

## Researchers identify proteins that might contribute to memory loss and Alzheimer's disease

*TGen-led team finds 3 proteins that dismantle 'bridges' within brain cells*

**PHOENIX, Ariz. — Jan. 15, 2009** — A scientific group led by the Translational Genomics Research Institute (TGen) have identified three kinases, or proteins, that dismantle connections within brain cells, which may lead to memory loss associated with Alzheimer's disease.

These findings, the results of a multi-year TGen study, are published in this month's edition of *BMC Genomics* in a paper titled: *High-content siRNA screening of the kinome identifies kinases involved in Alzheimer's disease-related tau hyperphosphorylation.*

The three kinases were found to cause a malfunction in tau, a protein critical to the formation of the microtubule bridges within brain cells, or neurons. These bridges support the synaptic connections that, like computer circuits, allow neurons to communicate with each other.

“The ultimate result of tau dysfunction is that neurons lose their connections to other neurons, and when neurons are no longer communicating, that has profound effects on cognition — the ability to think and reason,” said Dr. Travis Dunckley, an Associate Investigator in TGen's Neurodegenerative Research Unit and the scientific paper's senior author.

Tau performs a critical role in the brain by helping bind together microtubules, which are sub-cellular structures that create scaffolding in the neurons, allowing them to stretch out along bridges called axons. The axons support the synaptic, or chemical, connections with other neurons.

Under normal circumstances, kinases regulate tau by adding phosphates. This process, called tau phosphorylation, enables the microtubules to unbind and then bind again, allowing brain cells to connect and reconnect with other brain cells.

“That facilitates synaptic plasticity. It facilitates the ability of people to form new memories — to form new connections between different neurons — and maintain those memories. So, it's an essential function,” Dr. Dunckley said.

However, sometimes the tau protein becomes hyperphosphorylated, a condition in which the tau creates neurofibrillary tangles, one of the signature indicators of Alzheimer's.

“When tau protein is hyperphosphorylated, the microtubule comes apart — basically destroying that bridge — and the neurons can no longer communicate with each other,” Dr. Dunckley said.

TGen investigators created sophisticated tests to look at all 572 known and theoretical kinases within human cells. They identified 26 associated with the phosphorylation of tau. Of these 26, three of them — EIF2AK2, DYRK1A and AKAP13 — were found to cause hyperphosphorylation of tau, permanently dismantling the microtubule bridges.

“This paper shows, for the first time, these three kinases affect Alzheimer’s disease-relevant tau hyperphosphorylation, in which most of the tau protein is now driven into a permanently phosphorylated form,” Dr. Dunckley said.

Dr. Eric Reiman, clinical director of TGen's Neurogenomics Division and executive director of the Banner Alzheimer's Institute, explained that tau holds together the skeleton inside neurons. When phosphate molecules stick to tau proteins, the skeleton falls apart and the neurons begin to retract their synaptic branches and die, leading to memory loss and thinking problems.

In this study, researchers used a molecular tool called siRNA to screen the entire human genome, said Dr. Reiman, a co-author of the scientific paper. This tool enabled the TGen-led team to discover which proteins, when genetically turned off, prevent phosphate molecules from sticking to tau. The three kinases, or proteins, that appear to contribute to the formation of brain tangles, can now be targeted by protein-inhibitor drugs.

“This study used a powerful tool to discover three proteins that may be involved in tangle formation. If safe and well-tolerated tangle-busting medications can be developed, they offer great promise in the treatment of Alzheimer’s disease,” said Dr. Reiman, who also is Director of the Arizona Alzheimer’s Consortium.

The next step will be to identify drug compounds that can negate the effects of the three kinases linked to tau hyperphosphorylation.

“The reason that we did this study was to identify therapeutic targets for Alzheimer’s disease, whereby we could modify the progression of tau pathology,” Dr. Dunckley said. “This was a screen to identify what the relevant targets are. Now, we want to match those targets to treatments.”

TGen’s collaborators in the study included: the Department of Neurology at the Mayo Clinic in Jacksonville, Fla.; the Center for Alzheimer’s Research at the Sun Health Institute in Sun City, Ariz.; Banner Alzheimer’s Institute in Phoenix, Ariz.; the Department of Psychiatry at the University of Arizona; and the Arizona Alzheimer’s Consortium, a group of nine institutes that cooperatively study Alzheimer’s disease.

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### **About TGen**

The Translational Genomics Research Institute (TGen) is a Phoenix, Arizona-based non-profit organization dedicated to conducting groundbreaking research with life changing

results. Research at TGen is focused on helping patients with diseases such as cancer, neurological disorders and diabetes. TGen is on the cutting edge of translational research where investigators are able to unravel the genetic components of common and complex diseases. Working with collaborators in the scientific and medical communities, TGen believes it can make a substantial contribution to the efficiency and effectiveness of the translational process. TGen is affiliated with the Van Andel Research Institute in Grand Rapids, Michigan. For more information, visit: [www.tgen.org](http://www.tgen.org).

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**About the Arizona Alzheimer's Consortium**

The Arizona Alzheimer's Consortium (AAC) is the nation's leading model of statewide collaboration in Alzheimer's disease research. Established in 1998, the Consortium capitalizes on its participating institutions' complementary strengths in brain imaging computer science, genomics, the basic and cognitive neurosciences and clinical and neuropathology research to promote the scientific understanding and early detection of Alzheimer's disease and find effective disease-stopping and prevention therapies. It also seeks to educate Arizona residents about Alzheimer's disease, research progress in the state and the resources needed to help patients, families and professionals manage the disease. The Consortium is determined to find effective treatments to halt the progression and prevent the onset of Alzheimer's disease in the next 12 years.

The Arizona Alzheimer's Consortium is a 501(c)(3) organization that includes the state-supported Arizona Alzheimer's Research Center (AARC), the National Institute on Aging (NIA)-funded Arizona Disease Core Center (Arizona ADCC), and independently funded research programs. Its seven member institutions include: Arizona State University, the Barrow Neurological Institute, the Mayo Clinic Arizona, the Sun Health Research Institute, the Translational Genomics Research Institute (TGen), the University of Arizona, and the recently established Banner Alzheimer's Institute. Its three affiliated institutions include Banner Good Samaritan Medical Center, the Southern Arizona Veterans Administration Health Care System and the University Physician's Hospital at Kino.

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