



MIND MATTERS

Commemorating 30 Years of
Alzheimer's Disease Research at UCI

SPRING 2015

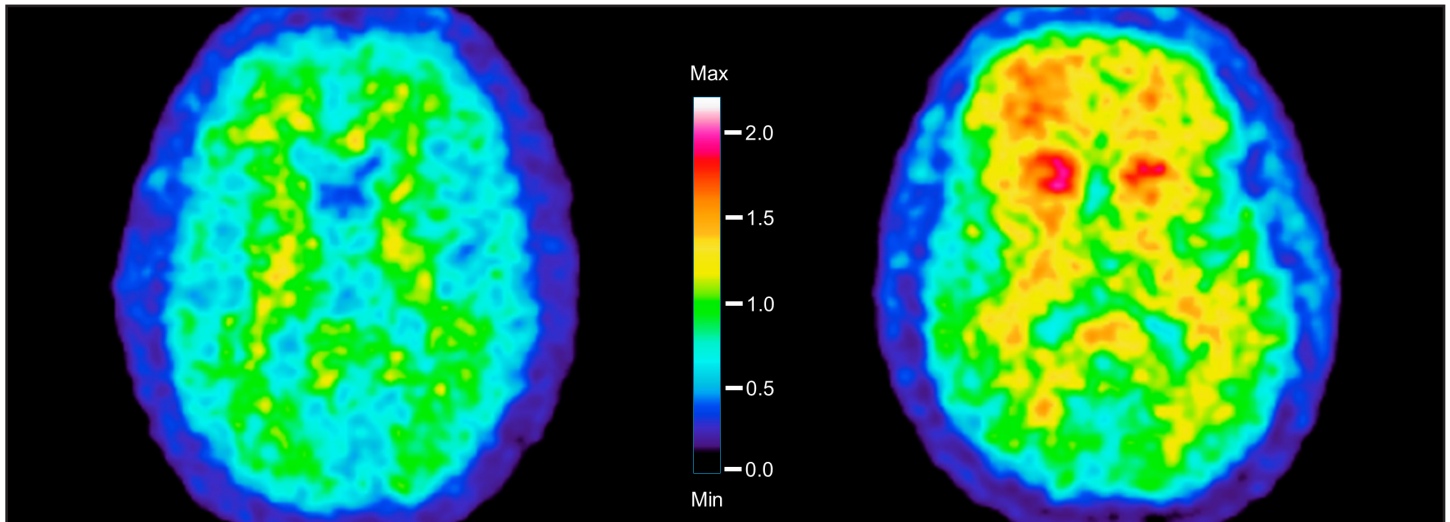


Celebrating 30 Years of Scientific Advancement in Alzheimer's Disease By Cordula Dick-Muehlke, Ph.D.

For a moment, step into the time machine of your mind and journey back to 1984, when Tina Turner's song, "What's Love Got to Do With It" was at the top of the charts and the movie "Ghostbusters" was a box office hit. Where was Alzheimer's disease? It was dawning upon scientists that the condition Dr. Alois Alzheimer had identified in 1907 was the most common cause of cognitive impairment in the elderly, then known as "senility." It hadn't even been settled whether Alzheimer's was a disease or just a normal part of aging. While a few scientific papers described the classic neuropathology of senile plaques and neurofibrillary tangles, no one had explored the prevalence, risk, and fundamental mechanisms of Alzheimer's disease (AD). Now, as science pursues multiple hopeful targets for intervention to delay or slow AD, imagine a world in which there were no treatments or promising therapeutic leads and the best we could offer was humane care. In this world, cognitively impaired older adults came to diagnosis late, when already moderately to severely impaired, and families truly had nowhere to turn, given the lack of experts and specialized resources.

