Charles F. and Joanne Knight
Alzheimer Disease Research Center (ADRC)

Knight ADRC and the Memory & Aging Project

HORIZONS

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New Technique Clarifies Methods of Protein Clearance

New Alzheimer disease research details a technique that speedily measures levels in the brain of a damaging protein fragment, and insight into why mutations in a specific gene increase the risk of developing the disease.

The new measuring technique could lead to a better understanding of how amyloid beta, a key protein associated with Alzheimer disease, is produced in and removed from the brain, which would help scientists design treatments to limit the protein's accumulation.

Carla Yuede, PhD, Assitant Professor of Neurology and John Cirrito, PhD, Associate Professor of Neurology, Washington University School of Medicine look at the tiny probe they used to measure the damaging protein. *(Photo: Robert Boston)*

When you use your brain – planning a meal, remembering the route to the store – your neurons release a sticky molecule known as amyloid beta, as a byproduct of their normal functioning. In healthy people, the protein fragment is cleared before it can do any damage. In people with Alzheimer disease, clearance is impaired, and amyloid beta builds up into clumps known as plaques.

Many of the treatments being studied for Alzheimer's are designed to reduce amyloid beta in the brain. John Cirrito, PhD, an associate professor of neurology, Carla Yuede, PhD, an instructor in neurology, and colleagues have developed a new technique that measures minute-by-minute changes in amyloid beta levels in the brain. Previous techniques had allowed measurements only once an hour.

"For the last 14 years we had a technique in which we would do something to the mouse – give it a drug, have it perform a certain behavior – and we'd find out what happened to its amyloid beta levels an hour later," said Cirrito. "Waiting that long just wasn't good enough. Neural activity happens on a rapid time scale, and we needed to see a direct connection between the intervention and the amyloid beta levels."

The researchers attached antibodies that specifically detect amyloid beta onto a tiny electrode, zapped it with a small amount of voltage and measured the resulting current.

"People have used this approach for other molecules, but the detectors were the size of a microscope slide," Cirrito said.

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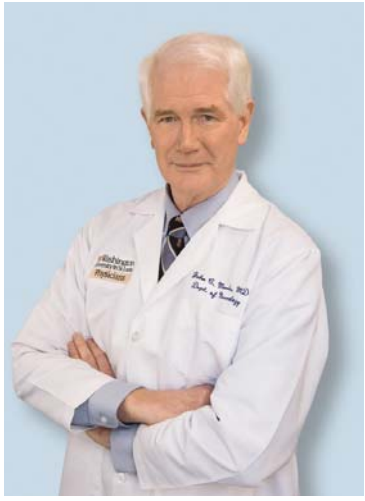
Update from the Director



All of our research volunteers are extremely valuable to the work of the Knight Alzheimer Disease Research Center. Building on a theme first discussed at our annual Participants' Breakfast in June, I write now to emphasize the importance of each participant remaining fully active over time. It is only when we are able to detect change over time (such as in our clinical assessments, cognitive testing, imaging, and analysis of biofluids such as cerebrospinal fluid) that we can capture the initial occurrence of Alzheimer disease (AD). We want to detect AD when it first appears, as we believe that initiating therapies at that point, before there is substantial brain damage, holds the promise of delaying or even preventing Alzheimer dementia. Following healthy individuals over time also provides us with the opportunity to note what is "normal" as we age. Hence, I write to underscore the immense value of your participation in our studies over time.

I appreciate that we ask a great deal from you. I also appreciate that life brings conditions (such as an illness or death in the family) that unavoidably interfere with participating in our studies at a particular point in time. What I ask of you is to make all reasonable efforts when you are available to schedule and complete your assessments. In that way, we will move much closer to finally defeating this terrible disease.

