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*“Brain-State and Vascular
Regulation of Periarterial
Cerebrospinal Fluid Transport”*

Seminar Abstract:

The glymphatic system is a brain-wide network of perivascular pathways that facilitates the exchange of cerebrospinal fluid (CSF) and interstitial fluid, contributing to metabolic waste clearance and brain homeostasis. Glymphatic transport is strongly influenced by vascular dynamics and brain state, yet the mechanisms governing periarterial CSF flow remain debated. This thesis investigated how these physiological processes regulate periarterial CSF transport. In Chapter 2, we tested whether directional CSF flow after intracisternal tracer administration is an artifact of injection-induced intracranial pressure changes. Using a dual-syringe infusion paradigm eliminating net volume change, we confirmed that periarterial CSF flow remained pulsatile, synchronized with the cardiac cycle, and directed with arterial blood flow, demonstrating that this directional flow is not driven by tracer injection. In Chapter 3, we incorporated measured hydraulic resistance and compliance into theoretical and computational models of perivascular pumping. Realistic boundary conditions reconciled discrepancies between predicted and observed flows, supporting arterial pulsations as an important driver of periarterial CSF transport. In Chapter 4, we provided the first high-resolution characterization of periarterial CSF flow in rats and identified conserved and species-specific transport features. Rats exhibited larger, lower-resistance perivascular spaces and greater CSF volume flow rates than mice, while flow in both species remained advection-dominated and strongly coupled to cardiac pulsatility. Because glymphatic transport is enhanced during sleep but suppressed during wakefulness, Chapter 5 examined how awakening regulates glymphatic transport. Awakening from sleep or anesthesia produced coordinated neural and vascular changes, including arterial dilation, suppression of arterial pulsatility, and collapse of penetrating perivascular spaces. Rather than merely reducing influx, these changes reversed periarterial CSF flow. Neural activity changes preceded vascular responses and flow reversal, supporting a model in which brain-state-dependent neurovascular dynamics regulate glymphatic transport. These findings suggest that repeated awakenings may disrupt sustained unidirectional CSF influx and help explain how sleep fragmentation impairs brain clearance. Collectively, this work validates direct measurements of periarterial CSF flow, strengthens the mechanistic basis for vascular-driven transport, identifies cross-species scaling principles, and reveals flow reversal as a previously unrecognized mechanism by which awakening suppresses glymphatic function, providing a foundation for future studies of glymphatic dysfunction.

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