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Ultrasonic Drug Delivery to Tumors Via Stealth Liposomes

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Ultrasonic Drug Delivery to Tumors Via Stealth Liposomes

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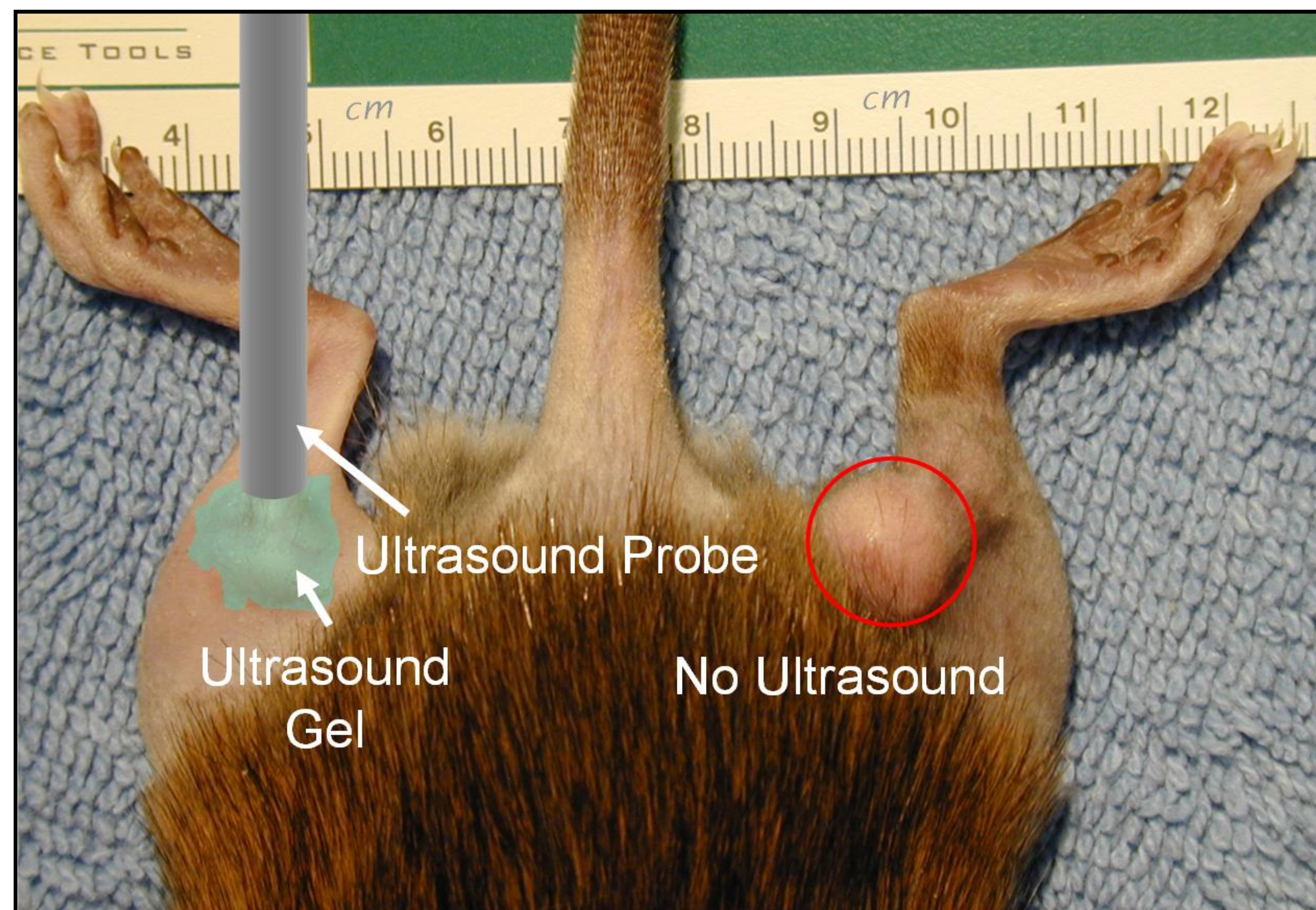


Figure 1. Application of 20 kHz US to 1 of 2 bilateral tumors on the legs of a rat: 15 min, 1 W/cm², CW.

