervised aerobic exercise can improve cognition, slow brain atrophy, or mitigate Alzheimer's pathology in older adults with MCI, a condition that often progresses to Alzheimer's disease. For more information about ADCS projects funded by the NIH, see <http://www.nia.nih.gov/newsroom/2013/01/nih-supported-alzheimers-studies-focus-innovative-treatments>.

UCI MIND INVESTIGATORS TO PRESENT FINDINGS AT PRESTIGIOUS CONFERENCE

The 2013 Alzheimer's & Parkinson's Conference (AD/PD™) will take place in Florence, Italy from March 6 - 10, and will unite international medical professionals for a dynamic scientific program revealing cutting-edge research and discoveries in diagnosing, preventing and treating neurodegenerative diseases. Multiple members of UCI MIND, including Drs. Frank LaFerla, David Cribbs and Charles Glabe, will be attending and presenting their innovative research at the AD/PD Conference. By serving as both an Alzheimer's disease and Parkinson's disease conference, the AD/PD 2013 will offer attendees a greater variety of new data, a truly multi-disciplinary scientific agenda, and enhanced opportunities to network with leaders in the field of these distinct neurodegenerative diseases.



Dr. Charles Glabe, one of three UCI MIND presenters at the 2013 AD/PD Conference

VIORELA POP, PH.D.



Viorela Pop, Ph.D., is the new Clinical Research Coordinator for the UCI MIND Alzheimer's Disease Research Center (ADRC). During a short stint as the Institute's education coordinator in the fall of 2012, it became obvious that Dr. Pop's unique skill set was perfectly suited for the newly vacated clinical research coordinator position. Dr. Pop brings an enthusiasm for academic research that aims to promote brain health and increase the well-being of those affected by cognitive decline. As a young adult, Dr. Pop also gained direct experience with patients and families through her involvement with local board and care facilities that provide care for persons with dementia.

Dr. Pop has studied neurobiology and brain diseases throughout her academic career. As an undergraduate student at UCLA, she performed research evaluating vascular changes in the brains of Alzheimer's disease patients and studied cellular activity in mouse models of Huntington's disease. During her tenure as a graduate student at UCI in the laboratory of Dr. Carl Cotman, the Institute's founder, she studied beta-amyloid neuropathology in the canine model of brain aging and dementia, and was mentored by several distinguished professors, including Dr. Frank LaFerla, Director of UCI MIND. As part of her post-doctoral training at Loma Linda University, she broadened her understanding of brain disorders in a laboratory studying the impact of traumatic brain injury on brain aging and Alzheimer's pathology. Her experience in laboratory research, with a clinical focus, has helped her develop an ability to translate basic science into common terms. She is passionate about making research findings accessible and useful to persons most in need of being aware of the data so they can apply new information to their specific circumstances.

Dr. Pop is thrilled to be part of UCI MIND, which is at the forefront of research on memory and aging, and poised to make the next big discovery in Alzheimer's disease.



MIND New and Events is a publication of the UCI Institute for Memory Impairments and Neurological Disorders in collaboration with the Alzheimer's Disease Research Center (ADRC) and the California Alzheimer's Disease Center (CADC). The ADRC is funded by a grant from the National Institute on Aging and supports and promotes interdisciplinary research on Alzheimer's disease. The CADC is funded by the California Department of Public Health. The CADC provides expert clinical assessments and diagnosis of memory complaints related to Alzheimer's disease and other dementias.

*Editor: Cordula Dick-Muehlke, Ph.D., Director of Education
Layout: Marcelo Soares, Education Coordinator*

MARCELO SOARES



In January of this year, Marcelo Soares joined the UCI MIND team as Education Coordinator. Marcelo has been a longtime supporter of UCI MIND and jumped at the opportunity to put his experience in healthcare and marketing to work on behalf of the Institute. In his new role, Marcelo will be involved in a spectrum of education and outreach activities, from coordinating educational events to enhancing the Institute's web and social media capacity. Additionally, Marcelo will take over design and layout of this newsletter, so watch out for his creative touch!

Marcelo has many years of experience in corporate marketing and project management, spending the last several years developing marketing strategy, brand messaging, and social media initiatives for Silverado Senior Living, a leading dementia-focused assisted living company. During his stint at Silverado Senior Living, Marcelo became acquainted with UCI MIND. Passionate about advancing research in Alzheimer's disease, Marcelo began volunteering his time to help with the Institute's annual "Time of Your Life" benefit event. Marcelo's talent for communicating ideas through creative mediums, especially online, is a natural strength he looks forward to sharing with UCI MIND.

During his college years, Marcelo learned firsthand about dementia when his father was diagnosed with Alzheimer's disease. Following the diagnosis, Marcelo joined his mother and siblings in caregiving until the disease took his father nine years later. Since then, Marcelo has dedicated his professional and personal time to supporting the search for a cure.

Marcelo resides in Costa Mesa with his partner and their two Boston Terriers. He is a transplant to Orange County and doesn't take it for granted. In his spare time, Marcelo enjoys getting outdoors whenever possible to hike, kayak or camp. When he can't do that, he enjoys reading philosophy with a nice glass of wine.



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**INSTITUTE for MEMORY IMPAIRMENTS
and NEUROLOGICAL DISORDERS**

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Research Today. Hope Tomorrow.