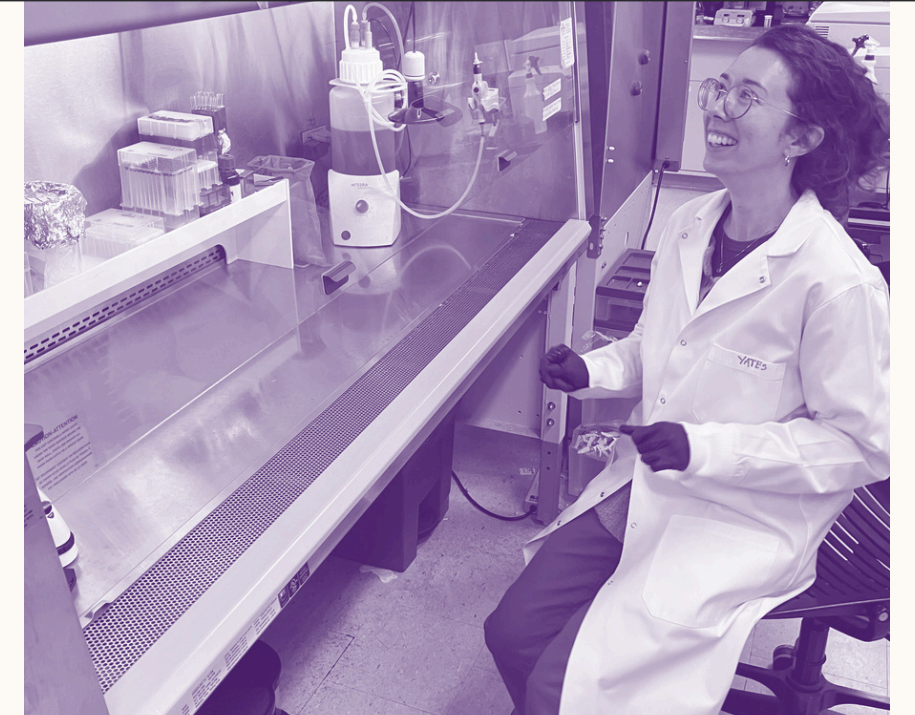




* dissertation

defense announcement



Investigating brain endothelial cell mechanics with engineered *in vitro* models

As life expectancy in the US has increased, a growing percentage of the adult population is expected to suffer from age-related neurodegenerative diseases, such as Alzheimer's disease (AD). Common vascular risk factors like hypertension and arterial stiffening are associated with vascular remodeling, cerebrovascular disease, and blood-brain barrier disruption. Brain endothelial cell dysfunction is the central driver of blood-brain barrier disruption and downstream neurodegeneration. Due to the clear associations between vascular basement membrane remodeling with blood-brain barrier disruption, we sought to investigate the consequences of mechanical inputs on cellular dysfunction using an *in vitro* model. Previous work has shown that brain endothelial cells exhibit sensitivity to both fluid shear stress and substrate stiffness, but no studies have examined the consequences of both factors in the same model, likely due to significant engineering challenges. In this dissertation, we examine the consequences of substrate stiffness and fluid shear stress on brain endothelial cell dysfunction, in addition to providing a design for a microfluidic splitter to increase experimental throughput. We show that brain endothelial cells have reduced membrane expression of a crucial junctional support protein, ZO-1, when cultured on 30 kPa hydrogels compared to 6 kPa hydrogels in static conditions. Exposure to physiological fluid shear stress impacts cell morphology, increasing cell size and elongation across both hydrogels. Further transcriptomic analysis and quantification of intracellular protein production revealed a distinct inflammatory response of cells cultured on 30 kPa hydrogels across both static and physiological fluid shear stress. To our knowledge, this is the first model to demonstrate a direct connection between substrate identity and brain endothelial inflammation in a perfused model, supporting the need for further investigation into mechanical regulation of brain endothelial cell dysfunction. We also demonstrate successful formation of a confluent 3D brain endothelial microvessel, fabricated from a cleanroom-free 3D-printed mold. This system represents an important step to overcoming technical limitations to the use of *in vitro* models.

April 7th, 2025

Featheringill Hall 298 at 1:30pm

Zoom Info:



Meeting ID: 970 4846 2694

Passcode: 714340

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**Under the direction of
Dr. Ethan Lippmann
& Dr. Angela Jefferson**