NIH Award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases

Principal investigator: John Varga, rheumatology
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- Project: Fibroblast TGF-Beta/Signaling in Scleroderma: Modulation by PPAR-Gamma
- Start Date: September 24, 2009
- Total Award Amount: $457,500

How the project will work:
We hypothesize that PPAR-g is an endogenous suppressor of fibrotic responses, and impaired expression or activity could be a factor in progressive fibrosis in SSc; thus PPAR-g may be a novel target for anti-fibrotic therapy. We will explore the anti-fibrotic role of PPAR-g and its mechanism in vitro and in vivo. In Specific Aim 1, we will characterize the anti-TGF-b mechanisms of action of PPAR-g in mouse and human cells with defective endogenous PPAR-g, and examine the modulation of TGF-b signaling by PPAR-g. In Specific Aim 2 we will examine the role of p300 in mediating TGF-b responses and in the antagonistic cross-talk with PPAR-g. In Specific Aim 3 we will examine the effect of PPAR-g ligands in mouse models of scleroderma, and study the fibrotic response in a novel transgenic mouse with fibroblast-specific conditional deletion of PPAR-g. In Specific Aim 4, we will examine the expression, activity and clinical correlates of PPAR-g in SSc. These studies will deepen our understanding of aberrant fibroblast activation in SSc, and provide the first insight into the role of PPAR-g in the process.

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How the results of this project will benefit society:
Systemic sclerosis (SSc) is an orphan disease with poorly understood pathogenesis and no disease-modifying treatment. Anti-fibrotic therapy could improve survival and quality of life in SSc as well as other fibrosing conditions. Recent studies indicate that PPAR-g is a potent negative regulator of fibrotic responses and may represent a novel target for therapy. Currently, nothing is known regarding the regulation and role of PPAR-g in SSc. The proposed studies will provide a better definition of fibrosis in SSc, the role of PPAR-g in regulating the response, and the potential clinical utility of therapies targeting PPAR-g in SSc.