Somatic gene therapy to treat heart failure is one step closer to reality

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This editorial refers to 'Prevention of cardiomyopathy in δ-sarcoglycan knockout mice after systemic transfer of targeted adeno-associated viral vectors' by C. Goehringer et al.,6 pp. 404–410, this issue.

Despite recent advances in heart failure therapy, patients with end-stage cardiac failure have a poor prognosis and die within 5 years. Diagnosis of the hereditary form of heart failure is becoming increasingly prevalent due to the identification of causative mutations in many structural genes encoding contractile and cytoskeletal proteins. The majority of muscular dystrophies including Duchenne muscular dystrophy (DMD) cause functional deficits not only in skeletal muscle but also in cardiac muscle since the proteins affected are normally present in all striated muscle. DMD is caused by mutations in the very large dystrophin gene. Dystrophin binds the submembranous cytoskeleton at one end and at the other end to a complex of membrane glycoproteins (Figure 1) called the dystrophin-associated glycoprotein complex (DGC). The DGC plays an essential role in maintaining the integrity of the cell membrane by forming a structural link between the extracellular matrix and the cytoskeleton, and in this way, the entire complex transduces the force of contraction and thereby protects the cell membrane from damage. Mutations in dystrophin and several other members of this complex, known as the sarcoglycans, destabilize the entire complex from the membrane and cause both skeletal and cardiac myopathies characterizing DMD and limb-girdle muscular dystrophies. In addition to causing muscular dystrophies, certain mutations in dystrophin and DGC lead primarily to cardiomyopathy. Dystrophin has also been shown to be present at reduced levels in human end-stage heart failure samples that do not have reductions in other cell membrane complexes, suggesting an even more prevalent role of this complex in heart failure.1

Patients with DMD or limb-girdle muscular dystrophies usually die from respiratory or cardiac failure and there are currently no long-term effective treatments for these diseases. During the last decade, gene therapy approaches for the treatment of DMD and the limb-girdle muscular dystrophies have been actively pursued in several disease models. They are an ideal target due to the prevalence of childhood mortality, the recessive nature of the diseases, and the wealth of animal models, reagents, and outcome measures available to test potential treatment approaches. The major advances of this research have led to curing muscular dystrophy by gene therapy in many mouse models.2,3 However, the major obstacle remaining for clinical efficacy is a systemic approach that can deliver a gene to the massive amount of skeletal muscle throughout the human body. Until recently, the other major obstacle was that of an immune response being elicited by the gene therapy vehicle. However, recombinant adeno-associated virus (rAAV) has shown great promise in this direction; wild-type AAV is a non-pathogenic virus in humans and in comparison to other vectors such as adenovirus, the rAAV capsid proteins cause relatively low immune responses. Another advantage is that rAAV vectors can display extremely stable expression in vivo, lasting the lifetime of mice and several years in larger animals.4 Moreover, rAAV vectors have been utilized in several clinical trials for various diseases without report of any serious adverse reactions.5

In this issue of Cardiovascular Research, Goehringer et al.6 address the prospects of gene therapy in treating the cardiomyopathy caused by deficiency of the δ-sarcoglycan protein. Heart is a much more readily targetable organ than skeletal muscle due to its compact size and the availability of cardiac-specific gene promoters. Years of refinement of gene therapy approaches in animal models together with transgenic studies showing sufficiency of re-expression of the missing gene in cardiomyocytes to rescue cardiomyopathy associated with these diseases have provided the foundation for pre-clinical gene therapy studies to improve cardiac function.7–11 These factors combined with increased recognition of heart failure in muscular dystrophy patients have resulted in mouse studies that demonstrate high-level gene expression and long-term efficacy of gene therapy for cardiomyopathy.12–14

The article in this issue by Goehringer et al.6 takes the cardiac gene therapy field one step further; in this study,
the authors employed rAAV-9 vectors but chose to drive the expression of the δ-sarcoglycan gene under the control of the cardiac muscle-specific myosin light-chain-2v gene promoter which is restricted to the heart tissue. Systemic delivery of this vector in a δ-sarcoglycan knockout mouse model showed that the sarcoglycan complex is reconstituted in the heart but not in skeletal muscle. Their study nicely demonstrates that rAAV gene therapy can prevent cardiomyopathy and improve ventricular function and exercise performance in this mouse model 6 months after the treatment. Although no data at time points after 8 months-of-age are included, these results are highly promising and suggest that somatic gene therapy to treat heart failure is one step closer to reality. This type of gene therapy targeted to cardiac muscle causes pathology.

With the many clinical trials currently ongoing using rAAV as a vehicle (clinicaltrials.gov), the overall clinical promise of this delivery system will soon be known. Clinical utility of this method will rapidly transform the vast amount of knowledge generated by pre-clinical studies in genetic animal models into a new age of personalized medicine. However, some challenges remain for rAAV gene therapy before it can become widely applicable to treat hereditary cardiomyopathies in patients. Expression constructs must be optimized when the entire protein coding sequence of the sarcoglycan-deficient cardiomyopathy.15

sufficient quantities for uniform expression throughout the heart must be achieved. However, this last challenge may be less of an issue when targeting cardiac muscle because of the ability to directly deliver vectors using catheters and the use of tissue-specific promoters optimized for cardiac expression as shown in this latest study.

References