



Embracing the Potential of
**YOUNG
INVESTIGATORS**

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Biomarker Discovery in Portopulmonary Hypertension

INTRODUCTION:

Pulmonary arterial hypertension (PAH) is a vascular disease characterized by progressive narrowing of the small pulmonary arteries. Portopulmonary hypertension (PoPH) is a type of PAH that occurs exclusively in patients with underlying liver disease, affecting up to 10% of all patients undergoing liver transplantation and exhibiting the highest morbidity and mortality of all PAH subtypes.

BACKGROUND:

Liver sinusoidal endothelial cell (LSEC) and pericyte injury are believed to play a central role in disease pathogenesis, potentially through the release of inflammatory vasoactive mediators acting on the matrix metalloproteinase 9 (MMP-9) and bone morphogenetic protein 9 (BMP-9) pathways, but the specific gene expression profiles, potentially mechanistic upregulated biochemical processes, and corresponding biomarkers unique to these cells in PoPH patients have not yet been studied. The advent of single-nucleus RNA sequencing (snRNAseq) technology provides an unparalleled opportunity to study the genetic profile of specific PoPH cellular populations in their native niche with an unprecedented degree of detail, allowing for the identification of transcriptomic profiles, signaling pathways, and potential circulating biomarkers that may be responsible for driving PoPH disease pathogenesis. We are in a unique position to apply this breakthrough technology to the study of hepatic endothelial and stellate cells in PoPH, which to our knowledge has not yet been attempted. We have recently completed snRNAseq on liver tissue obtained intraoperatively from a 55-year-old female with PoPH and identified a number of differentially expressed genes known to be associated with PAH endothelial cells (including epidermal and platelet-derived growth factor, genes for the Ras and metalloproteinase signaling pathways, and endoglin, an inhibitor of BMP-9) in both LSEC and pericyte cell populations.

HYPOTHESIS AND SPECIFIC AIMS:

We propose using snRNAseq to isolate and characterize gene expression patterns, signaling pathways, and receptor/ligand interactomes that are unique to PoPH and correspond to the MMP-9 and BMP-9 pathways; identify circulating biomarkers corresponding to these patterns; and validate the diagnostic and prognostic value of these biomarkers using the resources of the PAH Biobank.