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

September 8, 2017

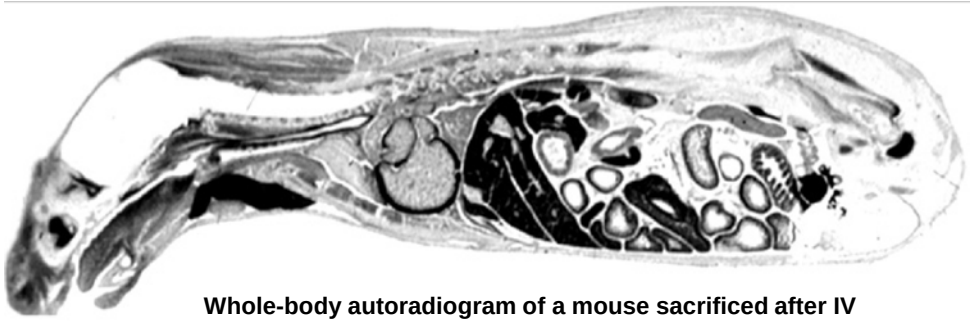
Alexandra Golby, MD

Nathan McDannold, PhD

Blood-brain barrier

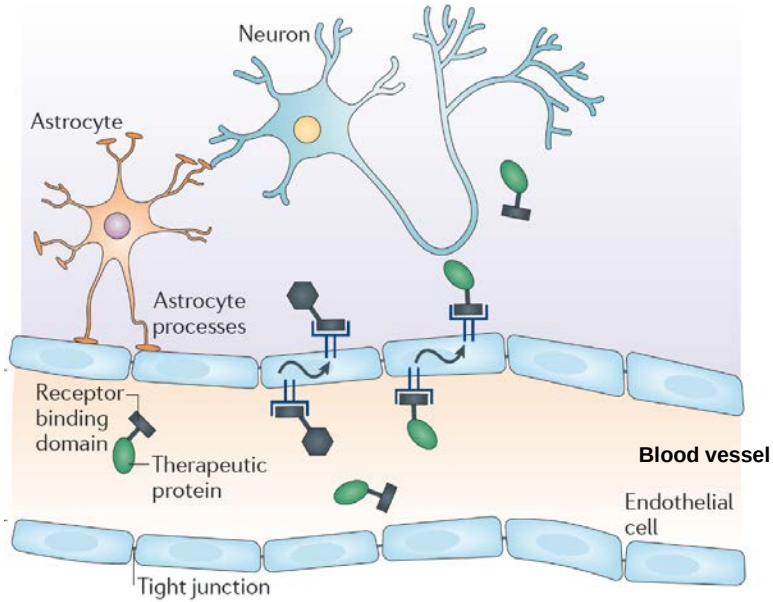
>98% of small molecule drugs do not cross the BBB

~100% of large molecule drugs do not cross the BBB



Whole-body autoradiogram of a mouse sacrificed after IV injection of a small molecule (histamine, 111 Da)

William M. Pardridge. “Blood–brain barrier delivery”
Drug Discovery Today Volume 12, Numbers 1/2 January 2007 p54-61

