Luminespib counteracts the Kifunensine-induced lung endothelial barrier dysfunction

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Introduction

- The lung endothelium is a dynamic semi-permeable barrier, which regulates the bidirectional transport of biological components (e.g. fluids, proteins, gases) through the vascular wall.
- Lung dysfunction due to endothelial hyperpermeability is a cause and consequence of the Acute Respiratory Distress Syndrome (ARDS), the most advanced and severe form of Acute Lung Injury (ALI).
- The development of medical countermeasures to oppose ARDS is of urgent need.
- Hsp90 inhibitors are potent anti-inflammatory compounds that enhance endothelial barrier function and activate unfolded protein response (UPR).
- UPR orchestrates the adaptive mechanisms that support an optimal protein production rate in response to diverse pathologic insults.
- UPR has been associated with the regulation of the endothelial barrier function and mild UPR activation supports endothelial barrier integrity in vitro.

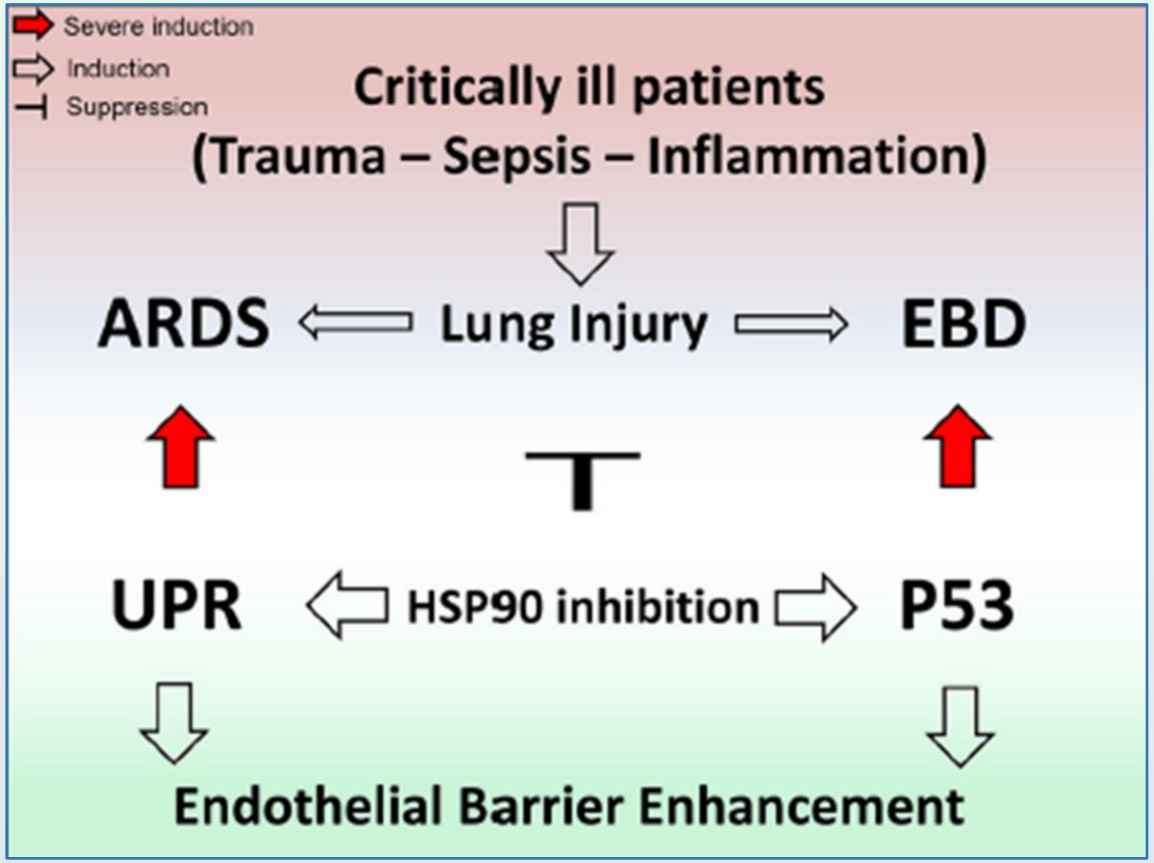
Hetz C. *et.al, Nat Rev Mol Cell Biol*, 2020

