Noninvasive and Targeted Brain Drug Delivery using Transcranial Focused Ultrasound

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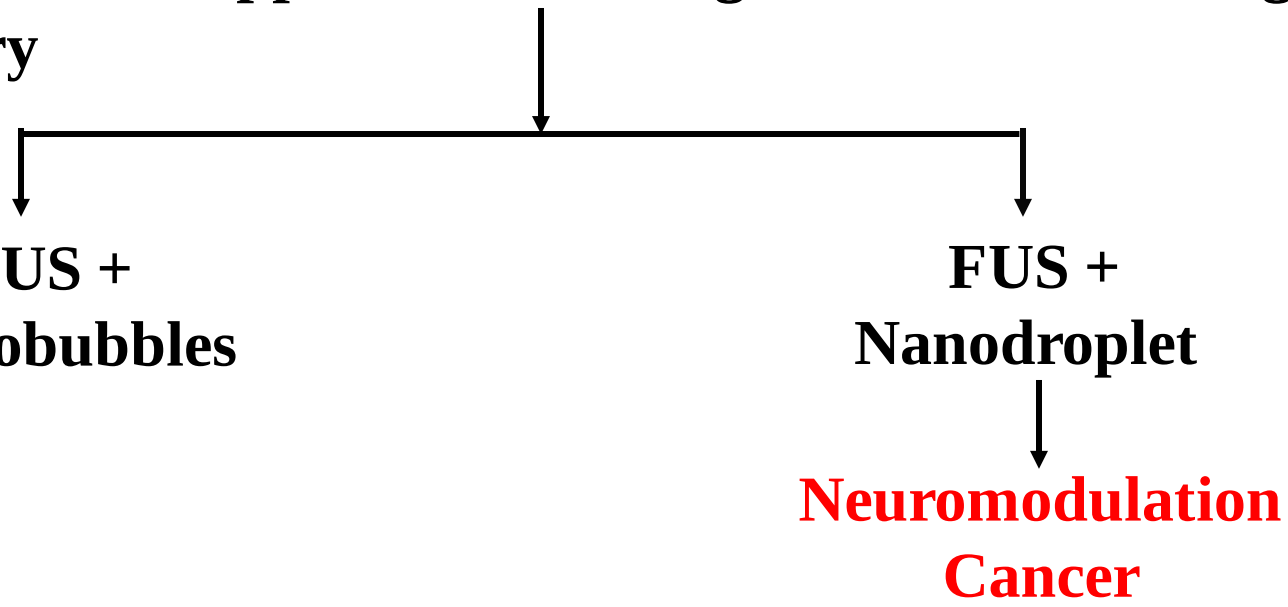
Stanford University

Outline

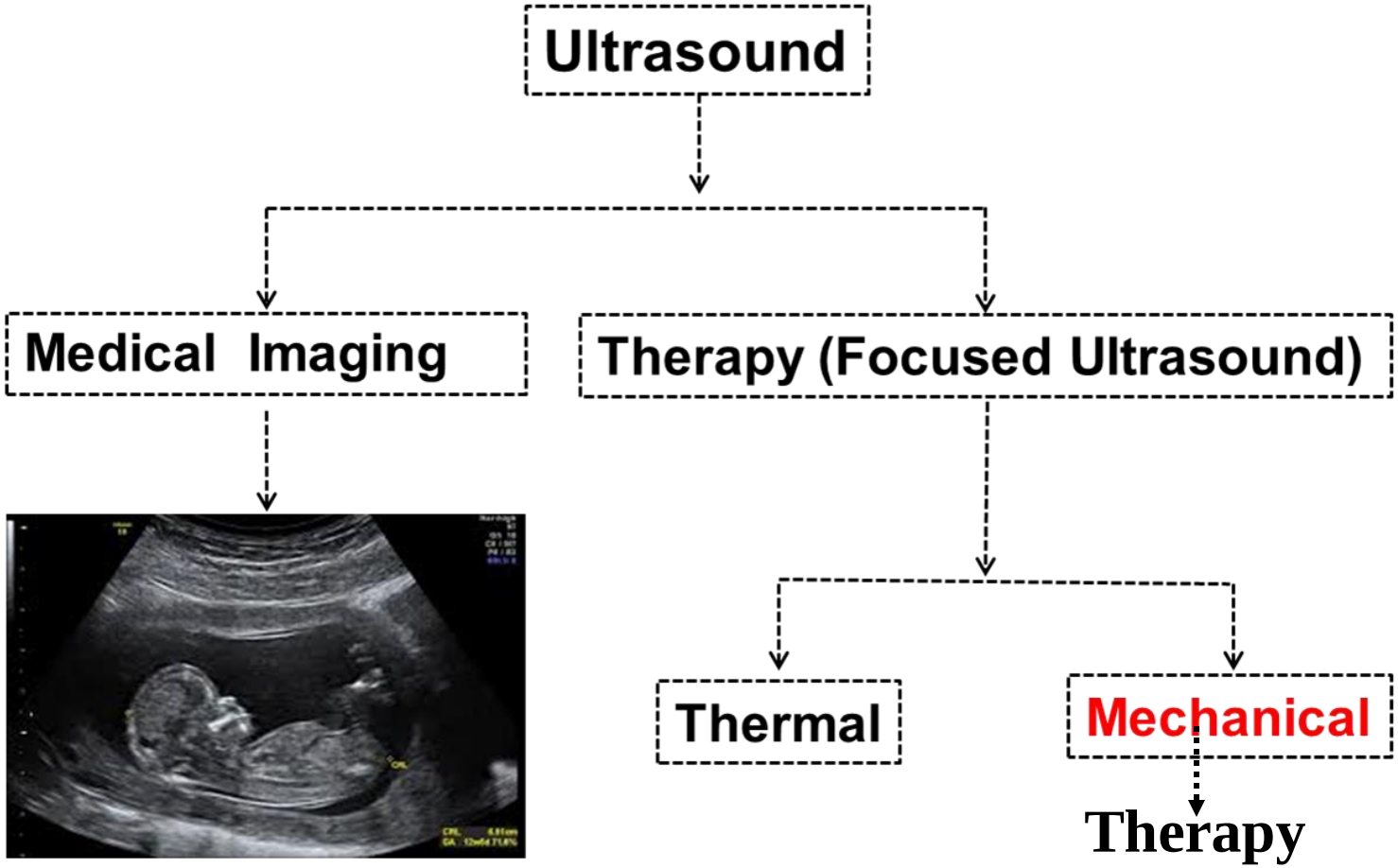
- **Introduction**
  Focused Ultrasound Technology (FUS)

