Biomedical ultrasound therapeutics

Biomedical ultrasound is widely employed as an imaging modality for anatomical assessment, as well as to provide information on blood flow characteristics. Focused, high intensity ultrasound is also gaining traction as a therapeutic tool, applications of which include tissue ablation (*e.g.* essential tremor treatment). For both diagnostic and therapeutic ultrasound, there is increasing interest in employing microbubble contrast agents. Unlike MR and CT agents, ultrasound contrast agents are comparable in size to a red blood cell and therefore provide a purely intravascular agent for clinical radiology. Under acoustic conditions comparable to those used in diagnostics, ultrasound can induce microbubbles to resonate around their equilibrium size (~1-5 μm), expanding and contracting in the sound field, as well as physically rupture. Microbubbles exhibit distinct nonlinear acoustic signatures when situated in an ultrasound field, and are currently clinically employed in echocardiography and liver applications as well as pre-clinically for the characterization of tumours and quantification of perfusion. These agents can also be functionalized to spatially target disease sites (*e.g.* angiogenesis), thereby enabling an ultrasound molecular imaging modality.

Recently, microbubbles have been exploited for therapeutic benefit by initiating transient, local increases in cell membrane and vascular permeability using sound (*i.e.* **sonoporation**)**.** This method has tremendous potential as a non-viral, image-guided and targeted delivery platform, for example in the selective delivery of cell lethal molecules into tumors or genetic material into deficient tissues. Indeed, the first in-human trial using ultrasound-triggered microbubbles to enhance drug delivery to the brain via transient opening of the blood-brain-barrier has recently been initiated in Canada. Despite promising initial results, *e.g.* pre-clinical work in animal models of cardiovascular disease and cancer, the nonlinear interactions between acoustically sensitive constructs and tissue remain poorly understood. Further, the mechanisms by which bubble oscillations within the microcirculation facilitate drug delivery into *extravascular* target cells is completely unexplored. A solid understanding of the mechanisms of therapeutic delivery with this approach is required to bring this platform to the clinical arena, and this cognizance will require fundamental explorations at the interface of ultrasound physics/acoustics and cell biology/physiology.

This talk will describe the latest research into the biophysics of sonoporation; from the microsecond timescale physics of bubble vibration, to the resulting effects on the biology of endothelial cells occurring on timescales of minutes to hours. After a brief background on the physics of ultrasound-stimulated microbubble dynamics, I will discuss my work using unique microscopy approaches to couple the salient biophysics of sonoporation over ten orders of magnitude in time, including cell membrane perforation and recovery, acute cytoskeletal disruption and re-organization, and shear-sensitive calcium influx dynamics.