Introduction to Nanomedicine

Applications in the Diagnosis and Treatment of Cancer

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NanoMedicine in Cancer

Controlling the composition and structure of a biomolecule at the nanoscale presents a plethora of diagnostic and therapeutic opportunities in cancer management

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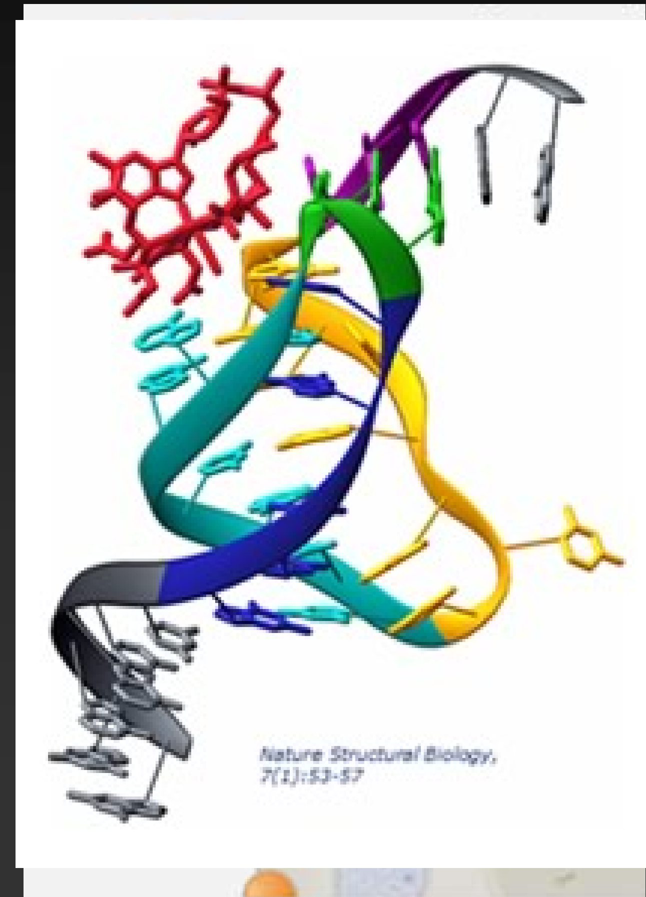
NanoMedicine in Cancer

- Aptamer
  - Short nucleic acids made of DNA or RNA composed from 15-40 nucleotides
  - Designed to bind with a specific protein, including enzymes, membrane proteins, and immunoglobulins
  - Include targeted localization of therapeutic agents and imaging of disease with high specificity

- Triggerable Drug Carriers
  - Nanoscale vesicles designed to respond to externally applied signal
  - Drugs, DNA, or siRNA can be encapsulated or incorporated within the shell
  - Targeting moieties can be
  - Can be conjugated with contrast agents for multimodal imaging



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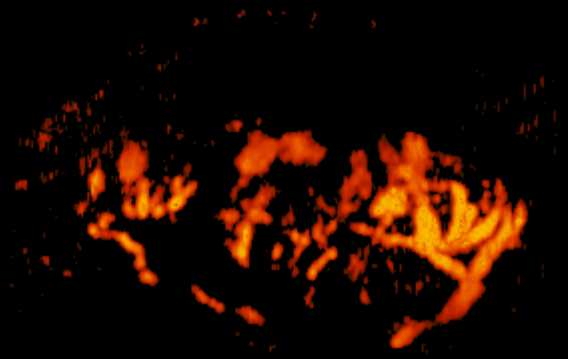
VEGF-R2 Targeted Contrast Agents in MeWo Tumor

- Region of Interest (ROI) is drawn for quantification
- Percentage of agents that bind can be quantified & graphed; 17.75%
- Visualization of bolus injection –"Wash-in"
- Avas12a1-avat ligand

