Heart Failure

A Silver bullet to treat heart failure

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Heart failure (HF) continues to be a progressive disease with ever increasing morbidity and mortality in the western world.¹ While progress in conventional treatment modalities is making steady and incremental gains to reduce HF mortality, there remains a need to explore new and potentially therapeutic approaches.¹ To that end, several animal models of heart failure have been used to test these novel therapies. A genetic strain of Syrian hamsters with a large deletion in the δ -sarcoglycan (SG) gene (TO-2 strain), are characterized by skeletal muscle myopathy, and severe cardiac dilation and cardiomyopathy, which primarily contributes to the very high mortality in these animals.² In a recent study, Zhu *et al.*³ reported that a single injection of adeno-associated type-8 vector carrying the human δ -SG gene enhanced contractile function in the hearts of these diseased hamsters, restored exercise capacity and survival to normal, and improved skeletal muscle function.

In these studies, the investigators used a novel AAV serotype, namely type 8, which they had previously shown to be highly efficient in crossing the blood vessel barrier and having great efficiency in transducing skeletal and cardiac muscles.⁴ Different AAV serotypes have different tropisms to various organs^{5,6} but the features of AAV8 made this specific vector ideal for targeting a disease state such as limb girdle muscular dystrophy (LGMD) that affects both cardiac and skeletal muscles. The authors further refined their AAV8 constructs by incorporating a double-stranded DNA vector for speedier and stronger expression and by using the synthetic muscle-specific promoter (SP) C5-C27.³ The experiments were carried out in neonates and in adult animals. In both groups, the reversal of cardiac and skeletal abnormalities were dramatic showing that gene transfer of the human SG gene by AAV8 pre-

vented the development of heart failure and skeletal abnormalities. One of the most exciting results was that long-term human δ -SG expression in these animals led to the prolongation of the lifespan of the diseased animals. In fact, TO-2 hamsters died of heart failure at 32–43 weeks of age (median survival time, 37 weeks), however, all of the AAV8-treated TO-2 hamsters survived beyond 48 weeks.

LGMD, however, represents only a very small fraction of HF in the general population.⁷

Most HF patients have various etiologies including coronary artery disease, hypertension, valvular disease, diabetes, infection, infiltrative syndromes or inflammation resulting in a myocardium with a mixture of replacement fibrosis, and dysfunctional myocytes.⁸ The abnormal contraction in these cardiomyocytes is caused by a wide variety of molecular changes with the dysregulation of thousands of genes.^{8,9} There are several mechanisms, however, that seem to be central to the pathogenesis of contractile dysfunction in heart failure. These include: (1) a defect in sarcoplasmic reticulum function, which is responsible for abnormal intracellular calcium handling, (2) activation of pro-apoptotic pathways, (3) dysregulation of beta adrenergic signaling, and (4) electrical remodeling.^{8,9} Targeting these pathways by gene transfer seems to improve overall function in failing hearts. Advances in the understanding of the molecular basis of myocardial dysfunction has, together with the evolution of increasingly efficient gene transfer technology, placed some cardiovascular pathophysiologies within reach of gene-based therapy.

The results of Zhu *et al.*³ will clearly pave the way for clinical gene therapy trials using AAV8 and δ -SG gene in human LGMD. More generally, it will allow new strategies with this and other novel vectors to be used to modulate various path-

ways in the more common forms of heart failure, ultimately providing novel therapeutic approaches for the management of the majority of heart failure patients. The recent description of AAV9 which has even higher cardiac tropism will further the drive towards clinical gene therapy for heart failure. ■

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