

LTRC Concept Sheet # 05-04-0002

Relationship between Gene Expression Profiles and Disease Activity in Idiopathic Pulmonary Fibrosis

Abstract: While the etiology of the disease remains obscure, increasing evidence suggests that disordered lung repair mechanisms contribute to the pathogenesis of IPF. There are no animal models available to study disease pathogenesis, so future advances in the understanding of this disease must increasingly rely on the collection of data from human subjects. Genomics offer a unique opportunity to conduct sophisticated analyses in lung tissues, and may offer insight into key molecular events especially when correlated with relevant clinical, radiographic, and physiologic data. The relationship between the histopathology of UIP and certain clinical, radiographic, and physiologic scores has been well established in a number of recently reported studies. However, there are no studies to date that have systematically correlated CRP scores with gene expression profiles in affected lung. The principal rationale for these experiments is to identify the subset of genes that correlate with identifiable clinical outcomes such as radiographic extent of disease, physiologic measures of lung function, and histopathologic scores. We have undertaken a similar analysis to identify transcriptional patterns that distinguish IPF from other interstitial lung diseases, but our resources are limited by a preponderance of samples from subjects with advanced disease. The LTRC resource will give us additional access to surgical biopsies from subjects with mild and moderate disease.

There are other histologic features that have been shown to appear concurrently in biopsy specimens of subjects with the histology of usual interstitial pneumonia. In one recent study, Flaherty et al. evaluated the impact of the concurrent appearance of NSIP (nonspecific interstitial pneumonia) histology in biopsies of patients with UIP on the clinical course of the disease. They found no statistically significant difference in survival between concordant UIP (all biopsies showing a UIP pattern) versus discordant UIP (those biopsies showing UIP in some areas and NSIP in others), although there appeared to be a trend toward a better clinical course for the latter group. However, the appearance of either concordant or discordant UIP histology was associated with a poorer long-term clinical prognosis than concordant NSIP. We will undertake an integrated approach that involves microarray analysis of distinct histopathologic regions of IPF tissues in order to identify key regulatory pathways that characterize these distinct lesions. We will focus on fibroblastic foci (from both concordant and discordant UIP), NSIP, and diffuse alveolar damage because the appearance of these histologic subtypes may influence the clinical course of the disease (most evident when DAD develops in IPF). The ultimate goal of this aim is to identify unique transcriptional networks associated with these histologic subtypes with the goal of identifying genes that may provide clues of their pathogenesis.