

LTRC Concept Sheet # 05-01-0001

Transforming Growth Factor- β Activity & Signaling In Idiopathic Pulmonary Fibrosis

Abstract: Idiopathic pulmonary fibrosis is a progressive and lethal disease with an overall five-year mortality of 50 to 70% (5). Recent investigations have more clearly defined these disorders. The most common histological pattern observed in IPF is termed usual interstitial pneumonitis (UIP). UIP is characterized by heterogeneously distributed fibroblastic lesions with surprisingly little inflammatory infiltrates. Mature fibroblastic regions contain mainly myofibroblasts, which deposit collagens and fibronectins. Treatment for UIP is limited, and the median survival after diagnosis of UIP is only 2.8 years (4). Distinct from UIP is a second form of interstitial fibrosis that has been termed non-specific interstitial pneumonitis (NSIP). In NSIP, tissue involvement is homogenous and contains abundant inflammatory infiltrates with variable deposition of matrix. Patients with NSIP often enjoy much better responses to treatment with frequent long-term survival (4). We hypothesize, that abundant TGF- β activity and signaling intermediates are present in regions of active pulmonary fibrosis in tissues from patients with idiopathic pulmonary fibrosis, driving myofibroblast accumulation and extracellular matrix deposition. We further postulate that the extent of TGF- β activity and TGF- β 1 signaling through SMADs and c-Abl in human pulmonary fibrosis, as well as circulating TGF- β 1 activity in plasma (3). The level of tissue activity of TGF- β 1 will be correlated to disease severity.

We will determine which TGF- β 1 signaling pathways (SMAD, c-Abl, or both) are active in pulmonary fibrosis. Next, we will utilize immunohistochemical and expression microarray strategies to contrast TGF- β 1 activity and signaling in the two major histological patterns of idiopathic interstitial fibrosis, namely the common usual interstitial pneumonitis (UIP) pattern and the less frequent non-specific interstitial pneumonitis (NSIP) (4). This will establish the role of TGF- β 1 activity in the pathogenesis and outcome of human IPF. We will determine the extent and regional localization of TGF- β 1 activity in lung tissues with pulmonary fibrosis of the common UIP type. These data will provide insights into TGF- β 1 activity in the pathogenesis and outcome of human idiopathic pulmonary fibrosis. We will also evaluate which mechanisms of TGF- β 1 signal transduction are functioning during UIP. Specifically, SMAD2 or SMAD3 phosphorylation and nuclear translocation will be assessed in these tissues.