With many thanks,

John C. Morris, MD, Friedman Distinguished Professor of Neurology

WU Students Win $10,000 Award for AD Diagnostic Tool

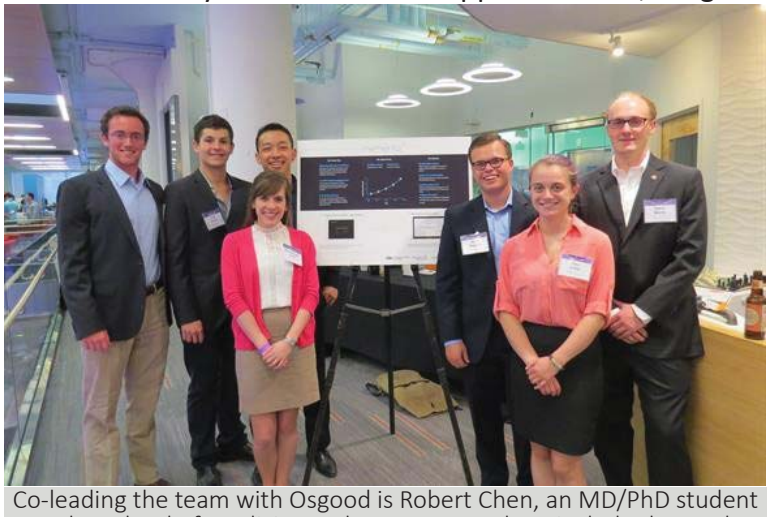
Memento, an interdisciplinary team of Washington University students, won $10,000 in a national competition for their mobile app designed to help diagnose Alzheimer disease more quickly.

The team is one of 10 finalists for the Student Technology Prize for Primary Healthcare, awarded by the Massachusetts General Hospital's Ambulatory Practice of the Future and sponsored by the Gelfand Family Charitable Trust.

To receive a formal Alzheimer disease diagnosis, patients must be referred from their primary-care physicians to a neurologist. However, due to significant backlog, patients and their families may wait from several months to one year for an appointment, during which time a patient's disease could rapidly progress.

To help shorten this process, the WashU team developed a mobile app to be completed by the patient's caregiver to help a primary-care physician more accurately determine if a patient needs to be referred to a neurologist for additional testing and diagnosis.

"The app replaces the 45 minutes of time spent by the physician interviewing the caregiver while simultaneously trying to scribble notes and answer the caregiver's questions," said Allen Osgood, co-lead of the team and a rising senior majoring in computer science in the School of Engineering & Applied Science. "By working through the app in advance, we give the physician, caregiver and patient more time to focus on the potential diagnosis and outcomes."



Co-leading the team with Osgood is Robert Chen, an MD/PhD student at the School of Medicine. Other team members include three additional Engineering students: Henry Morris and Matt Kramer, both majoring in biomedical engineering, and Rob Osorio, majoring in computer science; Mary Morgan Scott, a medical student; Hannah Bucklin, an MD/PhD student, and two May 2016 graduates: Dana Arditti, who earned a bachelor's degree in computer science, and Jenny Liu, who earned a bachelor's degree in biology with a concentration in neuroscience.

In addition to the mobile app, Memento is developing an objective cognitive assessment. The team is working with neurologists in the Knight Alzheimer's Disease Research Center, as well as the St. Louis chapter of the Alzheimer's Association, on both aspects of its work and is preparing for a future clinical trial.

By Beth Miller, first printed in Washington University Engineering News, August 2016.

Honors, Awards, and Funding

The **Adult Children Study** (ACS) received grant funding approval from National Institute on Aging in September. The grant, which was first funded in 2005, will be funded from 9/30/16 until 5/31/21 for total costs of $10, 313,347.

Congratulations to the 2016 Knight ADRC Pilot Grant Awardees:

- Identification of cell surface TREM-2 ligands involved in Alzheimer's Disease pathogenesis, **Thomas Brett**, Assistant Professor of Medicine, Biochemistry and Biophysics
- Decoding clinical and genetic contributions in Alzheimer disease dementia (A2D2), **Gregory Day, MD**, Instructor, Neurology
- Surveillance for Impending AD in Down Syndrome: A WU ADRC/IDDRC Feasibility Study, **Christina Lessov-Schlaggar, MD**, Assistant Professor, Psychiatry

Erik Musiek, MD, PhD and **Erik Herzog, PhD** received a 2016 Hope Center Pilot Award for their project: Fixing the Broken Clock: Optogenetic methods to restore circadian rhythms in a mouse model of Alzheimer's Disease.

Virginia Buckles, PhD (shown below) received the 2016 Harvey A. and Dorismae Hacker Friedman Award for Excellence in Service to Older Adults from the Friedman Center for Aging and the Foundation for Barnes-Jewish Hospital.

