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Protein inhibitor holds promise for heart disease treatment

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UC Davis scientists have developed a novel cardiovascular agent which, unlike currently available drugs for heart disease, does not target high blood cholesterol or high blood pressure. The experimental agent inhibits C-reactive protein (CRP), a biomarker of risk for heart attacks, strokes and unstable, or uncontrolled, chest pain.

The researchers reported their laboratory animal studies on the experimental agent in an article published online July 22 in the International *Journal of Cardiology*.

"There is an urgent need to develop inhibitors that specifically block the biological effects of C-reactive protein," said Ishwarlal Jialal, senior author of the article and professor of pathology and laboratory medicine at UC Davis.

Jialal said that his lab's development of the CRP inhibitor reflects the major shift that has occurred in how physicians and scientists view heart disease. The change is based on recent studies that have shown that the body's inflammatory response is pivotal to all phases of cardiovascular disease, from the development of fatty deposits, or plaques, in blood vessels to the onset of heart attacks and strokes, said Jialal, who directs UC Davis Medical Center's Laboratory of Atherosclerosis and Metabolic Research and holds the Robert E. Stowell Endowed Chair in Experimental Pathology.

"Numerous studies have shown that high levels of CRP result in a poorer

prognosis in patients with heart attack and unstable angina," he said. Unstable angina is unpredictable, frequent chest pain.

Research also has revealed that individuals whose blood CRP levels are high but whose blood cholesterol and blood pressure are normal are at risk for suffering a heart attack, stroke or sudden death from cardiovascular disease, said Jialal.

As an example, Jialal cited a major clinical trial of rosuvastatin that found the statin drug significantly reduced heart attacks, strokes, chest pains and other cardiovascular disorders in individuals with high CRP blood levels, but no other risk factors for cardiovascular disease.

An estimated 15 to 20 percent of heart attacks and strokes occur in patients without traditional cardiovascular risk factors such as high blood pressure and blood cholesterol, obesity, lack of regular exercise and cigarette smoking.

Jialal's lab synthesized the CRP inhibitor, a peptide, which is a small protein molecule, by using the one-bead-one-compound combinatorial library (bit.ly/14oGKR1) developed by study co-author Kit Lam, chair of the UC Davis Department of Biochemistry and Molecular Medicine and professor of hematology and oncology.

In laboratory cultures of human cells, the inhibitor—named CRP-i2—reduced CRP levels. These findings were reported in early 2013 in the journal Metabolic Syndrome and Related Disorders.

For the current study, Jialal's group injected the inhibitor CRP-i2 in one group of laboratory rats and compared the effects with a second group of lab rats that was not treated with the inhibitor. CRP from human cells was then administered to the animals because rodents do not normally produce the protein. Previous research by scientists in the United

Kingdom found that administering human CRP to rodents increased tissue damage from heart attacks or strokes in these animals.

Jialal and his colleagues found that CRP-i2 blunts the pro-inflammatory effects of CRP and significantly reduced biomarkers of inflammation, including nuclear factor kappaB, which he described as the master switch of inflammation. In addition, the inhibitor did not harm the animals.

Before CRP-i2 can be evaluated in human volunteers, Jialal and colleagues will conduct a series of studies over the next five years to evaluate the long-term effects of the agent on the pathobiology of the endothelial cells lining the blood vessels of rat models and on the extent of tissue damage caused by inducing heart attacks in the animals.

The agent developed by Jialal and his colleagues is the third known inhibitor of CRP under development as a potential treatment for cardiovascular disease.

CRP, which is normally present in trace levels in the blood, is produced by the immune system to clear dead and disintegrating cells. According to research at several labs, inflammation plays a role in Crohn's disease, diabetes, rheumatoid arthritis as well as heart disease. Physicians can measure CRP to determine the general level of inflammation in an individual's body.

The title of journal paper is "A Novel Peptide Inhibitor Attenuates C-Reactive Protein's Pro-Inflammatory Effects *in-vivo*."

Provided by UC Davis