Aims & Objectives

✓ **The α-mannosidases inhibitor and UPR suppressor Kifunensine (KIF) disrupted the lung endothelial barrier integrity.**

✓ **Hsp90 inhibition induces the Unfolded Protein Response, which in turn enhances endothelial barrier function (EBF).**

✓ **UPR induction due to Hsp90 inhibition counteracts the Kifunensine-induced endothelial barrier dysfunction.**

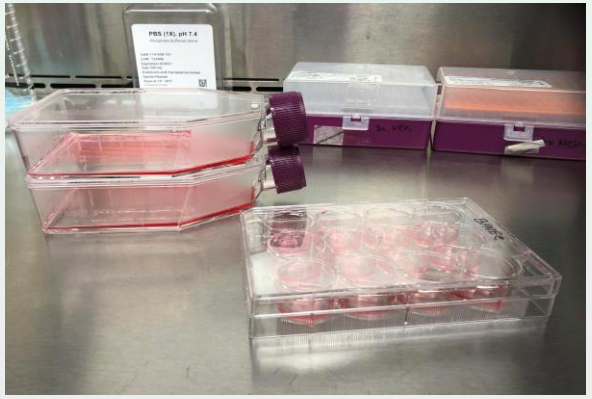


Barabutis, N., *Lung*,2019

Methods

Cell Culture

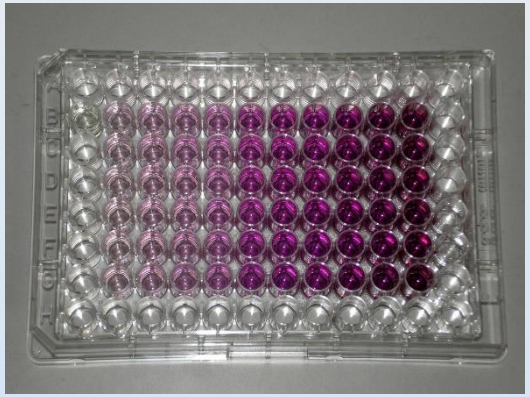
BPAEC
HMVEC-L



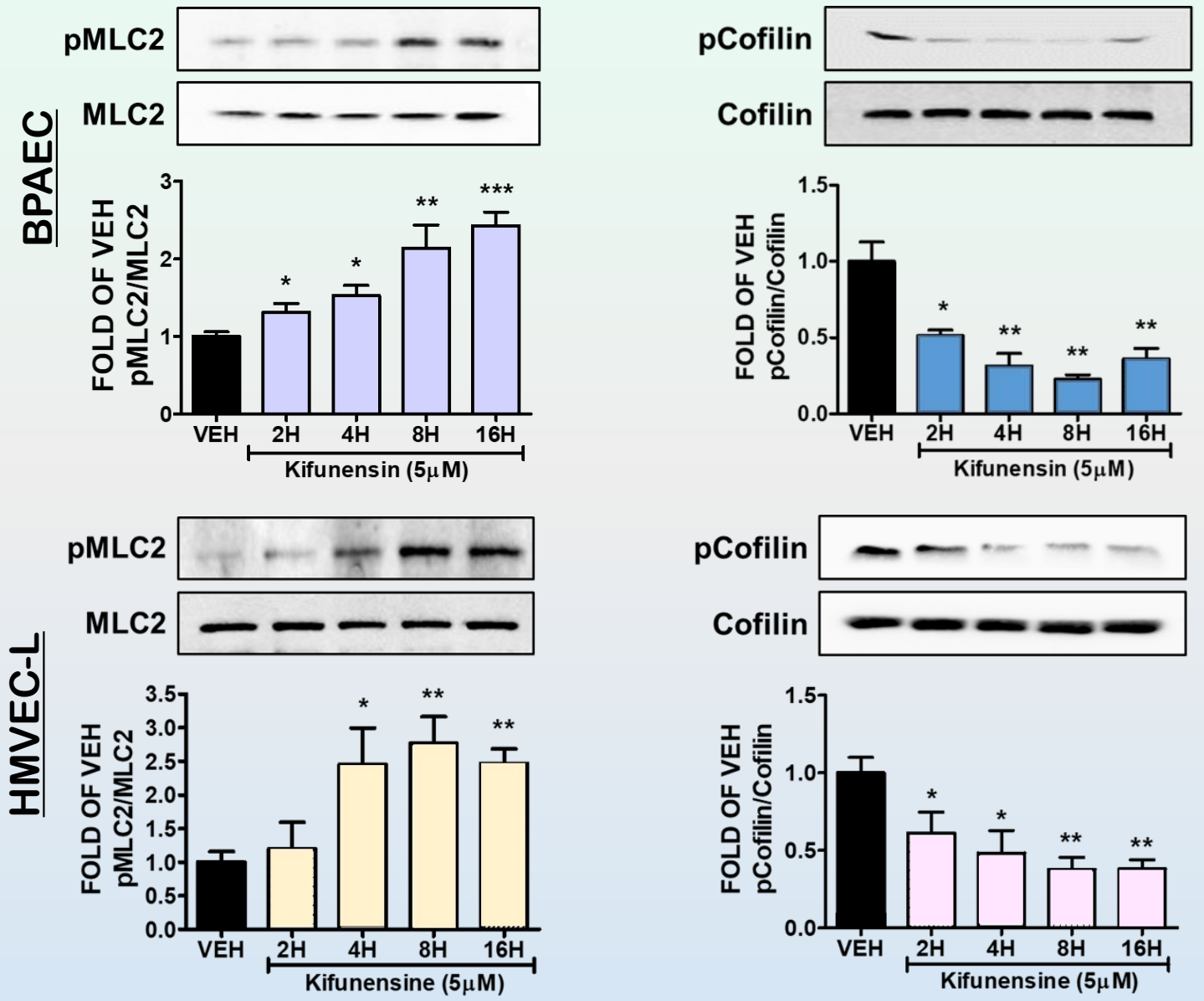
Measurement of endothelial barrier function

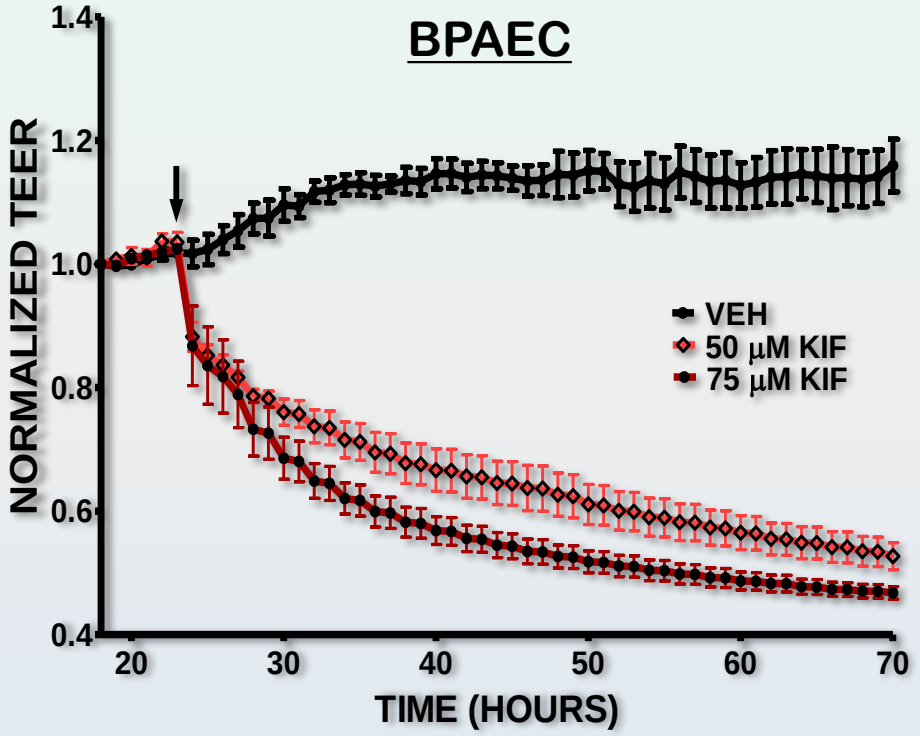
Protein isolation and Western Blot Analysis

