



Embracing the Potential of  
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*Investigation of calcium regulatory processes and their role in a natural large animal model of altitude-associated pulmonary hypertension sensitivity leading to heart failure*

### **INTRODUCTION:**

Polygenic in nature, the pathophysiological development of pulmonary hypertension (PH) creates a gap in knowledge between the pathology and genes involved in response to hypoxia. We will utilize a natural animal model to investigate the role intra- and extracellular calcium gene expression differences of PH susceptibility at high altitude.

### **BACKGROUND:**

Pulmonary hypertension (PH) resulting in heart failure not only occurs in humans, but also in cattle and represents a significant burden for the beef cattle industry. Heart failure as a result of PH commonly occurs in beef cattle herds at high altitude (> 1,500 m), with mortality rates of 3 to 5%. Cattle share parallel pathologic mechanisms of pulmonary hypertension with humans and can serve as a natural model to study development and progression of the disease. Typically in beef cattle, we evaluate ontogeny (changes with age or growth of the animal). This model offers unique opportunities to investigate mechanisms of pulmonary vascular pathology, such as end-arterial remodeling and large artery stiffening that are not accessible in humans. Previous research suggests a putative role for calcium in PH sensitivity. Calcium is a key mediator of the physiology of the heart, including myocardial depolarization involved with contraction and relaxation. Parathyroid hormone modulates calcium availability affecting cardiovascular inotropic and chronotropic actions. Gene expression results from RNA-sequencing and genome-wide association data comparing cattle with high and low pulmonary arterial pressures identified genes with functional roles in calcium signaling, homeostasis, and utilization. Differentially expressed genes including solute carrier family 8 member A1, troponin I, calcium/calmodulin dependent protein kinase, and ATPase sarcoplasmic reticulum Ca<sup>2+</sup> transporting 1 were identified in multiple functional pathways associated with cardiac and pulmonary vascular physiology. Limited knowledge exists regarding the role of calcium regulatory processes in determining susceptibility to PH and their influence on the development and progression of the disease.

### **HYPOTHESIS AND OBJECTIVES:**

Intra- and extracellular calcium availability and usage plays a role in the development and susceptibility of an individual to PH. The identification of tissue-specific genes pre- or -post-transcriptionally regulated by calcium will aid in differentiation of cattle susceptible to pulmonary hypertension, as well as ontogeny-associated expression differences.

### **SPECIFIC AIM 1:**

Characterize and compare the ontogeny of gene expression (RNA-seq) related to calcium signaling, homeostasis, and utilization in the regulation of PH susceptibility in cattle.

### **SPECIFIC AIM 2:**

Determine if ontogeny-related differences in available and (or) utilized calcium exists with PH sensitivity by examining blood-based biomarkers and their association with tissue-specific expression changes.