Ultrasound-Mediated Drug Delivery to the Spinal Cord: Preclinical Findings and Clinical Scale Advances

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FOCUSED ULTRASOUND LAB

Barriers of the CNS:

Blood-Brain and Blood-Spinal Cord Barriers (BBB and BSCB)

- CNS endothelia
  - Presence of t
  - Reduced num
- Restricts entry solubility[2]

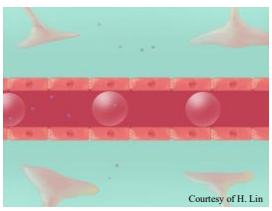
>98% of small molecule drugs and **100%** of large molecule drugs **do not pass the BBB or BSCB** in therapeutically relevant quantities

Abbott, *Nature Reviews* (2006)

[1]Reese and Karnovsky, *J Cell Biol* (1967); [2]Pardridge, *NeuroRx* (2005)

Ultrasound-Mediated Barrier Opening

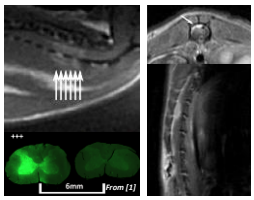
- Ultrasound can stimulate microbubbles in the circulation to cause transient opening[1]
  - Bubble interactions with the vessel walls induce bioeffects



[1]Hynynen et al., *Radiology* (2001)

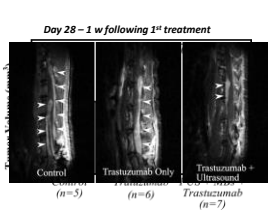
Drug Delivery to the Spinal Cord

- BBB opening has reached clinical investigations
  - Limited work to date in spinal cord[1-4] despite clinical need
- Leptomeningeal Metastases (LM)
  - Impacts ~ 5% of solid tumor patients w/ incidence rates increasing[5]
  - Greatest # cases = breast cancer

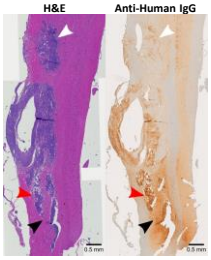


[1]Weber-Adrian et al., *Gene Therapy* (2015); [2]Payne et al., *Neural Regen Res* (2017); [3]O'Reilly et al., *Sci Reps* (2018); [4]Montero et al., *Ultrasound Med Biol* (2019); [5]Chamberlain, *Curr Opin Neurol* (2009);

Trastuzumab Delivery to LM Tumors



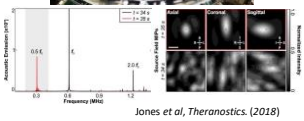
O'Reilly et al., *Scientific Reports* (2018)



Developing Robust Clinical-Scale Systems

Requirements:

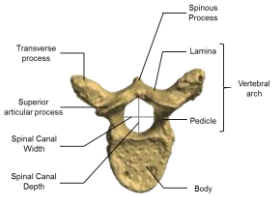
- Precise transmit control
  - Treatment planning models
  - Aberration correction capabilities
- Treatment monitoring/control
  - Detection and localization of bubble activity
  - Feedback control based on bubble activity



Jones *et al*, *Theranostics.* (*2018*)

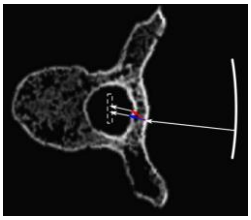
Clinical Scale Challenges

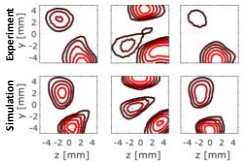
- **Complex bone geometry**
  - Beam attenuation and distortion
  - Attenuation of microbubble signals for treatment monitoring
- **Narrow spinal canal**
  - Standing wave formation



Thoracic spinal canal depth < 20mm

Numerical Modelling using Ray Acoustics

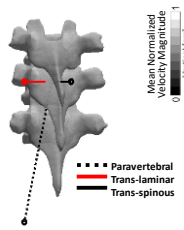


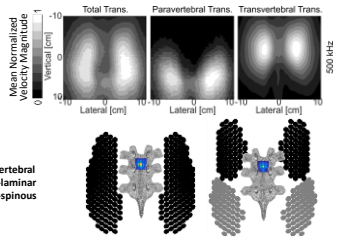


Normalized cross correlation:
87.2 ± 7.0 % (N=90)

Xu and O'Reilly, *Phys Med Biol* (2018)

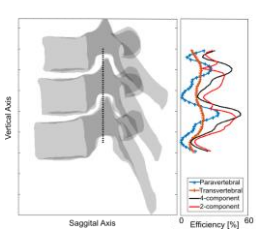
Spine-Specific Phased Array Design

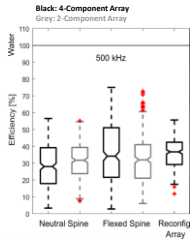




Xu and O'Reilly, *IEEE Trans Biomed Eng* (2019)

Array Performance

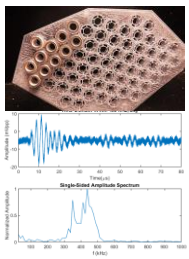




Xu and O'Reilly, *IEEE Trans Biomed Eng* (2019)

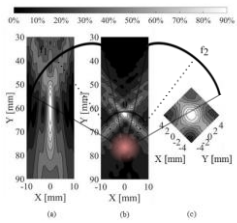
Array Fabrication

- 3D printed housing with 400 kHz PZT-4 tube elements
  - Centre frequency lowered to improve transvertebral transmission
  - Center space reserved for future integration of receiver array
- Backing yields ~ 40% bandwidth
  - Implementation of short bursts to mitigate standing waves



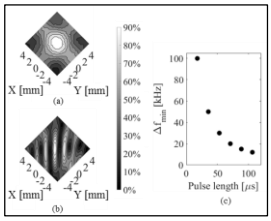
Standing Wave Mitigation

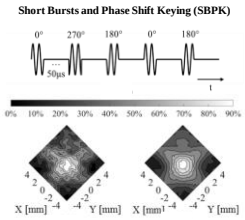
- Dual aperture, dual frequency FUS can reduce focal depth of field[1]
- ***Can we combine this with a pulse scheme that mitigates standing waves?[2]***



[1]Sun et al., *Appl Phys Lett* (2017); [2]Fletcher and O'Reilly, *IEEE TUFFC* (2018)

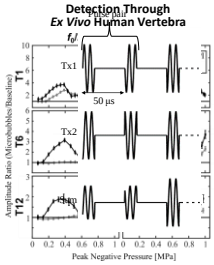
Standing Wave Mitigation

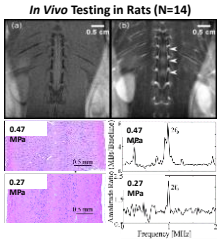




Fletcher and O'Reilly, *IEEE TUFFC* (2018)

Bubble Detection and BSCB Opening with SBPK





Fletcher et al, *In Revision at IEEE Trans Biomed Eng*

Summary

- *In vivo* results demonstrate potential of FUS+MBs in the spinal cord
- A clinical scale device has been designed to capitalize on optimal transmission pathways
- Short burst, phase keyed pulse trains mitigate standing waves in the human spinal canal
  - In vivo studies demonstrate safe opening can be achieved
- **Future work includes:**
  - Fabrication and testing of the phased array
  - Implementation of Short Burst Phased Keying with real-time feedback control
  - Cavitation mapping using receiver arrays

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