

**Dr. Tom Wynn**

**INTERLEUKIN-13 ANTAGONISM AS A TREATMENT FOR ESTABLISHED AND PROGRESSIVE LIVER FIBROSIS INDUCED BY *Schistosoma mansoni***

T.A. Wynn, A.W. Cheever, D.D. Donaldson, M.G. Chiaramonte

In several allergic, autoimmune, and infectious diseases, fibrosis is a major cause of morbidity and mortality. Here, using a model of infection induced liver fibrosis we show that IL-13 is required at all stages of *S. mansoni* infection to trigger fibrosis. IL-4 production was preserved in IL-13-deficient mice, yet failed to significantly contribute to the fibrotic response in either acute or chronic infection. Significant fibrosis develops in all infected mice, although the magnitude of the response varies widely in inbred mice. C3H/HeN, BALB/c and C57BL/6 mice develop high, intermediate, and low levels of fibrosis, respectively. Despite these differences, IL-13 blockade resulted in a marked amelioration of fibrosis in all strains. The fibrotic mechanism in the high and low responder strains was unrelated to their tissue eosinophil or mast cell responses, but did strongly correlate with their patterns of IL-13, IL-10, and IFN- $\gamma$  mRNA expression. Indeed, severe fibrosis correlated with a high IL-13 and low IFN- $\gamma$ /IL-10 mRNA response. Because fibrotic diseases are typically progressive disorders, an important issue was to determine whether IL-13 inactivation might be used to treat an established and ongoing fibrotic disease. Here, IL-13 antagonism was highly efficacious, even after fibrosis and the Th2 cytokine response were firmly established. These studies demonstrate the central role played by IL-13 in the pathogenesis of schistosomiasis and suggest that therapeutic approaches aimed at disrupting the IL-13 pathway will be highly effective at preventing fibrotic disease caused by chronic Th2-mediated inflammatory reactions.