



Embracing the Potential of
**YOUNG
INVESTIGATORS**

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Investigating Altered Right Ventricular Myocardial Gene Expression and Biomarkers Patterns Associated with Adaptive and Maladaptive Remodeling in Diverse Human Models

INTRODUCTION AND BACKGROUND:

The mechanisms of adaptive remodeling and pathologic right ventricular (RV) remodeling, which lead to preserved RV function (pRV) or RV failure (RVF) respectively, are poorly understood despite RVF being the primary cause of hospitalization and mortality in PAH. The molecular mechanisms that drive adaptive and pathologic RV remodeling in PAH have remained incompletely characterized due to lack of tissue availability, particularly for pRV. However, given that previously implicated pathways in RV remodeling appear to be involved in multiple etiologies, we will use the availability of RV tissue from left ventricular failure (LVF) to our advantage. From more than 150 ischemic (ICM) and 200 dilated cardiomyopathy (DCM) patients in the Penn Human Heart Tissue Bank, we will identify pRV and RVF using preexplant hemodynamics and compare to nonfailing (NF) controls as a discovery cohort. We will leverage ongoing bulk RNAseq to identify representative age, gender, and ethnicity-matched DCM-pRV, DCM-RVF, ICM-pRV, and ICM-RVF samples to assess using a single nuclear RNAseq method sNucDrop-seq. sNucDrop-seq will provide unique insight into cell population source for differential gene expression, the role of cardiomyocyte and noncardiomyocyte heterogeneity in adaptive and pathologic remodeling, and uncover the role of noncardiomyocyte cell populations that can be averaged out at the bulk RNAseq level.

Next, novel RV remodeling targets will be tested against clinically used and recently identified biomarkers of ventricular remodeling (NT-proBNP, MMP1, MMP9, and GAL3) using echocardiographic indices of RV remodeling and function in two pediatric cohorts. The first will be comprised of Nice classification group 1 PAH serum and the second will be comprised of serial tetralogy of Fallot (TOF) preoperative serum, RV tissue collected at surgery, and serum at one year follow up.

OBJECTIVES:

Through these studies, we hope to identify novel prognostic and therapeutic targets of RV remodeling, which will have broad applicability across multiple etiologies and demographics groups, and will ultimately lead to improved clinical outcomes for all patients with RVF.

SPECIFIC AIM 1:

Determine the cell-specific transcriptional signature of RV myocardium in pRV and RVF in the setting of LVF as a discovery cohort.

SPECIFIC AIM 2:

Test novel, cardiomyocyte and non-cardiomyocyte RV remodeling expression targets and biomarkers in pediatric PAH and TOF.