

# More human-like model of Alzheimer's better mirrors tangles in the brain

November 16 2016

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Credit: Human Brain Project

Tangled up brain fibrils made up of a rogue protein known as tau are the hallmark of Alzheimer's disease (AD) that likely hold the key to treatments, making them of great interest to researchers. Mimicking the formation and spread of these tangles in animal models with greater accuracy allows scientists to better investigate new therapies to stop or

slow their spread.

A new animal model developed at Penn Medicine using tau tangles isolated from the brains of Alzheimer's patients rather than synthetic tau tangles paints a closer picture of the tau pathology in the AD brain, researchers from the Center for Neurodegenerative Disease Research (CNDR) at the Perelman School of Medicine at the University of Pennsylvania reported in the print issue of the *Journal of Experimental Medicine*. Seeding normal, wildtype mice with the highly potent Alzheimer's brain-tau (AD-tau) protein induced damaging tangles in their brains for study, mirroring a more realistic progression of tau tangles seen in AD patients' brains.

Importantly, the mice used in the experiment were non-transgenic, meaning they did not overexpress tau protein. Past animal studies, including research from Penn Medicine, using synthetic tau fibrils provided an explanation for the progression of Alzheimer's and other related tauopathies by implicating the cell-to-cell transmission of pathological tau. However, this phenomenon was only demonstrated in models overexpressing tau. But increased tau expression is not a cause of Alzheimer's or other conditions involving misshapened tau protein.

"Alzheimer's patients don't generally overexpress tau or harbor tau mutations, so it was important to develop a model that can recreate the pathology in a setting that more closely resembles what's happening in patients," said senior author Virginia M.-Y. Lee, PhD, MBA, CNDR director and a professor of Pathology and Laboratory Medicine. "This model will open up many new directions and opportunities for not just Alzheimer's, but also for other pathological tau disorders, such as corticobasal degeneration [CBD] and progressive supranuclear palsy [PSP], conditions which cause Parkinson-like symptoms, but CBD and PSP also are associated with cognitive impairments that mimic Alzheimer's."

Normal tau keeps nerve cells functioning properly, but pathological tau can cause the protein to go rogue, or misfold, triggering the formation of protein clumps known as [neurofibrillary tangles](#), which are tightly linked to AD. It has been shown to move from cell to cell to form tangles in the brain, first in the areas that make memories, and then outward to areas associated with remembering.

Synthetic tau tangles have been used in transgenic mice to pattern this spread by Penn and others in the field, but until now, it couldn't produce enough misshapened [tau protein](#) in normal mice to fully support this hypothesis.

This is the first time, to the authors' knowledge, researchers have shown abundant amounts of [tau tangles](#) convincingly induced in multiple brain regions within a few months after inoculation of AD-tau. This observation provides the strongest support thus far for the physiological relevance of cell-to-cell transmission of pathological tau in human tauopathies, the authors said.

"This relevant mouse model will allow us to better study the architecture of tau and its physiological consequence in mechanistic and therapeutic investigations," Lee said, "but it also provides an experimental paradigm to examine how other factors, such as amyloid plaques, another hallmark of AD, contribute to the spreading, and how tau spreads in other diseases, like CBD and PSP, among other important questions that need to be answered."

Provided by Perelman School of Medicine at the University of Pennsylvania

Citation: More human-like model of Alzheimer's better mirrors tangles in the brain (2016, November 16) retrieved 5 May 2024 from <https://medicalxpress.com/news/2016-11-human-like->

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