The Zagzebski/Carson Distinguished Lecture on Medical Ultrasound:

Image Guided Ultrasound Therapy

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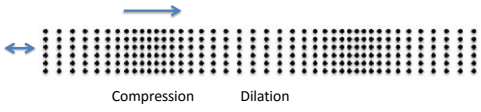
Ultrasound

= sound with a frequency above the hearing range

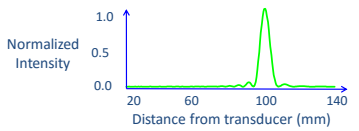
Therapy: 0.2 – 10 MHz, Diagnostic: 1-50 MHz

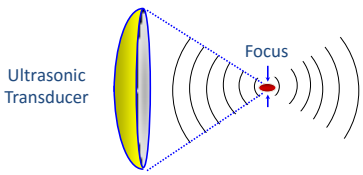
Longitudinal Wave



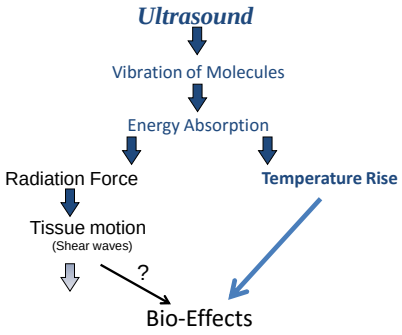
Compression Dilation

Focused Ultrasound

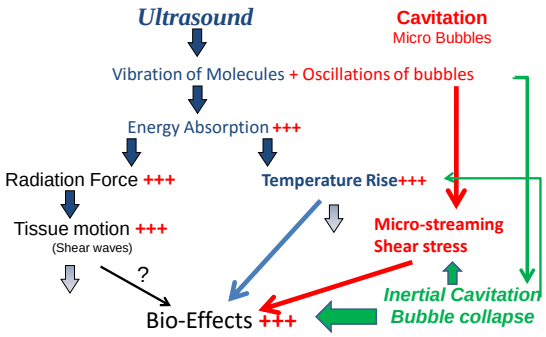




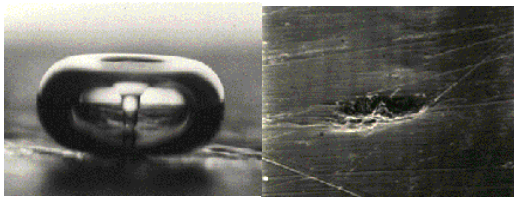
Ultrasound Interactions with Tissue



Ultrasound Interactions with Tissue



Jet formation



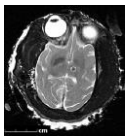
L.Crum

Ultrasound Therapies

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

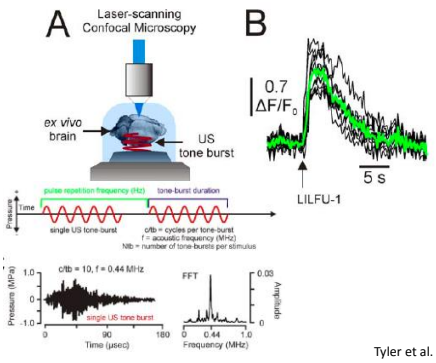
2. Gas bubble mediated
   - Histotripsy
   - Thrombolysis
   - Apoptosis
   - Enhancement of Radiation effects
   - Thermal enhancement
   - Drug delivery

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



Roberts et al. 2014

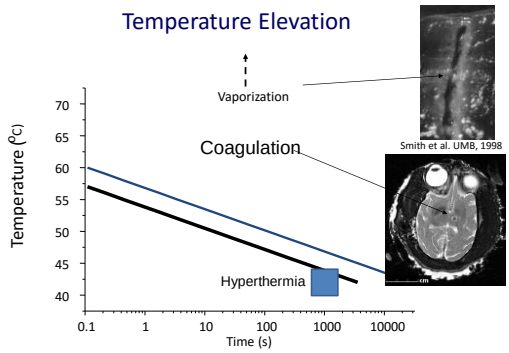
Neuromodulation



Tyler et al. PloS ONE 2008

Ultrasound Bioeffects

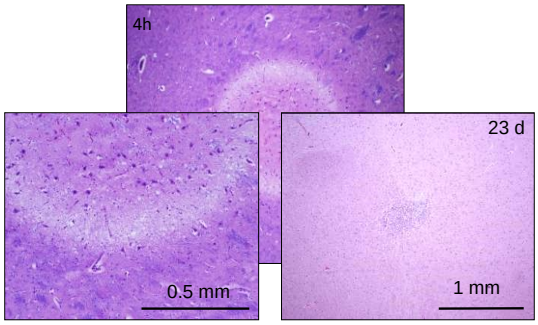
Temperature Elevation



Smith et al. UMB, 1998

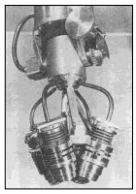
Dewhirst, et al. Int.J.Hyperthermia 19 (3):267-294, 2003.
Sapareto and Dewey Int.J.Radiation Oncology Biol.Phys. 10:787-800, 1984.

Focused Ultrasound Induced Tissue Coagulation
Rabbit Brain in Vivo



Vykhodtseva et al., *Ultrasound.Med.Biol. 26:871.-80, 2000.*

"Fry's monster"

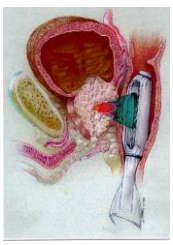


- The devise was made in the form of a double-deck arrangement
- Four ultrasound beams could be brought into coincidence to produce focal point

From: Fry et al., *J Exp Med. 1956,1;104(3):337-60.*

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.

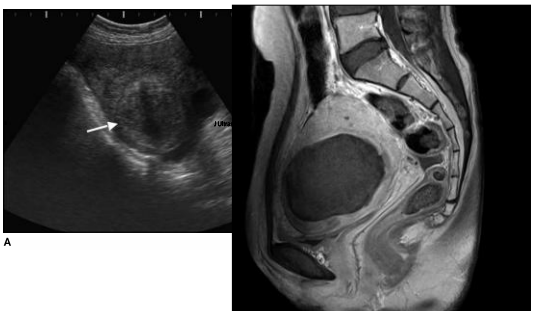
Sanghvi et al.,

Focused Ultrasound Treatments: Image Guidance

- Targeting
- Monitoring
- Control
- Verification

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

UF ablation with US-guidance



Cho et al. J. Ultrasound in Medicine, 32, 397-406, 2013

MRI vs. US Guidance

- Targeting

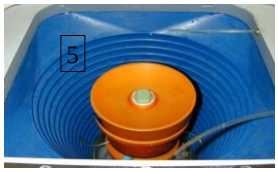
Target	Problem	Ultrasound	MRI
Prostate	Tumor/nerves	++	+++
Uterine Fibroid	Fat/nerves	+++	+++
Liver	Motion	+++	++
Breast	Tumor/Fat	++	+++

Haifu Model JC Focused Ultrasound Tumour Therapeutic System

Courtesy of J. Kennedy, F. Wu

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/cm^2 to 25000 W/cm^2
Therapeutic frequency:
0.8MHz—2.4MHz

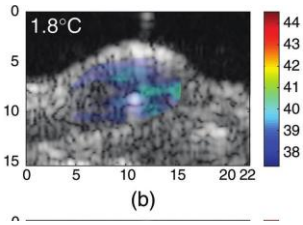
Thyroid System

Courtesy of Jean-François Aubry

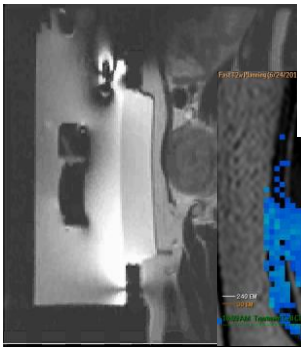
IEEE TRANSACTIONS ON ULTRASONICS, FERROELECTRICS, AND FREQUENCY CONTROL, VOL. 57, NO. 12, DECEMBER 2010

Noninvasive Thermometry Assisted by a Dual-Function Ultrasound Transducer for Mild Hyperthermia

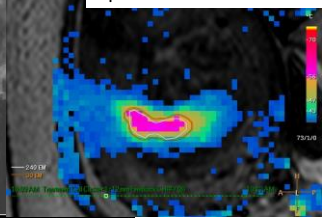
Chun-Yen Lai, Dustin E. Kruse, Charles F. Caskey, Douglas N. Stephens, *Member, IEEE*, Patrick L. Sutcliffe, *Member, IEEE*, and Katherine W. Ferrara, *Fellow, IEEE*