It was in this context that Dr. Carl Cotman, then in the Department of Psychobiology (now Neurobiology and Behavior) at UCI, became interested in studying aging and started "scrambling" to get human brain tissue to conduct research at the molecular level. Now available through the nationwide network of Alzheimer's Disease Research Centers, of which UCI has been a part for the past 30 years, brain tissue collected in a standardized fashion was difficult if not impossible to obtain in the 1980s. "I begged and borrowed to get tissue," Dr. Cotman recalls, "and once I got ice crystals." Dr. Cotman's growing interest in aging and AD was fueled by Dr. Zaven Khatchaturian, whose pioneering efforts led to the creation of the Alzheimer's Disease Research Centers in the National Institutes of Health (NIH). Leaders at the time envisioned a clinical and scientific infrastructure within which knowledge about AD could grow and be shared nationally and ultimately worldwide. Dr. Khatchaturian established the structure of the Alzheimer's Disease Research Centers that remains to this day, a Clinical Core for the identification and characterization of individuals with cognitive impairment due to AD or a related disorder, a Neuropathology Core to collect and distribute brain tissue, an Education Core to create community-wide awareness about AD and engage the public in research, and an Administrative Core to ensure smooth operations.

Dr. Khatchaturian used his "powerful and innate ability at persuasion," as Dr. Cotman recalls, to convince him to join the nascent effort to study aging and cognition. Dr. Cotman notes, "I kind of liked the idea of studying aging because



everyone gets older, and it was an open field with a lot of opportunity.” Already a widely recognized neuroscientist, Dr. Cotman brought his ability to drive basic research into the field. Now 30 years strong, the UCI Alzheimer’s Disease Research Center (ADRC) was created through an initial collaboration with USC, led there by Dr. Caleb Finch. At the beckoning of Dr. Khachaturian, Dr. Cotman and Dr. Finch, who has since become renowned for his work on the basic mechanisms in the human biology of aging and AD, applied to establish the Alzheimer’s Disease Research Center Consortium of Southern California. By this time, Dr. Cotman had already started a brain repository, a key component of the Neuropathology Core of the proposed Alzheimer’s Disease Research Centers. An October 10, 1984 article in the Los Angeles Times announced the team’s success, with T. Franklin Williams, then director of the National Institute on Aging, noting that the consortium would “foster collaboration among multidisciplinary groups of investigators, thus making possible achievements that could not be realized by individual researchers working alone.”

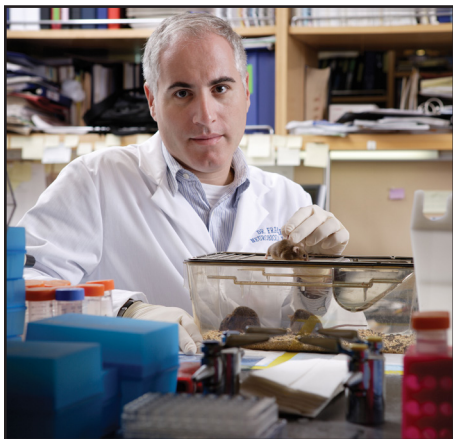
In a parallel, other opportunities were arising, including creation of the State of California Alzheimer’s Disease



Diagnostic and Treatment Centers, now known as the California Alzheimer’s Disease Centers. Through Dr. Cotman’s drive and leadership another first was achieved. With UCI hosting one of the first California Alzheimer’s Disease Centers, Dr. Cotman started building an infrastructure within the university to sustain science directed at understanding aging and neurodegenerative diseases for the long-term. His goal was to recruit at least one new investigator per year. A handful of interested scientists and clinicians evolved first into the Irvine Research Unit in Brain Aging and Alzheimer’s Disease and then into an organized research unit, initially known as the Institute for Brain Aging and Dementia and now as the Institute for Memory Impairments and Neurological Disorders (UCI MIND). Leveraging funding from multiple

public and private sources, Dr. Cotman and his successors, Dr. Frank LaFerla and then Dr. Andrea Tenner, built the organizational infrastructure in UCI MIND to sustain and nurture the ADRC as it advances into its fourth decade.

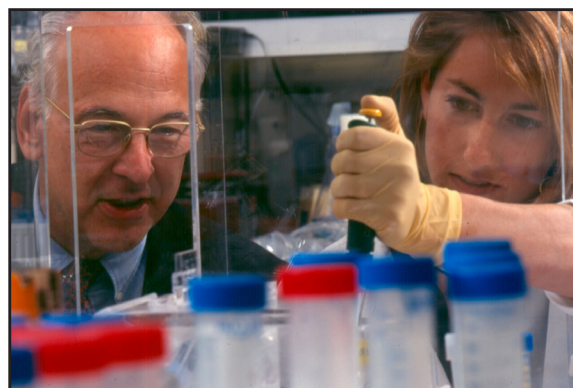
By the late 1990s, the initial Southern California Alzheimer’s Disease Research Center Consortium had grown substantially. At the urging of the NIH, Dr. Cotman applied for and received independent funding for UCI as an ADRC in 2000. All the while, Dr. Cotman had started recruiting and growing a world-class team of scientists and clinicians who were propelling research forward in areas that remain a major focus within the science of neurodegenerative diseases. In addition to Dr. Cotman, who is known for his work in neuroplasticity and the benefits of behavioral interventions, particularly exercise, the UCI ADRC has generated scientific leaders such as **Dr. Charles Glabe**, who has dedicated his research efforts to understanding the role of amyloid in AD; **Dr. Frank LaFerla**, who developed the first transgenic



