The Zagzebski/Carson Distinguished Lecture on Medical Ultrasound:

**Image Guided Ultrasound Therapy**

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Ultrasound

= sound with a frequency above the hearing range

Therapy: 0.2 – 10 MHz, Diagnostic: 1-50 MHz

Longitudinal Wave

![Diagram of ultrasound wavefronts and intensity profile]

Focused Ultrasound

![Diagram of focused ultrasound transducer and intensity profile]
Ultrasound Interactions with Tissue

Ultrasound
Vibration of Molecules
Energy Absorption
Radiation Force
Tissue motion (Shear waves)

Temperature Rise
Bio-Effects

Bio-Effects
Radiation Force
Tissue motion (Shear waves)

Cavitation
Micro Bubbles

Energy Absorption
Temperature Rise

Inertial Cavitation
Bubble collapse

Jet formation

L.Crum
Ultrasound Therapies

1. Thermal tissue interactions
   - Thermal ablations
   - Hyperthermia
   - Drug delivery

2. Gas bubble mediated
   - Histotripsy
   - Thrombolysis
   - Apoptosis
   - Enhancement of Radiation effects
   - Thermal enhancement
   - Drug delivery

3. Radiation force/Other
   - Sonodynamic therapy
   - Neuromodulation
   - Cardiac spacing
   - Drug delivery
   - Thrombolysis acceleration

Neuromodulation

Ultrasound Bioeffects

Temperature Elevation

- Coagulation
- Vaporization
- Hyperthermia

Temperature (°C)

Time (s)
Focused Ultrasound Induced Tissue Coagulation
Rabbit Brain in Vivo


“Fry’s monster”

- The device was made in the form of a double-deck arrangement
- Four ultrasound beams could be brought into coincidence to produce focal point


Prostate Device

A novel patented technology that combines both imaging and therapy elements on a single ultrasound crystal.

- Therapy Element: 4.0 MHz, Curved Rectangular
- Imaging Element: 4.0/6.0 MHz, Curved Circular

B-Mode Imaging With Treatment Monitoring.

Sanghvi et al.,
Focused Ultrasound Treatments: Image Guidance

- Targeting
- Monitoring
- Control
- Verification

- MRI
- Ultrasound
- X-rays
- PET/Spect

UF ablation with US-guidance

MRI vs. US Guidance

- Targeting

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Cho et al. J. Ultrasound in Medicine, 32, 397-406, 2013
Haifu Model JC Focused Ultrasound Tumour Therapeutic System

Integrated Treatment Transducer (diagnostic US probe and HIFU transducer) in degassed water reservoir

Courtesy of J. Kennedy, F. Wu

Ideal focal region for treatment:
1.1mm × 3.3mm

Range of acoustic intensity within focal field:
5000 W/cm² to 25000 W/cm²

Therapeutic frequency:
0.8MHz—2.4MHz

Thyroid System

Courtesy of Jean-François Aubry
Noninvasive Thermometry Assisted by a Dual-Function Ultrasound Transducer for Mild Hyperthermia

InSightec

MRI-guided Focused Ultrasound Thermal Ablation
Uterine Fibroids - 15 years

Approximately 150 sites > 10,000 patients
Limited Phased Arrays

Element size >> wavelength

=> limited steering

N= number of elements

NRF- signals

Cain and Umemura, IEEE Trans. Microwave Theory Tech. MTT-34:542-552, 1986

MR-Guided FUS

Uterine Fibroid Treatments

- All the image-guidance advantages
- No tissue penetration
- Reduced risk of infections
- Fast recovery

Carls et al., JOURNAL OF WOMEN’S HEALTH, 17, 7, 2008
Stewart et al., Obstet Gynecol 2007;110(2 Pt 1):279-287

InSightec: FDA approved 2004

Potential advantages:

- Provides better accessibility to lateral limbs to provide easy and comfortable access to multiple anatomical locations
- High density electronically steerable 1000 elements transducer
- Water-permeable membrane to provide acoustic coupling
- Integrated built-in skin cooling system
- Automatic transducer tracking

Current status:
First feasibility study completed outside the USA.

Caution - Investigational Device
Limited by United States Law to Investigational Use.
MRgFUS Intra-cavitary Prostate System

1000-channel phased array:
- Flat, rectangular, 2.3 MHz

Uses:
- Focusing
- Steering in depth direction
- Increasing focal volume per sonication

Exablate 2000, iSightec, Haifa, Israel

MRI-controlled Transurethral Prostate Ablation

Chopra and Bronskill

Atrial Arrhythmia treatment by Pulmonary Vein Isolation

ProRhythm, Inc.