The Journal of Alzheimer's Disease applied bibliometric analytics to identify 300 highly cited papers relevant to AD research, published in the last 5 years. Members were invited to vote for their top 10 most influential papers of the last five years, and to comment on why they selected a particular article - what made it outstandingly influential or how it changed the field. Congratulations to the following Knight ADRC investigators who were recognized: **Drs. Morris, Holtzman, Roe, Head, Bateman, and Cruchaga**.

Pastor Douglass Petty, PhD has been appointed Chair of the African American Advisory Board (AAAB). **Reverend C. Jessel Strong** will serve as AAAB Vice-Chair, and **Mary Harper Thomas** and **Mary Attyberry Polk** have accepted positions as members.

John Cirrito, PhD received the 2016 MetLife Promising Investigator Award in Alzheimer Disease, presented July 25, 2016 in Toronto, Canada. Cirrito also received an Alzheimer's Association research for his project *Role of Glucocorticoid Receptors in Sex-Related Differences in Alzheimer Disease.*

Andrea Denny, JD, MSSW received a $40K grant from the Missouri Department of Transportation to implement the project Older Driver Fitness Assessment Training to clinicians throughout the state.

Chengjie Xiong, PhD received the Biostatistics Department Faculty of the Year Award for the 3rd time since 2011.

Catherine Roe, PhD was awarded $25,000 for her project *Evaluation of Global Positioning Data Acquisition to Assess Driving in Older Adults With and Without Preclinical Alzheimer Disease*, from the University Research Strategic Alliance (URSA) program.

Five Knight ADRC faulty and staff members were recognized for years-of-service to Washington University. 10 years: **Mary Creech**, 15 years: **Ron Hawley**, 20 years: **Linda Amos** and **Howard Palmer**, 30 years: **Betsy Grant.**

Ellen Binder, MD was awarded an NIA R01 grant to fund her research *Exercise and Intensive Vascular Risk Reduction in Preventing Dementia.*

Beau Ances, MD, PhD is a new member of the NIH NeuroAIDS and Other End-Organ Diseases Study Section, Center for Scientific Review, for the term July 01, 2015-June 30, 2021.

Gregory Day, MD partnered with Queen's University, Kingston, Ontario to present a brief review of dementia as a part of its open-source medical education initiative, MedSkl. MedSkl is designed to facilitate learning of medical students, residents and members of the general public through succinct reviews of critical topics. Online access is free, but does require learners to open up an account.

John C. Morris, MD agreed to serve on the New York State Center for Excellence in Alzheimer's Disease (CEAD) Advisory Board.

Shannon Macauley-Rambach, PhD received the following funding awards:

- McDonnell Center for Systems Neuroscience award of $80,000 for 2 years for the project *Mapping glucose utilization in a mouse model of beta amyloidosis*.
- NIH/NIA K Award of $572,335 for 5 years to fund the project *Effects of Hyperglycemia on Neuronal Activity, Cerebral Metabolism, and Amyloid-beta Levels.*
- New Vision Award through Donors Cure Foundation award of $50,000 for one year to find the project: *Targeting the Link between Alzheimer's Disease and Diabetes with KATP Channel Modulators.*

New Additions

Bridget Blaes, Research Nurse Coordinator

Dranette Branson, MAP Secretary

Gigi Flynn, DIAN Senior Clinical Research Coordinator

Jee-young Han, MD, Visiting International Scholar and Fellow, Korea

Sarah Hartz, MD, PhD, MAP Physician Clinician

Deborah Kemp, MAP Research Nurse Coordinator

Eric McDade, DO, Assistant Professor in Neurology and DIAN-TU

Madeline Paczynski, Psychometrician

Michelle Randall, Receptionist and MAP Secretary

Marta Santos, MAP Research Nurse Coordinator

David Winkfield, Research Coordinator

Fond Farewells

Nupur Ghoshal, MD, PhD, MAP clinician, joined the Barnes Jewish Hospital Neurohospitalist section in July.

Faye Harvey, Data Entry Specialist.

Annelise Hernandez, Psychometrician, relocated to be closer to her family.

Doris Jones, MAP Supervisor of Clerical Positions, completed her degree and accepted a position in her new field.

Renee LaBarge, left the Memory and Aging Project and transitioned to the Memory Diagnostic Center.

Brianne Newman, MD, MAP clinician, accepted a position at St. Louis University.

