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Nano-Polymeric Carrier Influences Ultrasonic Drug Delivery to Tumors

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Introduction

Our overall research goal is to alleviate the severe side effects of chemotherapy while enhancing the effectiveness of the treatment by localizing the delivery of anti-cancer drugs to the cancer tissue only. To this end we are synthesizing ultrasonically-activated delivery systems that can control drug delivery in space and time. Ultrasound (US) is non-invasive (no surgery required) and can be focused on the specific tissue to be treated. Our past research has developed a nano-sized polymeric drug carrier that sequesters the therapeutic drug, such as Doxorubicin (Dox), within the carrier and releases the drug upon insonation by ultrasound. This drug-containing carrier can be injected systemically into the blood stream; ultrasound is focused only on the tumor; and as the blood carries the delivery device through the ultrasonic field in the tumor, the drug is released there. We have shown this technology to be effective in treating colon tumors in a rat model, but may questions remain to be answered to optimize chemotherapy with this delivery system.

In this work, we investigated the reduction in tumor size in a rat model of colorectal carcinoma [1] using ultrasound of 20 kHz applied to drug delivered with or without the acoustically active drug carrier. We found that the drug carrier is required to produce a reduction in tumor growth rate.

Methods

NanoDeliv™ drug carrier was made as described previously [2]. NanoDeliv™ was made by polymerizing N,N-diethyl-acrylamide (NDEA) in the presence of 10% Pluronic P105 in water using AIBN as an initiator and N,N'-bis-(acryloyl)-cystamine as a cross-linking agent. Following a nitrogen purge polymerization was conducted at 65 °C overnight in the presence of N_2 gas and magnetic stirring to create an interpenetrating crosslinked network of poly(NDEA) in the core of the P105 micelles. At 37 °C these stabilized micelles were between 50 and 100 nm in diameter and do not dissolve immediately upon dilution because polymerized poly(NNDEA) entangles the Pluronic chains. However there are no covalent bonds between the network and the Pluronic chains, so the latter can slowly diffuse away over time and be cleared from the circulatory system. The crosslinker allows the network to bio-degrade and be cleared. The Plurogel™ used herein have an *in vitro* half-life of approximately 17 hrs [2,3]. NanoDeliv™ readily sequesters Dox into its hydrophobic core (see Fig 1).

Four-wk-old BDIX rats were injected with DHD/K12 cancer cells on each hind leg to grow subcutaneous tumors. After 3 weeks of growth, Dox encapsulated in NanoDeliv™ was prepared and injected (2.67 mg/kg) via tail vein, and US at 20 or 476 kHz was applied for 15 minutes and 1 W/cm^2 (temporal average) to only one tumor, while the other tumor was an untreated control. In the 20 kHz experiments, half the rats received free drug, while the others received Dox in the Plurogel. Treatment was repeated weekly for 6 weeks. Both tumor sizes were measured weekly for bilateral comparison.

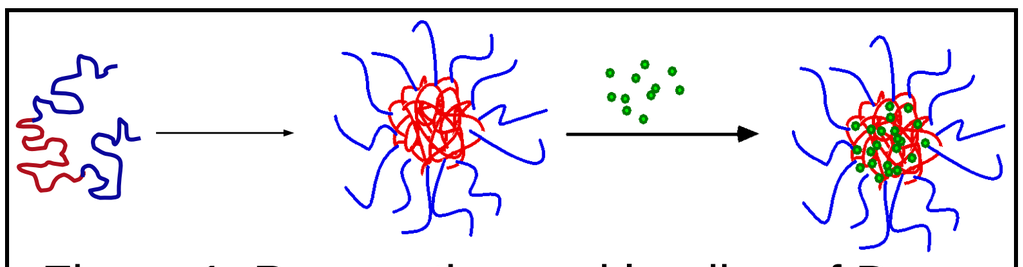

Figure 1. Preparation and loading of Dox into NanoDeliv™ micelles.

