# Transcranial Theranostic Ultrasound Pre-Planning and Blood-Brain Barrier Opening Using a Phased Array In Vitro and In Vivo

Alec Batts[1], Robin Ji[1], Alina Kline-Schoder[1], Rebecca Noel[1], and Elisa Konofagou[1,2]

[1]Department of Biomedical Engineering, [2]Department of Radiology, Columbia University, New York, USA

This study utilizes *in vitro* and *in vivo* theranostic ultrasound (TUS) treatment pre-planning to inform transcranial blood-brain barrier opening (BBBO) in mice with overlaid primate skull fragments using a single phased array.

*In vitro* experiments were conducted using a hydrophone (Fig. 1A) and microbubble flow channel (254 μm diameter, 8.0E8 microbubbles/mL) (Fig. 1B) to determine the expected transcranial pressure loss and focal shift induced by the skull, respectively. Simulations were conducted using the k-wave MATLAB toolbox with micro-CT scans (0.08 mm resolution) of primate skull fragments to evaluate steering angle-dependent attenuation and focal shift of the TUS beam. Synchronous *in vivo* transcranial BBBO and power cavitation imaging (PCI) was performed using the P4-1 phased array (1.5 MHz, 450 kPa derated peak-negative pressure, 35 mm focal depth, ±3.72 degree electronic steering angle), operated by a Verasonics ultrasound system (Vantage) (Fig.1C) in mice (C57BL/6J).

Simulations revealed significantly increased attenuation and axial focal shift magnitude with larger steering angle magnitudes through the non-human primate (NHP) skull (Fig.1D-E); no significant differences were observed through the human skull (Fig.1F-G). *In vitro* skull experiments demonstrated 0.3-1.5 mm axial and lateral focal shifts induced by the skull as confirmed by comparison between contrast-enhanced B-mode and PCI images acquired in the channel phantom. *In vivo* transcranial BBBO was achieved bilaterally, exhibiting high correlation between regions of contrast-enhancement on T1-weighted MRI and -6 dB regions in corresponding PCI (Fig.1H-M).

Feasibility for synchronous transcranial BBBO and PCI using a single theranostic phased array was demonstrated in mice *in vivo*.

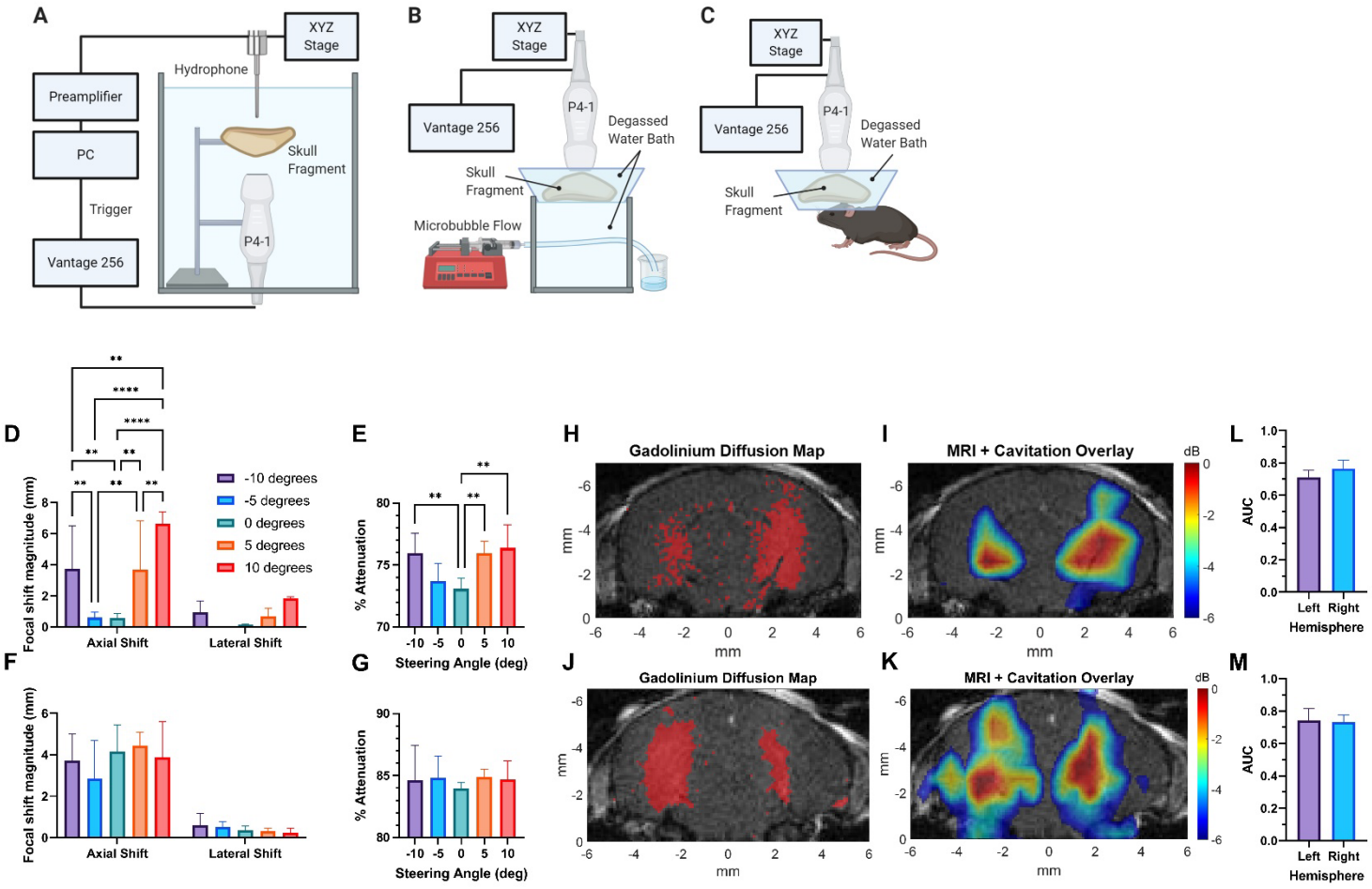


**Figure 1:** Experimental setup for **(A)** transcranial attenuation measurements, **(B)** *in vitro* cavitation mapping registration error calculations, and **(C)** *in vivo* transcranial BBB opening. Simulated steering angle dependent focal shift and attenuation through NHP skull fragment **(D-E)** and human skull fragment **(F-G)**. Statistical significance determined by a one-way ANOVA with post-hoc Tukey's multiple comparisons test where, $^{**}p<0.01$, $^{***}p<0.001$, $^{****}p<0.0001$, for n=6 simulation trials. Region of contrast enhancement on $T_1$-weighted MRI and corresponding cavitation map for BBB opening through the NHP skull **(H-I)** and human skull **(J-K).** Area under the receiver operator characteristic (ROC) curve depicting correlation between gadolinium diffusion maps and cavitation maps through **(L)** NHP skull and **(M)** human skull (n=4 mice per group). All error bars denote the mean ± standard deviation.