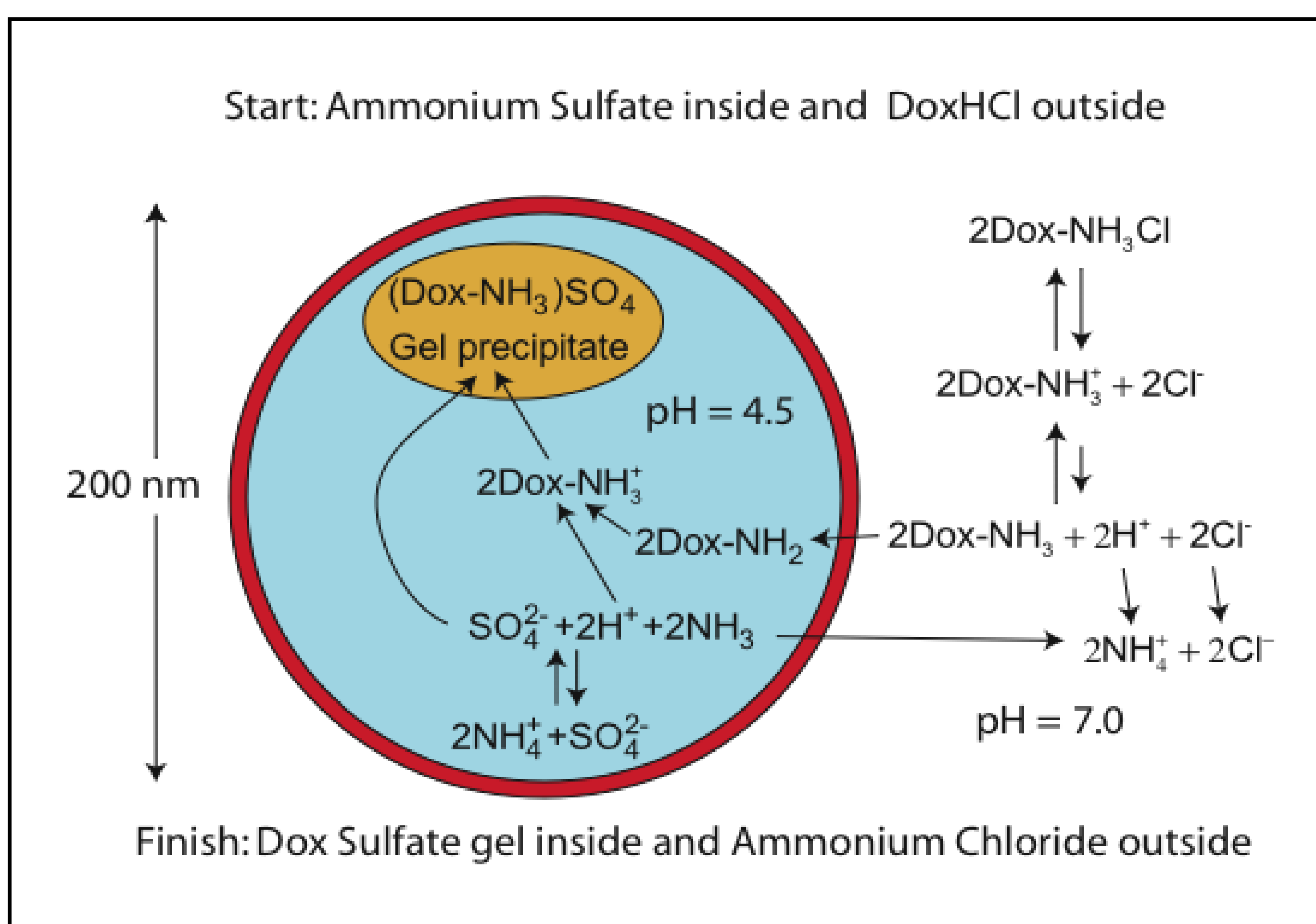


Figure 2. Preparation of stealth liposomes. Dox is loaded by the pH gradient [1]. Lipid bilayer has PEG2000 chains.

Conclusions

For this colorectal model, tumor growth is very dependent upon the application of ultrasound and the carrier. Ultrasound combined with Dox delivered in our stealth liposomes is much more effective in reducing tumor growth than Dox delivered from our micelles. More research will reveal the mechanisms by which ultrasound and liposomes effectively produce tumor regression.

References

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Introduction

Our research develops ultrasonically-controlled drug delivery systems. Previous micellar drug carriers released the drug upon ultrasonication. We have developed a liposomal drug carrier that is even more effective upon insonation in reducing tumors.

Methods

Doxorubicin (Dox) in stealth liposomes was made from phosphatidyl choline, cholesterol, and distearoyl-phospho-ethanolamine-PEG-2000 with internal ammonium sulfate buffer (pH~4.5). Liposomes were about 250 um in diameter. Dox was loaded by the pH gradient method [1] (Fig 2).

Four-wk-old BDIX rats were inoculated with DHD cancer cells on each hind leg to grow subcutaneous tumors. After 3 weeks of growth, Dox in stealth liposomes was injected (4.4 mg/kg) via tail vein, and US at 20 kHz was applied for 15 minutes and 1 W/cm² to only one tumor, while the other tumor was an untreated control (Fig 1). Treatment was repeated weekly for 4 wks. The volume was normalized by dividing by the volume on day 1. In this first study, only 6 rats were used.

Results and Discussion

Figure 4 shows the data from all rats in this study. Closed squares are the tumors receiving US, while open diamonds represents the tumors without insonation. In contrast to data from rats receiving micellar Dox, these data show that the tumor with US quickly regressed in size (Fig 3).

These results stand in stark contrast to our previous studies employing ultrasound with our micellar Dox [2]. Although the micellar formulation reduced the tumor growth rate, it rarely caused complete regression in such a high percentage of treated tumors. In the present study, five of six tumors regressed to non-measurable size within 4 weeks. Obviously something occurs upon insonation with Dox in our stealth liposomes that is very different than with micellar Dox. We are currently repeating this study on a larger population of rats.

