

# UCED

Ultrasound-assisted Convection Enhanced Delivery

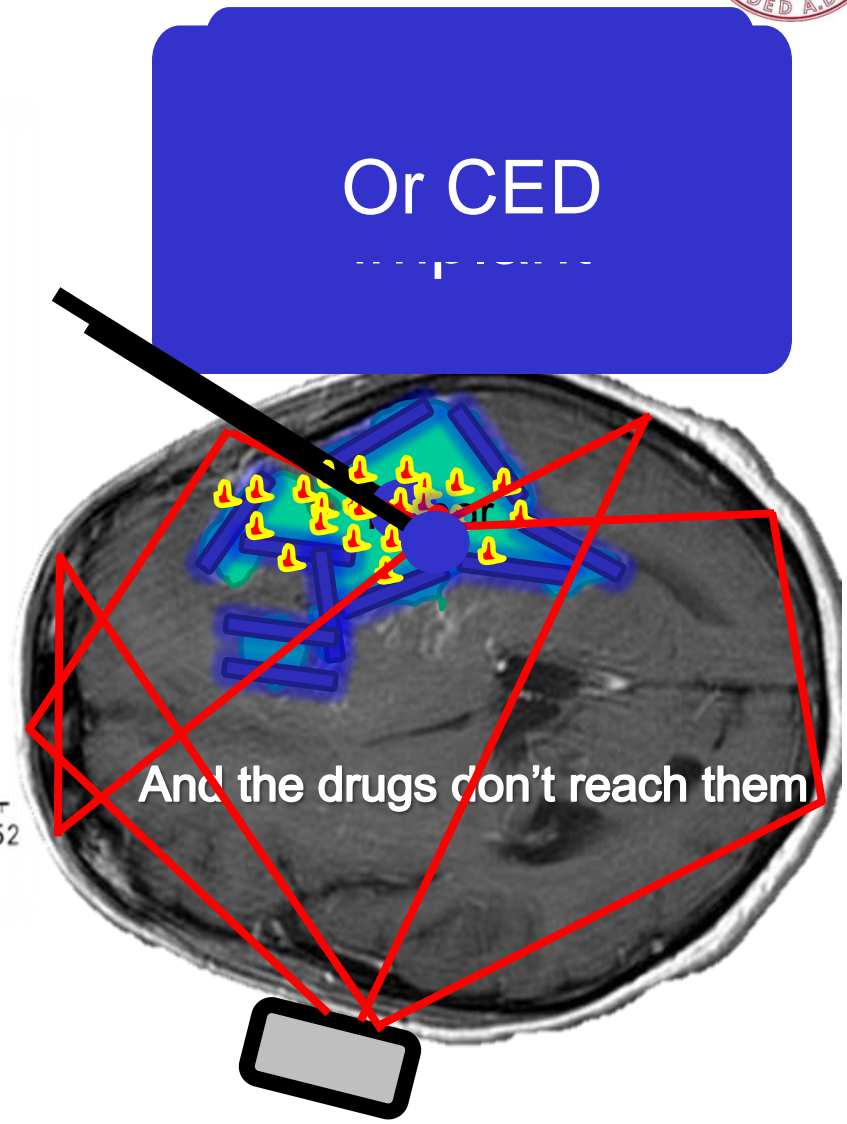
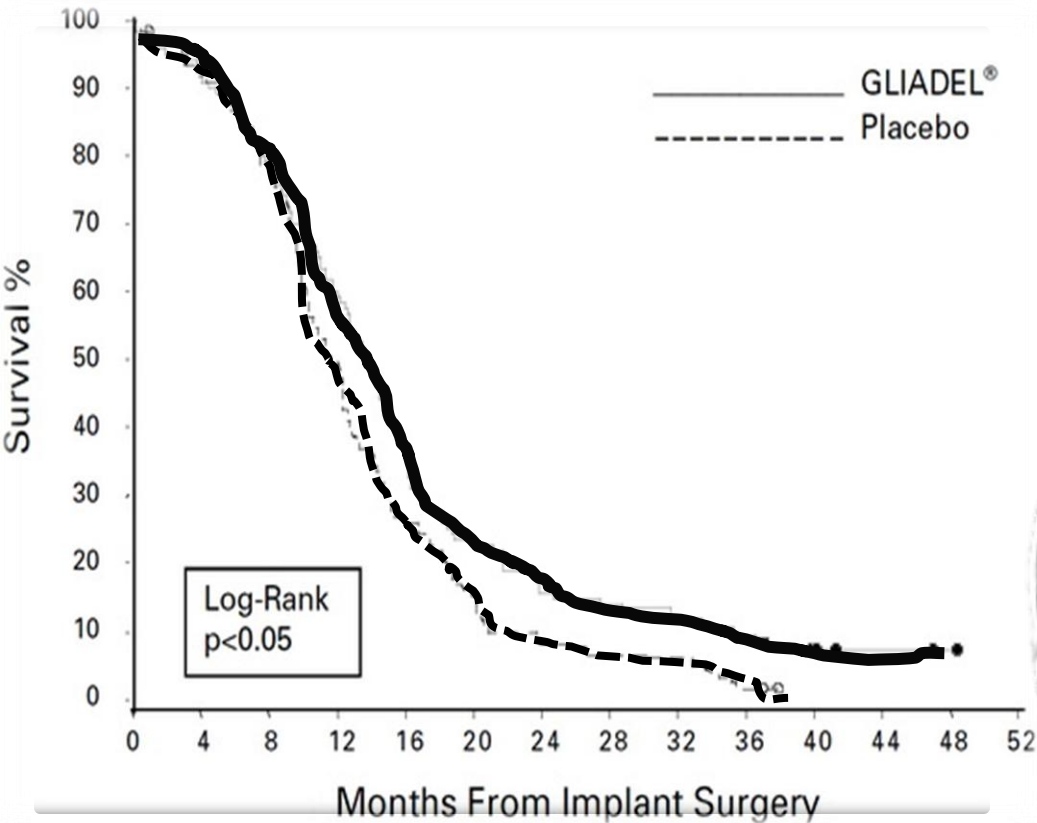
## Ultrasound-Assisted Convection-Enhanced Drug Delivery to the Brain

Dr. George K. Lewis, Dr. William Olbricht, Dr. Armen Sarvazyan, Dr. Teresa Southard, Dr. Susan Pannullo

