The Mary S. Easton Center for Alzheimer’s Disease Research at UCLA has very active teams working on basic research, drug discovery, biomarkers for early diagnosis and clinical activity including clinical trials, cognitive testing, and patient care.

Easton Center Welcomes New Members for the Clinical Programs

New Medical Director of the Clinical Program

Photo: Aaron McMurtray, M.D., Ph.D.

We are glad to announce that Aaron McMurtray, M.D., Ph.D., F.A.N.A. has joined the Mary S. Easton Center for Alzheimer’s Disease Research at UCLA (UCLA-Easton Center) as Medical Director for Clinical Programs on January 1, 2019. Dr. McMurtray is a board-certified neurologist who earned his medical degree in 2000 at Vanderbilt University and completed neurology residency training at Harbor-UCLA Medical Center, followed by fellowship in Behavioral Neurology and Neuropsychiatry at UCLA/West LA VA Medical Center. Dr. McMurtray will provide oversight for the Center’s clinical operations, as well as facilitate access for patients to clinical trials being conducted within the program.

Dr. McMurtray comes to us after having served as Medical Director of the Dementia Clinic at Harbor-UCLA Medical Center. He is committed to serving the patients and families seeking care at the Easton Center and expanding the clinical services to provide the best possible care to patients with Alzheimer’s disease and associated neurodegenerative diseases. Dr. McMurtray directs an active clinical research program at the Los Angeles BioMedical Research Institute, which has resulted in method of use and composition of matter patents related to the use of naphthalene derivatives in the treatment of neurodegenerative diseases.

New Nurse Practitioner of the Clinical Program

Photo: Kelsey Stander, N.P.

Kelsey Stander graduated from Indiana University with a B.S. Degree in Public Health in 2011. She continued her education at Massachusetts General Hospital Institute of Health Professions in Boston where she earned a Bachelor’s of Science in Nursing and a Master’s of Science in Nursing as an Adult and Geriatric Primary Care Nurse Practitioner. She worked as a Geriatric Nurse Practitioner in various settings firstly with Commonwealth Care Alliance in Boston providing primary care to homebound frail elders in the community and then in both the clinic and home setting for Mount Sinai Geriatrics in New York City. Kelsey’s interest in dementia and memory disorders lead her to pursue a career as a Nurse Practitioner with the UCLA Alzheimer’s
and Dementia Care Program and then to transition to her current role as a Nurse Practitioner in the UCLA Dementia and Memory Disorders Clinic.

If you would like to schedule an appointment with Dr. McMurtray, please call the Neurology Clinic at (310) 794-1195.

An Experimental Drug that Normalizes SirT1 Levels in the Presence of ApoE4 and Improves Memory

The Drug Discovery Lab (DDL) at the Mary S. Easton Center for Alzheimer’s Disease Research at UCLA recently reported on a first-in-class therapeutic candidate for Alzheimer’s disease (AD) in Nature Scientific Reports on December 4, 2018. The paper is authored by Jesus Campagna, a research associate in the DDL, which is led by Dr. Varghese John, an associate professor in the UCLA Department of Neurology. The promising compound, ‘A03’, increases levels of the enzyme Sirtuin1, or SirT1, a key regulator of healthy aging.