mouse model of AD exhibiting plaques and tangles, now used by investigators worldwide; **Dr. David Cribbs**, who is helping create safe immunotherapies that will clear the toxic beta-amyloid protein from the brain; **Dr. Andrea Tenner**, whose discoveries continue to reveal how the immune system goes awry in AD and causes harmful neuroinflammatory responses; **Dr. Claudia Kawas**, whose groundbreaking research into the oldest old has uncovered how aging and dementia differ after age 90; **Dr. Ira Lott**, who has increased our knowledge about the intimate relationship between Down syndrome and AD; and **Dr. Malcolm Dick**, who has provided excellence, distinction, and stability to the UCI ADRC Longitudinal Study on Aging while advancing knowledge of motor learning in AD and cross-cultural neuropsychological assessment. Among the many contributors to the ADRC during the past 30 years, these eight are featured in this newsletter for their dedicated service and lasting impact.

Surrounding these people, Dr. Cotman developed interdisciplinary connections within the university, particularly with the Departments of Neurobiology and Behavior, Neurology, Anatomy and Neurobiology, Chemistry, Cognitive Science, Developmental and Cell Biology, Molecular Biology and Biochemistry, Pathology, Physiology and Biophysics, Psychiatry and Human Behavior, and Statistics, in order to continuously cultivate and nurture young investigators.

While building this community of researchers within the university, Dr. Cotman extended outreach into the community through widespread education to the lay public and collaboration with like-minded organizations. In 1990, the UCI ADRC launched an annual conference on AD, now known as the Southern California Alzheimer's Disease Research Conference, which celebrated its 25th anniversary in September, 2014. Through this conference, a lasting collaborative partnership with the Alzheimer's Association, Orange County Chapter (AAOC) was born. From education to family support, the AAOC has enriched the UCI ADRC's capacity to achieve its goals. Additionally, the AAOC has generously helped fund cutting-edge research.



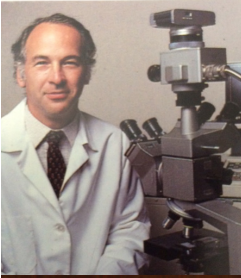
Since assuming directorship of the ADRC in 2012, Dr. Frank LaFerla has continued to build the center, most recently adding an Induced Pluripotent Stem Cell Core in 2014. Additionally, Dr. LaFerla has continued to expand awareness of the ADRC and, as federal research funding levels reached historic lows, has grown the effort to raise private



funding that would enable investigators to test new ideas. Building on its legacy and driven by insightful vision and leadership, the ADRC continues to prosper and make major contributions to the field on the basic mechanisms of neurodegeneration and neuroprotection, the ability of synaptic plasticity to maintain cognitive function with age and AD, behavioral and pharmaceutical interventions, and new techniques such as brain imaging and biomarkers to study the impairment of learning with age and AD.

As the UCI ADRC continues to pursue effective treatments and prevention strategies for AD, we reflect here on the leaders, like Dr. Cotman, that have advanced our understanding of neurodegenerative disorders over the past three decades. In Orange County, we can be forever grateful that Dr. Cotman recognized the potential of joining the effort to study aging and cognition, as 30 years later this community remains home to a stellar Alzheimer's Disease Research Center.

