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

David Geffen School of Medicine

Autumn 2022 Newsletter

The Mary S. Easton Center for Alzheimer's Research and Care 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.

Alzheimer's Disease Biomarkers

By: Maryam Beigi, MD

Professor Alois Alzheimer first described Alzheimer's disease in 1906. He called it "pre-senile dementia" as his case was in a 51-year-old female. Using a contemporary technique called silver staining, Professor Alzheimer was able to see deposits in the brain, that were later called amyloid plaques and neurofibrillary tangles (NFTs). In 1910 his coworker Emil Kraepelin further described the amyloid plaques and NFTs in brain autopsies of patients who had experienced similar symptom. At that time presence of amyloid deposits in the brains of older people was known, but NFTs were new. Professor Kraepelin named the disease Alzheimer's disease in honor of Professor Alzheimer's achievement.

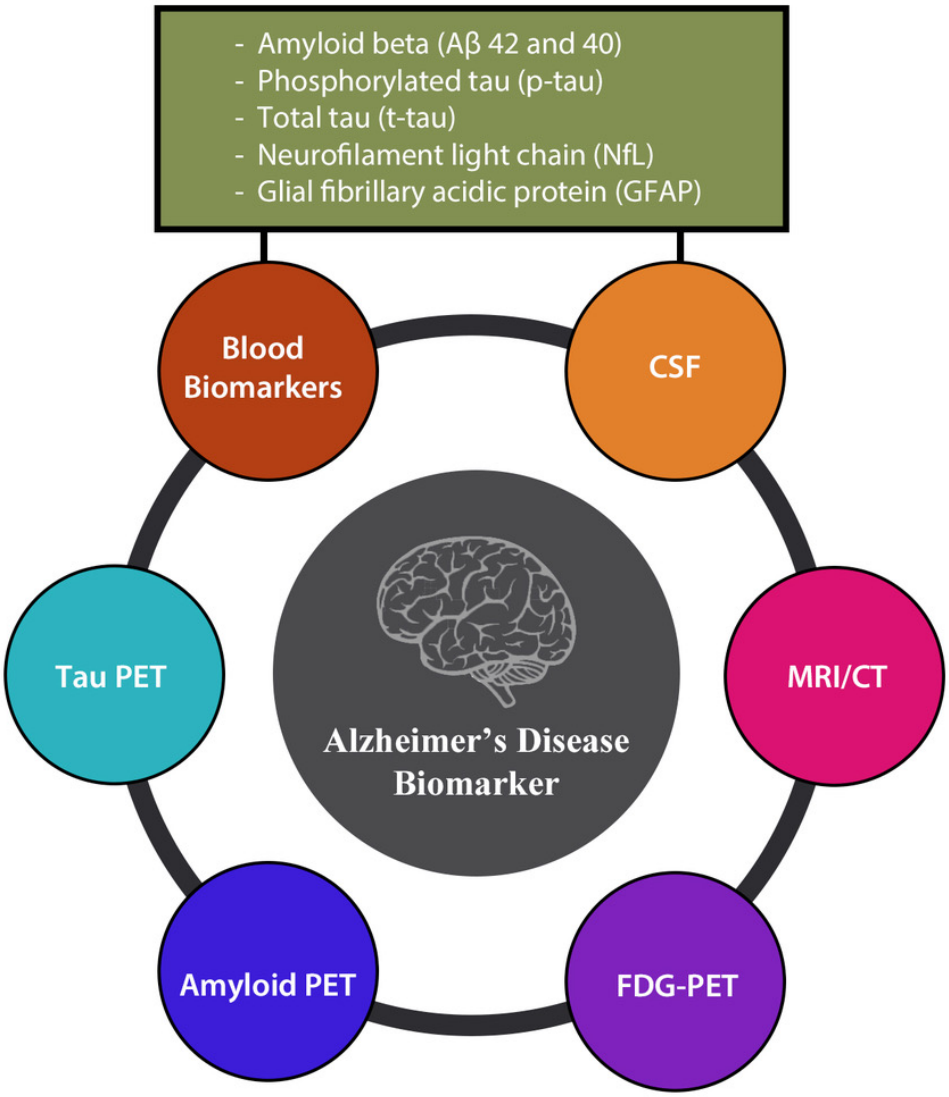
In 1963 electron microscopy of NFTs in brain biopsies from two patients with advanced Alzheimer's disease prompted more interest in the study of the disease. Since then, there has been significant progress in diagnosing the disease. Scientists have discovered that amyloid deposits are made up of the protein amyloid-beta and NFTs are composed of tau.

