

Preclinical Development of Gene Therapy

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VALORIZATION ADDENDUM

Patients with congestive heart failure (CHF) who have symptoms with mild activity or at rest (Class III and Class IV) have a poor long-term outcome, with up to 50% of patients dying within four years of symptom onset despite optimal pharmacological and device therapy. Heart transplantation has an 80% 5-year survival rate, but fewer than 2500 cardiac transplants are performed in the US each year, where the prevalence for CHF is estimated at 5.1 million patients, and 900,000 new cases are diagnosed annually. Angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, β -adrenergic receptor (β AR) antagonists, aldosterone inhibitors, implanted defibrillators, and biventricular pacing devices have improved survival — the 50% survival time in 1980 was 18 months while nowadays is 5 years. However, even with optimal medical and device management, heart failure is an inexorable disease associated with unacceptably high morbidity and mortality. Because the prevalence of CHF is increasing, and outlook remains dismal, we need new advances in heart failure treatment.

Although heart failure traditionally is defined as reduced contractile function, left ventricle (LV) dilation, and reduced ejection fraction, there is a growing epidemic of heart failure accompanied by preserved ejection fraction (HFpEF) and aging has been defined as one factor in the HFpEF epidemic. Echocardiographic studies often reveal normal or near-normal ejection fraction in elderly patients with heart failure, with abnormal diastolic relaxation and LV filling and cardiovascular stiffness.

Gene transfer for the treatment of cardiovascular diseases is justified because there is an unmet medical need for treating diastolic dysfunction, and, at least in theory, gene transfer has much to offer to reduce morbidity and mortality in patients with HFpEF. Cardiovascular gene transfer is conceptually attractive, but difficulty in obtaining high yield transgene expression in the heart in a manner that can be easily and safely applied has been a chief impediment to progress. Current methods of gene transfer for heart disease include intramuscular injection into heart muscle or intracoronary delivery, approaches that provide limited expression, and are cumbersome to apply. In previous studies and also in those presented in this thesis, we have discovered the usefulness of intravenous injection of a vector encoding a paracrine transgene. In this approach, the transgene encoding urocortin 2 or urocortin 3 peptide that act as hormones, having cardiac effects after being released to the circulation from a distant site. This approach would circumvent the problem of attaining high yield cardiac gene transfer and enable patients to be treated by a simple intravenous injection during an office visit.

Findings presented in this thesis are important and promising steps towards Ucn2 and Ucn3 gene transfer translation to clinical applications. It is verified that gene transfer of Ucn2 increased systolic and diastolic function in normal mice and in mice with age-related diastolic dysfunction. Additionally, Ucn2 gene transfer was able to decrease fasting glucose and improve glucose disposal in normal and diabetic mice, unlike Ucn3 gene transfer. Therefore, gene transfer of Ucn2 could be a viable treatment for elderly patients with either

systolic or diastolic dysfunction and also for patients with HF and diabetes. Ucn3 gene transfer was able to increase both systolic and diastolic function in normal young mice and also in a murine model of HFrEF, however it did not affect glucose homeostasis. According to these observations, Ucn3 gene transfer may be a viable treatment for HFrEF patients without diabetes. Verification of diastolic function improvement by Ucn3 gene transfer in undergoing studies using aged animals could further suggest its potential to be used as HFpEF treatment.

There are specific issues and requirements that will have to be addressed prior to the initiation of a clinical trial. Initially, the safety of our gene transfer approach has to be verified. It is necessary to meticulously investigate potential adverse effects caused by the sustained increases in plasma Ucn2 and Ucn3. We have recently accomplished this step via a biodistribution and toxicology study in which we tested the long term and dose related effects of Ucn2 gene transfer. A similar study testing Ucn3 gene transfer will be launched in the near future. Another important milestone that needs to be achieved is to prove that intravenous administration of an AAV8 encoding Ucn2 or Ucn3 gene transfer in different, preferably larger, species will still result in sustained elevation of plasma levels of Ucn2 or Ucn3. Additionally, we need to verify that elevation of plasma Ucn2 and Ucn3 can cause increases in systolic and diastolic heart function in normal animals, but most importantly in HF animal models different than mice. In the case that Ucn2 gene transfer is intended to be used as diabetes treatment, similar efficacy studies in different species with diabetes will also be required. If there is no observation of adverse effects in the biodistribution and toxicology study and the beneficial effects of Ucn2 and Ucn3 gene transfer are verified in a second animal model, there are great chances to get approval for the investigational new drug (IND) application. That will allow us to begin clinical studies and test the safety and efficacy of our gene therapy in human subjects.