MR GUIDED FOCUSED ULTRASOUND BLOOD BARRIER DISRUPTION FOR TARGETED DRUG DELIVERY

Enabling Novel Treatments for Nervous System Disorders by Improving Methods for Traversing the Blood-Brain Barrier
National Academies of Sciences Engineering and Medicine
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Alexandra Golby, MD
Nathan McDannold, PhD
Factors regulating BBB permeability, include:

- Modulation of membrane transporters & transcytotic vesicles
- Modulation of transcellular permeability

*Drug Discovery Today* Volume 12, Numbers 1/2 January 2007 p54-61
Barriers to drug delivery in brain tumors

• Tumors recruit blood vessels from surrounding tissue.
• Brain metastases are less permeable than those in other organs.
• Metastatic “seeds” will be protected by the BBB (BTB).

Glioma Challenges

• Infiltrate along white matter tracts, blood vessels
• Can be protected by BBB
• Extensive – after treatment recurrence occurs within several cm of margin

~90% of first recurrence after RT/TMZ was within 3cm of primary site (M. Chamberlain, J. Neuroonconology 2011)

Perhaps whole brain delivery is not necessary?

# APPROACHES TO OVERCOMING BBB

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct injection, convection-enhanced delivery, implantable devices</td>
<td>High local drug concentrations can be achieved; systemic administration avoided.</td>
<td>Invasive; side effects; challenging to control; not readily repeatable.</td>
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<tr>
<td>Intrathecal, intraventricular injection</td>
<td>Effectively delivers drugs to subarachnoid space, brain surface.</td>
<td>Little drug penetration beyond brain surface; invasive.</td>
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<tr>
<td>Trans-nasal delivery</td>
<td>Noninvasive; easy to administer; repeatable.</td>
<td>Small volume of drug delivered; interindividual variability.</td>
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<tr>
<td>BBB disruption via arterial injection of osmotic solution or other agents</td>
<td>Effectively delivers drugs to large brain regions; large clinical experience.</td>
<td>Invasive; requires general anesthesia; side effects; not readily repeatable.</td>
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<tr>
<td>Modification of drugs to cross barrier through endogenous transport mechanisms</td>
<td>Easily administered; delivered to whole brain.</td>
<td>Requires systemic administration; expensive; each drug requires new development; clinical data lacking.</td>
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<tr>
<td>BBB disruption via FUS and microbubbles</td>
<td>Noninvasive; readily repeatable; can target drug delivery to desired volumes; can control “magnitude” of disruption; can be combined with drug-loaded microbubbles or magnetic particles for additional targeting.</td>
<td>Requires systemic administration; currently technically challenging; large volume/whole brain disruption unproven; no clinical data.</td>
</tr>
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Focused ultrasound

Vibration → Energy absorption

Thermal Effects:
- Thermal ablation
- Enhance radiation, chemotherapy
- Heat-activated drugs, genes

Non-thermal:
- Enhance drug delivery
- Mechanical ablation
- Vessel occlusion
- Neuromodulation

Tissue
Water
• Occurs due to mechanically-induced changes and/or stimulation to vasculature
• Caused by microbubble/US interaction
• Not due to heating, inertial cavitation
• Exact mechanism(s) not known
BBB disruption with FUS

- Low-power (<1 MPa), pulsed exposures (~1% duty cycle)
- Combined with ultrasound contrast agent (Optison, Definity, Sonovue)
- Targeted
- Temporary (~4-6 hours)
- Localized, non-invasive

Microbubble-enhanced FUS appears to modulate both physical and functional BBB components

- Increase in number transcytotic vesicles
- Reduction in drug efflux (PgP)
- Increase transcellular permeability through widened tight junctions

Radiology 2001

Noninvasive MR Imaging-guided Focal Opening of the Blood-Brain Barrier in Rabbits

Trypan blue in rat
BBBD “magnitude”

- Amount of drug delivered
- Size of drug delivered
- Penetration depth
- Depends on acoustic parameters
  Particularly Pressure, Frequency, Burst length, Duration, Bubble Dose

BBBD Restoration

- Barrier “open” for several hours
- Closes exponentially
- Closing time depends on molecule size
- Low-level opening detected at longer time in some situations
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Dynamic study of blood–brain barrier closure after its disruption using ultrasound: a quantitative analysis

Benjamin Marty¹, Benoît Larmet¹,², Maxime Van Landeghem³, Caroline Rohic⁴, Philippe Robert⁵, Marc Port⁶, Denis Le Bihan⁷, Mathieu Pernot⁷, Mickaël Tanter⁶, Franck Lethimonnier⁵ and Sébastien Moraux⁴

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*Image showing a graph with data points labeled Dotarem, Magnevist (Park et al. J. Contr. Release)*

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Therapeutic agents delivered via FUS-BBBD

