

More evidence in quest to repurpose cancer drugs for Alzheimer's disease

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An FDA approved drug to treat renal cell carcinoma appears to reduce levels of a toxic brain protein linked to dementia in Alzheimer's and Parkinson's diseases when given to animals. This finding is the latest from Georgetown University Medical Center's Translational Neurotherapeutics Program (TNP) examining tyrosine kinase inhibitors in the treatment of neurodegenerative diseases.

The study, to be presented at the annual Alzheimer's Association International Conference in Toronto, found that the drug pazopanib decreases levels of phosphorylated Tau (p-Tau) in animal models genetically engineered to produce human mutant tau throughout their brains.

The TNP lab previously demonstrated in animal models that tau is a critical part of the "[garbage disposal](#) system," in cells allowing them to clear accumulated toxic proteins. In humans, p-Tau describes tau that has been abnormally modified, leaving it unable to do its job.

"Our lab has shown that functional tau is required for the clearance of [amyloid beta](#), which accumulates in sticky clumps called plaques. If tau stops functioning, the amyloid beta accumulation leads to cell death," explains Monica Javidnia, a pharmacology doctoral candidate at GUMC. "When tau is abnormally modified, it accumulates within neurons forming sticky tangles, and when the cell dies, it and the amyloid beta spill out into the brain. These are the plaques and tangles that are the hallmark of Alzheimer's disease." P-tau is also involved in other neurodegenerative diseases.

Previous research from the TNP has shown that when tyrosine kinases are inhibited, the garbage disposal system begins working, allowing cells to once again clear toxic proteins. Pazopanib is a known [tyrosine kinase](#) inhibitor.

The TNP, led by Charbel Moussa, MD, PhD, has identified several tyrosine kinase, which appear to play a role in neurodegeneration, protein clearance and inflammation. This work has led to clinical trials with the cancer drug nilotinib in both Parkinson's and Alzheimer's disease set to begin this summer. (Moussa is listed as an inventor on a patent application that Georgetown University filed related to nilotinib and the use of other tyrosine kinase inhibitors for the treatment of [neurodegenerative diseases](#).)

As Javidnia explains, there are two schools of thought in the Alzheimer's field as to the main culprit of the disease—tau or amyloid beta.

"Work from our lab and other groups shows tau pathology preceding amyloid beta. We believe tau is mainly responsible for dementia and exacerbates A-beta pathology," she says. "However, we are also studying the effects of pazopanib on amyloid beta to create a better understanding of how it works and what diseases it could potentially be used to treat."

Javidnia says analysis in this study shows pazopanib penetrates the mice's blood-brain barrier when given the equivalent of half of dose given for [renal cell carcinoma](#) treatment. Following treatment, the animal models showed significant decreases in levels of phosphorylated tau.

"In addition, the drug was safe and well-tolerated," Javidnia says. "Our next work will focus on the individual receptors pazopanib targets to better understand their role in protein clearance and inflammation."

More information: Poster # 8677: Abstract: Pazopanib Is a Potential Therapeutic for Tauopathies

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