Dr. Roger J. Hajjar of the Mount Sinai School of Medicine will present at the ASGCT 15th Annual Meeting during a Scientific Symposium entitled: *Cell and Gene Therapy in Cardiovascular Disease* on Wednesday, May 16, 2012 at 8:00 am. Below is a brief preview of his presentation.

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**Novel Developments in Gene Therapy for Cardiovascular Diseases**

Chronic heart failure is a leading cause of hospitalization affecting nearly 6 million people in the U.S. with 670,000 new cases diagnosed every year. Heart failure leads to about 280,000 deaths annually. Congestive heart failure remains a progressive disease with a desperate need for innovative therapies to reverse the course of ventricular dysfunction. The most common symptoms of heart failure are shortness of breath, feeling tired and swelling in the ankles, feet, legs and sometimes the abdomen. Recent advances in understanding the molecular basis of myocardial dysfunction, together with the evolution of increasingly efficient gene transfer technology have placed heart failure within reach of gene-based therapies.

One of the key abnormalities in both human and experimental HF is a defect in sarcoplasmic reticulum (SR) function, which controls Ca\(^{2+}\) handling in cardiac myocytes on a beat to beat basis. Deficient SR Ca\(^{2+}\) uptake during relaxation has been identified in failing hearts from both humans and animal models and has been associated with a decrease in the activity of the SR Ca\(^{2+}\)-ATPase (SERCA2a).

Over the last ten years we have undertaken a program of targeting important calcium cycling proteins in experimental models of heart by somatic gene transfer. This has led to the completion of a first-in-man phase 1 clinical trial of gene therapy for heart failure using adeno-associated vector (AAV) type 1 carrying SERCA2a. In this Phase I trial, there was evidence of clinically meaningful improvements in functional status and/or cardiac function which were observed in the majority of patients at various time points. The safety profile of AAV gene therapy along with the positive biological signals obtained from this phase 1 trial has led to the initiation and recent completion of a phase 2 trial of AAV1.SERCA2a in NYHA class III/IV patients. In the phase 2 trial, gene transfer of SERCA2a was found to be safe and associated with benefit in clinical outcomes, symptoms, functional status, NT-proBNP and cardiac structure.

The 12 month data presented showed that heart failure, which is a progressive disease, became stabilized in high dose AAV1.SERCA2a-treated patients: heart failure symptoms, exercise tolerance, serum biomarkers and cardiac function essentially improved or remained the same while these parameters deteriorated substantially in patients treated with placebo and concurrent optimal drug and device therapy. More recently, the 2-year CUPID data from long-term follow-up demonstrate a durable benefit in preventing major cardiovascular events.

The recent successful and safe completion of the CUPID trial along with the start of more recent phase 1 trials usher a new era for gene therapy for the treatment of heart failure. Furthermore, novel AAV derivatives with high cardiotropism and resistant to neutralizing antibodies are being developed to target a large number of cardiovascular diseases.