## OBJECTIVES

The primary goal of image guided drug delivery (IGDD) is to increase the therapeutic index of potent, often toxic treatments through personalized image-guided treatment, ultimately decreasing adverse effects of drugs by better controlling the pharmacokinetics (PK) and pharmacodynamics (PD) of therapy. Here, special attention is paid to the emerging field of ultrasound triggered IGDD, and the important role of multimodal imaging.

## INTRODUCTION

High frequency sound waves can lead to local tissue heating, cavitation, and radiation force in tissue, which can be used for 1) local drug release from nanocarriers circulating in the blood, 2) increased extravasation and crossing of the Blood-Brain-Barrier, 3) increased cellular uptake of drugs and/or carriers, and 4) enhanced diffusivity of drugs. Ultrasound can be focused within a region with a diameter of about 1 mm. Nanocarriers sensitive to mechanical forces, and/or sensitive to temperature can be used to release the content of the nanocarriers locally. Real-time imaging methods, such as MRI, optical and ultrasound imaging have led to novel insights and methods for ultrasound triggered drug delivery. Image guidance of ultrasound can be used for: 1) target identification and characterization; 2) spatio-temporal guidance of actions to release or activate the drugs and/or permeabilize membranes; 3) evaluation of biodistribution, pharmacokinetics and pharmacodynamics; 4) Physiological read-outs to evaluate the therapeutic efficacy.

## METHODS

Thermosensitive liposomes have been suggested for local drug release in combination with local hyperthermia more than 25 years ago. Liposomes may carry both hydrophilic and hydrophobic drugs, together with contrast agents, in their aqueous interior and lipid bilayer membrane, respectively. Iron oxide particles and/or conventional Gd based contrast agents can be used to track the particles with MRI, and monitor the release of the contents.Microbubbles are used clinically to increase contrast in ultrasound imaging. They can also be used therapeutically in IGDD. Drugs and imaging agents can be attached to the membrane surrounding the microbubble, they can be imbedded within the membrane itself, they can be bound non-covalently to the surface of the microbubble. Optical contrast agents can be used as model drugs that allow monitoring of extravasation and internalization in the cells. Labelling with radioactive nuclei allows the evolution of the biodistribution of particles and drugs.

## RESULTS AND CONCLUSIONS

Examples are given to illustrate the important role of multi-modal molecular imaging in the various aspects of ultrasound triggered IGDD. Ultrasound triggered IGDD has been shown to be feasible (1,2), and initial clinical applications have started. (Real-time) molecular imaging methods based on MRI, optical and ultrasound, are used for guidance of actions to release or activate drugs and/or permeabilize membranes, and for evaluation of biodistribution, PK/PD.

## REFERENCES


1) Deckers et al. JCR 2010
2) Lentacker et al. Adv Drug Del Rev 2014
3) Hijnen et al. Adv Drug Del Rev 2014