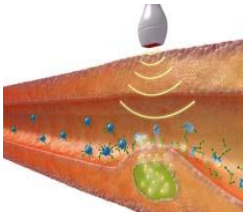
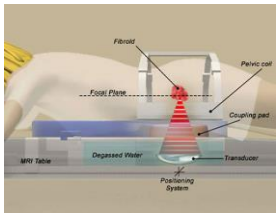
Ultrasound-triggered Drug Delivery



MRgFUS Tumor Ablation

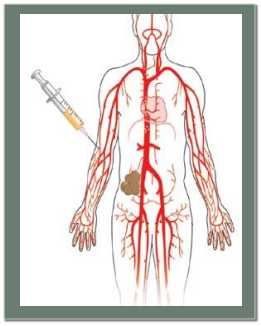


Stimuli-responsive colloids for ultrasound-mediated treatment of cancer

Tyrone Porter, Ph.D.
Associate Professor
Mechanical Engineering, Biomedical Engineering

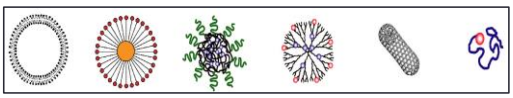
Combating Cancer

- Cancer is 2nd leading cause of death in the US
- Chemotherapy
  - i.v. administration of highly toxic drugs
  - Drug diluted and cleared from circulation
  - Large doses needed for adequate concentrations in tumor
  - Systemic toxicities limit dose delivered and consequently effectiveness of therapy



Nanomedicine

- Nanocarriers can be engineered to :
  - Protect drugs from enzymatic degradation or clearance from circulation
  - Target cancer cells specifically
  - Release drugs locally with well-defined kinetics
  - Entrap multiple drugs or a combination of drug(s) and image contrast material (theranostics)



DOXIL ®

- Clinically approved liposome encapsulated Doxorubicin (DOX)
- Surface modified with Poly(ethylene glycol) to avoid detection from MPS

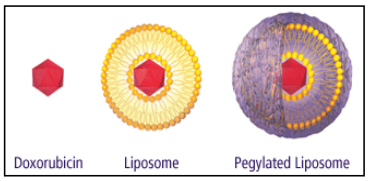


Figure adapted from Ortho Biopharmaceuticals, subsidiary of Johnson and Johnson ©2008

Slow drug release:

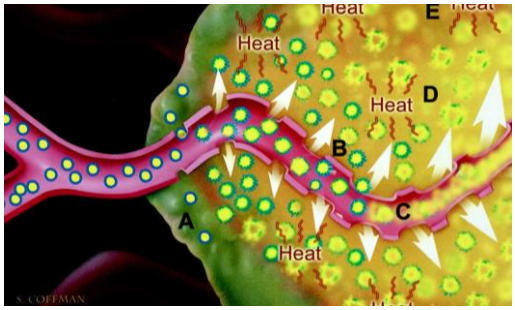
Passive diffusion

Degradation of lipid shell

Reduces side effects

Marginal improvement in therapeutic efficacy: drug release rate too slow; resultant intratumoral dose too low

Thermosensitive Liposomes



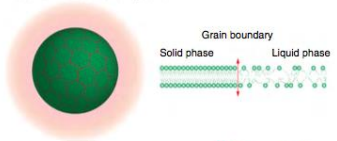
From Kong et al Cancer Research 2000

Criteria for Success

- Thermosensitive liposome must circulate for hours and be stable in blood
  - This will optimize extravasation and drug delivery to cancer cells
- Heating must be localized to tumor and sustained long enough to release > 50% of payload
  - An external noninvasive energy source is ideal
- Noninvasive method for measuring temperature elevation and feedback control of heating source
  - This is critical as the body will attempt to cool heated tissue

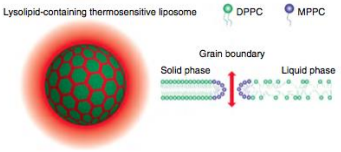
Documented Formulations

Traditional thermosensitive liposome



- DPPC is main lipid
  - T_{trans} = 42-44ºC
- Stably retains payload in blood until heated
- Long-circulating
- Slow release kinetics
  - Heat > 15 min