Faculty: Then and Now



Realizing a Vision

Carl Cotman, Ph.D., Founding Director of UCI MIND; Professor of Neurology; Neurobiology & Behavior

I arrived at UCI in 1968 straight out of graduate school and, as I recall, my first task was writing an NIH grant, a completely foreign concept. I got it funded – much to my surprise – and I continued to move forward, eventually conceptualizing and building what is now UCI MIND. In the early 80s, I envisioned that research on AD would be an exciting opportunity for my group and many other investigators at UCI. I had hoped we would reach where we have come today, but I must say we have exceeded expectations. Since its inception, the UCI ADRC and the Institute have served as the engine that drives basic and clinical research. I am very pleased to have nurtured and helped in this successful endeavor. Our program has opened multiple doors for continued discovery. And I believe we have now turned the corner for realizing the dream of slowing down the onset and progression of AD. It has been and continues to be rewarding and fun!



Discovering the Role of A β ₄₂ in Alzheimer's Disease

Charlie Glabe, Ph.D., Professor, Molecular Biology & Biochemistry

In 1989, as an assistant professor at UCI, I was investigating sea urchin fertilization. My career took a turn when Dr. Carl Cotman asked me to make a peptide for his lab. Well, this peptide turned out to be A β ₄₂, which is now thought to play a causative role in Alzheimer's disease (AD). At the time, I was told to be careful about how I handled this supposedly insoluble peptide which might cause AD. Naturally I was concerned about getting AD from the A β ₄₂ fragments floating in the air around the lab but doubted that the peptide was as insoluble as I'd been told. Hence, I hoped it wasn't infectious either. Because of this serendipity – of making a peptide for Dr. Cotman – I became one of the first people in the world to work on the role of A β ₄₂ in AD. While I can tell you that I haven't developed AD yet, I am currently working on the cell-to-cell transmission of amyloidosis between neurons.



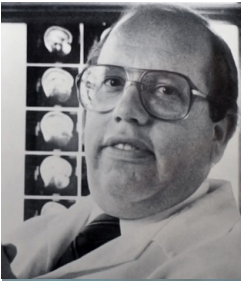
Discovering the Role of Inflammation in Alzheimer's Disease

Andrea Tenner, Ph.D., Director, UCI MIND; Professor, Molecular Biology & Biochemistry

In 1992, I was a new faculty member at UCI investigating the role of a powerful immune system pathway called “the complement system.” One day, Dr. Carl Cotman called me to discuss Alzheimer's disease (AD), as he had just seen a publication suggesting complement activation could play a role in this disorder. While the complement system evolved to protect the body from infection, uncontrolled activation of this pathway can cause detrimental inflammation. I knew very little about the brain, but Dr. Cotman, along with David Cribbs, who was doing a sabbatical in Carl's lab, pulled me into the exciting field of neuroscience. Through critical collaborations with Charlie Glabe and later Frank LaFerla and Claudia Kawas, we have demonstrated that the complement system is activated by amyloid fibrils, that this occurs in both human AD brain and mouse models of AD, and that it can contribute to the development and progression of AD in mouse models. Now we hope to determine if inhibition of this system can be a successful therapeutic intervention to substantially slow the progression of AD.



Faculty: Then and Now



Alzheimer Disease Research and Down Syndrome

Ira Lott, M.D., Professor & Chair, Pediatrics, School of Medicine

I joined the ADRC in 1985 and, with the support of Dr. Carl Cotman, established the first Down syndrome program within an ADRC. Even today, our ADRC is one of the few with a sustained and robust commitment to understanding the link between development and aging in Down syndrome. While focused on helping people with Down syndrome, we are also expanding knowledge about Alzheimer disease in the general population. Our contributions include the neurobiology of plaques and tangles, the role of oxidative stress in pathology formation, and multiple clinical trials. Involving numerous scientists from the ADRC, now under the guidance of Dr. Frank LaFerla, our work has resulted in significant publications as well as independent NIH grant funding. My research manager, Eric Doran, has made a career commitment to people with Down syndrome and their families – an example of the salutary effect people with Down syndrome have on investigators and caregivers.



Helping Families through State-of-the-Art Diagnostics

Malcolm Dick, Ph.D., Senior Neuropsychologist, UCI MIND

In 1984, I came to UCI to complete a postdoctoral fellowship and began researching preserved abilities in Alzheimer's disease, specifically motor learning. In 1989, Dr. Cotman asked me to help develop the neuropsychological test battery used at the UCI ADRC. At the time, clinicians were just figuring out the best tools and methods to identify dementia. Now 30 years later, I've had the opportunity to conduct over 7,000 assessments, helping patients and their families through state-of-the-art diagnostics and treatment recommendations to improve quality of life. As well, I've engaged in a variety of research activities over the years, such as helping develop the Cross Cultural Neuropsychological Battery. As part of the ADRC Clinical Core, however, it has been most meaningful to see patients benefit from our assessment and clinical care services while generously contributing the neurological, neuropsychological, and other data we collect, and ultimately their brains upon death, to our ADRC research effort.



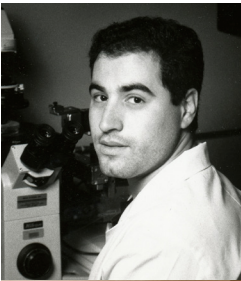
Immunotherapeutic Approaches for Treating Neurodegenerative Diseases

David Cribbs, Ph.D., Associate Director, UCI MIND; Neuropathology Core Co-Director

In November 1992, I came to UCI for an eight-month sabbatical from St. Mary's College of Maryland and the Naval Research Laboratory in Washington, DC. I had been collaborating with Professor Carl Cotman at UCI for some time on the development of chambers for growing brain cells (i.e., neurons) into organized networks, similar to the way the cells are connected in the brain, in order to better understand how the cells function. While working on this project, Dr. Cotman offered me a faculty position in the Department of Neurology at UCI. Eventually, this work led to a highly cited report in *Nature Methods* describing the chamber, which was patented and is widely used by other researchers. More recently, my laboratory has been involved in the development of novel vaccines for clearing the brain of Alzheimer's disease pathology.



Faculty: Then and Now



Building the ADRC for the Future

Frank LaFerla, Ph.D., Hana & Francisco J. Ayala Dean, Ayala School of Biological Sciences

I joined the faculty at UCI in 1995 as an assistant professor of Neurobiology and Behavior and shortly thereafter became involved in the ADRC, which at the time was a collaborative enterprise between USC and UCI. In 2000, the National Institute on Aging suggested that UCI establish its own ADRC to grow the research enterprise, capitalize on our strengths, and better position UCI to address the growing number of people with Alzheimer's disease (AD) in Orange County. One of my earliest accomplishments as part of the UCI ADRC was developing the first animal model to harbor both plaques and tangles. Through the UCI ADRC, we have been able to distribute this model to over 150+ investigators in more than 20 countries. Over the years, my involvement in the UCI ADRC has grown, not only scientifically but also administratively. Two years ago, I succeeded Dr. Cotman as the director of the UCI ADRC and now lead the Administrative Core, which oversees all of the strategic goals and financial aspects of the center. As director, I have been excited to play a major role in recruiting new faculty to the UCI ADRC and establishing a new national core focused on developing induced pluripotent stem (iPS) cells to better study AD.



Leading our Understanding of the Oldest Old

Claudia Kawas, M.D., Professor, Neurology; Neurobiology & Behavior

After 15 years on the faculty at Johns Hopkins School of Medicine, I came to UCI in 2000 as a geriatric neurologist and researcher. As Professor of Neurology and of Neurobiology and Behavior, I am delighted to lead the ADRC Clinical Core along with Dr. Aimee Pierce. With its outstanding physicians and scientists, my 14 years at the UCI ADRC have given me the unique opportunity to uncover the secrets of long life through The 90+ Study, focusing on the epidemiology of aging and Alzheimer's disease, the determinants of successful aging, longitudinal and clinical pathological investigations, clinical trials, and most recently, cognitive and functional abilities of the oldest old. I am excited and motivated by the lessons we are learning from individuals who have lived to 90 years and beyond. And with the incredible support of the ADRC participants and local community, the UCI ADRC will continue to be a leader in making life better for all of us as we age.



Our Commitment to Educating the Community

Since its beginning, the UCI Alzheimer's Disease Research Center has sought to bring the latest knowledge about Alzheimer's disease to the professional and lay community in Orange County through diverse and pioneering education and outreach activities. Involving widely recognized experts, the annual Southern California Alzheimer's Disease Research Conference offered, in partnership with the Alzheimer's Association, Orange County Chapter, has made cutting-edge findings available to our community for over 25 years. Since 1996, the quarterly Family Education Series has been a source of support and information for caregivers. And, starting in 2009, the popular and ongoing Ask the Doc forum has given audience members the opportunity to take the microphone and address their most pressing questions to a panel of UCI experts.

