Image-guided Histotripsy for Oncological and Vascular Applications

Session: Image-guided Histotripsy for Oncological and Cardiovascular Applications

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Disclosure

• Zhen Xu is one of the inventors of intellectual property licensed to Histosonics, Inc..
  – Co-inventors: Charles Cain, Tim Hall, Brian Fowlkes, and Will Roberts

• She is a co-founder and holds stock in Histosonics.

Histotripsy

• Mechanical Tissue liquefaction generated by inertial cavitation via microsecond-length, high-pressure, pulses at low duty cycle (<<1%)

Intrinsic Threshold: 1-2 cycle pulse, \( P > 30 \text{ MPa} \)
Shockscattering: \( P \sim 15-20 \text{ MPa} \), \( P+>50 \text{ MPa} \), 3-10 cycle pulse,

Xu et al. TUFFC 2004; Parsons et al. UMB 2006
**In Vitro Histotripsy Treatment**

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**Tissue-Fluid Interfaces: Erosion**

Porcine Atrial Wall

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**Bulk Tissue: Liquefaction**

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Bubble-cell Interaction

High strain produced by bubble expansion and collapse mechanically disrupts the cells.

Vlaisavljevich et al. UMB 2016;42(10):2466.

SAM Question

1. The mechanism of histotripsy-induced tissue disruption is:
   a. High mechanical strain produced by cavitation
   b. Heating by high energy of ultrasound delivered to the focus
   c. All of above

Answer: a)

BOILING HISTOTRIPSY

Boiling histotripsy process:
1. Shock-wave heating to 100°C within ms
2. Interaction of shocks with vapor cavity

Example: in vivo porcine kidney

Courtesy of Tanya Khokhlova from University of Washington
Ultrasound Image Guided Histotripsy System

Histotripsy for Cancer Applications
- Liver Cancer
- Renal Cancer
- Prostate Cancer
- Pancreatic Cancer
- Brain Cancer
- Thyroid Cancer

Cavitational Histotripsy in Porcine Liver

US

Cavitational Histotripsy in Porcine Liver

T2-weighted MRI  B-mode Ultrasound

Histotripsy Liver Tumor Ablation
N1-S1 rodent liver tumor model

MRI in 14/15 treated tumors (6 partial and 9 complete) demonstrated near complete resorption of the ablated tumor in 7-10 weeks.

SAM Question

- 2. What happens to the liquefied tissue homogenate after histotripsy ablation in long term?
  - a. Remains in situ and forms scar-like tissue in situ
  - b. Remains in situ but does not form scar
  - c. Goes to blood flow and gets reabsorbed by the body, results in reduction of the targeted tissue volume

- Answer: (c)
Histotripsy Induces Local Immune Response
(Murine Melanoma Model)

CD8+ Intratumoral T-cell Infiltration

HMGB1 Concentration Post-treatment

Histotripsy (HT) Induces Systemic Immune Response

CD8+ T-cell Infiltration

Histotripsy (HT) Induces Systemic Immune Response

Pulmonary Metastases

A) Control
B) Histotripsy
C) Control Histotripsy

# pulmonary metastases

Contralateral

Control ablated contralateral Histotripsy day

Tail-vein Injections Tumor and Lung harvest day

Tumor Inoculation day

Histotripsy Ablation day

Day 0

Day -10

Day 3

Day 10

Day 0

Day -7

Day 0

Day -7

Day 0

Tumor Inoculation
day

Histotripsy Ablation
day

Day 0

Day -7

Tail-vein Injections Tumor and Lung harvest
day

Tumor Inoculation
day

Histotripsy Ablation
day

Day 0

Day -7

Tail-vein Injections Tumor and Lung harvest
day

Tumor Inoculation
day

Histotripsy Ablation
day
BOILING HISTOTRIPSY
NON-INVASIVE LIQUID BIOPSY TOOL

Blood-based cancer biomarker – a cancer-specific molecule secreted by the tumor into the circulation
MicroRNAs – promising class of blood-based biomarkers, but low baseline release levels

MicroRNAs

Chevillet, Khokhlova et al. Radiology 2016

Thrombosis

Deep Vein Thrombosis
Large Hematoma Evacuation

Non-invasive Thrombolysis

- **Thrombosis** - blood clot formation, cause of many vascular diseases, such as deep vein thrombosis, stroke, etc.