Lysolipid-containing thermosensitive liposome

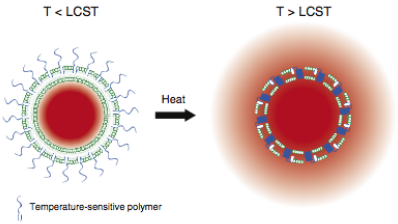


- Lysolipid (MPPC) added, drops T_{trans} to 39-40ºC
- Rapid release kinetics
  - Heat 1-2 min
- Unstable in blood, significant release within 60 minutes

From Ta and Porter J Cont Release 2013

Polymer-modified TSL

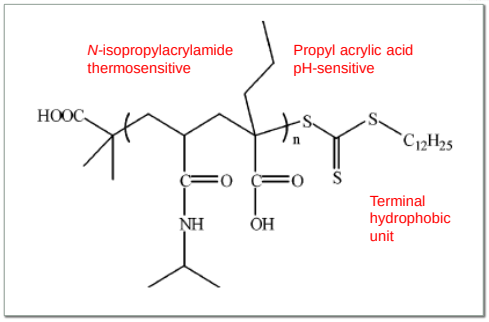
From Ta and Porter J Cont Release 2013



- DPPC main constituent…ensures stability in serum and sensitivity to heat
- PEGylated for long-circulation in blood
- Thermosensitive polymer terminated with fatty acid, which inserts into lipid bilayer
- Polymer goes from hydrophilic-to-hydrophobic when heated above LCST and disrupts lipid bilayer…enhances payload release

DOX Release as function of *T* and pH

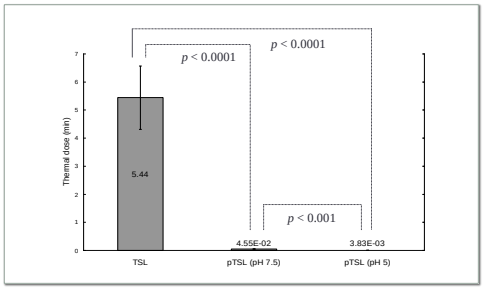
Copolymer Structure



DOX:lipid mass ratio ~ 6%

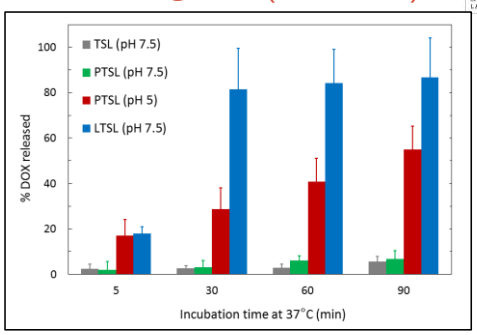
Ta et al Biomacromolecules 2010

Thermal Dose (50% DOX release)



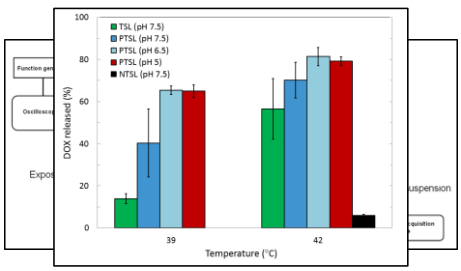
Ta et al Biomacromolecules 2010

DOX Release @ 37°C (20% serum)



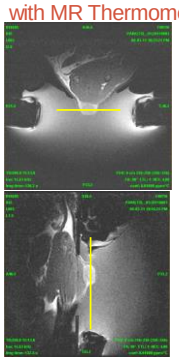
Ta et al Biomacromolecules 2010

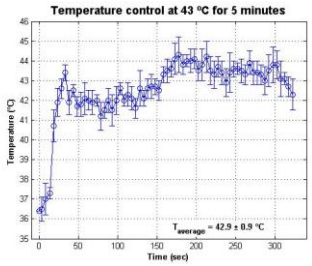
In vitro system for FUS-mediated heating



