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JULIE DILLARD, MD

St. Louis University
Saint Louis, Missouri

The Role of PDE3 Isoforms in a Murine Model of Bronchopulmonary Dysplasia-Associate Pulmonary Hypertension

INTRODUCTION:

Pulmonary hypertension (PH) is the leading cause of death in infants with bronchopulmonary dysplasia (BPD). Despite advances in medical care, the prevalence of BPD is rising, warranting further study of the pathobiology of BPD-PH. We aim to evaluate the role of phosphodiesterase 3 (PDE3) isoforms as therapeutic targets for BPD-PH.

BACKGROUND:

Bronchopulmonary dysplasia (BPD) is the most common type of chronic lung disease in infants, affecting 22-68% of premature infants. The median length of hospital stay at birth is 103 days, with an average cost over $357,000, representing a significant public health and economic burden. Pulmonary hypertension (PH) is a common complication of BPD and the leading cause of death in these infants, with nearly half dying within 2 years of the diagnosis of PH. Compared to BPD alone, infants with BPD-PH have higher rates of long-term cardiorespiratory morbidities and neurodevelopmental impairment. Pulmonary inflammation is a hallmark of the disease in both BPD and BPD-PH and leads to disruption in alveolar and microvascular development. Therapies aimed at improving BPD have shown a lack of efficacy or unacceptable risk profile, and care remains supportive. Thus, there is a critical need to develop novel therapeutic strategies to improve patient outcomes. In the lungs, Phosphodiesterase 3 (PDE3) regulates vascular tone and remodeling through hydrolysis of the cyclic nucleotides. PDE3 exists in two isoforms: PDE3A and PDE3B, each with cell-specific functions. PDE3A is implicated in vascular tone and smooth muscle cell proliferation, whereas PDE3B plays a role in energy homeostasis and inflammation. Multiple experimental animal studies have implicated dysregulation of PDE3 in the pathogenesis of both inflammatory airway disorders and pulmonary hypertension. Moreover, there is growing evidence that milrinone, a PDE3 inhibitor, improves PH in term neonates with hypoxic respiratory failure. However, the role of PDE3 isoforms in BPD-PH is an unexplored area of research.

HYPOTHESIS AND SPECIFIC AIMS:

We hypothesize that PDE3 isoforms play a role in the development of pulmonary inflammation and pulmonary vascular remodeling in BPD-PH. To test our hypothesis, we will utilize an established murine model of BPD in which Pde3a-/-, Pde3b-/-, or C57BL/6 wild-type (WT) offspring are exposed to intrauterine inflammation and postnatal hyperoxia.