- **Two different approaches of using FUS for brain drug delivery**



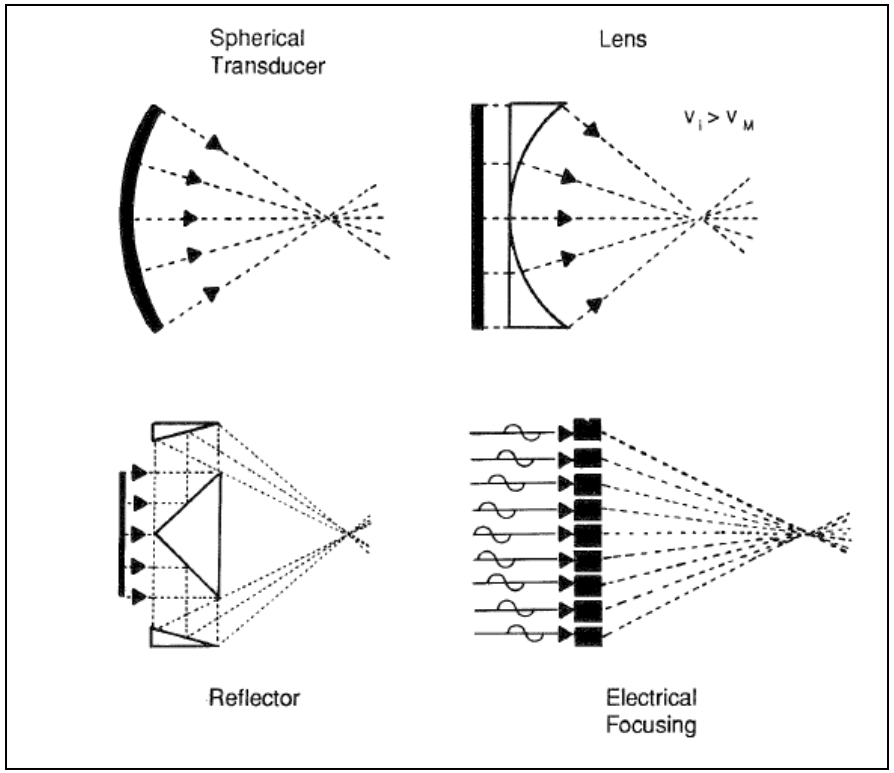
- **Conclusion**

Ultrasound , Medical Applications



Focused Ultrasound

- **Sound ($f = c/\lambda$)**
- **Ultrasound ($f > 20kHz$)**
- **How it can be generated?**
- **How it can be focused?**
- **Why it need to be focused?**



Focused ultrasound (FUS) is an application of ultrasound in which the wave energy is concentrated to provide **high gains** and **localized energy deposition**

