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Scientists identify protein that spurs formation of Alzheimer's plaques

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In Alzheimer's disease, the problem is beta-amyloid, a protein that accumulates in the brain and causes nerve cells to weaken and die. Drugs designed to eliminate plaques made of beta-amyloid have a fatal problem: they need to enter the brain and remove the plaques without attacking healthy brain cells. New research from the laboratory of Nobel Prize winner Paul Greengard, however, suggests that treatments modeled on the blockbuster cancer drug Gleevec could be the solution. The findings are reported in the Sept. 2 issue of the journal *Nature*.

Gleevec, it turns out, has the unique ability to bind to a protein that triggers the production of beta-amyloid plaques. The new research from Greengard's lab shows that this protein, called gamma-secretase activating protein (GSAP), dramatically and selectively increases the production of beta-amyloid peptide, which makes up the senile plaques found in the brains of most people with Alzheimer's. GSAP works through a mechanism involving its interactions with gamma-secretase, an enzyme that chops up the amyloid precursor protein, a large molecule produced naturally in the body and found in many different types of cells.

"Alzheimer's disease is a devastating disorder for which there are no satisfactory treatments," says Greengard, Vincent Astor Professor and director of the Fisher Center for Alzheimer's Research at Rockefeller. "Our findings reveal that gamma-secretase activating protein is a potential target for a new class of anti-amyloid therapies." Greengard won the 2000 Nobel Prize in Physiology or Medicine for research into

how neurons communicate.

Scientists have been searching for ways to reduce beta-amyloid production in Alzheimer's patients by blocking gamma-secretase, but most gamma-secretase inhibitors also block the cleavage of an important immune system molecule called Notch. Notch plays a pivotal role in the development of blood-forming organs and the immune system. Earlier research by Greengard and his colleagues showed that Gleevec, a drug used to treat leukemia and gastrointestinal stromal tumors, successfully inhibited the ability of gamma secretase to form beta amyloid without affecting the Notch pathway.

In the new study, led by Gen He, a research associate in Greengard's lab, the researchers showed that GSAP stimulates production of beta-amyloid in cell lines, and that reducing GSAP reduces beta-amyloid. The researchers also looked at GSAP's action in a mouse model of Alzheimer's disease. They knocked down the gene that codes for GSAP using RNA interference, and found that levels of beta-amyloid as well as plaque development decreased. Biochemical studies showed that Gleevec reduces beta-amyloid production by binding to GSAP and preventing its activation of gamma-secretase.

Unfortunately, the Gleevec molecule does not cross the blood-brain barrier, the gatekeeper that prevents some substances in the blood from entering the brain. Greengard, however, believes that it will be possible to design drugs that target GSAP but do not have this limitation.

"Anti-amyloid therapeutic drugs represent a valid approach to treating Alzheimer's disease, but their inability to accumulate in the brain has limited their usefulness," says Greengard, who is head of the Laboratory of Molecular and Cellular Neuroscience. "The development of compounds that work like Gleevec, but have the ability to pass the blood-brain barrier and target GSAP could revolutionize the treatment of this

disease."

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