

## **A New Combination Therapy for Pulmonary Arterial Hypertension: Bosentan and VIP**

### **Abstract**

Despite considerable advances in the treatment of pulmonary arterial hypertension (PAH), the condition remains highly fatal. The pathobiology of PAH, particularly pulmonary vascular remodeling, involves imbalances in several key endogenous mediators, which promote abnormal smooth muscle and other cellular proliferation within the pulmonary vascular walls. Used singly, many of the drugs available to treat PAH have limited efficacy, and are incapable of reversing or halting the progression of the disease over time. Consequently, there is now a growing tendency to combine agents from different classes, much as is currently accepted for the treatment of cancer.

Bosentan, an effective inhibitor of the endothelin system, has already been tried in combination with other agents, including the prostanoids epoprostenol, iloprost, and treprostinil, and phosphodiesterase-5 inhibitor sildenafil. We now propose to test the combination of Bosentan and Vasoactive Intestinal Peptide (VIP), a proven pulmonary vasodilator, inhibitor of vascular smooth muscle cell proliferation, and anti-inflammatory agent with beneficial therapeutic effects on hemodynamics and exercise tolerance in IPAH patients.

We recently reported that VIP KO mice show features of PAH: pulmonary hypertension, pulmonary vascular remodeling, right ventricular hypertrophy, and lung inflammation (*Circulation* 115: 1260-68, 2007). More recently, we found that VIP controls several of the major pathways that regulate pulmonary vascular remodeling: In the absence of the VIP gene, there was upregulation of genes that promote pulmonary vasoconstriction and vascular remodeling pathways, such as endothelin receptor A, PDGF $\beta$ /PDGF $\beta$ R, and RhoA/Rho kinase, and downregulation of genes that defend against PAH and vascular remodeling, including  $\beta_2$  adrenergic receptor, endothelial NOS, and prostacyclin synthase (*Eur. Resp. J.* 31:135-9, 2008). The combined use of Bosentan and VIP in 2 experimental models of PAH, VIP KO mice and monocrotaline-treated rats, should therefore be expected to target most of the pathways underlying the pathogenesis of PAH, and thus offer more promise of success.