



Use of thermosensitive liposomes in combination with ultrasound

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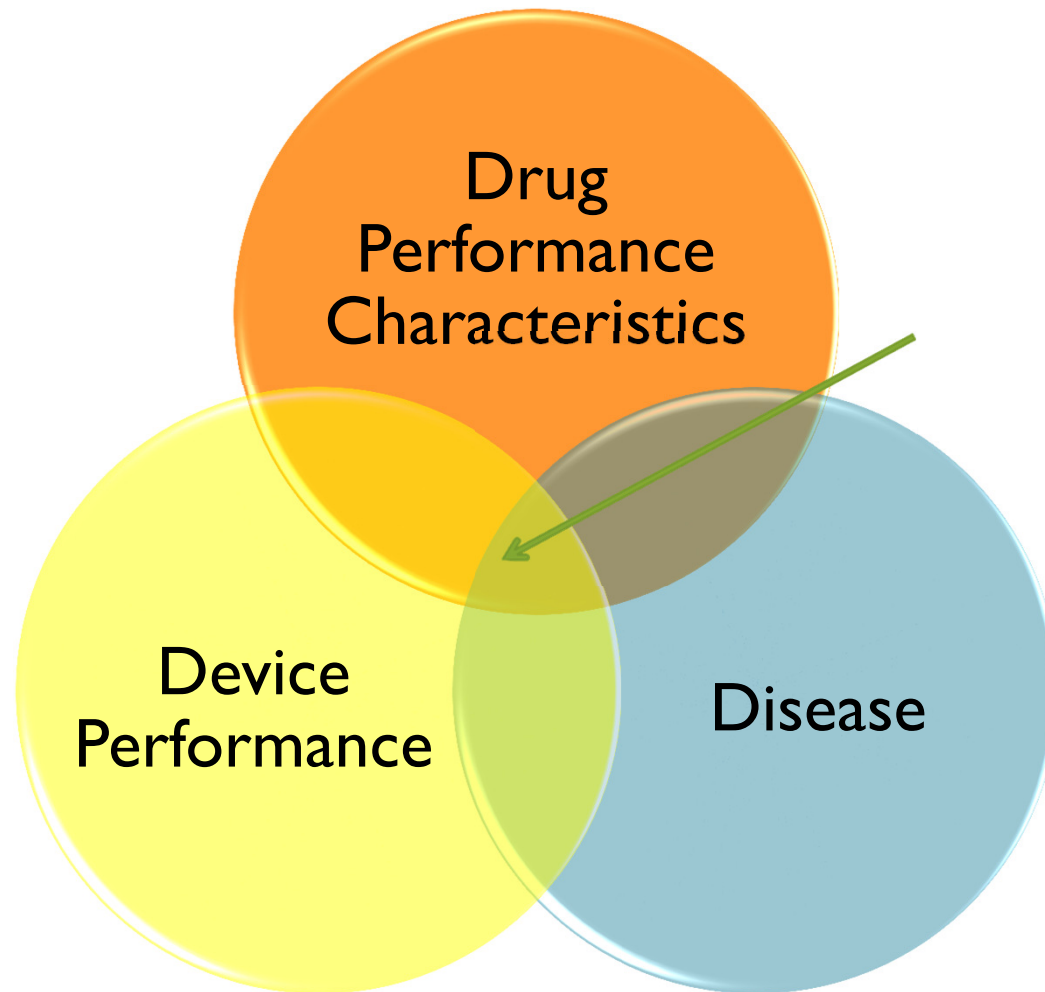
Duke University Health System



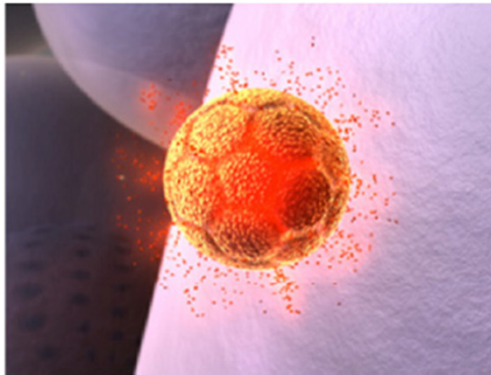
Conflict of Interest Statement

- I am a former consultant for Celsion
- I own stock in the Celsion Corporation
- I will discuss off-label use of liposomal drugs

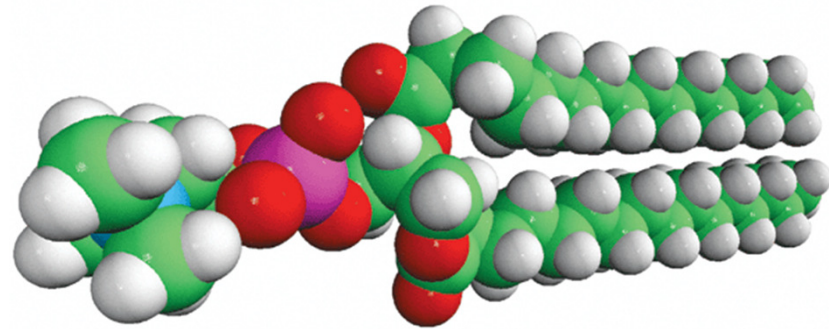
Drug – Device combinations require careful design



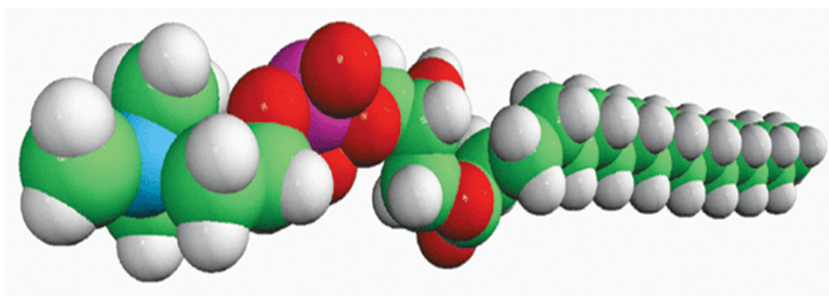
Low Temperature Sensitive Liposome (LTSL)



