Cell & Gene Therapy for Heart Failure

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While progress in conventional treatment modalities is making steady and incremental gains to reduce heart failure (HF) mortality, there remains a need to explore new and potentially therapeutic approaches. HF induced by genetic or specific conditions such as coronary artery disease, hypertension, diabetes, infection, or inflammation results in myocardium with a mixture of replacement fibrosis, dysfunctional, and normal myocytes. The normal myocytes that remain are under continuous stresses from hormonal and physical stimuli that can induce apoptosis and cell death or render them dysfunctional, and their preservation is the target of current therapies with neurohormonal blockade. Future HF therapy will be composed of efforts to "regenerate" the myocardium, with the target for stem cell therapy the replacement of lost myocytes, and the target for gene therapy the dysfunctional myocytes and the preservation of function for non-diseased myocytes. Recent advances in understanding of the molecular basis of myocardial dysfunction, together with the evolution of increasingly efficient gene transfer (GT) technology, has placed some cardiovascular pathophysiologies within reach of gene-based therapy.

One of the key abnormalities in both human and experimental HF is a defect in sarcoplasmic reticulum (SR) function, which is responsible for abnormal intracellular calcium handlin. 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 expression and activity of SR Ca^{2+}-ATPase (SERCA2a). Our preclinical laboratory is continuing to develop new vectors for GT, namely adeno-associated virus to enable long term expression and new techniques of GT in large models that can be readily applicable to humans. *We are initiating a Phase 1 clinical trial of dose escalation of AAV1.SERCA2a that will determine the optimal safe dose of AAV1 vector to be used in the Phase 2 trial described in this proposal.* This phase 2 trial will test the hypotheses that restoring SERCA2a levels by GT will improve ventricular function in patients with advanced HF and lead to improved exercise capacity.