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NEW TREATMENT REVERSES SIGNS OF ALZHEIMER'S DISEASE, PENN MEDICINE RESEARCH SUGGESTS

Penn Medicine researchers have found that a "chaperone" molecule that slows the formation of certain proteins in the aging brain can reverse signs of Alzheimer's disease (AD), including memory impairment, in a mouse model.

The study, led by **Nirinjini Naidoo, PhD**, a research associate professor of Sleep Medicine, found that injecting the molecule – a compound called 4-phenylbutyrate (PBA) which inhibits protein accumulation – into mouse models of AD "helped to restore signs of normal proteostasis in the animals' brains while also dramatically improving their performance on a standard memory test, even when administered late in the disease course," according to the Penn Medicine News Release.

"By generally improving neuronal and cellular health, we can mitigate or delay disease progression," said Dr. Naidoo. "In addition, reducing proteotoxicity—irreparable damage to the cell that is caused by an accumulation of impaired and misfolded proteins—can help improve some previously-lost brain functions."

Both early-life and middle-age treatment showed signs of inhibiting the process that forms amyloid beta plaques. For the later treatment, the amyloid plaque numbers themselves were also reduced.

These findings are exciting as they suggest PBA as a potential Alzheimer's disease treatment.

This study, which was published in *Aging Biology*, follows previous research by the team which found that PBA treatment improved sleep quality and cognitive test performance and helped normalize proteostasis in mouse models mimicking an normal human aging brain.

A LOOK INSIDE

Institute on Aging
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JUST ANNOUNCED! THE IOA'S FIRST ROUND OF FUNDED ALZHEIMER'S DISEASE THERAPEUTICS ACCELERATOR PROJECTS

IOA Co-Directors **David Wolk, MD** and **Edward Lee, MD, PhD** recently received a $5 million grant from the Delaware Community Foundation to support the development of the next generation of therapies for Alzheimer's disease and related dementias (ADRD).

This grant supports a new funding opportunity at the IOA, the **Alzheimer's Disease Therapeutics Accelerator Projects**, which support collaborative basic science and translational projects that focus on AD therapeutics including projects that address comorbid pathologies in the setting of Alzheimer's disease.

"It is our hope that the collaboration between basic scientists and clinicians at Penn Medicine will build on the already groundbreaking research on dementia and help us develop treatments that can one day stop the disease in its tracks," said Dr. Wolk.

The IOA is pleased to announce the first three projects that have been funded for this award.

» Monitoring neuroinflammatory and neurodegenerative treatment response to anti-amyloid therapy

Principal Investigators: Christopher Brown, MD, PhD, Dawn Mechanic-Hamilton, PhD, ABPP/CN, and David Wolk, MD

The goal of this study is to provide personalized monitoring of beneficial and adverse treatment response in individuals receiving anti-amyloid therapies for early Alzheimer's disease. Investigators hope to discover which neuroimaging, blood-based, and cognitive measures best predict beneficial outcomes after treatment and which measures predict development of adverse outcomes.

Results of this study could be used to help guide decisions around treatment cessation and continuation, provide personalized safety monitoring that is less burdensome than current requirements, and identify mechanisms that may help enhance beneficial effects and/or reduce adverse side effects of anti-amyloid therapy.

"This is the first study to examine detailed imaging and cognitive measures longitudinally and explore individual differences in treatment response to anti-amyloid therapies," said Christopher Brown, MD, instructor of Neurology at the University of Pennsylvania and principal investigator of the study. "Prior studies have been limited to looking at group effects that are not easy to translate to the individual patient level in the clinic."

» BlisRNAs as novel therapeutics for Alzheimer's Disease and related neurodegenerative diseases

Principal Investigators: Zissimos Mourelatos, MD, Kelvin Luk, PhD, and Virginia M.-Y. Lee, PhD

The overarching goal of this project is to develop novel RNA therapeutics for the major human neurodegenerative diseases such as Alzheimer's Disease (AD) and Related Dementias, Parkinson's Disease (PD) and related Synucleinopathies.

"We developed a new platform for potent, in vivo gene silencing based on bitargeting linked small interfering RNAs (BlisRNAs) that can simultaneously silence two genes," said principal investigator Zissimos Mourelatos, MD, Professor of Pathology and Laboratory Medicine. "BlisRNAs are simple and economical to synthesize and compatible with automated, large-scale production."