With invention of the CAT Scan and MRI machines, we could see volume loss in the brain, including thinning of the cortex and shrinkage of the hippocampus. This was important because, before that, we could not see these changes prior to death and brain autopsy.

Later, scientists came up with methods to measure the proteins amyloid-beta and tau in the cerebrospinal fluid (CSF) and correlate the concentration of these proteins with the diagnosis of Alzheimer's disease. Currently, there are three validated and FDA-approved CSF biomarkers of AD: amyloid-beta 42 (Aβ42), total tau (t-tau), and tau phosphorylated at threonine 181 (p-tau). CSF biomarkers are used in clinical practice to diagnose Alzheimer's diseases with atypical presentations, and are being increasingly used in clinical trials as inclusion criteria and/or outcome measures.

In recent years radioactive tracers have enabled us to look at the extent of glucose usage by the bran and the extent of amyloid and tau deposits in different parts of the brain. FDG-PET (fluorodeoxyglucose-positron emission tomography) measures the amount of glucose usage in the brain. Studies showed that glucose usage is decreased in specific brain parts in Alzheimer's disease and other neurodegenerative disorders. Amyloid-PET shows the extent of amyloid deposits in the brain, and we can detect people at risk for developing Alzheimer's disease years before they develop cognitive symptoms. Tau-PET shows the extent of tau deposits in different brain parts, and its elevation correlates with cognitive decline.

The diagnostic tools explained above are helpful for diagnosis, prognosis, and therapeutic clinical trials for Alzheimer's. However, public use of them is limited due to their cost and low accessibility. To overcome this challenge, scientists developed methods to measure the blood levels of amyloid beta, tau, and p-tau, as well as markers of neurodegeneration (NfL) and immune activation (GFAP). Although this has not been an easy path, extensive work made this possible, and currently, we can measure them in plasma with reasonable accuracy. By measuring the ratio of amyloid beta 42/40, we can diagnose



Alzheimer's disease and recognize people at risk of developing Alzheimer's disease years before they show cognitive symptoms. These blood measures (called biomarkers) are primarily used in clinical research, and we are hopeful that with arrival of new therapies for Alzheimer's disease, they will be used in doctors' offices to identify people at risk for Alzheimer's disease and to aid in clinical diagnosis.

In the end, I would like to thank participants in the ADNI (Alzheimer's Disease Neuroimaging Initiative) study, which is an observational research study at UCLA and all over the United States, Canada, and several other countries. I would like to also thank participants in other research studies that made it possible for scientists to come up with new techniques and diagnostic tools.

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Drug Discovery Lab Research on ApoE4-Targeted Therapeutics for Alzheimer's Disease Awarded Oskar Fischer Prize

By: Patricia Spilman, MA

Professor Varghese John and the Drug Discovery Lab (DDL) of the Mary S. Easton Center for Alzheimer's Research and Care in the Department of Neurology at UCLA, recently received one of the prestigious *Oskar Fischer Prize Awards* at the University of Texas, San Antonio (UTSA). This international award was named in honor of the Czech physician and neuropathologist, Dr. Oskar Fischer. Dr. Fischer's valuable publications from 1907-1924 that contributed to the first descriptions of what we know today as Alzheimer's disease (AD) were largely unrecognized until recently. The Oskar Fischer prize was awarded to ten researchers with hypotheses that may change how society and the medical community understands AD. Specifically, researchers were challenged to present new ideas concerning the causes of AD and how these ideas might lead to new treatments.

