# Effect of BMPR2 Mutation in FPAH on ET-1 and ET-1 Receptors and Smad/MAPK Activation by ET-1 Receptors in Lung ECs and PASMCs in the Mouse Model of PAH

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## Abstract

Familial pulmonary arterial hypertension (FPAH) is a progressive fatal disease and is associated with mutations in bone morphogenic protein type 2 receptor (BMPR2). Endothelin 1 (ET-1) has been implicated in the pathogenesis of PAH, which is mediated by activation of two G-coupled receptors endothelin A (ETA) and endothelin B (ETB). Increasing evidence suggests that ET-1 and mutations in BMPR2 contribute to pulmonary tissue remodeling, especially in endothelial cells (ECs) and smooth muscle cells (SMCs), by affecting downstream activation of SMAD and MAPK signaling pathways. Bosentan (dual ETA and ETB receptor antagonist) is a widely used drug in the treatment of PAH. However, its use in FPAH with BMPR2 mutations is not well studied. Our hypothesis is that mutations in the BMPR2 gene affect expression of ET-1 and ET-1 receptors, and modulate Smad/MAPK activation by ET-1 receptors in lung ECs and PASMCs. Our collaborator has developed a new ROSA26-tet- BMPR2R899X transgenic mouse model universally expressing an inducible BMPR2 allele identified in FPAH (R899X). Our studies will be conducted using pulmonary artery SMCs and lung ECs cultured from this mouse model. Our target goals are to understand interaction between BMPR2 mutant alleles, ET-1 and its receptors; how these interactions affect the downstream Smad/MAPK signaling pathways and whether Bosentan can modulate the expression of ET-1 receptors and activation of Smad/MAPK pathway. For the proposed research, we have the required expertise for each of the technique and have the required resources in this application.