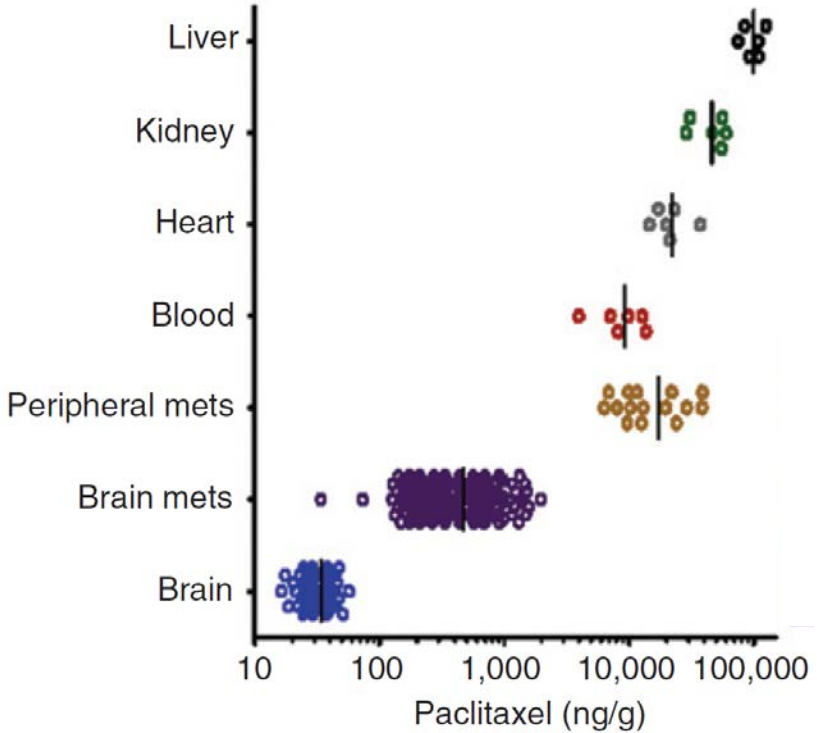


Factors regulating BBB permeability, include:

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

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).



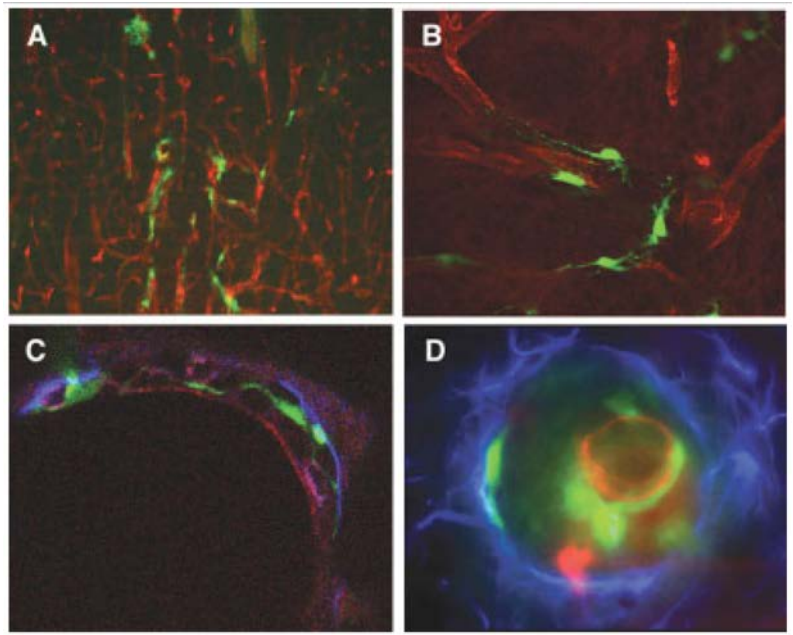
PR Lockman et al.”Heterogeneous Blood–Tumor Barrier Permeability Determines Drug Efficacy in Experimental Brain Metastases of Breast Cancer” Clin Cancer Res; 16(23) December 1, 2010

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?



C6-eGFP glioma cells migrate between endothelial cells and astrocyte end feet.

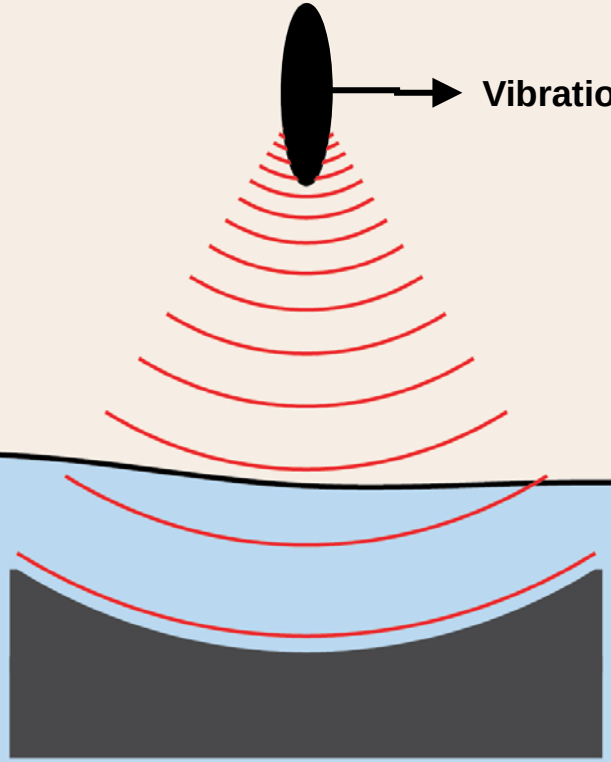
Red: Blood vessels
Green: Glioma cells
Blue: Astrocyte endfeet