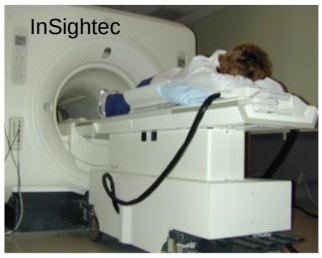
MRI-guided HIFU



Thermometry Problems:
-Fat
-Bone
-Motion
-Speed



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



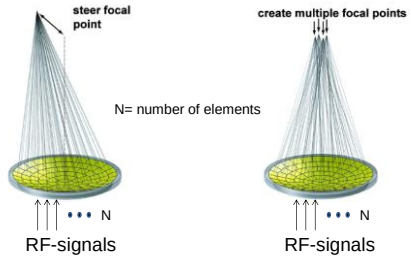
Approximately 150 sites > 10,000 patients

Philips

Limited Phased Arrays

Element size >> wavelength

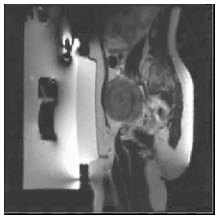
=> limited steering

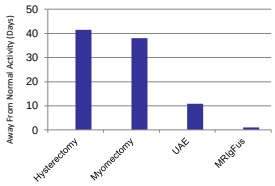


Cain and Umemura. *IEEE Trans.Microwave Theory Tech. MTT-34:542-551, 1986*
Fan et al., *Med.Phys. 22:297-308, 1995.*
Daum et al., *IEEE Trans Ultrason, Ferroelect, Freq Contr 46 (5):1254-1268, 1999.*

MR-Guided FUS

Uterine Fibroid Treatments

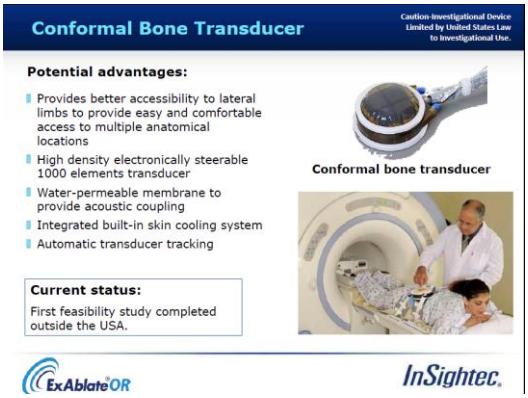




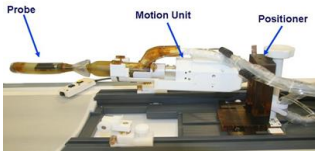
-All the image-guidance advantages
-No tissue penetration
⇒Reduced risk of infections
⇒Fast recovery

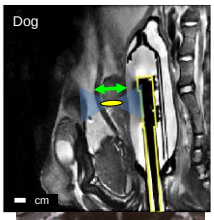
Carls et al., *JOURNAL OF WOMEN'S HEALTH, 17, 7, 2008*
Stewart et al., *Obstet Gynecol 2007;110(2 Pt 1):279-287*

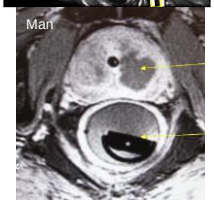
InSightec: FDA approved 2004



MRgFUS Intra-cavitary Prostate System





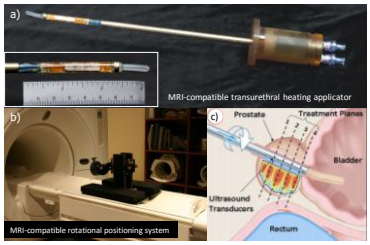


1000-channel phased array:
- Flat, rectangular, 2.3 MHz

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

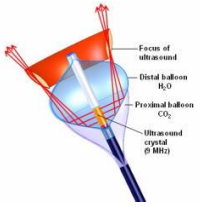
Exablate 2000, InSightec, Haifa, Israel

MRI-controlled Transurethral Prostate Ablation



Chopra and Bronskill

Atrial Arrhythmia treatment by Pulmonary Vein Isolation



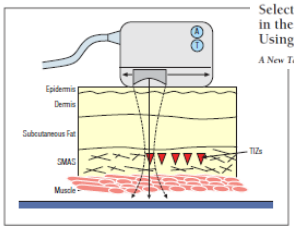
ProRhythm, Inc.

No exposure control => patient death

Cardiac Ablation-Epicor

http://www.youtube.com/watch?v=MkqriH9BGzM

Cosmetic Syrgery



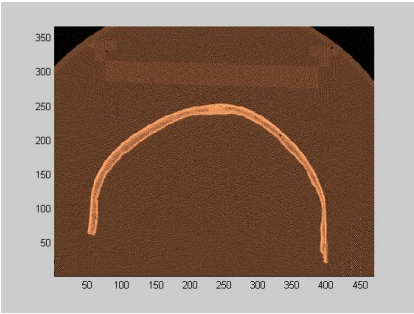
Selective Creation of Thermal Injury Zones in the Superficial Musculoaponeurotic System Using Intense Ultrasound Therapy

A New Target for Noninvasive Facial Rejuvenation

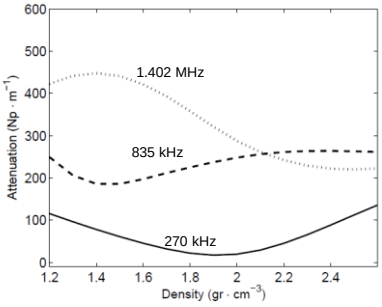
Figure 7. High-density line pattern of intense ultrasound exposures: left temporal area. The line of exposures is confined to the superficial musculoaponeurotic system (SMAS) layer (4.4 MHz/4.5 mm, 3.0 J). Dotted circles indicate thermal injury zones. Scale indicates 1 mm per division.

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

CT Calvaria image

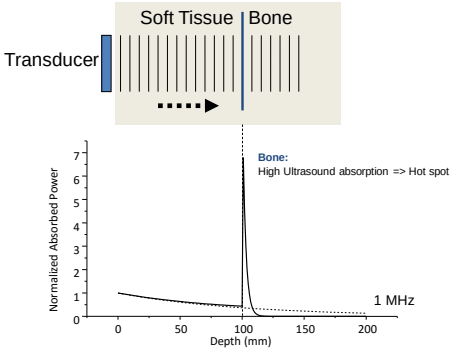


Attenuation in Human Skull Bone

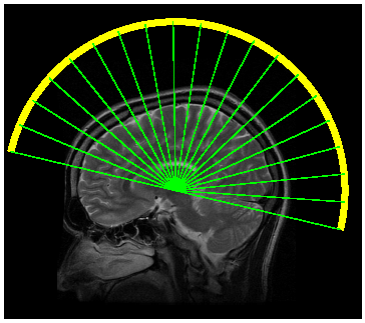


Pichardo et al.,Phys Med Biol. 2011;56(1):219-50

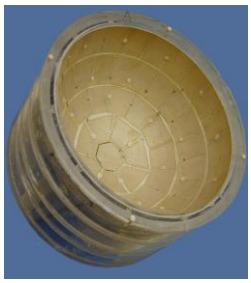
Ultrasound Propagation In Soft Tissue/Bone



Skull Heating Problem => Large Hemispherical Transducer



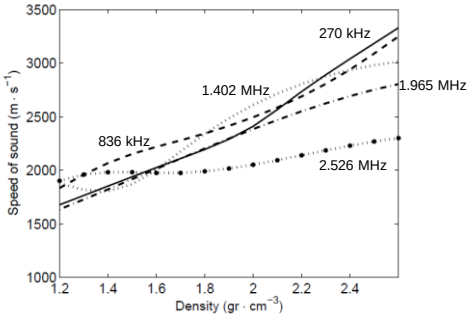
Prototype Hemispherical Arrays



64 elements
Clement et al., Phys.Med.Biol. 2000, 45, 3707

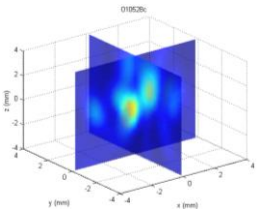
1372 elements
Song et al. IEEE Trans Biomed Eng. 2010, 57(1):124-33

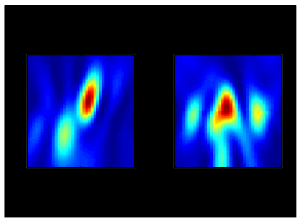
Speed of Sound in Human Skull Bone



Pichardo et al.,Phys Med Biol. 2011;56(1):219-50

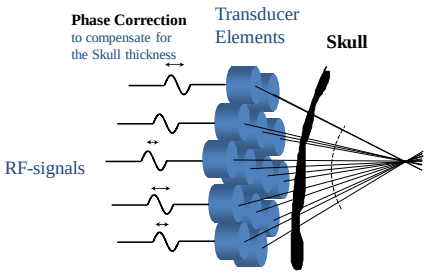
Sonication Through an ex vivo Human Skull
No Phase Correction





Skull Defocusing Problem

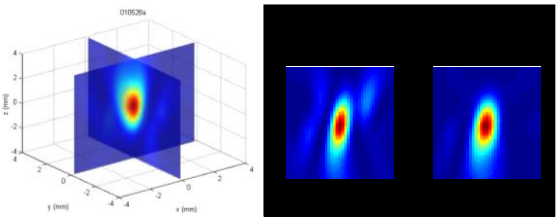
=> A Phased Array and Propagation Prediction



G. T. Clement and K. Hynynen, *Phys Med Biol*, vol. 47 2002, pp. 1219-1236.
J. F. Aubry, et al. *JASA*, vol. 113, no. 1, 2003 pp. 84-93.

