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Researchers create molecule that blocks pathway leading to Alzheimer's disease

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UC Davis researchers have found novel compounds that disrupt the formation of amyloid, the clumps of protein in the brains of people with Alzheimer's disease believed to be important in causing the disease's characteristic mental decline. The so-called "spin-labeled fluorene compounds" are an important new target for researchers and physicians focused on diagnosing, treating and studying the disease.

The study, published today in the online journal *PLoS ONE*, is entitled "The influence of spin-labeled fluorene compounds on the assembly and toxicity of the Aβ peptide."

"We have found these small molecules to have significant beneficial effects on cultured neurons, from protecting against toxic compounds that form in neurons to reducing inflammatory factors," said John C. Voss, professor of biochemistry and molecular medicine at the UC Davis School of Medicine and the principal investigator of the study. "As a result, they have great potential as a therapeutic agent to prevent or delay injury in individuals in the earliest stages of Alzheimer's disease, before significant damage to the brain occurs."

Amyloid is an accumulation of proteins and peptides that are otherwise found naturally in the body. One component of amyloid – the amyloid beta (Aβ) peptide – is believed to be primarily responsible for destroying neurons in the brain. Fluorene compounds, which are small three-ringed molecules, originally were developed as imaging agents to detect amyloid with PET imaging. In addition to being excellent for

detecting amyloid, fluorenes bind and destabilize Aβ peptide and thereby reduce amyloid formation, according to previous findings in mice by Lee-Way Jin, another study author and associate professor in the UC Davis MIND Institute and Department of Medical Pathology and Laboratory Medicine.

The current research studied the effects of fluorene compounds by attaching a special molecule to make their activity evident using electron paramagnetic resonance (EPR) spectroscopy. This technology allows researchers to observe very specific activities of molecules of interest because biological tissues do not emit signals detectable by EPR. Since Voss was interested in the activity of fluorenes, he added a nitroxide "spin label," a chemical species with a unique signal that can be measured by EPR.

The group found that spin-labeled compounds disrupted Aβ peptide formation even more effectively than did non-labeled fluorenes. In addition, the antioxidant properties of the nitroxide, which scavenge reactive oxygen species known to damage neurons and increase inflammation, significantly contributed to the protective effects on neurons.

"The spin-labeled fluorenes demonstrated a number of extremely important qualities: They are excellent for detecting amyloid in imaging studies, they disrupt Aβ formation, and they reduce inflammation," said Voss. "This makes them potentially useful in the areas of research, diagnostics and treatment of Alzheimer's disease."

Alzheimer's disease is the most common form of dementia and affects some 5 million Americans. Current medications used to fight the disease usually have only small and temporary benefits, and commonly have many side effects.

A major obstacle in developing Alzheimer's disease therapy is that most molecules will not cross the blood-brain barrier, so that potential treatments given orally or injected into the bloodstream cannot enter the brain where they are needed. Fluorene compounds are small molecules that have been shown to penetrate the brain well.

"We have brought together expertise from diverse fields to get to this point, and what was once a side interest has become a major focus," said Voss. "We are very excited and hopeful that these unique compounds can become extremely important."

Voss' group next plans to study the safety of spin-labeled fluorene compounds as well as their efficacy for treating models of Alzheimer's disease in small animals.

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