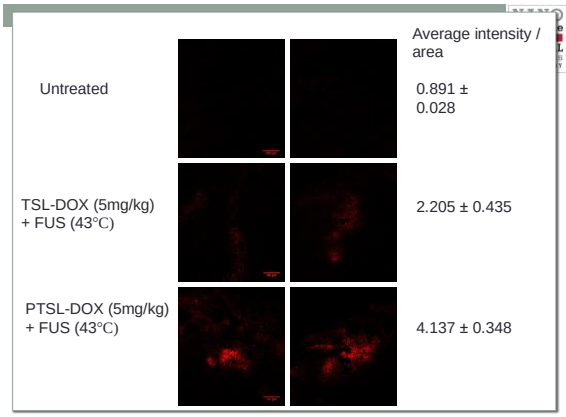
- 50% glycerol:saline attenuation coefficient @ 5 MHz: 0.795 dB/cm
- Mixture used to characterize FUS-mediated heating
- Optically transparent…ideal for quantifying DOX released from liposomes via spectrofluorophotometry

Ultrasound-induced heating measured with MR Thermometry

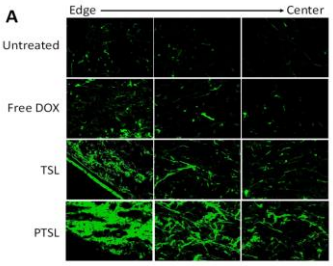




MR-guided ultrasound was used to heat implanted tumor to 42-44ºC for 5 min. MR thermometry used to measure temperature change.

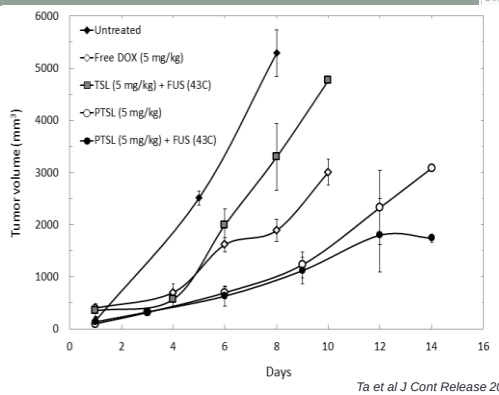


Evidence of Tissue Remodeling



Extracted tumors sectioned and stained for extra cellular matrix (ECM). More ECM was detected in tumors treated with pTSL and HIFU than other treatments, suggesting that this treatment combination was more effective.

Ta et al J Cont Release 2014



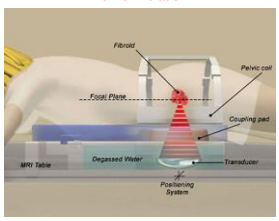
Ta et al J Cont Release 2014

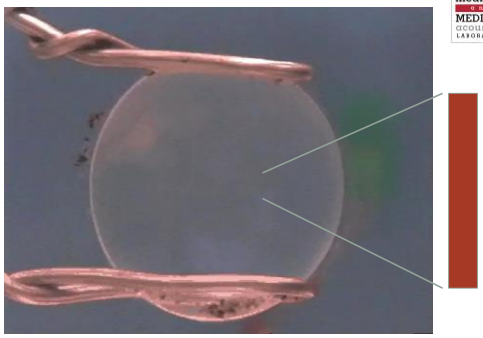
Summary

- Engineered nanocarrier that is responsive to both mild heating and mild acidity
- Incorporation of copolymer significantly reduced thermal dose required for triggered DOX release
- Sustained heating and pre-defined thermal dose delivered to solid tumor possible with MRgFUS
- pTSL released more DOX in solid tumors when heated to 43ºC for 5 min
- Combination of ultrasound-mediated heating and pTSL effective at slowing tumor growth significantly

