

## Wallace H. Coulter Foundation Biomedical Engineering Seminar Series

**DR. LINA SHEHADEH** The Shehadeh lab is focused on rare kidney disease, cardiovascular disease, Duchenne Muscular Dystrophy, and cardiac regeneration. The Shehadeh team investigates the role of Osteopontin (OPN) and its downstream effectors in a variety of small and large animal models. They utilize cutting-edge techniques such as antibody-, aptamer-, and AAV gene- therapy in surgical and genetic mouse models. They routinely use extracellular flux analysis, echocardiography, left ventricular catheterization, patient-derived iPSC differentiation, and a variety of biochemical assays to study cardiac/renal function, mitochondrial function and a variety of mechanistic studies.



### DR. LINA SHEHADEH

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#### Role of Osteopontin in Heart Failure with Preserved Ejection Fraction (HFpEF)

**ABSTRACT:** Background: Patients with chronic kidney disease (CKD) and coincident heart failure with preserved ejection fraction (HFpEF) may constitute a distinct HFpEF phenotype. Osteopontin (OPN) is a biomarker of HFpEF and predictive of disease outcome. We recently reported that OPN blockade reversed hypertension, mitochondrial dysfunction and kidney failure in Col4a3<sup>-/-</sup> mice, a model of human Alport Syndrome. Objectives: Identify potential OPN targets in biopsies of HF patients, healthy controls and human induced pluripotent stem cell-derived cardiomyocytes (hiPS-CMs). Characterize the cardiac phenotype of Col4a3<sup>-/-</sup> mice, relate this to HFpEF and investigate possible causative roles for OPN in driving the cardiomyopathy. Methods: 2-Oxoglutarate Dehydrogenase-Like (Ogdhl) mRNA and protein were quantified in myocardial samples from patients with HFpEF, HFrEF, and donor controls. OGDHL expression was quantified in hiPS-CMs treated ± anti-OPN antibody.

Cardiac parameters were evaluated in Col4a3<sup>-/-</sup> mice ± global OPN knockout or AAV9-mediated delivery of Ogdhl to the heart. Results: Ogdhl mRNA and protein displayed abnormal abundances in cardiac biopsies of HFpEF compared with donor controls or HFrEF patients. Blockade of OPN in hiPS-CMs conferred increased OGDHL expression. Col4a3<sup>-/-</sup> mice demonstrated cardiomyopathy with similarities to HFpEF including diastolic dysfunction, cardiac hypertrophy and fibrosis, pulmonary edema, and impaired mitochondrial function. The cardiomyopathy was ameliorated by Opn<sup>-/-</sup> coincident with improved renal function and increased expression of Ogdhl. Heart-specific overexpression of Ogdhl in Col4a3<sup>-/-</sup> mice also improved cardiac function and cardiomyocyte energy state. Conclusions: Col4a3<sup>-/-</sup> mice present a model of HFpEF secondary to CKD wherein OPN and OGDHL are intermediates, and possibly therapeutic targets.



Through the generous support of the Wallace H. Coulter Foundation the Department of Biomedical Engineering facilitates weekly lectures each year during academic terms. Experts in all areas of Biomedical Engineering are invited to campus to provide a research seminar and to meet with faculty and students and to tour our academic and research facilities.

Friday, February 21, 2020  
2:00PM-3:00PM MMC Everglades 141