

Ultrasound and microbubbles for anticancer drug delivery: From physics to clinics

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Ultrasound (US) in combination with gaseous microbubbles has come into focus as a potential new drug delivery technology. Indeed, beyond their exploitation for diagnosis, microbubbles and US, today represent an emerging technology for localized drug delivery. Recent research shows that under the action of US waves, microbubbles transiently perforate biological barriers (e.g. cell membrane, endothelial barrier) thus leading to the uptake and enhanced accumulation of drugs in the targeted region. Hence, the bioavailability of therapeutic agents is site- specifically augmented only in the zone where the US waves are focused. Commonly referred to as sonoporation, it offers real promises as a drug delivery tool with potential of alleviating the limitations encountered by traditionally available therapeutic arsenal.

Sonoporation can indeed potentiate the extravasation of a wide range of therapeutic molecules including chemotherapeutic agents, nucleic acids (e.g. siRNA, miRNA, mRNA, oligonucleotides, plasmid DNA), therapeutic peptides, and monoclonal antibodies. Preclinical studies demonstrating proof of concept have been shown in various organs as well as clinical indications in a number of small animal models including both ectopic and few orthotopic models.

Nevertheless, a number of evaluation and clinical validation issues need to be tackled including standardization of US parameters, selection of appropriate microbubbles, identification of optimal clinical indications and drugs before further translation to the clinic.

To facilitate US and microbubbles drug delivery to the clinic, a number of questions need to be addressed such as: which organ should be targeted? Which drugs are suitable for sonoporation drug delivery? If cancer is the clinical target, which lesions (solid tumors or metastases) should be considered? Since microbubbles need to be localized within the target organ or zone for better drug extravasation, should considerations concerning the perfusion of the target lesion take precedence? What US parameters (frequency, pressure/MI, exposure time and duty cycle) should be used to activate the microbubbles to induce drug uptake? A number of studies show that sonoporation efficiency is strongly correlated with the concentration of microbubbles in

the target zone, suggesting that UCA concentration is a crucial sonoporation parameter. Accordingly, what microbubble concentrations should be used? Similarly, the appropriate method of microbubble administration, that is, bolus injection or continuous infusion delivered intra-arterially or intravenously needs careful consideration. Likewise, the treatment schedule is of significant importance, since administration of microbubbles and drugs should be performed in a prescribed manner and US insonation timing (duty cycle) should be synchronized to coincide with the arrival of elevated microbubble concentrations in the targeted regions. The type of microbubbles employed is also of significant importance because their response to US activation depends on their physical properties. Recent data showed promising results using droplet activated microbubbles (e.g., ACT technology).

Pragmatically, it should be easier and faster to evaluate drug delivery using clinically available microbubbles, as that will facilitate quick translation to clinic. Whether US scanners operated in specific modes (such as Doppler mode) can deliver US sequences capable of inducing drug delivery; are just some of the questions that also need addressing for the effective translation of this therapeutic technology to the clinic.

In this lecture, we will discuss how this therapeutic approach developed from basic equation developments (Rayleigh-Plesset) to preclinical evaluation and to clinical proof of concept. We will show for the first time the results from the recent clinical trial (SONCHIMIO NCT03458975) carried out at the University Hospital in Tours France. We will also review on going and future clinical trials in the field of drug delivery using sonoporation.