PROJECT SUMMARY/ABSTRACT: COOK PROJECT

Marfan Syndrome (MFS) is a relatively common connective tissue disorder with an incidence of 1 in 5000 persons. This dominantly inherited disorder occurs secondary to mutations in the extracellular matrix (ECM) protein fibrillin-1. Thoracic aortic aneurysm with dissection or rupture and dilated cardiomyopathy with progression to heart failure are the leading causes of morbidity and mortality in afflicted patients. Fibrillin-1 microfibrils dictate both tissue integrity and local growth factor bioavailability and are widely expressed across a range of tissues including ECM surrounding the cardiomyocyte and within the aortic wall.

The long-standing understanding of MFS is that pleotropic manifestations are secondary to TGFβ overactivation due to poor ECM sequestration and that losartan, an angiotensin type 1 receptor (AT1R) antagonist, mitigates aortic aneurysm formation through reduction of TGFβ signaling. My work has revealed that the mechanisms are more complex. I was the first to identify dilated cardiomyopathy as a primary manifestation of a fibrillin-1 deficient cardiomyocyte ECM with accompanying abnormal cardiomyocyte-ECM signaling.

As a vascular surgeon, I am interested in understanding the development of cardiovascular disease in MFS to improve the care we provide to patients with MFS and other inherited and acquired aortopathies. My central hypothesis is that cardiovascular disease in MFS is the result of discrete tissue-specific loss of Fbn1 signaling that disrupts homeostasis to induce inflammation and maladaptive remodeling. The proposed studies represent a framework to interrogate the functional relationships among extracellular microfibrils, inflammation, and adaptation to stress that intersect vasculature and heart. My investigations will establish a foundation to identify molecular determinants underlying aortic aneurysm formation and stress-mediated cardiomyopathy that can be pharmacologically targeted to restore cardiovascular function in MFS and related conditions.