

## THE J. DAVID GLADSTONE INSTITUTES

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## GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

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### **GLADSTONE SCIENTISTS IDENTIFY ROLE OF FATTY ACIDS IN ALZHEIMER'S DISEASE**

#### ***Large-scale analysis of brain lipids identifies potential therapeutic strategy***

SAN FRANCISCO, CALIFORNIA—October 19, 2008--Scientists at the Gladstone Institute of Neurological Disease (GIND) and the University of California have found that complete or partial removal of an enzyme that regulates fatty acid levels improves cognitive deficits in a mouse model of Alzheimer's disease (AD). Their findings, which will be published in today's issue of *Nature Neuroscience*, identified specific fatty acids that may contribute to the disease as well as a novel therapeutic strategy.

AD causes a progressive loss of cognitive functions and results in death. Over 5 million Americans are living with this condition. Although there are treatments to ease the symptoms, these treatments are not very effective and researchers have yet to discover a cure.

"Several different proteins have been implicated in Alzheimer's disease," said Lennart Mucke, MD, GIND director and senior author of the study, "but we wanted to know more about the potential involvement of lipids and fatty acids."

Fatty acids are rapidly taken up by the brain and incorporated into phospholipids, a class of fats that form the membrane or barrier that shields the content of cells from the external environment. The scientists used a large scale profiling approach ("lipidomics") to compare many different fatty acids in the brains of normal mice with those in a mouse model of Alzheimer's disease that develops memory deficits and many pathological alterations seen in the human condition.

## Fatty Acids in Alzheimer's Disease

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“The most striking change we discovered in the Alzheimer mice was an increase in arachidonic acid and related metabolites in the hippocampus, a memory center that is affected early and severely by Alzheimer's disease,” said Rene Sanchez-Mejia, MD, lead author of the study.

In the brain arachidonic acid is released from phospholipids by an enzyme called group IVA phospholipase A<sub>2</sub> (or PLA<sub>2</sub>). The scientists lowered PLA<sub>2</sub> levels in the Alzheimer mice by genetic engineering. Removal or even partial reduction of PLA<sub>2</sub> prevented memory deficits and other behavioral abnormalities in the Alzheimer mice.

“Arachidonic acid likely wreaks havoc in the Alzheimer mice by causing too much excitation, which makes neurons sick. By lowering arachidonic acid levels, we are allowing neurons to function normally,” said Dr. Sanchez-Mejia.

Dr. Mucke added, “in general, fatty acid levels can be regulated by diet or drugs. Our results have important therapeutic implications because they suggest that inhibition of PLA<sub>2</sub> activity might help prevent neurological impairments in Alzheimer's disease. But a lot more work needs to be done before this novel therapeutic strategy can be tested in humans.”

John W. Newman, Sandy Toh, Gui-Qiu Yu, Yungui Zhou, Brian Halabisky, Moustapha Cissé, Kimberly Scarce-Levie, Irene H. Cheng, Li Gan, Jorge J. Palop, Joseph V. Bonventre, and Lennart Mucke also contributed to the study. The research was supported by the National Institutes of Health, the United States Department of Agriculture, and the Gladstone Institutes.

**About the Gladstone Institutes:** The J. David Gladstone Institutes is an independent, nonprofit biomedical research organization 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, affiliated with the University of California, San Francisco (UCSF), 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](http://www.gladstone.ucsf.edu).

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