University of Rochester

BME PhD Defense Seminar

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Supervised by
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MAY 04

"A Human Tendon-on-a-Chip for Investigating Vascular Inflammation and Synovial Crosstalk in Peritendinous Adhesions"

Seminar Abstract: Tendon injuries are among the most common musculoskeletal pathologies, accounting for 16 million cases in the U.S. each year and imposing a substantial healthcare burden. The tendon repair process is hindered by a chronic inflammatory response that promotes the formation of vascularized fibrotic scar tissue. This problem is particularly challenging in intrasynovial tendons, where immune cells from the vasculature and extrinsic synovial fibroblasts are thought to drive peritendinous adhesions. These restrictive adhesions cause recurring pain and reduced joint motion, and current treatment strategies often fail to prevent or resolve them. Despite the clinical significance, the multicellular interactions linking vascular inflammation, synovial activation, and fibrotic adhesions remain poorly understood.

To study cell crosstalk in a human-relevant context, microphysiological systems (MPS), or tissue chips, have emerged as powerful tools to recapitulate key features of tissue physiology and disease in vitro. In my thesis, I validate and advance a human tendon-on-a-chip (hToC) designed to model inflammatory and fibrotic processes in the tendon microenvironment. The hToC integrates a 3D tendon construct and a vascular compartment separated by an ultrathin nanomembrane. This system reproduces hallmarks of tendon fibrosis, including myofibroblast differentiation, tissue contraction, vascular activation, and monocyte recruitment. I then incorporated synovial fibroblasts to model the intrasynovial tendon niche. Synovial activation enhanced contraction, inflammatory cytokine secretion, and the deposition of fibronectin- and collagen III-rich matrix bridges between tendon and synovial compartments resembling nascent peritendinous adhesions. Importantly, these effects emerged even in the absence of exogenous TGF-β1, highlighting the role of synovial crosstalk in promoting adhesions. I also demonstrate suppression of inflammatory and adhesion phenotypes through pharmacological inhibition of the IL-6/JAK/STAT pathway, positioning the hToC as a drug-testing platform. Finally, I designed a manufacturable flow insert to enable vascular shear stress and circulating flow through the hToC vascular channel. Incorporating physiological flow increased endothelial activation and enhanced monocyte transmigration, demonstrating the importance of flow in modeling immune cell interactions in tissue inflammation. Together, this work advances a human microphysiological system to interrogate cellular crosstalk in the fibrotic tendon microenvironment, providing a new approach methodology to model peritendinous adhesions and evaluate anti-fibrotic therapeutics.

Monday, May 4, 2026 | 10:00 am EST | 1W-304 Helen Wood Hall
Zoom: https://rochester.zoom.us/j/91281547539

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