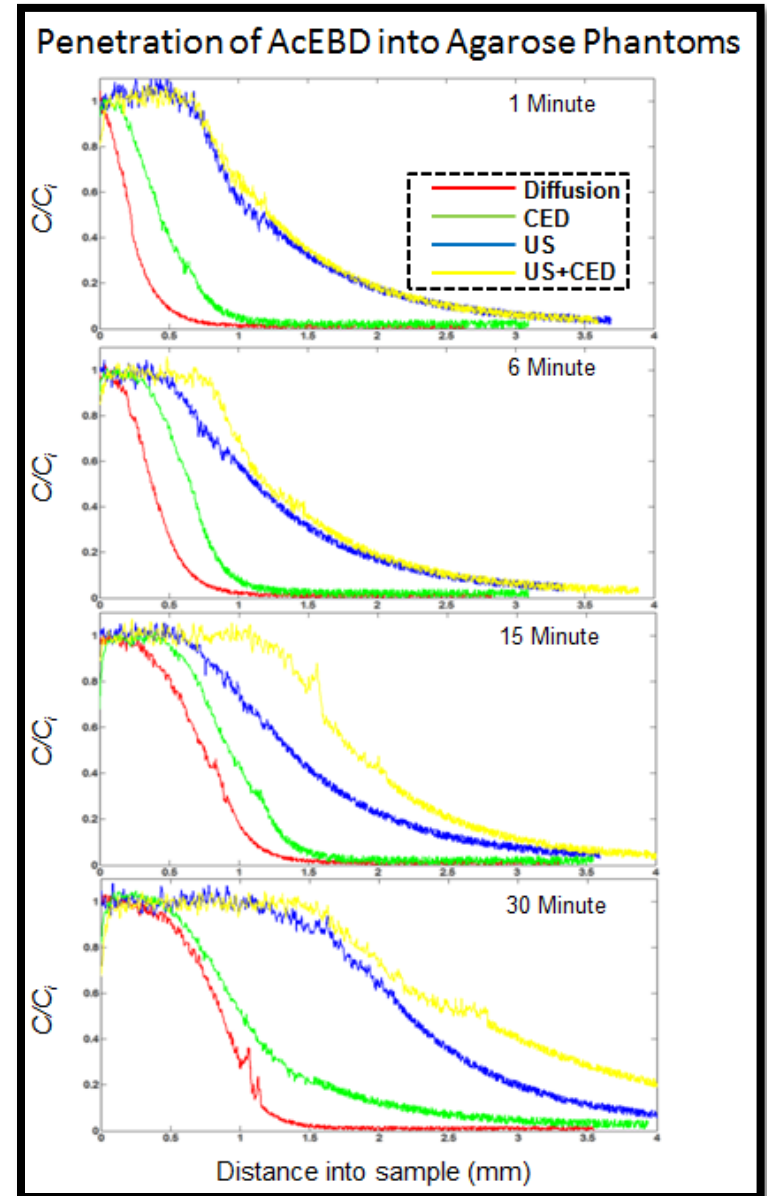
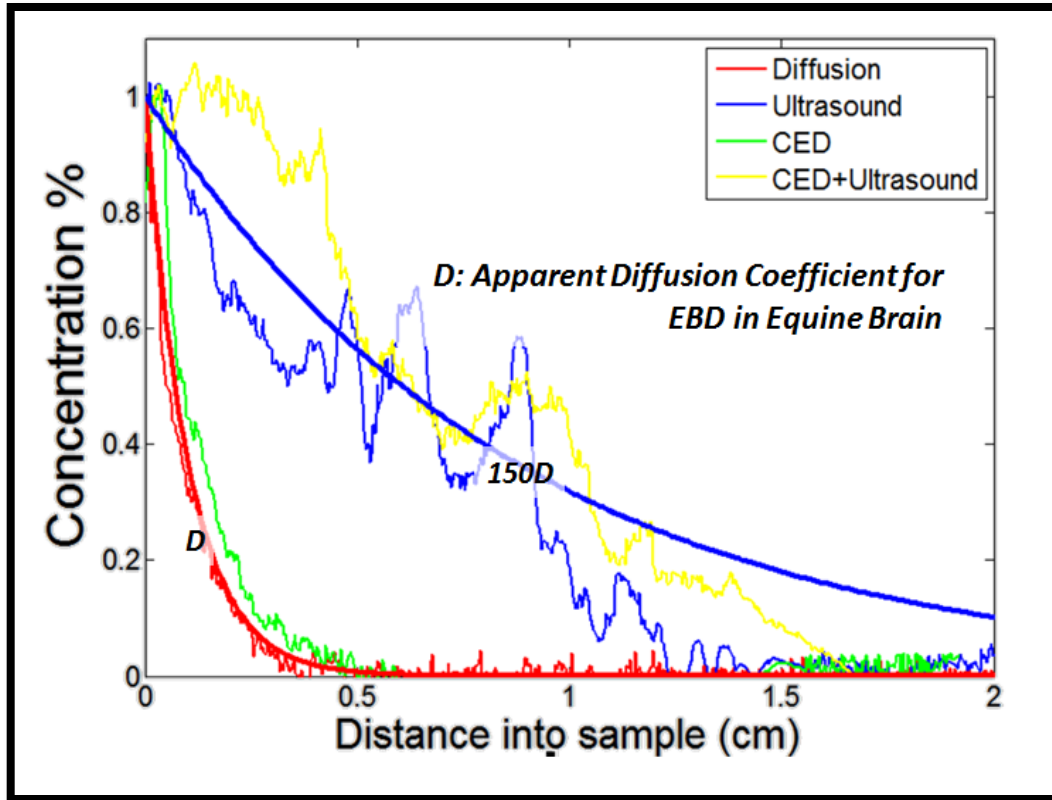
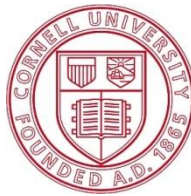
AIUM 2011, New York City

Research Fellow, Cornell University  
Vice Chair, TUS AIUM

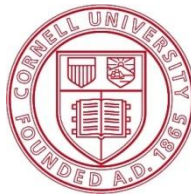
# Brain Cancer: Difficulty with Glioblastoma