A Farin et al. “Transplanted Glioma Cells Migrate and Proliferate on Host Brain Vasculature: A Dynamic Analysis” GLIA 53:799–808 (2006)

APPROACHES TO OVERCOMING BBB

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

Focused ultrasound



Vibration

Energy absorption

Thermal Effects:

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

Non-thermal:

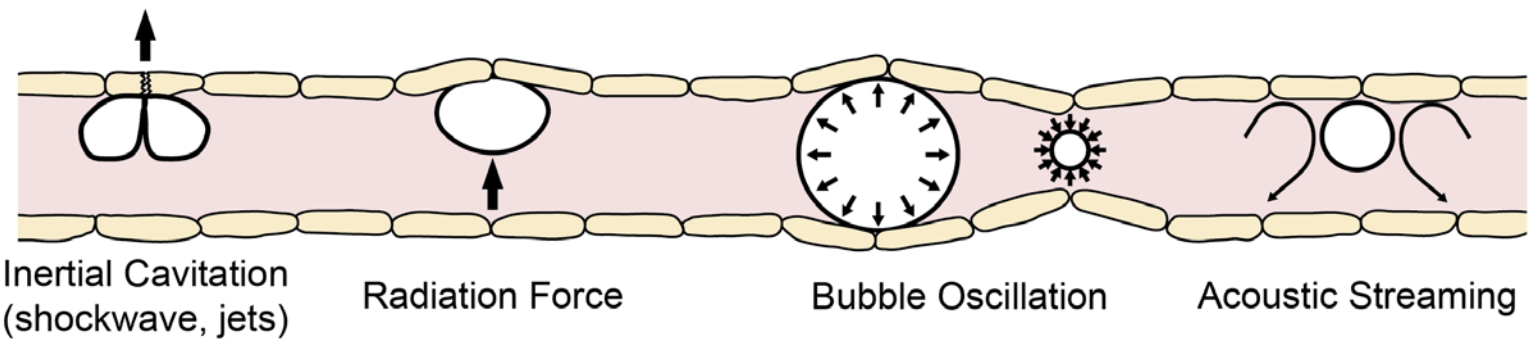
- Enhance drug delivery
- Mechanical ablation
- Vessel occlusion
- Neuromodulation

Tissue

Water

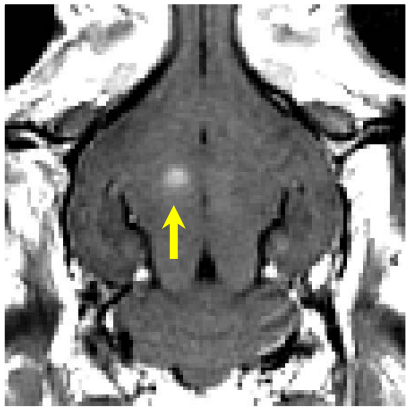
BBB disruption with FUS

- **Occurs due to mechanically-induced changes and/or stimulation to vasculature**
- **Caused by microbubble/US interaction**
- **<u>Not</u> 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



Rabbit MRI

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

Trypan blue in rat

Kullervo Hynynen, PhD
Nathan McDannold, BS
Natalia Vykhodtseva, PhD
Ferenc A. Jolesz, MD

Index terms:
Blood-brain barrier

Noninvasive MR Imaging–guided Focal Opening of the Blood-Brain Barrier in Rabbits[1]