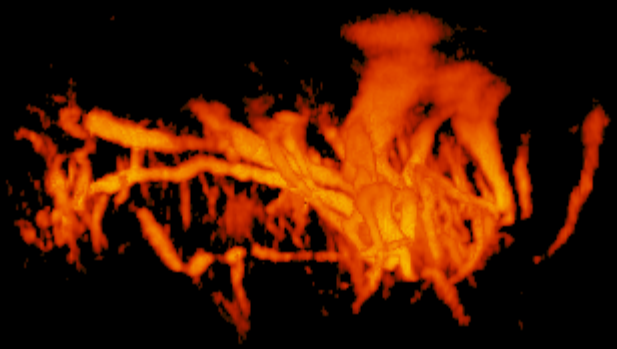
Adult Mouse Melanoma Relative Tumor Flow (3D)

Day 1



Percent Flow: 3.18%

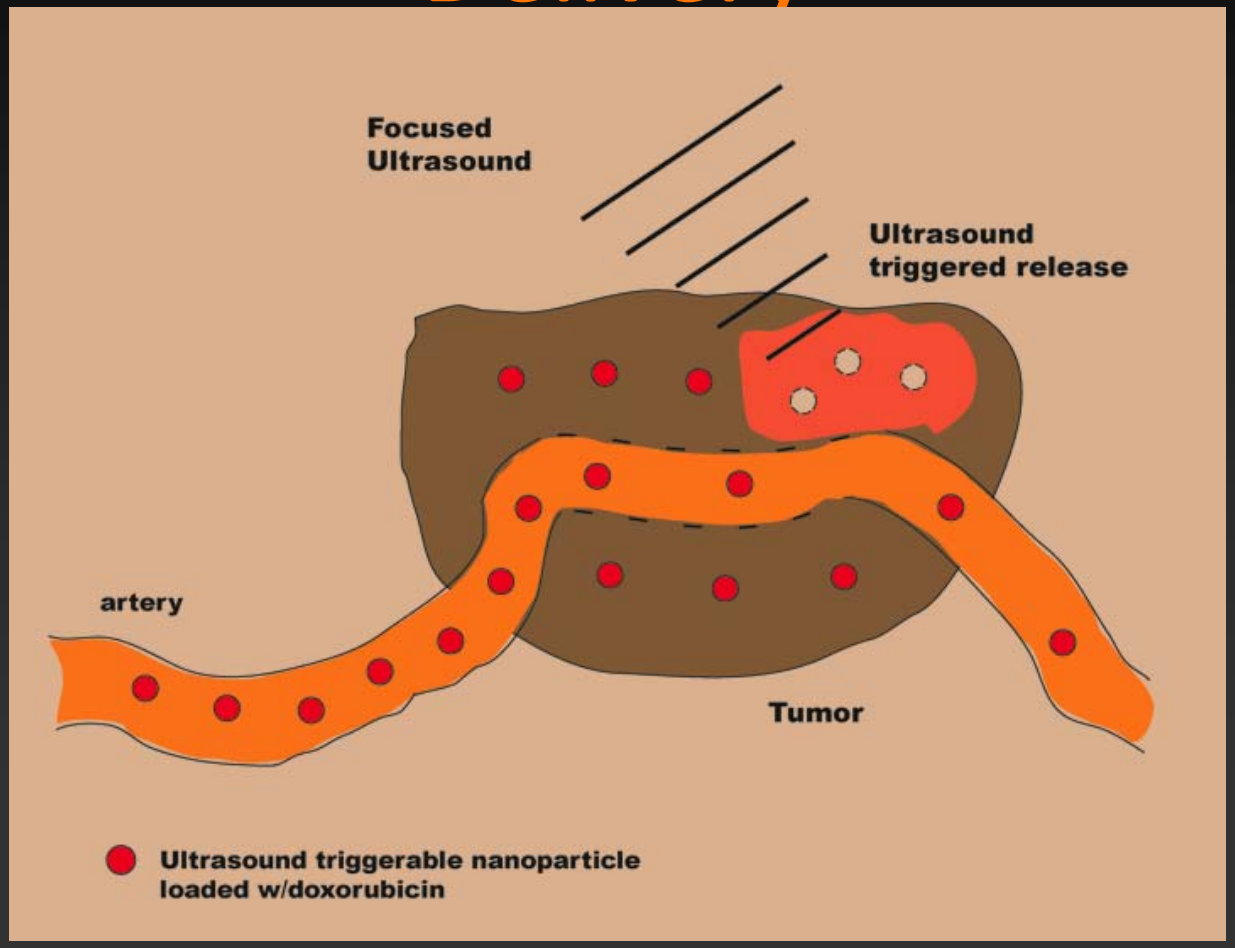
Day 4



Percent Flow: 11.22%

Image sequence courtesy of Hastie, Chambers, Lacefield and Fenster, Robarts Research Institute, London, 2005

Ultrasound-Triggered Drug Delivery