DPPC:MPPC:DPPC-PEG
90:10:4



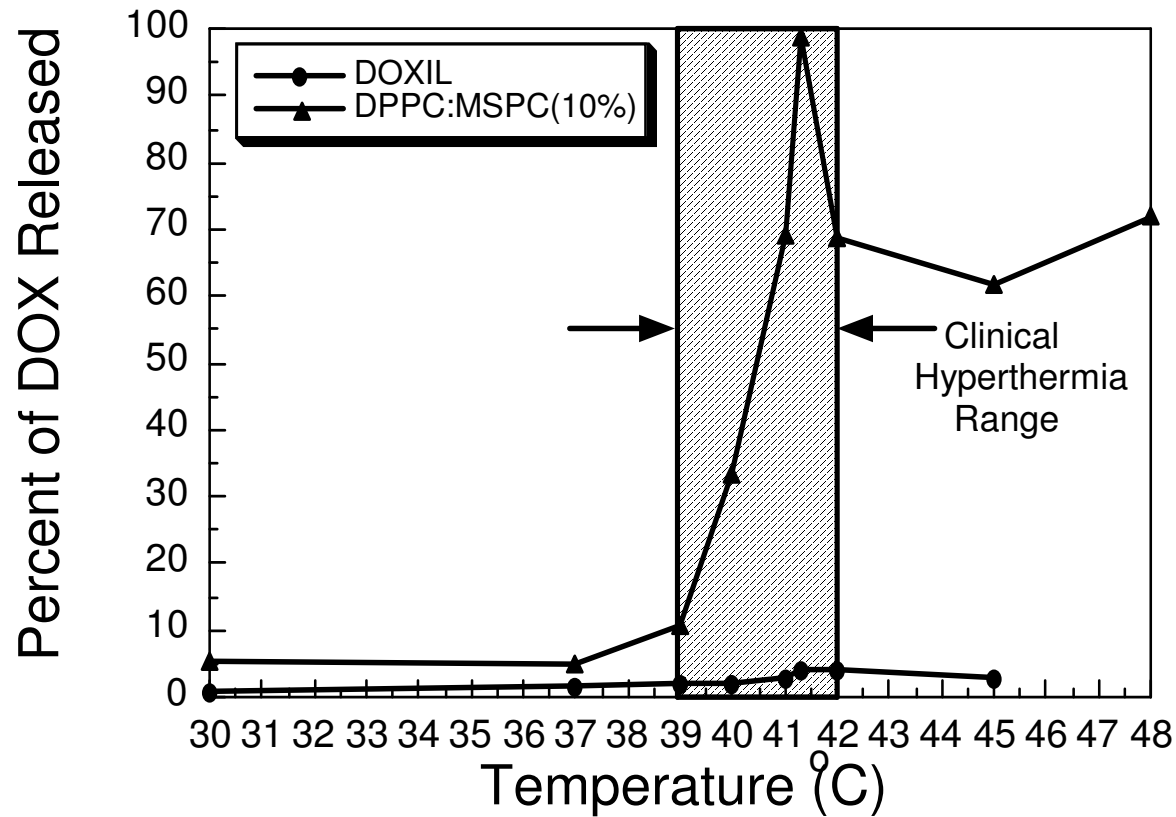
Typical phospholipid



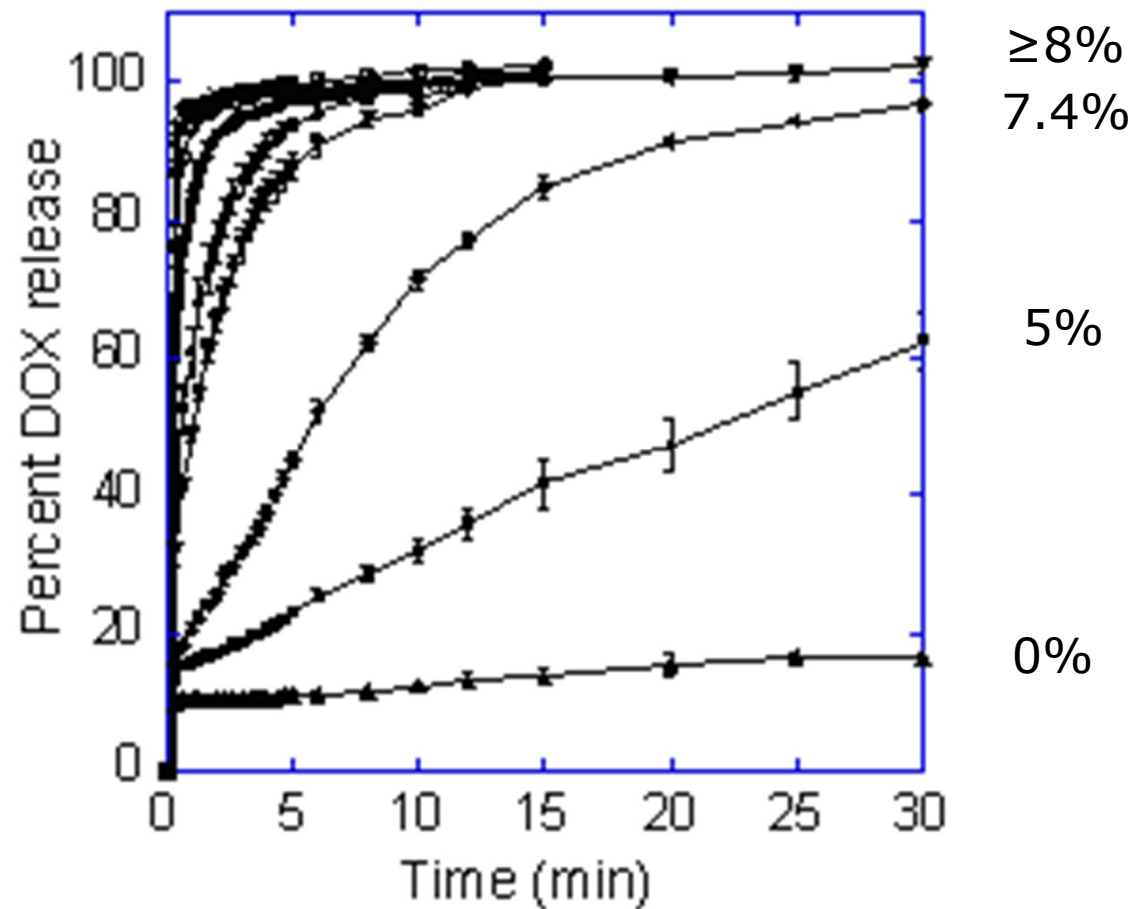
Lyso-phospholipid

DOX release temperature is clinically feasible

Percent of DOX Released for
DOXIL and DPPC:MSPC(10%) at t=4 minutes

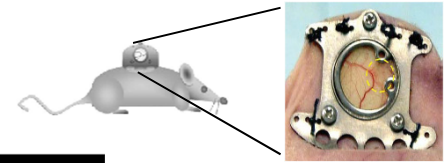


Drug release is very rapid upon reaching transition temperature



Increasing MSPC content

LTSL Dox delivery occurs via intravascular release



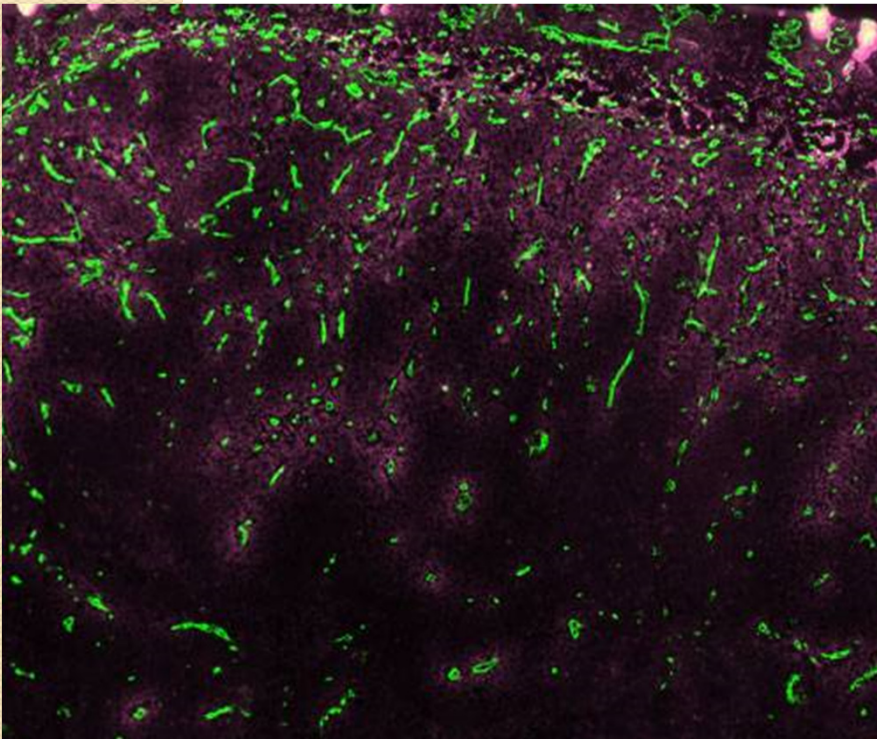
The video you are about to see shows real time delivery of free drug to heated tumor tissue.