Measurement of cell viability



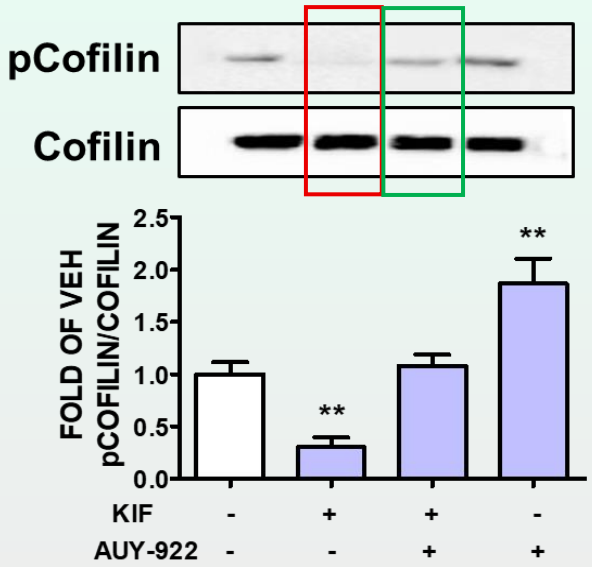
Results

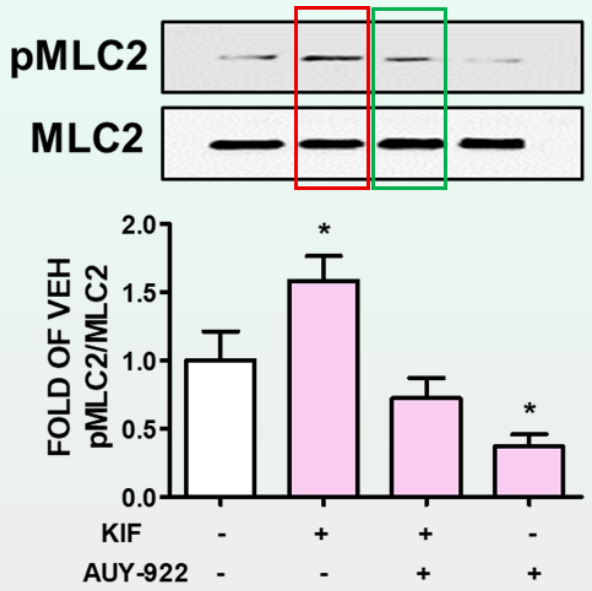


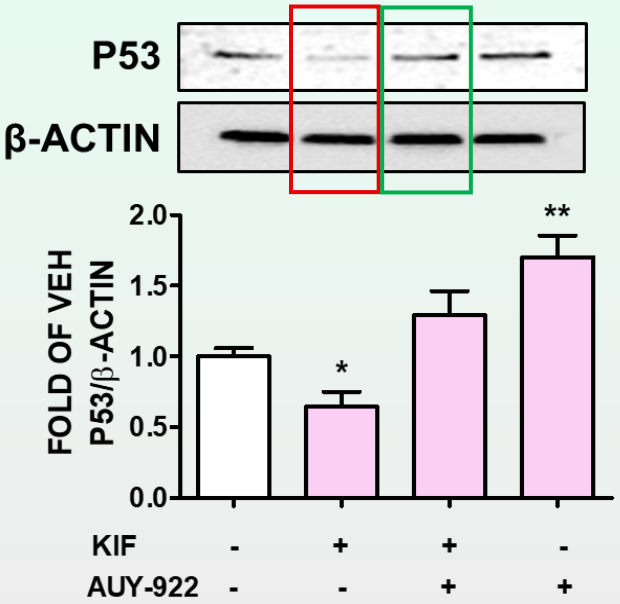


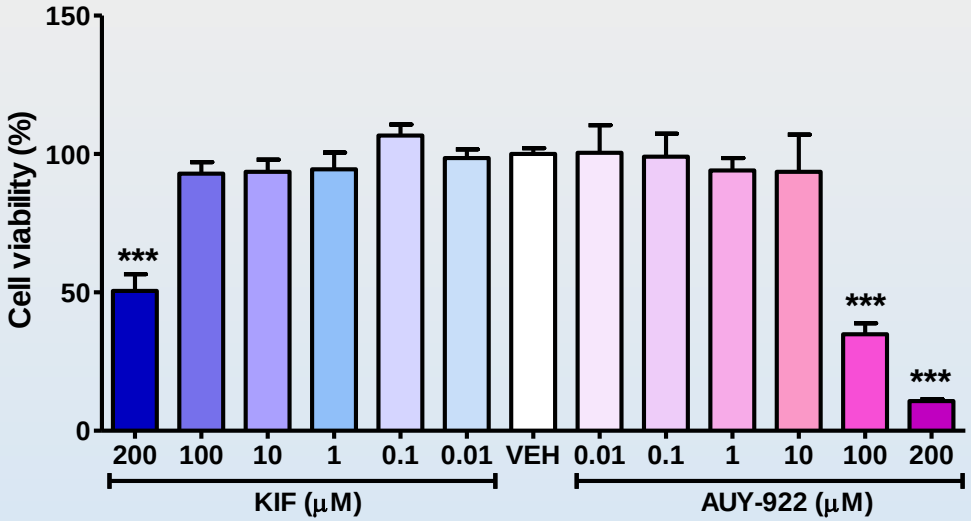
Kifunensine compromises lung endothelial barrier function

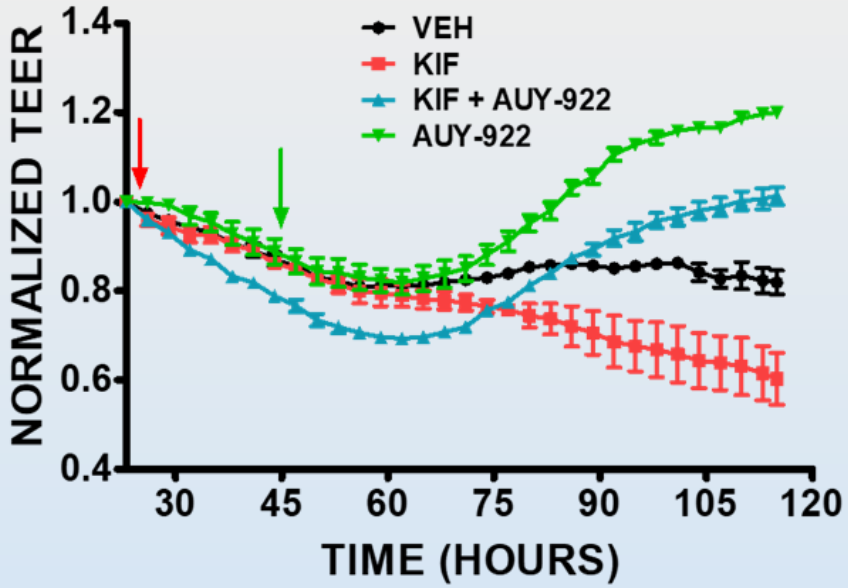
Results











Luminespib counteracts the KIF-induced EBD in BPAEC

Conclusions

- ❖ UPR is associated with the supportive effects of Hsp90 inhibitors in the barrier function

- ➢ UPR activation may serve as a promising therapeutic strategy against diseases related to endothelial barrier dysregulation.

- ❖ Future endeavors will focus on investigating the exact UPR components involved in the protection of the lung vasculature, by employing advanced models of genetically modified mice.

Acknowledgement

This study is supported by 1) R&D, Research Competitiveness Subprogram (RCS) of the Louisiana Board of Regents through the Board of Regents Support Fund (LEQSF(2019-22)-RD-A-26) (PI: NB) 2) Faculty Research Support Program from Dean's Office, College of Pharmacy, ULM (PI: NB) and 3) NIGMS/NIH (5 P20GM103424-15, 3 P20 GM103424-15S1)

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