# Ultrasound Enhances Transport in Tissues



Lewis G.K., Jr., Olbricht, W.L. (2007). LISSA, Lewis, G.K., Jr., Lewis, G.K., Sr., Olbricht, W.L. (2007). J. Acoust. Soc. Am. 122 3007, Lewis, G.K., Jr., Wang, P., Lewis, G.K., Sr., Olbricht, W.L. (2009). Symp. Theras. Ultras. AIP 1113, pp. 403-407



# UCED Drug Delivery Systems

**Targeted:** Technology that can target drugs or mediate delivery.

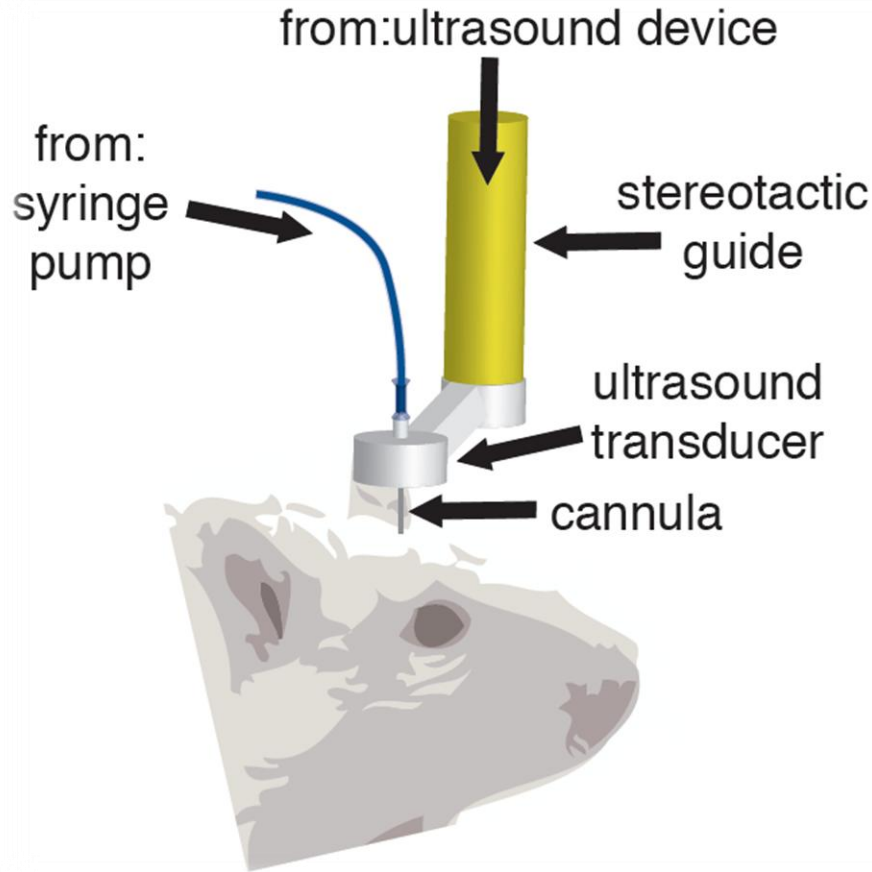
**1 MHz Ultrasound  
Needle—Transducer**



**1 MHz  
Time-reversal Needle**

# UCED Delivering Drugs to the Brain

## PLANE WAVE ULTRASOUND



**Ultrasound Exposure**

- 95mW/cm<sup>2</sup> acoustic intensity at 1.34 MHz (50mW/cm<sup>2</sup> at cannula tip)

$$I = \frac{P}{A} = \frac{P}{\pi r^2} = \frac{P}{\pi \left(\frac{B}{4}\right)^2} = \frac{4P}{\pi B^2}$$

$$T = \frac{f}{210210}$$

- Well below FDA guidelines and close to imaging intensities

3 mm

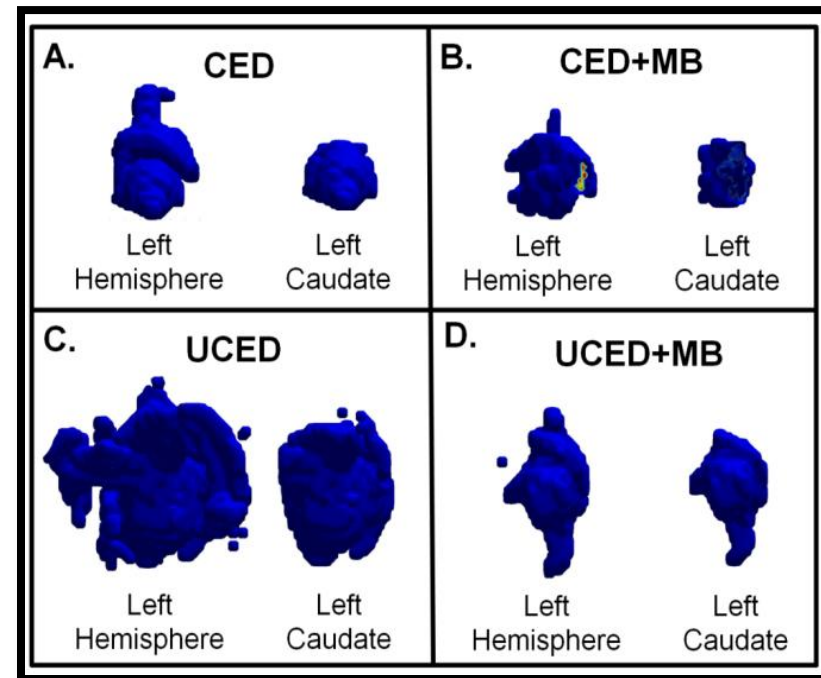
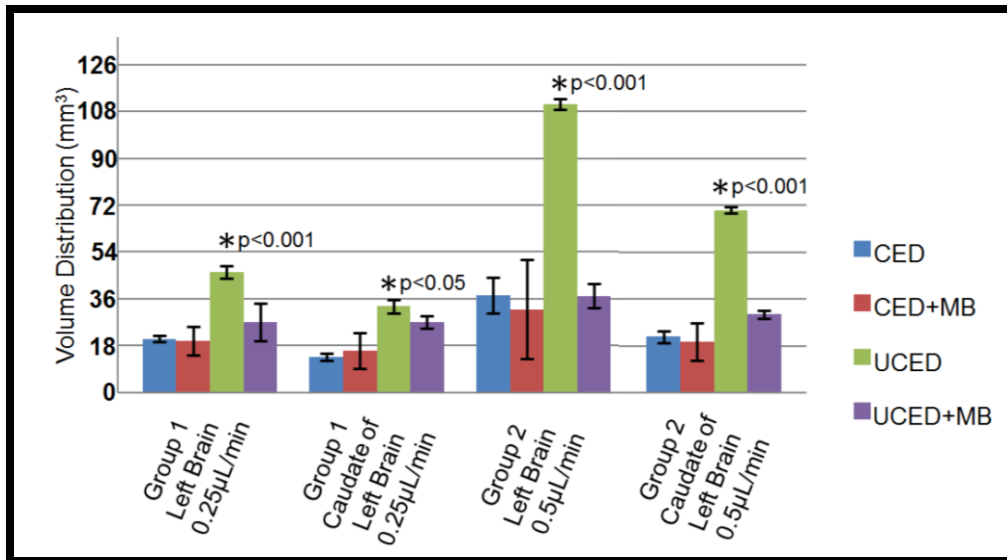
Schematic showing infusion coordinates ( $\beta +0$  mm)