Hynynen et al. Methods of External Hyperthermic Heating; 1990

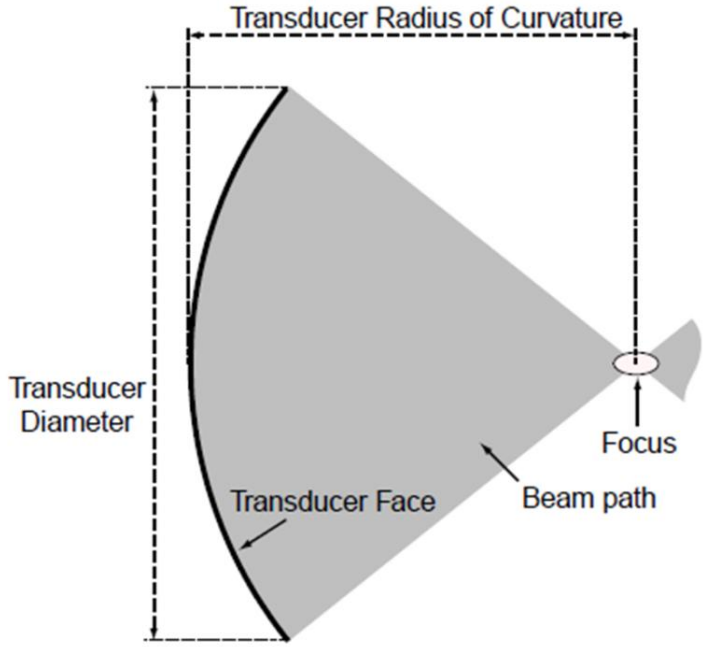
Focused Ultrasound

❖ Shape of focus

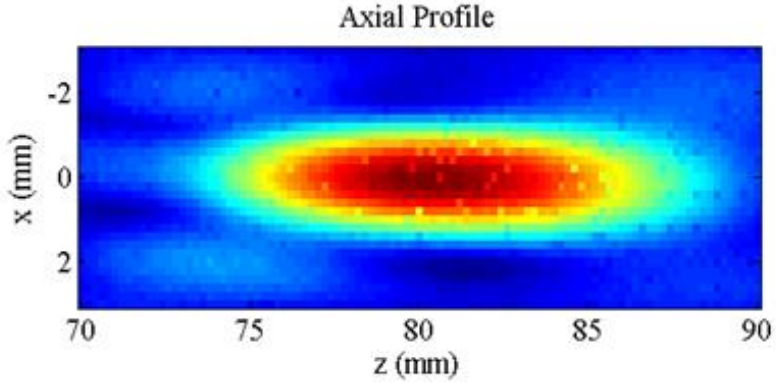
- $f-number = \dfrac{ROC}{diameter}$
- $Frequency$

❖ Diagram of focused transducer

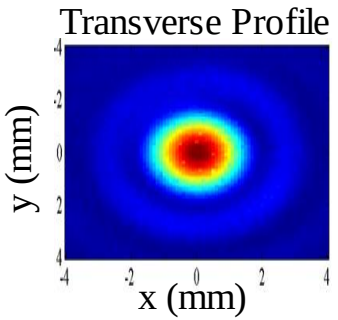
(Single element, PZT, f : 690 kHz, ROC: 8cm, d:10cm)



❖ Beam profile



$Focal\ Zone\ Length \approx 10\lambda\,(f-number)^2 \approx 12.8mm$



Focal diameter = FWHM of transverse profile (2.3mm)

Focused Ultrasound: Therapeutic Applications

InSightec ExAblate @ Stanford

- ✓ **Uterine Fibroid**
- ✓ **Essential Tremor**
- ✓ **Prostate**
- ✓ **Bone Metastases**

https://www.fusfoundation.org/diseases-and-conditions-all/overview

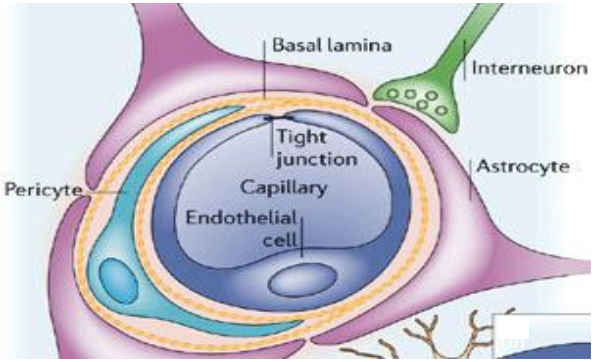
Brain Drug Delivery

Limitations

1. Blood Brain Barrier (BBB)

- ❖ Tight junction between two endothelial cells in the cerebral microvasculature
- ❖ Good for normal brain to maintain brain function by influx of nutrients & the efflux of wastes and toxins
- ❖ Decrease therapeutic efficacy in disease cases

2. Systemic Toxicity

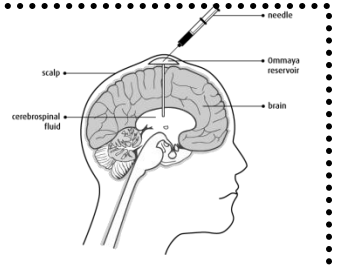


Abbott et al. Nature Reviews; 2006

Methods

Invasive Approaches

- Direct Injection
- Implantable devices
- Intrathecal/Intraventicular Injection
- BBBD via arterial injection of osmotic solution



Trans-Nasal Delivery

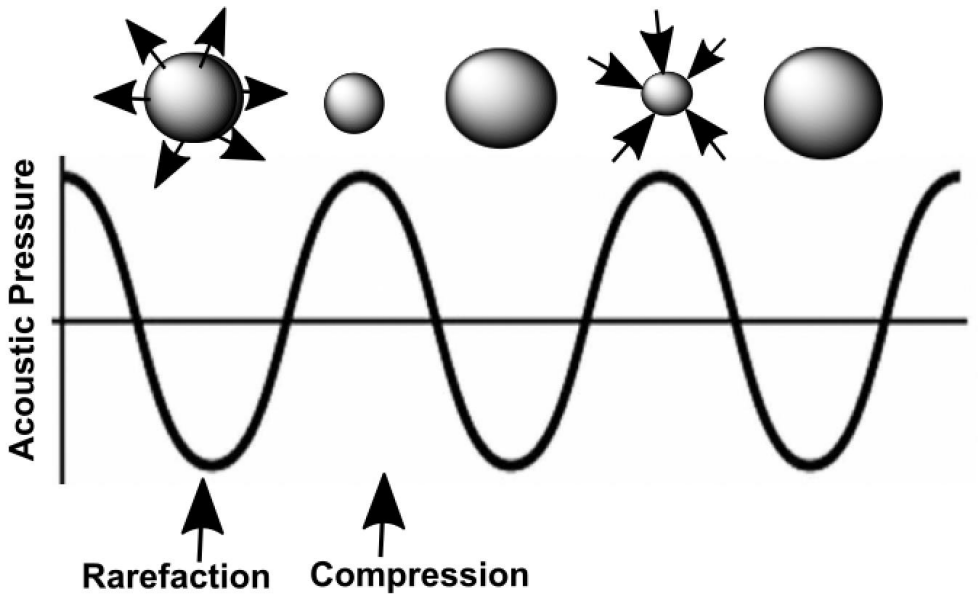
Biopharmaceutical Approaches

New Approach
Focused Ultrasound

Aryal et al. Advanced Drug Delivery Review; 2014

Drug Delivery

Focused Ultrasound + Ultrasound Contrast Agent (UCA / Microbubbles)