Radiology 2001

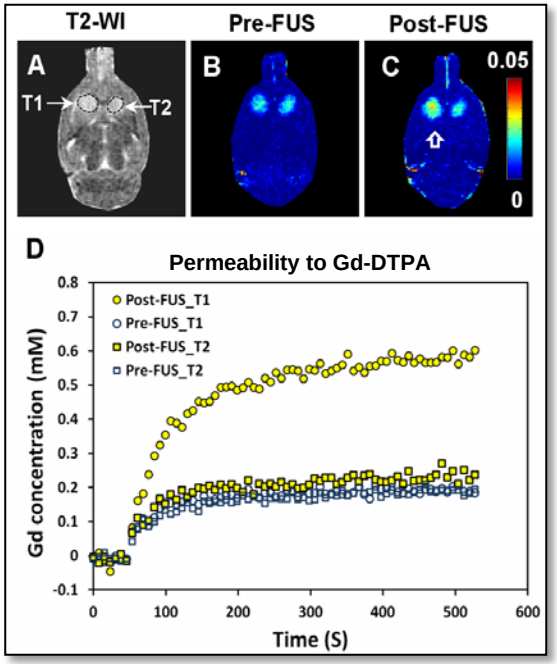
BBBD “magnitude”

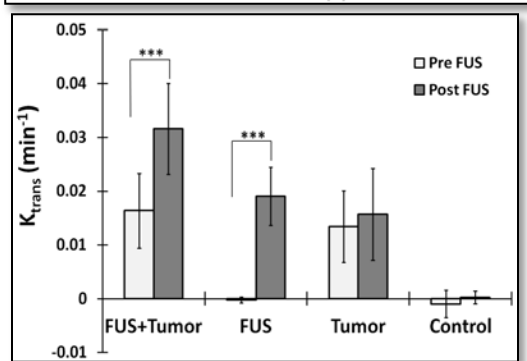
- Amount of drug delivered
- Size of drug delivered
- Penetration depth
- Depends on acoustic parameters

  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





JY Park et. al; J Controlled Release 2016

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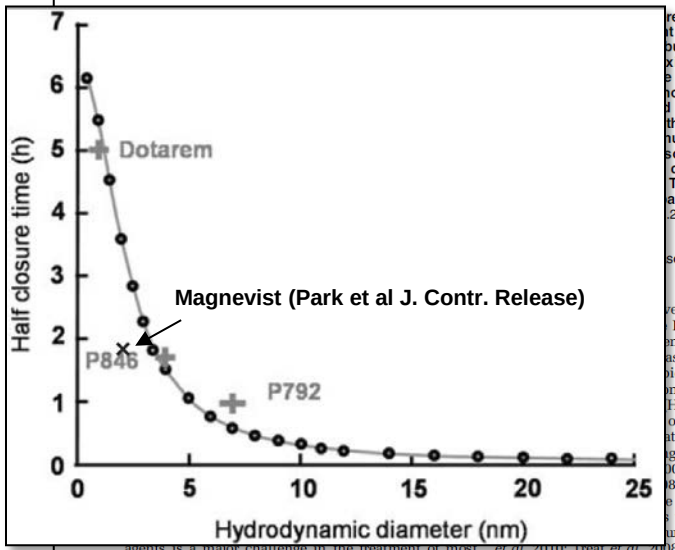
Journal of Cerebral Blood Flow & Metabolism (2012) 32, 1948–1958

www.jcbfm.com

Dynamic study of blood–brain barrier closure after its disruption using ultrasound: a quantitative analysis

Benjamin Marty[1], Benoit Larrat[1,2], Maxime Van Landeghem[3], Caroline Robic[4], Philippe Robert[4], Marc Port[4], Denis Le Bihan[1], Mathieu Pernot[2], Mickael Tanter[2], Franck Lethimonnier[1] and Sébastien Mériaux[1]

[1]*NeuroSpin, FBM, Commissariat à l'Énergie Atomique, Gif-sur-Yvette, France;* [2]*Institut Langevin, ESPCI ParisTech, CNRS UMR 7587, INSERM U979, Paris, France;* [3]*PPMD, ESPCI ParisTech, CNRS UMR 7615, Paris, France;* [4]*Guerbet Research Division, Roissy-Charles de Gaulle, France*



…red by the blood–brain …t disruption of the BBB …ubbles. However, BBB …ximum gap that may be …e BBB. Here, we studied …odel. First, MR contrast …d to estimate the largest …the duration of the BBB …nutes to 24 hours). A T_1 …sound (US) focal point. … curve was obtained to … These findings and the …articles to the brain.
…2012.100; published online

