Research shows that newly discovered drug reduces heart enlargement

January 29 2009

Researchers at the University of California, Davis have discovered that a prototype drug reduces heart enlargement, one of the most common causes of heart failure.

Heart failure, which occurs when the heart can't pump enough blood throughout the body, affects 5 million people in the United States. The condition contributes to 300,000 deaths each year.

The research in the laboratories of cardiologist and cell biologist Nipavan Chiamvimonvat, Department of Cardiovascular Medicine, UC Davis School of Medicine, and entomologist Bruce Hammock, Department of Entomology, showed that the new class of drugs reduces heart swelling in rat models with heart failure.

"This holds promise to treat heart failure and other cardiovascular as well as kidney problems," said nephrology professor Robert Weiss, Department of Internal Medicine.

Similar compounds are now in clinical trials.

Ding Ai of Beijing, senior author of the paper published recently in the *Proceedings of the National Academy of Sciences*, worked as a Ph.D. student in the Chiamvimonvat and Hammock laboratories for a year.

"The study of rat models showed that heart failure is driven by high angiotensin associated with high blood pressure, artery disease and some

kidney disease," Hammock said.

"When that occurs, a key enzyme called soluble epoxide hydrolase is increased."

The initial research on the enzyme sprang from studies on insect pest control in the Hammock lab.

"This enzyme," Chiamvimonvat said, "degrades anti-inflammatory and anti-hypertensive factors normally in the heart and blood, which may contribute to the pathological progression of heart failure."

Heart failure weakens the heart's pumping ability, she said. Blood and fluid can back up into the lungs; accumulate in the feet, ankles and legs (edema); and result in tiredness and shortness of breath. Coronary artery disease, high blood pressure and diabetes are the leading causes of heart failure.

The scientists showed they could inhibit the enzyme with a drug made by Paul Jones, a former postgraduate researcher at UC Davis. The swelling and ultimate failure of the heart is blocked and reversed, Hammock said.

"Interestingly, the increase in heart size associated with extreme exercise does not increase levels of the epoxide hydrolase, and exercise induced heart enlargement fortunately is not blocked by the drug."

This research follows earlier studies reported from the Chiamvimonvat laboratory on cardiac hypertrophy.

The two UC Davis laboratories collaborated with the laboratories of John Shyy at UC Riverside and Yi Zhu, Cardiovascular Sciences, Peking University Health Science Center. The 11-member research team also included Wei Pang, Nan Li, Ming Xu, Jun Yang and Youyi Zhang, all of

China.

In a November 2006 paper in the *Proceedings of the National Academy of Sciences*, the Chiamvimonvat and Hammock laboratories showed that these enzyme inhibitors both block and reduce heart enlargement and irregular heart rhythms in a mouse model. The more recent work with the Zhu and Shyy laboratories extends these studies to show the involvement of angiotensin dependent enzyme induction in the process.

At the time, Chiamvimonvat said: "We need a better way to control and prevent enlargement of the heart to improve treatment options for patients and reduce mortality." "By blocking the pathway that leads to overgrowth of cardiac cells, we have shown that it is possible to prevent the progressive deterioration of heart function and the development of abnormal hearth rhythms."

The prototype drug published this week appears to be that "better way," the scientists said.

The paper, "Soluble Epoxide Hydrolase Plays an Essential Role in Angiotensin II-Induced Cardiac Hypertrophy," is online at www.pnas.org/content/106/2/564.full .

Source: University of California - Davis