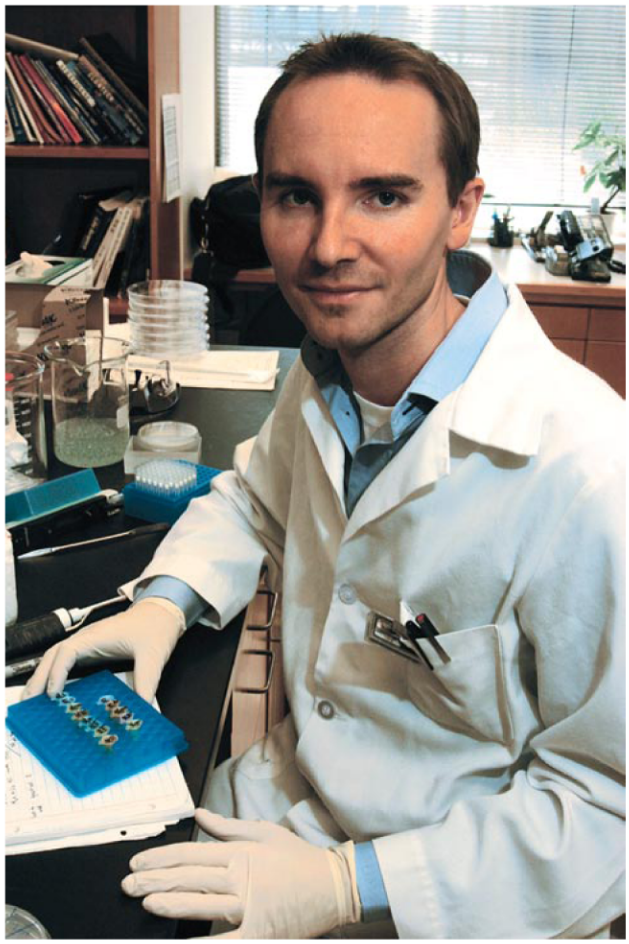
Drugs Without Side Effects?

A new therapeutic target for Alzheimer's could lead to drugs without side effects.

Researchers from the Fisher Center for Alzheimer's Disease Research at The Rockefeller University have identified a therapeutic target protein called casein kinase 1 that may be the key to halting the course of Alzheimer's disease. The findings, based on studies in the cells of mammals, show that chemicals that block casein kinase 1 don't interfere with an essential pathway that is often blocked by other experimental anti-amyloid compounds.

Alzheimer's disease is generally believed to be caused by a buildup of a small protein called amyloid-beta, which is formed when a larger protein is broken into pieces. But the enzyme that produces amyloid-beta is also responsible for cleavage (splitting) of another protein called Notch. The problem with current compounds that lower amyloid-beta production is that they also block the cleavage of Notch, which plays an important role in the development of healthy brain cells.

The new research, based on studies by lead author Marc Flajolet and from the Nobel Prize-winning laboratory of Paul Greengard, director of the Fisher Center for Alzheimer's Disease Research at Rockefeller, has identified casein kinase 1 that controls the regulation of these enzymes. When the researchers block casein kinase 1, production of amyloid-beta proteins goes down but Notch signaling is not affected.



Fisher Center Lab's Marc Flajolet, senior research associate

"Studies of brain tissue from Alzheimer's patients have shown an increase in casein kinase 1 expression," says Greengard, Vincent Astor professor and head of the Laboratory of Molecular and Cellular Neuroscience. "We found that the key enzymes involved in amyloid-beta production—called BACE and gamma-secretase—were targets of casein kinase 1, so we investigated what role it might be playing."

The scientists modified mouse cells to generate a form of casein kinase 1 that was always active, and found that these cells produced more amyloid-beta protein than normal. Then, using three different types of chemicals, they blocked the protein from functioning. When they did this, they were able to reverse the production of amyloid-beta protein without affecting the signaling of Notch proteins.

The studies suggest that an Alzheimer's therapy based on these chemicals could reduce or halt amyloid-beta buildup without causing side effects. "Numerous efforts have been directed at the development of drugs that inhibit gamma-secretase," says Greengard, "but there have been significant side effects in animal studies. Our hope is that this research might lead to drugs that don't have those problems." ■

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To learn more about ongoing Alzheimer's research, visit www.ALZinfo.org and click on "Alzheimer's Research."