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

David Geffen School of Medicine

Winter/Spring 2021 E-Newsletter

| 2020 Turken Research Award and Symposium |
| New Results Support Promising Drug Candidate Developed by UCLA Researchers |
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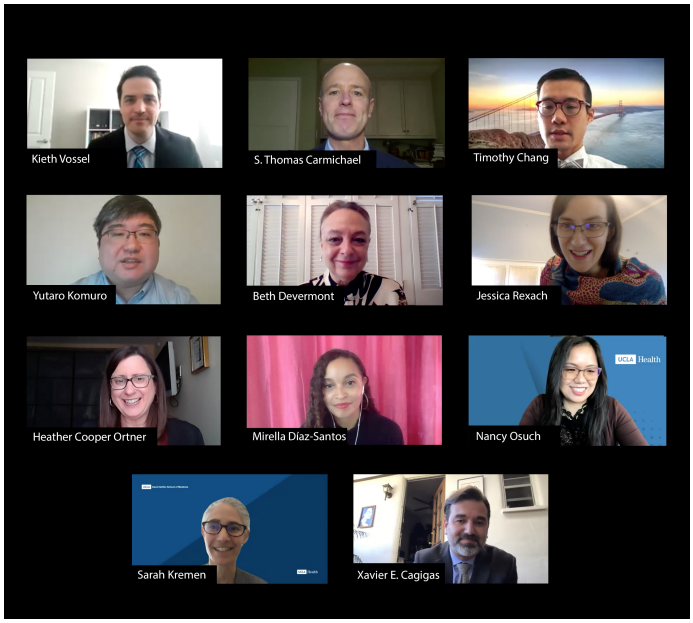
The Mary S. Easton Center for Alzheimer's Disease Research at UCLA has very active teams working on basic research, drug discovery, biomarkers for early diagnosis and clinical activity including clinical trials, cognitive testing, and patient care.

2020 Turken Research Award and Symposium



By: Keith Vossel, MD, MSc

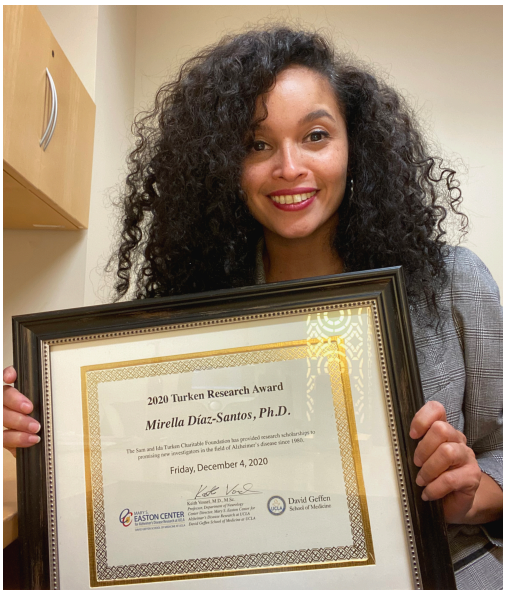
In December 2020, we held the 30th annual Turken Research Award Event via webinar. This event is made possible through the generous support of Beth Devermont and her foundation, the Sam and Ida Turken Charitable Foundation, gifted through Alzheimer's Los Angeles. The Turken foundation has sponsored this event since 1990 and supported a large number of accomplished scientists that have contributed breakthrough discoveries in the Alzheimer's field.

We had another outstanding program with UCLA clinicians and scientist presenting on a large range of topics in Alzheimer's research and care. The virtual format reached a wide audience, and 89 faculty, staff, and colleagues, attended the event. The event featured a virtual poster session where 20 presenters displayed their posters and took Q&A from the audience, as well as several featured speakers.

