Disease-Inspired Tissue Engineered Valves to Study Sex Bias in CAVD Progression
Lysmarie Figueroa, M.S.1, Marshall R. Walters1, Kristyn S. Masters, Ph.D.1
1University of Wisconsin-Madison, Madison, WI

Calcific Aortic Valve Disease (CAVD) is a prevalent valvular disease, but the development of effective treatments is limited by a gap in our understanding of the cellular and molecular mechanisms underlying the progression of this condition. During CAVD progression, changes in the phenotype of native valvular cells (VICs) and their extracellular matrix (ECM) occur, thus influencing CAVD pathogenesis. 3D scaffolds have previously been made to elucidate the cellular and molecular underpinnings of CAVD, but here we describe a unique approach to make stage-specific models of CAVD to investigate sex bias in disease progression.

We generated scaffolds that represent early and late stages of CAVD, as well as the healthy valvular state, by crosslinking gelatin and chondroitin-sulfate methacrylate in the presence of collagen fibers. Specifically, we mimicked the healthy/early disease transition by imitating pathological enrichment of glycosaminoglycans and the early/late transition by increasing collagen fiber content, both hallmarks of CAVD progression.

By seeding male or female VICs in these stage-specific disease models, we examined whether pathological ECM changes differentially affected males and females. We found that pathological changes in the ECM promote greater myofibroblastic differentiation in male VICs compared to females. Early and late-stage disease models stimulated significant increases in collagen and fibronectin in males, while females remained relatively unaffected. The impact of ECM pathology on VIC behavior was more influential than administration of a fibrotic stimulus, TGFbeta1. These results reveal new insight regarding sexual dimorphism in CAVD and highlight the potential for stage-specific disease models to decipher pathogenesis.