No exposure control => patient death
Cardiac Ablation-Epicor

http://www.youtube.com/watch?v=MkqriH986DqM

Cosmetic Syrgery

Arch Facial Plast Surg. 2007;9:22-29

CT Calvaria image
Attenuation in Human Skull Bone

![Graph showing attenuation in human skull bone with different frequencies (835 kHz, 1.402 MHz, and 270 kHz).](image)

Ultrasound Propagation In Soft Tissue/Bone

![Diagram showing ultrasound propagation in soft tissue and bone.](image)

Skull Heating Problem => Large Hemispherical Transducer

![Illustration of skull heating problem with a hemispherical transducer.](image)
Prototype Hemispherical Arrays

64 elements

1272 elements

Speed of Sound in Human Skull Bone


Sonication Through an ex vivo Human Skull
No Phase Correction
Skull Defocusing Problem

Phase Correction

to compensate for the Skull thickness

Transducer Elements

Skull

RF-signals


Model Corrected

SK12

Volume Maximum=4.158 x 10^6 mV^2


InSightec Exablate 4000

Brain system

Frequency: 220kHz and 660kHz
Number of Channels: 1000
Head fixation: pins
Essential Tremor

- 10 million in the US
- (0.5 mil Parkinson’s disease)
VIM Targetting

Immediate pre-operative

Intra-operative (in the scanner)

Immediate post-operative

Patient 5: Freehand Spirals

Lipsman et al., Lancet Neurology 2013
Thermal Treatments Close to Skull Base

Pulkkinen et al., ISTU10
MRI-Controlled Hyperthermia+ ThermoDox* => Localized Drug Delivery


Enhanced tumor drug concentration and antitumor effect (Kong et al, 2000)

Heat-Triggered Local Release

Local Heating (40-43°C)

Encapsulated Doxorubicin

Rapid Release of Doxorubicin at 40-43°C

Heat 10 mm region in VX2 tumor to 43°C for 20 min.

Thermosensitive liposomal doxorubicin (LTLD, ThermoDox) infused during heating (2.5 mg/kg over 8 min)

Transducer scans at 1 revolution per second, image every 5 seconds.

Heat 10 mm region in VX2 tumor to 43°C for 20 min.

Thermosensitive liposomal doxorubicin (LTLD, ThermoDox) infused during heating (2.5 mg/kg over 8 min)

Application: Thermally mediated drug delivery

Staruch et al, ISTU 2011

Setup (Axial T2w) Thermometry (Coronal FSPGR)

PI temperature control at 8 ROIs on periphery of 10 mm target region:

\[ P = K_1 (r - T) + K_2 \sum (T_0 - T) \]

Mean ± SD

Celsion

Transducer scans at 1 revolution per second, image every 5 seconds.

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Staruch et al, ISTU 2011

Setup (Axial T2w) Thermometry (Coronal FSPGR)
Biodistribution: Free vs. liposomal DOX

Drug formulation | Unheated tumor [DOX] | Heated tumor [DOX] |
--- | --- | --- |
Free DOX | 4.9 ± 3.5 μg/g | 7.9 ± 1.9 μg/g |
TSL-DOX | 3.4 ± 1.8 μg/g | 76.3 ± 27.9 μg/g* |

Staruch et al., Int J Hyperthermia 2012.

Drug distribution: Effect of triggered release

Rabbit VX2 Tumours: Survival

Staruch et al., Int J Hyperthermia, 2015
Heat Activated Gene Therapy

- Ad-HSP-Luc
  - an adenoviral vector
  - a firefly luciferase gene => therapy gene
  - a human hsp70B promoter


Spatial Control of Genetherapy by MR-HIFU

Deckers et al., PNAS 2009

2. Gas bubble mediated

Histotripsy

Histotripsy: Thrombolysis

High-Intensity Focused Ultrasound (HIFU) for Dissolution of Clots of Embolic Stroke.

