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Preface

Ultrasound assisted drug delivery ☆

Paul Ehrlich's magic bullet is still very much at the heart of today's pharmaceutical research. However, do the drugs really reach their target in sufficiently high concentrations? What can be done to improve the delivery, beyond drug formulation? From their entry in the human body, e.g. in the bloodstream for an intravenous injection, most drugs need to cross the epithelial cell layer, diffuse into the tissue, cross the cell membrane, enter the cells to find their target before being metabolized or excreted. Such barriers, in addition to others like the Blood–Brain Barrier, represent major obstacles for drug efficacy.

It has long been recognized that the mechanical vibrations of ultrasound, whether or not assisted by microbubbles, can help overcome such barriers [1]. Vibrating microbubbles can increase membrane permeability via a so-called sonoporation process. Microbubbles can also be used as drug carriers. Absorption of ultrasound energy can lead to temperature elevation that in turn can enhance the EPR effect and lead to accelerated drug extravasation and intratissue diffusion. Drugs can be released at locally elevated concentrations when using temperature sensitive drug carriers in combination with ultrasound generated hyperthermia. While the basic concepts have been known for some time, much progress has been made in recent years by major advances in ultrasound technology, drug nanocarriers, and multimodality imaging to assess PharmacoKinetics and PharmacoDynamics.

This special issue reviews the physics, mechanisms and applications of ultrasound assisted drug delivery via a series of papers by specialists in the field. State-of-the-art materials for ultrasound triggered drug delivery are reviewed by Sirsi et al. (http://dx.doi.org/10.1016/j.addr.2013.12.010) covering pressure and temperature sensitive carriers including the phase convertible systems that become gas bubbles in the body only at the ultrasound generated low pressure. The progress in ultrasound molecular imaging, multimodal imaging and theranostics is described by Kiessling et al. (http://dx.doi.org/10.1016/j.addr.2013.11.013), followed by the physics of microbubbles in an acoustic field for drug delivery (Kooiman et al.; http://dx.doi.org/10.1016/j.addr.2014.03.003). Sonoporation is still incompletely understood, and Lentacker et al. (http://dx.doi.org/10.1016/j.addr.2013.11.008) review the debate on whether drug delivery by cavitating microbubbles near membranes is caused by physical holes in them or endocytosis processes. High Intensity Focused Ultrasound (HIFU) is now clinically approved for ablation of prostate cancer and uterine fibroids and for palliative treatment of painful bone metastases. HIFU can also be applied for hyperthermia purposes. Hijnen et al. (http://dx.doi.org/10.1016/j.addr.2014.01.006) review the progress that has been made using HIFU to bring into practice the suggested use of temperature sensitive nanocarriers [2].

Applications of ultrasound assisted drug delivery are described in the next chapters. Several recent papers have shown enhanced uptake of genes as well as selective gene transcription as described by Rychak et al. (http://dx.doi.org/10.1016/j.addr.2014.01.009). Recent clinical HIFU studies in the brain have shown spectacular progress in essential tremor treatment [3]. Local temporary disruption of the Blood–Brain Barrier with HIFU, as reviewed by Aryal et al. (http://dx.doi.org/10.1016/j.addr.2014.01.008), is a highly promising field albeit still at the preclinical level. The cardiovascular system remains one of the most important targets for ultrasound assisted local drug delivery. Unger et al. (http://dx.doi.org/10.1016/j.addr.2014.01.012) describe recent progress including applications in stem cell therapies. Azagury et al. (http://dx.doi.org/10.1016/j.addr.2014.01.007) review the applications of ultrasound in transdermal drug delivery. Whereas image guided local drug delivery at the lesion site is crucial, it is also important to be able to treat lesions that cannot yet be visualized with imaging. Unga et al. (http://dx.doi.org/10.1016/j.addr.2014.03.004) describe how ultrasound can be used to stimulate the immune system for treating cancer metastases.

We hope that this special issue will further increase the enthusiasm for the multiple applications of ultrasound assisted drug delivery, and will contribute to clinical translation of these concepts as part of a move towards personalized medicine in which the drug treatment is not only biochemically but also spatially targeted and optimized with ultrasound after visualizing the lesion. In this regard it is important that HIFU instruments, whether guided by ultrasound or MRI imaging, are becoming increasingly available in the clinical setting for ablation purposes, and can be used for ultrasound assisted drug delivery with a spatial precision of the order of 1 to a few millimeters. Even regular ultrasound imaging instruments, in conjunction with clinically approved ultrasound contrast agents, gas microbubbles, as reviewed in this issue, can be used clinically to improve drug delivery as recently shown in a small number of pancreas cancer patients [4]. However, the various barriers to clinical translation of such concepts are still formidable. The reader is referred to recent recommendations, such as increasing public–private collaborations, to accelerate the field of image guided drug delivery that are very relevant to the exciting field of ultrasound assisted drug delivery [5].

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