The majority of high intensity focused ultrasound (HIFU) applications today involve relatively long, continuous exposures that produce significant temperature elevations for tissue ablation. In comparison, less is being done with pulsed exposures, where non-continuous energy deposition reduces the temporal average intensity and consequent formation of heat. Our pre-clinical investigations have shown that pre-treating both normal and cancerous tissues non-invasively with pulsed-HIFU can enhance the delivery of both systemically and locally injected materials to those targeted tissues in a non-destructive manner. This enhancement, which occurs reversibly, allows for improved efficacy of therapeutic agents possessing a variety of formulations, including soluble compounds, liposomes, nanoparticles, and plasmid DNA. Using murine xenograft, tumor models, we have shown that enhanced tumor growth inhibition can be obtained when combining the exposures with the systemically administered proteasome inhibitor, Velcade®, compared to the drug alone. Similar improvements in therapeutic efficacy were found when direct intra-tumoral injections of tumor necrosis factor alpha (TNF-α) plasmid were used. Additional studies demonstrated how the exposures improved delivery of tissue plasminogen activator (tPA) to blood clots in vitro, and consequently increased the rate of thrombolysis in both in vitro and in vivo models.

It is hypothesized that the delivery enhancement, and consequent improved therapeutic results, are directly linked to tissue displacement that occurs from locally-generated acoustic radiation forces, produced during each pulse. Shear forces are created between adjacent regions of tissue experiencing non-uniform displacement, where the resulting strain is capable of opening cellular junctions in the vasculature and the parenchyma, increasing extravasation and interstitial diffusion, respectively. In solid tumors, these structural alterations might also improve fluid exchange, especially at the tumor-host interface. As a result, a decrease in normally high interstitial pressures, which have been shown to adversely affect extravasation, might also occur. Improved diffusion through the interstitium, due to mechanical disruption of fibrillar collagen in the extracellular matrix, is another mechanism being investigated.

The effective use of pulsed-HIFU exposures to enhance delivery requires a basic understanding of the mechanisms by which the acoustic energy from the exposures interacts with the exposed tissues. Optimization of the exposure parameters, as well as their efficient translation from one tissue type to another, will be obtained through further experimentation and mathematical modeling. By selectively increasing the bioavailability of therapeutics in targeted tissues, pulsed-HIFU holds much promise to improve the treatment of cancer and other diseases.