Burgess et al. Plos One 2012

Through Skull Stroke Treatments Simulations

Pajek et al., PMB 2012
**Drug Delivery with Microbubbles**

- US + Bubbles+ free Drug
- US + Bubbles + Drug in free Liposomes/micelles
- US + Bubbles with Drug
- US + Targeted Bubbles with Drug
- US + Bubbles with Drug in liposomes/micelles
- US + Super heated droplets with drug


**Docetaxel (Taxotere) with the Antivascular Action of Ultrasound Stimulated Microbubbles**

![Graph showing tumor volume and percent survival over weeks for USMB and DTX treatment ends.](image)


**Radiation+MB+US**

Breast cancer MDA MB 231 model in vivo
- 500kHz,570kPa, 15 cycles, PRF=3kHz, 10% duty, Duration 50 ms,
- Repeat Frequency 0.5Hz, Total time ≤5 min

![Graphs showing blood flow and drug concentration over time with USMB and DTX treatment.](image)


Lai et al, Oncoscience 2016
Stem cells to infarcted heart using targeted microbubbles

Focal and Noninvasive MRI-guided Method for Drug Delivery into Central Nervous System

Cellular constituents of the blood-brain barrier.

Abbot et al., Nature Rev. 7:42, 2006
"Histological examination of lesions stained by trypan blue showed this method to be a reliable index of the area of tissue damage."

How Can Ultrasound Open the BBB?

Focused ultrasound opening of BBB
260 kHz:
0.3 MPa: BBB OPEN
Four hours after FUS:
NO EXTRAVASATION

Duration of the BBB open

How can BBB opening be used for therapy?

**Animal Experiments** (>150 studies):

*Effective Delivery of:*
- Chemotherapy*
- Antibody*
- siRNA
- Viral vectors
- Other agents
- Cells*

*Examples:*
Brain Tumours*
Alzheimer’s Disease*

* Effective treatments in animal models
Glioblastoma

T1W Contrast enhanced


MR-FUS-BBBD-enhanced chemotherapy
9L rat gliosarcoma-Survival

Pre BBBBD  Post BBBBD

Treat et al., UMB 2012

Three Weekly Treatments with FUS + DOX

Aryal et al., J Control Release, 2013
Can we use FUS for the delivery of antibodies against amyloid-beta peptides to reduce plaque pathology in Alzheimer’s disease?

Alzheimer's Disease

ABOUT 5.3 million Americans of all ages have AD in 2015.
- 1/9 people age 65 and older has AD
- 1/3 people age 85 and older has AD***
AD is a progressive and irreversible neurodegenerative disease that has no cure.
AD is characterized by the presence of β-amyloid plaques, neurofibrillary tangles, neuronal loss, and deficits in neurotransmitters

Long-term administration of high doses of antibodies against Aβ in the bloodstream remove the plaques has produced benefits in animals* but failed in patients**
<= BBB prevents large molecule penetration into the brain

*** Alzheimer's & Dementia 2015; 11(3)332+
FUS alone reduces pathology

Jordão et al., Exp Neurol (2013)

Is FUS effective for treatment of AD?

- 7 months at start of study
- Underwent treatment once per week
- 8 months: behavioral analysis
  histology analysis

Burgess et al., Radiology 2014

FUS improves performance in Y-Maze

Burgess et al., Radiology 2014
FUS improves performance in Y-Maze

Burgess et al., Radiology 2014

FUS reduces plaque load

Burgess et al., Radiology 2014

FUS increases neuronal plasticity

Burgess et al., Radiology 2014
Clinical trial of blood-brain barrier disruption by pulsed ultrasound

Carpentier et al., Science Translational Medicine 2016 Vol 8 Issue 343 343re2 1
Progress Towards Clinical Testing

First Patient Test
Gad Enhancement (T1)
Doxorubicin delivery

Axial
Coronal

Need to be able to motor and control of exposure
Localization and Control of the BBB Opening

Imaging of the bubbles and controlling their oscillations

Hossein-khan et al, 2013
O'Reilly et al., Radiology, 2011

How do we monitor and control cavitation?

