### Noninvasive and Targeted Brain Drug Delivery using Transcranial Focused Ultrasound

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# Outline

Introduction Focused Ultrasound Technology (FUS)



### **Ultrasound**, Medical Applications



## **Focused Ultrasound**



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

## **Focused Ultrasound**



#### Diagram of focused transducer

(Single element, PZT, f : 690 kHz, ROC: 8cm, d:10cm) Transducer Radius of Curvature Transducer Diameter Transducer Face Beam path

### ✤ Beam profile





Focal diameter = FWHM of transverse profile (2.3mm)

### **Focused Ultrasound: Therapeutic Applications**

Development stage:	Conceptual Pre-c	linical Anecdotal	Pilot Trials Pivotal Trials	Outside US Approvals FDA Appr	ovals US Reimbursement
Cardiovascular		Neurological		Pain	
Hypertension		Essential tremor		Back pain, facetogenic	
Peripheral artery disease		Depression		Neuropathic pain	
Arteriovenous malformations		Neuropathic pain		Osteoid osteoma	
Atherosclerosis		Obsessive-compulsive		Back pain, sacroiliitis	
Atrial fibrillation		disorder		Painful amputation stump	
Cardiac dysrythmias		Parkinson's disease		neuromas	
Congestive heart failure		Amyotrophic lateral sclerosis		Cancer pain	
Deep vein thrombosis		Alzheimer's disease			
Hypoplastic left heart		Brain cancer			
syndrome		Brain tumors, benign		Pediatrics	
Septal perforation		Dystonia		Osteoid osteoma	
		Epilepsy		Soft tissue tumors, benign	
		Painful amputation stump		Brain tumors, benign	
Endocrine Disorders		neuromas		Arteriovenous malformations	
Thyroid nodules		Trigeminal neuralgia		Neuroblastoma, pediatric	
Thyroid cancer		Hydrocephalus			
Diabetes		Stroke			
Obesity		Traumatic brain injury		Pulmonary	
		Multiple sclerosis	-	Lung metastases	
				Lung cancer	
Gastrointestinal					
Liver cancer		Oncological			
Pancreatic cancer		Bone metastases		Urological	
Malignant obstructive jaundice		Prostate cancer*		Benign prostatic hyperplasia*	
Colorectal cancer		Breast cancer		Lostate cancer*	
Esophageal cancer		Kidney concor		Kidney cancer	
		Liver cancer		Kidney stones	
Nai		Pancreatic cancer		Acute kidney injury	
Miscellaneous		C [1 1]	The second		
Soft tissue cancer		Soft tissue cancer		Acute tubular necrosis	
Soft tissue tumors, benign		Soft tissue cancer Bone cancer		Acute tubular necrosis Bladder cancer	
Head & neck cancer		Soft tissue cancer Bone cancer Brain cancer		Acute tubular necrosis Bladder cancer Ureterocele	>> >>
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InSightec ExAblate @ Stanford

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

# **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



### **Stanford University**

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

# **Brain Drug Delivery: Approach 1**

### **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

### Focused Ultrasound + Ultrasound Contrast Agents

(low frequency in pulse mode with very low pressure)



# **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 paclitaxelloaded nanoemulsions

## **Neuromodulation in Rat-Seizure Model**

### **Focused Ultrasound + Drug Loaded Ultrasound Sensitive Nanodroplets**



**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



**Physiochemical Properties of Nanodroplets** 

25 20 20 15 10 5 0 0.1 1 10 100 10000 Diameter (nm)

- ✤ Z-averaged diameter 397.3 ± 10.0 nm
- ✤ Polydispersity index 0.068 ± 0.023
- **\*** zeta potential -26.7  $\pm$  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.



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

- 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 <u>neuromodulatory</u> <u>effect in Canine model</u>
- 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

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Center for Cancer Nanotechnology Excellence for Translational Diagnostics

# Questions

Thank you