20 mins confocal imaging

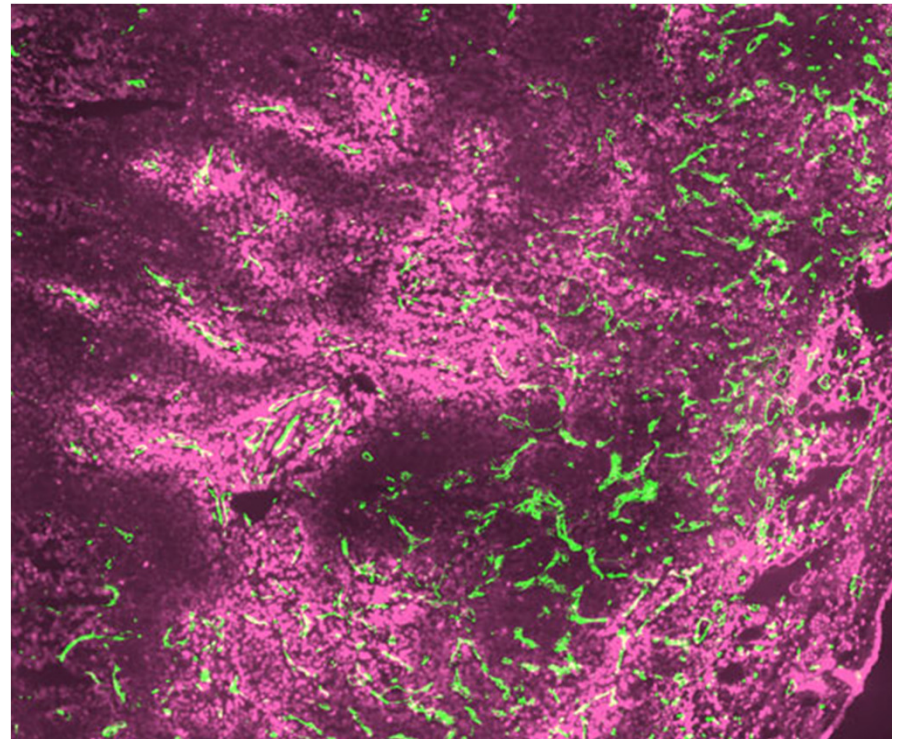
Manzoor et al, Cancer Res, 2012

Intravascular release enhances drug penetration distance into tumor

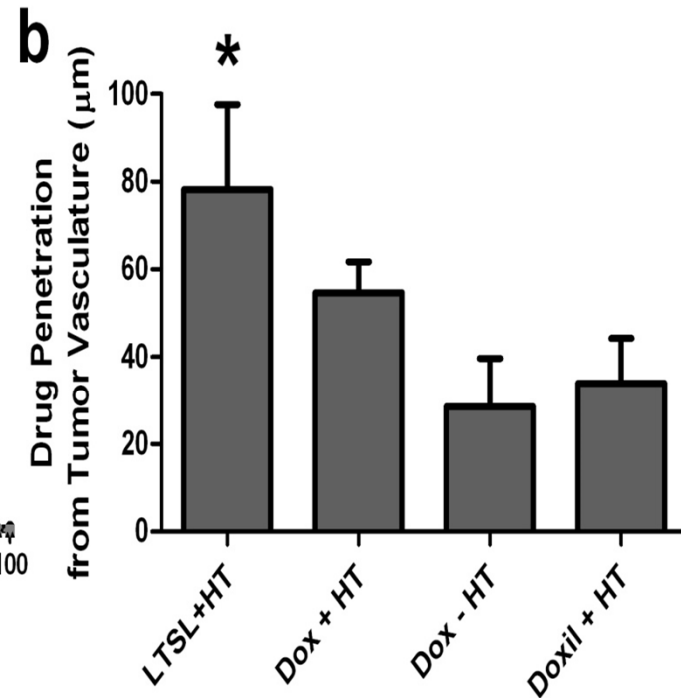
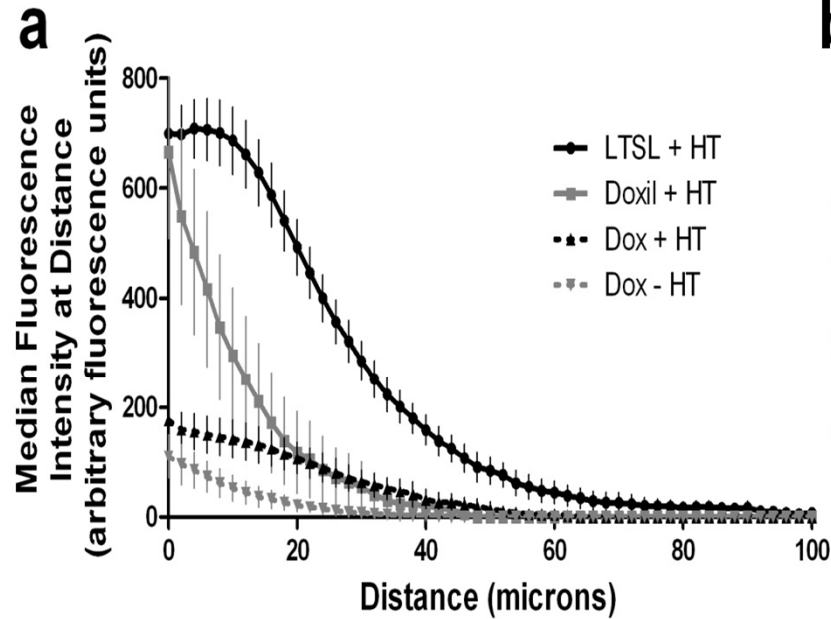
Free Dox + 42°C Heat