…sound

…ve finding an efficient mode … BBB.
…monstrated that the use of …asound combined with a …id- (or polymer-) shelled …ninvasive, local and transi- …Hynynen *et al*, 2001). Many …out to (1) establish optimal …t permit adequate tissular …g tissue damage (Choi *et al*, …005; O'Reilly *et al*, 2010, …8), (2) quantify permeability …e (Vlachos *et al*, 2010, 2011), … to treatments of particular …umors (Chen *et al*, 2010; Liu *et al*, 2010; Treat *et al*, 2008) and Alzheimer's disease (Jordao *et al*, 2010; Raymond *et al*, 2008). Most of these studies used magnetic resonance contrast agents (MR-CA) for monitoring the processes.

Despite a rapidly growing number of studies, the mechanism of ultrasound-induced BBB opening is understood only poorly. In particular, the maximum space that can be safely generated (ensuring reversi- bility) between endothelial cells, and the duration for

agents is a major challenge in the treatment of most brain disorders. Strategies to design specific drugs

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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

<u>One hour</u>: DOX delivered to normal brain after FUS

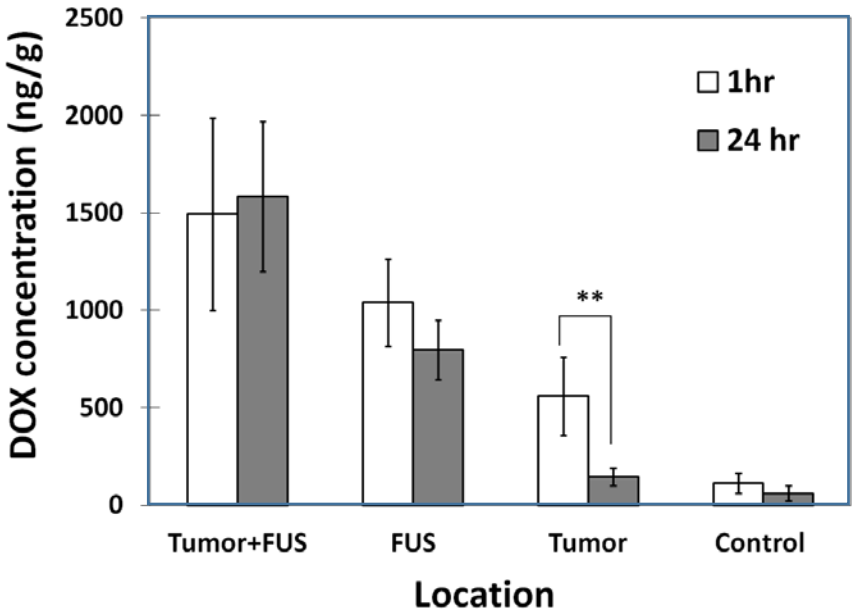
Some drug delivered to control tumor, but more with FUS

<u>24 hours</u>: DOX cleared from the control tumor

No apparent clearance from brain or tumor that received FUS

Results suggest FUS enhances drug retention

Delivery of free doxorubicin



JY Park et. al; J Controlled Release 2016

Enhanced Doxil delivery in a glioma model

Rat glioma model (9L)

3 weekly treatments with liposomal doxorubicin

Improved Survival

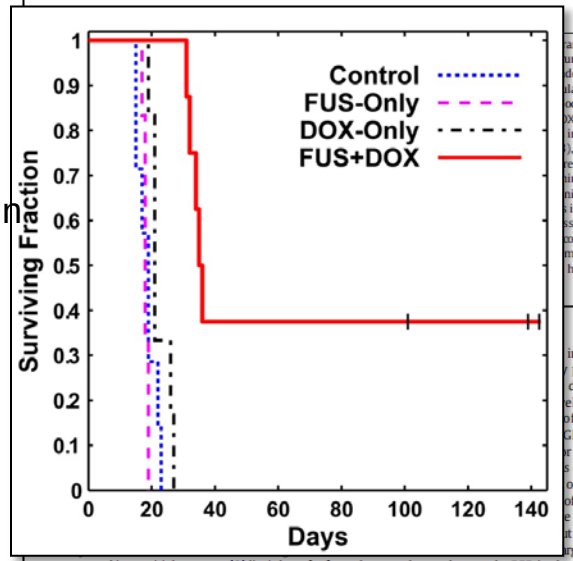
- **3 weekly treatments FUS+liposomal DOX improved survival by 100% compared to control**
- **7/8 animals in FUS+DOX group showed a strong treatment effect**

