



Embracing the Potential of
**YOUNG
INVESTIGATORS**

JONATHAN DAVIES, MD

Baylor College of Medicine
Houston, TX

The role of adenosine signaling in pulmonary hypertension associated with bronchopulmonary dysplasia

INTRODUCTION:

Bronchopulmonary dysplasia (BPD) is one of the most important morbidities in premature infants. Pulmonary hypertension (PH) is a complication of BPD and is a significant cause of morbidity and mortality in patients with BPD. This study will determine the role of adenosine signaling in the development of PH in BPD.

BACKGROUND:

BPD occurs in 1/3 of extremely low birth weight infants (<1000 grams) and remains a significant cause of mortality and morbidity in premature neonates. PH is recognized as one of the most important complications of BPD, occurring in 20-40% of patients with BPD. The presence of PH is associated with a four-fold increase in mortality for patients with BPD as well as increased morbidities, including longer initial hospitalization and higher medical costs in the first two years of life. The key regulatory pathways that lead to the development of BPD and PH remain unknown. There is a critical need to identify these signaling pathways to provide a foundation for the development of effective targeted therapies to prevent BPD associated PH and improve long term morbidity and mortality in premature neonates. One key regulatory pathway of lung development and pulmonary vascular remodeling is the adenosine signaling pathway. Lung injury is associated with increased extracellular adenosine and the activation of adenosine receptor-mediated signaling pathways. Sustained adenosine signaling contributes to the development of PH in chronic adult lung diseases. Additionally, our preliminary studies have demonstrated that activation of adenosine pathways contributes to ongoing inflammation and disruption of alveolar development in an animal model of BPD. However, the contribution of adenosine to disrupted vascular development and remodeling in BPD remains unknown. The goal of this project is to determine the extent to which the activation of adenosine signaling pathways contributes to the development of PH in BPD.

HYPOTHESIS AND OBJECTIVES:

We hypothesize that elevated levels of extracellular adenosine that result from hyperoxic lung injury activate specific adenosine-receptor signaling pathways in the developing lung to disrupt alveogenesis and inhibit normal pulmonary vasculogenesis. The combined effects of adenosine on alveolar and vascular development in the neonatal lung is the underlying cause for the development of PH in BPD.

SPECIFIC AIM 1:

To identify the pathways regulating extracellular adenosine production and signaling during hyperoxic lung injury in the developing neonatal lung. 1.1. Are transcript and protein levels of adenosine signaling mediators CD73, ENT, and adenosine receptors altered in an experimental model of BPD? 1.2. What is the effect of oxygen on adenosine signaling mediators in pulmonary vascular endothelial cells?

SPECIFIC AIM 2:

To determine the role of adenosine signaling in the disruption of pulmonary angiogenesis, vascular remodeling and development of PH in BPD. 2.1. Does decreasing extracellular adenosine levels in the lung improve pulmonary vascular density and attenuate vascular remodeling in a hyperoxia BPD model? 2.2. Will decreasing adenosine signaling decrease right ventricular systolic pressures in adult mice exposed to hyperoxia after birth?