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Pilot study to engage the Apelin-MEF2 signaling axis for myocardial preservation in a large animal model of right ventricle failure

INTRODUCTION:
Current therapies for pulmonary arterial hypertension (PAH) have largely neglected the role of right ventricular (RV) preservation in improving clinical outcomes associated with the disease. This proposal will utilize a highly innovative and translational large animal model to investigate the therapeutic efficacy of a novel strategy to preserve the RV function in PAH.

BACKGROUND:
Despite the existence of multiple FDA approved therapies for PAH, along with a wide body of literature demonstrating therapeutic efficacy of various molecular targets in small animal experimental models of PAH, there remains a clear, unmet need for novel strategies in our clinical management of disease, based on the fact that: 1) mortality remains remarkably high (up to 45% at 3 years after diagnosis), and 2) rodent based experimental models face a significant hurdle in translating to human efficacy. Moreover, the preservation of RV function, which in many aspects is the ultimate determinant of clinical outcome in PAH, is not targeted by any of the existing therapies. A number of molecular therapeutic targets have been identified through the use of experimental models and human patient samples. One such pathway is that represented by the GPCR pathway involving the ligand apelin and its receptor APLNR, and its downstream activation of the transcription factor myogenic enhancer factor-2 (MEF2). With respect to apelin, 1) circulating levels of apelin have been demonstrated to be decreased in multiple cohorts of PAH subjects, 2) apelin knockout mice develop worsening PAH, and 3) exogenous apelin can effectively rescue multiple models of PAH. Studies on MEF2 have also identified it to be a critical transcription factor that is impaired in PAH, and importantly, its activation can be achieved by either exogenous apelin, or by selective inhibitors of class IIa histone deacetylases (HDAC), which serve as negative regulators of MEF2 via direct protein-protein interaction. In particular to the RV, apelin expression has been found to be remarkably downregulated in RV failure, while mice with genetic deletion of either APLNR or MEF2 develop spontaneous RV failure, supporting a key potential role of augmenting this pathway as a strategy to preserve RV function.

HYPOTHESIS AND OBJECTIVES:
We hypothesize that engagement of the apelin-MEF2 signaling axis will achieve preservation of RV function in PAH. In this highly innovative, translational project, we will utilize a unique and clinically relevant pulmonary artery (PA) banding model in pigs to investigate the feasibility and efficacy of pharmacologically engaging the apelin-MEF2 axis to preserve RV function, perfusion and hemodynamics.

SPECIFIC AIM 1:
Establish the efficacy of PA banding in promoting RV failure in a chronic pig model.

SPECIFIC AIM 2:
Investigate the efficacy of liposomal nanoparticle encapsulated apelin in the preservation of RV function and perfusion.

SPECIFIC AIM 3:
Determine the efficacy of activating MEF2 via HDAC class IIa inhibition in RV preservation.