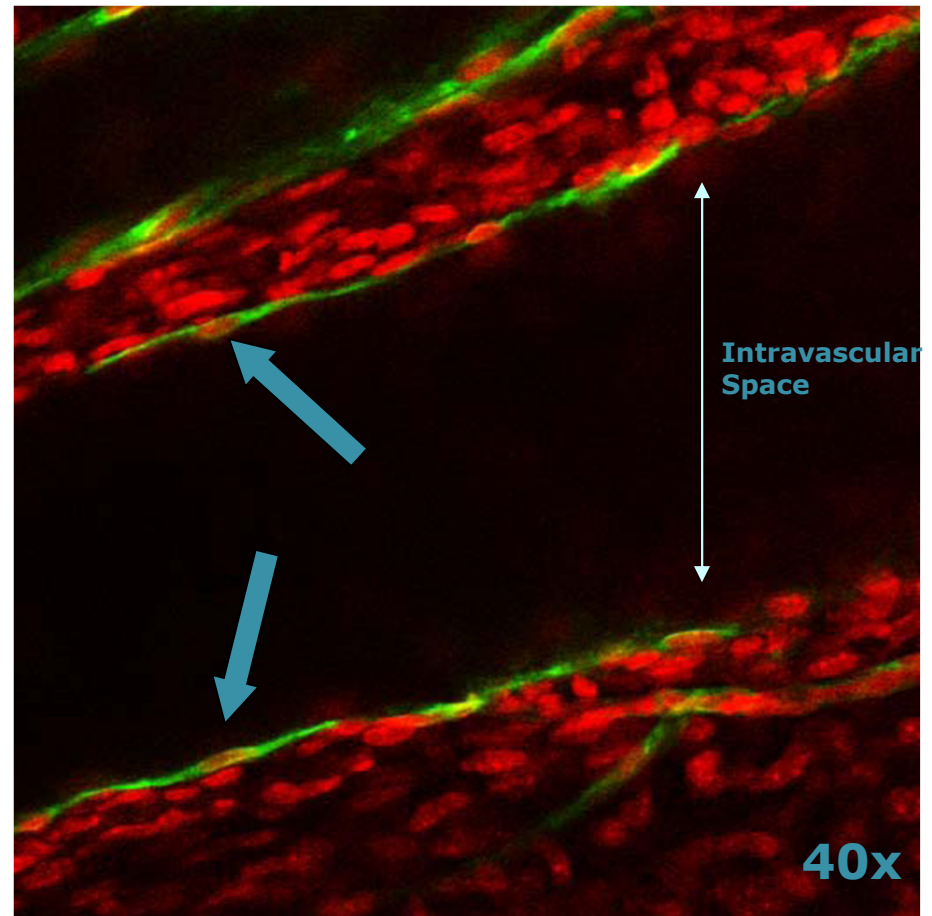
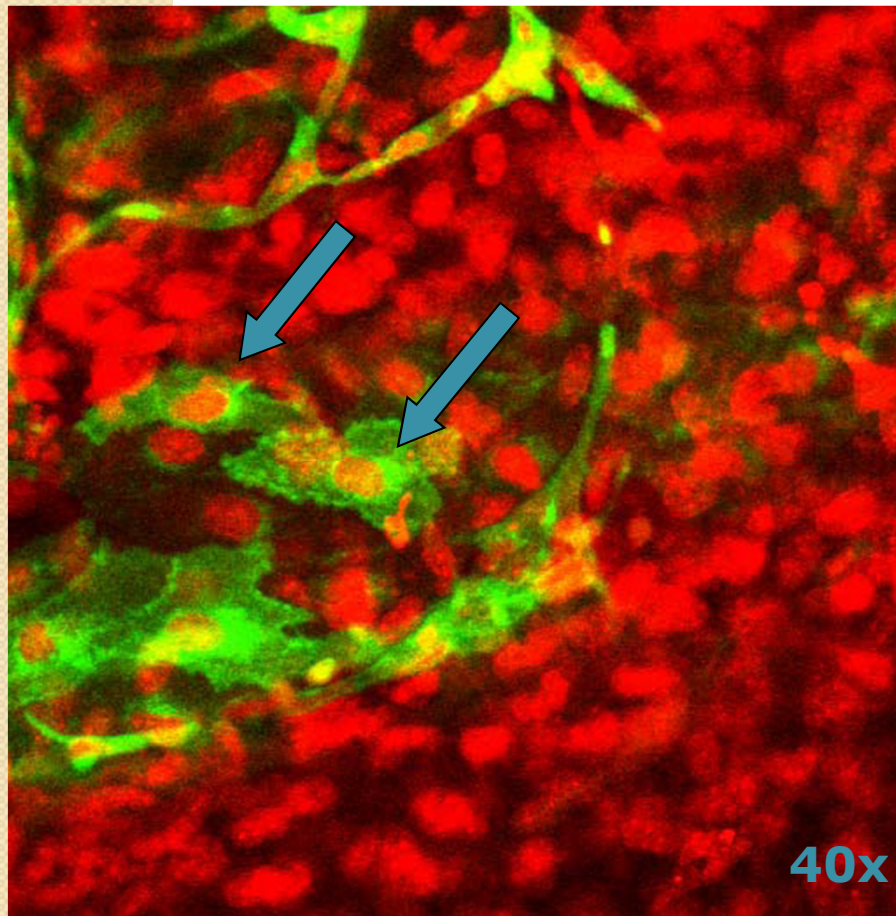
Dox-LTSL + 42°C Heat



Dox-LTSL yields higher drug concentration and greater depth of penetration



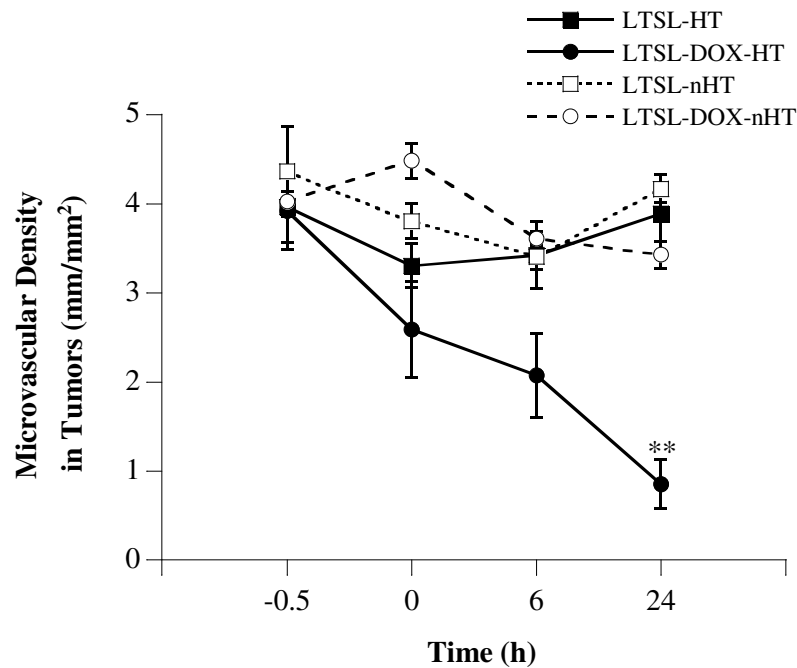
Dox from thermosensitive liposomes is taken up in high concentration by endothelial cells



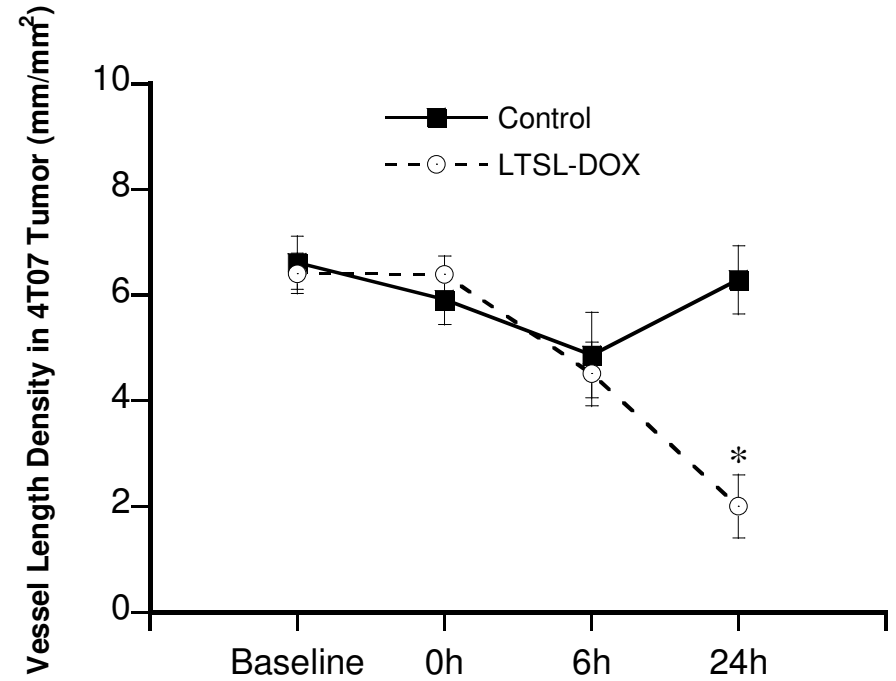
Courtesy Lars Lindner, from Manzoor et al, Cancer Res, 2012

