Targeted Drug Delivery with Focused Ultrasound-Induced Blood-Brain Barrier Opening Using Acoustically-Activated Nanodroplets

Cherry C. Chen\textsuperscript{a}, Paul S. Sheeran\textsuperscript{b}, Shih-Ying Wu\textsuperscript{a}, Oluyemi O. Olumolade\textsuperscript{a}, Paul A. Dayton\textsuperscript{b}, Elisa E. Konofagou\textsuperscript{a, c}

\textsuperscript{a} Department of Biomedical Engineering, Columbia University, New York, NY 10027
\textsuperscript{b} Joint Department of Biomedical Engineering, University of North Carolina and North Carolina State University, Chapel Hill, NC, 27599
\textsuperscript{c} Department of Radiology, Columbia University, New York, NY 10032

Keywords – Blood-Brain Barrier, Drug Delivery, Nanodroplets, Nanomedicine, Microbubbles

Background, Motivation and Objective – Focused ultrasound (FUS) in the presence of systemically administered microbubbles has been shown to locally, transiently and reversibly increase the permeability of the blood-brain barrier (BBB), thus allowing targeted delivery of therapeutic agents in the brain for the treatment of central nervous system diseases. Currently, microbubbles are the only agents that have been used to facilitate the FUS-induced BBB opening. However, they are constrained within the intravascular space due to their microscale size, limiting the delivery effect at or near the microvessels. In the present study, acoustically-activated nanodroplets were used as a new class of contrast agents to mediate FUS-induced BBB opening in order to study the feasibility of utilizing these nanoscale phase-shift particles for targeted drug delivery in the brain.

Statement of Contribution/Methods – 3-kDa dextran was used as the model molecule to confirm BBB opening after FUS was locally applied to target the left hippocampus of C57/BL mice in the presence of both nanodroplets and conventional microbubbles. The acoustic pressure was
varied between 0.15 and 0.60 MPa so as to be clinically relevant. The fluorescence intensity increase was quantified to compare the efficiency of FUS-induced delivery dose between these two contrast agents. Passive cavitation detection was used in the attempt to establish a correlation between the amount of dextran delivered in the brain and the acoustic emission recorded during sonication.

Results/Discussion – The BBB opening was consistently achieved using nanodroplets at pressures higher or equal to 0.45 MPa, while the pressure threshold was decreased to 0.30 MPa using microbubbles. The stable cavitation threshold for nanodroplets was found to be 0.48 kV·s², which was significantly lower than that of microbubbles (2.9 kV·s²). For each acoustic pressure, microbubbles produced greater fluorescence enhancement compared to nanodroplets. The normalized enhancement with pressure followed a linear relationship with correlation coefficients at 0.76 and 0.94 for nanodroplets and microbubbles, respectively. The dextran delivery achieved using nanodroplets was found to be more homogeneous within the targeted region, and no inertial cavitation was induced even at the highest pressure. Histological evaluation revealed minor damage when the animals were sonicated at 0.60 MPa using microbubbles, corresponding to the onset of inertial cavitation. The present study demonstrated, for the first time, the feasibility of nanodroplet-mediated FUS-induced BBB opening. Our results highlighted the possibility to develop this technology for potential extravascular targeted drug delivery in the brain, extending the delivery region beyond the cerebral vasculature. Future studies are needed to optimize the nanodroplet composition and the acoustic parameters in order to decrease the activation pressure and to achieve higher drug delivery efficiency.