

**LTRC Concept Sheet # 07-99-0006**

**Microvascular Injury as a Cause of Idiopathic Pulmonary Fibrosis: Retrospective Study**

**ABSTRACT**

Our group has recently published a manuscript in the American Journal of Respiratory and Critical Care Medicine that details the involvement of two important hematopoietic proteins [M-CSF and CCL2] in the pathogenesis of IPF. Specifically, using both M-CSF-deficient and CCL2-deficient mice, we observed that these mice were protected from bleomycin-induced pulmonary fibrosis. Furthermore, we also performed a retrospective study (n=50 patients: n=24 IPF, n=26 non-IPF) in collaboration with The University of Iowa and Dr. Gary Hunninghake that demonstrated elevated levels of M-CSF in bronchoalveolar lavage fluid in patients with IPF. Similarly, we also determined that CCL2 levels were also elevated, but the correlation to disease status was much stronger to the elevated M-CSF levels. Finally, taking into account the importance of these two hematopoietic proteins, we concluded the alveolar macrophages were a significant contributor to the development of pulmonary fibrosis in mice. I have attached this manuscript to this e-mail as a PDF file. Specific numbers for all observations and the number of observations in these studies are included in this manuscript.

Based upon the conclusions discussed in the above section, we now want to further define the role and importance of macrophages and these two proteins in the human disease. This pilot study, using lung tissue and RNA and plasma, will allow us to perform this analysis without the need for a long-term prospective study. We will determine mRNA and protein levels of M-CSF and CCL2 in the plasma and lung tissue, the appearance of macrophages and fibrocytes via immunohistochemistry. Although our group is currently performing this specific prospective study at The Ohio State University Medical Center, it will take some time before we enroll enough patients and obtain enough samples to adequately perform this study. We will perform correlative analyses between the IPF samples and emphysema samples and (if possible) normal samples, as we performed in the AJRCCM manuscript.

Our group is interested in defining the cellular and mechanistic properties associated with the development of IPF and emphysema. In short, we are interested in the contribution of monocytes, macrophages, myofibroblasts, and fibrocytes to these disease processes, along with the influences of cytokines, chemokines, microRNA, and mRNA. Resources from LTRC will allow us to correlate some of the findings we have acquired in animal models to the human diseases.