**Poster Abstract Submission for 2024 Indiana CTSI Annual Meeting**

|  |  |
| --- | --- |
| Poster Title: | Activation Of The Mitochondrial Unfolded Protein Response (uprMt) Promotes Vascular Remodeling In Pulmonary Arterial Hypertension. |
| Poster Presenter: | Last Name: Ssendawula  First Name: Arthur |
| Poster Presenter Institution: | Indiana University Indianapolis |
| Poster Authors: (please provide all authors’ names and institutions) | A. Ssendawula, A. Snow, T. Mubuuke, R. F. Machado, A. Lockett |

Please enter your poster abstract in the text box below. Use the subheadings listed. Do not remove any of the subheadings. Please limit your abstract to no more than 300 words (subheadings do not count against the 300-word limit). Upload the completed abstract with your poster submission in the REDCap poster submission survey.

|  |
| --- |
| Background/Significance/Rationale: Pulmonary Arterial Hypertension (PAH) is a severe and progressive disease which results in death due to increased pulmonary vascular resistance that leads to right heart failure. Increased vascular resistance occurs as a result of pulmonary arterial smooth muscle cells (PASMCs) and endothelial cells (PAECs) undergoing changes in intracellular signaling that leads to a proliferative, apoptosis resistant phenotype that causes remodeling and occlusion of the pulmonary vasculature. We demonstrated that the sphingosine-1-phosphate (S1P)/sphingosine kinase 1(SPHK1) signaling pathway promotes vascular remodeling, that it is upregulated in PAH patients and that inhibition of S1P mitigates PAH *in vivo*. Preliminary data from our lab demonstrates that the mitochondrial unfolded protein response (UPRmt) is activated by the S1P pathway. Hence, we hypothesized that the UPRmt induces vascular remodeling to promote PAH development. |
| Methods: Human PASMCs and PAECs were treated with S1P up to 6h or Lentiviral-Sphk1 was overexpressed for 48h at MOI 20. Western blotting was performed on whole cell extracts to assess regulation of the UPRmt pathway. Activation of UPRmt mediators was assessed by immunoblotting for mtHSP70, HSP60, ClpP and LonP1. The effect of UPRmt inhibition on proliferation was assessed by Western blotting for PCNA and Ki67 expression level. |
| Results/Findings: Activation of the Sphk1-S1P signaling axis promoted activation of the UPRmt pathway as we observed increased expression of UPRmt pathway mediators (mtHSP70, HSP60, ClpP and LonP1). There was also an increase in vascular remodeling as expression of proliferation markers was elevated. Inhibition of the UPRmt using the mtHSP70 inhibitor, MKT-077, mitigated the increase in proliferation. |
| Conclusions/Discussion: Aberrant regulation of mitochondrial function leading to activation of the UPRmt pathway promotes vascular remodeling. |
| Translational/Human Health Impact: Currently, no therapeutic interventions exist to treat vascular remodeling in PAH. These studies suggest that pharmacological interventions targeting the UPRmt pathway may improve PAH outcomes. |

(Note: Translation, in the last section, is the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public — from diagnostics and therapeutics to medical procedures and behavioral changes.)