MARY S. EASTON CENTER for Alzheimer's Disease Research at UCLA
DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA

David Geffen School of Medicine

Winter 2022 E-Newsletter

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.

2021 Turken Research Award and Symposium

By: Keith Vossel, MD, MSc

What is the future for precision medicine approaches in Alzheimer's disease? What are major barriers to receiving equitable health care and access to research opportunities in underserved communities, and how can we address them? How are brain autopsy samples utilized in research? These are just some of the exciting topics covered in the annual Turken Research Award Event, held by webinar in November 2021. We had lively program and discussion with UCLA clinicians and scientist presenting on a broad range of topics in Alzheimer's research. An audience of 83 faculty, staff, and colleagues attended the event, which included four featured speakers and 26 poster presenters.

Mirella Díaz-Santos, PhD, Assistant Professor in Neurology and 2020 Turken Research Award recipient, led off the event presenting an update on her research project, "By the Community with the Community: Ending Exclusionary Research in Latino/a/x Alzheimer's Disease." Between 2008 to 2030, the U.S. Hispanic/Latinx population aged 65 years and older will increase by 224% compared to a 65% increase for non-Latinx whites[1]. However, Hispanic/Latinx communities are not equitably represented in Alzheimer's clinical research, making up only 1% of research participants in clinical trials and 7.5% of participants in Alzheimer's Disease Research Centers. Dr. Díaz-Santos leads the Easton Center's Equity for Latinx-Hispanic Healthy Aging (ELHA) lab, which is addressing barriers to research participation in Hispanic/Latinx communities. She is developing an English-Spanish bilingual educational program on Latinx aging, brain health, and dementia; developing and validating a clinician fact sheet for primary care/family medicine to improve dementia recognition and diagnosis in primary care settings; and creating a short Spanish neuropsychological tool sensitive to detect Alzheimer's disease. We also learned about new efforts by the National Institute on Aging to diversify Alzheimer's disease research, which included a new online tool, Outreach Pro[2], to help researchers and clinicians increase awareness and participation in clinical trials on Alzheimer's disease and other dementias, especially among traditionally underrepresented communities.

The 2021 Turken Research Award Recipient, Shino Magaki, MD, PhD, Assistant Professor of Neuropathology, delivered an outstanding talk titled, "Neuropathology Core – Easton Center Brain Bank: Latest Advances in

Optimizing Tools to Study Neurodegenerative Diseases." Dr. Magaki is co-director of the Easton Center Brain Bank (ECBB) that has thousands of brain samples from patients with Alzheimer disease, Lewy body disease, and other neurodegenerative diseases, collected over many decades. Dr. Magaki has been a pioneer in developing novel ways to examine tissue and databasing the findings to be optimal for basic and translational investigators. Just in 2021 so far, the ECBB has distributed over 180 frozen tissue specimens and formalin fixed paraffin embedded sections/slides, performed 300 histochemical and immunohistochemical stains and provided over 130 mL of cerebrospinal fluid to Easton Center collaborators. The ECBB trains students, fellows, and faculty in neuropathological assessments through brain cutting sessions, slide review, and clinico-pathological conferences, and frequently helps optimize and troubleshoot immunohistologic protocols for other research labs.

Two students were selected as abstract awardee presenters. Crystal Shaw, MS, Graduate Student Researcher, Department of Epidemiology, and PhD Candidate, Department of Biostatistics, gave a talk titled, "A Bayesian Latent Class Mixture Modeling Framework for Algorithmic Dementia Classification in Population Representative Studies." Ms. Shaw is mentored by Dr. Elizabeth Rose Mayeda in the Department of Biostatistics and Dr. Thomas R. Belin, in the Department of Epidemiology. Her study uses sophisticated statistical modeling to extrapolate dementia classification from large datasets of medical records by incorporating cognitive neuropsychological measures and sociodemographic, health, and health behavior information. This multidisciplinary investigation will improve our understanding of population-level burden and determinants of dementia.

Amy Zhang, BS, a Research Coordinator in Dr. Zhefeng Guo's Lab presented her study, "An Aggregation Screening Platform that Distinguishes Oligomers from Amyloid Fibrils." The Guo lab investigates the structure and fibrillization mechanism of amyloid fibrils related to a wide range of human disorders such as Alzheimer's disease, Parkinson's disease, and prion diseases, with the goal of developing molecular diagnostics and therapeutics for amyloid diseases. Ms. Zhang presented a clever platform that uses bacterial growth to indicate the amount of protein aggregation, which enables low-cost and high-throughput screening of aggregation inhibitors and modulators.