Vascular targeting responsible for some of the anti-tumor effect of Dox-LTSL

FaDu



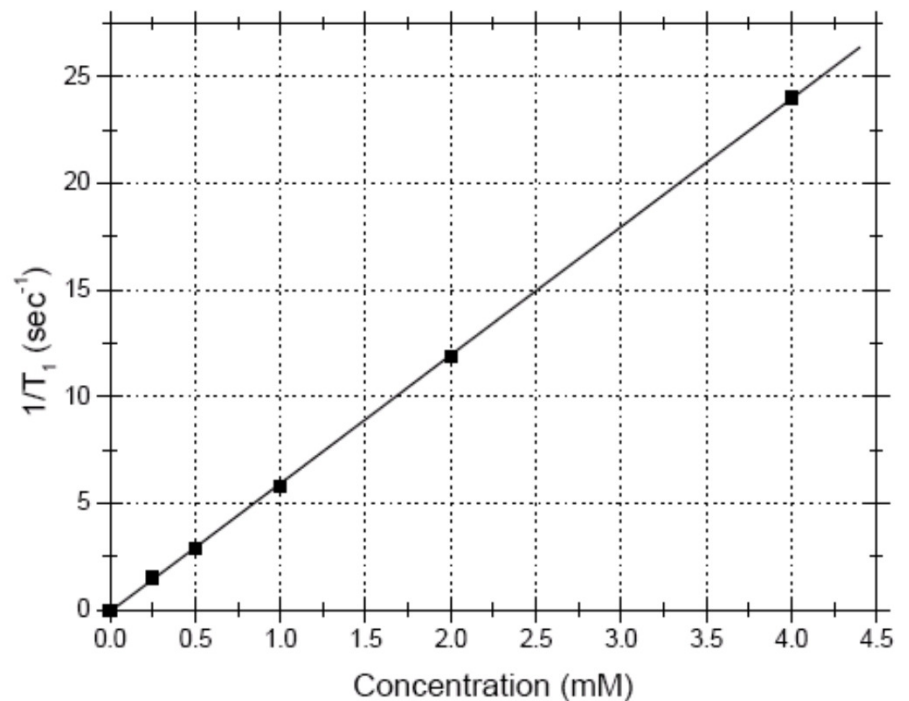
4T07



Chen et al., Mol Cancer Ther, 2004

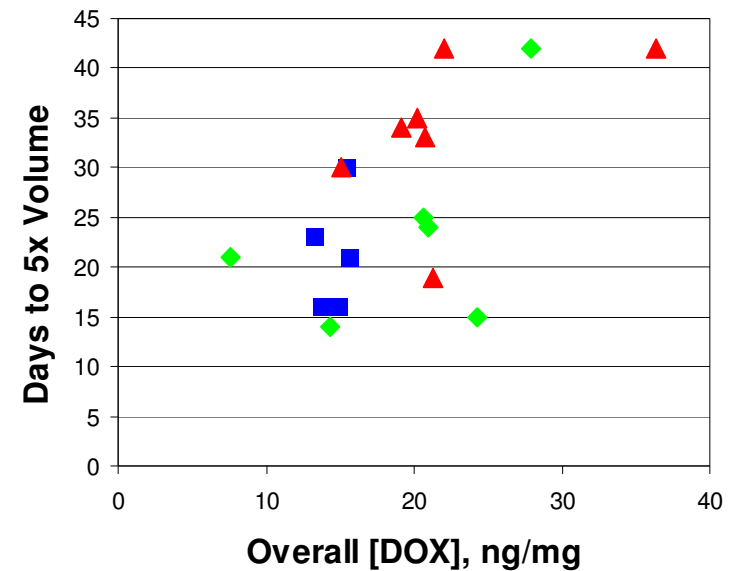
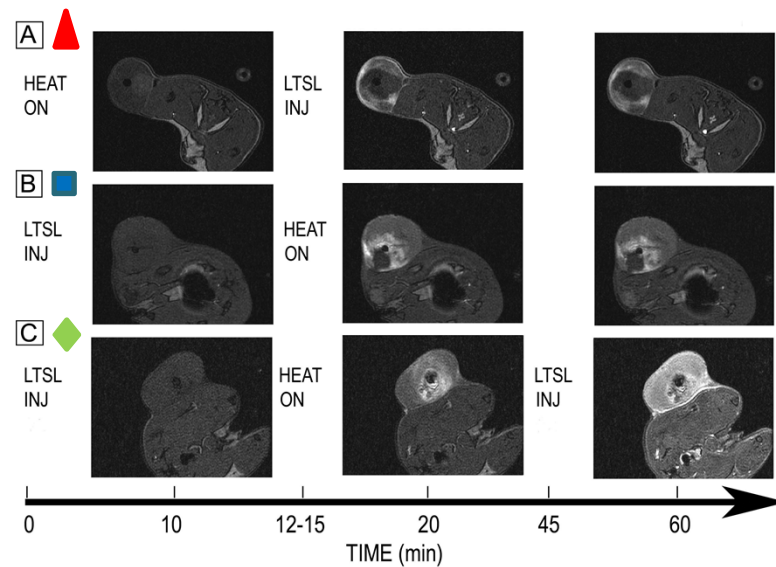
Manganese Loading Enables Liposome Visualization by MRI

- MnSO_4 gradient to actively load doxorubicin into LTSL
- Mn is paramagnetic MRI contrast agent



Viglianti et al, MRM, 2006

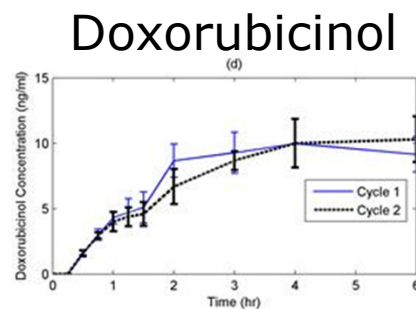
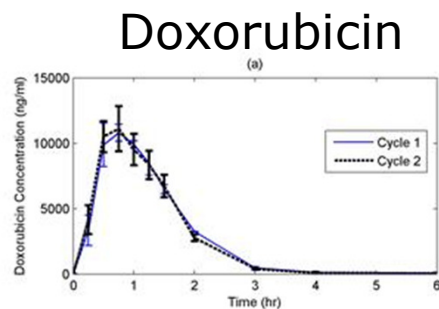
Amount *and* pattern of drug deposition predicts outcome



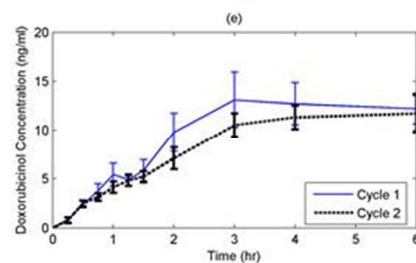
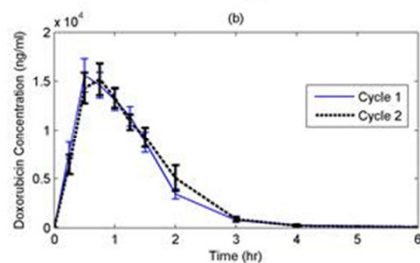
Ponce et al., JNCI, 2007

