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Scientists Discover that Three Molecules May be Developed into New Alzheimer's Drugs

A team of scientists has discovered three molecules --- from a search of 58,000 compounds --- that appear to inhibit a key perpetrator of Alzheimer's disease.

Each of the three molecules protects the protein called "tau," which becomes hopelessly tangled in the brains of patients with Alzheimer's. The finding is promising news for the development of drugs for the disease.

Ken Kosik, co-director of the Neuroscience Research Institute at the University of California, Santa Barbara, headed the effort to find these molecules. The results of the study are published in the July issue of the journal *Chemistry and Biology*, released on Friday, July 22.

As baby boomers grow older, the incidence of Alzheimer's, already increasing, will rise much more. "Our approaches to the disease are flagrantly inadequate," said Kosik. "There are a couple of FDA-approved drugs that help a little, but don't modify the disease. They give a little bit of symptomatic relief, but don't change the inexorable progression of the disease."

He said that new insights made over the past decade help to understand the molecular and genetic basis of the disease and these can now be built upon for the

development of treatments. "There is no doubt that we need new approaches," said Kosik. "The insights gained about the mechanisms of the molecular and genetic basis of the disease are beginning to add up and can be harnessed for treatments."

Alzheimer's involves a complicated, interwoven series of regulatory steps of genes and proteins "talking" to each other, he explained. "When the conversation goes awry the disease process begins. And it is not just one gene or one protein causing the damage."

The complexity of Alzheimer's means that several different medications will likely be needed to control it, said Kosik. The same is true for many other diseases --- from AIDS to cancer. "It is likely that we will need to strategically target different aspects of the disease and put them together."

Kosik and his team chose to focus on the neurofibrillary tangles of neurons in the brain that, along with senile plaques, characterize Alzheimer's disease. The tangles are made of "tau," a protein that is also present normally in the brain.

"Tau goes wrong and becomes pathological when it becomes intensely phosphorylated," said Kosik. "This means that many phosphate groups attach to tau --- modify it --- and cause it to become dysfunctional."

The culprit is an enzyme, called CDK5, that attaches the phosphate to the tau protein, facilitating the disease process. The researchers set out to find a way to inhibit this enzyme, to keep it from putting any phosphate on tau.

In the laboratory, they purified the enzyme and purified tau protein, and watched tau get phosphorylated by the enzyme. They then performed a library search of small molecules (58,000 of them) in an attempt to find those that would prevent phosphorylation. Small molecules are preferred because they are more easily used as a drug since they can get through the body and into cells. It is also important to find molecules that will cross the blood brain barrier.

They then set up a test of nearly 400 small molecules that fit their criteria. The test results showed three small molecules that can inhibit the enzyme. These are candidates for development as drugs.

Kosik explained that proteins are strings of amino acids folded into small globs. All proteins that happen to be an enzyme involved in phosphorylation have one thing in

common. They have a pocket that is almost always in the same place and this is where the phosphate attaches to the enzyme, in this case CDK5. To get a molecule that specifically prevents the enzyme from binding at the pocket is difficult.

Of the three compounds that the research group found, the scientists were able to locate where they bind. They found that one binds in the pocket, another binds at the edge of the pocket, and a third appears to bind completely outside the pocket. The scientists are most interested in the second and third compounds.

"This is the first demonstration that we can find small molecules that can more specifically affect the phosphorylation of tau by CDK5," said Kosik.

In terms of future directions, Kosik said, "There is lots to do here, lab testing, testing in animals, etc. But we have made an important step forward toward developing treatments for this disease."

He noted that this work is of a type usually performed by pharmaceutical companies, but in this case was completed in an academic environment.

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In addition to Kosik, authors of the paper include: Jae Suk Ahn, Sungwoon Choi, and Gregory D. Cuny of the Department of Neurology and Laboratory for Drug Discovery in Neuroegeneration of Brigham and Women's Hospital, Harvard Medical School; Mala L. Radhakrishnan of the Computer Science and Artificial Intelligence Laboratory, Department of Chemistry, Massachusetts Institute of Technology; Marina Mapelli and Andrea Musacchio of the Structural Biology Unit of the Department of Experimental Oncology, European Institute of Oncology, Milan, Italy; Bruce Tidor of the Computer Science and Artificial Intelligence Laboratory, Biological Engineering Division, Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology.

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