Neurons are stabilized by a cytoskeleton of microtubules. Tau protein is an important stabilizing protein for that cytoskeleton. When tau proteins become altered by various biochemical processes, such as acetylation or phosphorylation, they begin to form tangles, and the neuron cytoskeleton and subsequently, the neuron, cannot continue to function in a healthy way. SirT1 is important because it has a role in reversing acetylation of tau proteins, therefore stabilizing tau proteins and neuronal cytoskeletons. SirT1 levels decline with age, and this decline is more pronounced in people with the Apolipoprotein E4 (ApoE4) gene, the most common genetic risk factor for AD. Previous studies by Dr. John’s research group have shown that SirT1 levels are lower in mice with ApoE4. Lower SirT1 levels may contribute to increased risk for developing AD in ApoE4 carriers. Reduced SirT1 levels may also contribute to the spread of toxic tau pathology and loss of neurons, leading to the accelerated onset and subsequent decline in cognitive performance in AD. The DDL originally discovered A03 while screening a library of drug compounds for their ability to increase SirT1 in the presence of ApoE4 in cells. When the researchers treated living ApoE4 model mice with A03 for 56 days, they found that SirT1 levels were increased in the mice hippocampi, a brain region that suberves memory and that is often the first affected in AD. The researchers subjected A03 to a battery of tests to see if the compound could increase SirT1 and also improve memory in ApoE4 model mice. After two months of oral dosing, the DDL researchers found that A03 not only increased SirT1 enzyme levels in the mice hippocampi, but also improved scores on memory tests. Importantly, A03 treatment did not have any adverse effects on the mice by the end of the study. The lab has also shown that A03 is selective for boosting the levels of SirT1 while not increasing the levels of the Sirtuin2 (SirT2), a neurotoxic protein, which may make it safer for treatment of AD.
A03 was originally developed to treat depression as a selective serotonin reuptake inhibitor (SSRI). A03 has been tested in human clinical trials for depression as well as for treatment of dementia. In a small clinical study, it was reported that A03 elicited improvements on a test of global cognition, the Dementia Rating Scale, with no serious adverse symptoms.

Based upon the promising preclinical results reported in this newly published article, the DDL is conducting further research on A03 and its active enantiomer, (its mirror image molecule), to evaluate their potential for clinical testing in AD, especially in subjects who have an ApoE4 allele.

The DDL has an ongoing collaboration with renowned professor and chemist Michael Jung, Ph.D. in the UCLA Department of Chemistry and Biochemistry to synthesize new, possibly more effective analogs that increase brain SirT1 levels. The National Institute of Aging funded the reported studies.

Publication:
Our 2018 Turken Research Award and Symposium gathering emphasized the richly diverse basic and clinical research on Alzheimer’s disease (AD) performed by our Alzheimer’s Disease Research at UCLA (UCLA-Easton Center) and broader UCLA community. The Turken Research Award has been an inspiring UCLA tradition since the 1980s with continuous support from the Sam and Ida Turken Charitable Foundation, under the leadership of Ms. Beth Devermont. The core mission of this award and symposium is to bring our AD research community together collaboratively and to foster new investigators to continue to work in the field of Alzheimer’s disease research. The Turken event was attended by a broad range of academic researchers and clinicians from various academic departments in UCLA as well as community organization leaders, including Heather Cooper-Ortner, CEO of Alzheimer’s Los Angeles.

The morning program was comprised of short presentations by rising junior researchers, touching on topics from drug discovery and novel brain imaging techniques, to clinical research focusing on risk factors of dementia. The first presenter was Tina Bilousova, Ph.D., a research scientist in the Easton Drug Discovery Lab (DDL), led by Dr. Varghese John, who presented a new translational project entitled “Development of Dual nSMase2-AChE Inhibitors as a Novel AD Therapeutic Strategy”. This project is the result of Dr. Bilousova’s interdisciplinary work in the DDL and in the lab of Karen Gylys, Ph.D. (UCLA School of Nursing), where she has been studying the mechanism behind the release of tau-containing exosomes across synapses (gaps) between neurons. Exosomes are small bubble-like sacs that shuttle proteins, genetic material, or in the case of neurons, neurotransmitters, across synapses. Misfolded tau is a key protein thought to cause cognitive decline in AD and may spread from neuron to neuron via exosomes. Dr. Bilousova has studied an enzyme, nSMase2 (neutral sphingomyelinase-2), that controls the production and release of exosomes from nerve terminals, including those containing mis-folded tau. The DDL team searched for compounds that inhibit nSMase2 and found one that not only can inhibit this enzyme, but which can also inhibit acetylcholinesterase (AchE), an enzyme that breaks down synaptic acetylcholine. Acetylcholine has been shown to be important to memory pathways, and current FDA-approved drugs target AchE to prevent breakdown of acetylcholine and allow the synapses to have longer access to acetylcholine in an attempt to boost memory pathways. Unfortunately, these drugs do not stop disease progression. This new Easton discovery is exciting in that it may be able to prevent the spread of tau, thereby affecting disease progression, as well as boosting memory pathways.