  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)



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Multiple treatments with liposomal doxorubicin and ultrasound-induced disruption of blood–tumor and blood–brain barriers improve outcomes in a rat glioma model☆

Muna Aryal [a,b,*], Natalia Vykhodtseva [b], Yong-Zhi Zhang [b], Juyoung Park [b], Nathan McDannold [b]

[a] Department of Physics, Boston College, Chestnut Hill, USA
[b] Department of Radiology, Brigham & Women's Hospital, Harvard Medical School, Boston, USA

creased interstitial pressure [3] limit how far from the vasculature the drugs can penetrate. Furthermore, efflux pumps, which are present at

☆ Conflict of interest: The last author holds two patents on the ultrasound technique evaluated in this work. The other authors have no conflicts of interest to report.

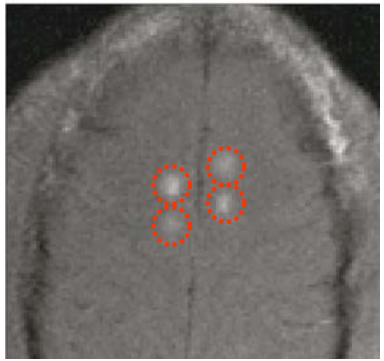
the BBB in the surrounding brain could enable the use of a wide range of anticancer agents for GBM and other brain tumors.

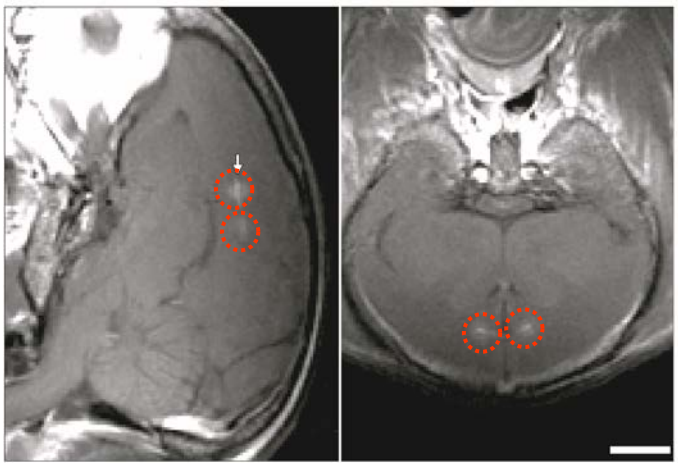
The use of focused ultrasound (FUS) combined with a circulating microbubble agent is an emerging technique to disrupt the BBB temporarily in a localized and non-invasive manner [10]. The microbubbles, which are constrained to the vasculature, interact strongly with even

M. Aryal et al. J. Controlled Release 2013

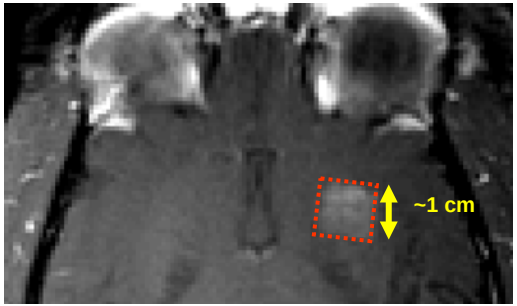
BBB disruption with ExAblate Neuro in macaques

