Image-guided ultrasound facilitated drug delivery into tumors: optimization of treatment strategy based on quantitative measurement of cavitation

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Background

- **Cavitation**: expansion, contraction, collapse of air encapsulated microbubbles

- **Sonoporation**: cavitation \(\rightarrow\) cell/vessel disruption \(\rightarrow\) delivery of therapeutics into target cells/tissues
Goal

• Optimize treatment strategies for US-assisted delivery into tumor
  – Effects of acoustic and microbubble parameters
  – *In vivo* treatment platform
  – Image guidance of treatment
Phantom study: Experimental setup

- L7-4 probe $\rightarrow$ ACTIVE cavitation monitoring
- P4-1 probe $\rightarrow$ cavitation
- MB injection
- Active/passive cavitation detector
- Cavitation generation
- MBs
Passive cavitation detection (PCD)

- Incident US
- Scattered US
- Bubble response
- Power spectrum
- Frequency [MHz]
- Norm magnitude [dB]
- Time [µs]
- Pressure [MPa]
- Bubble radius [µm]
Quantification of cavitation

Temporal integral ➔ inertial cavitation dose (ICD)

(2) Duration of cavitation

(3) Mean RMS value during onset of cavitation
Active cavitation detection

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Presence of MBs $\rightarrow$ high image intensity and acoustic shadowing

US $\rightarrow$ destruction of MBs

Destruction of MBs $\rightarrow$ reduced image intensity

B-mode image intensity $\downarrow$ $\rightarrow$ MB destruction
### Experimental series

*Total treatment time = 2 sec (200 pulses).*

<table>
<thead>
<tr>
<th>Series</th>
<th>Frequency (MHz)</th>
<th>P- Pressure (MPa)</th>
<th>PD (cycles)</th>
<th>PRF (Hz)</th>
<th>MB (BR38) (count/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Series 1</td>
<td>1.8</td>
<td>0.6 – 5.4</td>
<td>5</td>
<td>100</td>
<td>$1 \times 10^8$</td>
</tr>
<tr>
<td>Series 2</td>
<td>1.8</td>
<td>2.4</td>
<td>3, 5, 7, 10, 15</td>
<td>100</td>
<td>$1 \times 10^8$</td>
</tr>
<tr>
<td>Series 3</td>
<td>1.8</td>
<td>3.0</td>
<td>5</td>
<td>10, 20, 50, 100</td>
<td>$1 \times 10^8$</td>
</tr>
<tr>
<td>Series 4</td>
<td>1.8</td>
<td>3.0</td>
<td>5</td>
<td>100</td>
<td>$4 \times 10^6 \sim 2 \times 10^8$</td>
</tr>
</tbody>
</table>
Passive cavitation detection in tissue phantoms

- Pressure (MPa) vs. ICD (V·s)
- Pulse length (cycles) vs. ICD (V·s)
- PRF (Hz) vs. ICD (V·s)
- MB concentration (count/mL) vs. ICD (V·s)
Active cavitation detection in tissue phantoms

5.4 MPa

1.8 MPa

MB destruction zone
Active cavitation detection in tissue phantoms

Post-treatment image magnitude

Bubble destruction zone (width)

Image magnitude (A.U.)

Pressure (MPa)

Bubble destruction zone (mm)

Pressure (MPa)

N=4 for each

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In vivo treatment platform

- MBs: PFC core, lipid shelled MBs
- Tumor model: Subcutaneous tumor on mice
- Model drugs:
  - 40nm polymer NPs
  - 130nm PLGA NPs
Active cavitation detection \textit{in vivo}

MB destruction @ 3 MPa
Active cavitation detection

- Treatment monitoring

MB destruction @ 3 MPa
Control: tail vein injection, 4hrs

Penetration depth <2 cell layers near the vessels

Small amount of leakage due to EPR
Penetration at least 3 cell layers with high dose
Ultrasound + microbubble, 24 hrs

Penetration depth: 5 cell layers with high dose
Summary

• Ultrasound image-guided drug delivery platform in vivo allows for treatment monitoring in real-time.
• Successful microbubble cavitation was achieved in phantoms and in vivo.
• Detectable delivery of 40-nm polymer nanoparticles into tumors with US and MB treatments.
Future work

• Effects of acoustic parameter, MB parameters, scanning protocol in drug delivery in vivo
• Spatial extent of drug distribution
• Maximum deliverable size of drugs