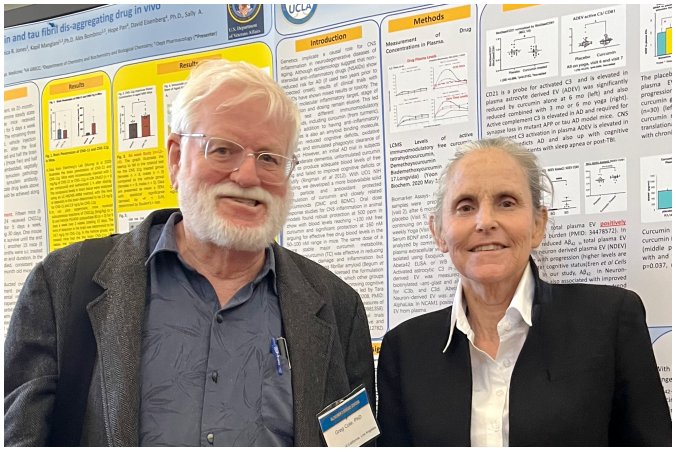
MARY S. EASTON CENTER for Alzheimer's Research and Care at UCLA
DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA

David Geffen School of Medicine

Summer 2024 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.

Targeting Zombie Proteins in the Bullseye of the Easton Center



By: Sally A. Frautschy, PhD, and Greg M. Cole, PhD, Professors of Neurology at UCLA

Here, we highlight a collaborative project to develop new treatments for Alzheimer's and Parkinson's diseases. This initiative was supported by generous donations from Jim and Phyllis Easton, who have a history of building successful teams in both their Easton companies and various sports initiatives, including national and international support for archery and the Olympics, as well as UCLA athletics. The Easton Family founded and continues to support the Mary S. Easton Alzheimer's Center to encourage interdisciplinary collaboration and teamwork among multiple laboratories across campus and to foster innovative breakthroughs in understanding and treating neurodegenerative diseases.

We sought to design and test a drug targeting the misshapen or misfolded proteins responsible for Alzheimer's, Parkinson's, and various other neurological diseases collectively known as 'proteinopathies.' While each disease involves unique misshapen proteins, all share the common feature of forming elongated strands or "amyloid fibrils." Like zombies, they transform normal proteins into new zombie-like fibrils, a process called 'seeding.' The fibrils then spread from nerve cell to nerve cell, irreversibly disrupting circuits as the diseases progress.

Three collaborative teams spearheaded this project. Dr. David S. Eisenberg, a leading structural and computational biologist at UCLA Molecular Biology Institute, led his team to identify key toxic regions in protein structures and design drugs to target these regions to slow or reverse toxic fibril formation and spreading. Dr. Harry Vinters and his group at the UCLA Neuropathology Core used brain extracts of

deceased patients to ensure that these drugs directly bound and destroyed human fibrils. Because of our expertise in developing some of the first AD mouse models with protein aggregates and bringing safe drugs to clinical trials (such as n-3 fatty acids, turmeric-derived curcumin that also specifically targets misfolded proteins), our team supervised, assisted, and trained Drs. Ke Hou and Hope Pan from the Eisenberg team to test these drugs in animal models.

The Eisenberg team utilized brains from patients with Alzheimer's, Parkinson's, Huntington's, and other less common brain disorders, employing advanced atomic-level techniques to identify exposed sticky regions in the three-dimensional structure responsible for aberrant protein-protein self-assembly into fibrils. This particular project first focused on the role of misfolded tau, pivotal in diseases known as tauopathies, including AD, frontotemporal dementia, and chronic traumatic encephalopathy, a disease caused by frequent concussions common in football players and Veterans. Tau fibrils twist into tangles inside neurons and spread through circuits.

Using computer models, the Eisenberg team designed small proteins (short chains of amino acids, the building blocks of proteins) to interfere with aggregation. The peptide that best halted tau protein aggregation and seeding was a six-amino acid chain named "D-peptide." Our team then set out to determine whether D-peptide could be effective in aged mice genetically engineered to express human tau. Since small peptides circulating in the blood may not reach the brain, we inserted a small pump under the skin to directly deliver D-peptide into the brain. In just two weeks, D-peptide reduced tau aggregates and pathology. It is also protected in a fruit fly tauopathy model.

Seeking alternative and practical delivery methods, the Eisenberg team added a chain of amino acids that codes for cell penetration of the D-peptide. We then used this to explore intranasal administration in a different model with more severe tau pathology. Following six weeks of treatment, cognition only slightly improved, and tau aggregates were only partially reduced.

