Subject: Dissertation defense - Jorge G. Fernandez Davila, PHD Biosciences
Date: Thursday, April 4, 2024 at 1:00:10 PM Eastern Daylight Time
From: SSB Faculty List on behalf of Diane St. Germain
To: SSB-FACULTY-LIST-L@LISTSERV.GMU.EDU

Dissertation Defense Announcement
To: The George Mason University Community

Candidate: Jorge G. Fernandez Davila

Program: PhD Biosciences

Date: Friday, April 19, 2024

Time: 10:00 AM

Location:
In person - Conference room 1003
IABR, Science & Tech campus

All are invited to attend the defense.

Committee chair: Dr. Geraldine Grant
Committee members: Dr. Luis Rodriguez, Dr. Mikell Paige, Dr. Jeffrey Moran

Title: "Investigating Extracellular Matrix-Derived Hydrogels From the Lungs of Patients with Idiopathic Pulmonary Fibrosis as an *In Vitro* Disease Model"

Abstract:
Idiopathic pulmonary fibrosis (IPF), one of the most common forms of interstitial lung disease, is a poorly understood, chronic, and often fatal condition with only two FDA-approved medications. IPF is characterized by excessive matrix production that leads to the loss of lung architecture and physiology, eventually resulting in death. The primary disease-causing cell in IPF is the fibroblast, which is responsible for depositing matrix components in the lung interstitium. Understanding the pathobiology of the fibroblast is critical to evaluating and discovering novel therapeutics. Unfortunately, our ability to interrogate this biology *in vitro* is greatly limited by the effects of tissue culture (TC) plastic on the fibroblast phenotype. Previously, we observed a dramatic change in gene expression when culturing fibroblasts on TC plastic. Additionally, it has been well documented that mechanobiological signals derived from stiff substrates such as TC plastic result in the transition of fibroblasts to an α-smooth-muscle-actin expressing phenotype called the myofibroblast (highly migratory and contractile), thus masking *in vivo* expression of fibroblast markers intrinsic to IPF. To overcome the changes in the mechanobiology from TC plastic and to better understand the fibroblast in the IPF lung microenvironment *in vitro*, we decellularized lung matrices derived from IPF patients to generate three-dimensional (3D) hydrogels as *in vitro* models of lung physiology. In this project, we characterize the phenotype of fibroblasts seeded into the hydrogels. First, we validate that our methodology preserves native collagen, and our soluble ECM becomes a gel-like material under physiological temperature. We also demonstrate that the mechanical properties of our hydrogel are comparable to established hydrogel models. Second, we show that when cultured in our hydrogels, IPF fibroblasts display differential contractility compared to their normal counterparts, lose the myofibroblast phenotype, and increase expression of proinflammatory cytokines compared to fibroblasts seeded two-dimensionally (2D) on TC dishes. We validate this

proinflammatory state in fibroblast-conditioned media studies with monocytes and monocyte-derived macrophages. Finally, we utilize FDA-approved drugs in our hydrogel system to verify and confirm drug testing capability. Our results demonstrate that a Janus Kinase inhibitor reduces our system's proinflammatory state. Additionally, we observed that fibroblasts cultured in the IPF ECM hydrogel were responsive to pro-fibrotic and anti-fibrotic compounds. These findings 1) reaffirm the crucial limitations of the traditional 2D plastic TC model and their significant effect on fibroblasts, 2) add to a growing understanding of the lung microenvironment effect on fibroblast phenotypes, and 3) shed light on the potential of therapeutic intervention in fibroblast-immune cell crosstalk in the IPF lung.

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