Knight ADRC Loses Two Longtime Supporters

The Knight ADRC mourns the passing of two key community members and longtime supporters of the Knight ADRC.

Ida Goodwin Woolfolk was often called "St. Louis' Mistress of Ceremonies" because of the way she could command important events with humor, grace, and her special personal touch.

African American Advisory Board Chair I**da Goodwin Woolfolk** died unexpectedly in her home March 23, 2016 at age 72. It was said that "Ida knows everyone and everyone knows Ida." Ida had the honor of being the first Saint Louis citizen to lie in state at City Hall prior to her burial. She was a force of nature, working tirelessly for the betterment of us all, and she is greatly missed.

Mildred Poletsky presented the annual Poletsky Award in October, 2015. From left to right, John C. Morris, MD, Poletsky, and award recipient Matthew Brier, PhD.

Mildred Poletsky died on May 13, 2016 at age 92. Mrs. Poletsky was involved in the Memory and Aging project first as a collateral source for her husband and then as a participant herself for the last 28 years. In the 1990s she established the Richard and Mildred Poletsky Award, which provides an annual cash award to further the educational goals of a student (master's degree, resident, fellow) working in a field related to AD-research. She was an inspiration, a supporter, a participant, and most of all, a friend.

Alzheimer's Association Funds Local AD Research

The DIAN-TU Next Generation Prevention Trial (NexGen), led by **Randall Bateman, MD**, was awarded a $4.3 million grant by the Alzheimer's Association, in part through a gift from Edward Jones, to expand the DIAN-TU prevention trial to international sites.

Additionally, the Alzheimer's Association Research Grant program awarded three recent grants to investigators from Washington University:

Ganesh Babulal, PhD

Ganesh Babulal, PhD, 2016 Alzheimer's Association Research Fellowship to Promote Diversity —$145,000 over 3 years for his project *Racial Differences in Alzheimer's Disease Biomarkers and Driving Behavior.*

Nicholas Barthelemy, PhD, 2016 Alzheimer's Association Research Fellowship —$174,999 over 3 years for his project *Quantitative analyses of tau isoforms in human Brain, CSF and Plasma by MS.*

Thomas Brett, PhD, 2016 Alzheimer's Association Research Grant —$150,000 over 3 years for his project *Structural and Functional Basis for TREM2/ApoE/Lipid interaction in AD.*

Construction Notice: Kingshighway / Forest Park Avenue Intersection Remake

Forest Park Parkway between DeBaliviere and Kingshighway will be closed about one year (from late fall 2016 to the following year) to reconfigure the intersection. Forest Park Parkway will be closed for the entire construction period from DeBaliviere and Kingshighway; there also will be traffic restrictions on Kingshighway.

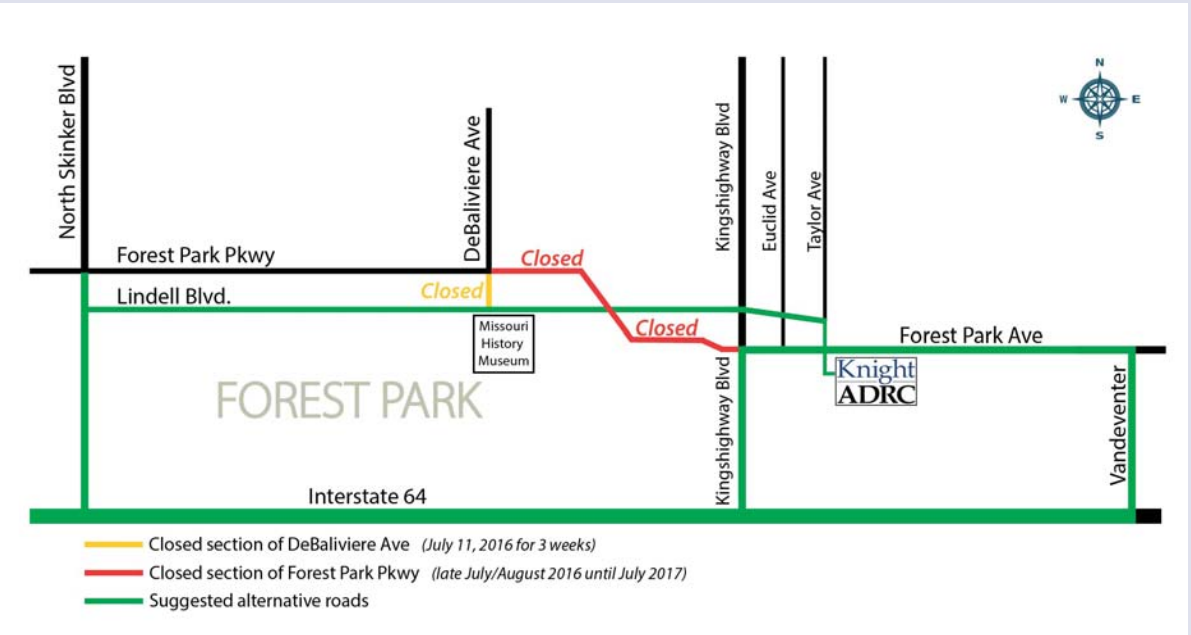
As this construction will affect many Memory and Aging Project participants, we have identified some alternate routes that will allow volunteers to access our center while avoiding construction delays. As always, please allow plenty of time for travel, and drive safely!