Beth Devermont, President and Director of the Sam and Ida Turken Charitable Foundation, greeted everyone and gave us a historical context of the award ceremony. Ms. Devermont is the daughter of Phyllis Turken Shamberg who began donating funds to Alzheimer's research on behalf of the Sam and Ida Turken Charitable Foundation in the 1990's. Ms. Devermont is continuing her mother's legacy by generously providing an annual gift to support early career researchers at UCLA who are committed to studying Alzheimer's disease.

Photo (Left to right): Ms. Heather Cooper Ortner, President & CEO of Alzheimer's LA; Dr. Keith Vossel, Professor of Neurology, and Center Director for the Mary S. Easton Center; Dr. Shino Magaki, Assistant Professor of Neuropathology, and the 2021 Turken Research Award recipient; Ms. Beth Devermont, President and Director of the Sam and Ida Turken Charitable Foundation; Dr. Debra Cherry, Executive Vice President of Alzheimer's LA; Dr. Harry Vinters, Distinguished Emeritus Professor of Pathology and Laboratory Medicine of Neurology.

The event concluded with an outdoor gathering where Beth Devermont met with the Turken Awardees and their mentors and offered encouragement to us all. The Turken Research Award Event is gifted through Alzheimer's Los Angeles, and we were delighted to have Debra Cherry, PhD, Executive Vice President, Alzheimer's L.A., in

attendance. Dr. Cherry described the many important ways that Alzheimer's L.A. is serving patients suffering from dementia and their families.

We owe sincere gratitude to Nancy Osuch, Media and Communications Manager for the UCLA Easton Center, who organized the event and found creative ways to keep everyone engaged in the virtual format. It was a great meeting with much thought-provoking discussion on a broad array of timely topics in the Alzheimer's field.

References:

1. Administration on Aging, U.S. Department of Health and Human Services 2009. *"A Profile of Older Americans: 2009."* https://acl.gov/sites/default/files/Aging%20and%20Disability%20in%20America/2009profile_508.pdf
2. National Institute on Aging. "Outreach Pro." https://outreachpro.nia.nih.gov

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2021 Clinical Trials on Alzheimer's Disease (CTAD) Conference

By: Maryam Beigi, MD

The Clinical Trial on Alzheimer's Disease (CTAD) Conference is a three-day meeting held annually. It is attended by scientists, experts in the field of Alzheimer's disease, and pharmaceutical companies from all over the globe.

CTAD 2021 was held on November 9th – 12th in Boston. A wide variety of topics were discussed, and the results of many new research and clinical trials on Alzheimer's disease were presented.

Here is a short-list of topics that were presented or discussed at this year's conference:

1. Anti-amyloid therapies
2. Anti-tau therapies
3. GLP1 receptor agonists (diabetes drugs)
4. Repurposed FDA-approved medications: Levetiracetam, Riluzole, Rotigotine
5. Small molecules
6. Dietary supplements
7. Blood biomarkers
8. Treatment of the bacteria P. Gingivalis (GAIN study)
9. Virtual Clinical trials
10. Virtual cognitive testing

Overall, there has been significant progress in Alzheimer's disease diagnosis. In near future, we will be able to recognize people at risk for Alzheimer's disease years before the onset of the symptoms by a simple blood test.

In the field of therapeutics, there has been great progress. As you may have heard, the first disease modifying treatment, Aducanumab (Aduhelm), a monoclonal antibody targeting amyloid-β, received accelerated, conditional FDA approval on June 6, 2021. Although this drug is not ready for widespread use in Alzheimer's disease, this is a promising new step towards disease-modifying therapies in Alzheimer's disease. On the heels of Aducanumab are three more amyloid-β monoclonal antibodies: Donanemab, Lecanemab, and Ganterunemab. The result of phase 2 clinical trials are encouraging, and phase 3 trials are ongoing. The results of phase 3 should be released in the 3rd or 4th quarter of 2022. All three drugs have been filed for accelerated FDA approval.