Ultrasound-triggered Drug Delivery

MRgFUS Tumor Ablation

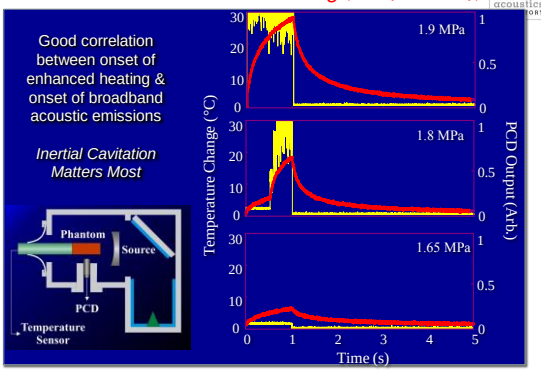




Cavitation-enhanced HIFU Heating *(courtesy of Holt & Roy)*

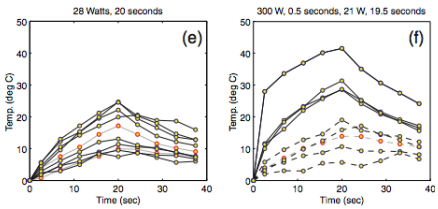
Good correlation between onset of enhanced heating & onset of broadband acoustic emissions

Inertial Cavitation Matters Most



Bubble-enhanced Heating at 1.1-MHz in Rabbit Thigh

(from Sokka et al Phys Med Biol 2003)



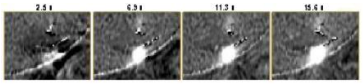
CW exposure for 20 s

0.5 s tone burst; 19.5 s CW

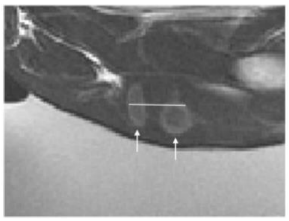
Cavitation was initiated with 0.5 s 300 W tone burst, followed by 19.5 W continuous wave exposure for ablation.

MR Thermometry Temperature Maps

(*from Sokka et al Phys Med Biol 2003*)



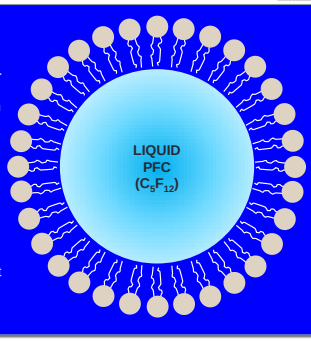
1.7 MHz
0.5 s pulse @ 300 W
19.5 CW @ 14 W



Lesion on left is control…no cavitation activity.
Lesion on right results from bubble-enhanced heating. Note circular shape and prefocal location.

Phase-Shift Nanoemulsion (PSNE)

- **PSNE: liquid perfluorocarbon nanodroplets**
- Size: 150-200 nm in diameter
  - Small size desired for passive accumulation in tumors through enhanced permeability and retention (EPR) effect
- Droplets are stabilized by phospholipid shell (DPPC/DSPE-PEG2000)
- Droplets contain non-toxic liquid perfluorocarbon with low boiling point (~29ºC)
  - Liquid perfluorocarbon droplets can be vaporized into microbubbles *in situ* using short acoustic pulses



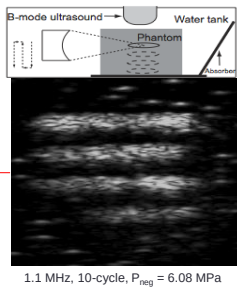
PSNE in acrylamide gel phantom

Basic properties of PSNE

- Submicron perfluorocaborn droplets
  - mean diameter around 250nm at 20°C
- Well-defined high-amplitude pressure threshold
  - 4.62 MPa Pk_{neg} at 1.1 MHz
- Predictable microbubble nucleation
  - On site
  - On-demand

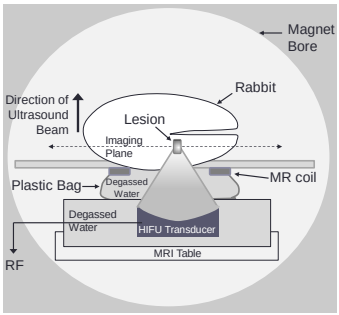
Guiding Principle

The ability of to control nucleation provides greater spatial and temporal control of bubble-enhanced heating and lesion formation.



