Regenerative Medicine

- Bone Healing
- Hyperthermia
- Enhancing Homing and Retention of Stem Cell
Bone Healing

- Approximately 5.6 m fractures occur in the US annually
- 5-10% don’t heal by themselves
- Low intensity pulsed ultrasound can accelerate healing

- accelerates healing by 38%
One set of Parameters

- 1.5 MHz
- 20% duty cycle
- \( I_{\text{sata}} \) 30 mW/cm\(^2\)
- 20 minutes/day
- 1 kHz PRF
Bone Fractures

During normal healing, a series of physiological events:
- Inflammation
  - release of inflammatory cytokines and growth factors
  - migration and differentiation of stem cells to the site of injury
- Repair
- Remodeling

In the aging population
- lower capacity for stem cell division and differentiation
- impaired angiogenesis
- reduced levels of growth factors
Bone Healing Mechanism

- Repetitive mechanic stimulus
- Bone cells can sense microforces and adjust their microenvironments (mechanoreceptors)
- Stimulates VEGF (vascular endothelial growth factor)
- Enhances osteoclast formation, calcium signaling, calcified matrix production
Bone Remodeling after MR Imaging–guided High-Intensity Focused Ultrasound Ablation: Evaluation with MR Imaging, CT, Na\(^{18}\)F-PET, and Histopathologic Examination in a Swine Model\(^1\)

- Both ablations show mixed endosteal sclerosis and lucency (arrows).
- Distal lesions also demonstrated a subtle focus of new bone density along the cortical margin.

- All ablations show dense subcortical sclerosis
- Distal lesions also show a larger focus of new bone density along the cortical margin compared with the appearance at 3 weeks.
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**Temperature**

**Figure 3.** Frequency distribution of 700 baseline oral temperature observations obtained at various times during two consecutive days from 148 healthy volunteers. The arrow indicates location of 37°C (98.6°F). Reprinted with permission from the *Journal of the American Medical Association* 1992;268:1578–80. ©1992, American Medical Association.
"Old people," according to Wunderlich, "present a temperature 0.5°C = 0.9°F less than younger persons". In a study reported in the Lancet in 1948, Howell confirmed this observation.
Hyperthermia

There is a reason why we develop fever when we get sick (wikipedia):

- Increased mobility of leukocytes
- Enhanced leukocyte phagocytosis
- Increased proliferation of T cells

Hippocrates used heat for treatment of a wide variety of inflammatory diseases and cancer.

Over 100 years ago Dr. William Coley witnessed a significant improvement in tumor control and overall survival in patients who were inoculated with bacterial cultures. Those patients who achieved the longest duration of remission experienced the highest fevers.
Hyperthermia

1) Improves radiotherapy in hypoxic tumors by
   - increasing blood flow
   - increasing oxygenation
   - decreasing tumor pressure
   - interferes with DNA damage repair
2) Improves Chemotherapy
Augments drug uptake into tumor cells and can reverse drug resistance
Hyperthermia

3) Enhances immune response by
- promotes infiltration of tumor-specific cytotoxic CD8T cells into the tumor microenvironment
- decrease in Tregs
- enhancing entry of naive T-cells into lymph nodes and Peyer's patches

4) enhances sensitivity to immune cell recognition and killing
- HSP70 family members expressed on the tumor cell surface may activate NK cells via specific receptor interactions.
- HSP70 stimulates the proliferation and activation of NK cells while binding to Granzyme B, rendering tumor cells more sensitive to NK cell–mediated cytotoxicity.
Focused ultrasound induced hyperthermia accelerates and increases the uptake of anti-HER-2 antibodies in a xenograft model.

Centelles MN¹, Wright M¹, Gedroyc W², Thanou M³.

Fig. 2.
NIRF in vivo imaging of mice with bilateral implanted tumours (IGROV-1) at time point post-injection of XI750-trastuzumab (~8 mg/kg). FUS induced hypothermia treatment was either omitted (top) or applied at 1 h (middle) or 1 h, 2 h, and 3 h 30 (bottom) on the right tumour. The difference in labelled antibody uptake is clear and lasts for more than a week.
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Pulsed Focused Ultrasound Pretreatment Improves Mesenchymal Stromal Cell Efficacy in Preventing and Rescuing Established Acute Kidney Injury in Mice


**SCOTT R. BURKS,** a,b **BEN A. NGUYEN,** a **PAMELA A. TEBEBI,** a,c **SAEJEONG J. KIM,** a **MICHELE N. BRESLER,** a **ALI ZIADLOO,** a **JONATHAN M. STREET,** d **PETER S. T. YUEN,** d **ROBERT A. STAR,** d **JOSEPH A. FRANK,** a

**pFUS Technique**

pFUS was administered with a Sonoblate 500 (Focus Surgery, Indianapolis, IN, sonacaremedical) or VIFU 2000 (Alpinion Medical Systems, Bothell, WA, www.alpinionusa.com) under ultrasound imaging guidance [21]. pFUS exposure parameters were: peak rarefaction amplitude, 8.9 MPa; pulse repetition frequency, 5 Hz; duty cycle, 5%; number of pulses per site, 100. Six raster points in a $2 \times 3$ pattern with an elemental spacing of 2 mm were used to treat kidneys. Kidneys were treated unilaterally for molecular analyses and quantification of MSC homing, where untreated contralateral kidneys were internal controls. Bilateral pFUS was performed in mice used to assess functional outcomes. Control groups received sham pFUS exposures (transducer power = 0 W).

Scott R. Burks, a,b Ben A. Nguyen, a Pamela A. Tebebi, a,c Saejeong J. Kim, a Michele N. Bresler, a Ali Ziadloo, a Jonathan M. Street, d Peter S. T. Yuen, d Robert A. Star, d Joseph A. Frank, a,a

B

cisplatin  
<p>|</p>
<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<td>pFUS+MSC</td>
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<td>pFUS+MSC</td>
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<tr>
<td>Time (days)</td>
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MSC homing to AKI kidneys

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<th>Days post-cis-platinum</th>
<th>Control</th>
<th>pFUS Treated</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Day 4</td>
<td>+</td>
<td>*</td>
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</tbody>
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D

Day 1

Control  
pFUS

Day 4

Ex Vivo 7T MRI

E

Cell Count

Day 1  

Day 3  

Day 7  

*p<0.01  

Treated  

Control
Pulsed Focused Ultrasound Pretreatment Improves Mesenchymal Stromal Cell Efficacy in Preventing and Rescuing Established Acute Kidney Injury in Mice

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Percent survival

Time (days)

Cis / pFUS / MSC

Cis / MSC

Cis

\[ p < 0.0001 \]

\[ p = 0.0292 \]

\[ p = 0.0247 \]