Many scientists believe that the aggregation and deposits of amyloid-β in the brain are major contributors to the development and progression of Alzheimer's disease. Amyloid-β is formed from amyloid precursor protein (APP); it is present on the membrane surface of many cells of the body and nervous system. Two main physiological functions of APP are cell adhesion and regulation of cell growth. APP is cleaved by three different enzymes called alpha secretase, beta secretase, and gamma secretase (see Figure 1)[1]. Sequential breakdown of APP by beta and gamma secretases produces segments that are 40 to 42 peptide units long. These peptide monomers have a strong tendency to aggregate and form oligomers which are believed to be the most toxic form of amyloid-β. Oligomers are further aggregated and form protofibrils, fibrils, and finally amyloid plaques (see Figure 2)[2], that are insoluble and deposit in the brain. The amyloid plaques in the brains of people who developed Alzheimer's disease during life can be identified under the microscope (see Figure 3)[3]. The process of amyloid-β deposition starts 15-20 years before the person develops memory loss. Also, deposition of amyloid-β can activate a cascade of events leading to loss of synapses, brain atrophy, and cognitive decline.

Anti-amyloid-β monoclonal antibodies are a class of medications that are infused monthly or biweekly and clear amyloid from the brain. Clearing amyloid plaques and earlier amyloid-β structures from the brains of individuals with early stages of Alzheimer's disease may slow cognitive decline to a modest degree. If amyloid-β therapies become a mainstay of Alzheimer's treatments, newer therapies will need to be added to these therapies for maximum benefit.

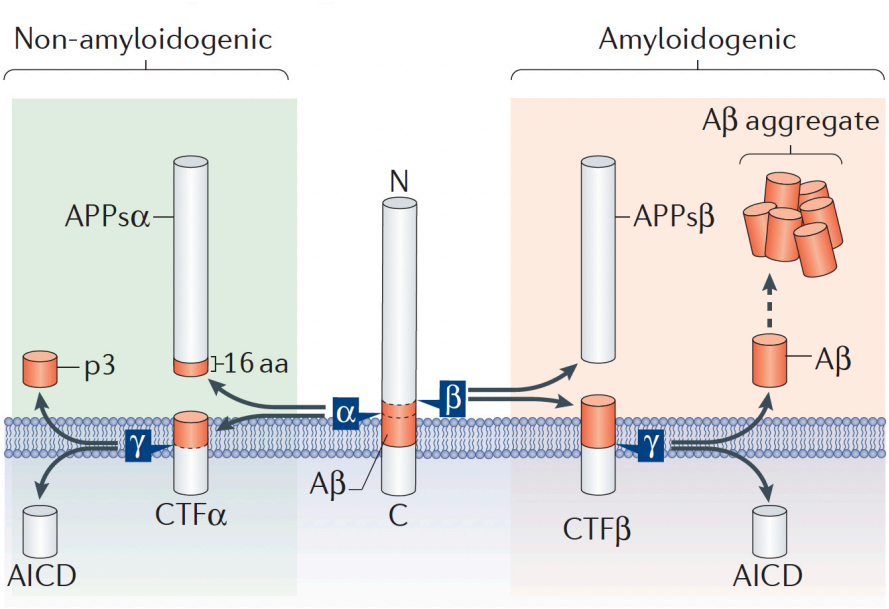

Figure 1: Amyloid precursor protein (APP) processing Pathways. The schematic shows the canonical amyloid precursor protein (APP) processing pathways. Processing by α-secretase along the non-amyloidogenic pathway (green background) occurs in the amyloid-β (Aβ) region (shown in red), liberates APPsα (α-secretase-generated APP ectodomain fragment) and generates p3. By contrast, processing along the amyloidogenic pathway (red background) generates Aβ (through β-secretase and γ-secretase cleavage) and liberates APPsβ. An intracellular fragment (APP intracellular domain (AICD)) is released in both pathways. The positions of cleavage sites are indicated. Image is from reference 1.