Tracking and Destroying the target.

Since intranasal administration was only partially successful, the next step was to improve delivery to the brain. We chose a two-tiered approach, first to deliver the drug through the tail vein, and second to tag the protein with a small iron particle (magnetic nanoparticle) that could allow us to track delivery to the brain as well as use magnetic resonance imaging (MRI) to track progression in live animals. First, Dr. Ke Hou and her colleagues in the Eisenberg lab coated the magnetic NPs with the D-peptide that can bind to the tau lesions (tangles). There was a catch to adding an amino acid to connect the particle with the peptide. All six amino acids in D-peptide are required for activity. Would the extra amino acid diminish activity? It turned out that the new seven amino acid peptide (D7) not only retained the tau fibril binding and halted fibril growth and seeding, but it also improved activity! In fact, adding D7 to synthetic tau fibrils alone in a test tube or with cells in a culture dish disappeared them! But would it do the same thing with tau from disease patients? It did! Fibrils isolated directly from AD patient brains, collected by Dr. Vinters and his team, were also rapidly fragmented.

The next step was determining if NP attached to D7 could work in live animals to bind and clear abnormal tau. Drs. Ke Hou and Hope Pan, an MD student who just completed her PhD, worked with our lab using a tau model with accelerated (severe) disease caused by a single injection of tau aggregates into the brain of young mice expressing human tau. Then, every week for three months, we injected into their

tail veins D7-coated NPs. The D7-NPs were demonstrated to penetrate the brain and worked to significantly reduce tau aggregates and improve cognition, as featured in Alz Forum[1] and published this year in Science Advances[2]. The Eisenberg team also produced a paper detailing a molecular mechanism for fragmenting and breaking down pre-existing fibrils, which is under peer review at a leading journal, and the preprint is posted online[3].

Tracking and Treating Parkinson's Disease (PD) pathology.

Using computer models based on diseased human aggregates, the Eisenberg team used a similar approach to develop a drug for Parkinson's. Instead of tau, the misfolded protein in Parkinson's is called alpha-synuclein (aSyn). They designed a peptide called R8, which team member Dr. Melinda Balbirnie showed specifically binds and caps aSyn fibrils, halting their growth and seeding in a dish. She then coupled R8 with magnetic NPs. Working with Dr. Hope Pan, we aged Parkinson's Disease (PD) model mice with aSyn fibrils and motor deficits. Dr. Pan found that, after a single injection, the R8-NPs entered the brain and bound aSyn fibrils, and because of the NPs, we were able to image pathology in live animals using MRI. This was a major breakthrough since, unlike AD, there is no specific neuroimaging diagnostic for PD. Our revised paper is under review at Science Advances[4]. We also tested repeated administration of R8-NPs for treatment efficacy in live animals. While this dose and formulation was ineffective with advanced disease, it reduced pathology in early disease. We wanted it to be effective for both, leading to the next step.

Small molecule solutions that dissolve alpha-synuclein and tau fibrils.

Peptide drugs can be difficult to formulate for brain penetration and stability and costly for patient use. So Drs. Paul Seidler (now at USC) and Kevin Murray (now at Brown University), when working in the Eisenberg lab, sought to identify small molecules with similar properties that were also stable, penetrated the brain, and amenable to frequent dosing. First, they identified that the green tea molecule EGCG fit perfectly into the vulnerable tau and aSyn folds and dissolved their aggregates. Although EGCG has other properties and is poorly brain penetrant without formulation, we tested an EGCG formulation proven to deliver EGCG to the brain. Unfortunately, it failed to improve motor deficits with this dose and formulation.

The poor EGCG drug properties led the Eisenberg team to use computer modeling to simulate the precise atomic level fit for EGCG in the fibril's vulnerable pocket. Then, they found a series of compounds that break down aSyn fibrils. The resulting drug candidates were also screened for the theoretical properties needed to penetrate the brain. They named the molecule showing the best results for aSyn CNS11g, which Dr. Hope Pan found readily entered the brain. Then, in our group, Dr. Zuo formulated it for injection under the skin to allow frequent dosing, which Drs. Cansheng Zhu and Kapil Manglani used to treat very advanced-stage PD model mice. We were excited to see that it corrected impaired mobility and reduced brain and spinal cord levels of neurotoxic soluble aSyn aggregates.

