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GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

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FOR IMMEDIATE RELEASE

**GLADSTONE SCIENTISTS IDENTIFY NEW STRATEGY FOR PREVENTING
ACUTE AND CHRONIC BRAIN DISEASE**

Mice lacking tau protein can resist seizures and Alzheimer-related memory loss

SAN FRANCISCO, CA – May 4, 2007 – Scientists at the Gladstone Institute of Neurological Disease (GIND) have discovered that reducing levels of the protein tau can prevent seizures and neurological deficits related to Alzheimer’s disease. The findings, reported today in the journal *Science*, demonstrate that when tau is removed from mice genetically engineered to simulate Alzheimer’s disease, their memory function is retained and they live a normal lifespan. Reducing tau levels also made mice more resistant to epileptic seizures.

“This is the most striking therapeutic effect I have ever seen in our disease models,” said Lennart Mucke, MD, GIND director and professor of neurology at the University of California, San Francisco (UCSF), and senior author of the study. “A lot more work needs to be done, of course. But if this strategy also works in humans, it could enable a major leap forward in our ability to treat and prevent devastating neurological diseases.”

Although Alzheimer’s disease (AD) was first described over a hundred years ago, there is still no effective way to prevent it. Many investigational therapies for AD aim to reduce levels of amyloid- β proteins ($A\beta$), because $A\beta$ builds up to abnormally high levels in the brains of people with AD and is widely suspected to cause the disease.

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“We wanted to pursue a complementary strategy and try to make the brain more resistant to A β without having to change the levels of A β itself,” said the study’s lead author, Erik Roberson MD, PhD, Gladstone staff scientist and assistant professor of neurology at UCSF. “Amazingly, even partial reduction of tau prevented memory problems and premature deaths in our Alzheimer mice, even though their brains were full of A β .”

The Gladstone team used a mouse model of AD in which memory deficits are triggered by a human gene that causes overproduction of A β . The key finding was that cognitive and neuronal deficits in these mice were prevented when one or both copies of the tau gene were eliminated.

Tau is made normally by brain cells and regulates the stability of their internal skeleton. In AD, tau is altered in a way that makes it aggregate into clumps, called tangles. A lot of effort has been devoted to finding ways to specifically eliminate these abnormal forms of tau, but this has been difficult. The current study suggests that lowering overall tau levels may be a good alternative, especially since even partial tau reduction was effective and very well tolerated, at least in the mice.

A breakthrough came when the researchers identified a mechanism by which tau reduction could protect the brain. They found that tau reduction protects brain cells against overstimulation, which can interfere with the brain’s normal functioning and even cause seizures. Indeed, mice with reduced levels of tau were also resistant against epileptic seizures.

“This connection between tau and neuronal overexcitation was really unexpected,” said Dr. Roberson. “It opens up totally new ways of thinking about tau and its involvement in neurological disease.”

Because overstimulation of brain cells contributes to a variety of major neurological diseases, these findings may have broad therapeutic implications.

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“We still have hurdles to cross before this discovery is translated into something that is ready for patients,” said Dr. Mucke, “but there is an urgent need for better treatments in this field, so it is really exciting to have identified such a promising approach.”

The Gladstone research team also included Kimberly Scearce-Levie, Jorge J. Palop, Fengrong Yan, Tiffany Wu, Irene H. Cheng, Hilary Gerstein and Gui-Qiu Yu. The research was supported by grants from the National Institutes of Health, the Giannini Foundation, and an S.D. Bechtel Jr. Young Investigator Award.

About the Gladstone Institutes

The J. David Gladstone Institutes, affiliated with the University of California, San Francisco (UCSF), is dedicated to the health and welfare of humankind through research into the causes and prevention of some of the world’s most devastating diseases. Gladstone is comprised of the Gladstone Institute of Cardiovascular Disease, the Gladstone Institute of Virology and Immunology and the Gladstone Institute of Neurological Disease. More information can be found at www.gladstone.ucsf.edu.

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