Model Corrected

SK12

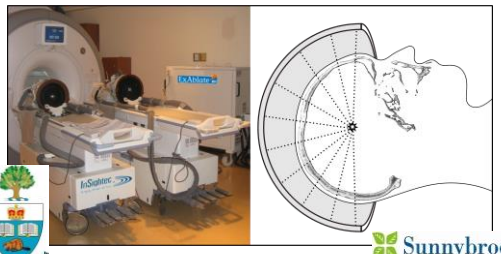


Volume Maximum=4.158 x 10^6 mV^2

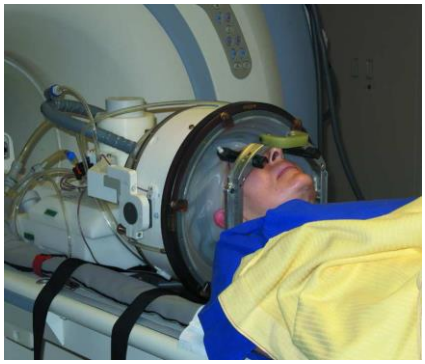
Clement et al., . *Phys.Med Biol* 47 (8):1219-1236, 2002.

InSightec Exablate 4000 Brain system

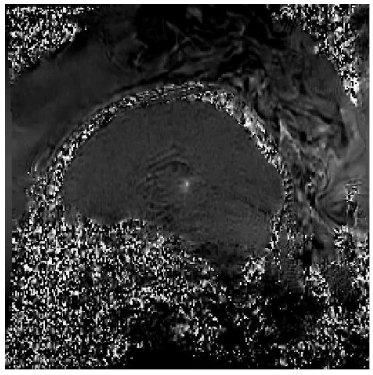
Frequency: 220kHz and 660kHz
Number of Channels: 1000
Head fixation: pins



Sunnybrook
HEALTH SCIENCES CENTRE

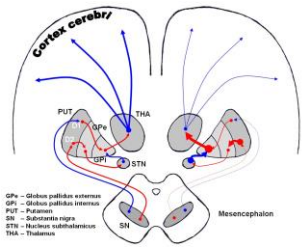


Martin et al., Annals of Neurology (in print)
Courtesy University Children's Hospital, Zurich

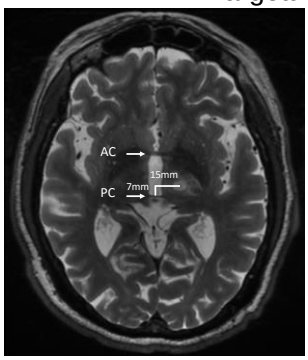


Essential Tremor

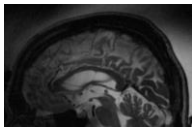
- 10 million in the US
  (0.5 mil Parkinson's disease)

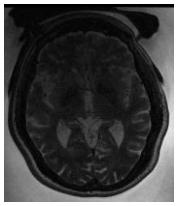


VIM Targetting



Intra-operative MR



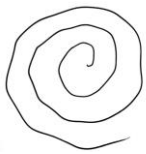


Patient 5: Freehand Spirals

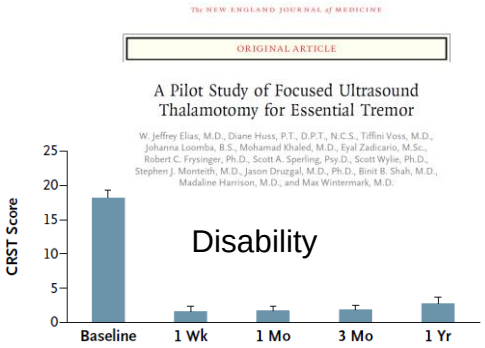
Immediate pre-operative

Intra-operative (in the scanner)

Immediate post-operative

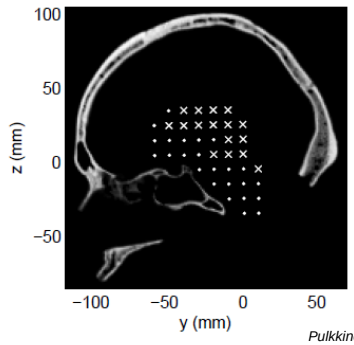


Lipsman et al., Lancet Neurology 2013



FDA Approval July 2016

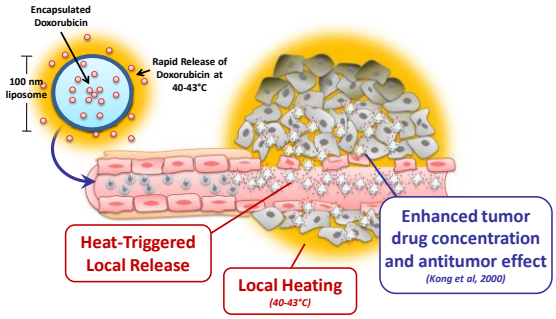
Thermal Treatments Close to Skull Base



Pulkkinen et al ., ISTU10

MRI-Controlled Hyperthermia+ ThermoDox*

=>Localized Drug Delivery

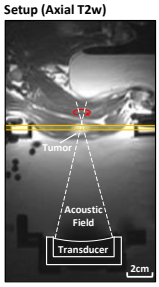


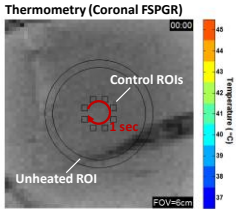
Yatvin MB, Weinstein JN, et al. Science. 1978

*Celsion

Application: Thermally mediated drug delivery

Setup (Axial T2w) | Thermometry (Coronal FSPGR)





Transducer scans at 1 revolution per second, image every 5 seconds. PI temperature control at 8 ROIs on periphery of 10 mm target region:

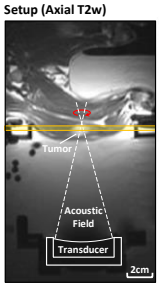
$$P = K_P(T_g - T) + K_I \sum (T_g - T)$$

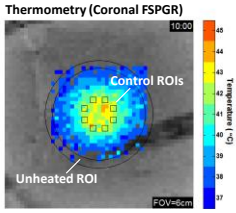
Heat 10 mm region in VX2 tumor to 43°C for 20 min. Thermosensitive liposomal doxorubicin (LTLD, Thermodox) infused during heating (2.5 mg/kg over 8 min)

Staruch *et al*, ISTU 2011

Application: Thermally mediated drug delivery

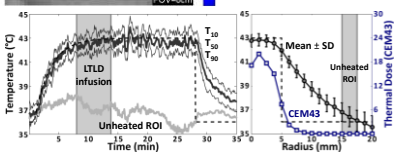
Setup (Axial T2w) | Thermometry (Coronal FSPGR)





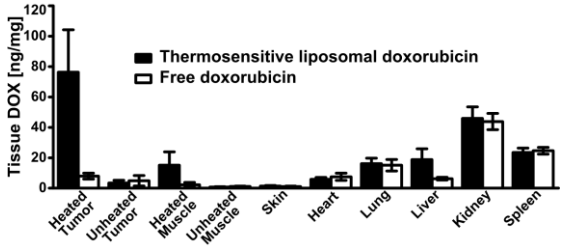
Transducer scans at 1 revolution per second, image every 5 seconds. PI temperature control at 8 ROIs on periphery of 10 mm target region:

$$P = K_P(T_g - T) + K_I \sum (T_g - T)$$



Staruch *et al*, ISTU 2011

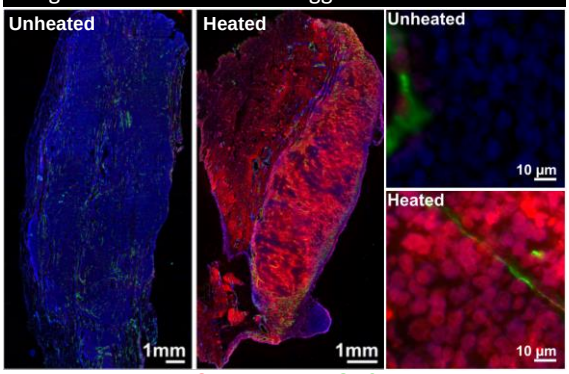
Biodistribution: Free vs. liposomal DOX



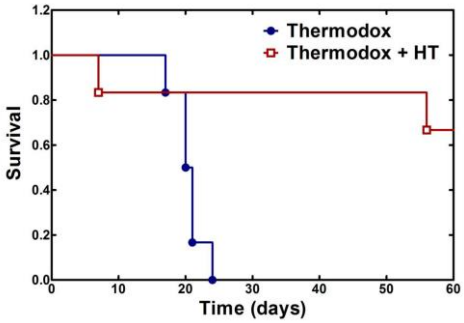
Drug formulation	Unheated tumor [DOX]	Heated tumor [DOX]
Free DOX	4.9 ± 3.5 µg/g	7.9 ± 1.9 µg/g
TSL-DOX	3.4 ± 1.8 µg/g	76.3 ± 27.9 µg/g*

Staruch *et al*, Int J Hyperthermia 2012.