Example of Commercially Produced UCA

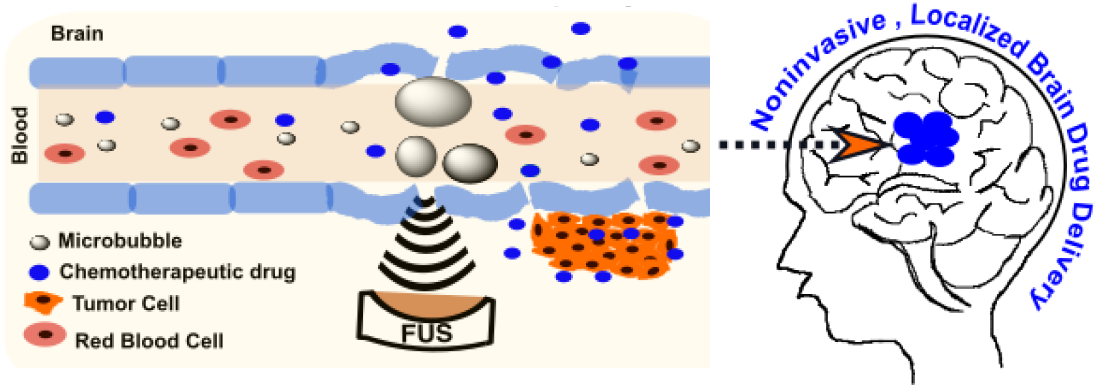
Name	Shell	Gas	Size, µm
Optison*	Albumin	Octafluoropropane	2 – 4.5
Definity*	Lipid/surfactant	Octafluoropropane	1.1 – 3.3
Imagent*	Lipid/surfactant	Perfluorohexane	6
SonoVue	Lipid	Sulfur Hexafluoride	2 - 3
BR38	Lipid	Decafluorobutane	< 4
Imagify	PLGA polymer	Perfluorocarbon	
Sonazoid	Lipid	Decafluorobutane	2 - 3

* Approved for use by US FDA for LV opacification

Goldberg et al. UMB, 1994

Brain Drug Delivery: Approach 1

Focused Ultrasound + Ultrasound Contrast Agents
(low frequency in pulse mode with very low pressure)



Open Blood-Brain Barrier (BBB)

- Deliver bigger molecules through

Bioeffects

- Immediately open & recover in 4 -24 hrs
- Opening magnitude depend on anatomy, FUS parameters & microbubble concentrations

Mechanism is not known

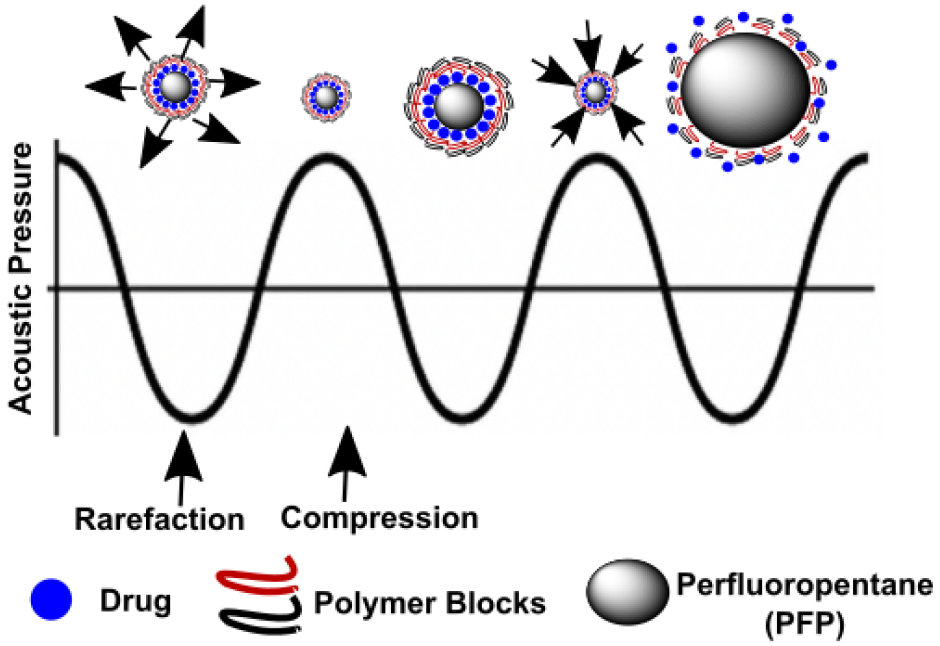
- Bubble grow with rectified diffusion,
- Interact with vessel wall by oscillatory and radiation force
- Exert indirect shear force due to microstreaming in the surrounding medium

