



*Enriching Research in Pulmonary Vascular Medicine*

*Embracing the Potential of*

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*Iron deficiency and hypoxic signaling in pulmonary hypertension*

### **INTRODUCTION:**

There is increasing evidence of importance of iron in pulmonary arterial hypertension (PAH); Iron deficiency is associated with worse outcomes, and current trials are addressing the benefit of iron repletion (clinical trials.gov #NCT01447628). However, how iron affects the pulmonary circulation remains unclear.

### **BACKGROUND:**

Iron deficiency is present in up to 63% of patients with idiopathic PAH, and correlates with worsened functional class and mortality independent of anemia – though a causative relation has not been demonstrated. Small clinical trials of iron supplementation in PAH have demonstrated both a small increase and no change in functional capacity. Further, published studies in animal models of pulmonary hypertension (PH) have shown conflicting improvement or worsening of pulmonary artery pressures and vascular remodeling with induction of iron deficiency. The discordant findings highlight the complexity of the role of iron in the pathobiology of PAH. Iron is a cofactor for over 1000 enzymes, a source of oxidative stress, and essential for cellular proliferation. Further, iron has the ability to drive and inhibit hypoxia inducible factor (HIF) signaling – strongly implicated in the pathobiology of PH – through iron regulatory protein and prolyl hydroxylase (PHD)-mediated mechanisms. Utilizing the hypoxic mouse model of PH, I have preliminarily identified a significant protective effect of iron deficiency on the development of PH. Further, I have found that pulmonary HIF transcriptional activity is not altered by iron depletion. Rather, iron depletion leads to a robust increase in renal HIF activity with an increase in serum erythropoietin (EPO) levels – a canonical HIF target. Pleiotropic effects of EPO on vascular cells are well described, and these findings bring forward the paradigm of systemic integration between the lung and kidney potentially mediating the protecting effects of iron depletion.

### **HYPOTHESIS AND OBJECTIVES:**

I hypothesize that in murine chronic hypoxic pulmonary hypertension, iron depletion leads to increased renal HIF availability via decreased PHD activity, resulting in increased production of EPO. This EPO then attenuates pulmonary hypertension through increased eNOS signaling in the pulmonary vasculature.

### **SPECIFIC AIM 1:**

To determine that low iron availability in chronic hypoxic PH increases renal HIF2 stability via decreased PHD activity, resulting in increased serum EPO levels.

### **SPECIFIC AIM 2:**

To determine that blocking circulating EPO, by administering exogenous soluble EPO receptor, results in loss of protective effect of iron deficiency in PH.

### **SPECIFIC AIM 3:**

To determine that EPO signaling in pulmonary vascular endothelial cells results in activation of eNOS signaling.