



## 2014 ABSTRACTS



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#### *Role of Macrophage ET1 Expression in the Pathogenesis of Persistent Pulmonary Hypertension of the Newborn (PPHN) Caused by Perinatal Inflammation*

PPHN affects 2-6% of births and is the most common cause of cardiopulmonary failure in the neonate. Of these patients, >40% fail medical therapy and need ECMO or die. Although exposure to inflammation (chorioamnionitis, sepsis) causes 30% of the cases of PPHN, the specific cells and signaling pathways mediating this response are poorly understood. **The significance of this proposal is that we will identify novel therapeutic targets for these critically ill neonates by defining the mechanistic link between perinatal inflammatory stress and PPHN.**

Whether inflammatory stress-induced ET-1 expression contributes to PPHN, and whether the use of ET receptor antagonists is indicated in these patients remains largely unexplored. Although the pulmonary endothelium has been considered the primary source of ET-1, macrophages secrete ET-1 in response to pro-inflammatory stimuli. With inflammatory stress, there is a massive influx of macrophages into the fetal lung. Additionally, the rate-limiting step of ET-1 bioavailability is gene transcription. Determining the transcriptional regulation of inflammatory-stress induced ET-1 expression may identify additional therapeutic targets. The dimeric transcription factor NF $\kappa$ B regulates the cellular response to inflammatory stress, and the ET-1 promoter is known to have NF $\kappa$ B binding sites. **We hypothesize that antenatal inflammation causes PPHN in part due to NF $\kappa$ B regulated ET-1 expression from fetal lung macrophages.**

#### **Specific Aims:**

##### **1. Demonstrate that TLR4-NF $\kappa$ B signaling drives LPS-induced macrophage ET-1 expression.**

LPS-stimulated macrophages will be tested for NF $\kappa$ B activation and ET-1 expression. The effect of attenuated TLR4/NF $\kappa$ B signaling on LPS-induced ET-1 expression will be tested.

##### **2. Establish that antenatal inflammation induces NF $\kappa$ B-regulated ET-1 expression in fetal lung macrophages.**

The effect of antenatal inflammation (intraamniotic [IA] lipopolysaccharide [LPS]) on pulmonary macrophage NF $\kappa$ B activation, ET-1 expression and PPHN will be determined. Mice with macrophage-specific disrupted TLR4/NF $\kappa$ B signaling will be assessed.

##### **3. Test whether pharmacologic NF $\kappa$ B or ET receptor blockade will attenuate antenatal inflammation-induced PPHN.**

The effect of postnatal ETA or nonselective ET receptor blockade on PPHN will be compared to global NF $\kappa$ B inhibition in newborn mice exposed to IA LPS.