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GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

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SCIENTISTS ZERO IN ON MEMORY-RELATED PROTEINS AT THE CORE OF ALZHEIMER'S DISEASE

New research sheds light on how the formation of long-term memories may be blocked in Alzheimer's disease.

Reporting in two companion papers in the October 19 issue of the *Journal of Neuroscience*, investigators from the Gladstone Institute of Neurological Disease show in genetically engineered mouse models of the disease that the accumulation of Alzheimer-related neurotoxic amyloid- β peptides ($A\beta$) can deplete key proteins in a specific memory center of the brain. They also report that this process can be worsened by increased activity of an enzyme called Fyn.

The inability of Alzheimer's patients to remember events from a few days ago may be linked to the lack of proteins that strengthen the contact points, or synapses, between neurons in the brain, according to study findings.

Much research points to the idea that, far from having a single cause, Alzheimer's disease is typically brought on by a combination of risk factors. In keeping with that model, these papers show that the depletion of memory proteins can require the interaction of different disease-promoting molecules, explains GIND Director Lennart Mucke, MD, the Joseph B. Martin Distinguished Professor in Neuroscience at the University of California, San Francisco, and senior author of the papers.

The researchers found that memory proteins can be depleted not only by high levels of $A\beta$ but also by low levels of $A\beta$ in combination with high levels of Fyn activity.

"Like partners in crime, $A\beta$ and Fyn appear to cooperate to cause Alzheimer-like changes in the brain," says Mucke. The findings may eventually help identify novel therapeutic targets and biomarkers for emerging treatments.

Scientists in Mucke's laboratory were among the first to generate genetically engineered mice that produce human $A\beta$, providing a powerful tool to study the devastating disease. Using a technique called gene expression imaging to profile molecular changes in millions of neurons throughout the brain, they unexpectedly found $A\beta$ -induced deficits in a very specific neuronal population in the hippocampus, a brain region that serves as a gateway to the complex system that helps lay down new memories.

"The most striking changes within the brain were found in hippocampal granule cells, the specialized neurons that help convert new information into a format for long-term storage," says Jorge J. Palop, PhD, lead author of one of the papers. "That conversion requires proteins that

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help strengthen the synapses between neurons.” These important proteins, which included two called Arc and Fos, were found to be depleted in mice that produced Alzheimer’s-related A β peptides in the brain.

The investigators have good leads on exactly how the memory proteins are depleted in Alzheimer’s disease, adds Jeannie Chin, PhD, lead author of the companion paper. They have discovered that changing the activity of the enzyme Fyn can drastically alter the susceptibility of granule cells to the A β -induced depletion of memory proteins.

“Fyn is strategically located at the synapses, where it regulates the activity of several memory-related proteins,” explains Chin. The scientists found that increases in Fyn activity markedly enhanced the susceptibility of granule cells to the A β -induced depletion of memory proteins and, in fact, triggered prominent deficits in memory retention, even in mice with low levels of human A β .

Further studies are now underway to determine whether treatments aimed at A β and at Fyn-related pathways will together enhance the level and function of memory proteins, thereby providing synergistic benefit in the fight against Alzheimer’s disease.

Palop, Chin and Mucke will present their work at Neuroscience 2005, the Society for Neuroscience’s 35th Annual Meeting, to be held in Washington, DC, November 12-16.

The research was supported in part by grants from the National Institutes of Health and by fellowships from the John Douglas French Alzheimer’s Foundation and the Academy of Finland.

One paper is titled “Vulnerability of Dentate Granule Cells to Disruption of Arc Expression in Human Amyloid Precursor Protein Transgenic Mice.” Co-authors are GIND staff members Jorge J. Palop, Jeannie Chin, Nga Bien-Ly, Catherine Massaro, Bertrand Z. Yeung, Gui-Qiu Yu and Lennart Mucke.

The companion paper is titled “Fyn Kinase Induces Synaptic and Cognitive Impairments in a Transgenic Mouse Model of Alzheimer’s Disease.” Co-authors are GIND staff members Chin, Palop, Jukka Puoliväli, Massaro, Bien-Ly, Hilary Gerstein, Kimberly Scarce-Levie, and Mucke, as well as Eliezer Masliah of the UC San Diego Department of Neurosciences and Pathology.

Palop, Chin, and Mucke are additionally associated with the UCSF Department of Neurology, and Massaro and Mucke are associated with the UCSF Neuroscience Program.

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