Maladaptive hypertrophic changes in the right ventricle (RV) are the primary cause of morbidity and mortality in patients with pulmonary arterial hypertension (PAH). RV hypertrophy (RVH) usually progress to myocardial apoptosis and fibrosis, resulting in RV dilation, hypokinesis, and eventually RV failure and death. Both endothelin (ET) and protein kinase C (PKC) have been shown to be involved in the pathophysiology of RVH in animal models. ET-mediated PKC activation, particularly the α and δ isoforms, has been demonstrated in cardiomyocytes. Recent studies, in rats, have found that PKCδ has the greatest increase in RV PKC activity in response to pulmonary artery banding, suggesting the importance of this isoform in RVH.

We hypothesize that ET-1 induces pathologic hypertrophic changes in the RV by activating PKCδ. We aim to determine if bosentan mitigates maladaptive hypertrophic responses in the RV by inhibiting PKCδ expression and/or activity that in turn may attenuate myocardial apoptosis, fibrosis and decreased contractility. Two models of RVH will be studied, one with pulmonary hypertension (chronic hypoxia) and another with increased RV afterload in the absence of pulmonary hypertension (PA banding).

Aim 1: Determine the effect of ET receptor antagonism on PKCδ expression and activity in the RV of rats treated with chronic hypoxia and with pulmonary artery banding; correlating these changes with the degree of RV hypertrophy, RV apoptosis, RV fibrosis, RV function and PA pressure.

Aim 2: Determine if the effect of ET receptor antagonism on maladaptive RV hypertrophic responses is attenuated in PKCδ deficient mice.