

**LTRC Concept Sheet # 08-99-0031**

**Fibroblast Activation Protein- $\alpha$  and Severity of Disease in Idiopathic Pulmonary Fibrosis**

**Abstract:**

Idiopathic pulmonary fibrosis (IPF) is a devastating disease with poor patient survival rates. The etiology of IPF is unknown and there is no effective treatment. However, it is well known that IPF is associated with proliferation of lung fibroblasts and exaggerated deposition of extracellular matrix (ECM) proteins, especially collagen and fibronectin. ECM proteins interact with integrins on cell membrane and thus initiate focal adhesion kinase (FAK) signaling cascades involved in cell proliferation, leading to fibrosis.

The proper assembly of fibronectin and collagen matrix requires the presence of von Hippel Lindau protein (pVHL), and loss of pVHL prevents fibroblast proliferation. Thus, we reason that pVHL plays a role in the development of IPF. Our preliminary data show that overexpression of pVHL increases primary lung fibroblast proliferation and activates FAK. **Therefore, we hypothesize that in IPF patients; pVHL is overexpressed, facilitating aberrant ECM assembly. ECM interacts with integrins and activates FAK, leading to lung fibroblast proliferation and fibrosis.**

We propose following experiments to test this hypothesis. As an exploratory step, we will collect lung tissue samples of 10 control patients and 10 IPF(UIP) patients to examine whether lungs of IPF patients have increased levels of pVHL. These samples will be used for quantitative real time RT-PCR (qPCR) analysis to examine pVHL mRNA levels. We will extract total RNA from frozen tissue samples and synthesize cDNAs reverse transcription. The cDNAs will be used as templates for qPCR to detect pVHL mRNA. Human ribosomal protein L19 (hRPL19) will be employed as the internal control.

Expected outcomes

We anticipate that lungs from fibrotic patients have higher levels of pVHL. We expect that pVHL overexpression stabilizes the fibronectin matrix and increases its association with integrin, leading to the activation of FAK and pVHL-mediated fibroblast proliferation.