- DOX loaded onto pressure or temperature-sensitive nanoparticles
- Local changes in pressure and temperature due to focused ultrasound delivered noninvasively
- Trigger release of DOX when and where needed

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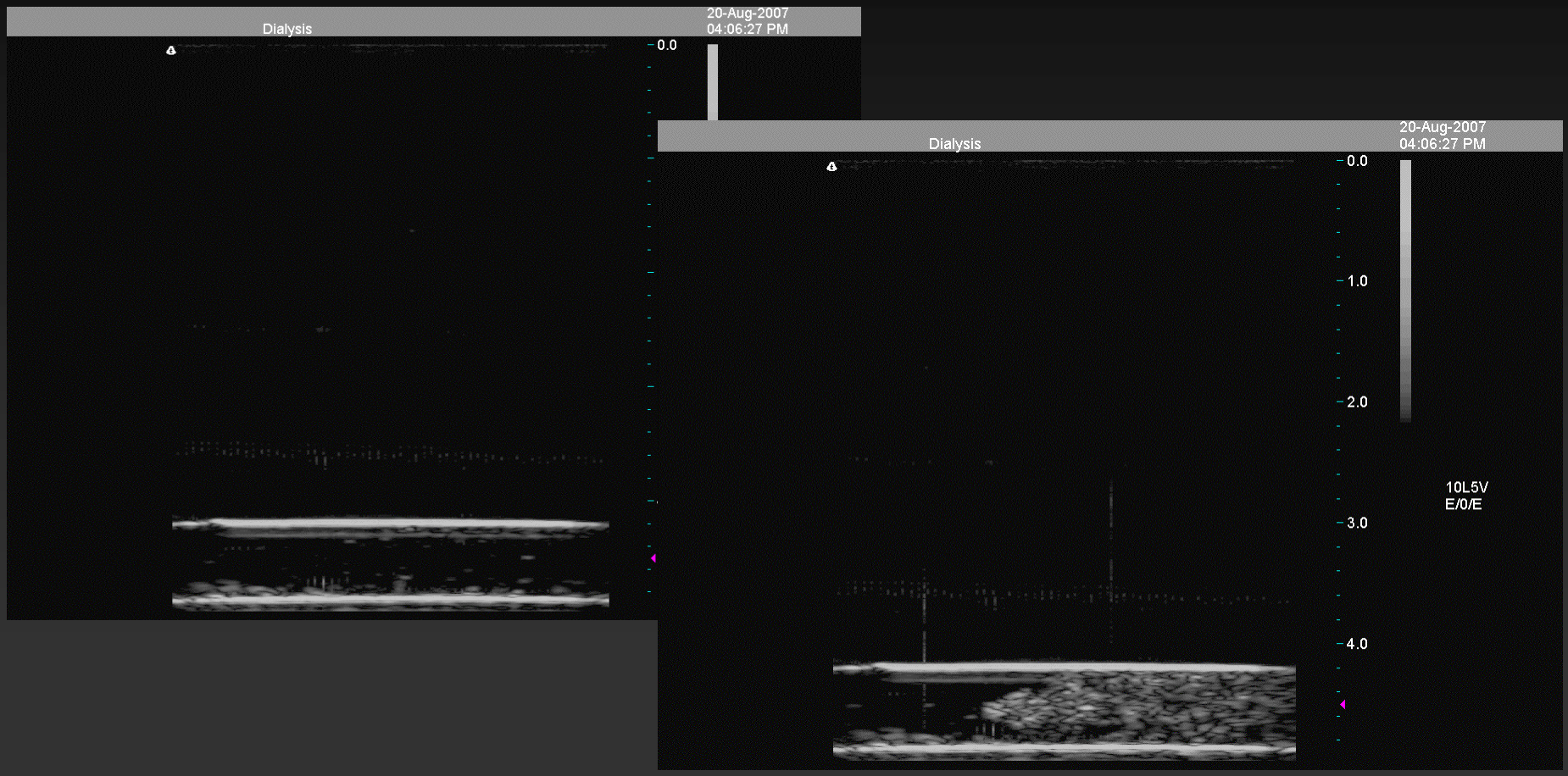
Acoustic Vaporization of Nanoemulsions