*Lewis et al. Int. Thera. Ultras 2008, Lewis et al. Am. Inst Ultras Med. 2010, Lewis et al. USPCT 2010, Lewis et al. Acous. Soc. Am. 2010, Lewis et al. J. Neuro Surg. 2011*

# UCED Delivering Drugs to the Brain

## UCED of Evans blue dye

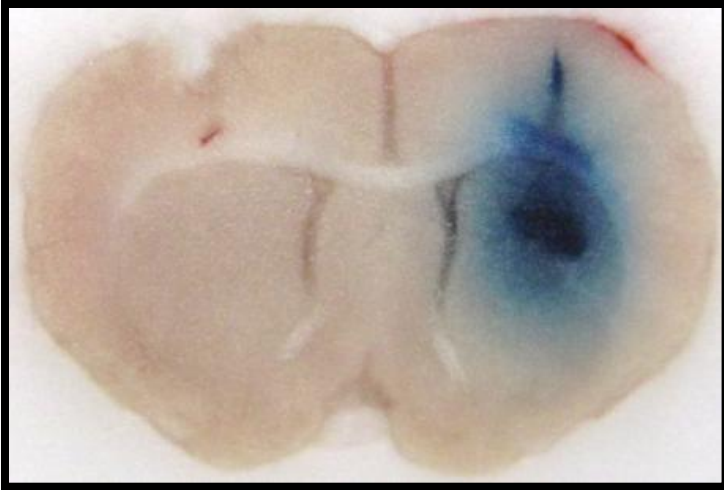
- Greater distribution volume 2 to 3 times
- Trends with reduced back flow
- Microbubbles provide concentrated delivery



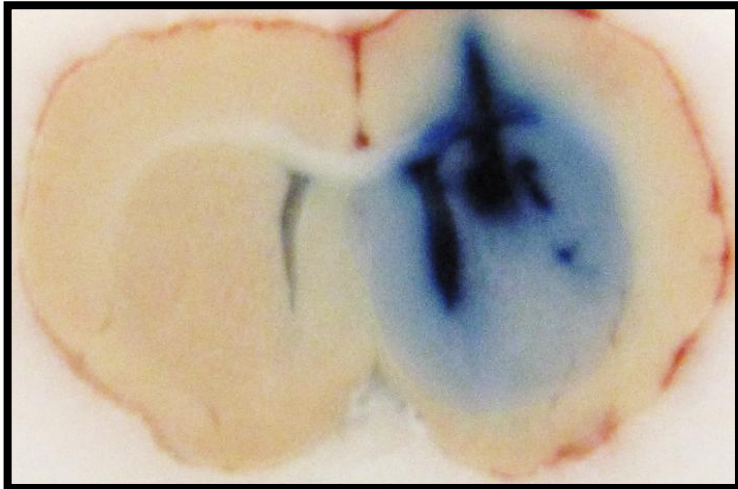
# A Closer Look at the Brains

## Ultrasound

0.25 uL/min

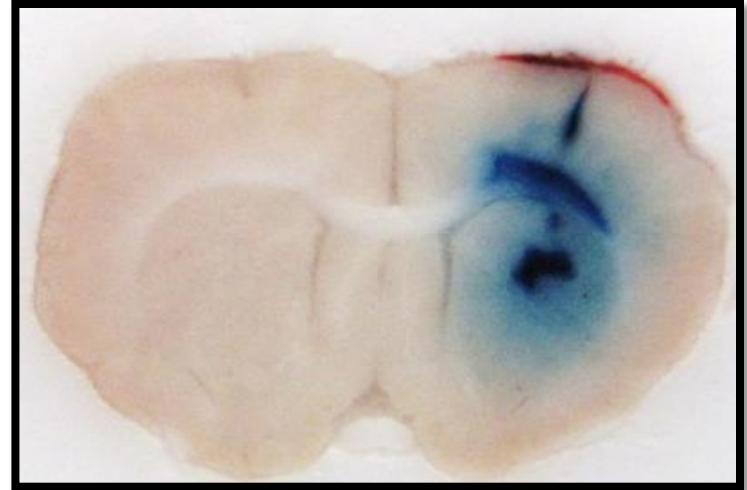


0.5 uL/min

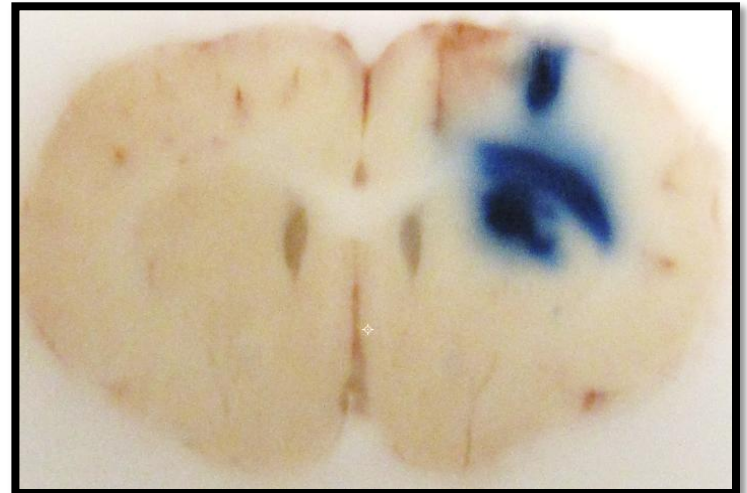


## Control

0.25 uL/min

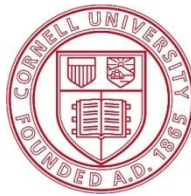


0.5 uL/min



Lewis, G.K. Jr., Olbricht, W.L. (2010). United States Provisional Patent Application. 61311064, Lewis, G.K., Jr., Schulz, Z., Pannullo, S., Southard, T., Olbricht, W.L. (2011). *JNS*

