Title: Optimization of blood brain barrier opening using laser-activated perfluorocarbon nanodroplets

Authors: Kristina Hallam[1,2] and Stanislav Emelianov[1,2]
[1]*Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University School of Medicine, Atlanta, GA, USA*
[2]*School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA, USA*

Background, Motivation, and Objective:

Perfluorocarbon nanodroplets (PFCnDs) are used in ultrasound (US) as a contrast agent and therapeutic delivery vehicle. When loaded with a photoabsorber and upon pulsed laser irradiation, PFCnDs undergo a laser-triggered phase change from droplet to bubble and provide photoacoustic (PA) and ultrasound contrast. We have previously demonstrated the ability of laser-activated PFCnDs to open the blood brain barrier (BBB) and deliver various agents across the BBB by harnessing the PFCnD phase-change ability. In these studies, we examine the effect of laser pulse parameters used for PFCnD triggering on BBB opening. As a result, the studies provide guidelines on how to safely and effectively open the BBB using laser-activated PFCnDs. Optimization of this method of BBB opening could enable non-invasive delivery of contrast or therapeutics to the brain tissue under US/PA image guidance, resulting in a safe and efficient approach to studying neurological diseases.

Statement of Contribution/Methods:

A solution of Evans Blue (EB) dye and PFCnDs, composed of liquid perfluorohexane, a lipid shell, and a 1064 nm NIR dye for laser triggering, was introduced via systemic delivery. Injected PFCnDs had a distribution of 265 ± 65 nm in size. To activate PFCnDs, a pulsed laser (1064 nm, 10 Hz PRF) was used to deliver light through a 1.5 mm diameter optical fiber positioned over the right side of the mouse brain (Fig. 1A). Mice (n = 3 per group) were exposed to one of three laser fluences (70, 56, and 38 mJ/cm^2) and one of three laser pulse groups (1200, 600, and 300 pulses). After 4 hours, mice were sacrificed, and brains were excised. BBB opening at different laser fluences and number of laser pulses was evaluated qualitatively and quantitatively using EB staining of the tissue (Fig. 1B), fluorescence from the extravasated antibody immunoglobulin G (Fig. 1C), and via US/PA imaging of the delivered 1064 nm NIR dye (40 MHz, Vevo LAZR, Fig. 1D).

Results/Discussion, and Conclusions:

Overall, these studies serve as a guideline to choosing suitable laser parameters for safe and effective BBB opening using laser-activated PFCnDs. The results of these studies show trends between increased laser fluence and increased BBB opening as well as between an increased number of laser pulses and increased BBB opening, however, with limitations on the extent of BBB opening after a certain number of pulses. Thus, laser-activated PFCnDs have the potential to deliver various sized agents across the BBB, allowing for real-time, US/PA guided monitoring and treatment of neurological disease.

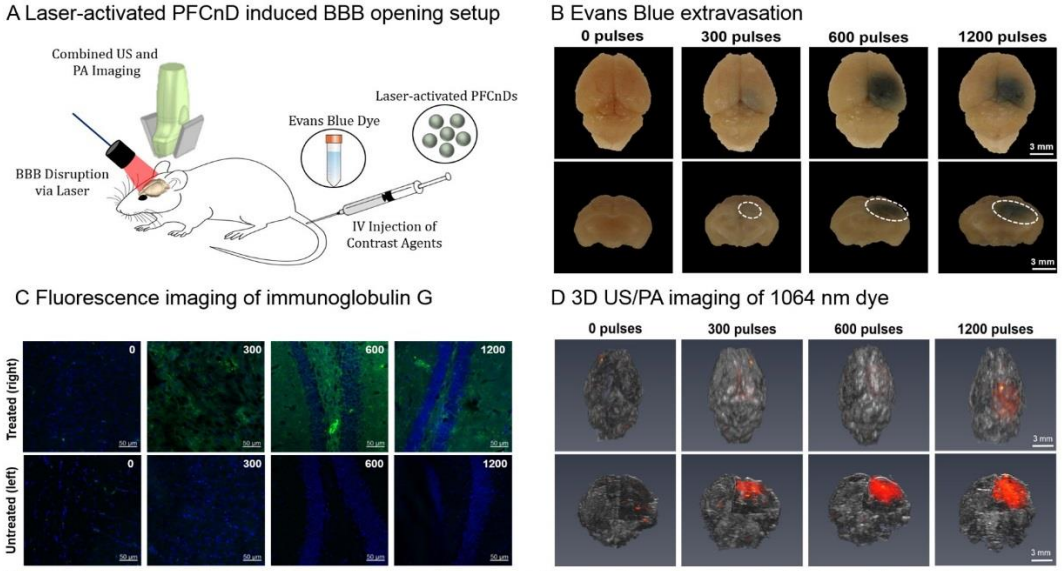

Figure 1. A Experimental setup for laser-activated perfluorocarbon nanodroplet induced blood brain barrier opening. B-D Brain images showing Evans Blue extravasation, immunoglobulin G extravasation for both treated (right) and untreated (left) sides of the brain, and 1064 nm dye extravasation, all for a varying number of laser pulses and a fluence of 56 mJ/cm².