37°C, 2-MHz, 6-cycle, 10ms pulse repetition period ADV pulse

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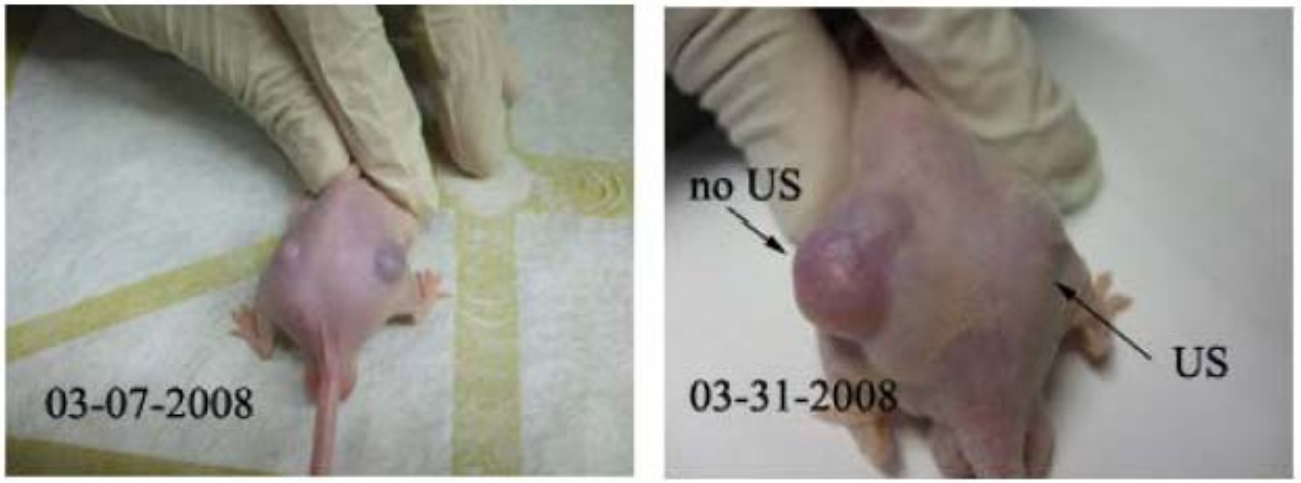
Chemotherapy of Ovarian Cancer Using Paclitaxel-Loaded PFP/PEG-PLLA nanoemulsions/US



N. Rapoport et al., J. Control Release 2009, in press

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Temperature-Sensitive Liposomes

Targeting tumor microvessels using doxorubicin encapsulated in a novel thermosensitive liposome

