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FOR IMMEDIATE RELEASE
May 19, 2004

ALZHEIMER'S PATHOLOGY CAN BE REDUCED, LONGEVITY IMPROVED IN MOUSE MODEL, BY BLOCKING PROTEIN REGULATION PATHWAY, GLADSTONE STUDY SHOWS

Removal of an enzyme that regulates the activity of many proteins can suppress key features of Alzheimer's disease in experimental models, researchers at the Gladstone Institute of Neurological Disease (GIND) recently reported in the *Journal of Neuroscience* (May 12, 2004).

Using well-established mouse models of Alzheimer's disease, the investigators examined how changing levels of the enzyme Fyn affects key aspects of the disease, including accumulation of large clumps of amyloid proteins in the brain (so-called plaques) and changes in the complex neuronal networks in which memories are formed and stored. Genetic engineering strategies were used to increase or decrease the expression of Fyn, which regulates many other proteins through the attachment of specific groups of atoms known as phosphate groups.

The researchers determined that changing levels of Fyn had no effect on plaque formation or aberrant sprouting (the abnormal growth of nerve terminals, in which neurochemical messages are stored), indicating that these pathologies involve discrete molecular mechanisms. However, they observed that blocking Fyn expression prevented amyloid proteins from damaging synapses, the specialized connections between brain cells, and improved the longevity of mice. (Experimental mice with Alzheimer's-like disease otherwise die prematurely.) In contrast, increasing Fyn in the brain worsened synaptic damage, and also increased the number of premature deaths in the mice.

Loss of synapses and abnormal outgrowth of nerve terminals occur both in people with Alzheimer's disease and in transgenic mice producing human amyloid proteins in the brain (the model used in the study). Humans with the disease, like mice, die prematurely.

"Synaptic degeneration in Alzheimer's disease is like electrical circuits in a computer becoming faulty -- signals can no longer be transmitted through broken connections," says senior author and GIND director Lennart Mucke, MD, who is also Joseph B. Martin Distinguished Professor of Neuroscience at the University of California, San Francisco.

"Our results suggest that Fyn plays a key role in Alzheimer's-related synaptic impairments, and that it can worsen the toxicity of amyloid proteins," says lead author Jeannie Chin, PhD, a GIND postdoctoral fellow. "We are excited about the possibility that pharmacological modulation of Fyn might be of therapeutic benefit in this disease."

Because Fyn is involved in many different processes related to normal neuronal functioning, complete suppression of its activity might have detrimental side effects, says Mucke. Thus, he says, the

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researchers will be examining whether partial suppression of Fyn is beneficial. They also will be testing the therapeutic potential of manipulating some of the more specific pathways that Fyn regulates.

This work was supported by C. Lester and Audrey Hogan, the National Institutes of Health, the John Douglas French Alzheimer's Foundation, and the Hillblom Center for the Biology of Aging.

The paper, "Fyn Kinase Modulates Synaptotoxicity, But Not Aberrant Sprouting, in Human Amyloid Precursor Protein Transgenic Mice," was co-authored by Mucke and fellow GIND staff members Jeannie Chin, Jorge J. Palop and Gui-Qiu Yu; Nobuhiko Kojima of the Neuronal Circuit Mechanisms Research Group, RIKEN Brain Science Institute, Japan; and Eliezer Masliah of the Departments of Neurosciences and Pathology, University of California, San Diego.

The Gladstone Institute of Neurological Disease is one of three research institutes of The J. David Gladstone Institutes, a private, nonprofit biomedical research institution affiliated with UCSF. For further information, visit www.gladstone.ucsf.edu.

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