1.1 MHz, 10-cycle, P_{neg} = 6.08 MPa

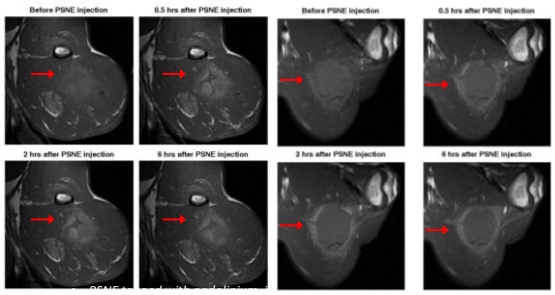
Experimental Setup



GE Signa 3T MRI System

MR-compatible, 1.5 MHz HIFU Transducer

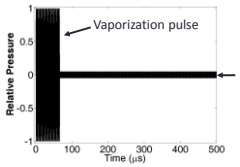
PSNE Accumulation



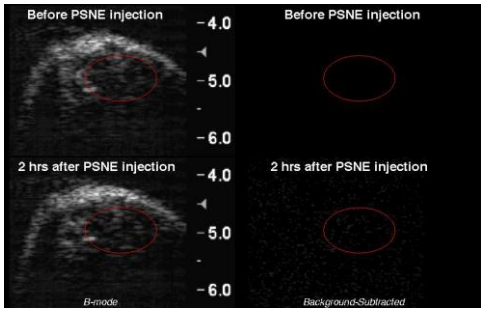
Kopechek et al J Heathcare Eng 2013

HIFU Parameters

- Center Frequency: 1.5 MHz
- Pulse Repetition Period: 670 ms
- Total Sonication Time: 30 s
- Pulsing Scheme:
  1. Short, high-amplitude pulse (100 cycles) to vaporize PSNE
  2. Long (1 million cycles), low-amplitude pulse to drive inertial cavitation and accelerate heating