Timothy Chang, MD, PhD, Assistant Professor of Neurology, led off the event with a talk titled "Rare Variant Network Analyses in Progressive Supranuclear Palsy." The genetic causes of Alzheimer's disease and related disorders, such as progressive supranuclear palsy, are complex, and require advanced computational tools to assess. Dr. Chang presented his novel approach to discovering rare genetic risk factors for dementias, combining biomedical informatics and genetics. By studying large sets of genetic data from patients with Alzheimer's disease, progressive supranuclear palsy, and healthy controls, Dr. Chang has identified clusters of genes within specific brain cells, that are associated with dementia risk. Dr. Chang's findings will help predict diagnosis, progression, and treatment response in neurodegenerative diseases.

Yutaro Komuro, PhD, Postdoctoral Research Fellow of Neurology, presented a talk titled, "Tauopathy-induced Gliovascular Dysfunction Identified by Cell-specific Viral TRAP-Seq." Dr. Komuro's presentation demonstrated how a viral toolbox called translating ribosome affinity purification (TRAP) can identify genetic expression within specific cells of the brain. Neurons, support cells, and vascular cells in the brain work together as a unit, and Dr. Komuro's work is revealing in intricate detail how this cellular unit becomes altered in Alzheimer's disease.

Jessica Rexach, MD, PhD, Assistant Professor of Neurology and 2019 Turken Research Awardee, presented a talk titled, "Functional Genomics Quest for Causal and Regulatory Mechanisms of Dementia." Dr. Rexach's research uses human genetics and systems biology to understand immune signaling in Alzheimer's and associated dementias with the goal of developing immune-targeted therapies. Dr. Rexach's investigation has pinpointed a micro-RNA called miR-203 which contributes to inflammation, DNA damage, and cell death in models of Alzheimer's disease. This micro-RNA is an attractive drug target due to its contributions to a myriad of disease pathways.



Mirella Díaz-Santos, PhD, received the 2020 Turken Research Award for her project titled "By the Community with the Community: Ending Exclusionary Research in Latino/a/x Alzheimer's Disease." Dr. Díaz-Santos is a bilingual neuropsychologist in the UCLA Easton Center with an expertise in Alzheimer's disease and related dementias in the Latinx older adult community and their families. She holds appointments of Adjunct Assistant Professor in the UCLA Department of Psychiatry and Behavioral Sciences and Director of Research for the Hispanic Neuropsychiatric Center of Excellence at the Jane and Terry Semel Institute for Neuroscience and Human Behavior at UCLA. Dr. Díaz-Santos gave an outstanding presentation of her creative approaches to providing education on aging, brain health, identifying symptoms of dementia, and diagnostic differentials of Alzheimer's disease and related dementias while ruling out other competing diagnoses in the Latinx community. She is working to improve healthcare for Latinx patients by developing cognitive screening tools in Spanish as well as a clinician fact sheets in the detection of cognitive decline and dementia in Spanish-speaking individuals. We are excited that the Turken Award will support this important endeavor.

Heather Cooper Ortner, President and CEO of Alzheimer's Los Angeles, provided a broad overview of the many ways that Alzheimer's L.A. is serving patients suffering from dementia and their families. These services include evidence-based caregiver education, support groups, social worker family support, outreach through a large network of dementia care providers, partnership with philanthropic organizations to fund promising new investigators, and strong advocacy for federal and state funding for Alzheimer's disease and related dementias.

Finally, Beth Devermont, President and Director of the Sam and Ida Turken Charitable Foundation, presented a hopeful message with encouraging words for the Turken Awardees, past and present, and challenged us all to keep up the great work as we work together to make major steps towards eradicate dementia. We are deeply grateful to Ms. Devermont for her generosity and continuing her family's legacy of supporting bright and promising new scientists devoted to Alzheimer's disease research and care.

This was the first Turken Award meeting to be held online, and it went smoothly thanks to the great efforts of Nancy Osuch, Media and Communications Manager for the UCLA Easton Center. It was great to see each other and catch up on everyone's progress.