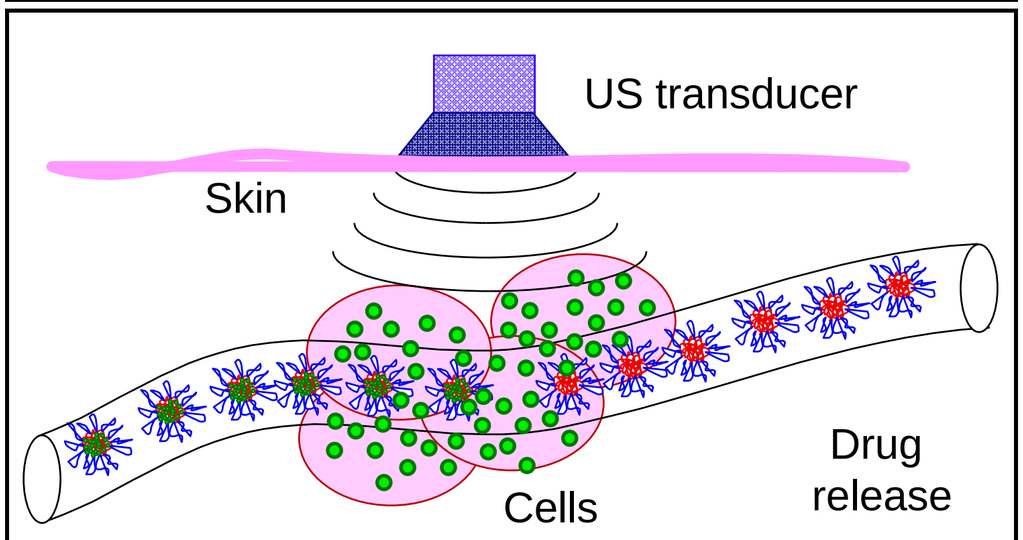

Figure 2. Schematic illustrating ultrasonic drug release from NanoDeliv™ micelles.

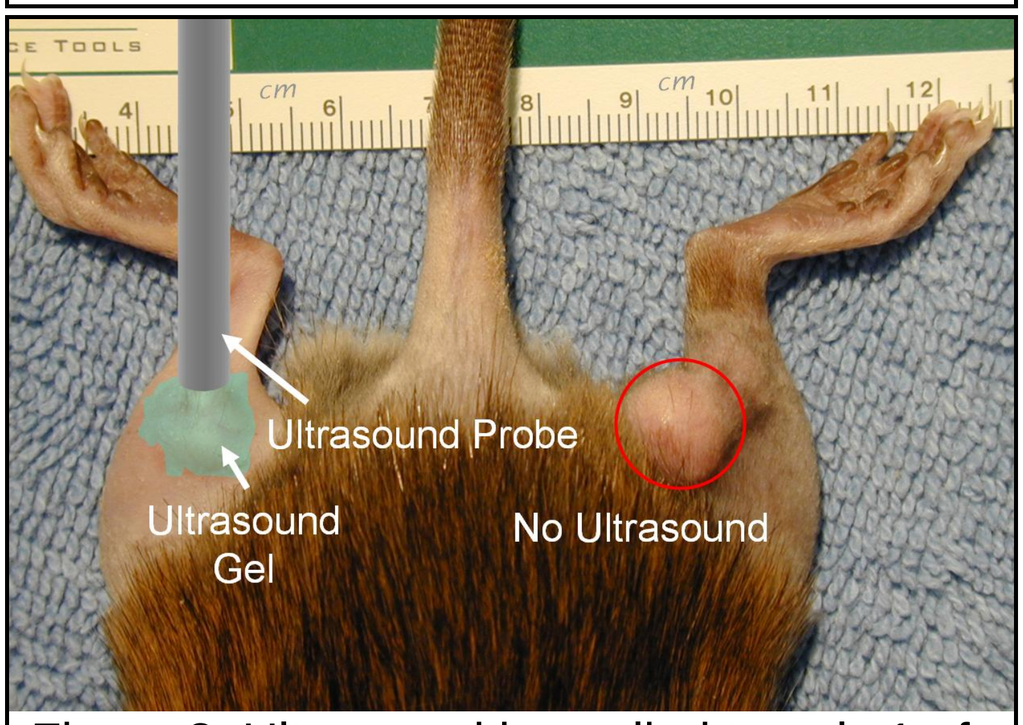

Figure 3. Ultrasound is applied to only 1 of bilateral tumors on hind legs of BDIX rats.

Results

A statistical analysis of the tumor growth showed that application of US significantly reduced the tumor growth rate when the Dox was delivered from the Nanodeliv™ carrier (p=0.0047), at either 20 kHz or 476 kHz. However, when Dox was given in free form (without any carrier), there was no reduction in growth rate of the US-treated tumor (p=0.92). Also, with NanoDeliv™ there was no difference in tumor growth at the two different frequencies (p=0.94).

This is a very significant result that shows that the Nanodeliv™ carrier is required for the tumor reduction therapy to be effective. A previous pharmacokinetics study showed that there was a small increase in the amount of Dox in the tumor that was sonicated, compared to the bilateral control. The data also showed that there appears to be an accumulation of Dox in the tumor that increases with time after injection during the first 12 hours, and then decreases, suggesting an enhanced permeation and retention (EPR) effect with the Nanodeliv carrier. Therefore the use of Nanodeliv™ as a carrier has a significant impact. The Nanodeliv™ carrier appears to be helpful in enhancing the regression, and most importantly, helpful in sequestering the drug from harmful interactions with non-targeted tissues.

It is also significant that there was an equal reduction in tumor growth rate at both frequencies, even though the frequencies were very different and were applied from different instruments. The average ultrasonic intensity was the same at each frequency, so there may be a correlation with growth rate reduction and average intensity, but this remains to be studied further.

Conclusions

Colorectal model tumor growth in a rat model is very dependent upon the application of ultrasound and the manner in which the Dox is delivered. Ultrasound combined with Dox delivered in Nanodeliv™ is effective in reducing tumor growth, whereas US combined with free Dox does not change growth rate compared to free Dox without US.

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