Cyrus Raji, M.D., Ph.D., who completed his neuroradiology fellowship at UCLA and is now an assistant professor of Neurology and Neuroradiology at Washington University in St. Louis, presented a talk entitled “Machine Learning of MR Neuroimaging Automated Volumetric Data for Diagnostic Delineation for Alzheimer’s Dementia and Mild Cognitive Impairment in ADNI”. This project was a collaboration with Dr. Meysami (Harbor-UCLA), Dr. Porter (UCLA Neurology) and Dr. Merrill (UCLA Psychiatry). He described the use of artificial intelligence algorithms and an app called Neuroreader that recognizes the pattern of brain shrinkage associated with Alzheimer’s disease using magnetic resonance imaging (MRI) data. 1143 brain
MRI scans were obtained from ADNI, the Alzheimer’s Disease Neuroimaging Initiative, a multicenter collaboration ongoing since 2004, that longitudinally follows people with normal cognition, mild cognitive impairment (MCI) and dementia due to AD. This data set included 261 normal controls, 310 individuals with early MCI, 223 with late MCI, and 349 with AD dementia. Dr. Raji used the Neuroreader software to evaluate the size of different brain regions, and then used an IBM machine learning program to define patterns of change in these regions and attribute possible clinical diagnoses corresponding to these patterns of change. The automated program was able to pick out AD dementia patterns with 85% sensitivity and 79% specificity, in other words, it was correct about 4 times out of 5. For early MCI, this dropped to 76% sensitivity and 70% specificity. While not perfect, this automated approach to disease pattern recognition using routine MRI scans already approaches the accuracy of the average specialist. Because MRI is a widely available and routine tool typically used to rule out other causes of cognitive dysfunction, such as tumors or strokes, this approach or another similar to it has the potential to be widely implemented in the future for analysis of brain scans looking for incipient AD.

Elizabeth Rose Mayeda, Ph.D., M.P.H., as assistance professor in the UCLA School of Public Health, described her study with Dr. Rachel Whitmer of Kaiser Permanente entitled: “Cumulative Exposure to Elevated Blood Pressure throughout Adulthood and Late-life Dementia Risk.” Drs. Mayeda and Whitmer examined blood pressure history on in the records of 28,147 Kaiser members 50 years and older; 4,840 of these patients went on to develop dementia. Dr. Mayeda was able to show that small increases in mid-life blood pressure (bp) increased dementia risk. Specifically, compared with those with bp<120, those with bp 120-129 had ~4% increased risk, and those with bp 130-139 had ~10% increased risk per decade of exposure. These small increases in risk could only be reliably detected by examining the long-term electronic record data from a large population. The results are significant for dementia prevention programs as current practice has aimed to keep bp below 140, and this study reflects the importance of tighter control over small increases in blood pressure much earlier in life.

The afternoon program kicked off with an update from last year’s Turken Award winner- Dr. Eric Hayden. Dr. Hayden presented on work with the Teplow Laboratory on surface-enhanced Raman spectroscopy as biophysical tool capable of distinguish aggregate assembly states of Aβ40 from Aβ42 which provides a useful new label-free method of distinguishing different forms of the amyloid beta (Aβ) peptides implicated as causal in AD. Dr. Hayden also described work on a mouse model related to ApoE4 interactions with vascular dementia performed with Dr. Jason Hinman. They observed unexpected positive amyloid reducing effects of focal sub-cortical stroke in mice with amyloid and ApoE4.

Following Dr. Hayden, the 2018 Turken Awardee was announced as Dr. Paul Seidler, Postdoctoral Fellow at the Eisenberg Laboratory, UCLA Molecular Biology Institute. Dr. Seidler presented his lecture on “Development of a Structure-based Panel of Tau Inhibitors for Probing Structural Polymorphs in Neurodegenerative Disease.” Tau protein is normally either bound to microtubules or quickly degraded but in AD, it self-aggregates to form tangled intraneuronal filaments or “neurofibrillary tangles.” Other rarer diseases including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and some forms of frontotemporal dementia (FTD), also feature tau aggregate accumulation that appears to cause the different symptoms of the diseases by forming in different circuits and parts of the brain. Dr. Seidler described how these tau proteins from patients with different diseases can aggregate to form different structures, or “polymorphs”. He then explained how his team has developed a series of different tau aggregation inhibitors that specifically target and “cap” the aggregates to block the recruitment of normal tau to form new aggregates. Because this is an exciting new approach to blocking the development of AD, Drs. Seidler and Eisenberg are already collaborating with other UCLA groups on testing this in animal models. Dr. Seidler has recently received new Bright-Focus and National Institutes of Health (NIH) funding to support this work which was developed with the aid of generous pilot support from Phyllis and Jim Easton through their gifts to support UCLA research teams working on Neurodegeneration.
Turken Day was rounded out with a poster session and a luncheon, which offered opportunities for attendees to discuss their research projects and interests within the Alzheimer’s disease arena. In his closing remarks, Dr. Eisenberg, UCLA’s Paul D. Boyer Professor of Biochemistry and Molecular Biology, stated that it truly takes the scientific depth of field and teamwork that we have here at UCLA to make and develop groundbreaking discoveries. As we continue to revitalize the Easton Center, we expect to broaden our collaborative research across departments and build a team working to defeat Alzheimer’s disease.