New Results Support Promising Drug Candidate Developed by UCLA Researchers

By: Gal Bitan, PhD

The Bitan group has published a new paper reporting the therapeutic effect of their drug candidate, CLR01, against toxic clumps of the protein tau. Protein molecules sticking to each other to form toxic clumps is a pathological phenomenon underlying more than 50 diseases, including Alzheimer's, Parkinson's, and Lou Gehrig's disease. In each of these diseases, a particular protein forms toxic clumps that attack and kill specific groups of cells. Alzheimer's disease is unique in being a "double whammy", in which two different proteins, beta-amyloid and tau, form toxic clumps, launching a coordinated assault on the brain, in which beta-amyloid acts as the instigator of the attack, whereas tau is the propagator of the pathology throughout the brain.

Several years ago, the group tested CLR01 in a mouse model of Alzheimer's disease genetically engineered to have both of the offending proteins in the brain and found that after treating the mice with CLR01, the toxic clumps of both beta-amyloid and tau were dramatically reduced (Attar et al., 2012). Later, they showed that similar therapeutic effects could be found in a rat model (Malik et al., 2018). However, because the toxic clumps of tau are believed to form in response to those of beta-amyloid, those studies left open an important question: Can CLR01 directly reduce pathological clumps of tau in the absence of beta-amyloid? Answering this question may have far-reaching consequences. First, if the drug candidate can act directly on both of the rogue proteins, its chances of having a meaningful therapeutic impact in patients with Alzheimer's disease are much higher than drugs that affect only one of the offenders. Second, a direct therapeutic effect on tau means that CLR01 could be used not only for Alzheimer's, but also for other diseases caused by toxic tau clumps, such as frontotemporal dementia, progressive supranuclear palsy, and chronic traumatic encephalopathy – the disease that can cause depression and dementia in football players, professional boxers, soldiers, and other people exposed to repeated head injury.

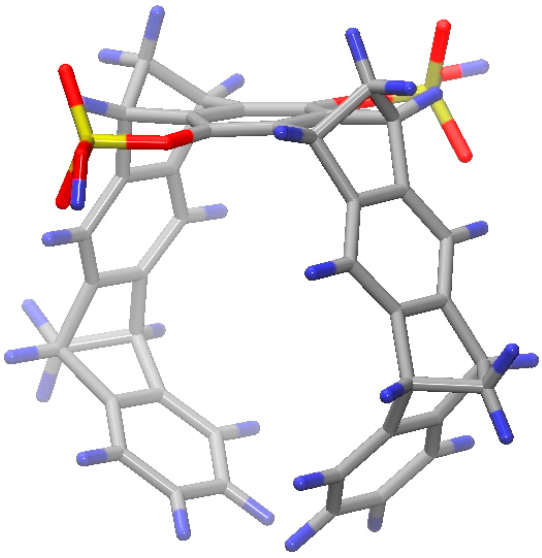


Figure 1: A schematic structure of CLR01. Gray color represents carbon atoms, blue represents hydrogen, yellow represents phosphorous and red represents oxygen.

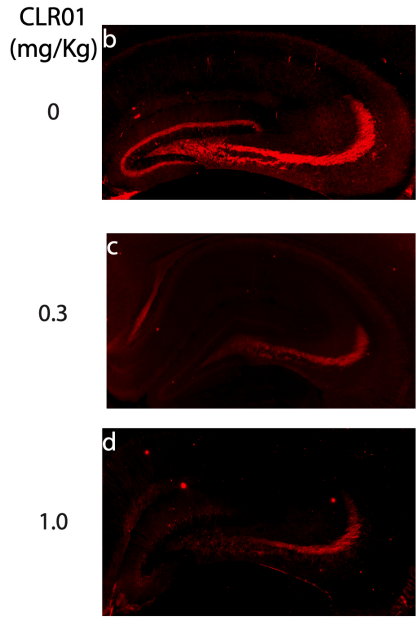


Figure 2: Brain section of mice that received placebo (top image), low dose (middle), or high dose (bottom) of CLR01. The red color represents the tau pathology in the brain.

