Prostacyclin Analog Treprostinil Enhances Neonatal Rat Lung Endothelial Cell Growth And Angiogenesis In Vitro

Kisha G. Thayapran, Gregory Seedorf, Steven H. Abman
Pediatric Heart Lung Center, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO

**Background**

Bronchopulmonary Dysplasia (BPD) is a chronic lung disease of premature newborns associated with mechanisms such as postnatal hyperoxia and the risk of significant co-morbidities such as pulmonary hypertension (PH).

**Treprostinil (TRE),** a synthetic prostacyclin analog, is recommended for treating pulmonary hypertension in older children and adults. However, the effect of TRE on lung structure is uncertain.

TRE Preserves Lung Structure in Experimental BPD

Previously, we found that TRE preserves lung structure and function, improves vascular growth, and prevents right ventricular hypertrophy in a hyperoxia-induced neonatal rat BPD model in vivo.

**Is the effect of Treprostinil on neonatal lung development due in part to stimulation of angiogenesis?**

**Methods**

- **2 wk old rats**
- **2.5% FBS**
- **3d in normoxia**
- **Cells/Well**

**Results**

- **Cell Proliferation**
  - CONTROL
  - TRE 1uM
  - AX 10nM
  - TRE + AX

- **TRE increased LEC growth by 109% (p<0.01)**
- **AX alone did not decrease LEC growth**
- **TRE administration with AX did not attenuate effect of TRE**

- **Tube Formation**
  - CONTROL
  - TRE 1uM
  - AX 10nM
  - TRE + AX

- **TRE increased tube formation by 51% (p<0.05)**
- **AX alone decreased tube formation by 38% (p<0.01)**
- **TRE administration with AX restored tube formation to control**

**Conclusions**

1. TRE enhances both LEC growth and angiogenesis in vitro.
2. VEGF receptor blockade reduces tube formation but not cell growth, and this effect can be reversed by TRE.

**Speculations**

1. This in vitro data supports our previous findings that TRE improves lung alveolar and vascular growth in vivo.
2. We speculate that these suggests interactions between the VEGF and prostacyclin pathways that can be targeted to develop novel therapies to prevent BPD and BPD-associated PH.

**Future Directions**

1. Elucidate a further understanding of the signaling pathways at play by performing Western Blots on LEC cell homogenates.
2. Perform cell proliferation assays, tube formation assays, and Western Blot on LEC cells isolated from animals grown in hyperoxic conditions that mimic BPD.

**Acknowledgements**

1. United Therapeutics provided investigational drug Treprostinil
2. Steven H. Abman, MD, Gregory Seedorf, BS, and the Pediatric Heart Lung Center
3. Allan Prochazka, MD and the CUSOM Medical Research Track