THE SCIENCE OF AGING

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// An Institute on Aging Newsletter

Developing a Novel Gene Therapy for Alzheimer's Disease

It is widely understood that Alzheimer's disease (AD) is a disorder of protein misfolding and aggregation – but there is limited knowledge of what drives this protein aggregation and how protein homeostasis can be therapeutically restored in the brains of patients with AD. Xiaolu Yang, PhD, Professor of Cancer Biology at the Perelman School of Medicine, is investigating exactly this in a recent research project working to develop a gene therapy that restores protein homeostasis in AD, addressing the underlying cause of the disease.

Together with his lab, Dr. Yang has recently discovered a novel system comprised of TRIM proteins that can function as both molecular chaperones to prevent protein aggregation and disaggregates to dissolve pre-existing amyloid deposits, thereby maintaining solubility of normal proteins. They found that TRIMS also promote proteasomal degradation of defective proteins and directly activate the proteasome linking misfolded proteins with the proteasome. Findings suggest that these TRIM activities provide several safeguards that may synergize to buffer the toxicity of misfolded proteins.

As gene therapy has become an important approach in the treatment of central nervous system diseases, TRIM activities and their downregulation of neurodegenerative diseases make them especially attractive as transgenes to restore protein homeostasis and address the root cause in the disease. Dr. Yang and his team found that intracranial delivery of the TRIM11 gene improved pathology, neuroinflammation, and cognitive impairments in multiple animal models of tauopathies and synucleinopathies providing a proof of concept for a gene therapy for AD.

To translate this work from bench to bedside, the team plans to propose additional research looking at different animal models while testing different vectors. Upon completion of the proposed experiments, next steps would include performing an IND-enabling study for this novel gene therapy approach.

This research is supported by the IOA's Alzheimer's Disease Therapeutics Accelerator Projects.

A LOOK INSIDE

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NEWLY IDENTIFIED COMPOUND, CNDR-51997, COULD OFFER POTENTIAL TREATMENT FOR ALZHEIMER'S DISEASE AND RELATED DISORDERS

A collaborative, multi-disciplinary team led by Penn Medicine's **Kurt Brunden, PhD**, Director of Drug Discovery at the Center for Neurodegenerative Disease Research (CNDR), and University of California San Diego's Carlo Ballatore, PhD, Professor in the Skaggs School of Pharmacy and Pharmaceutical Sciences are working on a potential disease-modifying Alzheimer's disease (AD) treatment for future clinical trials. According to the study, the team discovered that the new compound called CNDR-51997 -- which was identified through a joint drug discovery program at Penn and UC San Diego -- is effective in reducing both Aβ plaques and tau pathology, ultimately restoring brain health in mouse models of AD.

The researchers believe that their compound could not only be a future treatment for Alzheimer's, but also for other related diseases such as traumatic brain injury, chronic traumatic encephalopathy (CTE), frontotemporal lobar degeneration, progressive supranuclear palsy, corticobasal degeneration, and Pick's disease -- collectively called tauopathies.

This research, which is supported by a recent $6.9 million grant from the National Institute on Aging (NIA), aims to demonstrate the drug's safety in formal studies required by the U.S. Food and Drug Administration (FDA) prior to the initiation of human testing. Researchers hope that by the end of the three-year grant period that they will be able to submit an Investigational New Drug (IND) application to the FDA that will allow for Phase 1 clinical studies.

WHAT CAUSES COGNITIVE DECLINE IN LEWY BODY DISEASES?

Cognitive decline is a common symptom in individuals with Lewy body diseases such as Parkinson's disease and Penn Medicine researchers are working hard to uncover the underlying cause.

A new $18 million grant from the National Institutes of Health (NIH) and National Institute on Aging (NIA) will support continuing research to help advance the teams understanding of the factors that determine who develops dementia, and how quickly, in hopes of developing therapies that might slow the progression of disease.

Parkinson's disease and dementia with Lewy bodies are both caused by the buildup of a-synuclein (αSyn) which forms clumps called Lewy bodies leading to issues with movement and cognition. However, individuals with these diseases can experience symptoms differently and at different stages.