Status: Phase 0/1 clinical trials for Alzheimer and cancer treatments in US

Hynynen et al. 2001

Brain Drug Delivery: Approach 2

Focused Ultrasound + Drug Loaded Ultrasound Sensitive Nanodroplets



Ultrasonic Drug Uncaging (mechanism unknown)

- PFP core expands with enough pressure
- Weaken the emulsifying polymer layer
- Allow drug to debris from the encapsulation

Bioeffects

- Immediately release drug in the blood pool
- Drug release event depend on anatomy FUS parameters & nanodroplet concentrations

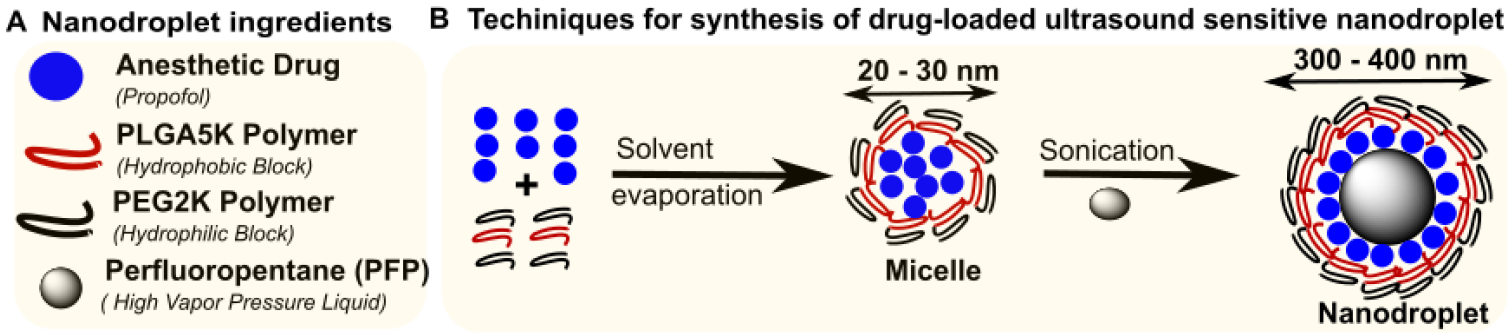
Status (in preclinical model)

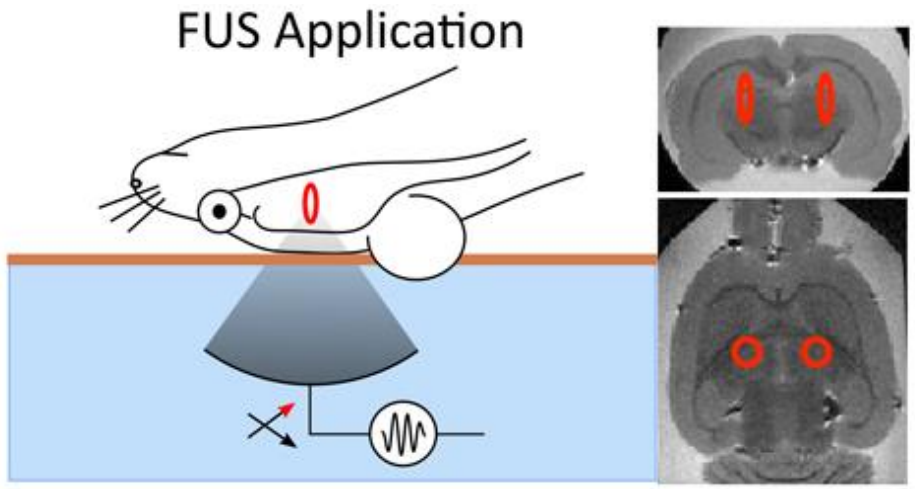
- Therapeutic benefit in ovarian, breast, & pancreatic cancerous tumors by paclitaxel-loaded nanoemulsions

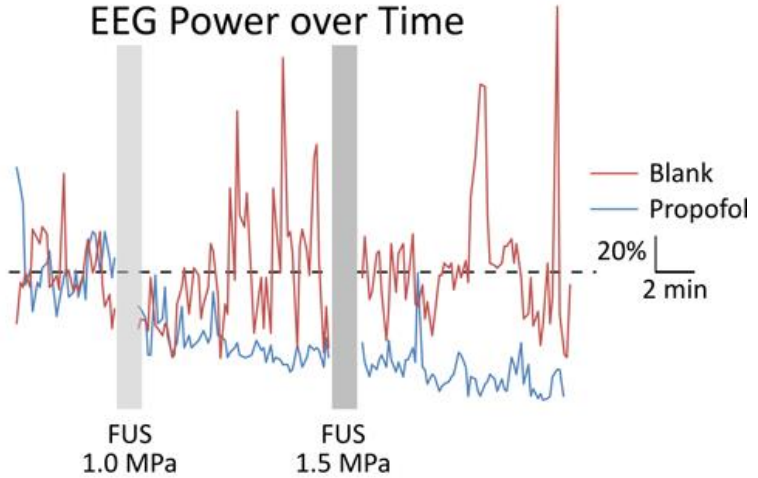
Rapoport et al. JCR, 2009

Neuromodulation in Rat-Seizure Model

Focused Ultrasound + Drug Loaded Ultrasound Sensitive Nanodroplets







Airan et al. Nanoletter, 2017

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Temporal Resolution & Specificity of Neuromodulatory Effects via Ultrasonic Drug Uncaging