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Abstract

Liposomal drugs accumulate only in perivascular regions in tumors after i.v. injection. Thus, they cannot kill tumor cells in deeper tissue layers. To circumvent this problem, we investigated effects of doxorubicin (DOX) encapsulated in a lysolecithin-containing thermosensitive liposome (LTSL) on tumor microcirculation because damaging microvessels would stop nutrient supply to deeper tumor cells. We used LTSL-DOX in combination with hyperthermia to treat a human squamous carcinoma xenograft (FaDu) implanted in dorsal skinfold chambers in nude mice. Before the treatment, the RBC velocity in tumors was 0.428 ± 0.037 mm/s and the microvascular density was 3.93 ± 0.44 mm/mm^2. At 24 hours after the treatment, they were reduced to 0.003 ± 0.003 mm/s and 0.86 ± 0.27 mm/mm^2, respectively. The same treatment, however, caused only 32% decrease in the RBC velocity and no apparent change in microvascular networks in normal s.c. tissues over the same period. LTSL and LTSL-DOX alone had no effect on tumor microcirculation, and LTSL

microvessels (1–7), and the release of the drugs from liposomes can be controlled either chemically or physically (8–10). Despite these advantages, liposomal drugs have not yet led to a significant improvement in the clinical outcome in cancer treatment (11–13). The lack of improvement is likely to be due to the low concentration of free drugs in tumor tissues, although the total concentration of drugs (i.e., free plus liposome-associated drugs) may not be low.

Liposomes are nanoparticles (~100 nm in diameter). They can accumulate only in perivascular regions in tumors after i.v. injection (7, 14, 15). The smaller drug molecules released from liposomes may penetrate into deeper tissue layers, but the penetration depth is often limited. This is because (*a*) the interstitial concentration gradient of free drugs is greater in the direction toward the microvessel wall than away from it and (*b*) many anticancer drugs bind strongly to tumor tissues. For example, >80% of doxorubicin (DOX) molecules in tumors are bound to proteins, membranes, and nucleic acids (16, 17). The binding hinders or even prevents interstitial transport of drugs.

To circumvent the penetration problem, we proposed to use liposomal drugs to target endothelial and tumor cells in perivascular regions because the damage of these cells may shutdown tumor blood flow, which in turn will kill deeper tumor cells through reducing the nutrient supply. To significantly damage perivascular cells, free drugs must be

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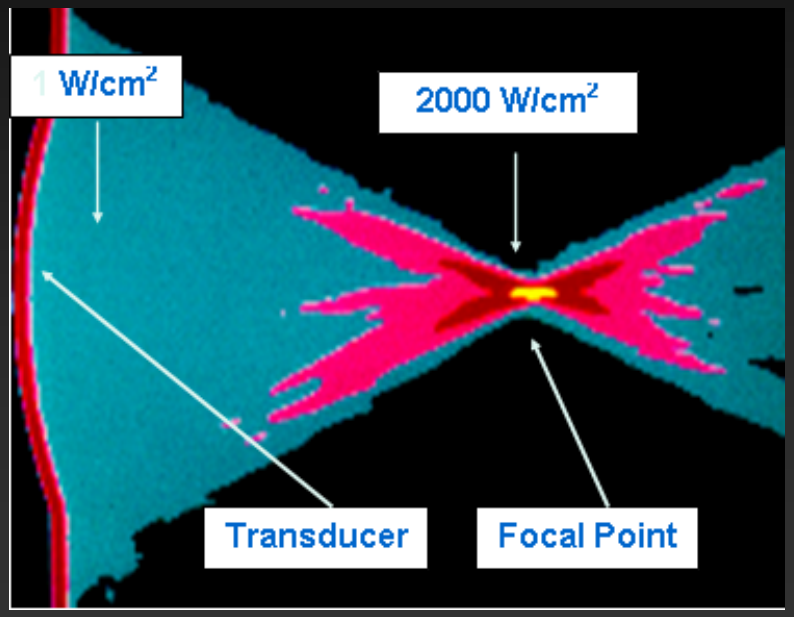
Energy Sources for Heating



