Researchers develop new gene therapy for heart failure

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Researchers at Mount Sinai School of Medicine have found in a Phase II trial that a gene therapy developed at Mount Sinai stabilized or improved cardiac function in people with severe heart failure. Patients receiving a high dose of the therapy, called SERCA2a, experienced substantial clinical benefit and significantly reduced cardiovascular hospitalizations, addressing a critical unmet need in this population. The data are published online in the June 27 issue of the American Heart Association journal *Circulation*.

SERCA2a is delivered via an adeno-associated virus vector—an inactive virus that acts as a medication transporter—into cardiac cells. The therapy stimulates production of an enzyme within these cells that enables the heart to pump more effectively in people with advanced heart failure. After one year, patients who were administered a high dose SERCA2a demonstrated improvement or stabilization. Gene therapy with SERCA2a was also found to be safe in this sick patient population, with no increases in adverse events, disease-related events, laboratory abnormalities, or arrhythmias compared to placebo.

"Few treatment options have shown such improved clinical outcomes in this patient population in the last decade," said Roger J. Hajjar, MD, Research Director of Mount Sinai's Wiener Family Cardiovascular Research Laboratories, and the Arthur and Janet C. Ross Professor of Medicine, and Gene and Cell Medicine, Mount Sinai School of Medicine. "This study establishes a new paradigm for the treatment of heart failure by clinically validating SERCA2a as a novel target. In

addition, by showing that adeno-associated vectors are safe to use in patients with advanced heart failure, this study ushers a new era for gene therapy for the treatment of failing hearts."

The CUPID (Calcium Up-regulation by Percutaneous administration of gene therapy In cardiac Disease) trial is a randomized, double-blind, placebo-controlled study, which enrolled 39 patients with advanced heart failure to study the safety and efficacy of SERCA2a. Patients were randomized to receive SERCA2a gene delivery in one of three doses or placebo, and were evaluated over one year. The treatment is delivered directly to the patient's heart during a routine outpatient cardiac catheterization procedure.

Patients in the high-dose SERCA2a group demonstrated improvement and/or stabilization in symptoms, overall heart function, biomarker activity, and ventricular mechanics and function. They also saw a dramatic reduction in cardiovascular hospitalizations, averaging 0.4 days versus 4.5 days in the placebo group.

"Even though heart failure mortality has decreased over the last decade with the help of standard pharmacological and device therapies, patients with advanced heart failure continue to die at high rates. The CUPID trial offers a new therapeutic option for these patients," said Dr. Hajjar.

Led by Dr. Hajjar, the Mount Sinai team discovered the landmark potential of the cardiac-specific target in 1999 and has been pursuing its potential as a treatment delivered via gene therapy in state-of-the-art custom built laboratories at Mount Sinai School of Medicine in New York.

According to the U.S. Centers for Disease Control and Prevention, about 5.8 million Americans suffer from heart failure, and 670,000 new cases are diagnosed each year. One in five people who have heart failure die

within one year of diagnosis. In 2010, heart failure will cost the United States $39.2 billion, including the cost of health care services, medications, and lost productivity. Heart failure is most often treated with aggressive medical and device therapy, but has no cure. The most common symptoms of heart failure are shortness of breath, feeling tired, and swelling in the ankles, feet, legs, and sometimes the abdomen.

Provided by The Mount Sinai Hospital