Drug distribution: Effect of triggered release



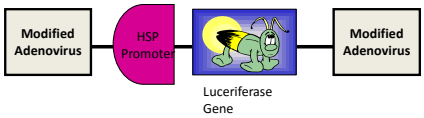
Rabbit VX2 Tumours: Survival



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

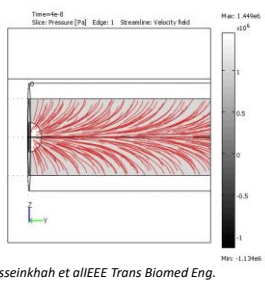


Silcox et al., Ultrasound Med. Biol. 2005 Jul. 31(7): 965-970.

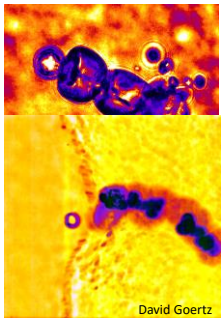
Spatial Control of Genetherapy by MR-HIFU

Deckers et al., PNAS 2009

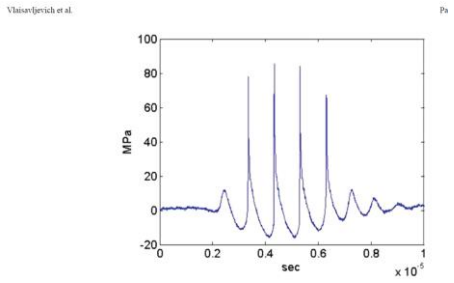
2. Gas bubble mediated



Hosseinkhah et alIEEE Trans Biomed Eng. 62(5):1293-304, 2015

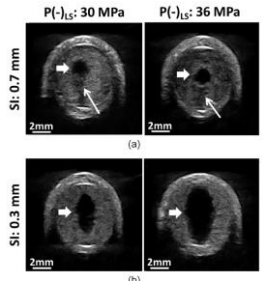


Histotripsy



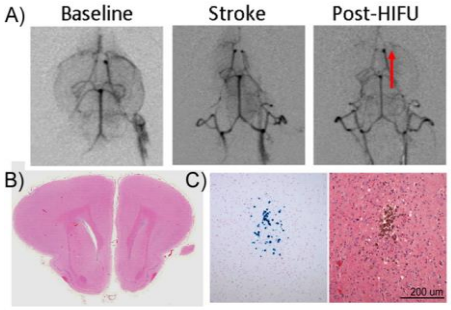
IEEE Trans Ultrason Ferroelectr Freq Control. 2014 February ; 61(2): 341–352

Histotripsy: Thrombolysis



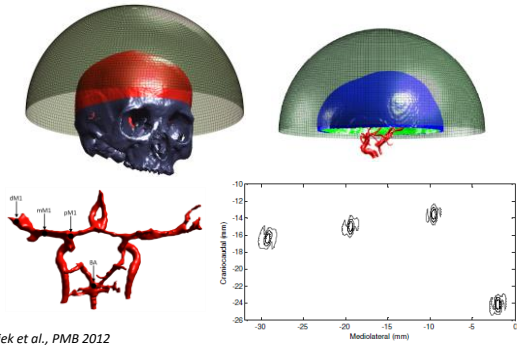
Zhang et al., IEEE TRANSACTIONS ON ULTRASONICS, FERROELECTRICS, AND FREQUENCY CONTROL, vol. 62, no. 7, 2015

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



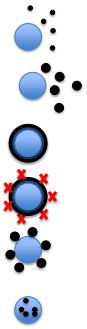
Burgess et al. Plos One 2012

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

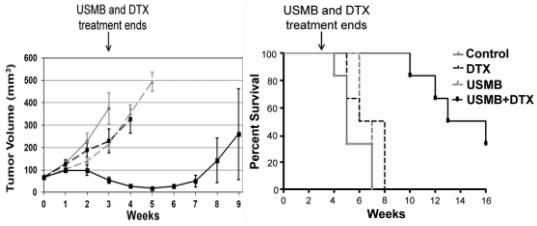
US + Targeted Bubbles with Drug

US + Bubbles with Drug in liposomes/micelles

US + Super heated droplets with drug

Review: Wood and Sehgal, UMB., 41,905–928, 2015

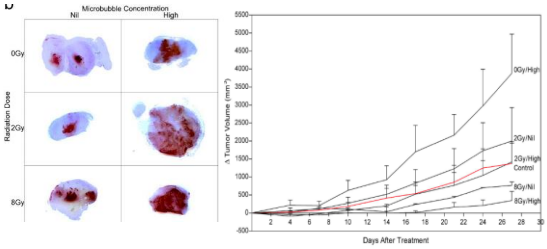
Docetaxel (Taxotere) with the Antivascular Action of Ultrasound Stimulated Microbubbles



Goertz DE et al., . PLoS One. 2012;7(12):e52307

Radiation+MB+US

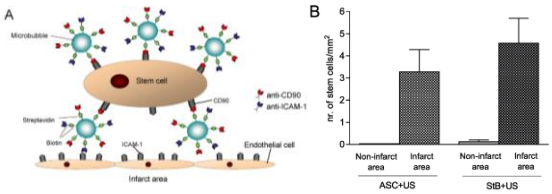
Breast cancer MDA MB 231 model in vivo
500kHz,570kPa, 15cycles, PRF=3kHz, 10% duty, Duration 50 ms,
Repeat Frequency 0.5Hz, Total time =5 min



First paper: Czarnota et al.,Proc. Natl Acad. Sci, 2012;109: E2033-E2041

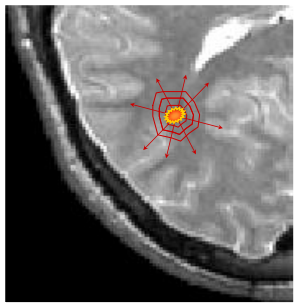
Lai et al, Oncoscience 2016

Stem cells to infarcted heart using targeted microbubbles



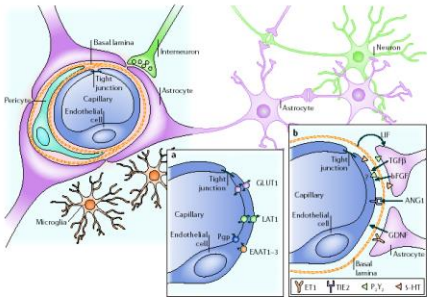
Stem Cell Research 17 (2016) 6–15

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



68

Cellular constituents of the blood–brain barrier.



Abbot et al., Nature Rev. 7,42,2006

FOCAL DESTRUCTION OF NERVOUS TISSUE BY FOCUSED ULTRASOUND: BIOPHYSICAL FACTORS INFLUENCING ITS APPLICATION*

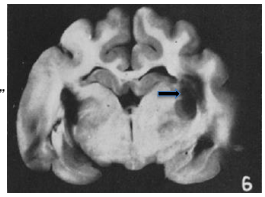
By H. T. BALLANTINE, Jr., M.D., T. F. HUETER‡, Ph.D., W. J. H. NAUTA,§ M.D., and D. M. SOSA, M.D.

(*From the Medical Acoustics Research Group, Department of Neurosurgery, Massachusetts General Hospital, Boston*)

Plates 28 to 30

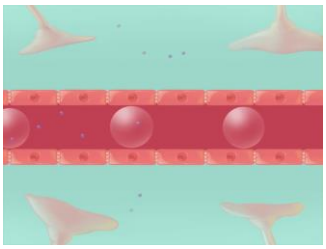
(Received for publication, May 3, 1956)

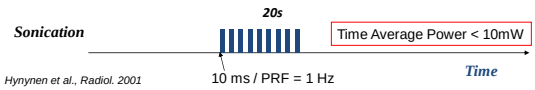
"Histological examination of lesions stained by trypan blue showed this method to be a reliable index of the area of tissue damage."