The DDL's research proposal, "*ApoE4-Targeted Therapeutics to Prevent the Onset and Progression of Alzheimer's Disease*", submitted in response to the challenge, focused on current research in the lab concerning the effects of the lipoprotein apolipoprotein E4 (ApoE4) on sirtuin 1 (SirT1) - a major factor regulating lifespan and metabolism. Expression of ApoE4 is the greatest genetic risk factor for sporadic AD (AD not caused by a genetic mutation). People have 2 copies of the apolipoprotein E gene, with the most common form being for ApoE3; about 25% of people carry one copy for ApoE4 (with the other copy being for ApoE3), and 2 to 3% carry two copies for ApoE4, putting them at significantly higher risk for developing AD.

As part of the DDL investigation of the effects of ApoE4 on SirT1, they have identified several novel small molecule compounds that may be developed as candidates for clinical testing. They have also identified a novel mechanism by which ApoE4 decreases SirT1 and could confer increased risk for onset and progression of AD. The lab found that ApoE4 can bind to the promoter DNA region of the SirT1 gene (the region of the gene that acts as an 'on' switch) and reduce SirT1 production. Treatment with the small molecule candidates may reverse or prevent that binding, resulting in an increase in SirT1 levels.

To discover potential new AD therapeutics that target ApoE4 effects, particularly ApoE4's exacerbation of tau pathology, the DDL leverages its drug discovery development skills including screening, using medicinal chemistry to create drug analogs, and computer modeling, as well as testing in cellular and animal models. The lab's current approaches include the following: 1) identifying brain-permeable

enhancers of SirT1, 2) identifying small molecule enhancers of soluble amyloid precursor protein alpha (sAPPα) to support synapses and combat amyloid-β (Aβ) and tau pathology, 3) creating mimetics of the mitochondrial-derived peptide humanin to restore neuronal function, and 4) developing dual neutral sphingomyelinase2/acetylcholinesterase inhibitors that may slow the spread of tau pathology. The lab is also developing 'synthetic exosome' technology to deliver potential therapeutics to the brain and is using it to deliver CRISPR components to modify ApoE4 to ApoE3 to prevent its pro-AD effects.

The lab has additional projects funded by the National Institutes of Health to identify small molecules that could modulate two other known risk factors for AD and reduce amyloid and tau pathology: sortilin-related receptor (SORLA) and secreted clusterin. (**Figure**).

The DDL's view is that AD is a multi-factorial disease that is exacerbated by the effects of ApoE4, some of which have been revealed, others yet to be elucidated. The lab's ongoing drug discovery efforts could provide greater understanding of some of these effects leading to new therapeutic approaches – *using drug discovery as a tool to reveal and target new biological mechanisms in AD*. The DDL's ultimate goal is to discover potential new drugs that may effectively be used as mono-therapy or in combination as multi-modal therapy to successfully prevent or treat Alzheimer's disease.