In the new study (Di et al., 2021), led by postdoctoral fellows, Drs. Jing Di and Ibrar Siddique, mice genetically engineered to produce tau clumps in the brain were treated with CLR01 for 35 days. The treatment results in a significant rescue of muscle strength, which deteriorates in these mice starting at 7-months of age, and reduced anxiety and disinhibition, a behavior similar to that displayed by patients with frontotemporal dementia. Pathological examination showed that CLR01 reduced several different toxic forms of tau clumps in the brain and suppressed the brain inflammation that results from the offending action of these clumps. These results suggest that CLR01 is a promising drug candidate for Alzheimer's disease and other diseases involving toxic tau clumps and support the development of CLR01 toward human clinical trials.

References:

Attar, A., Ripoli, C., Riccardi, E., Maiti, P., Li Puma, D.D., Liu, T., Hayes, J., Jones, M.R., Lichti-Kaiser, K., Yang, F*., et al.* (2012). Protection of primary neurons and mouse brain from Alzheimer's pathology by molecular tweezers. Brain *135*, 3735-3748.

Di, J., Siddique, I., Li, Z., Malki, G., Hornung, S., Dutta, S., Hurst, I., Ishaaya, E., Wang, A., Tu, S*., et al.* (2021). The molecular tweezer CLR01 improves behavioral deficits and reduces tau pathology in P301S-tau transgenic mice. Alzheimers Res Ther *13*, 6.

Malik, R., Di, J., Nair, G., Attar, A., Taylor, K., Teng, E., Klärner, F.G., Schrader, T., and Bitan, G. (2018). Using Molecular Tweezers to Remodel Abnormal Protein Self-Assembly and Inhibit the Toxicity of Amyloidogenic Proteins. Methods Mol Biol *1777*, 369-386.

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New Addition to the Easton Center

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

Photo: Kwaku Addo-Osafo, MSc

Kwaku Addo-Osafo, MSc, has joined the Mary S. Easton Center as a Senior Scientist in the Vossel Lab. Kwaku received his Bachelor of Health Science and MSc with Thesis in Neuroscience from Calgary University. Under the mentorship of Dr. Gordon Teskey, he studied epilepsy and hippocampal learning and memory. Kwaku is excited to contribute to the research on Alzheimer's and related disorders at the UCLA Easton Center. Outside of research, he enjoys outdoor activities and has an interest in sports as a former track and field hurdler.

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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.

EASTON CENTER KAGAN CLINICAL TRIALS PROGRAM

- Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Protocol

BEHAVIORAL NEUROLOGY PROGRAM

- Early-onset Alzheimer's Disease Phenotypes: Neuropsychology and Neural Networks

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

Living a Brain Healthy Lifestyle

Date: Thursday, March 8, 2021
Time: 1:30 P.M. – 2:30 P.M. (PST)
Virtual Forum

Presenter: Monica Moore, MSG
This presentation is in partnership with California State University Dominguez Hills (CSUDH) Osher Lifelong Learning Institute (OLLI). Please register at https://bit.ly/csudholli-UCLAHealth-Sp21 or contact Monica Moore at MRMoore@mednet.ucla.edu for more information.

COVID and its Implications on Brain Health

Date: Thursday, March 10, 2021
Time: 5:30 P.M. – 7:00 P.M. (PST)
Virtual Forum

Presenter: Mirella Díaz-Santos, PhD
This presentation is in partnership with South Bay Dementia Education Consortium. Please RSVP with Monica Moore at MRMoore@mednet.ucla.edu.

COVID on the Brain: Implications for Dementia Diagnosis and Treatment

Date: Thursday, March 25, 2021
Time: 5:30 P.M. – 7:00 P.M. (DST)
Virtual Forum

This presentation is in partnership with UCLA Health. Mirella Díaz-Santos, PhD, will discuss how diagnosing and treating dementia has been affected by COVID-19.

RSVP at: (800) 516-5323
For more information, please visit: https://connect.uclahealth.org/calendar/

Stress Reduction for Dementia Caregiver

Date: Thursday, April 15, 2021
Time: 1:30 P.M. – 2:30 P.M. (DST)
Virtual Forum

Caring for dementia sufferers is stressful and can have negative health implications on the caregiver. This presentation will discuss practical tips and tools that can reduce and better manage caregivers' stress.

RSVP at: (800) 516-5323
For more information, please visit: https://connect.uclahealth.org/calendar/

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