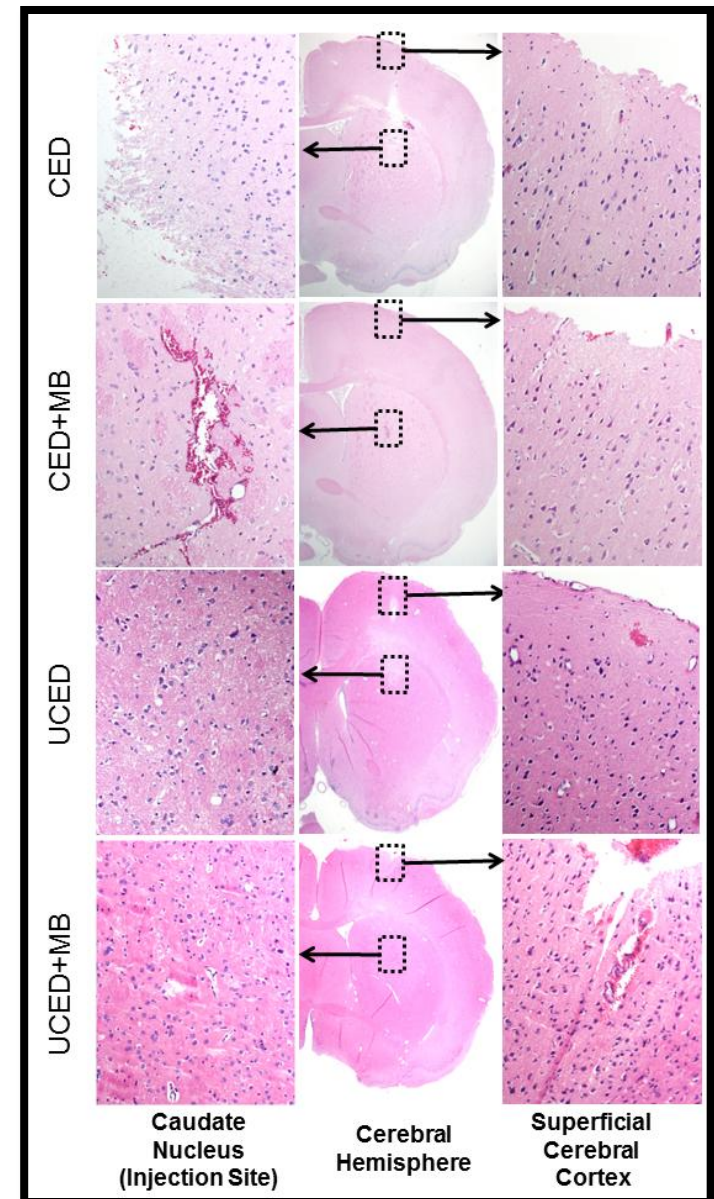
# Histology



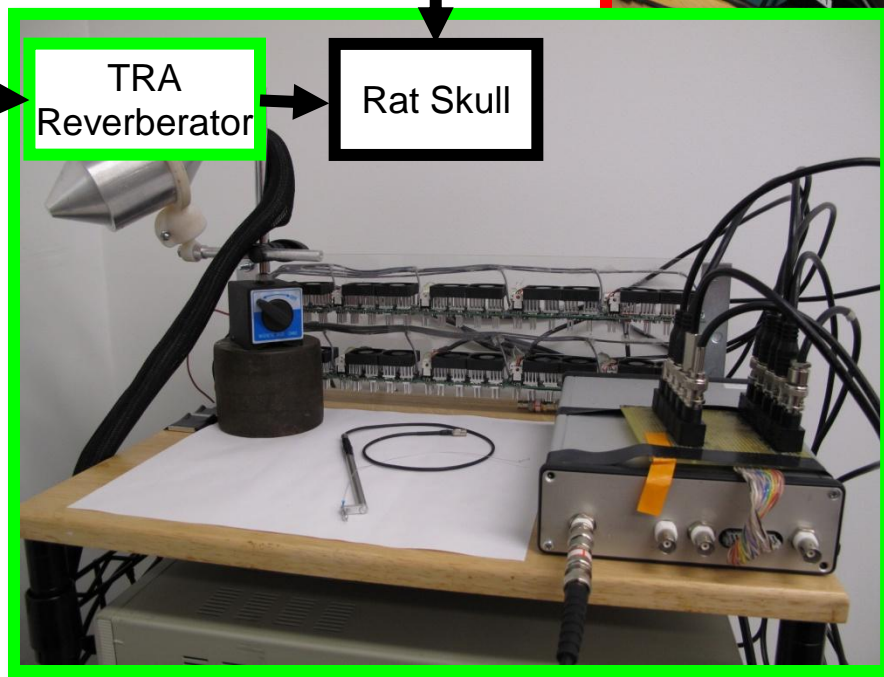
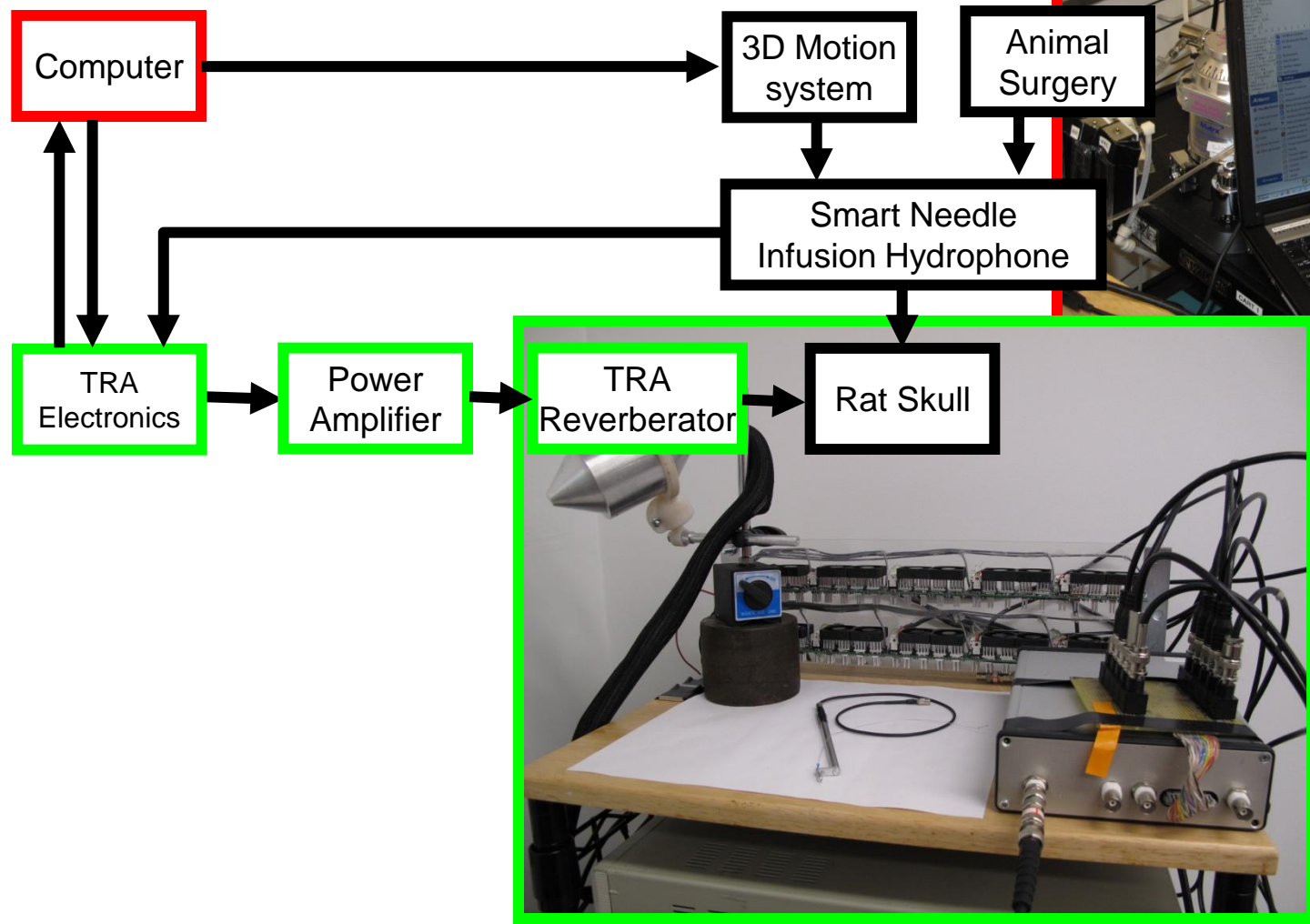
## Cornell Veterinary Medicine

- *Hematoxylin and eosin stain of rodent brains (10 um coronal slices) in the cannula insertion path*
- *CED, CED+MB, UCED and UCED+MB show similar histological results in both the cortex and caudate of the rodent brains*
- *Mild parenchymal disruption, edema and hemorrhage around the needle track and injection site are equivalent for the group*

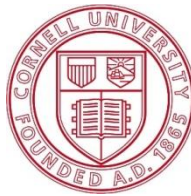
Lewis, G.K., Jr., Schulz, Z., Pannullo, S., Southard, T., Olbricht, W.L. (2010). *In preparation*, Schulz, Z., Lewis, G.K., Jr., Olbricht, W.L. (2011) JNS.



