

LTRC Concept Sheet # 07-99-0010

Roles of Angiotensin in Idiopathic Pulmonary Fibrosis

ABSTRACT

In several animal models, angiotensin (ANG) II has been shown to play an essential and causative role in experimental pulmonary fibrosis (PF), but the potential role of ANGII in human PF has not been vigorously explored. Earlier work by the applicant showed that in Idiopathic Pulmonary Fibrosis, lung myofibroblasts synthesize the precursor of ANGII, angiotensinogen (AGT), constitutively in response to TGF- β 1. Newer data show that the TGF- β 3 response of AGT is regulated by a small domain in the AGT core promoter. Exciting new Preliminary Data obtained from DNA samples from Spanish IPF patients show that one of three single nucleotide polymorphisms (SNPs) in the AGT core promoter (the G-6A SNP) strongly associates with faster IPF disease progression measured by widening of the alveolar-arterial (A-a) oxygen gradient. The G-6A SNP often, but not always, occurs together with SNPs at the -20 and -18 positions in AGT that impart higher rates of AGT gene transcription. On that basis, this proposal is designed to use genotyping and clinical data analyses to examine the hypotheses that a) the G-6A SNP in AGT is associated with more severe IPF in U.S. patients; b) an "IPF Risk Haplotype" at base positions -20,-18 and -6 in AGT will be identified through the application of a new statistical method, developed at MSU, to U.S. IPF patients, and c) AGT core promoter SNPs at -20 and -18 may provide even stronger markers of IPF predisposition or severity than the G-6A SNP alone.