Gene therapy to reverse heart failure ready for clinical trials

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A promising gene therapy developed, in part, at Thomas Jefferson University's Center for Translational Medicine to prevent and reverse congestive heart failure is on the verge of clinical trials, after years of proving itself highly effective in the lab and a large animal study.

Reporting in the online July 20 issue of Science Translational Medicine, cardiology researchers have demonstrated feasibility, the long-term therapeutic effectiveness and the safety of S100A1 gene therapy in a large animal model of heart failure under conditions approximating a clinical setting.

"This is the last step you have to take to finish a very long line of research," said Patrick Most, M.D., adjunct assistant professor of medicine at Thomas Jefferson University, and lead author of the study who now heads the Institute for Molecular and Translational Cardiology at the University of Heidelberg, Germany. "The reversal of cardiac dysfunction in this pre-clinical heart failure model in the pig by restoring S100A1 levels in practically the same setting as in a patient is remarkable and will pave the way for a clinical trial."

The therapy works by raising diminished levels of the protein S100A1, a calcium-sensing protein in the diseased heart muscle cell, to normal. Previous research suggests this will prevent against heart failure development, particularly in people who have had a heart attack.

According to Dr. Most, "the therapeutic profile of S100A1 is a unique

one as it targets and reverses the underlying causes of heart failure: progressive deterioration of contractile performance, electrical instability and energy deprivation."

About six million people in the United States have heart failure, and it results in about 300,000 deaths each year.

Work on S100A1 started bench side 15 years ago with Dr. Most and Walter J Koch, Ph.D., now director of the Center for Translational Medicine in the Department of Medicine in Jefferson Medical College of Thomas Jefferson University, who, with his team, have moved the research closer to bedside ever since.

Five years ago, Jefferson researchers showed that increasing levels of the protein above normal helped protect mouse hearts from further damage after simulated heart attacks. The hearts worked better and had stronger contractile force.

"We have pursued a completely different path over the years," said Dr. Most. "We have set up a translational pipeline and don't stick to just one model system. We took it step by step, and did whatever was necessary to go to the next level. We realized early on that a mouse is not a man. You need to design target-tailored translational research strategies and work in human-relevant model systems to take molecular discoveries from bench to bedside.

"With such a translational roadmap at hand, we are in the unique position to accelerate future development of molecular therapies."

In their latest study in *Science Translational Medicine*, Drs. Koch and Most and their team of researchers used a pig model—this type more closely resembles human physiology, function and anatomy—to determine the effectiveness and safety of the S100A1 gene therapy.

Researchers were also able to administer it with certified catheters and delivery routes, just as a human patient would receive it. "We've shown its effectiveness in the lab. It worked in mice and rats, then pigs and now it's ready for humans," Dr Most adds.

Heart failure was induced in the pigs, and at 14 weeks showed significantly decreased S100A1 levels. Treatment, however, with the gene therapy prevented and reversed development of heart failure by restoring the S100A1 protein levels or getting them above normal.

"This therapy gets to the core of the disease," said Dr. Koch, who received the "Outstanding Investigator Award" for 2011 by the International Society for Heart Research for his work in heart failure gene therapy. "They are not just beta blockers or ancillary drugs, which only block the damage. This therapy makes the heart beats stronger and overcomes the damage from previous heart attacks. It's the next great thing in heart failure."

This is the final set of preclinical data needed to apply for investigational new drug status with the U.S. Food and Drug Administration and advance to a phase I clinical trial.

Researchers say one of the next steps is to find industry or private partners to help fund the work, as well as recruit eligible patients to enroll in the clinical trial.

"With National of Institutes of Health money in jeopardy, this could be translated faster with funds from other sources," said Dr. Koch. "It could fund both ongoing research with other targets using our translational roadmap and to take this particular target for heart failure into humans."

Provided by Thomas Jefferson University