Sara N. Fischer  
PhD Candidate  

“Electrospun Nanofiber Scaffolds as a Model of the Lung Microenvironment in Pulmonary Fibrosis”  

August 9th, 2011  
115 BRT  
9:00 a.m.
VITA

June 8th, 1985 ......................... Born – Dearborn, MI

2003-2007..............................B.S., Biological Sciences
                                     (Psychology Minor)
                                     University of
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2007-2011..............................Graduate Research
                                     Associate, Department of
                                     Pulmonary, Allergy,
                                     Critical Care and Sleep
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                                     The Ohio State University

COMMITTEE MEMBERS

Clay B. Marsh, MD, Advisor

Virginia Sanders, PhD

Michael Ostrowski, MD, PhD

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FUTURE PLANS

After obtaining her PhD, Sara plans to pursue a career in scientific communication and teaching.
ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a devastating interstitial lung disease of unknown origin that is characterized by irreversible scar tissue formation within the lungs. Collagen deposition, myofibroblast expansion, and the development of fibroblastic foci are hallmark pathological events that contribute to pulmonary fibrosis. The origin and mechanism of recruitment of myofibroblasts, the key cell leading to fibroblastic foci is unknown. We hypothesized that the fibrotic lung microenvironment causes the differentiation of bone marrow cells into myofibroblasts. In order to test this hypothesis, we developed a novel method of studying the effects of the fibrotic microenvironment on various cell types through the utilization of electrospun nanofiber scaffolds. Poly (e-caprolactone) nanofiber scaffolds were electrospun and coated with lung extracts from bleomycin or PBS-treated mouse lungs. Also, nanofibers of varying moduli were employed to determine the effect of matrix stiffness on bone marrow cell differentiation in our model. Bone marrow cells were harvested from wild-type mice, plated on the nanofiber scaffolds, and allowed to expand. After various time-points, cells were observed by scanning electron microscopy and changes in fibrotic gene expression were determined by real-time PCR.

Wild-type mouse bone marrow cells plated on the matrices coated with bleomycin- treated lung extract were observed by scanning electron microscopy to be secreting matrix materials and appearing more fibroblast-like after 8 and 14 days. These cells also had a significant increase in expression of the hallmark myofibroblast genes, type-I collagen and alpha-smooth muscle actin, as well as a significant increase in expression of connective tissue growth factor and tenascin-C. Similar results were observed when the modulus of the matrix was increased; suggesting that stiffness of substrate plays a role in bone marrow cell differentiation. These data underscore the importance of bone marrow derived cells in mediating pulmonary fibrosis.
We next determined the bone marrow-derived cell population that differentiated into myofibroblast-like cells when cultured in the \textit{ex vivo} fibrotic lung microenvironment system. Mesenchymal stem cells, and not hematopoietic stem cells, were able to differentiate into myofibroblast-like cells that were observed in previous studies, as demonstrated by morphology and increased expression of hallmark fibrotic genes described above. Further, monocyte/macrophage lineage cells were unable to differentiate into myofibroblast-like cells in our \textit{ex vivo} culture system. These data provide evidence that circulating mesenchymal stem cells are capable of providing a source of myofibroblast precursor cells that traffic to the lung during the pathogenesis of pulmonary fibrosis, and these cells may be manipulated and utilized for future therapeutic options for IPF.

We have recently demonstrated that the ubiquitous transcription factor ets-2 plays an important role in the pathogenesis of IPF. Mice with an inactive form of ets-2 due to a mutation (ets-2 \textit{A72/A72}) are protected from bleomycin-induced pulmonary fibrosis. To further elucidate the cellular mechanisms of protection from pulmonary fibrosis due to the ets-2 mutation, ets-2 \textit{A72/A72} bone marrow cells, fibroblasts, and mesenchymal stem cells were cultured in our \textit{ex vivo} fibrotic lung microenvironment system. In each of these cell types, ets-2 \textit{A72/A72} cells demonstrated a decreased response to the fibrotic microenvironment, as shown by morphology and real-time PCR. Fibroblasts generated from ets-2 \textit{WT/WT} and ets-2 \textit{A72/A72} mice were further tested with biomechanical assays to delineate how the ets-2 mutation alters responses to matrix proteins. Mutant fibroblasts were less adherent to collagen nanofiber scaffolds, had a decreased ability to contract the surrounding nanomatrix, were less migratory than ets-2 \textit{WT/WT} fibroblasts. However, ets-2 \textit{A72/A72} cells were more proliferative on both cell culture dishes and nanofiber scaffolds than ets-2 \textit{WT/WT} cells. These observations indicated that the ets-2 mutation resulted in a switch from a pro-fibrotic phenotype to a proliferative/protective phenotype in the affected cells. Furthermore, microarray analysis of ets-2 \textit{WT/WT} and

\section*{RECENT PUBLICATIONS}


**Presentations:**

1. “Electrospun nanofiber scaffolds as a model of the lung microenvironment in pulmonary fibrosis.” Pulmonary Grand Rounds, The Ohio State University Medical Center, Columbus, OH, 2011.

2. “Nanofiber scaffolds provide a novel system for studying the lung microenvironment in pulmonary fibrosis.” MVIMG Research in Progress, The Ohio State University, Columbus, OH, 2010.

Ets-2 ($^{A72/A72}$) myofibroblasts exposed to the *ex vivo* fibrotic microenvironment revealed several interesting new targets that may be related to the protective phenotype rendered by the ets-2 mutation. These studies provide evidence that ets-2 may be an attractive therapeutic target in IPF.

The studies presented herein describe the development of an *ex vivo* fibrotic lung microenvironment nanofiber scaffold system and the validation of this system as a model for studying pulmonary fibrosis. This model was utilized to gain insights into the role of bone marrow-derived mesenchymal stem cells in providing an external source of differentiating myofibroblasts in the fibrotic lung, as well as the role of the transcription factor ets-2 in driving cell mediated fibrotic processes. With further study, the present work may result in the development of new therapies for IPF.
RECENT ABSTRACTS AND PRESENTATIONS

Abstracts:


