Advances in Focused Ultrasound Brain Therapies

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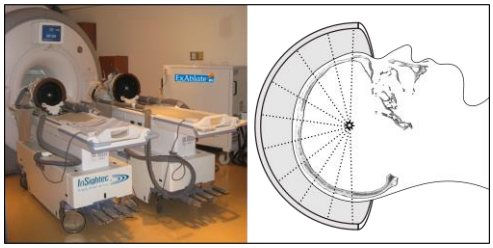
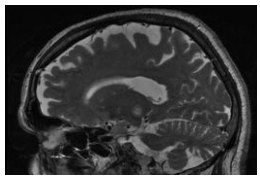
InSightec Exablate 4000 Brain system

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



Brain Patient Treatments

Patient Treatments:
~20 Hospitals >100 patients
Tumors: *McDannold et al, J. Neurosurgery 2010*
Chronic Pain: *Martin et al., Ann. of Neurol 2009*
Essential Tremor: *Elias et al., NEJM 2014*
Parkinson's Disease:



Can FUS be used for anything else in Brain?

Biological feasibility

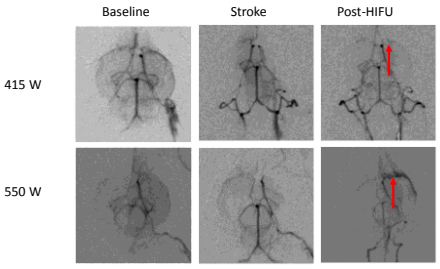
Embolic Stroke
Cancer
Alzheimer's Disease

Technical Requirements

Transmit Array Requirements
Exposure Monitoring and Control
Combined Array Feasibility

Stroke Treatment?
FUS fragmentation of a blood clot

1.5MHz transducer, 1ms pulses, PRF =1 Hz, F-number = 0.8, 20sec duration



Medical Biophysics UNIVERSITY OF TORONTO

Burgess et al, Plos One 2012

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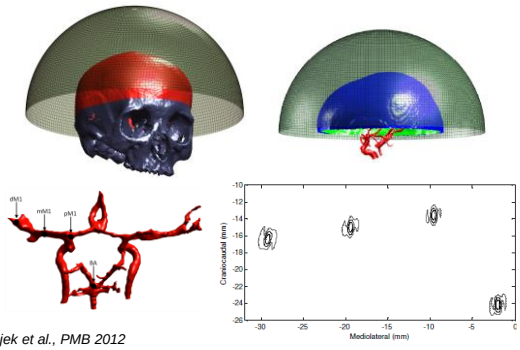
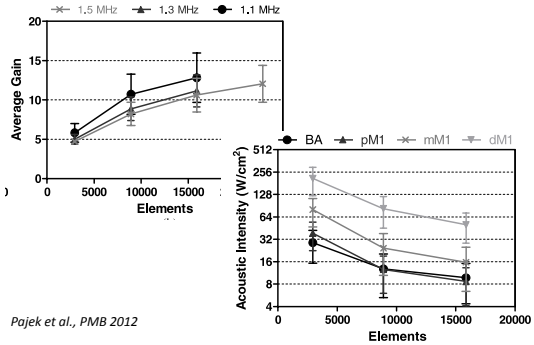
Through Skull Stroke Treatments Simulations



Pajek et al., PMB 2012

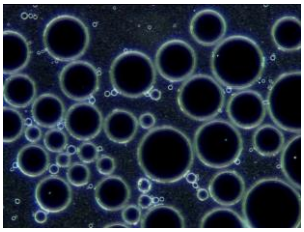
Through Skull Stroke Treatments Simulations



Pajek et al., PMB 2012

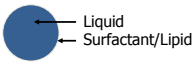
Problem:

How can we reduce the inertial Caviation threshold?



Sub-micron Droplets

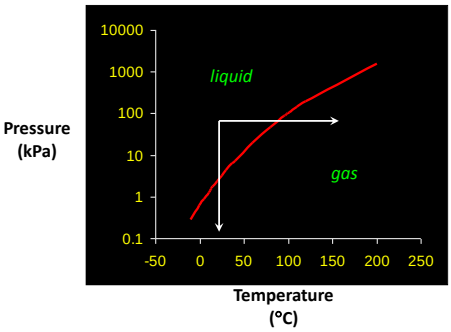
Sub-micron droplets are precursors to microbubbles



- **Low BP liquid PFC**
- **Micron to submicron size**

Benefit:
Can locally create microbubbles → Locally induce cavitation

Convert liquid droplet to gas bubble

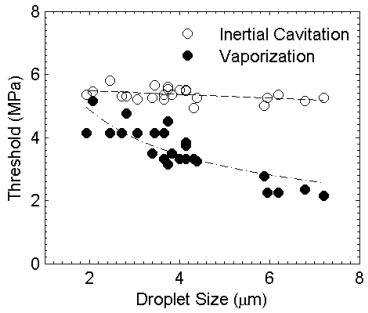


Manufacturing

Shell Material	[PFC]	[Shell material]	Method
Fluoro-surfactant	5% v/v	0.1 – 0.8 %	Microfluidizer
Bovine Serum Albumin	10% v/v	20mg/mL	Vialmix Microfluidizer

PFC	DDFP	PFH	FC84	FC77	FC40
Boiling Point (°C)	29	56	80	97	165

Perfluorocarbon droplet vaporization



Schad et al., UMB 2010

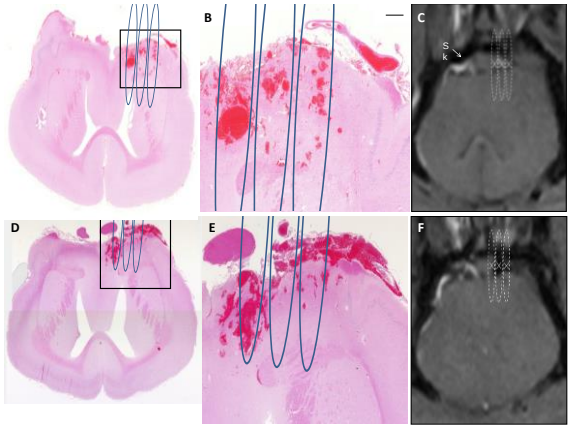
In Vivo Brain Sonications

Droplet diameter :156 - 207 nm
Sonication Duration: 20s
Burst Repetition Frequency: 1Hz

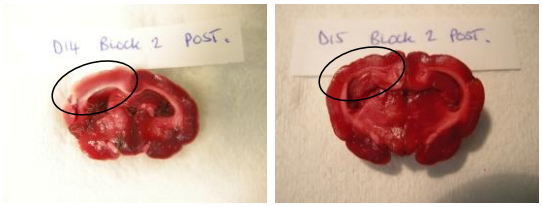
Experiment	Wait after injection	Focused placed away from skull	Pulse Length	Recanalization
88-111W	Yes	No	1 ms	2/2
88-137W	No	Yes	1 ms	5/7*
88W	No	Yes	0.1 ms	1/2
Ctrl	N/A	N/A	N/A	1/8

Compares well with no droplet experiments: 550 W
Burgess et al. Plos One 2012

Pajek et al, UMB 2014



Preliminary Analysis - Vital Stain



Control Sonicated

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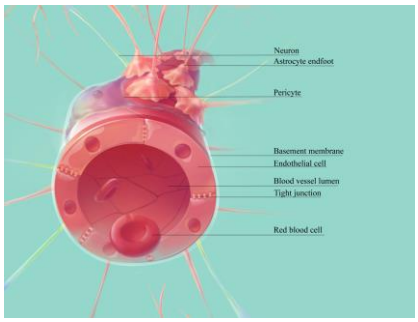
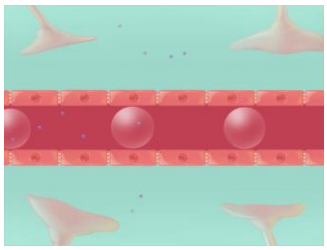
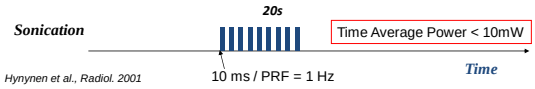
Blood-Brain Barrier



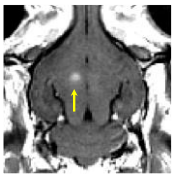
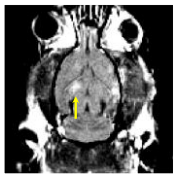
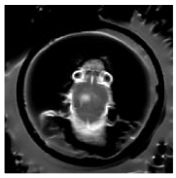
How Can Ultrasound Open the BBB?



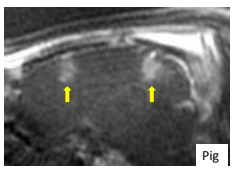


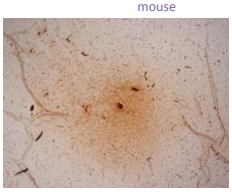
Hynynen et al., Radiol. 2001

Focused ultrasound opening of BBB

rabbit rat mouse





How can BBB opening be used for therapy?

Animal Experiments (>100 studies)**:**

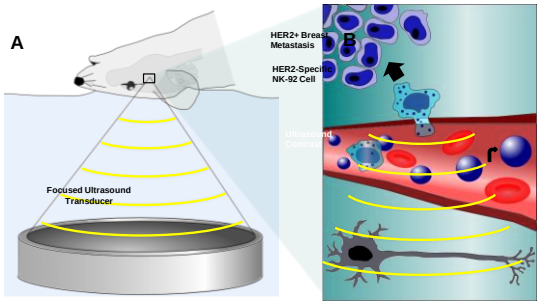
Effective Delivery of:

-Chemotherapy*
-Antibody*
-siRNA
-Viral vectors
-Other agents
-Cells*

Examples:
Brain Tumours*
Alzheimer's Disease*

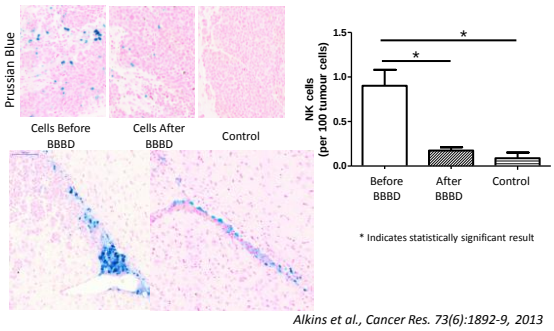
** Effective treatments in animal models*

Targeted NK-Cells



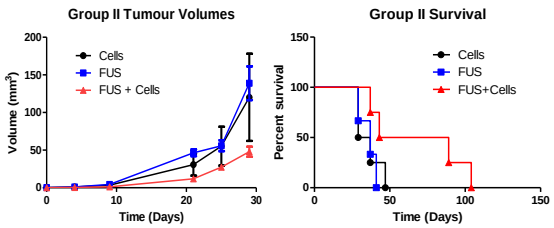
Alkins et al., Cancer Res. 73(6):1892-9, 2013

Her2-Targeted NK-92 Cells



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

Targeted NK-Cells: In Vivo Tumours



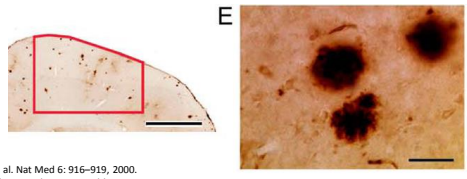
Alkins et al., submitted

Alzheimer's Disease

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

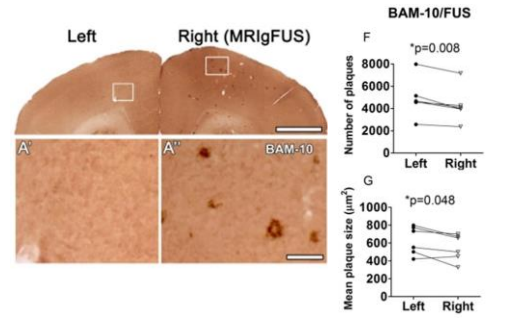
AD is characterized by the presence of β-amyloid plaques, neurofibrillary tangles, neuronal loss, and deficits in neurotransmitters

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



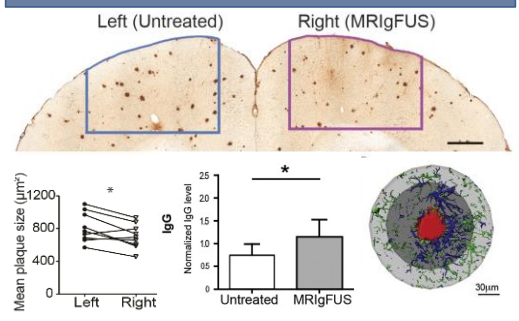
*Bard et al. Nat Med 6: 916–919, 2000.
**Grundman et al. *J Nutr. Health Aging.*, 17, 51-53, 2013.

FUS-mediated antibody delivery



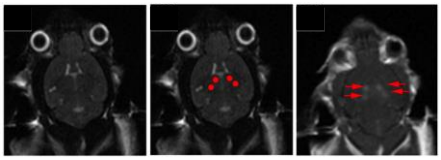
Jordão et al., PLoS One(2010)

FUS Opening of the BBB alone Reduces pathology



Jordão et al., Exp Neurol (2013)

Is FUS effective for treatment of AD?

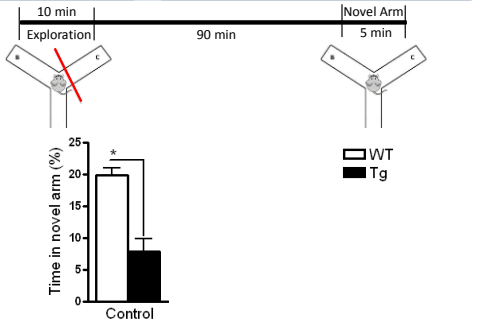


Wildtype	Transgenic
Untreated	Untreated
FUS treated	FUS treated

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

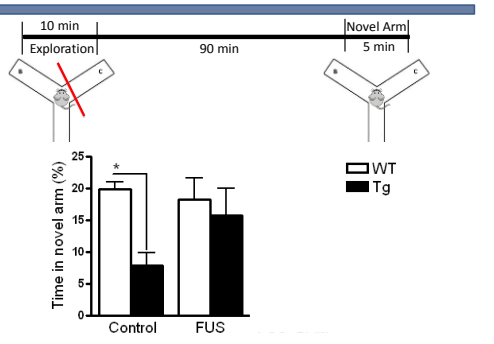
Burgess et al., Radiology 2014

FUS improves performance in Y-Maze



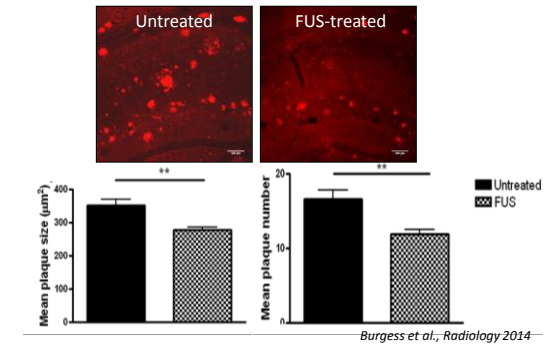
Burgess et al., Radiology 2014

FUS improves performance in Y-Maze



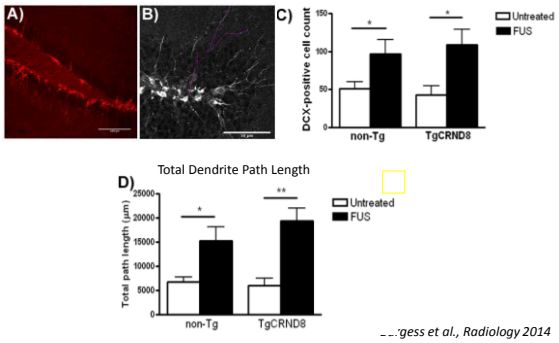
Burgess et al., Radiology 2014

FUS reduces plaque load



Burgess et al., Radiology 2014

FUS increases neuronal plasticity



Burgess et al., Radiology 2014

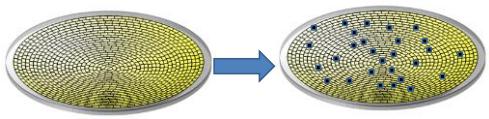
Challenges of translating FUS BBB Opening to the Clinic

- Monitoring and control of the bubble activity
  - Human skull highly variable
  - Too low exposure => no opening
  - Too high exposure=> vascular, and neuronal damage
  - No temperature elevation
- Large volume treatments required with high precision
  - Close to bone and other critical structures
  - Large electronic steering range
  - Large number of focal exposures needed
    => fast electronic scanning required

Full-Scale Arrays: Problem

Large number of:

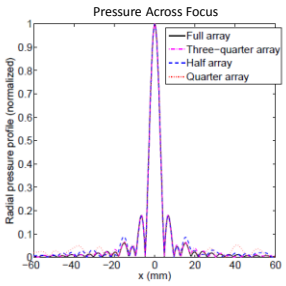
-small elements
- RF-drivers
- Interconnects
=>cost

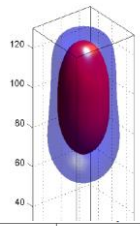


Sparse Array

Goss et al., 1996

Sparse Arrays



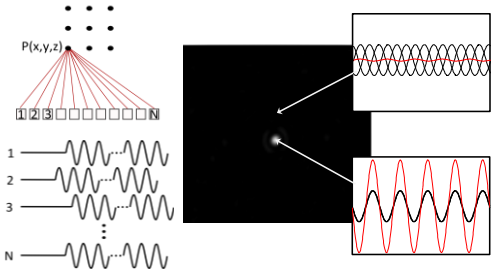


Array fraction	Power (W)	
	500 kHz	1000 kHz
Full	85.4-1210	61.2-898
Three-quarter	113-1600	81-1200
Half	170-2420	122-1790
Quarter	334-4750	237-3490

Ellens et al, PMB 2011

Bubble location and activity monitoring

Passive Acoustic Mapping (PAM)

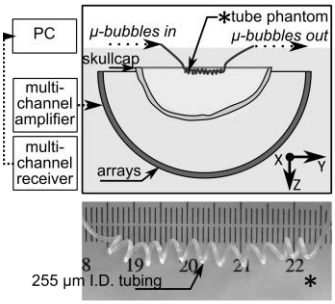


*T. Sato, K. Uemura, K. Sasaki, JASA **67**, 1802 (1980).*
*S. J. Norton, I. J. Won, IEEE T Geosci Remote **38**, 1337 (2000).*

Trans-skull Imaging of the Bubbles:

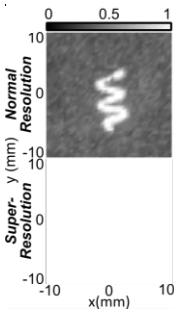
- Wide aperture transcranial array
  - 128 passive receive elements (612 kHz)
  - 306 kHz prototype brain therapy array [1]
- 3D bubble activity maps reconstructed
  - passive imaging techniques

