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**IN THE PIPELINE: Gene Therapies May Reverse Heart Failure**

**By Dinah Wisenberg Brin**

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Scientists are finding growing evidence that a genetically engineered virus can significantly reverse heart failure.

Two separate groups of researchers using different gene therapies have reported progress recently in reversing heart damage. One group already is testing its treatment in humans and aims to get a product on the U.S. market within a few years; another is testing its therapy in animals and hopes to start human clinical trials in a year or two.

Heart failure, for which there are treatments but generally no cure, affects nearly 5 million Americans, according to the Heart Failure Society of America. The progressive condition, which can lead to transplants and other expensive procedures, costs about \$38 billion annually to treat in the U.S., according to Celladon Corp., a venture-backed concern conducting the gene-therapy human clinical trials.

"We are able to improve the function of the failing heart," said Dr. Roger Hajjar, co-founder of Celladon and director of the Cardiovascular Research Center at Mount Sinai School of Medicine in New York.

By injecting into patients' hearts a genetically altered virus that doesn't cause disease in humans, the Celladon scientists say they are able to replace an enzyme, SERCA2a, that decreases in heart failure. The enzyme is a key driver of calcium movement that drives contraction of heart muscle cells, said Krisztina Zsebo, Celladon's chief executive and president.

Celladon, whose investors include Enterprise Partners Venture Capital, Venrock Associates and Johnson & Johnson's (JNJ) venture capital subsidiary, reported at the American Heart Association Scientific Sessions in November promising results from the first nine advanced-heart-failure patients treated with its Mydicar genetically targeted enzyme replacement therapy.

Celladon said early results from the clinical trial, known as CUPID, or Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease, showed Mydicar was safe and improved cardiac function and the overall condition of some patients; "and this just means an enormous amount to their quality of life," Zsebo said, noting that patients had limited mobility before the treatment.

"It looks like it has a very strong safety profile," she said. The treatment is delivered on an outpatient basis in about a half-hour, with the patient awake and mildly sedated. The positive effects have endured in six- and 12-month followups, according to Zsebo, who said trials of genetically altered virus for other diseases have shown long-lasting effects.

CUPID has dosed 19 patients, aims to complete enrollment in its Phase II study by midyear and is working with about 15 cardiology and heart transplant centers around the U.S., Zsebo said. She noted that the principal investigator, Dr. Mariell Jessup of the Hospital of the University of Pennsylvania, also is an officer of the American Heart Association.

If the treatment proves successful in trials, the earliest a product might be approved for the U.S. market would be 2012 or 2013, unless the government adopts an accelerated approval pace, Zsebo said. European approval could come earlier, as the European Union has a conditional approval process for the sickest patients with no other options, she said. Celladon is preparing briefing packages to submit to European authorities. The company also is seeking to raise private-sector investments.

The gene therapy shouldn't be expensive compared with heart transplants and mechanical hearts, which can cost upwards of \$200,000, Zsebo said.

## Other Therapy

Meanwhile, researchers at Thomas Jefferson University's Center for Translational Medicine in Philadelphia recently published results of a study showing reversal of damage in the hearts of rats treated with a similar noninfectious virus that was genetically engineered to perform a different cellular task. They're now testing the therapy on pigs and sheep.

The virus generates a peptide called BARKct that inhibits activation of a kinase, or enzyme, linked to deterioration of the heart during heart failure, according to center director Walter Koch, whose research team conducted the study. This enzyme, known as GRK2, increases in heart failure.

"Our hypothesis is that if you inhibit this kinase, the heart will do better as far as its contractile function," Koch said. "We've set out to try to correct that at a molecular level."

The research, published recently in *Circulation*, is significant because the team used a virus that stays in the animal permanently, he said.

"It is a simple model in the rat, but we think it is translatable in the human," Koch said.

When the BARKct peptide is in the heart cell, the cell no longer is failing and the heart beats more strongly, Koch said. The sick animal "basically got better, heart function reversed."

The healthier heart then appeared to send signals to other organ systems in the body to correct defects associated with the heart failure, he said. The genetic profiles of the animals were better and fewer toxic genes were being expressed, according to Koch.

"These viruses actually last pretty much forever. They're very stable," he said.

Celladon's Hajjar said Celladon and the Jefferson researchers are using similar viruses to target the heart, while aiming for different physical and functional areas of cardiac cells.

The BARKct peptide is compatible with beta blockers, a standard treatment for heart failure that stops disease progression but doesn't reverse the damage, according to Jefferson's Koch.

Koch hopes to get a clinical trial on humans going in another year or two. He said Genzyme Corp. (GENZ), while not involved with the research, has the license for the peptide, which Koch developed in the 1990s while at Duke University. Genzyme hasn't decided whether to conduct clinical trials or take any other steps to advance the research, a spokeswoman said.

"We think it's interesting. We're evaluating it, but we haven't made any decisions yet," said Erin Emlock of Genzyme.

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