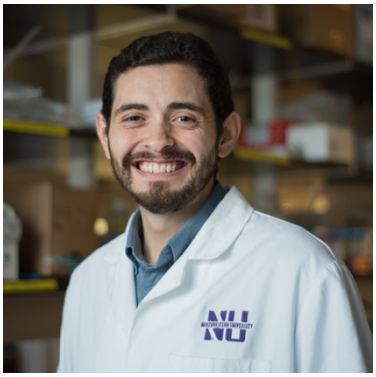
CHEMICAL ENGINEERING

DISTINGUISHED YOUNG SCHOLARS SERIES



BRIAN AGUADO

August 12, 2019

Postdoctoral Fellow
University of Colorado

Precision biomaterial platforms to probe myofibroblast activation

ABSTRACT: Aortic valve stenosis (AVS) is a progressive disease characterized by aberrant stiffening of the aortic valve, leading to inadequate blood flow from the left ventricle and eventual heart failure. AVS is currently treated exclusively with valve replacement surgeries, which may be avoided if effective small molecule therapeutics could be identified to slow or reverse AVS progression. During AVS progression, a large fraction of valvular interstitial cells (VICs) differentiate into pathogenically activated myofibroblasts, which contribute to excessive matrix deposition and eventual valve leaflet stiffening. Effective small molecule therapeutics intended to reverse myofibroblast activation remain elusive, owing to the inherent heterogeneity of the cellular microenvironment from patient to patient. For example, male patients show increased calcification and female patients show increased tissue fibrosis in the aortic valve microenvironment, leading to differential drug responses. Considering these clinical observations, we seek to engineer precision biomaterial microenvironments to recapitulate sex- and patient-specific AVS progression in vitro and identify molecular mechanisms that mediate reversal of myofibroblast activation. Precision biomaterials are defined here as engineered environments that enable the evaluation of how sex- and/or patient-specific variables may influence disease progression. As a strategy to evaluate molecular mechanisms guiding AVS progression, we utilize poly(ethylene glycol) (PEG) hydrogels as precision in vitro platforms to probe various biochemical and mechanical cues that activate male and female VICs to a myofibroblast state, as well as cues that reverse activation (Fig. 1A). My talk will focus on three vignettes where PEG hydrogels were used to evaluate how male and female VICs activate to and reverse from a myofibroblast state in response to different cues, including serum factors from AVS patients before and after a valve replacement procedure (Fig. 1B), small molecule inhibitors of myofibroblast activation (Fig. 1C), and nanoscale stiffness cues to mimic valve calcification (Fig. 1D). Collectively, our work demonstrates how engineered hydrogel matrices enable an increased

understanding of the molecular mechanisms guiding myofibroblast activation and reversal, which may provide a critical bridge toward sex- and patient-specific small molecule AVS therapies.

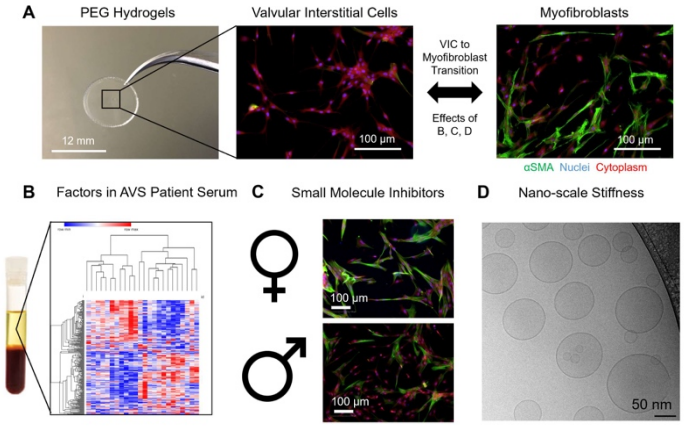


Figure 1: Precision biomaterial strategies to model myofibroblast activation and reversal. (A) VICs are seeded on PEG hydrogels of varied stiffness to either maintain VICs in a quiescent state or activate them to a myofibroblast state. Biochemical and mechanical cues are then delivered to manipulate VIC phenotype. (B) Patient serum factors before and after a valve replacement procedure differ in composition, which alter myofibroblast differentiation. (C) Male and female VICs respond differentially to inhibitors of myofibroblast signaling as a function of material stiffness. (D) PEG hydrogel nanoparticles of varied stiffness, shown in the TEM image, manipulate male and female VIC phenotype differentially.

BIOGRAPHY: Dr. Brian Aguado is currently an NIH and Burroughs Wellcome Fund postdoctoral fellow at the University of Colorado. His current research is focused on developing precision biomaterials for applications in personalized medicine. Dr. Aguado completed his MS and PhD in biomedical engineering from Northwestern University and his BS degree in biomechanical engineering from Stanford University. He also obtained his certificate in Management for Scientists and Engineers from the Kellogg School of Management at Northwestern. Dr. Aguado is also a dedicated science communicator outside of the lab and seeks to engage underrepresented populations in the sciences. He is the former president of the Postdoctoral Association of Colorado, organized seminars featuring underrepresented thought leaders in STEM for CU Café, and served on the executive board for Project Bridge Colorado. Most recently, he co-founded LatinXinBME, a new social media initiative dedicated to building a diverse and inclusive community of Latinx biomedical engineers and scientists to support each other personally and professionally through their careers.

LECTURE 4:00 – 5:00 (PAA) A118
Happy Hour in Benson Hall Lobby Following

CHEMICAL ENGINEERING
UNIVERSITY of WASHINGTON
Knowledge and solutions for a changing world