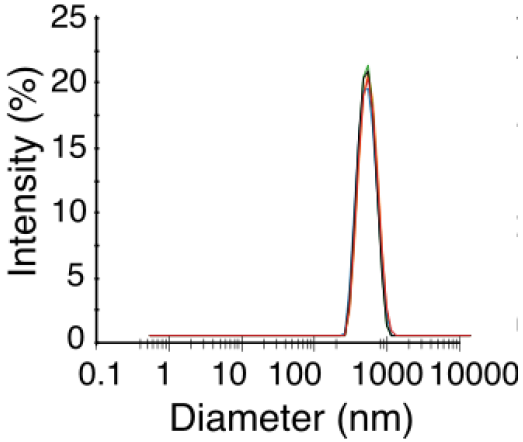
Objective 1: To determine temporal resolution & specificity of neuromodulatory effect

Hypothesis: Ultrasonic drug uncaging is **precisely limited** spatially and temporally by the **ultrasound focal zone and timing of sonication**

Test: Tested that hypothesis on normal rodent model (**N = 18 Rats**) using **electrophysiological** (EEG) readout

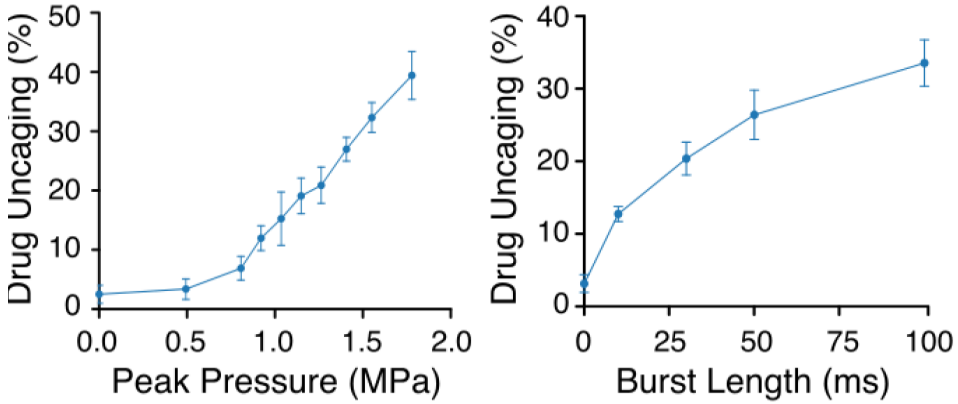
Temporal Resolution & Specificity of Neuromodulatory Effects via Ultrasonic Drug Uncaging

Physiochemical Properties of Nanodroplets



- Z-averaged diameter 397.3 ± 10.0 nm
- Polydispersity index 0.068 ± 0.023
- zeta potential -26.7 ± 0.6 mV

In vitro efficacy of drug uncaging

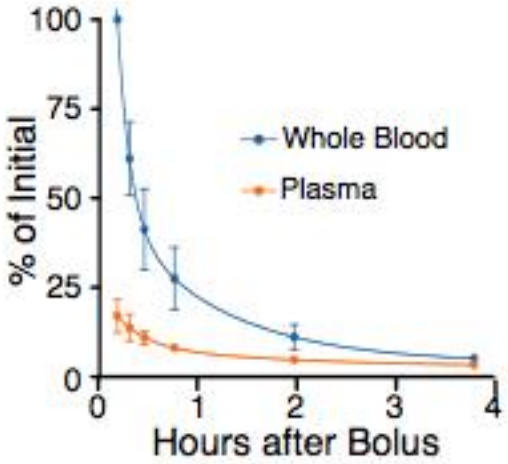


650 kHz at 1 Hz PRF for 1 min

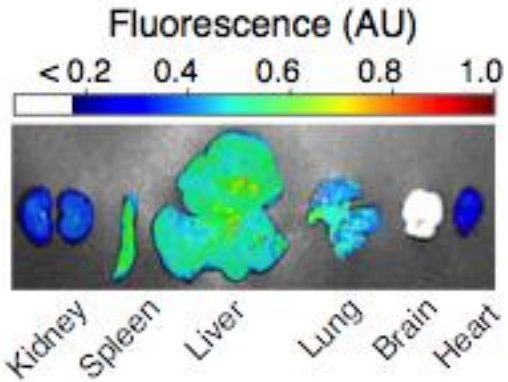
Zhong Q, Yoon BC, **Aryal M**, Wang JB, Airan RD. "Polymeric perfluoropentane nanoemulsions are a versatile platform for ultrasonic drug uncaging", **bioRxiv, doi: https://doi.org/10.1101/315044: Under Revision.**

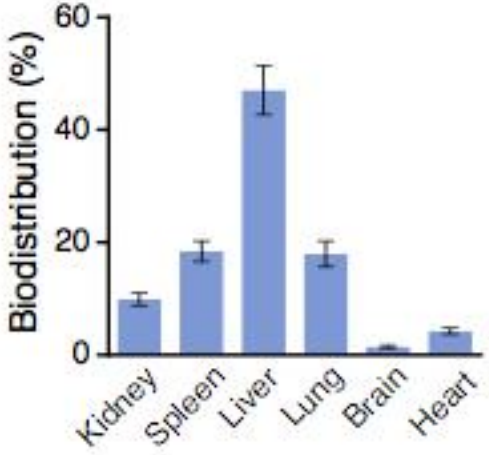
Temporal Resolution & Specificity of Neuromodulatory Effects via Ultrasonic Drug Uncaging

