CARDIAC AAV6-BETAARKCT GENE THERAPY RESCUES FAILING MYOCARDIUM AND NORMALIZES NEUROHORMONAL SIGNALING IN A CLINICALLY RELEVANT SWINE HEART FAILURE MODEL

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Background: Failing myocardium is characterized by marked upregulation of G protein-coupled receptor kinase 2 contributing to dysfunctional beta-adrenergic receptor (betaAR) signalling and cardiac dysfunction. The GRK2-inhibitor peptide betaARKct could rescue disparate small animal heart failure models. This study was designed to evaluate long-term betaARKct expression in a clinically relevant large animal heart failure model with the use of stable myocardial gene delivery with adeno-associated virus serotype 6 (AAV6).

Methods: A porcine model of left ventricular myocardial infarction was used. Two weeks after left circumflex myocardial infarction we measured baseline cardiac function (hemodynamics, echocardiography) and delivered AAV6-betaARKct (n=8) or AAV6-Luciferase (n=8) as control by retrograde injection into the anterior interventricular vein. 6 weeks later, cardiac function was assessed and hearts were harvested for further analyses.

Results: Robust and long-term betaARKct expression was found after AAV6 mediated delivery. Interestingly, AVV6-betaARKct gene transfer significantly improved left ventricular hemodynamics and ejection fraction, whereas in AAV6-Luciferase treated control animals a decline in cardiac function was observed. The neurohormonal axis was virtually normalized in AAV-betaARKct treated animals, represented by reductions in plasma normetanephrine and plasma brain natriuretic peptide levels. Furthermore, significant repression of adverse left ventricular remodelling was observed after betaARKct treatment represented by reduction in heart-to-body weight ratio and repression of the activation of the fetal gene program (atrial natriuretic factor, beta-myosin heavy chain).

Conclusions: Myocardial AAV6-betaARKct gene therapy in a clinically relevant large animal heart failure model resulted in sustained improvement of global cardiac function, normalization of the neurohormonal signalling axis, and repression of adverse left ventricular remodelling.