Decoupling Mechanical and Thermal Effects of Ultrasound Enhanced Local Drug Delivery Systems

Selva Jeganathan[1], Emily Budziszewski[1], Peter Bielecki[1], Michael Kolios[2], Agata Exner[1]
[1]Case Western Reserve University, Cleveland, United States, [2]Ryerson University, Toronto, Canada

Background, Motivation and Objective

Systemic chemotherapy has been shown to deliver less than 1% drug to tumor cells. Local drug delivery systems, such as *in situ* forming implants (ISFIs), potentially allow for 100% drug delivered to the tumor site, but still, suffer from poor therapeutic outcome. The poor outcome can be attributed to insufficient drug diffusion due to tumor microenvironment. Ultrasound (US) has been shown to improve drug distribution and intracellular uptake of particles. Prior work has shown that US enhances drug distribution in gels (Manaspon et al, *Annal Bioeng 2017)* and subcutaneous space (Bielecki et al, *IEEE* 2017). In this study, we aim to design experiments to probe the ultrasonic mechanical and thermal effects that led to increased drug distribution.

Statement of Contribution/Methods

ISFIs consist of poly(lactic-co-glycolic acid) and Doxorubicin (Dox) dissolved in N-methyl-2-pyrrolidone. Subcutaneous colorectal tumors (HCT-15) grown in athymic mice received an ISFI, ISFI + 30 min US (5% duty factor, Δ 2°C), ISFI + 5 min hyperthermia (H) (heated rice pack, Δ 20°C), or ISFI + 5 min US (H) (33% duty factor, Δ 20°C). Mice received a single ISFI injection and one exposure to US (4 cm^2 surface probe, 3 MHz, 2.2 W/cm^2) / hyperthermia. Thermocouples measured tumor temperature changes. Dox distribution in-vivo was measured with an optical imaging system (Maestro, Life Science) and analyzed in ImageJ (radial profile plugin, NIH). ISFIs were harvested from the tumor at 1 and 8d and Dox release was measured on a plate reader (Tecan, Infinite Series) (Fig 1A).

Results/Discussion

1d release of Dox from the ISFI was equivalent for all groups, yet a significant change in Dox distribution can be seen in the ISFI+ 5 min US group up to 0.4 cm (Fig 1B). At 8d, a significant release of Dox with 5 min US is seen compared to all other groups (96.31 ± 3.59 %, $p < 0.05$) and the Dox intensity increased 10-fold at 0.6 cm radial penetration with all treatment groups compared to ISFI alone (Fig C, black arrow in inset). Mechanical and thermal effects each contribute to the increased drug distribution seen in the optical images (Fig D). These two effects combine to increase the release of Dox at 8d that correlates to greater optical Dox tumor intensity. This synergy helps explain the reduced tumor growth rate seen with ISFI + 5 min US (Jeganathan et al, *IEEE* 2018). Future work will examine the acoustic radiation force effects on drug penetration.

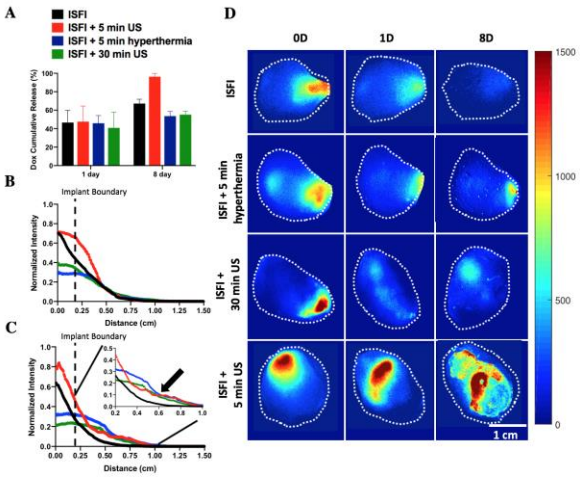

Figure 1: (A) Dox release from ISFIs, legend applies to Fig B and C. Radial Dox penetration at (B) 1d and (C) 8d. (D) Representative heat maps of optical images of tumors injected with ISFIs.