THE SCIENCE OF AGING

TRIM11: A promising target for developing Alzheimer's Disease treatment

Penn Medicine researchers have identified TRIM11 – a tau-regulating protein – as a promising target for developing Alzheimer's disease (AD) treatment.

According to the Penn Medicine News Release highlighting the study, which is led by senior author **Xiaolu Yang, PhD**, a professor of Cancer Biology at Penn Medicine, TRIM11 was found to suppress deterioration in small animal models of neurodegenerative diseases similar to AD, while improving cognitive and motor abilities. It also appears to play a key role in removing the protein tangles that cause neurodegenerative diseases like AD.

After examining postmortem brain tissue of 23 individuals with AD and 14 healthy controls from Penn's Center for Neurodegenerative Disease Research (CNDR) brain bank and finding substantially reduced levels of TRIM11 in AD brains vs the healthy controls, Yang and his team used adeno-associated viral vector (AAV) to deliver the TRIM11 gene into the brains of multiple mouse models. Findings showed that mice with tau pathologies receiving the TRIM11 gene experienced a decrease in the development and accumulation of neurofibrilary tangles (NFTs), and had much improved cognitive and motor abilities.

While other studies have previously reported various connections between TRIM genes and tau or other proteins associated with neurodegeneration — such as TRIM28 and TRIM21 — this study reveals a direct role for TRIM11 in suppressing tau aggregation and the underlying mechanism.

"Most organisms have protein quality control systems that remove defective proteins, and prevent the mis-folding and accumulation of tangles — like the ones we see with tau proteins in the brain of those with taupathies — but until now we didn't know how this works in humans, or why it malfunctions in some individuals and not others," explained Dr. Yang in the News Release.

"For the first time, we have identified the gene that oversees tau function, and have a promising target for developing treatments to prevent and slow the progression of Alzheimer's disease and other related disorders," he said.

This study was published in *Science*.

A LOOK INSIDE

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Detailed 3D Mapping of AD Pathology Using Ex Vivo Imaging of the MTL

One of the challenges of Alzheimer's Disease is the presence of co-pathologies; this means patients with AD tend to have other neurodegenerative pathologies present in their brains in addition to tau. To address this, researchers at Penn, in collaboration with researchers at University of Castilla-La Mancha, Spain are working to improve imaging-based biomarkers for AD by better understanding the spread of tau and its specific effects on neurodegeneration using postmortem, or ex vivo, MRI and histological imaging.

Using these unique imaging techniques, **Sadhana Ravikumar, PhD,** a postdoc working in the Penn Image and Computing Science Lab, and her team are able to look directly at the underlying pathology in patients to understand what co-morbid pathologies they have, and link this information to structural changes they are seeing with MRI. Much of their work is developing tools and methods for analyzing and linking 3D postmortem MRI and histology images, and doing further analyses to identify which regions of the brain are most tied to tau pathology in Alzheimer's disease versus other neurodegenerative pathologies.

While the lab also does whole hemisphere high resolution postmortem imaging, Ravikumar's work focuses mostly on MRI and histology imaging of the medial temporal lobe (MTL) – the earliest cortical region affected by Alzheimer's disease. Through this method she is able to visualize the MTL anatomy and pathology in great detail and describe for the first time, differences in the 3-D topography of tau pathology between early and late Braak stages.

In this particular research project, Ravikumar and her team are studying 25 subjects postmortem, which is a relatively large number in this type of research. To handle this data, Ravikumar developed a computational atlas of the MTL to combine the data from the 25 subjects and perform group comparisons.

What she is finding is that a lot of the work points to the entorhinal cortex (EC) as being affected very early on within the MTL, as well as high levels of pathology very early on in certain subfields in the hippocampus such as the CA1 subfield. "We also found that we see a lot more pathology in the anterior MTL than the posterior MTL in the early stages, so it is kind of pinpointing the trajectory of tau pathology accumulation across different Braak stages," she explains.

Ravikumar's hope is that identifying these regions that are affected early on in the disease will inform biomarker development and help pinpoint what regions can be used as biomarkers within the clinical trial framework. For example, when looking at clinical trials in patients where you want to track if a drug is working or not, you can evaluate the reduction in neurodegeneration in these specific regions that you know are affected by tau pathology in AD.