"Regardless of timing, these symptoms appear to share some underlying processes. We hope that the differences in individuals' diseases can illuminate the root cause of neurodegeneration and help us develop therapies that delay the onset of cognitive decline," said Alice Chen-Plotkin, MD, the Parker Family professor of Neurology, director of the Molecular Integration in Neurological Diagnosis (MIND) Initiative, and principal investigator on the grant in the official Penn Medicine News Release.

"Ideally, instead of Parkinson's being a disease that eventually may disrupt all aspects of an individual's life, we could slow its progression so much that it would just be a minor inconvenience."

The grant will support four different projects at Penn Medicine:

» **Project 1**, led by **David Irwin, MD**, associate professor of Neurology, will investigate how aSyn buildup interacts with b-amyloid plaques and tau neurofibrillary tangles to impact loss of cognition.

» **Project 2**, led by **Virginia M.-Y. Lee, PhD**, Director of the Center for Neurodegenerative Disease Research (CNDR), will examine how the misfolding and clustering of proteins contributes to the rate at which they spread through the brain.

» **Project 3**, led by **Alice Chen-Plotkin, MD**, begins with leads derived from Lewy body dementia genomic studies and large-scale biomarker screens and aims to explain the role of specific genes and proteins in the uptake of fibrillar aSyn, development of aSyn pathology, and cell-to-cell transmission of aSyn pathology.

» **Project 4**, led by **Kelvin Luk, PhD**, professor of Pathology and Laboratory Medicine, will use gene-editing techniques on mice to study the possibility of altering genetic variations to slow disease progression.

The goal is that this multidisciplinary approach will allow for collaboration and opportunity to learn how the different systems work together in order to accelerate the development of novel therapies.

PENN MEDICINE EXPANDS ACCESS TO GERIATRIC CARE IN EASTERN PENNSYLVANIA

A newly funded program called Advancing Geriatrics Education with Strategic, Multi-dimensional, Age-friendly Resources and Training (AGE SMART) led by Penn Medicine Chief of Geriatric Medicine **Lisa Walke, MD,** will expand access to geriatric care for adults over 65 and their families in eastern Pennsylvania.

AGE SMART, which is supported by the Geriatrics Workforce Enhancement Program (GWEP) grant from the federal Health Resources & Services Administration, will train primary care providers in aging-related medicine, and educate older adults and their caregivers on topics of health and aging.

There are three focus areas of the program: provider training, trainee education, and community education. The training portion will educate existing providers on common conditions and complications of the aging population, as well as guidance on appropriate care, while the community education portion maximizes Penn Medicine's existing relationships with organizations across eastern PA. Partnering with the Philadelphia Free Library and advanced care facilities, AGE SMART will feature events and programming on topics like cognitive assessments, guardianship, avoiding financial exploitation, and promoting vaccinations for common conditions.

"We're planning for a massive population shift and proactively training primary care providers to incorporate geriatric medicine into their practice organically, to make sure the needs of that population are met," said Dr. Walke in the official Penn Medicine News Release. "We also hope that by directly educating individuals and their caregivers, we can arm them with the information they need to prepare for how normal aging might impact their health, as well as warning signs for disease to discuss with their providers."

DECISION-MAKING FOR AGING IN PLACE

A recent study conducted by researchers at the Penn Memory Center (PMC) and Leonard Davis Institute of Health Economics (LDI) investigates the decision-making process of aging in place.

The study involved interviewing 74 key stakeholders – 14 people living with dementia, 36 family care partners of persons living with dementia, and 24 dementia clinicians. Findings showed not only that those living with dementia preferred aging in place, but also revealed some driving factors behind that preference.

Common factors included desire to preserve independence by the person with dementia, perceptions that the best care is delivered by loved ones in the home, distrust and fear of residential facilities, and caregiver guilt if transitioning to care in a residential facility.

However, while most older adults including those with dementia prefer to age in place, it is not necessarily their "choice." Cost and accessibility of both home support services and residential facilities are often common roadblocks.