Trypan blue

How Can Ultrasound Open the BBB?

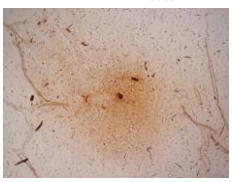


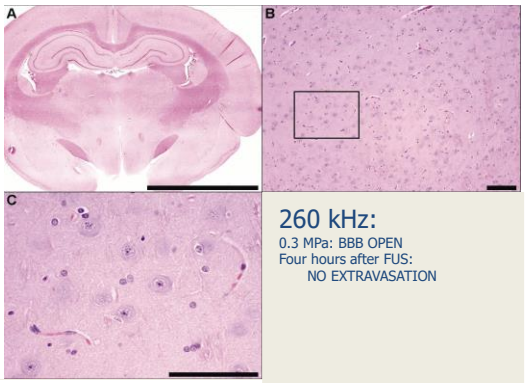


Hynynen et al., Radiol. 2001

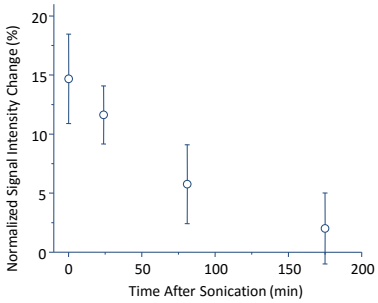
Focused ultrasound opening of BBB

rabbit rat mouse





Duration of the BBB open



How can BBB opening be used for therapy?

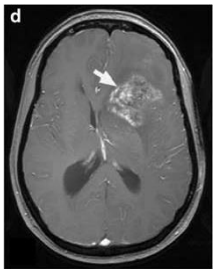
Animal Experiments (>150 studies)**:**

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

Examples:
Brain Tumours*
Alzheimer's Disease*

** Effective treatments in animal models*

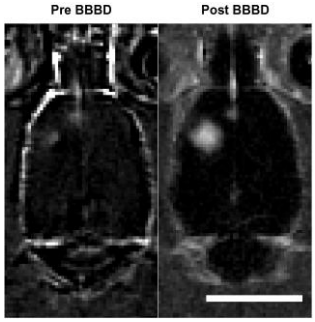
Glioblastoma



T1W Contrast enhanced

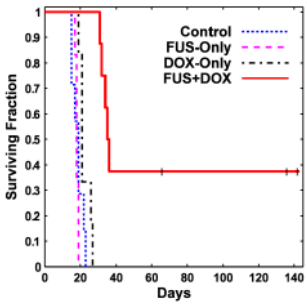
Daniel J Brat and Erwin G Van Meir, Laboratory Investigation (2004) 84, 397–405

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



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?

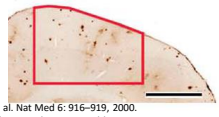
Alzheimer's Disease

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***

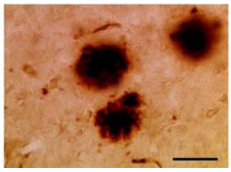
AD is a progressive and irreversible neurodegenerative disease that has no cure.

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

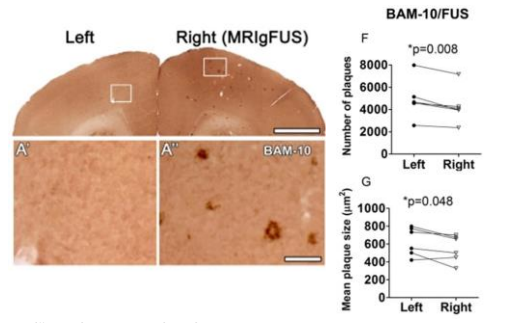


E



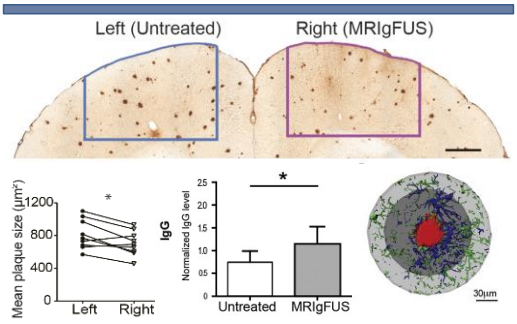
*Bard et al. Nat Med 6: 916–919, 2000.
**Grundman et al. *J Nutr. Health Aging.*, 17, 51-53, 2013.
***Alzheimer's & Dementia* 2015; 11(3)332+

FUS-mediated antibody delivery



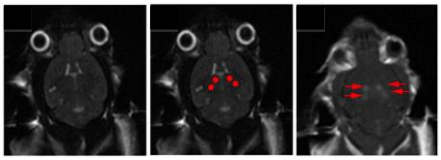
Jordão et al., PLoS One(2010)

FUS alone reduces pathology



Jordão et al., Exp Neurol (2013)

Is FUS effective for treatment of AD?

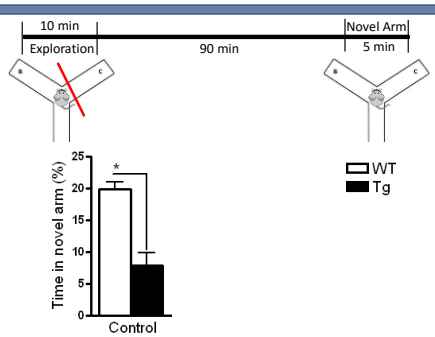


Wildtype	Transgenic
Untreated	Untreated
FUS treated	FUS treated

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

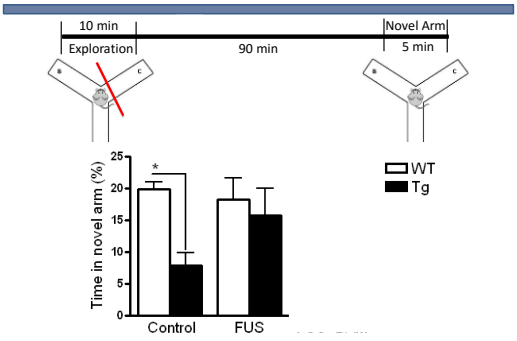
Burgess et al., Radiology 2014

FUS improves performance in Y-Maze



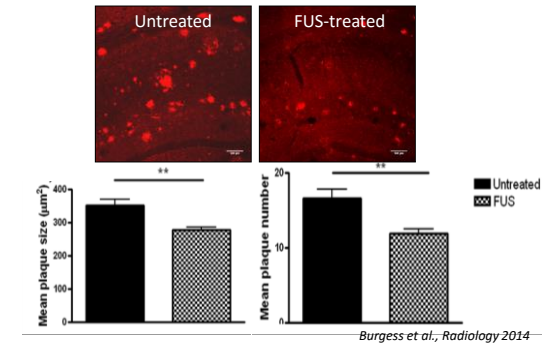
Burgess et al., Radiology 2014

FUS improves performance in Y-Maze



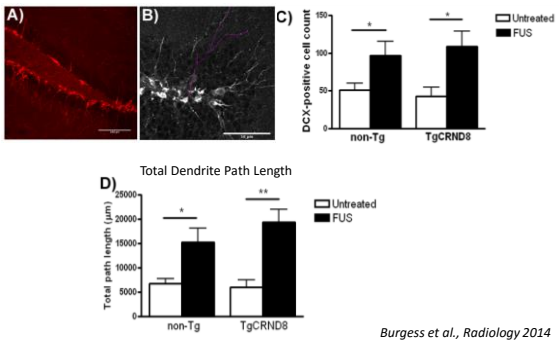
Burgess et al., Radiology 2014

FUS reduces plaque load



Burgess et al., Radiology 2014

FUS increases neuronal plasticity



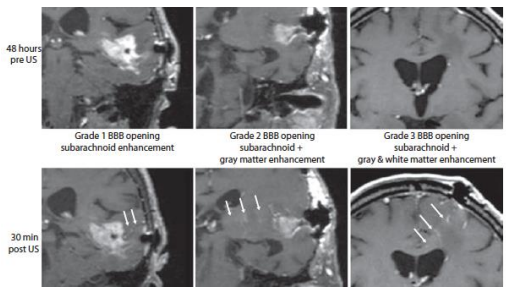
Burgess et al., Radiology 2014

Clinical trial of blood-brain barrier disruption by pulsed ultrasound

Alexandre Carpentier, Michael Canney, Alexandre Vignot, Vincent Reina, Kevin Beccaria,1Catherine Horodyckid, Carine Karachi, Delphine Leclercq, Cyril Lafon, Jean-Yves Chapelon, Laurent Capelle, Philippe Cornu, Marc Sanson, Khê Hoang-Xuan, Jean-Yves Delattre, Ahmed Idbaih

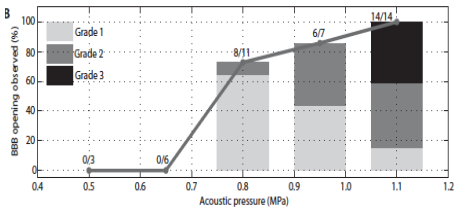
Science Translational Medicine 15 June 2016 Vol 8 Issue 343 343re2 1

Clinical trial of blood-brain barrier disruption by pulsed ultrasound



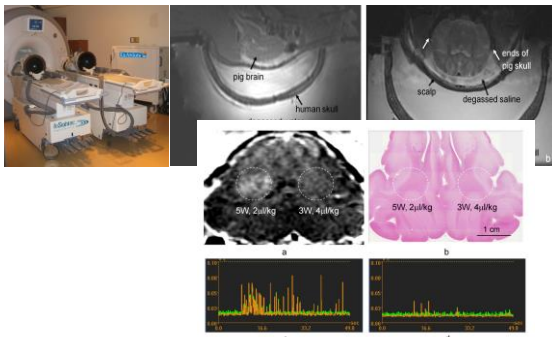
Carpentier et al., Science Translational Medicine 2016 Vol 8 Issue 343 343re2 1

Clinical trial of BBB disruption by pulsed ultrasound



Carpentier et al., Science Translational Medicine 2016 Vol 8 Issue 343 343re2 1

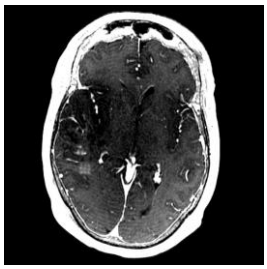
Progress Towards Clinical Testing



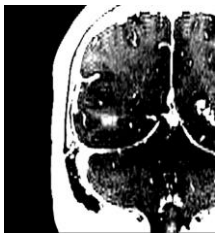
First Patient Test

Gad Enhancement (T1)
Doxorubicin delivery

Axial



Coronal

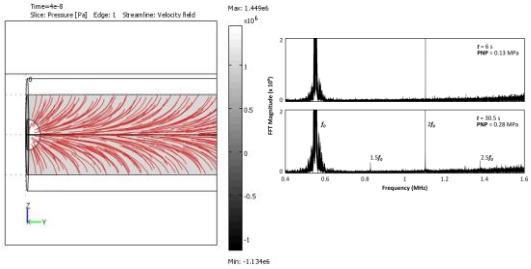


Huang, Mainprize et al., ISMRM 2016

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

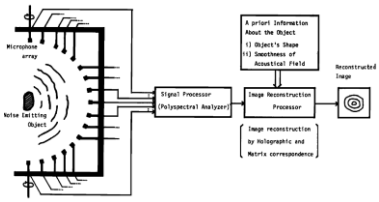


Hossein-khan et al 2013

O'Reilly et al., Radiology, 2011

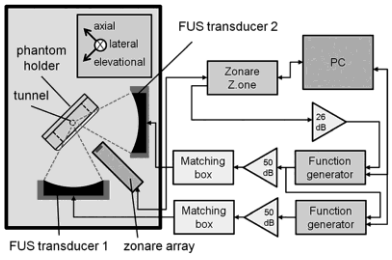
How do we monitor and control cavitation?

Oscillating Bubble Emits Ultrasound



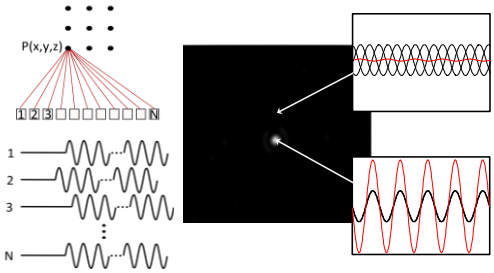
"Super-resolution acoustical passive imaging system using algebraic reconstruction"
Sato et al., *JASA* (1980)

Passive cavitation detection



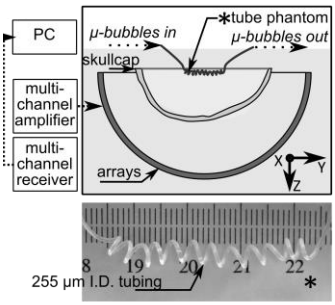
James J. Choi[a] and Constantin-C. Coussios
J. Acoust. Soc. Am. **132** (5), November 2012

Passive Acoustic Mapping (PAM)



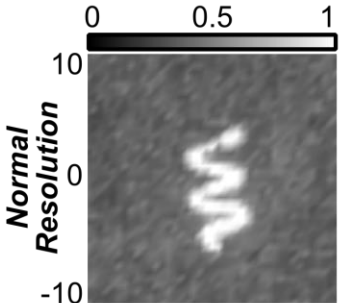
*T. Sato, K. Uemura, K. Sasaki, JASA **67**, 1802 (1980).*
*S. J. Norton, I. J. Won, IEEE T Geosci Remote **38**, 1337 (2000).*