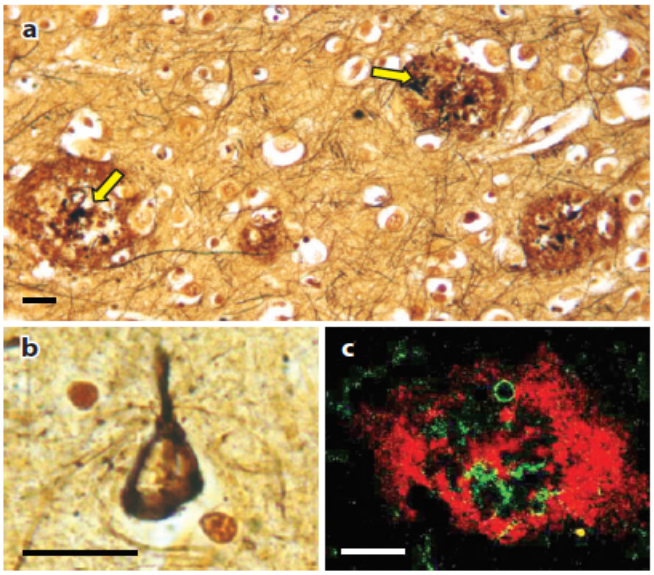

Figure 2: Pathology of Alzheimer's disease. **(a, b)** Brain sections from a patient with dementia are stained with silver, revealing amyloid plaques in panel **a** and a neurofibrillary tangle in panel **b**. The plaques in panel **a** consist of an amorphous reddish protein (amyloid-ß) with disrupted neural projections (yellow arrows, dark black material). The neurofibrillary tangle consists of the tau protein. **(c)** An amyloid-ß plaque stained with an anti-amyloid-ß antibody (red) shows infiltrating support cells (microglia) stained with an IBA1 antibody (green). Microglia are part of the brain's defense system and they can engulf amyloid plaques. Each line is 40 microns. Images are from reference 2.

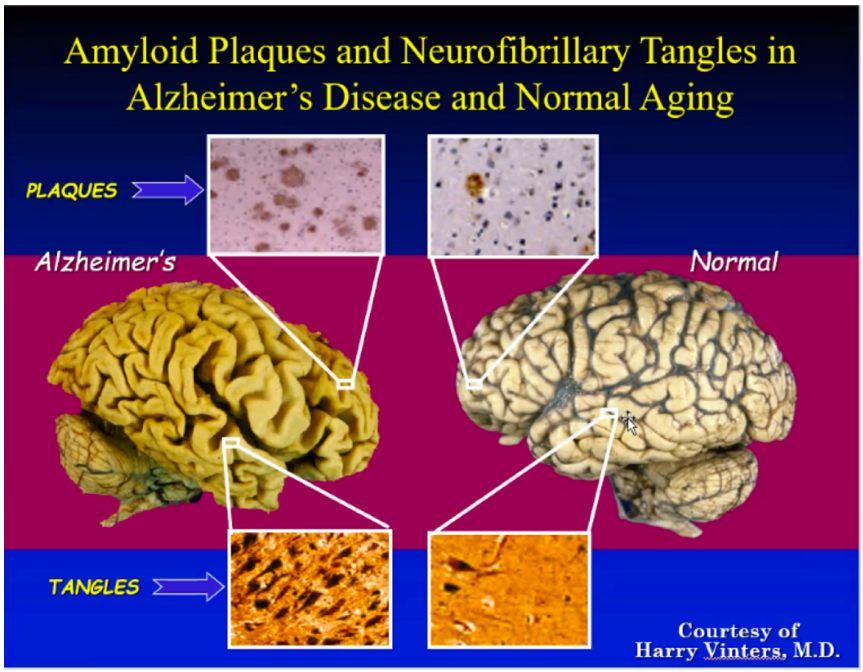

Figure 3: Comparison of aged normal brain and Alzheimer's disease brain. Image courtesy of Harry Vinters, M.D.

References:

1. Ulrike C Müller[1], Thomas Deller[2], Martin Korte[3,4]. Not just amyloid: physiological functions of the amyloid precursor protein family. Nat Rev Neurosci 2017; 18(5): 281-298. doi: 10.1038/nrn.2017.29.
2. Richard J. O'Brien[1] and Philip C. Wong[2]. Amyloid Precursor Protein Processing and Alzheimer's Disease. Annual Review of Neuroscience 2011; 34: 184-204.
3. Image courtesy of Harry Vinters, MD.

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New Additions to the Easton Center

Please join us in welcoming new staff members to the Easton Center.

Photo: Mariane C. Vicente, PhD, Postdoctoral Researcher, Vossel Lab

Dr. Mariane Vicente joins the Department of Neurology as a Postdoctoral Researcher in Dr. Keith Vossel's lab. Dr. Vicente is a graduate in Biological Science from Sao Paulo State University, Brazil (UNESP) (2013), and earned a Master's (2016) and PhD (2021) in Animal Physiology from Federal University of São Carlos (UFSCar), Brazil. She completed a PhD sandwich scholarship program at A.T. Still University, Kirksville, MO (2018). Before joining the lab, she was focused on respiratory dysfunction during sleep and wakefulness in a model of Alzheimer's Disease. She is excited to contribute to the Alzheimer's research at the Vossel Lab. Outside of the lab, she enjoys movies, shows, and the gym.