- **Chemotherapy**
  - BCNU, methotrexate, doxorubicin, liposomal doxorubicin

- **Antibodies**
  - Herceptin, BAM10 (Alzheimer’s)

- **Nanoparticles**
  - Magnetic nanoparticles
  - Gold nanoparticles

- **Neuroprotective agent**
  - BDNF, GDNF (Parkinson’s, stroke, traumatic brain injury)

- **Viruses**
  - siRNA for Htt (Huntington’s disease)

- **Cells**
  - Neural precursor cells (stem cells)
  - Natural killer cells

- **Nothing!**
  - BBBD *alone* might help Alzheimer’s disease, induce neurogenesis
Enhanced chemotherapy delivery to brain tumors

One hour: DOX delivered to normal brain after FUS

Some drug delivered to control tumor, but more with FUS

24 hours: DOX cleared from the control tumor

No apparent clearance from brain or tumor that received FUS

Results suggest FUS enhances drug retention

JY Park et al; J Controlled Release 2016
Rat glioma model (9L)

3 weekly treatments with liposomal doxorubicin

Improved Survival

- 3 weekly treatments FUS+liposomal DOX improved survival by 100% compared to control
- 7/8 animals in FUS+DOX group showed a strong treatment effect
  - 6 animals had no tumor or only a tiny cluster of cells in histology; 1 was shrinking

Adverse events

- Consistent with large tumor burden, DOX effects
  - skin toxicity, hemorrhagic tumor in one animal, poor health

M. Aryal et al. J. Controlled Release 2013
BBB disruption with ExAblate Neuro in macaques

Point-by point sonication

Volumetric sonication

~1 cm
HISTOLOGIC CHANGES

Cingulate Cortex @ 2h
BBBD 9x over 7 months

Erythrocyte extravasation (petechia)

McDannold et al. Cancer Res. 2013
FUS delivery in AD models

- rabbit anti-Aβ antibodies injected immediately before FUS-MB
- signal is significantly stronger in the treated (C) versus untreated (B) hippocamp

TECHNOLOGY

Non-invasive therapy platform that combines two proven technologies - High intensity focused ultrasound and Magnetic Resonance Imaging.

The high intensity focused ultrasound (FUS) delivers energy to a focal point in the target tissue.

The MRI enables:

1. Identification and targeting
2. Monitoring the treatment progress in real time, using MR imaging
CLINICAL BRAIN DEVICE

1024 element spherical transducer

Active cooling

Based on patient bone characteristics, beams are refocused to a common focal point

Phased array: beams individually corrected

At the focal point temperature increase creates thermal ablation/tissue changes

Interfaces with GE MRI scanners (1.5T and 3T scanners)

220KHz allows whole brain treatment
## Clinical Neuro Treatments to Date

### Essential Tremor
- ~ 650 treatments
- Unilateral thalamotomy (VIM)
- Multiple prospective studies – US, EU, Japan
- Multi-center pivotal trial – NEJM
- > 350 clinical treatments to date

### Tremor Dominant PD
- ~ 100 treatments
- Unilateral thalamotomy (VIM)
- Single site, randomized pilot trial
- Ongoing clinical use

### BBB Disruption
- 3 treatments
- Using FUS and microbubbles
- Single site feasibility study
- Deliver chemotherapy & other therapeutics in the brain

### Parkinson's Disease
- ~ 30 treatments
- Unilateral pallidotomy pilot
- Multi-center pivotal trial in planning
- Unilateral subthalamotomy pilot

### Neuropathic Pain
- ~ 70 treatments
- Central lateral thalamotomy (bilateral).
- Single site prospective study published
- Modest clinical use: EU

### OCD
- ~ 15 treatments
- Bilateral capsulotomy
- Single center pilot trial published

### Total Treatments Performed
- > 1000 treatments
- Various neurological disorders treated in commercial (750) and clinical research (~300)

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Slide courtesy InSightec
Gadolinium uptake enhanced within a 3x3 array of targets pre-treated with MRgFUS to open the BBB - demonstrating the proof of concept and the spatial resolution of the technique.

Todd Mainprize MD
Sunnybrook Health Science Center
Toronto, Ontario

CTV News    November 8, 2015
CHALLENGES

- Significant infrastructure requirements
- Time consuming treatment
- Presently requires head fixation
- Hair must be shaved
- Limits on volumetric coverage
- Unknown safety profile, especially for repeated treatments
FUTURE DIRECTIONS FUS ENHANCED DRUG DELIVERY

- MRg FUS with microbubbles, carriers
- Different locations
- Volume of delivery
- Assess safety
- Drug concentration
  - Preliminary results in brain tumor patients
  - Imaging of drug delivery in humans
- Agents to be delivered
- FDA challenges
  - Device + drug + imaging agent
THANK YOU!

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