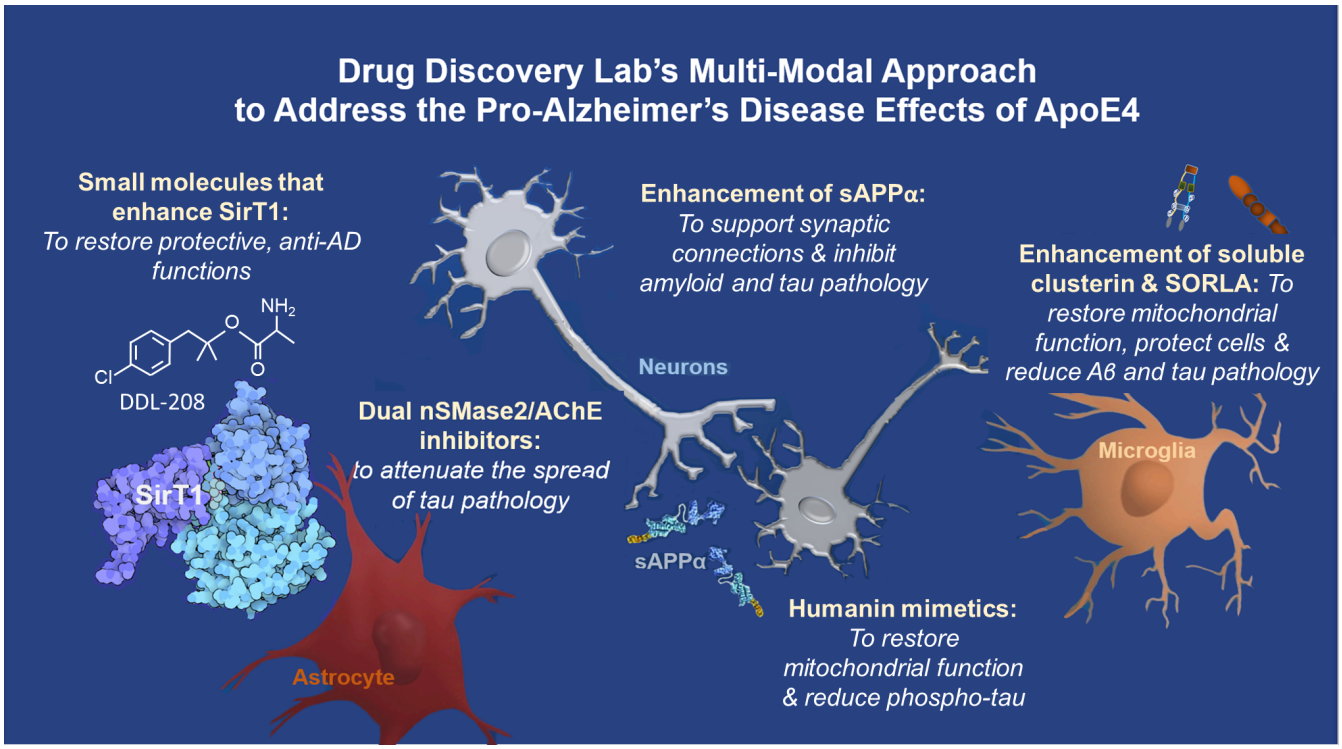

Figure. The Drug Discovery Lab's (DDL) therapeutic approach to overcoming the pro-Alzheimer's disease (AD) effects of apolipoprotein E4 (ApoE4). Current targets for DDL efforts include: enhancing protective SirT1 to reverse effects of ApoE4; identifying dual neutral sphingomyelinase2/acetylcholinesterase (AChE) inhibitors to support cognitive improvement and slow the spread of tau pathology; enhancing soluble amyloid precursor protein alpha (sAPPα) to protect neuronal synapses and reduce Aβ and tau pathology; identifying humanin mimetics to enhance function and reduce tau pathology; enhancing sortilin-related receptors (SORLA) and soluble clusterin to protect cells and reduce Aβ and tau pathology.

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Thank You for Making a Difference!

The Mary S. Easton Center for Alzheimer's Research and Care at UCLA provides expert diagnosis and care as well as access to the latest clinical trials and research for persons living with Alzheimer's disease and related dementias. We are rising to the challenge to combat this devastating disease in all its complexity and are making inroads into finding effective treatments. And successful therapies cannot come soon enough. An estimated 6.5 million people in the United States are living with Alzheimer's disease, and, with the growth of the aging population, this number is expected to surge to 14 million by the year 2050.

Our world leading physician-scientists are vigorously working to combat Alzheimer's and related dementias through a number of innovative approaches. Along with treating some of the most complicated cases of Alzheimer's and related dementias, we conduct genetic studies, basic research into disease pathways and progression, and rapid translation of discoveries and ideas into novel treatments from our drug discovery lab and clinical trials. The close teamwork of clinicians and basic scientists at UCLA greatly enhances our ability to solve Alzheimer's disease. Some of the research studies on Alzheimer's disease include:

- Improving early diagnosis of Alzheimer's and related dementia in primary care: Early detection and accurate diagnosis of Alzheimer's and related dementias is crucial for a number of reasons including: 1) getting people on the right medications, 2) intervening on lifestyle modifications to optimize cognitive and motor function, 3) reducing family/caregiver burden through appropriate counseling and planning, and 4) offering participation in clinical trials. In an initiative led by Dr. Timothy Chang, we are implementing a new dementia screening toolkit in a primary care clinic. This clinic serves a wide population including people that do not have ready access to dementia experts. We designed the toolkit in English and Spanish, and doctors conduct the screening in 5 minutes at annual wellness visits. It is fully integrated into the electronic health record.
- Developing effective treatments for silent seizures and associated memory loss in Alzheimer's disease: This investigation, led by Dr. Keith Vossel, bridges exciting discoveries in scientific models with human clinical trials targeting seizures and silent epileptic activity that occurs in up to 60 percent of Alzheimer's patients. We have found that treatment with an antiseizure drug can improve memory and other cognitive functions in Alzheimer's patients with detectable epileptic activity.
- Developing new genetic approaches to study Alzheimer's disease. The center is pioneering methods to determine genetic risk factors for Alzheimer's disease and using this information to develop treatments. We envision a clinic where information from a genetic screening exam, along with other medical information, will be used to provide information about risk of Alzheimer's disease and tailor treatments for specific disease pathways.

The generosity of our donors allows the Mary S. Easton Center for Alzheimer's Research and Care at UCLA to honor its commitment to:

- Improve the quality of life for patients through compassionate care
- Support psycho-social needs of Alzheimer's disease families and caregivers
- Develop new medications and treatments for Alzheimer's disease and related conditions
- Continue the relentless pursuit of a cure

We would like to express our gratitude to the supporters of the Mary S. Easton Center. Your philanthropy truly makes an impact on our progress and ongoing research.

Questions? Please contact: **Chris Carbado**, Director of Development, at **(310) 562-6498** or ccarbado@mednet.ucla.edu or **Iris Lopez**, Development Coordinator, at **(424) 325-9310** or Ijl@mednet.ucla.edu.

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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 https://eastonad.ucla.edu.

OBSERVATIONAL STUDIES:

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

INTERVENTIONAL STUDIES:

- A Study of JNJ-63733657 in Participants with Early Alzheimer's Disease (Autonomy)
- Clinical Trial of Oxytocin for Frontotemporal Dementia (FOXY)

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

Caregiver Wellbeing: Your Mental Health Matters

Date: Thursday, October 6, 2022
Time: 3:00 PM – 4:30 PM (PDT)
Virtual Forum

In partnership with South Bay Dementia Education Consortium.
A discussion on managing stress, anxiety, and depression while caring for a loved one with dementia.

Registration required:
https://uclahs.zoom.us/meeting/register/tJEtd-yopjgqGtR3P5qbxjrvndUXUm8a6vZ0

Update on Alzheimer's Disease Research

Date: Tuesday, October 18, 2022
Time: 10:30 AM - 12:00 PM (PDT)
Virtual Forum

In partnership with UCLA Osher Lifelong Learning Institute (OLLI).
As part of Beyond the Headlines, POLI SCI 747, Monica Moore, MSG, Community Health Program Manager, will present an update on Alzheimer's disease research.

https://www.uclaextension.edu/osher-olli/lecture-courses/course/beyond-headlines-pol-sci-747
(*Open to UCLA OLLI members only)

Alzheimer's Association Santa Monica Walk to End Alzheimer's

Date: Sunday, October 23, 2022
Time: 9:00 AM - 12:00 PM (PDT)
Location: Crescent Bay Park
2000 Ocean Avenue
Santa Monica, CA 90405

Join the Easton Center as we walk to raise funds and awareness for the Alzheimer's Association.
http://act.alz.org/goto/UCLAEastonCenter

Care. Cure. Prevent. Part 2

Date: Thursday, November 10, 2022
Time: 3:00 PM - 4:30 PM (PST)
Virtual Forum

In partnership with Kensington Senior Living.
Dr. Leila Parand will be a part of an esteemed panel of Neurologists across the state to discuss the latest in Alzheimer's research and care.

Virtual forum- please rsvp at:
https://us02web.zoom.us/webinar/register/WN_vlXDDWB6SFS1cWBzEYmiHA

Alzheimer's Los Angeles Making Memories Festival

Date: Sunday, November 13, 2022
Time: 12:00 PM - 5:00 PM (PST)
Location: LA State Historic Park
1245 N. Spring Street
Los Angeles, CA 90012

A celebration of food and music and visit our booth for information about brain health, Alzheimer's disease-related dementia prevention and management, and involvement with clinical research.
https://www.alzheimersla.org/get-involved/events/making-memories-festival/

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