Photo: Stephanie Ovalle Eliseo, BA, Clinical Research Associate, Community Engagement/Outreach Core and Equity for Latinx-Hispanic Healthy Aging (ELHA) Lab

The Easton Center welcomes Stephanie Ovalle Eliseo. Stephanie obtained her Bachelor's degree in Anthropology with a minor in Society and Genetics from UCLA in 2020. Throughout her undergraduate career, Stephanie served marginalized communities in Los Angeles as a member and then board director of the student-led organization, Latinxs and Chicanxs for Community Medicine (LLCM). Prior to graduating, Stephanie took an opportunity to work as a pediatric-study research assistant that helped her understand how qualitative research can inform policy implementations that affect communities of color on a macro scale. As she engaged in sensitive, health-related conversations with participants from underserved communities, Stephanie found a calling that motivates her to pursue a career in Public Health and Policy. Stephanie joins the Easton Center's Latinx-Hispanic Healthy Aging Lab (PI: Mirella Díaz-Santos, PhD) after completing a service term with the United Farm Workers Foundation's Workers' Rights team. In her free time, she enjoys practicing yoga, spending time with her two dogs, retail therapy on a budget, and watching History channel documentaries or reading.

Photo: Maribel Hernandez, BA, Dementia Care Team Navigator at UCLA – Olive View

Maribel Hernandez joins the Easton Center as its new Dementia Care Team Navigator at UCLA-Olive View. Maribel received her Bachelor of Arts degree in Sociology from UCLA in 2019. As an undergraduate student, she gained valuable experience as a research assistant for the Center of Latino Health and Culture where she focused on assisting with published work regarding important figures who contributed to Latino healthcare issues. After graduating, Maribel gained a background in applied behavior analysis working with children and adolescents with autism spectrum disorders. She then moved onto case management working with people experiencing homelessness and tackling the homeless crisis in Los Angeles working under Council District 1. With a passion for serving vulnerable populations and focusing on health disparities among disenfranchised populations, Maribel is excited to contribute to the mission of UCLA Easton Center and Olive View-UCLA Medical Center. Outside of work, she enjoys hiking, fitness, and partakes in powerlifting competitions.

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Clinical Research Opportunities

If you would like to advance Alzheimer's disease research, please consider being a study participant. Below are the current recruiting trials. For a complete list of enrolling studies, visit our website at www.eastonad.ucla.edu.

OBSERVATIONAL STUDIES:

- Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Protocol
- Alzheimer's Disease Research Center - Biomarkers in Neurodegenerative Disease (ADRC-BIND)
- NIA-AD-FBS (National Institute on Aging Alzheimer's Disease Family Based Study)
- Vascular Contributions to Cognitive Impairment and Dementia (MarkVCID)
- ALLFTD (ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration)

INTERVENTIONAL STUDY:

- Autonomy Study

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For more information on our upcoming lectures and events, please visit the Easton Center Community Calendar.

Alzheimer's Los Angeles Visionary Virtual Women's Afternoon Tea

Date: Thursday, March 11, 2022
Time: 4:00 P.M. (PST)
Virtual Forum

For more information please visit: https://www.alzheimersla.org/get-involved/events/visionary-women/

Pathways to Care: A Conversation on Dementia and Behaviors

Date: Wednesday, March 23, 2022
Time: 6:00 P.M. - 7:30 P.M. (PDT)
Location: Joslyn Community Center
1601 N. Valley Drive
Manhattan Beach, CA 90266

In partnership with Always Best Care Senior Services, Alzheimer's Association, Beach Cities Health District, City of Manhattan Beach.

Caring for the Caregiver

Date: Monday, April 4, 2022
Time: 1:00 P.M. - 2:30 P.M. (PDT)
Virtual Forum

Virtual presentations in partnership with CSUDH- OLLI register at: https://bit.ly/csudholli-uclahealth-sp22

Memory Matters

Date: Beginning Thursday, April 7, 2022
Time: (TBA)
Virtual Forum

Memory Matters is a virtual 8-week evidence-informed program for people with early memory loss resulting from Mild Cognitive Impairment, Alzheimer's disease, or another dementia.

To register or for more information please email Dr. David Hart at DHART@ABC-SENIORS.COM or call (424) 323-3518.

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