# Time Reversal Brain Drug Delivery System

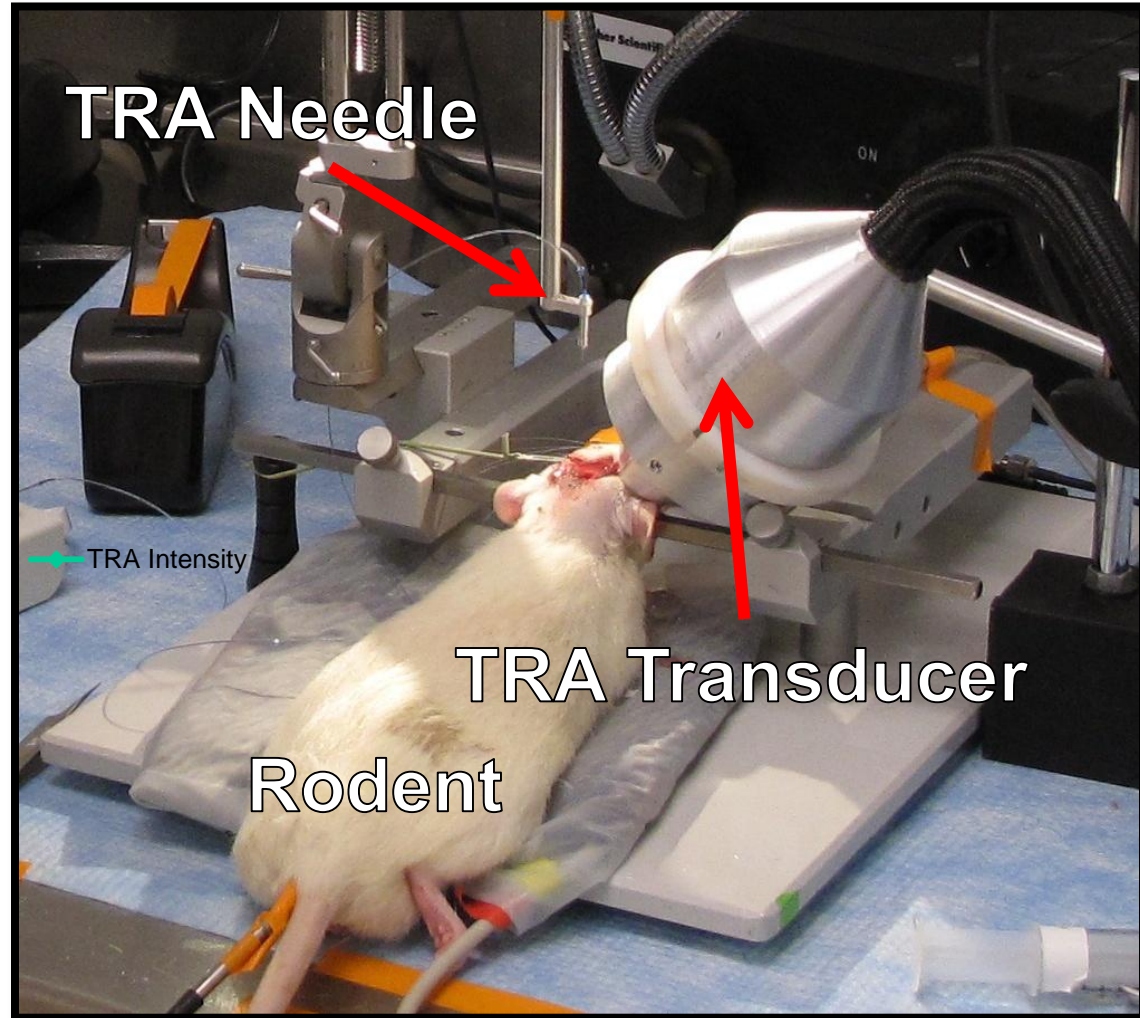
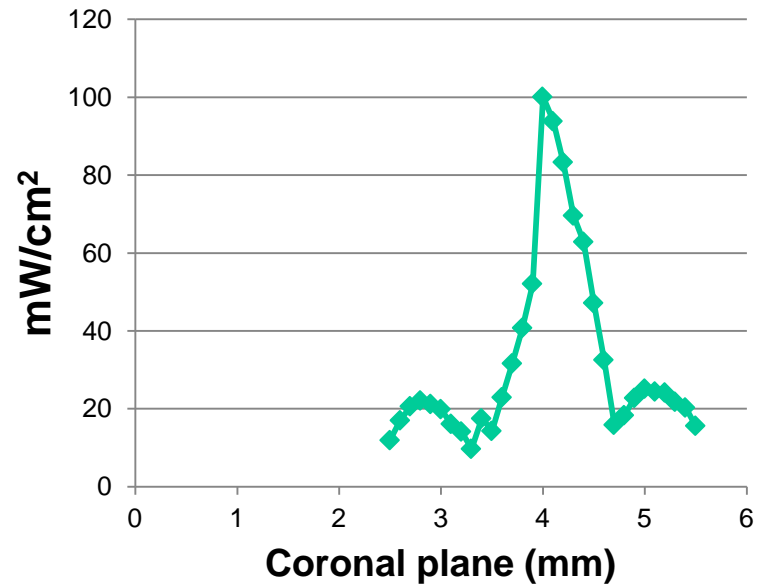


