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CARDIAC FUNCTION AND HEART FAILURE

CARDIAC-TARGETED AAV-S100A1 HEART FAILURE GENE THERAPY: TRANSLATION OF A NOVEL MOLECULAR TARGET TOWARDS CLINICAL CARE

ACC Poster Contributions
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Session Title: Emerging Nonpharmacological Treatment for Heart Failure
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Authors: *Sven T. Pleger, Jan Kszienyk, Raffi Bekeredjian, Gang Qiu, Christophe Weber, Hugo Katus, Walter J. Koch, Oliver Müller, Patrick Most, Center for Molecular and Translational Cardiology, Internal Medicine III, University of Heidelberg, Heidelberg, Germany, Center for Translational Medicine, Dept. of Medicine, Thomas Jefferson University, Philadelphia, PA*

Background: Heart failure (HF) is a major cause of morbidity and mortality in western societies. This dilemma reflects a lack of innovative therapies targeting the underlying root causes of the disease. A key underpinning of HF is the depletion of S100A1 in cardiomyocytes, which results in abnormal intracellular calcium (Ca2+) cycling and poor contractility. As a prerequisite to clinical application, we sought to determine therapeutic effectiveness and safety of S100A1 gene therapy using adeno-associated viral serotype 9 (AAV9) in a preclinical large animal HF model recapitulating the human HF phenotype.

Methods and Results: HF in domestic pigs was induced by ballon-occlusion of the left circumflex coronary artery (LCx) resulting in myocardial infarction (MI). 2 weeks post-MI, when infarcted animals (n=32) displayed significant left ventricular (LV) contractile dysfunction compared to sham-operated (n=13) animals, retrograde coronary venous delivery of AAV9-S100A1 (1.5x1013 viral particles, n=9) to LV non-infarcted remote myocardium was performed while AAV9-luciferase (AAV9-luc, n=9) and saline (n=14) treatment served as control. At 14 weeks post-MI, both HF-control groups showed significantly decreased myocardial S100A1 protein along with progressive deterioration of cardiac performance, LV hypertrophy and sympathetic activation. In contrast, AAV9-S100A1 treated HF swine exhibited enhanced cardiac S100A1 protein levels resulting in significantly improved cardiac performance, reversed LV remodeling, improved inotropic reserve in response to dobutamine and restored cardiac energetics at whole heart and isolated cardiomyocyte level. Cardiac-restricted transgene expression and uncompromised extra-cardiac organ function indicated a favorable safety profile.

Conclusions: Our translational study shows long-term therapeutic effectiveness and a favorable safety profile of AAV9-S100A1 gene therapy in a preclinical HF model emanating from the unique molecular profile of S100A1. Employing cardiac-targeted gene delivery techniques and a gene dosage directly applicable to humans, these results pave the way for clinical application of S100A1 gene therapy in human HF.