SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS FIND PROTEIN THAT INHIBITS CARDIAC HYPERTROPHY, HEART FAILURE

DALLAS – March 13, 2001 – The over-expression of a protein produced naturally in the human body inhibits cardiac hypertrophy and ultimately heart failure in transgenic mice, according to a study conducted by researchers at UT Southwestern Medical Center at Dallas.

This finding could potentially lead to the development of novel therapies to prevent heart disease in humans, said Dr. R. Sanders Williams, chief of cardiology and lead author of the study.

The protein, MCIP1, which is expressed normally in the cardiac and skeletal muscles of mice, humans and other animals, is activated as a protective mechanism when the heart is subjected to a stress. But it is inadequate when the stimulus is strong and sustained, Williams said.

"We showed that you can prevent cardiac abnormalities resulting from several different stresses by increasing the abundance of this protein beyond that which occurs naturally," he said.

The researchers produced transgenic mice that over-expressed the MCIP1 protein. This overexpression inhibited the activity of calcineurin, a signaling protein that controls enlargement of the heart, which can progress to heart failure. When calcineurin is activated, a condition known as hypertrophic cardiomyopathy – a heart defect characterized by increased thickness of the wall of the left ventricle – progresses.

The researchers reported their findings in the March 13th issue of the *Proceedings of the National Academy of Sciences.*

"The effects of MCIP1 were consistent in blocking enlargement of the heart produced in the several models of cardiac hypertrophy in mice," said Williams. "If you increase the level of MCIP1 above what nature will do, no harmful effects are apparent, and it will prevent

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hypertrophy and heart failure when the heart is presented with a stressful condition," he said.

Heart disease affects some 5 million Americans, and as many as 400,000 new cases of heart failure will be diagnosed in the next year, according to the Heart Failure Society of America. Because its symptoms – fatigue and shortness of breath – are sometimes mistaken as normal signs of aging, many people are unaware that they have heart disease.

"It must still be proven that these findings are relevant to heart disease in humans, but the results suggest that a drug capable of increasing the abundance or function of MCIP1 conceivably could prevent heart failure in at-risk individuals," Williams said. "We need to hunt for ways in which one can increase the function or abundance of MCIP1 in a way that can be transferred safely to humans."

Other UT Southwestern researchers participating in the study were Christopher Antos, student research assistant in molecular biology; Dr. Rhonda Bassel-Duby, associate professor of internal medicine; Drs. Pradeep Mammen and John Yang, postdoctoral trainees in clinical research; Drs. Timothy McKinsey and Rebekka Nicol, postdoctoral researchers in molecular biology; Dr. Eric Olson, chairman of molecular biology; Dr. Beverly Rothermel, assistant professor of internal medicine; John Shelton, research scientist in internal medicine; and Dr. Rick Vega, postdoctoral research fellow in internal medicine.

The study was supported by funds from the National Institutes of Health and UT Southwestern's Donald W. Reynolds Cardiovascular Clinical Research Center, which is headed by Williams. He also directs the Frank M. Ryburn Jr. Cardiac Center at UT Southwestern.

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