Pharmacokinetics

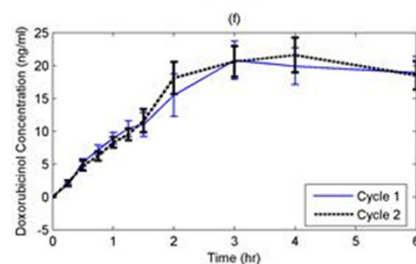
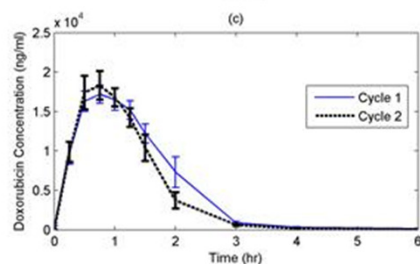
20mg/M²



30mg/M²



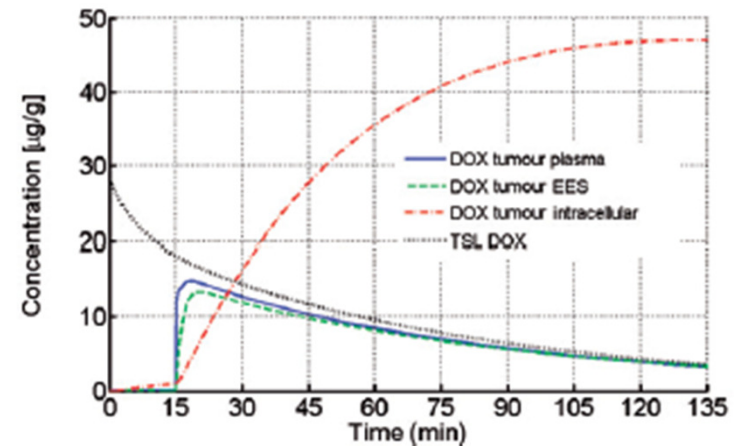
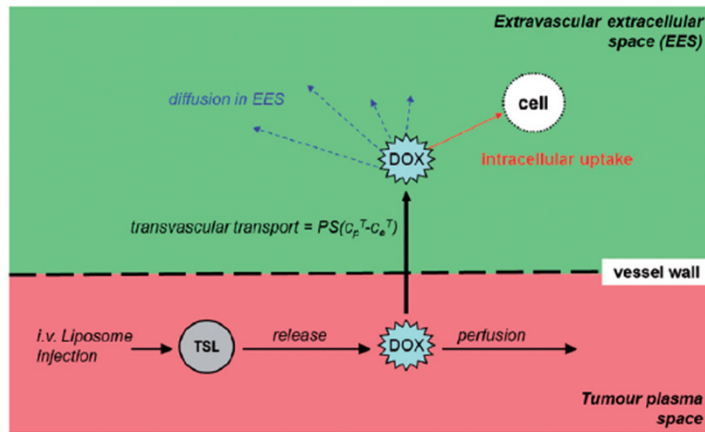
40mg/M²



$t_{1/2} = 35$ min-
Independent
of dose

Zagar et al., Two phase I dose escalation/pharmacokinetics studies of low temperature liposomal doxorubicin (LTLTD) and mild local hyperthermia in heavily pretreated patients with local-regionally recurrent breast cancer, In review

Alternate LTSL formulations may provide more flexibility in sequencing drug and treatment; modeling may provide important insights



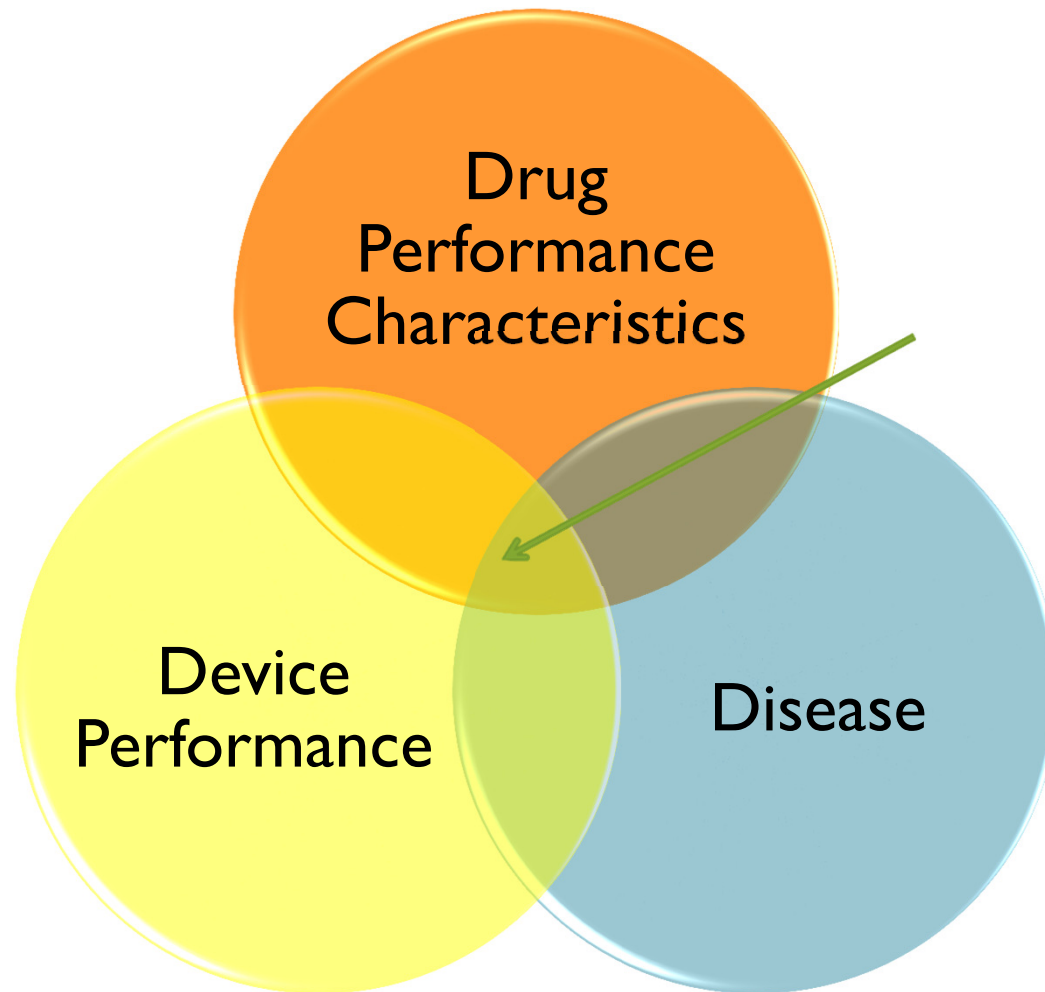
Gasselhuber et al, Int J. Hyperthermia, 2012



