

LTRC Concept Sheet # 08-99-0002

Gene Deficiency of Vasoactive Intestinal Peptide in COPD Patients with Pulmonary Arterial Hypertension

**ABSTRACT**

Pulmonary artery remodeling and inflammation occur spontaneously in mice with targeted deletion of the gene for Vasoactive Intestinal Peptide (VIP) (Said et al, Circulation, 2007). In patients with COPD, pulmonary artery vessel remodeling may be associated not only with hypoxic vasoconstriction, but also may be modulated by upregulation of the gene for Nuclear Factor of Activated T Cells (NFAT), a pro-inflammatory and pro-remodeling master controller.

To test the hypothesis that NFAT activation is linked to pulmonary artery vessel thickening/remodeling and inflammation-and possibly airway remodeling/inflammation, we are requesting 1) RNA later fixed COPD lung tissue for gene microarray to check for upregulation of the gene for NFAT and related pro-inflammatory, pro-remodeling genes, and 2) paraffin blocks from these patients for hematoxylin and eosin staining to grade histological severity of pulmonary artery vessel thickening and inflammation, as well as airway remodeling and inflammation.

Clinical indices (severity of spirometric obstructive ventilatory defect, smoking history, 6 minute walk, St. George's Respiratory Questionnaire, available cardiopulmonary exercise testing) will be correlated to NFAT expression, as well.

We will determine if there is a strong relationship between expression of a single gene, the pathological features noted above, and clinical manifestations of disease.

The significance of the study is that selective NFAT inhibitors (VIVIT) are now available, so that this study may raise the possibility of new treatments for COPD. VIP, which modulates these same pathological and physiological features (Szema et al, AJP-Lung Cell Molec Physiol, 2006) exerts its "anti-asthma gene" and "anti-pulmonary hypertension gene" functions via NFAT (unpublished data). VIP, an endogenous modulator with minimal side effects, may therefore have use as a novel COPD drug.