

Promising new drug target discovered for treatment and prevention of heart failure

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A promising new drug target for the treatment and prevention of heart failure has been discovered by researchers at Mount Sinai School of Medicine in New York, NY, US. The study was presented at the ESC Congress 2012 by principal investigator Professor Roger J. Hajjar, MD.

According to the US 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 with heart failure die within one year of diagnosis. 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.

In this study presented at the ESC Congress 2012, researchers identified a new [drug target](#) that may treat and/or prevent heart failure. The team evaluated failing human and pig hearts and discovered that SUMO1 (small ubiquitin-like modifier), a small protein that regulates the activity of key transporter genes, was decreased in failing hearts. When the researchers injected SUMO1 into these hearts via gene therapy, [cardiac function](#) was significantly improved.

"This indicates that SUMO1 may play a critical role in the pathogenesis of heart failure," said Professor Hajjar, who is research director of Mount Sinai's Wiener Family [Cardiovascular Research Laboratories](#).

Led by Professor Hajjar, the team has been evaluating the transporter gene SERCA2a in patients with severe heart failure as part of the CUPID (Calcium Up-regulation by Percutaneous administration of gene therapy In [cardiac Disease](#)) trial. When delivered via an adeno-associated [virus vector](#)—an inactive virus that acts as a medication transporter—into [cardiac cells](#), SERCA2a

demonstrated improvement or stabilisation with minimal side effects. But Professor Hajjar said: "We found that while injection with SERCA2a restored cardiac function, over time the new SERCA2a became dysfunctional. This indicated that something else upstream from SERCA2a was causing the dysfunction in the heart."

Dr Changwon Kho, PhD, and Dr Ah Young Lee, PhD, two experts in the study of cardiac proteins at Mount Sinai School of Medicine, identified SUMO1 as the regulator of SERCA2a, showing that it enhanced its function and improved its stability and enzyme activity. When Professor Hajjar and his team studied human and animal models, they found that when SUMO1 was decreased, SERCA2a became dysfunctional in human hearts, showing that SUMO1 plays a protective role. When the team injected SUMO1 as a gene therapy, they found that it protected SERCA2a from oxidative stresses that are prevalent in heart failure.

"Our experiments over the last four years beginning with the discovery of SUMO1 as an interacting protein of SERCA2a have shown that it plays a critical role in the development of heart failure," said Professor Hajjar. "In fact, SUMO1 may be a therapeutic target at the earliest signs of development and may be beneficial in preventing its progression, a much needed advance for the millions suffering from this disease."

Dr Lisa Tilemann extended the experiments performed in mice and rats in a preclinical model of heart failure in porcine models.

Professor Hajjar said: "We have now clearly shown that SUMO1 gene delivery can enhance cardiac function and stabilize the deteriorations of left ventricular volumes in large animals with severe heart failure. We have also shown that delivering SUMO1 and SERCA2a concomitantly can have synergistic benefits on overall function in heart failure."

Led by Professor Hajjar, the Mount Sinai team discovered the landmark potential of SERCA2a in 1999 and since then has been pursuing its potential as a treatment delivered via gene therapy. The next stages in the research include testing a novel gene therapy construct which will combine both SUMO1 and SERCA2a within one gene therapy vector that will enable the investigators to express both genes simultaneously. Similar to their efforts in the CUPID trial they will explore the delivery of SERCA2a and SUMO1 via [gene therapy](#). Additionally, the research team has developed a cellular test to screen for compounds that may increase the interaction of SERCA2a with SUMO1, evaluating SUMO1 as an adjunctive therapy to SERCA2a.

Professor Hajjar concluded: "While this study re-affirms the importance of SERCA2a as a target in heart failure, our discovery of the critical role that SUMO1 plays in improving SERCA2a function in heart failure will hopefully lead to novel treatment strategies for patients with [heart failure](#)."

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