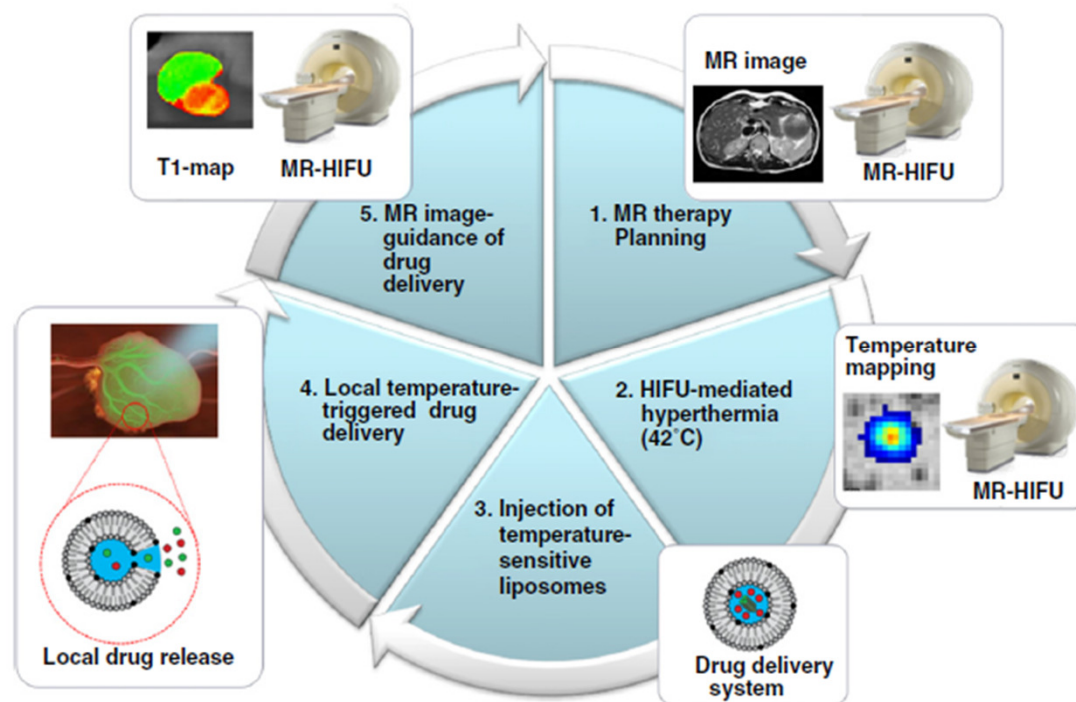
Summary

- LTSL exhibits maximal drug release between 41-43°C, some enhanced release at 40°C
- Rapid release kinetics enables intravascular drug release
 - Intravascular drug delivery targets vascular endothelium – adding to cytotoxic effects
 - Drives drug farther into extravascular space
- Short plasma half-life of Dox-LTSL
 - Give drug during heating to maximize drug delivery

Drug – Device combinations require careful design

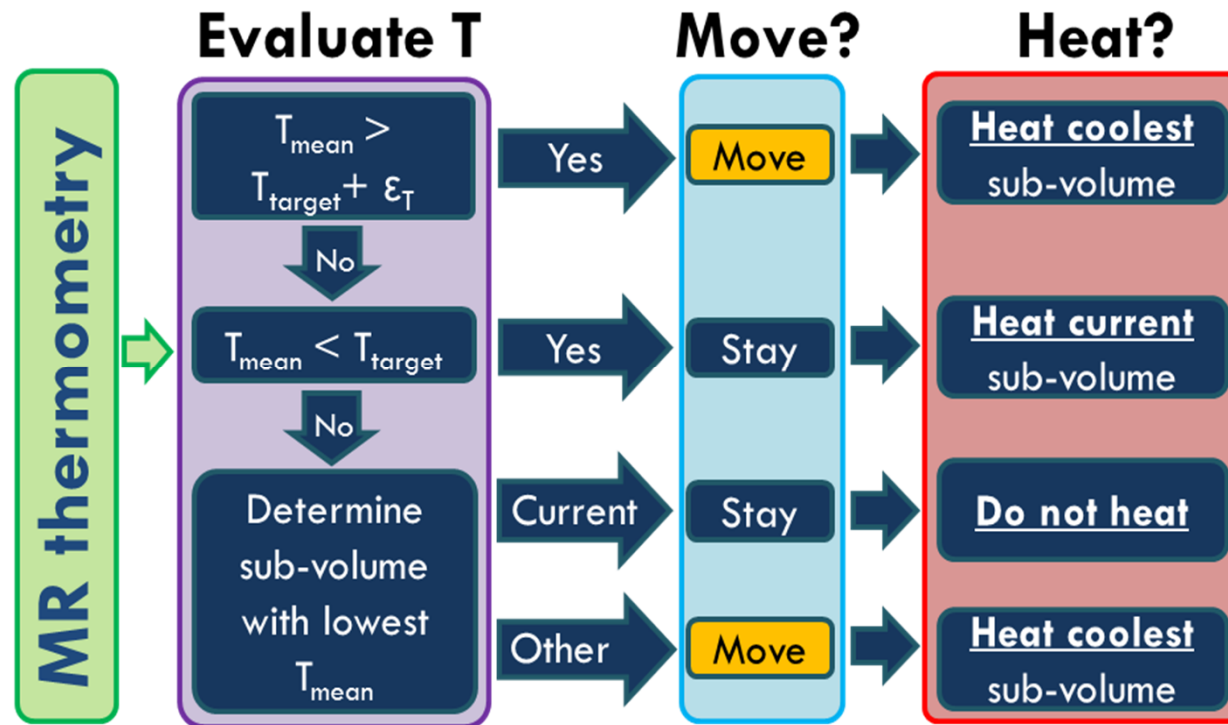


Implementation of LTSL drug release with ultrasound



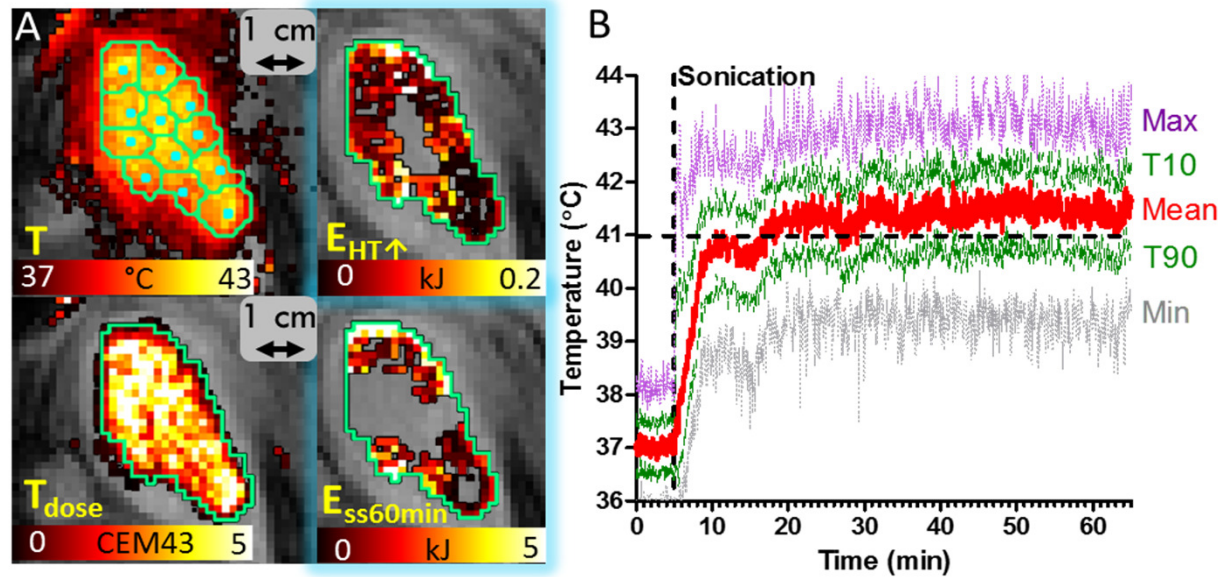
Grüll and Langereiss, J. Contr. Release 2012