According to an article published by LDI, the study's investigators found that "patients and families often feel forced to pursue one path or the other, and few can make the informed decision to seek care in a residential facility or make home adaptations." With that in mind, the researchers believe that it is necessary to report not only on time spent at home as a positive outcome for studies or policy initiatives in dementia care, but to also measure caregiver wellbeing, patient distress, financial burdens, and more to better support patients and caregivers and improve the decision-making process in this area.

Authors listed on this study include IOA Members Jason Karlawish, MD, and Catherine Auriemma, MD, MSHP.

MISSION

The mission of the Institute on Aging (IOA) at the University of Pennsylvania is to improve the health of older adults by increasing the quality and quantity of clinical and basic research as well as educational programs focusing on normal aging and aging-related diseases across the entire Penn campus.

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LEARN MORE

Learn more about the IOA, including our annual events and Members Program at:

www.med.upenn.edu/aging

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((IN CASE YOU MISSED IT))

ICYMI @ THE IOA

IOA CO-DIRECTOR DAVID WOLK, MD, TO SERVE ON ADRC EXECUTIVE COMMITTEE

Dr. Wolk will serve a three-year term on the ADRC Executive Committee, as well as a three-year term on the National Alzheimer's Coordinating Center Steering Committee, ending Fall 2027.

IOA CO-DIRECTOR EDDIE LEE, MD, PHD, KICKS OFF AAIC 2024 WITH PLENARY SESSION

Dr. Lee kicked off the plenary sessions at this year's AAIC with a presentation titled "Neuropathology in a Multidisciplinary Age." His lecture discussed neuropathology, the study of diseases through brain tissue analysis, and how it intersects with a wide variety of other disciplines to inform our understanding of Alzheimer's disease and related dementias (ADRD).

MEET THE 2024/2025 IOA-FUNDED PENN PREP SCHOLAR

This year's IOA-funded PennPREP Scholar is Gabriel Elias. During his time as a PennPREP Scholar, Gabriel will work in the neuroscience lab of David J. Irwin, MD, Associate professor of Neurology at Penn Medicine and Co-director of the Penn Frontotemporal Degeneration (FTD) Center. His work will focus on incorporating histopathology of human brain tissue to understand brain-behavior correlations to neurodegenerative disease diagnosis with a particular emphasis on Primary Progressive Aphasia (PPA).

PENN MEDICINE'S 13TH ANNUAL 5K FOR THE IOA AND THE MEMORY MILE WALK

Over $43,000 was raised at Penn Medicine's 13th Annual 5K for the IOA & Memory Mile Walk which took place on October 6, 2024. This year, 227 runners and walkers and 52 volunteers gathered once again at Penn's Franklin Field for the event which raises funds to support Alzheimer's and aging-related research at Penn through the IOA's Joseph A. Brennan Research Scholar Award.

PENN NEURODEGENERATIVE DISEASE GRAND ROUNDS KICKED OFF WITH IOA VISITING SCHOLAR YAAKOV STERN, PHD

The new Penn Neurodegenerative Disease Grand Rounds kicked off in early October with it's first lecture "Studying Cognitive Reserve" by IOA Visiting Scholar, Yaakov Stern, PhD of Columbia University. The grand round lectures take place every other Tuesday at noon unless otherwise noted. Visit the IOA website for more information including schedules and registration information.

THE IOA RELEASED OUR 2023/2024 ANNUAL REPORT

The 2023/2024 IOA Annual Report is now available. From receiving a major grant to support research on next-generation therapies for Alzheimer's disease to making noteworthy progress in the efforts of our Strategic Plan for ADRD, the IOA has reached several significant milestones in the past year. Learn more in the full report available on our website.

THE AGE OF AGING PODCAST

The Age of Aging, a podcast about living well with an aging brain, is now in its second season. Supported by the Penn Memory Center, Penn FTD Center, Penn Institute on Aging, and Alzheimer's Disease Research Center, this podcast is available to listen on all major podcast platforms.

FULL STORIES AVAIABLE AT: WWW.MED.UPENN.EDU/AGING/BLOG

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