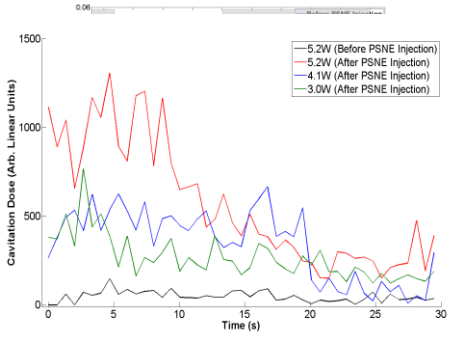


B-mode Imaging: PSNE Vaporization



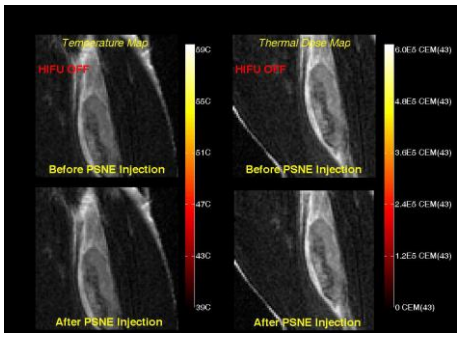
Kopechek et al J Ther Ultrasound 2014

Detection and Analysis of Inertial Cavitation

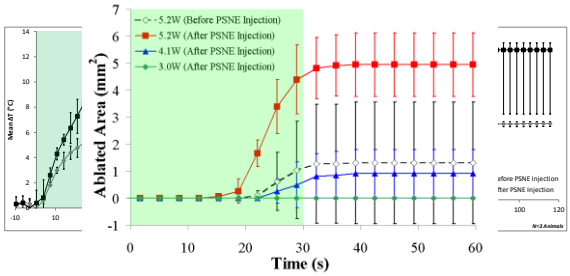


Kopechek et al PMB 2014

MR Thermometry: PSNE-enhanced Heating

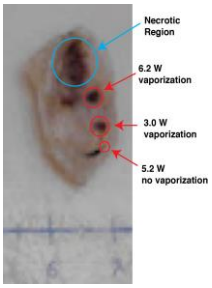


PSNE-enhanced Heating



Kopechek et al PMB 2014

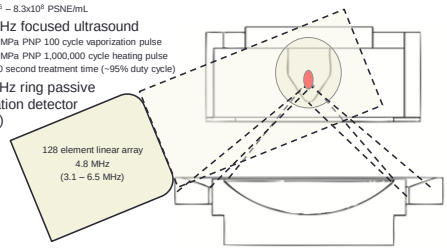
Cavitation-enhanced Lesion Formation



- Typically, tumors are treated with > 10 W of HIFU for ablation
- It was possible to ablate tumor in the presence of vaporized PSNE with acoustic power as low as 3 W
- Size of ablated volume depended upon acoustic power

Integrated MR Thermometry and Cavitation Monitoring

- Polyacrylamide gel phantom
  - Mean size: 208 nm (+/- 23 nm)
  - $8.3x10^6$ – $8.3x10^8$ PSNE/mL
- 1.6 MHz focused ultrasound
  - 5 MPa PNP 100 cycle vaporization pulse
  - 2 MPa PNP 1,000,000 cycle heating pulse
  - 50 second treatment time (~95% duty cycle)
- 600 kHz ring passive cavitation detector (PCD)

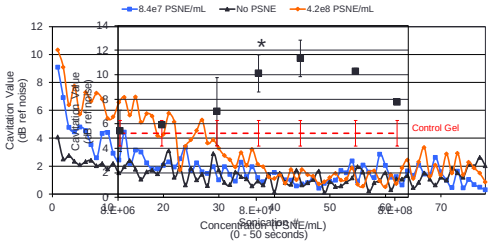


- Passive Cavitation Mapping
- MR Imaging and Thermometry
  - Proton resonant frequency (PRF) shift

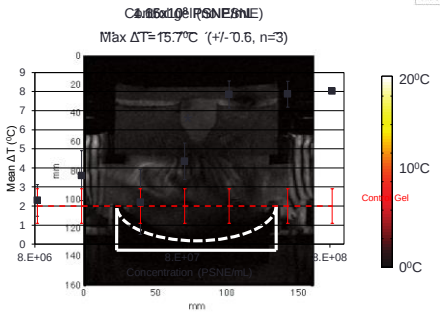
Cavitation Activity

- Data collected throughout entire treatment (50 seconds, 78 sonications)
- Each sonication time trace was enveloped and summated

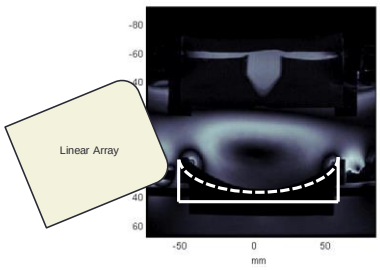
$$\text{Cavitation Value (dB)} = 20\log_{10}\left(\frac{c_{sum}}{c_{noise}}\right)$$



MR Thermometry



Passive Cavitation Mapping



Summary

- PSNE can accumulate in established tumors and seed inertial cavitation
- PSNE-nucleated cavitation enhanced heating, applied thermal dose, and reduced acoustic intensity required for lesion formation *in vivo*
- Combined MR thermometry and ultrasound monitoring in PSNE-loaded hydrogels:
  - Capture cavitation and heating migration
  - Multimodality feedback control of cavitation-enhanced tumor ablation
- Ongoing work for treatment of established tumors in rabbit kidney

Acknowledgements

- Nanomedicine and medical acoustics laboratory
- Focused ultrasound laboratory
- National Institute of Health (NIH)
  - Grant #: R01EB016102
- Focused Ultrasound Foundation