Building on this history, UCI MIND continues to develop innovative experiences that bring understanding and awareness about aging, memory, and cognitive disorders to the community. We encourage you to learn more about the education programs at UCI MIND by visiting <http://mind.uci.edu/community>.

Institute Highlight: Dick and LaVonne Holmes



Dick and LaVonne Holmes

Across the past 30 years, over 105,000 Americans have joined the effort to advance our knowledge of Alzheimer's disease (AD) and related dementias by volunteering to participate in research at one of the now 29 Alzheimer's Disease Centers nationwide. Dick Holmes is one of those individuals.

Dick joined the ADRC in 2013, but his journey there started in 2008 after a physician diagnosed him with MCI. During the next five years, Dick experienced a variety of health problems, leaving him and LaVonne wondering about how his cognition was being affected.

On a search for answers, LaVonne attended the 2010 Southern California Alzheimer's Disease Research Conference, where she first learned about UCI MIND. From there, she started attending the Institute's quarterly Family Education Series. After pursuing two referrals that weren't a good match for Dick, LaVonne brought him to UCI MIND for an assessment. About the assessment, Dick jokes, "They know more about me than I know about myself." Humor aside, LaVonne notes, "We appreciate the effort that goes into the evaluation and the expertise that we don't have."

As a participant in the UCI ADRC, Dick, who has mild cognitive impairment (MCI), is assessed annually and contributes all the findings from the neurological and neuropsychological evaluations, brain imaging, blood tests, and family interviews to a national database accessible to researchers worldwide. As well, Dick, like the other ADRC participants nationwide, has agreed to donate his brain upon death for research.

Dick was inspired to join the ADRC, as well as other UCI-based research studies, by his mother, who had cancer and was always ready to undergo experimental treatments to help. Her attitude, as LaVonne recalls, was, "This would help somebody else. We knew it would never benefit her in any way. But only this mass of material that they are accumulating will help someone down the line." And so it is with Dick today; he knows he's making a difference for future generations.

These days, Dick, a banker for 42 years, still enjoys playing bridge, being with friends, and most of all, spending time with his constant companion, Benji, a 12-year-old rescue dog who is always by his side. And, he is forever grateful to LaVonne, his wife of 58 years, for being his care partner.

Without people like Dick, who voluntarily and generously participate in research, we wouldn't know what we do today about the development and progression of AD as well as its treatment and prevention.

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Research Today. Hope Tomorrow.

Investing in Discovery

Through the years, UCI MIND has made great strides in research on Alzheimer's disease (AD) and related cognitive disorders which affect millions of Americans and their families. From the beginning, this work has been accomplished through ongoing public and private funding. UCI MIND research scientists rely on this combination of support to take the bold steps needed to conquer AD.

Through the generous support of our community, UCI MIND has been able to sustain the only Alzheimer's Disease Memory Assessment and Research Center in Orange County despite the recent difficult years of federal and state budget cuts. Notably, UCI MIND has been able to leverage individual private donations while establishing the first federally funded AD iPS Stem Cell Bank and also fund three junior investigators to conduct pilot projects that use banked stem cells.

Now with support from the private sector, UCI MIND will begin recruiting cognitively normal individuals at high risk for developing AD into a registry for studies on the preclinical stage of the disease, during which biological symptoms are taking place but symptoms are not yet evident. With an increasing focus on early intervention, clinical researchers at our Alzheimer's Disease Research Center will quickly match highly qualified research volunteers with appropriate clinical trials and research studies as soon as they are available.

As UCI commemorates its 50th anniversary and UCI MIND celebrates 30 years of Alzheimer's disease research, we reflect on a bright past – but the story isn't over. We need your support to ensure a brilliant future in which memories last a lifetime. Invest in discovery today by making a contribution to UCI MIND. We value your donation of any amount to support research.

Make a donation online by going to our website at www.mind.uci.edu and clicking on Donate to find the e-giving page.

Alternatively, mail a check made out to UCI MIND to Linda Scheck, Director of Development and Donor Stewardship, at UCI MIND, 2646 Biological Sciences III, Irvine, CA 92697-4545. Or you may contact Linda for more information at 949-824-3251 or lscheck@uci.edu.