Pharmacokinetic

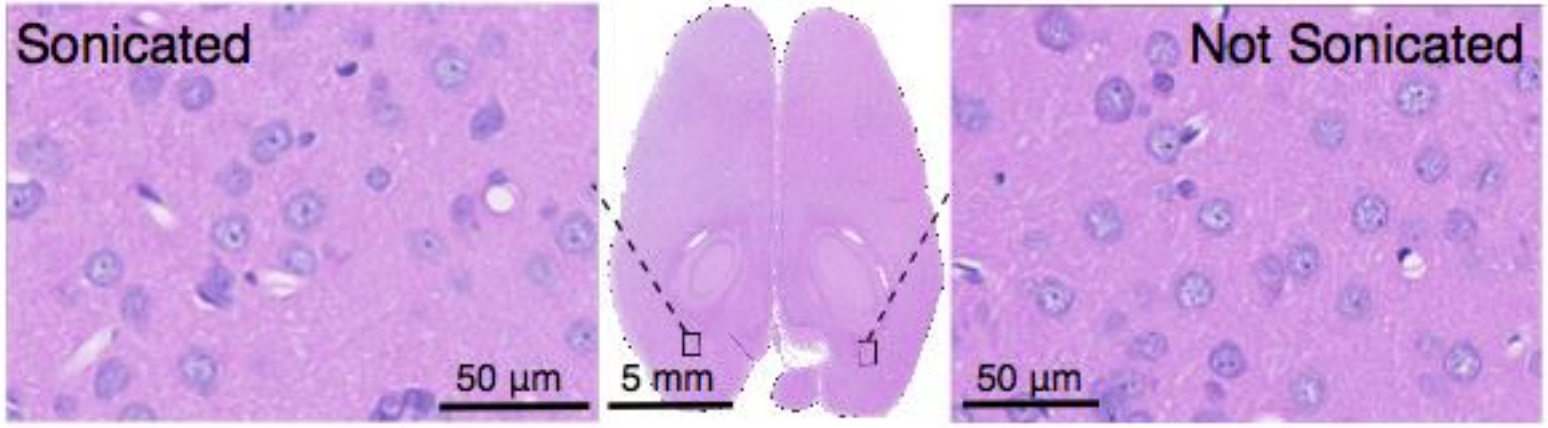


Biodistribution





Safety



Wang* JB, **Aryal* M**, Zhong Q, Vyas D, Airan RD. "Noninvasive neuromodulation with ultrasonic drug uncaging", **Under Revision.** * *authors contributed equally to this work*

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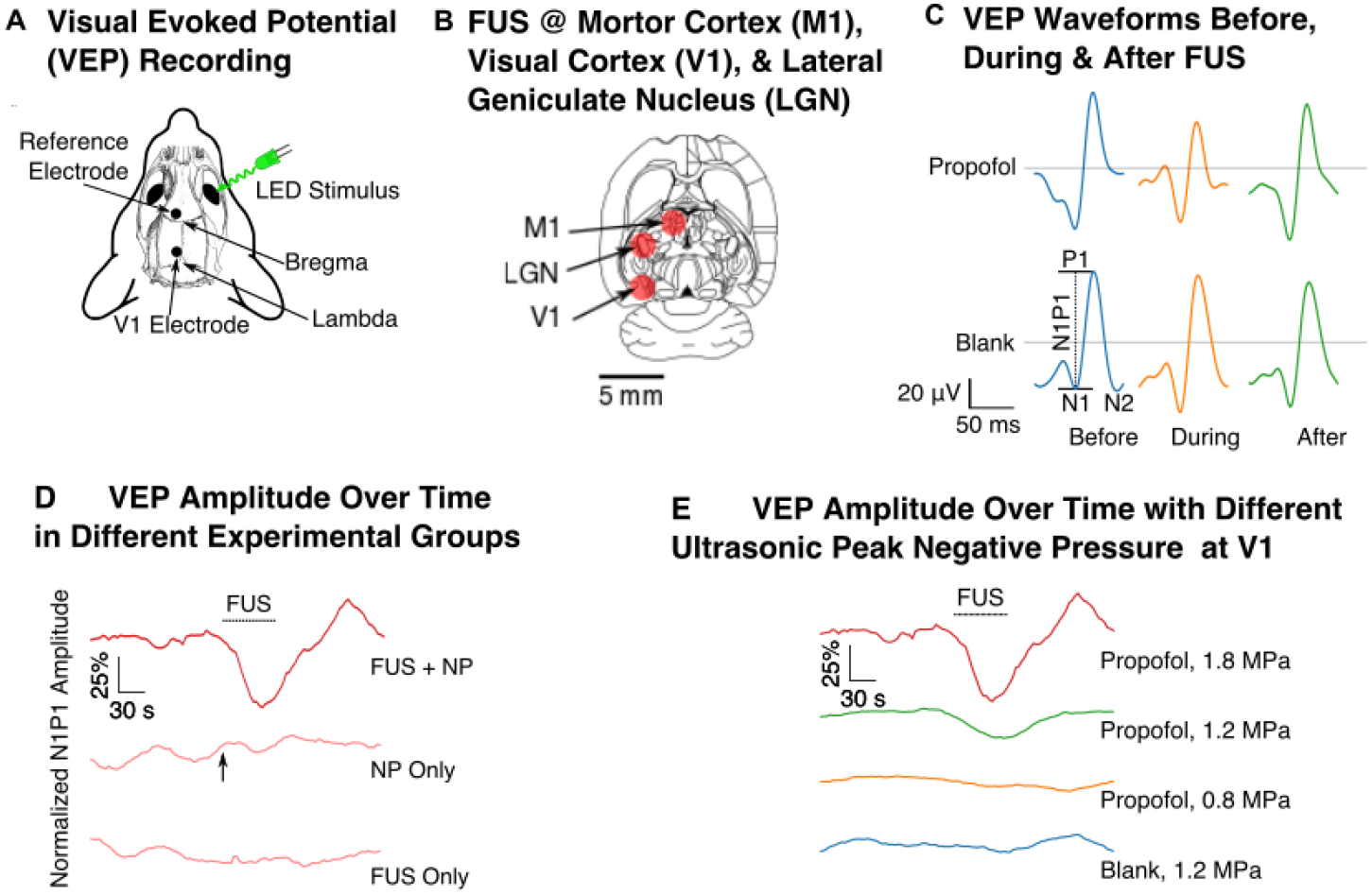
Temporal Resolution & Specificity of Neuromodulatory Effects via Ultrasonic Drug Uncaging



