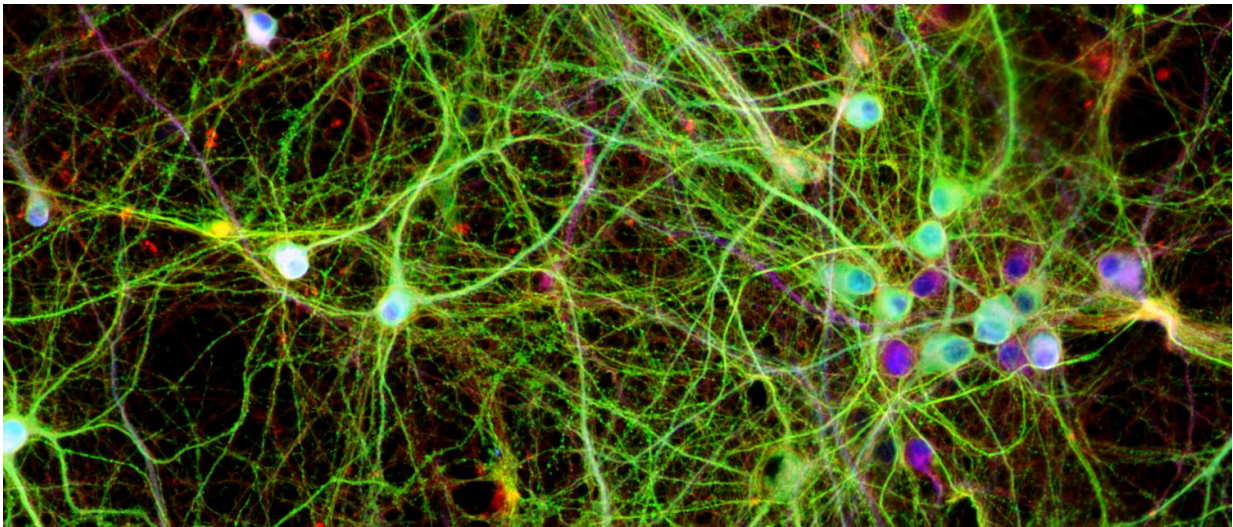


Discovery opens door to new Alzheimer's treatments

November 17 2016



Neurons in culture dishes. The colors highlight the human tau protein in green, a structural component in red and the DNA inside the cell nucleus in blue. Credit: UNSW/Lars Ittner

Australian researchers have shed new light on the nerve cell processes that lead to Alzheimer's disease (AD), overturning previously held ideas of how the disease develops and opening the door to new treatment options that could halt or slow its progression.

The study is published today in the prestigious journal *Science*.

Studying human [brain tissue](#), the UNSW and Neuroscience Research Australia research team identified a protein, kinase p38 γ , which is lost as AD progresses. When they reintroduced the protein into the brains of mice, it was shown to have a protective effect against [memory deficits](#) associated with the disease.

"This study has completely changed our understanding of what happens in the brain during the development of Alzheimer's disease," said lead author UNSW Professor Lars Ittner.

Two of the hallmarks of Alzheimer's are the presence of protein plaques (made up of amyloid-beta) and tangles (made up of [tau protein](#)) in the brain. The accumulation of these plaques and tangles is associated with cell death, brain atrophy and memory loss.

The research team has revealed that a crucial step in the process that leads to tangles has been misunderstood. Previously, scientists believed the plaque-forming protein, amyloid-beta, caused a modification - called phosphorylation - to the tau protein resulting in [cell death](#) and, ultimately, Alzheimer's disease. Increased phosphorylation of tau eventually leads to its accumulation as tangles.

Results from the new study suggest that the phosphorylation of tau initially has a [protective effect](#) on neurons, and that amyloid-beta assaults the protective functionality until it is progressively lost. This is the stage at which toxicity levels cause the destruction of neurons and results in the cognitive deficits associated with Alzheimer's disease.

"Amyloid-beta induces toxicity in the neurons but the first step in tau phosphorylation is actually to decrease this toxicity," said Professor Ittner.

"This is a completely new mindset; that the reason tau becomes modified

is actually to protect from damage."

The study used different mice models and human brain tissue from the Sydney Brain Bank to identify a [protein](#) called kinase p38 γ , which assisted the protective phosphorylation of tau and interfered with the toxicity created by amyloid-beta.

"We used mice to screen for a very specific toxicity that we knew from previous work is involved in the progression of the disease," said Professor Ittner.

"We set out to find mediators of this progression, which led us quickly to our surprising finding. It was the opposite of what we expected. It was only when we changed our view of the process involved in the development of AD that these results started to make sense."

Studying [human brain](#) tissue, Professor Ittner and his team identified that p38 γ is lost as AD progresses, however a small amount does remain in the brain.

"We found that p38 γ , which initially offers protection, fades away early in the brains of people with AD, suggesting a loss of protection," he said.

"Part of our study involved reintroducing p38 γ and increasing its activity. We saw that, in mice, it could prevent memory deficits from happening, so it has true therapeutic potential. If we can stimulate that activity, we may be able to delay or even halt the progression of Alzheimer's disease."

The next step for the researchers will be to develop their patented discoveries into a novel treatment for humans, subject to new funding.

More information: [DOI: 10.1126/science.aah6205](https://doi.org/10.1126/science.aah6205) "Site-specific

phosphorylation of tau inhibits amyloid- β toxicity in Alzheimer's mice,"
Science, [science.sciencemag.org/cgi/doi ... 1126/science.aah6205](https://science.sciencemag.org/cgi/doi/10.1126/science.aah6205)

Provided by University of New South Wales

Citation: Discovery opens door to new Alzheimer's treatments (2016, November 17) retrieved 5 May 2024 from <https://medicalxpress.com/news/2016-11-discovery-door-alzheimer-treatments.html>

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