Transcranial Imaging

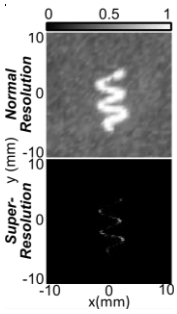


O'Reilly et al., Medical Physics 2014

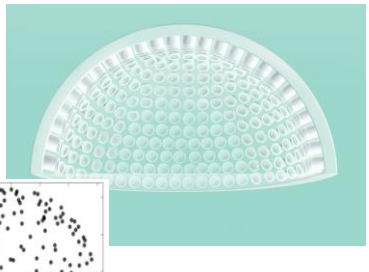
Transcranial Imaging

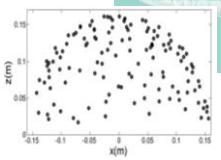


Transcranial Super-Resolution Imaging



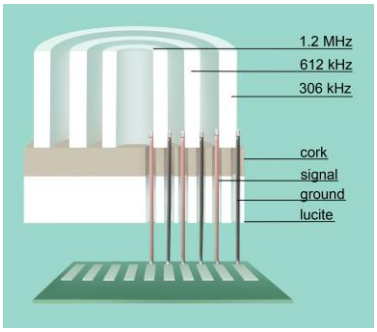
Multi-Frequency Transmit-Receive Phased Array



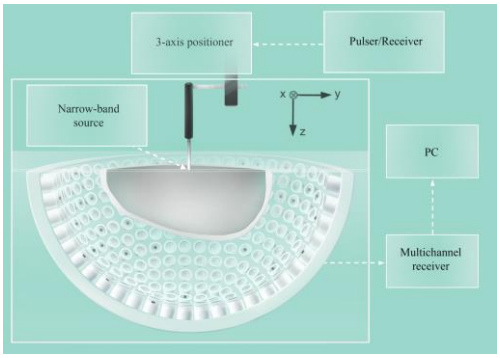


128- elements in simulation optimized locations

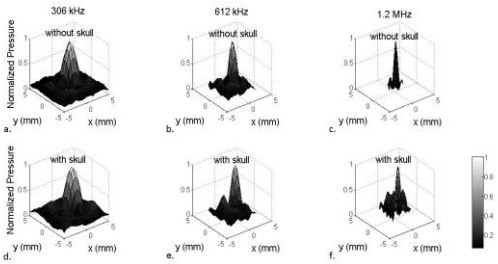
Transducer Element



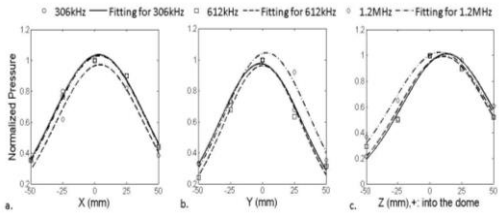
PAM Benchtop Set-Up



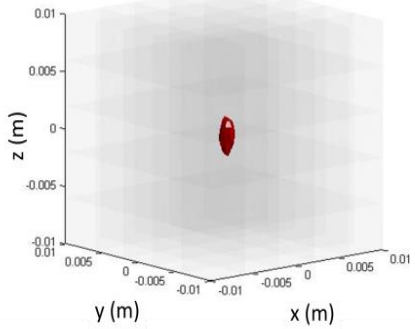
Transmit Focus in Water and Through a Human Skull



Transmit Electronic Beam Steering



Through Skull Single Bubble Image at 612 kHz



Conclusions
Brian Treatment Phased Arrays

Thermal ablations
Skull heating is a limiting factor
=>require fully populated arrays
=> Mechanically moved
=>Limited phased arrays (~1000 elements)
-distortion correction, limited steering

BBB opening
-Transmit/Receive Arrays
-Very low time average power
=> skull heating not a problem
=>Sparse arrays feasible
=> multi-frequency arrays practical

Embolic Stroke
Inertial cavitation
High precision
⇒ High pressure amplitude
⇒ Large number of elements
⇒ Droplets, nano-bubbles?

Many New Treatments Possible in the Future => FUS could have a huge impact

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Thank You!