CHEMICAL ENGINEERING
UNIVERSITY of WASHINGTON

SEMINAR

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Breaking (Blood-Brain) Barriers: MRI-guided Focused Ultrasound as a Novel Treatment Option for Cerebral Cavernous Malformations and Enhanced Drug Delivery

Monday August 7th
Lecture 4:00-5:00 p.m. | Physics/Astronomy Auditorium (PAA) A110
Reception 5:00-6:00 p.m. | Benson Hall Lobby

Bio

Delaney Fisher is an American Heart Association Pre-Doctoral Fellow pursuing her Ph.D. in the Department of Biomedical Engineering at the University of Virginia. Her research in the Price Lab centers on leveraging the non-invasive, therapeutic technology of focused ultrasound to overcome challenges in treating disorders of the brain. Specifically, her dissertation work bridges the fields of biomedical engineering, neuroscience, and radiology to develop MRI-guided focused ultrasound platforms for the treatment of cerebral cavernous malformation, a disease that causes hemorrhagic, vascular growths in the brain. Previously, Delaney received her B.S. in Chemical and Biomolecular Engineering from the University of Tennessee. She is passionate about effective communication and diversity, equity, and inclusion practices. During her term as president of the University of Virginia's Graduate Biomedical Engineering Society, she aided in the implementation of department initiatives to foster conversation and connection around DEI efforts, including the installment of the Candid Conversation series, faculty-student lunches, and DEI townhall.

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Abstract

Disorders of the brain remain a challenge to treat due to the impervious blood-brain barrier (BBB) that limits passage of therapeutics into and clearance of toxins from the brain[1]. Focused ultrasound (FUS) is a non-invasive treatment method that leverages pressure waves to oscillate simultaneously administered, gas-filled microbubbles within brain capillaries[2] (**Fig. 1, Left**). This FUS technique temporarily opens the BBB, allowing ordinarily impenetrable agents across the vessel walls and can stimulate secondary neuroprotective effects[3] (**Fig. 1, Right**). Under magnetic resonance image (MRI) guidance, FUS BBB opening (BBBO) enables targeting—localizing these effects to precise diseased brain regions. Using FUS BBBO, we have sought to develop a novel treatment option for cerebral cavernous malformations (CCMs)—a disease that causes mutated cells of the brain vasculature to undergo cancer-like signaling changes, resulting in the formation of hemorrhage-prone, vascular growths. Patients with CCM can sustain incapacitating, life-threatening neurological symptoms. Currently, resection of CCMs via invasive neurosurgery is the only treatment, and preclinical pharmacological agents have had minimal success[4]. By using MRI-guided FUS BBBO to increase delivery of therapeutics to CCMs, better therapeutic outcomes may be achieved in addition to unlocking new therapies like higher-molecular weight biologics (i.e. antibodies, drug/gene-loaded nanoparticles) that have restricted transport across the BBB[5-6]. Thus, we tested whether FUS BBBO could be deployed therapeutically in a clinically-relevant mouse model of CCM, which could establish the first incisionless treatment for CCM. To this end, CCM was induced in mice by the knock down of the CCM1 gene in vasculature cells. FUS BBBO was applied over a range of peak-negative pressures (0.2-0.6 MPa), affecting the degree of expected BBBO by modulating the maximum microbubble diameter (**Fig. 1**). MRI was used to guide sonications and evaluate the safety and longitudinal changes after BBBO, and MRI contrast agent (gadolinium, ~1kDa) was administered to confirm BBBO, visible as a bright T1 MRI signal (**Fig. 2A**). We found that FUS BBBO increased contrast delivery to the CCM, with delivery localizing primarily to the boundaries of CCMs rather than the dark CCM cores (**Fig. 2B**). Acutely (24h post-FUS), CCMs exposed to FUS BBBO remained structurally stable, with no signs of hemorrhage or increases in volume (**Fig. 2C**). Longitudinal MRI revealed that FUS BBBO controlled the growth of CCMs, when compared to non-sonicated lesions of similar volumes and anatomical locations (**Fig. 2D**). Indeed, after 30 days, sonicated lesions were on average 95% of their pre-sonication volume, while non-sonicated control lesions grew to 880% of their initial volume. Strikingly, in mice receiving multiple BBBO treatments, the formation of new CCMs was significantly reduced by 81% (**Fig. 2E**).