Remarkably, despite their differences, aSyn and tau aggregates share one similar fold. Thus, the designer drug CNS11g used in the Parkinson's study also successfully targeted tau aggregates. This is exciting because 25% of Alzheimer's patients have a "Lewy Body Variant," a type of aSyn pathology in addition to the amyloid plaques and tangled tau present in all AD cases, indicating that the drug is likely to target both pathologies.

Why does this matter? Moving to Trials.

Even after successful treatment with the expensive FDA-approved anti-amyloid antibodies that remove this one aggregated protein after repeated intravenous infusions, the other aggregated protein tau, which also causes memory decline, remains. For Parkinson's, there is no approved treatment that breaks apart aSyn aggregates. Further development of the peptides and CNS series of small molecules will facilitate getting these into the clinic.

References:

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2. Hou K, Pan H, Shahpasand-Kroner H, Hu C, Abskharon R, Seidler P, Mekkittikul M, Balbrinie M, Lantz C, Sawaya MR, Dolinsky JL, Jones M, Zuo X, Loo JA, Frautschy SA, Cole GM, Eisenberg DS. D-peptide-magnetic nanoparticles fragment tau fibrils and rescue behavioral deficits in a mouse model of Alzheimer's disease Sci Adv. 2024, 10(18): eadl2991. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11062580/
3. Hou K, Ge P, Sawaya MR, Dolinsky JL, Yang Y, Xiao JY, Lutter L, Boyer DR, Cheng X, Pi J, Zhang J, Lu J, Yang S, Yu Z, Feigon J, Eisenberg DS. How short peptides can disassemble ultra-stable tau fibrils extracted from Alzheimer's disease brain by a strain-relief mechanism. https://www.biorxiv.org/content/10.1101/2024.03.25.586668v1.full
4. Pan H, Balbirnie M, Hou K, Sta Maria NS, Sahay S, Denver LS, Mychica JM, Zuo Z, Zhu C, Mirbaha H, Shahpasand-Kroner H, Mekkittikul M, Hu C, Cheng Z, Abskharon R, Sawaya MR, Williams CK, Vinters HV, Jacobs R, Harris NG, Cole GM, Frautschy SA, Eisenberg DS. Functionalized magnetic nanoparticles for magnetic resonance imaging of α-synuclein. (Submitted. In Review.)

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Research MD Fellows

Tirth Patel, MD, PhD
Resident Physician | PGY-4
Department of Neurology | UCLA Health

Tirth's interest in neurology stems from his time as an undergraduate student at UCLA when he participated in the Student Stroke Team, where he had the unique opportunity to get involved in the care of acute stroke patients and learn from UCLA's top stroke neurologists. After graduating, he took this passion for neurology with him to Washington University in St. Louis. There, he joined the MD/PhD program, obtaining his PhD in the laboratory of Dr. David Holtzman. His research there focused on the role of tau protein in the pathogenesis and therapeutics of Alzheimer's disease and other neurodegenerative diseases. He returned to UCLA for his neurology residency. He will be joining the Easton Center as a neurobehavior fellow starting July 2024 while performing postdoctoral research in the laboratory of Dr. Jason Hinman. His research will focus on the molecular mechanisms of lymphovascular dysfunction in tauopathy.

Tien-Phat (Phat) Huynh, MD, PhD
Resident Physician | PGY-4
Department of Neurology | UCLA Health

Phat was born and raised in Nha Trang, a tropical paradise on the central coast of Vietnam. His immediate family moved to Orange County when he was 14, where he attended high school and dreamed of becoming an architect. However, the stark contrast in health disparities between the United States and his home country that Phat observed on a home visit prompted him to look into a career in medicine where he thought he could make a greater impact. Phat attended UCLA as an undergraduate with a major in Molecular biology and a minor in biomedical research, where he first discovered his love for the latter. Phat pursued several independent research projects in the Teplow lab, studying the role of protein misfolding in the context of Alzheimer's disease. Phat's interests in the field of neurodegeneration led him to attend the MD-PhD program at Washington University in St. Louis, where he completed a PhD thesis in the laboratory of David M. Holtzman. Phat's graduate works examined the role of apolipoprotein E in the pathogenesis of Alzheimer's disease and the potential of antisense oligonucleotides as therapeutic revenue for neurodegenerative diseases. Phat is a proud Bruin, and he returned to southern California to join the neurology residency at UCLA. Following residency, Phat is staying at UCLA to pursue a combined clinical research fellowship in memory and dementia. To this end, Phat was awarded the UE5 (formerly R25) training grant from the NINDS and will be investigating the role of astrocytes in the pathogenesis of Alzheimer's disease under the mentorship of Dr. X. William Yang and Baljit Khakh. As a physician-scientist, Phat hopes to develop a translational research program that allows him to utilize a multi-disciplinary approach to model and understand disease mechanisms, spanning across disciplines of cellular and systems neuroscience. In his spare time, you can find him shredding on the slopes at Big Bear or Mammoth in the Winter or falling off his surfboard at San Onofre in the Summer. He occasionally enjoys more mundane activities such as hiking, camping, and cooking (mostly Vietnamese food).