High Intensity
Focused Ultrasound

Extracorporeal application of HIFU
Absorption of propagating waves results in rapid heating

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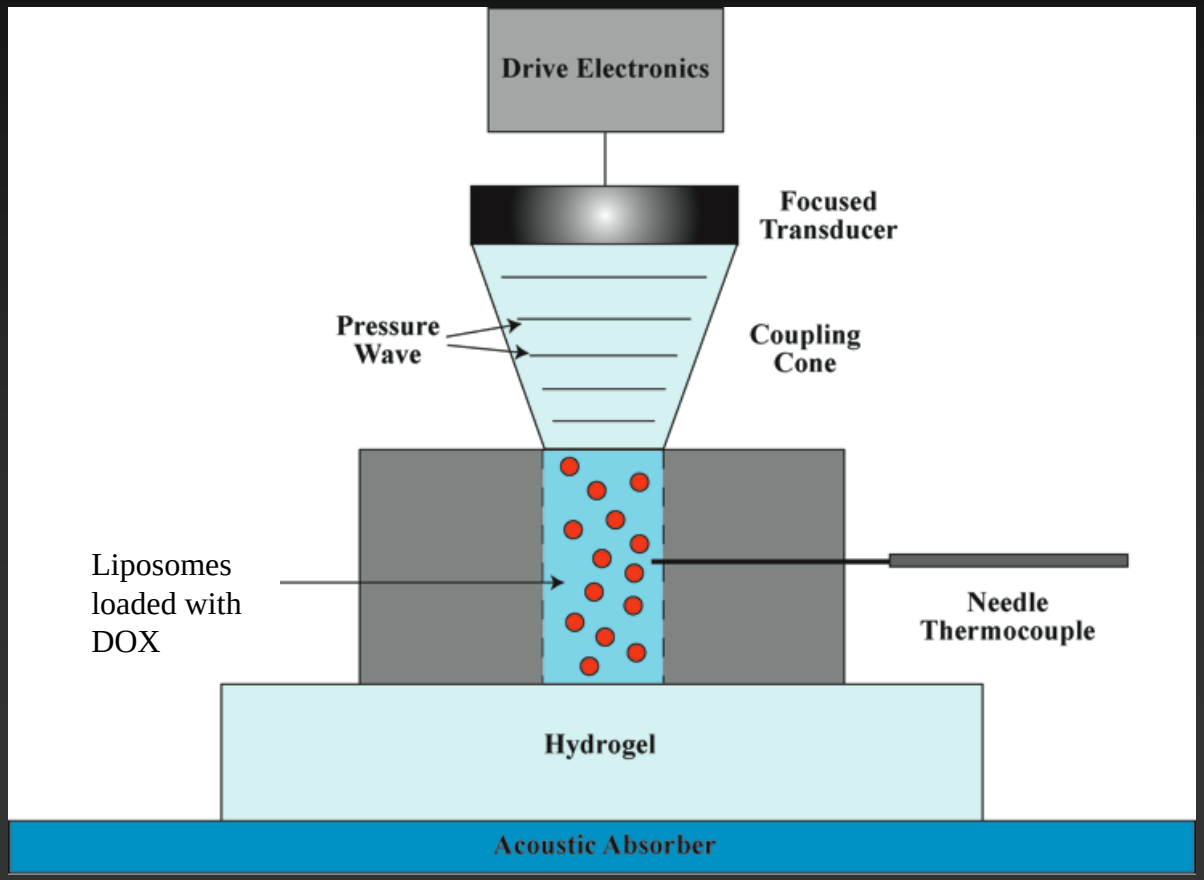
DOX Release From Temperature-sensitive Liposomes