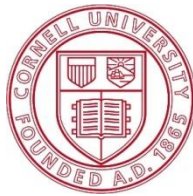
# Time Reversal Based UCED



## FOCUSED ULTRASOUND

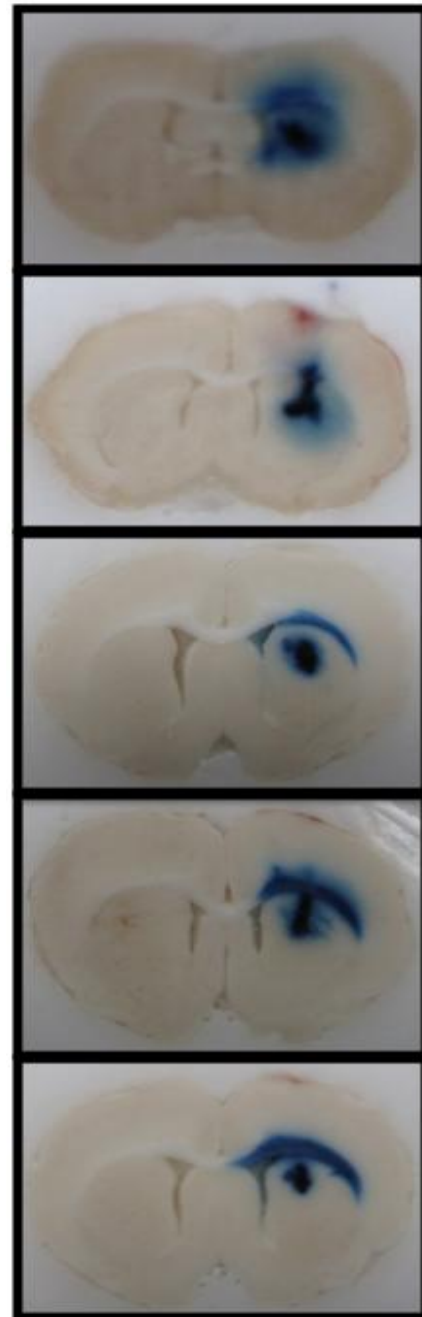
### TRA Focus in Rodent Brain





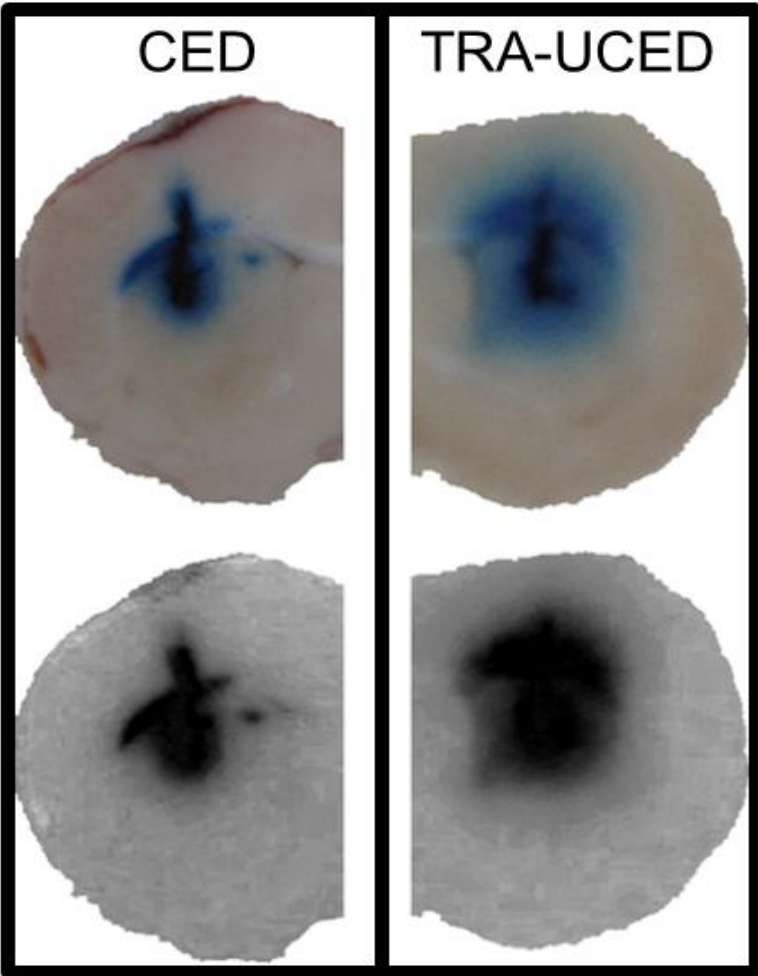
## TRA-CED

30.1 mW/cm<sup>2</sup> 16.7 mW/cm<sup>2</sup> 1.15 mW/cm<sup>2</sup> 0.337 mW/cm<sup>2</sup> 0.307 mW/cm<sup>2</sup> *Inte.*



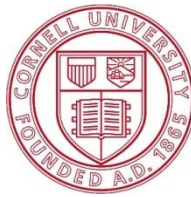
## CED

## TRA-UCED

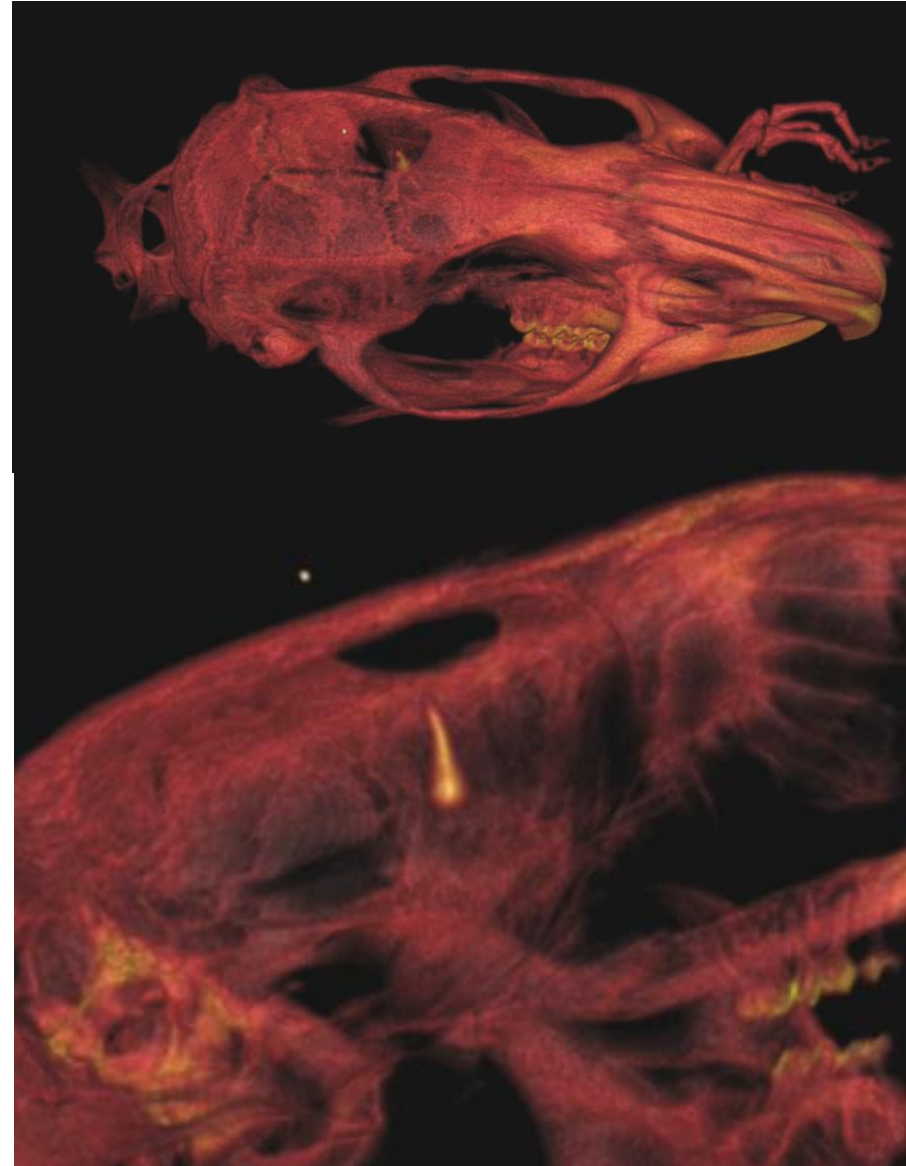


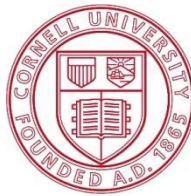
Lewis G.K., Filing L., Olbricht W.L., Lewis Sr. G.K., Sarvazyan A. (2010) J. Acoust. Soc. Am., Lewis G.K., Pannullo S. (2010) USPCT *In prep.*

# Conclusions



- Ultrasound may enhance the distribution of tracers and drugs in brain.
- Safe levels of ultrasound exposure to the brain need to be accessed.
- Methods for measuring distribution non invasively (MRI/uCT) for chronic experiments.
- Larger animal models to asses scalability of the approach.





# Acknowledgements



## CLINICAL RESEARCH TEAM

*Brain: Susan Pannullo and Mark Souweidane*

## PRECLINICAL RESEARCH TEAM

*Brain: Zach Schulz, Sabrina Guarino, Allison Jagoe, Brian Aguilare, Saran Baskaran, John Foo and Sruthi Chandran*

**Research supported by:**

National Institutes of Health, *Grant #1R43NS065524-01*

Weill Cornell Brain Tumor Project

# Questions?