Transcranial Imaging



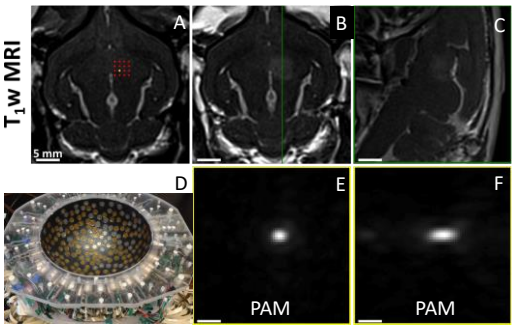
O'Reilly et al., Medical Physics 2014

Transcranial Imaging



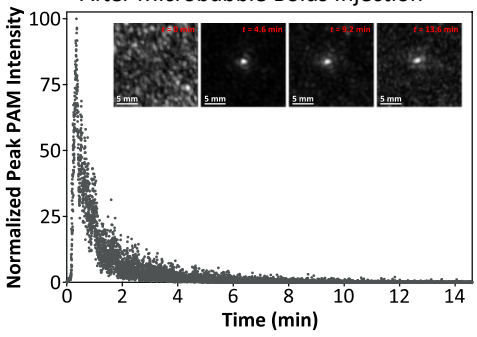
Transcranial Super-Resolution Imaging

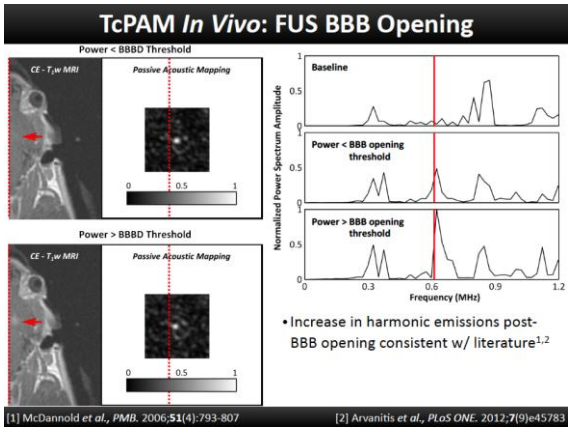
Rabbit Brain in vivo



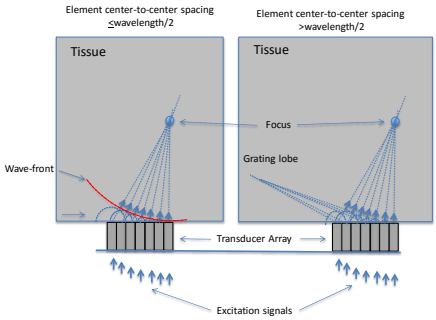
Rabbit Brain in Vivo

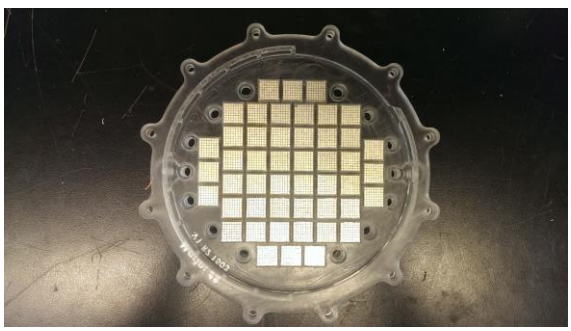
After Microbubble Bolus Injection

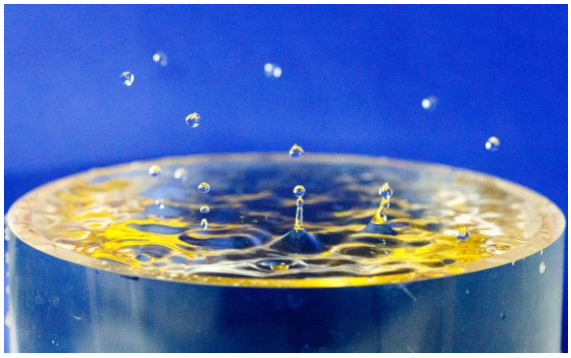




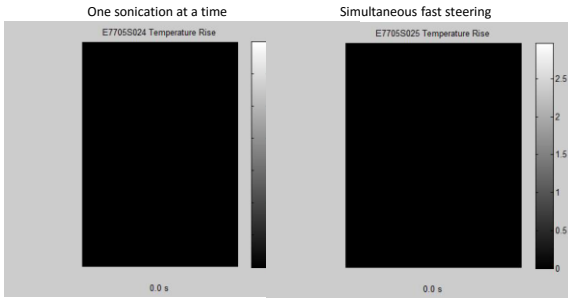
Focusing Using Phased Arrays



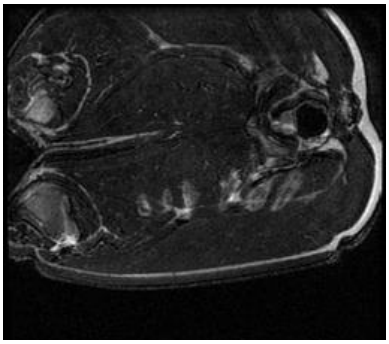




Full-Scale Phased Array
MRI Thermometry in a Phantom



Fully Electronically Steered Array
Muscle *in vivo*



Conclusions

- Ultrasound can be used to focus energy deep into the brain
- Thermal surgery has a vide 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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Funding:
Canada Foundation for Innovation
Canadian Institutes of Health Research
Focused Ultrasound Foundation
Canada Research Chair Program
Natural Sciences and Engineering
Research Council of Canada
Ontario Research Fund
Ontario Institute of Cancer Research
National Institutes of Health
Weston Brain Institute

Industry:
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InSightec
Philips
Celsion
Artenga
Fus Instruments
Harmonic Medical

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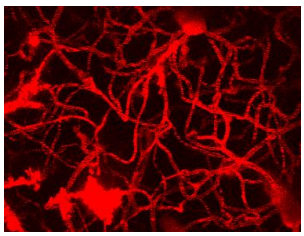
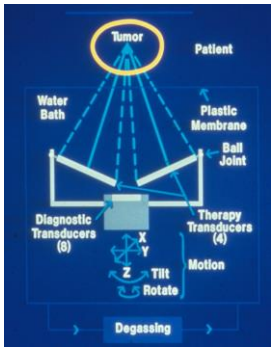
D.Mainprize, MD
J. McLaurin, PhD
M.Schwartz, MD
B. Stefanovic, PhD
G.Wright, Ph.D.

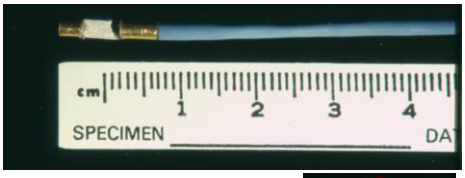
BWH
N. McDannold
G. Clement
N. Vykhotdseva





Hynynen et al., 1987

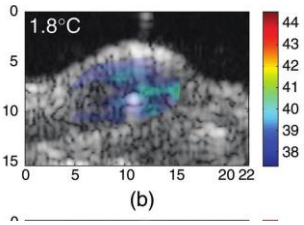
Intra-cardiac ablation



IEEE TRANSACTIONS ON ULTRASONICS, FERROELECTRICS, AND FREQUENCY CONTROL, VOL. 57, NO. 12, DECEMBER 2010

Noninvasive Thermometry Assisted by a Dual-Function Ultrasound Transducer for Mild Hyperthermia

Chun-Yen Lai, Dustin E. Kruse, Charles F. Caskey, Douglas N. Stephens, *Member, IEEE*, Patrick L. Sutcliffe, *Member, IEEE*, and Katherine W. Ferrara, *Fellow, IEEE*

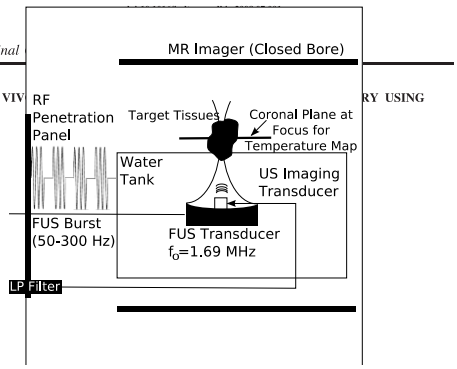


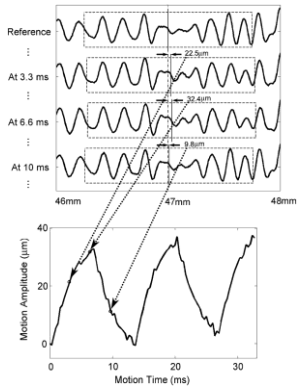
Ultrasound in Med. & Biol., Vol. 35, No. 1, pp. 65–78, 2009

0301-5629/09/$–see front matter

• *Original*

IN VIV RY USING

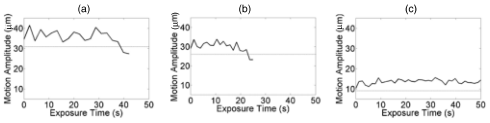




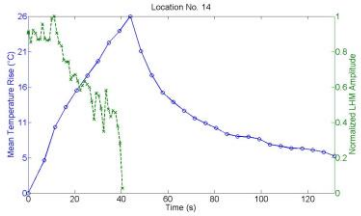
IOP Publishing | Physics in Medicine and Biology
Phys. Med. Biol. 54 (2009) 3405–3419 | doi:10.1088/0031-9155/54/11/009

Focused ultrasound treatment of VX2 tumors controlled by local harmonic motion

Laura Curiel[1,2,4], Yuexi Huang[1], Natalia Vykhodtseva[3] and Kullervo Hynynen[1]



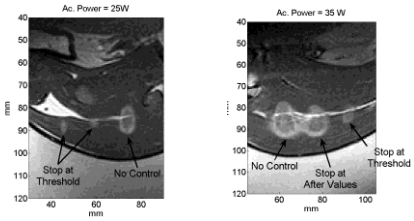
In Vivo Experiments
Rabbit Muscle



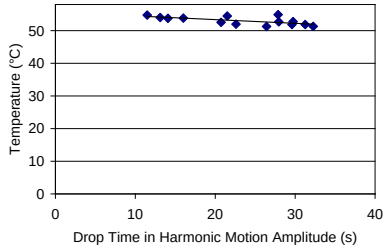
- Peak temperature rise of 26 °C at 43.8 s
- LHM amplitude: initial value of 25.01±1.34 mm, starts dropping at 13.5 s, final value of 16.3±1.63 mm (p=0.01)

Results: Using Control During Lesion Formation

Lesions controlled by LHM threshold

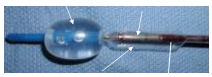


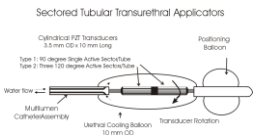
Lesion Formation Threshold vs. MRI Thermometry In Vivo Muscle

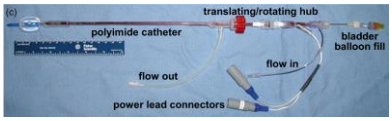


Multi-Sectored Tubular Transurethral Applicator

Dynamic Angular & Length Control Without Movement





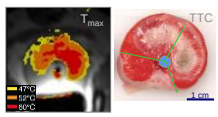


Chris Diederich

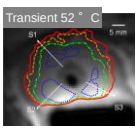
Tri-Sectored Tubular Transurethral Applicator

In Vivo Canine Prostate Evaluations (n=3) with MRTI

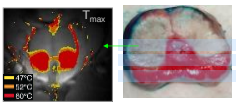
Case 1 – Dual-sector Control

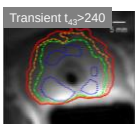


Case 3 – Tri-sector Control



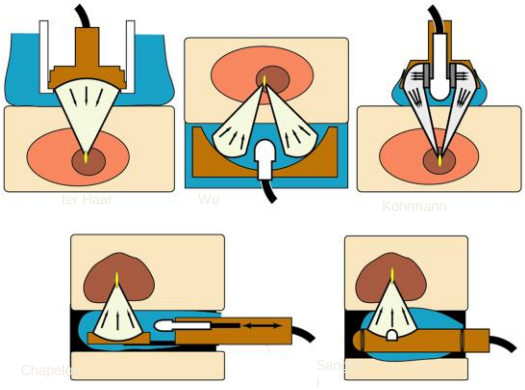
Case 2 – Translation w/ Coronal MRTI





Kinsey et al. 2008

Phys Med Biol. 2003 Aug 21;48(16):2577-89.
High power transcranial beam steering for ultrasonic brain therapy.
Pernot M, Aubry JF, Tanter M, Thomas JL, Fink M