So far, Dr. Mourelatos and his team have developed potent BlisRNAs that silence Microtubule-associated protein tau (MAPT), amyloid precursor protein (APP) and Synuclein Alpha (SNCA).

They are conducting biodistribution, safety, and efficacy studies of their BlisRNAs in relevant mouse models of AD and PD with the hope that this BlisRNAs will reduce pathology in a sustainable manner, without toxicity. "Since we developed each BlisRNA to be able to target all mRNA isoforms of human, mouse and primate ortholog genes, we can quickly test the same BlisRNAs in primates and ultimately in human clinical trials, if our studies in mice are successful," explained Dr. Mourelatos.

» Microglia cell therapy with protective APOE genetic variants for the treatment of Alzheimer's Disease

Principal Investigators: Michael Haney, PhD, Saar Gill, MD, PhD, and Frederick "Chris" Bennett, MD

"Variants in the gene APOE have been shown to dramatically decrease the risk of developing Alzheimer's disease (AD), however there are severe lipid related side effects outside the brain due to APOE expression in the peripheral immune system," said Michael Haney, PhD, Assistant Professor of Pathology and Laboratory Medicine and principal investigator of this study. "The goal of this project is to develop engineered myeloid cell therapies that introduce AD-protective APOE variants into brain resident immune cells while sparing the peripheral immune system."

Dr. Haney and his fellow investigators are examining whether replacing microglia with protective APOE variants is sufficient to inhibit progression of AD pathology in mouse models of AD -- and if so, which APOE variants are most effective in this.

Their work combines recently developed microglia replacement approaches with large scale CRISPR based gene editing of stem cells which enables them to quickly test the effect of many different variants of the APOE gene in AD progression. "This combination of this cell therapy approach with gene editing of the APOE gene is the first of its kind," said Dr. Haney.

PENN LEADS LARGEST-EVER STUDY OF PALLIATIVE CARE TO INCREASE SUPPORT FOR SERIOUSLY ILL PATIENTS

In the largest-ever study of its kind, Penn Medicine researchers have found that ordering a palliative care consultation by "default" via an automatic order is an effective strategy to give more hospitalized patients the opportunity to benefit from palliative care.

Study authors **Scott D. Halpern, MD, PhD**, the John M. Eisenberg Professor of Medicine, Epidemiology, and Medical Ethics and Health Policy, and **Kate Courtright, MD, MS**, an assistant professor of Critical Care and Palliative Medicine and IOA Member, found that implementing the automatic order – with the option for doctors to opt out and cancel the order – increased palliative care consultation rates from 16.6 percent to 43.9 percent and decreased the time to consultation by 1.2 days.

The study included more than 34,000 patients with chronic obstructive pulmonary disease (COPD), dementia, or kidney failure at 11 hospitals in 8 states. While these specific patient groups often experience challenges with coping, as well as breathlessness, anxiety, pain, and other symptoms that palliative care can help address through medications, other treatments, and/or referrals to other specialists, they have been previously underrepresented in past studies of palliative care delivery.

During a secondary outcomes analysis, the investigators found that for patients who only received palliative care consultation thanks to the default order, such care reduced the median length of stay by 9.6 percent, according to a Penn Medicine News Release highlighting the study. They also found that the default orders led to more patients being discharged from the hospital to hospice care without affecting mortality, suggesting that such orders improved the quality and patient-centeredness of end-of-life care.

This study was published in *JAMA*.

CAREGIVER MASTERY MAY HELP LOWER ANXIETY FOR THE COGNITIVELY IMPAIRED

According to findings from a recent study conducted by Penn Nursing's **Nancy Hodgson, PhD, RN, FAAN** and **Adriana Perez, PhD, ANP-BC, FAAN** interventions that support and enhance caregivers' skills and confidence may lower anxiety levels in individuals with cognitive impairment.

"Accurately assessing the needs of those living with cognitive impairment is crucial, especially since many may struggle to verbalize their requirements," explained Dr. Hodgson in a recent Penn LDI article highlighting the study. "Caregivers with lower levels of mastery might fail to connect their care recipients' symptoms with indicators of unmet needs. If caregivers do not promptly identify and address these needs, it could lead to increased anxiety in their care recipients."