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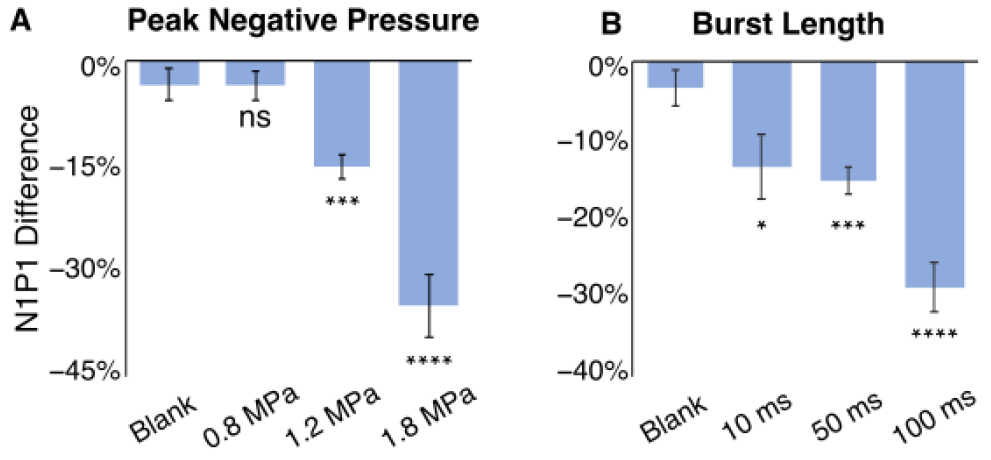
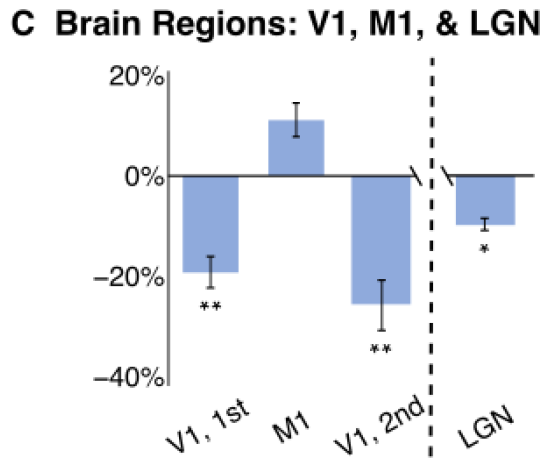
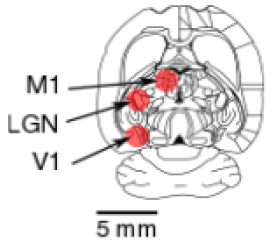




D Temopral Resolution

Condition	Effect Half-life (s)
1.8 MPa, 50 ms	8.8 ± 3.5
1.2 MPa, 100 ms	14.8 ± 2.5



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Temporal Resolution & Specificity of Neuromodulatory Effects via Ultrasonic Drug Uncaging

Determined temporal resolution & specificity of **neuromodulatory effect in *rodent*** i.e. produced by ultrasonic uncaging of anesthetic Propofol from polymeric perfluropentane nanodroplets

1. Zhong Q, Yoon BC, **Aryal M**, Wang JB, Airan RD. "Polymeric perfluoropentane nanoemulsions are a versatile platform for ultrasonic drug uncaging", **bioRxiv, doi: https://doi.org/10.1101/315044: Under Revision.**
2. Wang* JB, **Aryal* M**, Zhong Q, Vyas D, Airan RD. "Noninvasive neuromodulation with ultrasonic drug uncaging", **Under Revision.**

* *authors contributed equally to this work*

Temporal Resolution & Specificity of Neuromodulatory Effects via Ultrasonic Uncaging in Canine Model

Objective 2

- To determine the spatiotemporal resolution of the ***neuromodulatory effect in Canine model***

- To develop an **imaging method** to determine a physical model of the drug uncaging event, to guide further nanodroplet optimization

Conclusions

- Introduced **two different approaches** of using FUS on brain drug delivery
- Showed **spatiotemporal resolution of neuromodulatory effect** using ultrasonic drug uncaging in *rodent model*
- Potential implication of the ultrasonic drug uncaging technique in **cancer and imaging**

Acknowledgement

Airan's Lab

Questions

Thank you