Oscillating Bubble Emits Ultrasound

"Super-resolution acoustic passive imaging system using algebraic reconstruction"
Sato et al., JASA (1980)

Passive cavitation detection

James J. Chmi and Constantin-C. Cvasaies
Passive Acoustic Mapping (PAM)


Transcranial Imaging

O’Reilly et al., Medical Physics 2014
Transcranial Super-Resolution Imaging

Rabbit Brain in vivo

Rabbit Brain in Vivo
After Microbubble Bolus Injection
Excitation signals 
Transducer Array 
Wave-front 
Focus 
Grating lobe 
Tissue 
Element center-to-center spacing < wavelength/2 
Element center-to-center spacing > wavelength/2 

Focusing Using Phased Arrays 

*Increase in harmonic emissions post-BBB opening consistent w/ literature.1,2*
Full-Scale Phased Array
MRI Thermometry in a Phantom

Fully Electronically Steered Array
Muscle in vivo
Conclusions

• Ultrasound can be used to focus energy deep into the brain
• Thermal surgery has a wide range of clinical applications
• Preclinical studies show potential for thermal drug release
• Microbubble excitation:
  - Tissue disintegration/ablation
  - Increased blood vessel permeability
  - FUS induced drug release from bubbles/carriers
• Many devices are in clinical testing
• Many new potential therapies => Huge impact

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- InSightec
- Philips
- Celsion
- Artega
- Fus Instruments
- Harmonic Medical

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- S. Stefanovic, PhD
- G. Wright, Ph.D.

BWH
- K. McDannold
- G. Clement
- N. Vykhotdseva
Intra-cardiac ablation
Focused ultrasound treatment of VX2 tumors controlled by local harmonic motion

Larisa Orzel, Yeazi Hang, Natalia Yihchihova and Kulbinder Bhayana

In Vivo Experiments
Rabbit Muscle

- Peak temperature rise of 26°C at 43.8 s
- LHM amplitude: initial value of 25.01±1.34 mm, starts dropping at 13.5 s, final value of 16.3±1.63 mm (p=0.01)

Results: Using Control During Lesion Formation

Lesions controlled by LHM threshold
Lesion Formation Threshold vs. MRI Thermometry In Vivo Muscle

![Graph showing temperature vs. drop time in harmonic motion amplitude.](image)

Multi-Sected Tubular Transurethral Applicator
Dynamic Angular & Length Control Without Movement

![Image of Multi-Sected Tubular Transurethral Applicator](image)

Tri-Sected Tubular Transurethral Applicator
In Vivo Canine Prostate Evaluations (n=3) with MRTI

Case 1 – Dual-sector Control
Case 2 – Translation w/ Coronal MRTI
Case 3 – Tri-sector Control

![Images of evaluation cases](image)

Kinsey et al. 2008
MRI vs. US Guidance

- Monitoring/control

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**2D Correlation as Control**

- Select reliable frames for temperature visualization

  Motion case 1 (transitory): 4 mm cell, 30 W, 20 s.

  - 20 s (peak). R=0.75
  - 30s (cooling). R=0.93

**Delivery of Trastuzumab Through BBB into a Mouse Brain**

- Herceptin (ng/g tissue)

**Volumetric Heating**

- Increased Ablation Volume

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<th>Diameter (mm)</th>
<th>Length (mm)</th>
<th>Volume (ml)</th>
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<tr>
<td>4</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>0.6</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>2.3</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>5.4</td>
</tr>
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For details see:
M. Köhler et al., Med. Phys. 36 (8), 3521, August 2009
BBB disruption by Ultrasound

BBB disruption has been long known to result from focused ultrasound exposures in the brain.

- Associated with damage:
  - Bakay et al. Arch Neurol 1956, 1959
  - Ballantine et al. J Neurosurg 1960
  - McDannold et al. Magn Reson Med 2004

- Some animals without damage:
  - Vykhodtseva. The 5th International Symposium on Ultrasound in Biol Med Puschino, Russia 1981
  - Vykhodtseva et al. Ultrasound Med Biol 1995

Targeted NK-Cells

Alkins et al., Cancer Res. 73(6):1892-9, 2013

Her2-Targeted NK-92 Cells

Alkins et al., Cancer Res. 73(6):1892-9, 2013
**Targeted NK-Cells: In Vivo Tumours**

Alkins et al., submitted

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**Super-Resolution Imaging**

- Position of sources can be estimated beyond the diffraction limit\(^1\)
- Re-plot images of single bubbles at higher resolution (PALM)
  - Estimate source position
  - Re-plot with width equal to uncertainty on fit


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**Electron Microscopy**

Lanthanum (MV139 D)

EM: Arteriola
Transport via Caveolae

Clinical Therapy Ultrasound Systems

Scanned Focused Ultrasound Hyperthermia
1975 - 1995
1.63 MHz:
Small regions with extravasation blood cells
Negligible effects to brain parenchyma

0.8 MPa, 100 ms pulses
Time-averaged acoustic power: 50 mW

Hynynen et al., Radiology 2001