The study suggest that improving the level of caregiver mastery – a positive perception of one's efficacy in caregiving – by providing psychoeducational programs and resources that family caregivers need will help reduce the frequency of anxiety in individuals with cognitive impairment.

"Making educational programs available at the community level is crucial for the well-being of both caregivers and individuals living with dementia," said Hodgson. "Policymakers are encouraged to allocate grants for research into nonpharmacological interventions for dementia, such as sensory stimulation, reminiscence therapy, and meaningful structured activities, and recognize their potential impact on care."

THE MALAWI LONGITUDINAL STUDY OF FAMILIES AND HEALTH (MLSFH) SHIFTS RESEARCH FOCUS TO AGING

As life expectancy continues to increase, The Malawi Longitudinal Study of Families and Health (MLSFH) – a 25+ year cohort study done in collaboration between the University of Pennsylvania and researchers in Malawi, one of the world's poorest countries – has shifted their research focus from HIV/AIDS to concerns about aging.

"Aging in high-income countries has been studied for many years, and it's a big and prominent and important research agenda, and we know a lot about this. Aging in poor countries is really understudied," says Penn sociology professor **Hans-Peter Kohler, PhD**, director of the MLSFH, co-director of the Population Aging Research Center, and IOA Member, in a Penn Today feature on the study.

Iliana V. Kohler, PhD, practice associate professor of sociology and IOA Member, leads the evolution of the project into an aging study, leveraging two-and-a-half decades of health and social data that provides a critical foundation for current and future research. This research is funded by a new $10 million grant from the National Institutes of Health's National Institute on Aging.

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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SCAN ME

"TRAILBLAZERS IN NEURODEGENERATIVE DISEASE RESEARCH"

PENN MEDICINE HONORS DRS. LEE AND TROJANOWSKI WITH PORTRAIT CELEBRATING THEIR EXCEPTIONAL CAREERS

Virginia Lee, PhD, and the late **John Q. Trojanowski, MD, PhD**, partners in life and in science, have long been recognized as trailblazers in the field of neurodegenerative disease research. Now, their legacy will be immortalized in the halls of the University of Pennsylvania, as they join the list of leaders at Penn who have been celebrated with portraits to honor their impacts and contributions not only to the university, but to their respective fields.

Drs. Lee and Trojanowski spent nearly 4 decades working together at the University of Pennsylvania accomplishing one groundbreaking discovery after the other, all in hopes of solving the puzzle of neurodegenerative disease. On Thursday, January 25, 2024, the legacy of this remarkable team was celebrated at their portrait unveiling.

"[This] event honors and celebrates, probably – not an exaggeration – one of the most successful partnerships in neurodegenerative science, and potentially in science in general," said **George Netto, MD**, Chair of the Department of Pathology and Laboratory Medicine at the University of Pennsylvania. "Not only a scientific partnership but also a life partnership that will leave a legacy beyond description."

Dr. Lee attributes much of her career in neurodegenerative disease research to her late husband. "If it wasn't for John, this would have never happened," she said. "I didn't know much about neurodegenerative diseases and John said "Look, I'll do all the neuropathology and I'll get you all the brain tissue that you want, but you have to do your magic, be able to isolate this disease protein, and then we can get started to build models", and he was absolutely right."

With the inspiration from Dr. Trojanowski on her side, Dr. Lee continues to be recognized for her outstanding work. She recently recieved the prestigious **2024 Rainwater Prize for Outstanding Innovation in Neurodegenerative Disease Research**, an $400,000 award aimed at honoring scientific advancements in primary tauopathies and highlighting significant accomplishments that drive us closer to treatments and a cure for disorders like progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and frontotemporal dementia (FTD).

"I really think it can't be overstated; John and Virginia broke open the field of neurodegeneration," said **Jon Epstein, MD**, Interim Executive Vice President of the University of Pennsylvania for the Health System and Dean of the Perelman School of Medicine. "And for many years they laid the fundamental groundwork through careful, painstaking basic science that we now see bearing fruit."

The beautiful portrait of Drs. Lee and Trojanowski can be viewed in its new home on the second floor of the Biomedical Research Building at the University of Pennsylvania.

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

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