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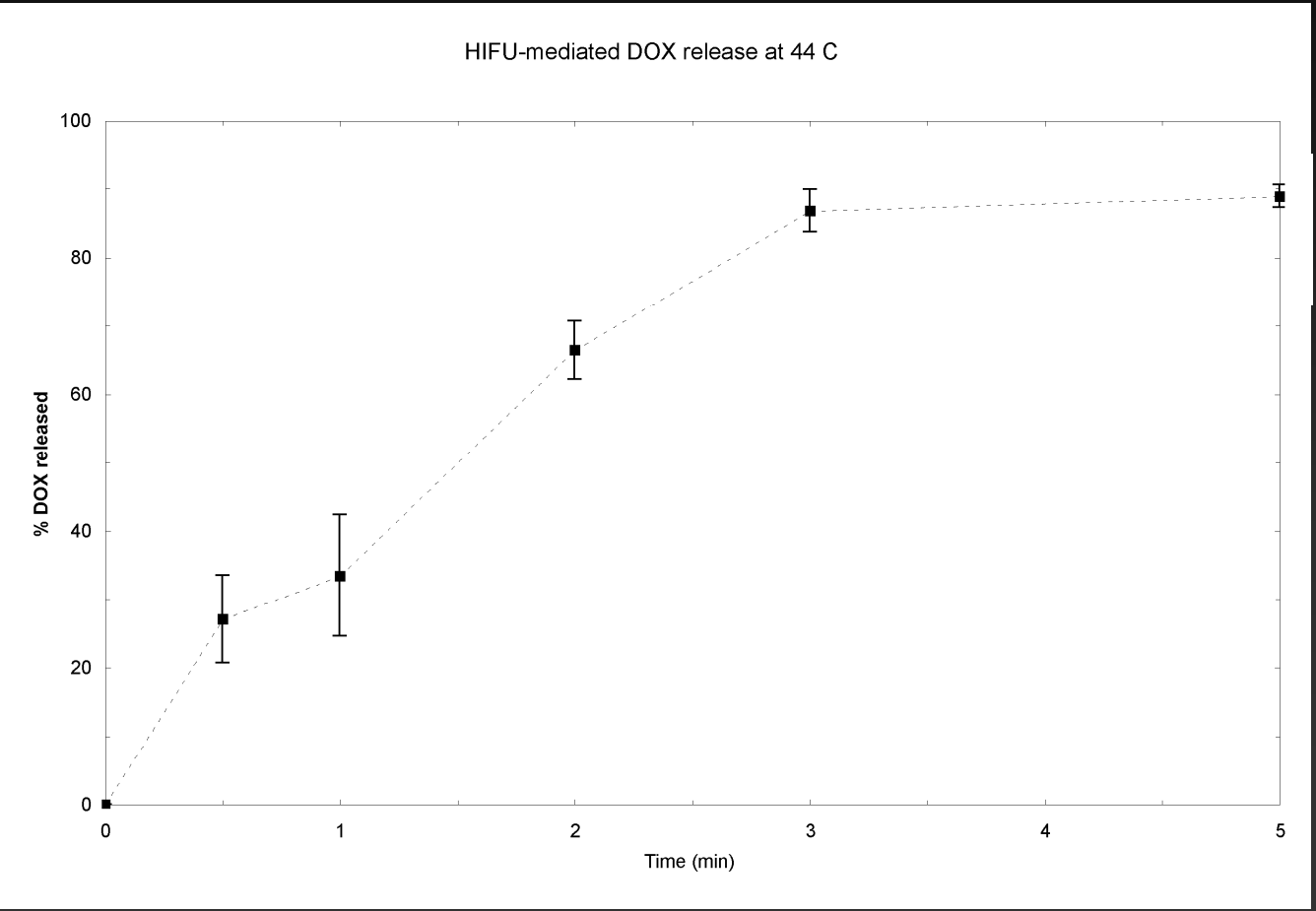
DOX Release From Temperature-sensitive Liposomes



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Ideas for the Future

- Synthesize and test targeted ultrasound contrast agents for monitoring angiogenesis in tumors
- Synthesize and test two classes of temperature-sensitive liposomes (polymer-modified and paramagnetic)
- Investigate ultrasound-triggered DOX release in animal model

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