Using focused ultrasound requires algorithm for large volume heating



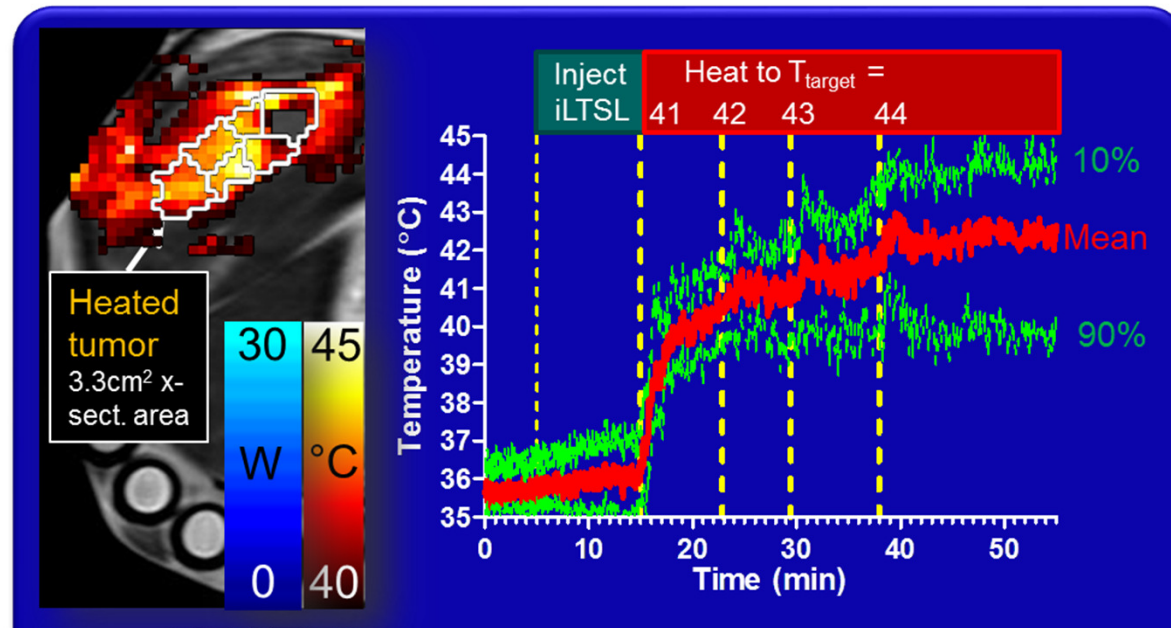
Algorithm for large volume heating

Using focused ultrasound requires algorithm for large volume heating



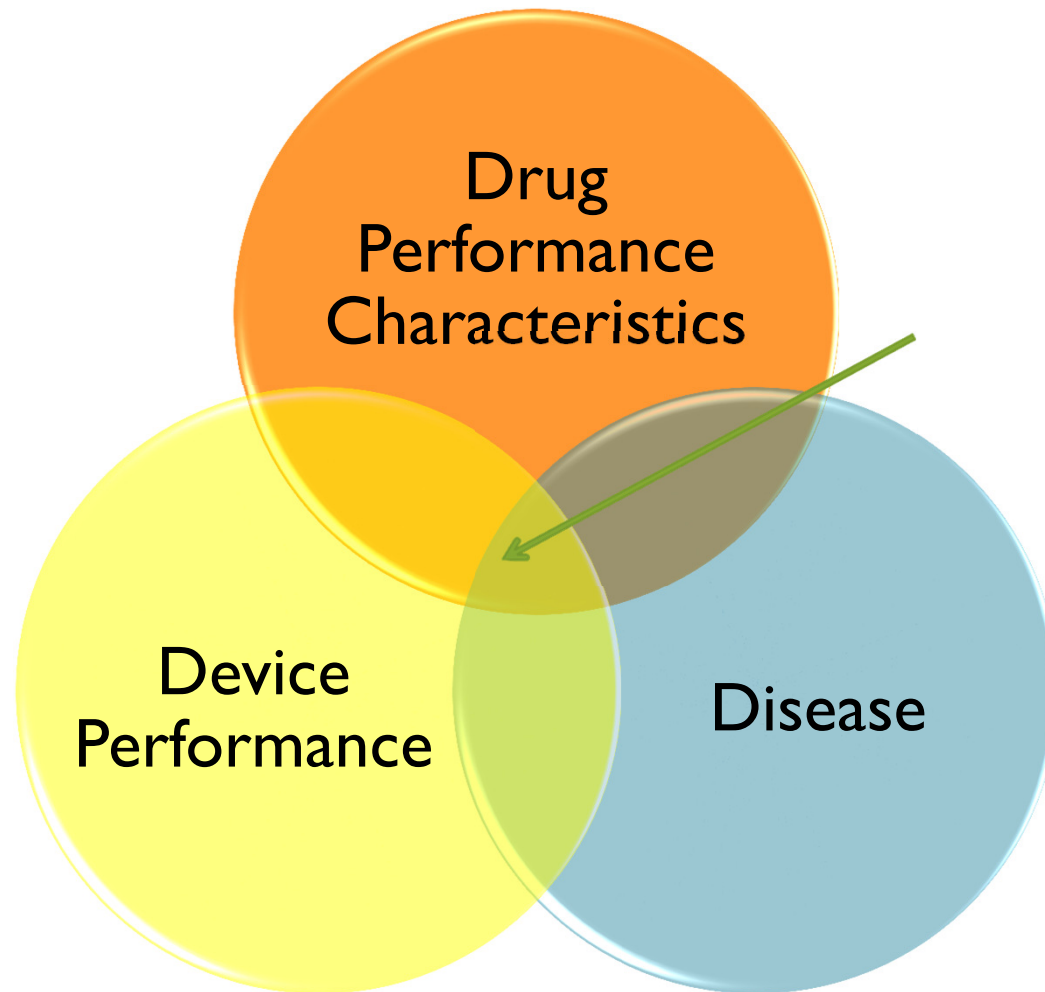
Example heating for 5cm diameter
VX2 carcinoma – rabbit thigh

Arrival of LTSL encapsulated contrast agent causes PRFS thermometry error



Tumor at thermal steady state, but arrival of MR contrast containing Liposome appears to show temperature elevation

Drug – Device combinations require careful design





Selection of diseases to use with US + LTSL -

Sites where conventional treatment is not satisfactory and where failure to control local disease causes morbidity or mortality

- Brain
- Liver
- Bone metastases
- Prostate
- Soft tissue sarcoma
- Locally advanced breast
 - Recurrent chest wall disease
- Pancreas
- Muscle invasive bladder cancer



Human Clinical Trials with Doxorubicin thermally sensitive liposome (TSL-Dox)

- Phase I
 - TSL-Dox + thermal ablation for colorectal liver metastases
 - NIH, Hong Kong
- Phase III
 - TSL-Dox + thermal ablation for primary HCC
- TSL-Dox + local hyperthermia for chest wall recurrences of breast cancer
 - Duke
 - Celsion

New phase III trial design for HCC

Phase 3 Design



Gen Eligibility:

- non-resectable HCC
- single lesion 3-7 cm
- no previous treatment
- Child-Pugh A

Stratification

Lesion Diameter: 3-5 v. 5-7
RFA approach: Perc, Lap, Surg

R
a
n
d
o
m
i
z
e

n= 275

ThermoDox®
plus standardized RFA

n= 275

standardized RFA alone

End Points

Primary: Overall Survival

Secondary: PFS, Safety



Future Directions for Liposome Studies

- The future, according to some scientists, will be exactly like the past, only far more expensive.
 - John Slaydek
- The future will be better tomorrow
 - Dan Quayle
- The best way to predict the future is to invent it
 - Alan Kay



Acknowledgements

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- **M. Dreher**



Future Directions: Liposome Development

- **Cisplatin liposome**
 - Has been formulated and is in pre-clinical studies
- **Clinical applications**
 - Bladder Cancer
 - Locally advanced rectal cancer, with RT
 - Pancreatic, with RT
 - Head and Neck with RT
- **Doxorubicin – Gadoteridol formulation**
 - For imaging with HIFU
- **Additional drugs being considered**