Inhibition of YAP/TAZ Signaling by the FDA Approved Drug Verteporfin Attenuates Fibrosis in Mouse and Human Tissue

N. Mitash[1], H. N. Alsafadi[2], R. H. Pineda[1], K. Kohler[1], M. Ishizuka[3], J. Sembrat[1], M. Lehmann[4], R. Chambers[5], D. E. Wagner[6], M. Koenigshoff[1]; [1]Pulmonary Allergy and Critical Care Medicine, Div of Pulmonary, Allergy & Critical Care Med, Univ of Pittsburgh Medical Center, Pittsburgh, PA, United States, [2]Department of Experimental Medical Science, Lund University, Lund, Sweden, [3]Respiratory Medicine, Tokyo Medical and Dental University, Tokyo, Japan, [4]Helmholtz Zentrum Munchen, German Research Center for Environmental Health Research Unit Lung Repair and Regeneration, Munich, Germany, [5]Division of Medicine, University College London, London, United Kingdom, [6]Faculty of Medicine, Lund University, Lund, Sweden.

Corresponding author's email: nim109@pitt.edu

Rationale: Idiopathic pulmonary fibrosis (IPF) is a chronic disease with median survival of 3-5 years post-diagnosis. It is characterized by altered cellular composition and dysfunction of the lung epithelium, which leads to excessive extracellular matrix, progressive scarring, and rapid decline in lung function. We previously reported increased nuclear localization of Yes associated protein (YAP) and transcriptional co-regulator with PDZ-binding domain (TAZ), co-transcriptional activators of the Hippo pathway, in fibrotic epithelial cells in IPF. Here, we aimed to elucidate the therapeutic potential of interfering with YAP/TAZ signaling in IPF using the FDA approved compound Verteporfin (VP), a well-known YAP/TAZ inhibitor. Materials and Methods: Different models to assess the effects of VP were used: 1) in vivo Bleomycin induced lung fibrosis model with therapeutic treatment with VP (7μM daily from day 7- day 14) and 2) ex vivo precision-cut lung slices (PCLS) were generated from murine and human tissue, respectively, and treated with fibrotic cocktail (FC) as described previously (Alsafadi et al. 2017). Verteporfin treatment was added 48 hours post-FC treatment and analysis was done after a total of 5 days. Fibrosis was assessed by trichrome staining and hydroxyproline measurements, gene and protein expression by qPCR, Western Blotting, 3D immunofluorescence and second harmonic imaging. YAP/TAZ localization was assessed by immunofluorescence imaging. Results: We observed increased survival of animals receiving bleomycin and were therapeutically treated with VP as compared to those animals who received vehicle only. Furthermore, a significant decrease in Ctgf, a known downstream target of YAP/TAZ, and reduced nuclear translocation of YAP/TAZ was found. The anti-fibrotic effect of VP was corroborated by a reduction of well-known fibrotic markers Acta2, Wisp1, and Cdkn2a, a marker of senescence and accelerated aging in IPF, as well as a reduction in cellular infiltrates and tissue density in fibrotic animals treated with VP. Total collagen content of the lungs of animals treated with bleomycin followed by VP was significantly decreased. Along with known fibrotic changes, YAP/TAZ signaling was further induced in the murine and human FC-PCLS model, and pharmacological intervention with VP, but not nintedanib or pirfenidone, significantly reduced Ctgf as well as other fibrotic marker, such as Fn1 and Col1a1. Conclusion: Therapeutic targeting of the YAP/TAZ pathway using an FDA approved drug resulted in attenuated fibrosis in an in vivo mouse and in the ex vivo human tissue-based FC-PCLS model. Targeting of YAP/TAZ using VP may represent a new therapeutic strategy for IPF.

This abstract is funded by: Helmholtz Association