"Some studies have already started using some of the regions that we've pinpointed through these ex vivo analyses to inform other in vivo analyses," she said. "Since this is all done post mortem, the hope is to translate our findings into an in vivo space where we're actually applying it to clinical data."

This research project, Ex vivo MRI atlas of the human medial temporal lobe: characterizing neurodegeneration due to tau pathology, was published in *Acta Neuropathologica Communications* (2021) and presented as a Featured Research Session by Ravikumar at this year's Alzheimer's Association International Conference (AAIC) 2023.

PENN MEDICINE RESEARCHERS TO LEAD $40 MILLION, MULTISITE STUDY ON ASIAN COHORT FOR ALZHEIMER'S DISEASE

Penn Medicine's **Li-San Wang, PhD**, the Peter C. Nowell M.D. Professor of Pathology and Laboratory Medicine, is set to lead the Asian Cohort for Alzheimer's Disease (ACAD) study, a project at Penn Medicine and 15 other academic research centers across the U.S. and Canada. The study is funded by a $40.5 million grant from the National Institute on Aging (NIA).

ACAD represents the first major Alzheimer's disease genetics cohort for Asian Americans and Asian Canadians, which are two populations currently underrepresented in Alzheimer's disease (AD) research. "This is a very ambitious project because we need to gather a critical mass of data on lifestyle and genetic risk factors to have enough statistical power to understand causes of the disease and strategies for treatment that may be specific to these Asian populations in the U.S. and Canada," said Dr. Wang in the Penn Medicine News Release announcing the grant.

Researchers will analyze genetic data from cohort samples to identify risk variants in both U.S. and Canadian Asian populations, compared to other populations and to those living in Asia. They hope to use this information to help develop blood biomarker benchmarks and a polygenic risk score model to measure the risk for AD specifically among Asian Americans and Asian Canadians. Additionally, they will look at non-genetic biomarkers in combination with lifestyle and clinical information for clues suggesting other contributing factors to AD.

"A major priority of this project is to help the community – we're not just going in and taking samples. The response during the pilot phase was incredible excitement to participate, which reinforced why we're doing this and the need for health equity in Alzheimer's disease research," said Dr. Wang.

Dr. Wang also serves as the co-lead of the Data Management and Statistical Core at the Penn Alzheimer's Disease Research Center and is an IOA Member.

FDA FULLY APPROVES LECANEMAB FOR TREATMENT OF ALZHEIMER'S DISEASE

This Summer, the U.S. Food and Drug Administration converted Leqembi (lecanemab-irmb), the first drug indicated to treat adult patients with Alzheimer's by slowing the disease, to traditional approval following a determination that a confirmatory trial verified clinical benefit.

"The decision for full FDA approval of lecanemab marks a major milestone in the fight against Alzheimer's Disease," said researcher and clinician **David Wolk, MD**, Co-Director of the Institute on Aging and Director of the Alzheimer's Disease Research Center.

"In addition to being the first approval in ~20 years, it is the first drug to demonstrate clear alteration of the biology of the disease and modify the speed of progression," he explained. "While there remains much work to be done, this foothold in more specific molecular therapies for AD will usher in an era of precision medicine that I believe will greatly accelerate progress in the field over the next 5-10 years. This is a time to be very hopeful!"
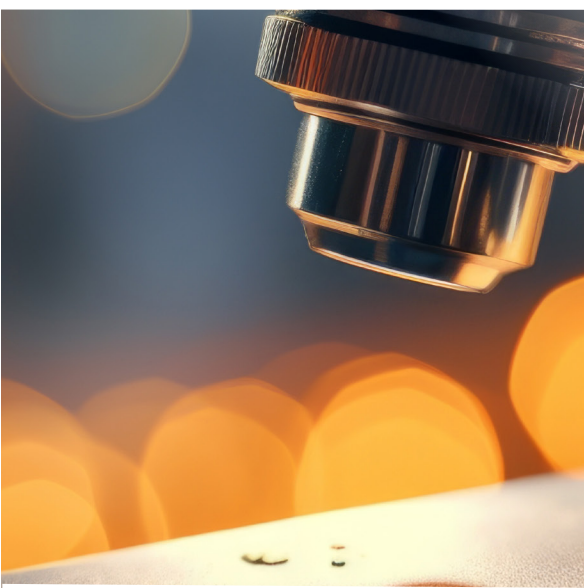
INTRODUCING THE NEW **IOA MEMBERS RESEARCH DATABASE**

The IOA is pleased to announce the launch of the **IOA Members Research Database**. This database will serve as a resource for those interested in aging and neurodegenerative disease-related research at Penn. The goal is to foster potential collaborative opportunities between IOA Members and those with similar research interests not only at Penn but at institutions nationwide.