We would like to thank the following people for helping us make this year’s Turken Symposium a success:

- **Ms. Beth Devermont**, President and Director, Sam and Ida Turken Charitable Foundation.
- **Dr. S. Thomas Carmichael**, Chair, Department of Neurology.
- **Dr. Greg Cole**, Interim Director, The Mary S. Easton Center for Alzheimer’s Disease Research at UCLA.
- **Easton Center and Kagan Program staff**: Nancy Osuch, Monica Moore, Celine Ossinalde, Lauren Garcia, Lorena Hernandez, Rachel Schade, Michelle Torreliza.

**Clinical Research Opportunities**

*If you would like to advance Alzheimer’s disease research, please consider being a participant. Below are the current recruiting trials. For a complete list of enrolling studies, visit our website at [www.eastonad.ucla.edu](http://www.eastonad.ucla.edu).*

**EASTON CENTER KAGAN CLINICAL TRIALS PROGRAM**

- Alzheimer’s Disease Neuroimaging Initiative 3 (ADNI3) Protocol
- NEAT (Nicotinamide as an Early Alzheimer’s Disease Treatment) Study
- Phase 2 Study of BIIB092 in Participants with Early Alzheimer’s Disease (TANGO)

**BEHAVIORAL NEUROLOGY PROGRAM**

- Early-onset Alzheimer’s Disease Phenotypes: Neuropsychology and Neural Networks
- Neuropsychological Test Measures in Behavioral Variant Frontotemporal Dementia (bvFTD) and Healthy Subjects

**OTHER PROGRAMS**

- Curcumin and Yoga Therapy for Those at Risk for Alzheimer’s Disease
- E2609 Study for MCI and Early Alzheimer’s Disease (MissionAD1)
- Effect of Grapes Dietary Supplement on Brain Metabolism and Cognition
- The UCLA Caregiver Sleep (CARES) Study
For more information on our upcoming lectures and events, please visit the Easton Center Community Calendar.

Alzheimer’s Los Angeles Early Memory Loss Conference  
**Date:** Saturday, April 6, 2019  
**Time:** 9:00 A.M. – 3:00 P.M. (PDT)  
**Location:** Torrance Memorial Hoffman Health Conference Center  
3315 Medical Center Drive  
Torrance, CA 90505

Please register by visiting AlzheimersLA.org/EMLC or call 844.HELP.ALZ (844-435-7259). [Flyer]

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24th Annual UCLA Research Conference on Aging  
**Date:** Wednesday, May 29, 2019  
**Time:** 8:00 A.M. – 12:30 P.M. (PDT)  
**Location:** UCLA David Geffen School of Medicine Geffen Hall, Room B-36  
885 Tiverton Avenue  
Westwood, CA 90095

Please register by visiting https://www.uclahealth.org/geriatrics/rcoa [Flyer]

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**Newsletter Editorial Team:**  
Co-Directors of Training and Education Activities: Sarah Kremen, M.D. and Monica Moore, M.S.G.  
Editor: Nancy Osuch, B.A.

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**Mailing Address:**  
Mary S. Easton Center for Alzheimer’s Disease Research at UCLA  
710 Westwood Plaza, Room C-224  
Los Angeles, CA 90095-1769

| [https://eastonad.ucla.edu/](https://eastonad.ucla.edu/) | Phone Number: (310) 794-3665 / Clinic Appointments: (310) 794-1195 |  
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