- **Current techniques have drawbacks:**
  - **Thrombolytic Drugs** – Slow reperfusion, excessive bleeding
  - **Catheters** – Invasiveness, bleeding, and infection
Histotripsy Thrombolysis
Porcine Deep Vein Thrombosis Model


Histotripsy Thrombolysis
Porcine Deep Vein Thrombosis Model


Histotripsy Thrombolysis
Porcine Deep Vein Thrombosis Model

Histotripsy Thrombolysis
Porcine Deep Vein Thrombosis Model


Histotripsy Thrombolysis: B-mode and Doppler Post-treatment

Before Treatment
Right After Treatment
2 Weeks After Treatment

Zhang et al. UMB 2017

Histotripsy Thrombolysis: Vessel Damage (2 weeks)

2 Weeks After Microtripsy Thrombolysis Treatment
Boiling Histotripsy For Liquefaction And Aspiration Of Large Hematomas

Large (up to 1-2 L) hematomas often caused by trauma or post-surgical bleeds

Health effects:
• pain
• compartment syndrome
• organ failure
• risk of infection

Clinical management:
• Surgery
• Indwelling drain (ineffective)

Approach: fast liquefaction with boiling histotripsy, simultaneously drain with fine needle

In vitro phantom

Highest liquefaction rate achieved to date: 16 mL/min

Courtesy of Tanya Khokhlova from University of Washington

Histotripsy for Brain Applications

Brain Tumor
Hemorrhagic Stroke

Transcranial (Cavitational) Histotripsy

250/500kHz 256E hemispherical array
30 cm diameter
15 cm focal distance
Can ablate brain tumor or liquefy clot through human skull in deep and shallow locations in the brain

Sukovich et al. TUFFC 2016; Gerhardson et al., TUFFC; 2017
Transcranial Histotripsy
In vitro bovine brain ablation through human skull

Capability to
• ablate a volume
• ablate near skull surface (5mm)
• Skull heating (<4°C)

Gerhardson et al., UMB, 43(10):2302-17

Histotripsy in the In Vivo Porcine Brain

Sukovich et al., J. Neurosurgery, 2018

Acknowledgement

• Scientific Collaborators (PhD)*
  – Charles A. Cain (BME)
  – Timothy L. Hall (BME)
  – J. Brian Fowlkes (Radiology)
  – Jonathan Sukovich (BME)
  – Eric Johnsen (ME)
  – James Balter (Radiation Oncology)

• Ph.D. Students and Postdocs
  – Jonathan Lundt
  – Jonathan Macockey
  – Tyler Gerhardson
  – Hedefe Tamaddoni
  – Yige Li
  – Sang Won Choi
  – Tejwai Warlikar
  – Ryan Hubbard
  – Ellen Yeats
  – Ning Lu
  – Greyson Stocker

• Clinical Collaborators (MD)
  – Aditya Pandey (Neurosurgery)
  – Gabe Owens (Pediatric Cardiology)
  – William Roberts (Urology)
  – Clifford Cho (Surgery)
  – Mishal Mendiratta-Lala (Radiology)
  – Fred Lee (Radiology – U. Wisconsin)
  – Hitinder Gurm (Interventional Cardiology)

• Funding Support
  – NIH (R01 CA 211217, R01 EB 008998, R01 NS108042, R01 DK 091267)
  – American Cancer Society (RSG-13-101-01- CCE)
  – Focused Ultrasound Foundation
  – American Heart Association
Brain Diseases and Treatment Options

- Brain Tumor Treatment
  - Craniotomy surgery - invasive
  - Chemotherapy – blood brain barrier
  - Radiation therapy – normal brain structure susceptible to radiation damage

- Hemorrhagic stroke treatment
  - Medical management – no active clot reduction
  - Craniopuncture (tPA + catheter drainage) – Slow

- MR guided Focused Ultrasound (MRgFUS)
  - Essential Tremor
  - Can only treat a small volume in the central region of the brain

Thank you!
Questions?