Options coming from the West:

- Take Forest Park Pkwy to right on Skinker. Turn left onto Lindell. Take Lindell and turn right onto Taylor.
- Take Skinker to Interstate 64. Proceed east to the Kingshighway exit. Turn left onto Kingshighway and then turn right onto Forest Park. Participants exiting at Kingshighway should anticipate heavy traffic volume.
- Take Interstate 64 east and exit at Vandeventer. Turn left on Vandeventer and proceed to Forest Park Ave. Turn left onto Forest Park Ave.

Options coming from the East:

Participants coming from East will not be in the direct path of construction but should anticipate delays. Participants exiting at Kingshighway should anticipate heavy traffic volume.



New Technique, *continued from page 1*

"We adapted it into a five-micron fiber, which is way thinner than a human hair, so it could be implanted into the brain."

The experiment revealed something surprising: One clearance pathway rapidly cleared amyloid beta at higher levels, but a different, slower one became dominant later as the levels dropped. These results contradicted research that Cirrito himself, among others, had published that suggested that the rate of clearance and the relative importance of the different pathways did not depend on the amyloid beta concentration.

"This is important if you're devising a therapeutic strategy against Alzheimer disease," said Cirrito. "If you hit the first pathway, you might have an effect quickly, but you may not be able to lower amyloid beta levels beyond a certain point. You'd have to consider targeting multiple pathways." *-By Tamara Bhandari for Washington University.*

ACS Breakfast Welcomes Guests

The 2016 Adult Children Study (ACS) Breakfast and Research Update was held in September at the St. Louis Zoo Rivercamp. In addition to scientific talks by Knight ADRC faculty, the audience was treated to a very special update: a visit from Dr. Morris' grandson Jack, shown left with Dr. Morris and his daughter, Carrie.

HORIZONS is the newsletter of the Charles F. and Joanne Knight Alzheimer Disease Research Center (Knight ADRC) — a research program in the Department of Neurology, Washington University School of Medicine, funded by grants from the National Institute on Aging and private donations. The Knight ADRC supports and promotes interdisciplinary research on Alzheimer Disease. The Memory & Aging Project (MAP) — the clinical research office of the Knight ADRC — provides expert clinical assessments of cognitive functioning in normal aging and dementia. Knight ADRC leadership:

John C. Morris, MD, Director, Knight ADRC; Director, MAP; Administration Core and Clinical Core Leader.

Eugene M. Johnson, PhD, Associate Director

David M. Holtzman, MD, Associate Director

Virginia Buckles, PhD, Executive Director

Krista Moulder, PhD, Associate Executive Director

Carlos Cruchaga, PhD, Genetics Core Leader

Jason Hassenstab, PhD, Psychometric Core Leader

Nigel J. Cairns, PhD, FRCPath, Neuropathology Core Leader

Tammie Benzinger, MD, PhD, Neuroimaging Core Leader

Chengjie Xiong, PhD, Data Management and Biostatistics Core Leader

Anne Fagan, PhD, Biomarker Core Leader

Andrea Denny, JD, MSSW, Outreach, Recruitment, and Education Core Leader

John C. Morris, MD, Interim African American Outreach Core Leader

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