



## GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

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### GLADSTONE RESEARCHERS IDENTIFY ENZYME THAT MAY PROTECT AGAINST PLAQUE BUILD UP ASSOCIATED WITH ALZHEIMER'S DISEASE

Researchers at the Gladstone Institute of Neurological Disease (GIND) have identified a potential new avenue for reducing the build up of toxic amyloid  $\beta$  ( $A\beta$ ) proteins, which are suspected of causing Alzheimer's disease (AD). They discovered that the enzyme cathepsin B (CatB) effectively destroys small as well as large clusters of  $A\beta$ . Previously, CatB had been suspected of increasing  $A\beta$  production in AD patients.

"We were very surprised and excited to find that CatB might be protective," said senior author Li Gan, Ph.D., a staff research investigator at the Gladstone Institute of Neurological Disease and an assistant professor of neurology at University of California, San Francisco (UCSF). "The number of drugs for the treatment of AD is very small. CatB's ability to remove  $A\beta$  may lead to another strategy for treating this disease."

Since Alzheimer's disease was first characterized 100 years ago, many studies have implicated  $A\beta$ , in the large insoluble clusters called plaques, and in more soluble forms, in the pathogenesis of AD, and the logical conclusion has been that getting rid of  $A\beta$  would be beneficial. The key question has been how to do it.

In general, levels of  $A\beta$  proteins, which are created by nerve cells, are determined by the balance between their production and removal. Therefore,  $A\beta$  build-up might be prevented by blocking the production of  $A\beta$  or by enhancing its clearance. While most work has focused on the first approach, the latter has been problematic. For example, efforts to develop a vaccine that would stimulate the host immune system to remove  $A\beta$  met with unexpected complications.

To test whether the enzyme CatB is involved in  $A\beta$  regulation in the brain, Gan's team inactivated CatB in mice genetically engineered (transgenic) to produce high levels of human  $A\beta$  in the

brain. With CatB inactivated, the mice had increased A $\beta$  levels, more plaques, and more severe neuronal deficits. The scientists then took the opposite tack.

They used gene therapy to express CatB in the brain of aged transgenic mice and found that even the preexisting plaques were markedly reduced.

In complementary experiments, carried out in cell-free conditions in the test tube, Gan's team was able to show that CatB effectively truncates the most dangerous A $\beta$  variety, generating shorter A $\beta$  peptides that result in fewer plaques and are less toxic.

"The finding that CatB can so effectively break down many different types of A $\beta$  aggregates is very exciting," said Lennart Mucke, M.D, Director of Gladstone Institute of Neurological Disease and an author of the study. "As the Baby Boom generation is entering the age of greatest risk for AD, it is critical that we aggressively pursue new therapeutic targets, including this powerful enzyme."

The research results are reported in the September 21 issue of *Neuron*.

Research co-authors are postdoctoral fellows Sarah Mueller-Steiner, Ph.D. Erik D. Roberson, M.D., Luke Esposito, Ph.D., Binggui Sun, Ph.D. and Jennifer Chen, Ph.D. visiting scientist Hideaki Arai, Ph.D, and research associates Yungui Zhou, Xin Wang, and Gui-qiu Yu.

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The Gladstone Institute of Neurological Disease is one of three research institutes of The J. David Gladstone Institutes, a private, nonprofit biomedical research institution. It is affiliated with UCSF, a leading university that consistently defines health care worldwide by conducting advanced biomedical research, educating graduate students in the life sciences, and providing complex patient care. For further information, visit [www.gladstone.ucsf.edu](http://www.gladstone.ucsf.edu) and [www.ucsf.edu](http://www.ucsf.edu).