"We are so excited to launch the IOA Members Research Database. We often get requests from faculty who are looking for collaborators in a specific area and now we have a resource to easily identify them," said **Kathy Jedrziewski, PhD**, IOA Deputy Director.

The IOA Members Research Database is accessible through our IOA website.

((IN CASE YOU MISSED IT))
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IOA STRATEGIC PLAN FOR ADRD

In May, The Institute on Aging launched the IOA Strategic Plan for Alzheimer's Disease and Related Dementias (ADRD). This plan aims to promote, facilitate and enhance the use of multidisciplinary research approaches to achieve groundbreaking discoveries that can advance the field.

MEET OUR 2023-2024 PENNPREP SCHOLAR

The IOA's 2023-2024 PennPREP Scholar is **Annie Abioye**, a recent graduate from Indiana University with a B.S. in neuroscience. Annie will be working in cognitive research at the Kable Lab at the University of Pennsylvania. A main focus of this lab is to understand how people make decisions, and to trace out the psychological and neural mechanisms of choice.

IOA DIVISION HIGHLIGHTS

> **David Wolk, MD**, IOA Co-director and leader of the IOA's Division of Clinical and Translational Neurodegenerative Disease Research, co-authored a review in *Annals of Neurology* arguing the clinical importance of limbic-predominant age-related TDP-43 encephalopathy (LATE). The review argues that LATE is a common mimic of Alzheimer's Disease based on shared signs and symptoms, but that there are potential diagnostic tools that help with diagnosis. They also discuss potential treatment implications for LATE that may be beneficial for physicians, patients, and families. Dr. Wolk also co-chaired a National Institute on Aging (NIA) workshop on the topic last Spring.

> **Eddie Lee, MD, PhD**, IOA Co-director and leader of the IOA's Division of Basic Neurodegenerative Disease Research, helped organize the AAIC Neuroscience Next events hosted at the University of Pennsylvania in April. The conference showcased the work of students, postdoctoral researchers and early career research professionals in cognitive, computational, behavioral, and other areas of neuroscience research. Dr. Lee also received the Alzheimer's Association Excellence in Neuroscience Mentoring Award for his dedication to educating the next generation of neuroscientists and physician-scientists.

> **Anne R. Cappola, MD, ScM**, a Professor of Medicine in the Division of Endocrinology, Diabetes and Metabolism and division co-leader of the IOA's Division of Geroscience, Gerontology, and Geriatrics, recently chaired the Scientific Statement from the Endocrine Society, "Hormones and Aging: An Endocrine Society Scientific Statement", published in the *Journal of Clinical Endocrinology and Metabolism*. "The goal of this statement is to inform future research that refines prevention and treatment strategies in age-associated endocrine conditions," explained Dr. Cappola.

> "Racial and Ethnic Disparities in Access to and Enrollment in High-quality Medicare Advantage Plans," co-authored by **Norma B. Coe, PhD,** Co-Director of Penn's Population Aging Research Center (PARC) and leader of the IOA's Division of Epidemiology, Social Science, and Policy, was selected as *Health Services Research*'s 2023 John M. Eisenberg Article of the Year.

> Work by **Brad Johnson, MD, PhD**, Professor of Pathology and Laboratory Medicine and co-leader of the IOA's Division of Geroscience, Gerontology, and Geriatrics, and his team was recently published in *Cellular and Molecular Gastroenterology and Hepatology*. The work highlighted in the paper, Patient-Induced Pluripotent Stem Cell-Derived Hepatostellate Orgaoids Establish a Basis for Liver Pathologies in Telomeropathies, contributes to the understanding of age-related liver diseases, and to potential novel approaches to their treatment, explained Dr. Johnson.

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

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