Here, we show that FUS BBBO can non-invasively increase the delivery of a small molecule MRI contrast agent and can reduce lesion growth and formation even in the absence of paired therapeutically-active agents. Ultimately, the innate protective effect of FUS BBBO for CCM and its ability to seamlessly integrate with antibody, gene, and nanocarrier delivery generates an immeasurable potential to vastly expand the therapeutic options for CCM and revolutionize the treatment paradigm for brain disorders.

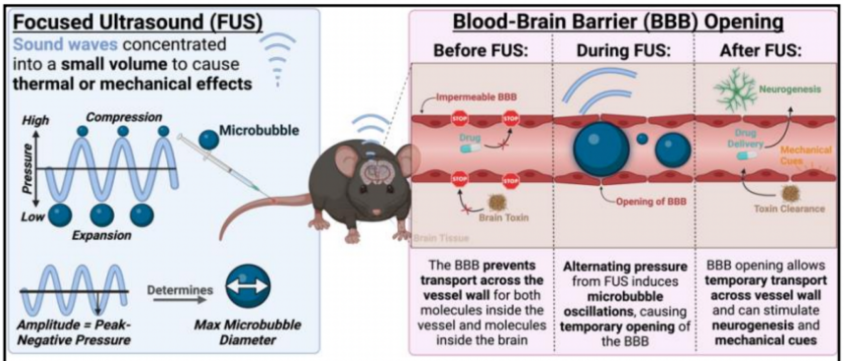

Figure 1. Schematic depicting FUS BBBO physical and biological effects.

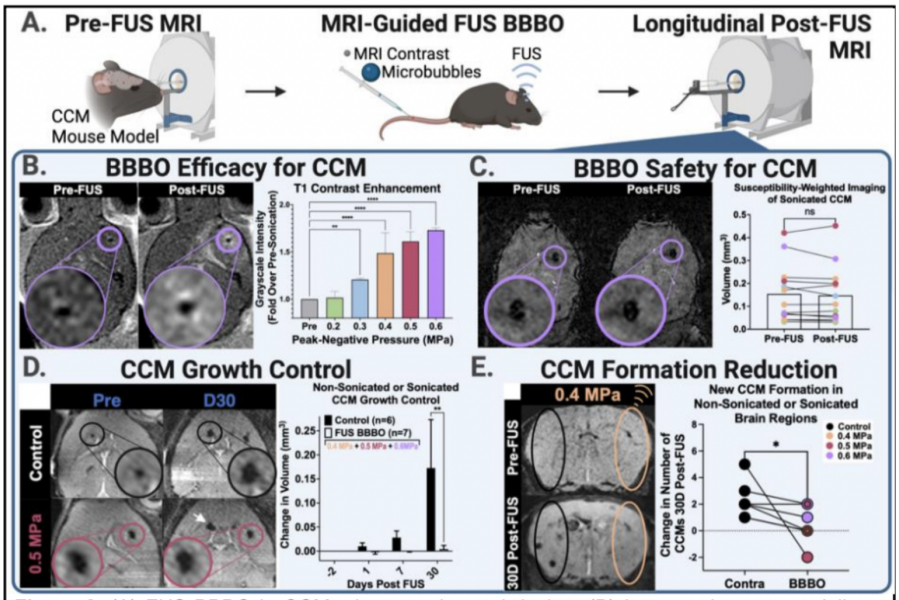

Figure 2. (A) FUS BBBO in CCM mice experimental design. (B) Increase in contrast delivery post-FUS. (C) No acute hemorrhage or volume change post-FUS. (D) FUS BBBO controls growth of sonicated CCMs and (E) reduces CCM formation in sonicated brain area.

References: (1) Patel, MM and Patel, BM. CNS Drugs, 2017; (2) Konofagou, EE et al. Theranostics, 2012; (3) Todd, N et al. JCR, 2020; (4) Snellings, DA et al. Circ Res, 2021. (5) Nance, E et al. JCR, 2014; (6) Mead, BP et al. Nano Lett, 2017.