Replacing Microbubbles with Nanofluids:  
Development of Stable Ultrasound Triggered Drug Delivery Vehicles

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Summary: A new stable nanofluid payload has been used to create drug delivery vehicles which rupture upon exposure to low intensity ultrasound. The introduction of the nanofluid changes the field of microbubble-based ultrasound triggered drug delivery by allowing these new vehicles to have both the ultrasound triggerability of a microbubble and the stability of a traditional liposome.

The harmful side effects of chemotherapy originate from the indiscriminate exposure of healthy tissue to the anti-tumor drugs. The goal of targeted drug delivery is to reduce these side effects by encapsulating the drug in a vehicle which releases the drug only in the tumor region. The trick is to find a fundamental difference between the tumor tissue and the healthy tissue which can be used as a trigger for this release. There are many challenges to relying on inherent properties of the tumor itself to make this differentiation because they often do not provide sufficient contrast [1]. Tumors are also biochemically different from patient to patient [2] which makes determining the properties of a specific patient’s tumor a difficult and lengthy process. To address these challenges, the tumor region can be highlighted by an artificial trigger creating a stark differentiation from the healthy tissue which can be applied to a wide range of tumors and patients. The best method of depositing significant amounts of energy into small regions of the body in a safe and controllable manner is the use of low intensity focused ultrasound. This is the ideal artificial trigger to activate vehicles in deep tissue with pinpoint accuracy.

![Fig. 1 Images of both nanoparticle and microbubble based drug delivery particles before and after low intensity ultrasound exposure](image)

We have developed a new injectable drug delivery vehicle which encapsulates a chemotherapy payload as well as a stable ultrasound sensitizing nanofluid as shown in Fig. 1A. The ultrasound interacts with the internal nanofluid of each particle creating a localized shockwave which shatters the outer lipid membrane of the vehicle leaving a debris field of lipid particles and internal contents as shown in Fig. 1B. No microbubbles were present to cause this effect, however the activation of these particles is the same as those made from less stable conventional microbubbles. Fig. 1C shows a delivery vehicle made with a microbubble encapsulated within a liposome. Fig. 1D shows that vehicle explode when exposed to low intensity ultrasound. The introduction of these nanofluids to drug delivery vehicles is a game changing event for the field of ultrasound triggered delivery. The nanofluid allows particles to be designed which have both the ultrasound triggerability of a microbubble and the stability of a traditional liposome. This could allow them to be made significantly smaller and increase their circulation times overcoming the hurdles of using microbubbles.