

Combining ultrasound with chemo and immunotherapy to cure cancers



Ultrasound imaging is widely valued for its low cost, simplicity, real time capabilities, and safety. Ultrasound waves compress and rarefy tissue and the resulting mechanical and thermal effects can be exploited to modify tissue and drug delivery vehicles. Mechanisms by which ultrasound facilitates drug and gene delivery can be summarized as direct changes in the biological or physiological characteristics of tissues facilitating transport, direct changes in a drug or drug carrier increasing bioavailability or enhancing efficacy, and indirect mechanisms by which ultrasound acts on an exogenous material (such as a microbubble) to produce changes in the surrounding tissue. Approaches using these mechanisms to enhance delivery vary in the optimal parameter settings and in efficiency. Early, small scale clinical trials are now underway to extend the use of ultrasound in the guidance and enhancement of drug delivery mechanisms. Our laboratory has synthesized unique drug delivery particles and created technologies to further such delivery methods. In this lecture, we will particularly focus on the technologies that are the basis of recent and near term clinical trials.

Methods to monitor treatment efficacy using ultrasound or MR-based imaging techniques have also been a focus of our laboratory and will be reviewed. Magnetic resonance-guided focused ultrasound (MRgFUS) facilitates noninvasive image-guided conformal therapy and can provide precise control of ultrasound treatment. Ultrasound-guided ultrasound therapy can also be applied, particularly for the treatment of superficial lesions. Optimized transducer design for image-guided therapy is a crucial aspect of such strategies and the designs created for our studies will be reviewed.

While ultrasound ablation can be curative for some cancers, in many scenarios sensitive surrounding tissues constrain the margins of ablation and therefore augmentation with chemotherapy may be required to destroy remaining tumor. Both mechanical and thermal effects of ultrasound can be exploited and can also enhance the accumulation of nanoparticles via release of the drug from a particle or by changing properties of the vasculature. In our laboratory, we combine the use of positron emission tomography (PET) and optical imaging to quantify delivery, the use of magnetic resonance imaging (MRI) for anatomic and functional imaging and to assess local temperature and the use of ultrasound to enhance delivery. We have demonstrated a five-fold and fifty-fold enhancement of liposome and drug concentration, respectively, within MRgFUS thermal ablation-treated tumors, with dense accumulation within the surrounding tissue rim. Ultrasound-enhanced drug accumulation is rapid and durable, greatly increasing total tumor drug exposure over time. In addition, we found that the small molecule gadoteridol accumulates around and within ablated tissue for short periods after treatment. We demonstrate that mechanisms for the enhanced accumulation of liposomes and small molecule probes include dilated vasculature, loss of vascular integrity resulting in extravasation of blood cells, stromal inflammation, and loss of cell-cell adhesion and tissue architecture. The locally-enhanced accumulation was preserved even after a multi-week protocol of drug-loaded liposomes and partial ablation. By supplementing ablation with concurrent liposomal drug therapy, a complete and durable response in local cancers was obtained using protocols for which a sub-mm rim of tumor remained after ablation.

Finally, we will describe methods to activate the immune system such that local ultrasound-based therapies can achieve a systemic cure for a multi-focal cancer.