Cancer drug could treat early-stage Alzheimer's disease, study shows

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Using preclinical models — in vitro cellular models with amyloid and tau proteins, in vivo mouse models and in vitro human cells from Alzheimer's patients — the researchers demonstrated that stopping IDO1 helps restore healthy glucose metabolism in astrocytes, the star-shaped brain cells that provide metabolic support to neurons. Credit: Michelle Bixby/Penn State

A type of drug developed for treating cancer holds promise as a new treatment for neurodegenerative diseases such as Alzheimer's, according to a study by researchers at Penn State, Stanford University and an international team of collaborators.

The researchers discovered that by blocking a specific enzyme called indoleamine-2,3-dioxygenase 1, or IDO1 for short, they could rescue memory and brain function in models that mimic Alzheimer's disease.

The findings, published Aug. 22 in the journal *Science*, suggest that IDO1 inhibitors currently being developed as a treatment for many types of cancer, including melanoma, leukemia and breast cancer, could be repurposed to treat the early stages of neurodegenerative diseases—a first for the chronic conditions that lack preventative treatments.

"We're showing that there is high potential for IDO1 inhibitors, which are already within the repertoire of drugs being developed for cancer treatments, to target and treat Alzheimer's," said Melanie McReynolds, the Dorothy Foehr Huck and J. Lloyd Huck Early Career Chair in Biochemistry and Molecular Biology at Penn State and co-author on the paper.

"In the broader context of aging, neurological decline is one of the biggest co-factors of being unable to age healthier. The benefits of understanding and treating metabolic decline in neurological disorders will impact not just those who are diagnosed, but our families, our society, our entire economy."

Alzheimer's disease is the most common type of dementia, an umbrella term that refers to all age-associated neurodegenerative disorders, McReynolds explained. In 2023, as many as 6.7 million Americans were living with Alzheimer's disease, according to the Centers for Disease Control and Prevention, and its prevalence is expected to triple by 2060.

"Inhibiting this enzyme, particularly with compounds that have been previously investigated in human clinical trials for cancer, could be a big step forward in finding ways to protect our brains from the damage caused by aging and neurodegeneration," said Katrin Andreasson, the Edward F. and Irene Pimley Professor of Neurology and Neurological Sciences at the Stanford University School of Medicine and the study's senior author.

Alzheimer's disease affects the parts of the brain that control thought, memory and language, the result of progressive and irreversible loss of synapses and neural circuitry.

As the disease progresses, symptoms can increase from mild memory loss to losing the ability to communicate and respond to the environment. Current treatments for the disease are focused on managing symptoms and slowing progression, through targeting the build-up of amyloid and tau plaques in the brain, but there are no approved treatments for combating the onset of the disease, McReynolds said.

"Scientists have been targeting the downstream effects of what we identify as an issue with the way the brain powers itself," said Praveena Prasad, doctoral student at Penn State and co-author on the paper.

"The therapies that are currently available are working to remove peptides that are likely the result of a bigger issue we can target before those peptides can start forming plaques. We're demonstrating that by targeting the brain's metabolism, we can not only slow, but reverse the progression of this disease."

Using preclinical models—in vitro cellular models with amyloid and tau proteins, in vivo mouse models and in vitro human cells from Alzheimer's patients—the researchers demonstrated that stopping IDO1 helps restore healthy glucose metabolism in astrocytes, the star-shaped

brain cells that provide metabolic support to neurons.

IDO1 is an enzyme that breaks down tryptophan, the same molecule in turkey that can make you sleepy, into a compound called kynurenine. The body's production of kynurenine is the first part of a chain reaction known as the kynurenine pathway, or KP, which plays a critical role in how the body provides cellular energy to the brain.

The researchers found that when IDO1 generated too much kynurenine, it reduced glucose metabolism in astrocytes that are required to power neurons. With IDO1 suppressed, metabolic support for neurons increased and restored their ability to function.

The researchers conducted the study in several models of Alzheimer's pathology, namely amyloid or tau accumulation, and found that the protective effects of blocking IDO1 cut across these two different pathologies.

Their findings suggest that IDO1 may also be relevant in diseases with other types of pathology, such as Parkinson's disease and dementia as well as the broad spectrum of progressive neurodegenerative disorders known as tauopathies, explained Paras Minhas, current resident at Memorial Sloan Kettering Cancer Center who earned a combined medical and doctoral degree in neuroscience at Stanford School of Medicine and is first author on the paper

"The brain is very dependent on glucose to fuel many processes, so losing the ability to effectively use glucose for metabolism and energy production can trigger metabolic decline and, in particular, cognitive decline," Minhas said. "Through this collaboration we were able to visualize precisely how the brain's metabolism is impacted with neurodegeneration."

More information: Paras S. Minhas et al, Restoring hippocampal glucose metabolism rescues cognition across Alzheimer's disease pathologies, *Science* (2024). DOI: 10.1126/science.abm6131. www.science.org/doi/10.1126/science.abm6131

Lance A. Johnson et al, Alzheimer's and metabolism wed with IDO1, *Science* (2024). DOI: 10.1126/science.adr5836

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