Compared to our previous studies using ultrasound and micellar Dox delivery [2], tumor regression is quick and very obvious. A statistical comparison (paired t-test) on the ultrasonicated vs non-treated tumor shows that the treated side has smaller tumors ($p < 0.0001$).

Although we are still exploring mechanisms, we hypothesize that the ultrasound enhances the delivery of Dox to the tumors by 2 possible mechanisms. First, we think that ultrasound is causing cavitation that breaks open the liposomes at the insonated tumor. We also postulate that ultrasound is rendering the tumor capillaries more permeable and liposomes are extravasating more into the insonated tumor than the non-treated control.



Figure 3. Rat with tumors on each leg was given Dox-liposomes weekly. Ultrasound (20 kHz, 1 W/cm²) was applied weekly for 15 min to the right tumor only.

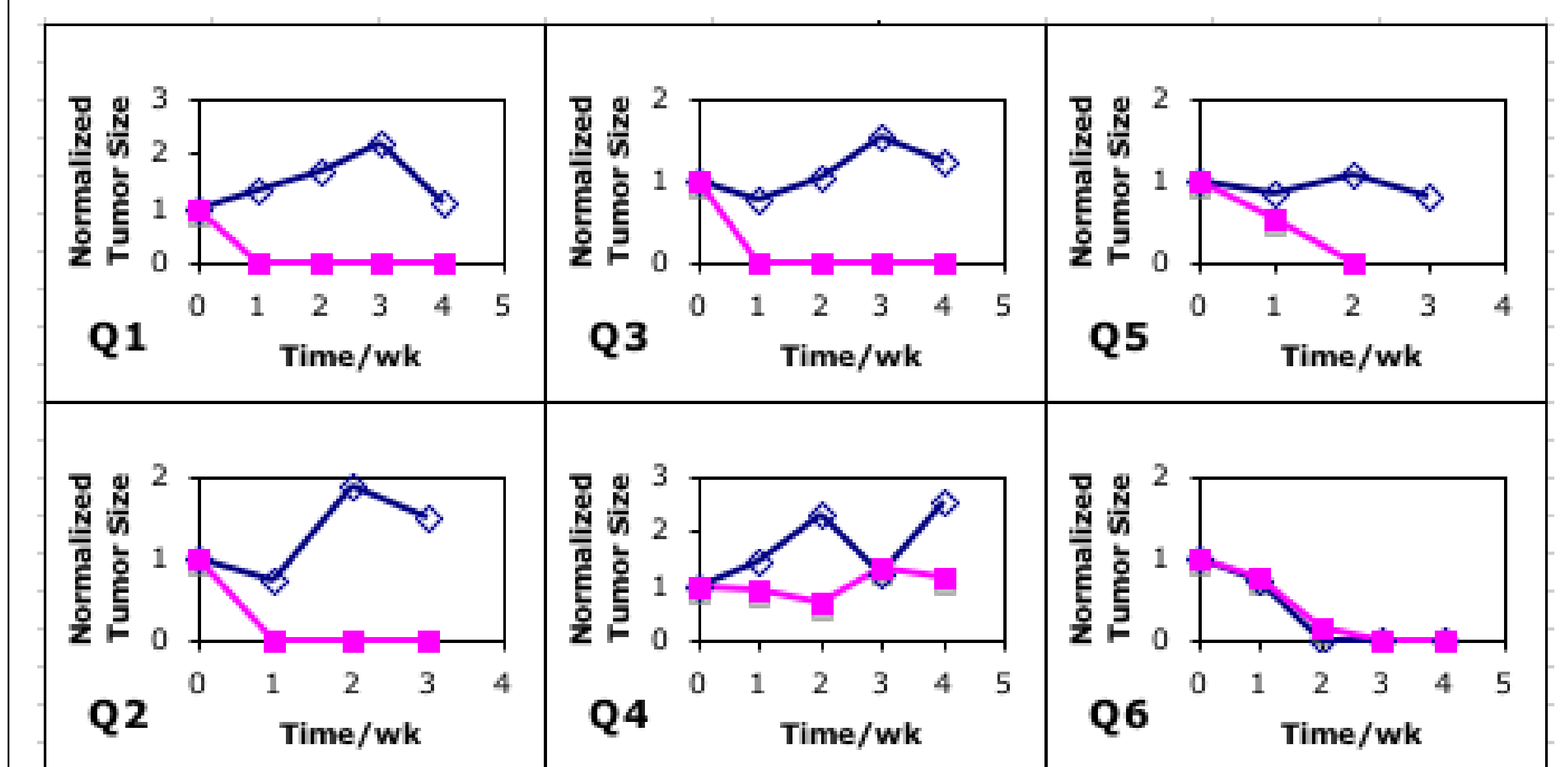


Fig 4. Normalized tumor volume of 6 rats. The red squares are treated tumors, and the blue triangles are non-treated tumors.