

The role of ultrasound in image-guided drug delivery

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Outline



- Use thermal or mechanical effects of ultrasound, in combination with drug or immunotherapy to cure cancers
- Temperature sensitive liposomes + hyperthermia
- Long circulating liposomes + hyperthermia
- Long circulating liposomes + ablation

MRfUS

Collaboration with Image-Guided Therapy (IGT)



- 16 element annular array
- Diameter: 45mm
- Radius of curvature: 35mm
- Operating frequency: 3MHz
- Acoustic efficiency > 65%
- Power rating: 150Wacoustic
- Bandwidth: 300KHz.
- Focal spot size (approx.) : 1.5mm x 1.5mm x 2mm



Fite, PLoS One, 2012



Mild hyperthermia with ultrasound reduces CD4+



Stabilized temperature sensitive liposomes Treat 2x/week, 4 weeks, 6 mg/kg



Enhanced delivery to tumors- highly stably and thermally sensitive particles



toxicity

Small molecule can penetrate tissue

Complexation of Cu(II) and Dox within liposomes



US 40 min

Dox fluorescence validates delivery

Lasic, D.D. et al., Biochimica Biophysica Acta (1995) vol. 1239, 145-156











(Cu)











Long Circulating Liposomes + Hyperthermia



Optimize <u>ultrasound-enhanced</u> <u>permeability and retention</u> <u>effect</u> (U-EPR)

(Red arrow shows insonified tumor)







Cumulative Equivalent Minutes at 43°C Comparison



PNP (MPa) 1.1 1.1 2.4 2.4

*p<0.01, **p<0.005, ***p<0.001

Combination of thermal and mechanical effects



Combination therapy regressed epithelial tumors



N= 32 mice

Dox: 33 mg/m², twice a week (intravenous injection, iv)
Rapa: 0.9 mg/kg, 3 times a week (intraperitoneal injection, ip)
US: 1.5 MHz, 42°C for 2 min, MI 1.9

*p < 0.05

Histological & immunohistochemical evaluation



Long Circulating Liposomes + Ablation



Ultrasound ablation (CEM43>200 for 2-3 seconds)



LCL + Ablation Unilateral Tumors (ablate 1x1x2 mm), 4x ablation, 8x drug



LCL + Ablation Histology



Conclusion



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Single ablation + long circulating nanodrug



Epithelial



EMT



Max Accumulation
 Max Accumulation Time



CuDox-LTSLs 40 min US



Dox fluorescence validates delivery



Dox spectrum

Thermal effects



MRI maps temperature and drug release



Mechanical disruption of RBC phantom (>12 MPa)