L. Brian Hickman, MD, MSc
Resident Physician | PGY-4
Department of Neurology | UCLA Health

Dr. L. Brian Hickman is an R25 trainee and epilepsy fellow at UCLA studying Alzheimer's disease as a cause of epilepsy in adulthood. Dr. Hickman completed medical school at Washington University in St. Louis. While in medical school, he also obtained a master's degree in clinical investigation via the NIH TL1 clinical and translational research training program and investigated altered electrocerebral activity after anesthesia and seizures. He completed his neurology residency at UCLA and served as chief resident during the 2023-2024 academic year.

Supported by the NIH R25 research training program, Dr. Hickman is investigating fluid biomarkers and neuroimaging markers of Alzheimer's disease in older adults with epilepsy. Growing evidence shows that

epilepsy and Alzheimer's have a bidirectional relationship, with epilepsy increasing the risk of Alzheimer's disease and vice-versa. Dr. Hickman aims to identify patients with early stages of Alzheimer's causing their seizures. Early identification may facilitate treatments that can prevent both seizures and cognitive changes in these patients. His current work includes the use of ultrasensitive biomarker assays of amyloid-beta and tau, PET neuroimaging targeting amyloid and tau, quantitative MRI analyses using FreeSurfer neuroimaging software, and EEG recordings of seizures and abnormal cerebral discharges to study abnormal cerebral activity and brain structure in patients with late-onset epilepsy. His mentorship team and collaborators include Dr. Keith Vossel, Dr. Jason Hinman, Dr. John Stern, and Dr. Daniel Silverman, who represent an interdisciplinary group of expert investigators across clinical neuroscience at UCLA.

Dr. Hickman's research has been published in JAMA Neurology, Neurology Clinical Practice, Clinical Neurophysiology, and the British Journal of Anaesthesia. His clinical training includes the diagnosis and treatment of epilepsy, including interdisciplinary epilepsy surgery planning, seizure localization, and EEG interpretation. He will be staffing a clinic at UCLA specifically treating older adults with epilepsy to provide specialized treatment needs for this group.

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New Addition to the Easton Center

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

Photo: Natalie Perez, Clinical Research Liaison

Natalie has a bachelor's degree in biochemistry from Loyola Marymount University. Upon graduation from LMU, she started her professional career at a biotech startup in Santa Monica that focused on using modern science to help farmers protect crops in a naturally effective and sustainable way. Natalie is thrilled to join the Kagan team and begin her contribution to Alzheimer's research at the UCLA Easton Center.

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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 4 (ADNI4) Protocol
- Alzheimer's Disease Research Center - Biomarkers in Neurodegenerative Disease (ADRC-BIND)
- ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD)
- Dementia Research Focus Group
- Dementia Research, Education, and Advancement in Los Angeles (DREAM-LA)

- Music Stimulation to Improve Cognition (MUSIC)
- National Institute on Aging Alzheimer's Disease Family Based Study (NIA-AD-FBS)

INTERVENTIONAL STUDIES:

- SUVEN-502 Study
- [18F]PI-2620 Phase 3 Histopathological Study
- LIFUP-MCIAD Study

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

2024 Mental Health Awareness Community Fair

Date: Saturday, August 3, 2024
Time: 9:00 AM – 12:30 PM (PDT)
Location: Robert F. Kennedy Institute
544 N. Avalon Blvd., Ste., #309
Wilmington, CA 90744

The ELHA Lab is looking forward to returning to Wilmington for a second time this summer to join the Robert F. Kennedy Institute's Mental Health Awareness Community Fair! This event will host a variety of informational resources for the entire family as well as ensure a quality social outing for its guests.