MRI vs. US Guidance

- Monitoring/control

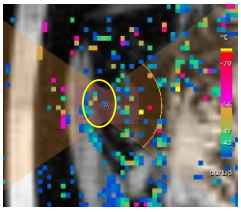
Target	Problem	Ultrasound	MRI
Prostate	Nerves/fat	++	+++
Uterine Fibroid	Fat/nerves	+++	+++
Liver	Motion/Fat/Bone	++	+
Breast	Tumor/Fat	++	++

2D Correlation as Control

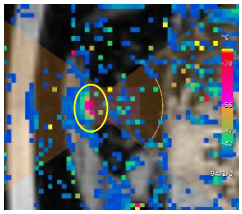
- Select reliable frames for temperature visualization

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

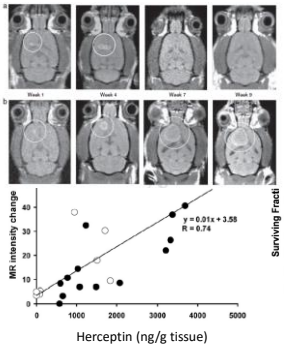
20 s (peak). R=0.75



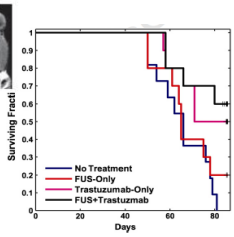
30s (cooling). R=0.93



Delivery of Trastuzumab Through BBB into a Mouse Brain



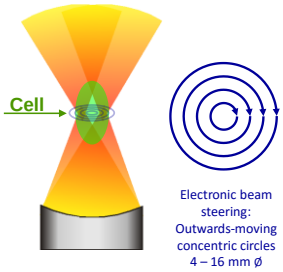
Kinoshita et al, PNAS, 2006



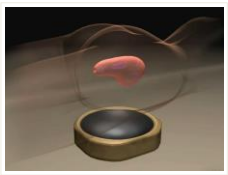
Park et al., Control Release 2012

Volumetric Heating

Increased Ablation Volume



Electronic beam steering:
Outwards-moving concentric circles
4 – 16 mm Ø



Diameter (mm)	Length (mm)	Volume (ml)
4	10	0.1
8	20	0.6
12	30	2.3
16	40	5.4

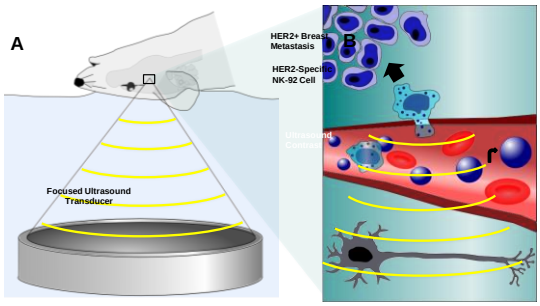
For details see:
M. Köhler et al., Med.Phys. 36 (8),3521, August 2009

BBB disruption by Ultrasound

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

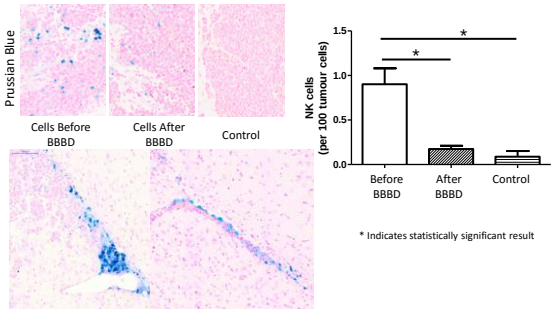
- Associated with damage:
  - Bakay et al. Arch Neurol 1956, 1959
  - Ballantine et al. J Neurosurg 1960
  - Patrick et al. Adv Exp Med Biol 1990
  - McDannold et al. Magn Reson Med 2004
- Some animals without damage:
  - Vykhodtseva. The 5th International Symposium on Ultrasound in Biol Med Puschino, Russia 1981
  - Vykhodtseva et al. Ultrasound Med Biol 1995
  - Mesiwala et al. Ultrasound Med Biol 2002

Targeted NK-Cells



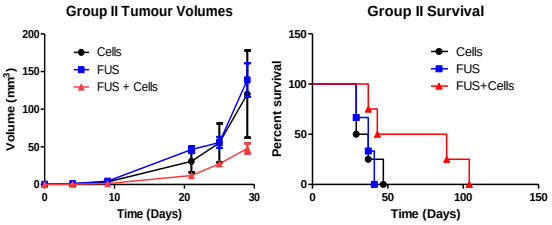
Alkins et al., Cancer Res. 73(6):1892-9, 2013

Her2-Targeted NK-92 Cells



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

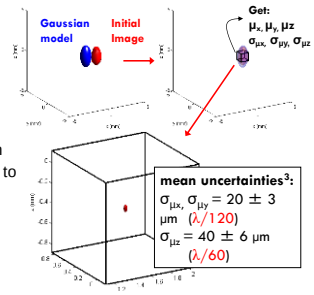
Targeted NK-Cells: In Vivo Tumours



Alkins et al., submitted

Super-Resolution Imaging

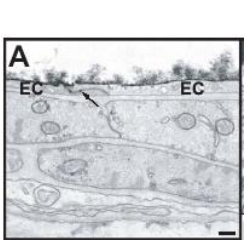
- Position of sources can be estimated beyond the diffraction limit[1]
- Re-plot images of single bubbles at higher resolution (PALM[2])
  - Estimate source position
  - Re-plot with width equal to uncertainty on fit



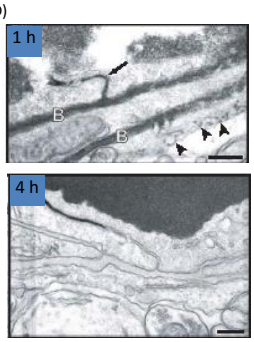
[1]Bobroff, *Rev. Sci. Instrum.* (1986) [2]Betzig *et al.*, *Science* (2006) [3]O'Reilly and Hynynen, *Med. Phys.* (2013)

Electron Microscopy

Lanthanum
(MV139 D)



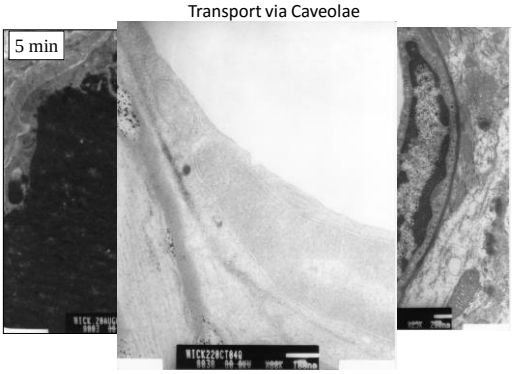
No US



Sheikov et al., UMB, 2004,2006,2008

EM: Arteriola

Transport via Caveolae



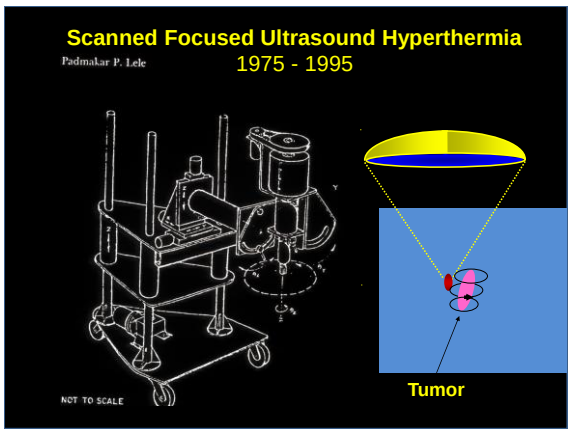
Clinical Therapy Ultrasound Systems

Focus Surgery
Edap
Profound Medical
UltraShape

Scanned Focused Ultrasound Hyperthermia

Padmakar P. Lele

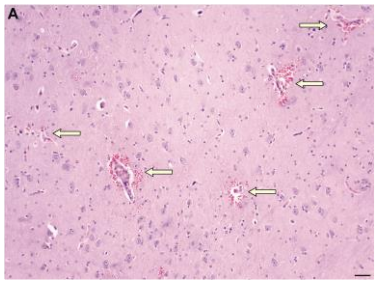
1975 - 1995



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