To register, please contact Demi Prado at: rfkihealthfair@gmail.com

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Festival Cultural para el Adulto Mayor

Date: Monday, August 5, 2024
Time: 9:00 AM – 1:00 PM (PDT)
Location: Lakewood Masonic Center
5918 Parkcrest Street
Long Beach, CA 90808

Dr. Mirella Díaz-Santos, director of the ELHA Lab, will be a guest speaker at a cultural celebration for older adults in the Long Beach community! Join us for a great time and an opportunity to learn about why strengthening ties with our cultural roots helps increase our brain health! [Spanish Flyer]

To register, please contact Angelica Arias at: aarias@alzla.org

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Living a Brain-Healthy Lifestyle

Date: Wednesday, August 7, 2024
Time: 12:00 PM – 1:00 PM (PDT)
Location: Bella Vida SCV Senior Center
27180 Golden Valley Road
Santa Clarita, CA 91350

For information or to rsvp, please call: (661) 259-9444.

Did you know that what is good for the body is also good for the brain? Monica Moore, MSG, will discuss the latest research on brain health and the information that has been discovered about reducing one's risk of developing dementia.

Bernardi Multipurpose Senior Center's 2nd Annual Block Party

Date: Friday, August 9, 2024
Time: 9:00 AM – 12:30 PM (PDT)
Location: Bernardi Senior Center
6514 Sylmar Avenue
Van Nuys, CA 91401

The ELHA team is happy to be back with the Bernardi Center during their 2nd annual block party! We will be sharing important brain health and healthy lifestyle tips with the community. [Flyer]

7th Annual Senior Briefing and Health Fair

Date: Friday, August 16, 2024
Time: 9:00 AM – 2:00 PM (PDT)
Location: Congresswoman Juanita Millender McDonald Community Center (CJMMCC)
801 E. Carson Street
Carson, CA 90745

The ELHA team is excited to return to Carson this summer. This is one of our busiest events of the year and one of the most interactive and fulfilling. Join us on August 16th at Carson's Community Center. [Flyer]

Caregiver Experts Discuss: Male Caregivers and Dementia

Date: Wednesday, September 4, 2024
Time: 3:00 PM – 4:00 PM (PDT)
Platform: Virtual Forum

Please join the Easton Center's Monica Moore, MSG, in a discussion along with the Caregiver Experts of Kensington Senior Living about the unique needs faced by male caregivers.
Presented by Kensington Senior Living

To register, please contact Monica at: mrmoore@mednet.ucla.edu

Mental Health Resource Fair

Date: Saturday, September 7, 2024
Time: 10:00 AM – 12:00 PM (PDT)
Location: Salt Lake Recreation Center
3401 E. Florence Avenue
Huntington Park, CA

The ELHA Lab team will be present for the first time at a community resource fair in Huntington Park! In partnership with the city's Health and Education Commission, ELHA's team will share the importance of catering to our brain health as an important component of caring for one's mental health. This is a community event you don't want to miss! [Flyer]

Registration: https://docs.google.com/forms/d/e/1FAIpQLSfEe07MXdHWyx35CtUkRQoaz0ZXVEJOxVAF6h8XV12f07jemw/viewform

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Advanced Health Care Planning

Date: Tuesday, September 17, 2024
Time: 10:00 AM – 11:00 AM (PDT)
Platform: Virtual Forum

Our partners at the UCLA Emeriti Retiree Relation Center are offering a course on **Advanced Health Care Planning.**

Desired future health states (for example, being able to carry out certain activities) and what situations you want to avoid (for example, being kept alive on machines while in a coma). You can discuss your wishes with your healthcare team and record them.

Speaker: Delia Cortez, LCSW, Palliative Care Social Worker at UCLA Medical Center, Santa Monica
Please register at: https://retirees.ucla.edu/event-5803511 (open to all)

Update on Alzheimer's Disease Research

Date: Thursday, September 19, 2024
Time: 10:00 AM – 11:00 AM (PDT)
Location: Cerritos Senior Center
12340 South Street
Cerritos, CA 90703

Monica Moore, MSG, UCLA Easton Center, will present the latest findings related to the symptoms and causes of dementia and Alzheimer's disease. She will also address the latest treatments available, current clinical trials, and what research is currently being conducted for this devastating disease. No RSVP. Come with questions!

Update on Alzheimer's Disease Research

Date: Saturday, September 28, 2024
Time: 11:00 AM – 12:30 PM (PDT)
Location: Alhambra Public Library
101 S. 1st Street
Alhambra, CA 91801

Monica Moore, MSG, UCLA Easton Center, will present the latest findings related to the symptoms and causes of dementia and Alzheimer's disease. She will also address the latest treatments available, current clinical trials, and what research is currently being conducted for this devastating disease. No RSVP. Come with questions!

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