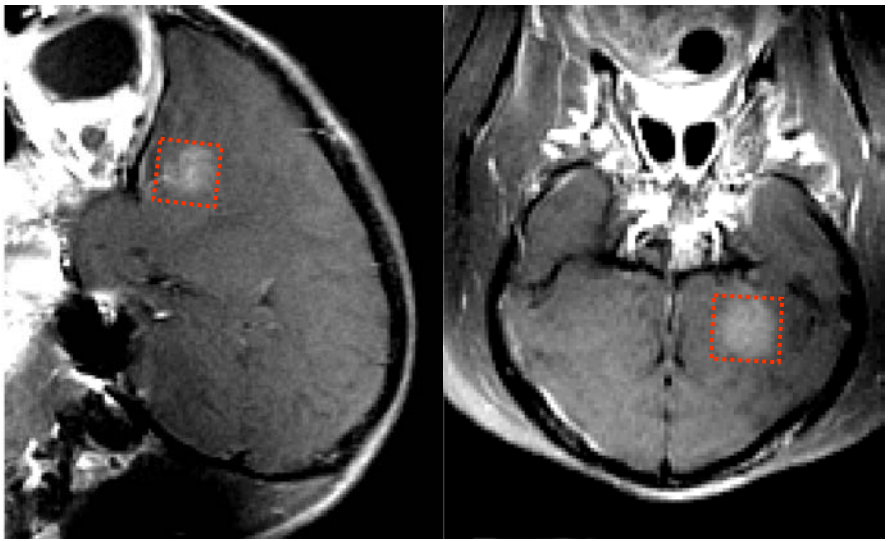
Point-by point sonication





Volumetric sonication

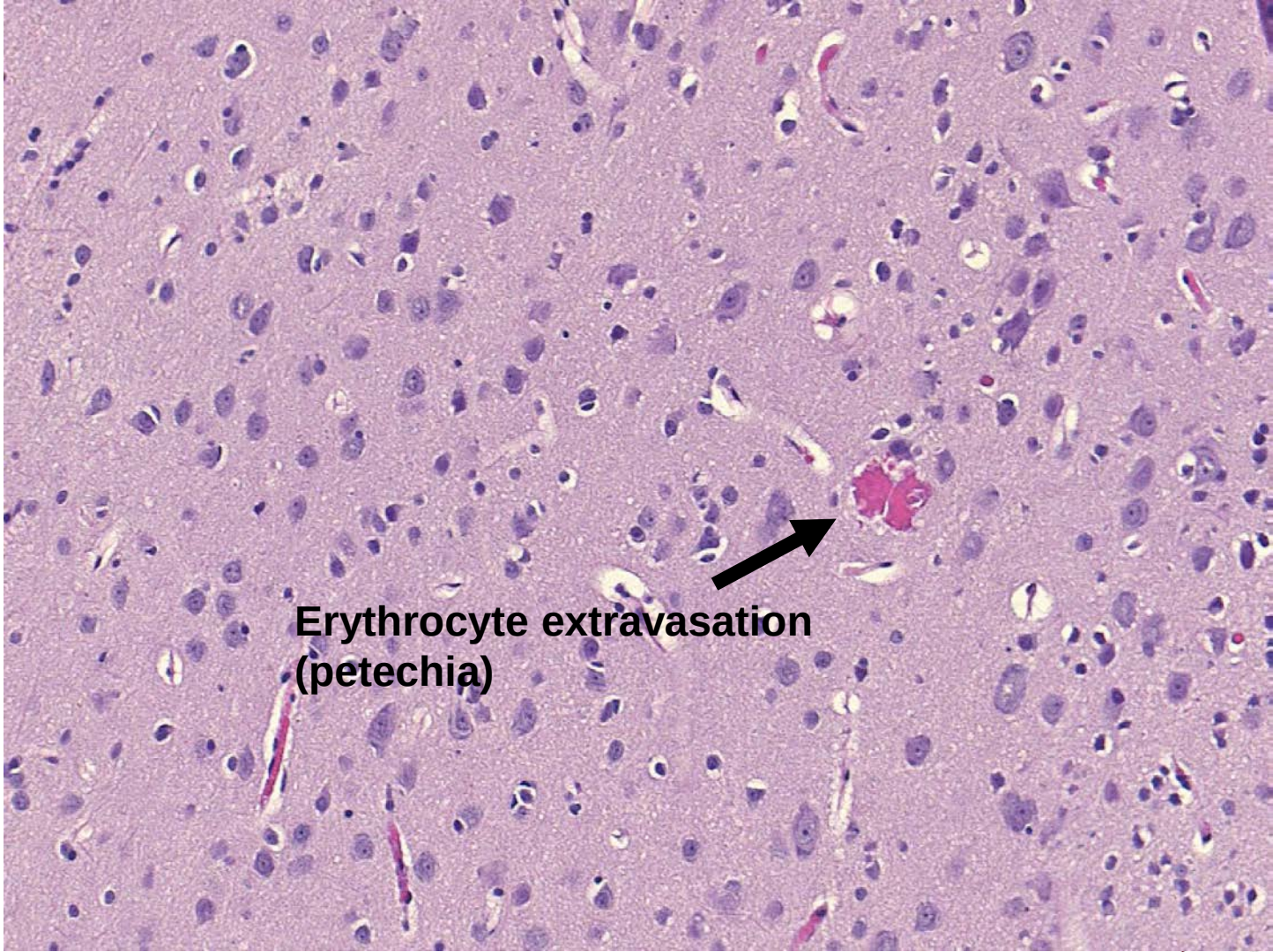




McDannold et al. *Cancer Res.* 2012

Nathan McDannold (njm@bwh.harvard.edu)

HISTOLOGIC CHANGES

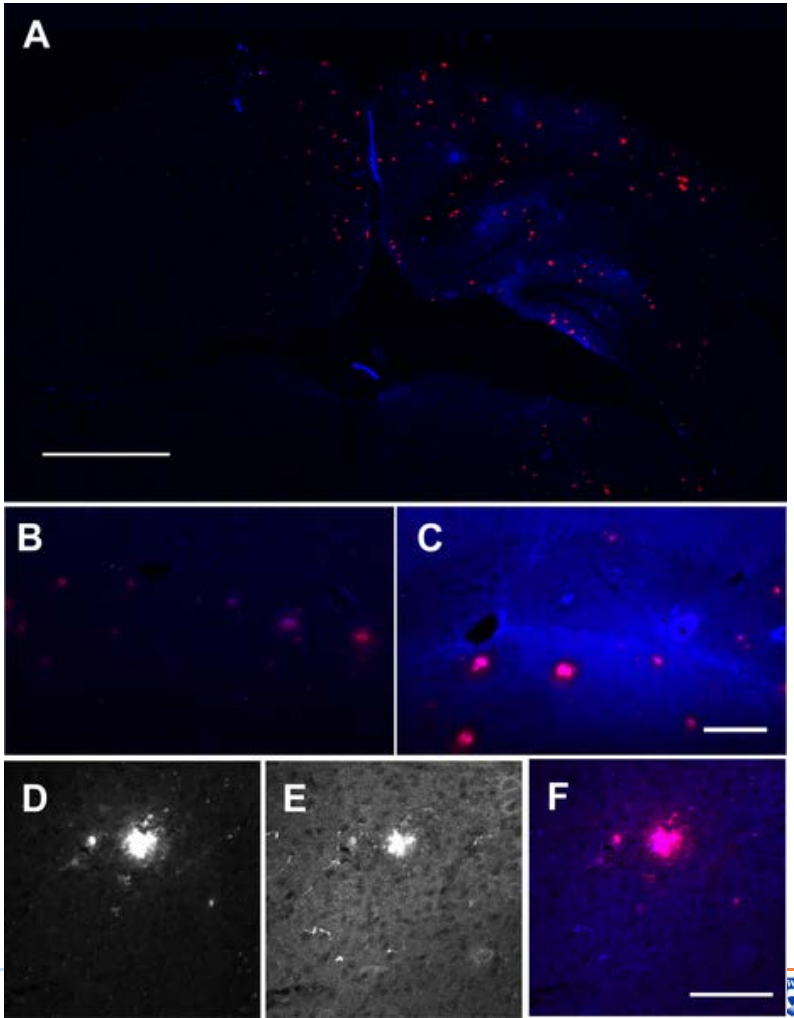


Cingulate Cortex @ 2h
BBBD 9x over 7 months

McDannold et al. Cancer Res. 2013

FUS delivery in AD models

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



Ultrasound Enhanced Delivery of Molecular Imaging and Therapeutic Agents in Alzheimer's Disease Mouse Models. Scott B. Raymond Lisa H. Treat Jonathan D. Dewey Nathan J. McDannold Kullervo Hynynen Brian J. Bacskai. PloS one. 2008 May 14;3(5):e2175.

Clinical MR Guided Focused Ultrasound

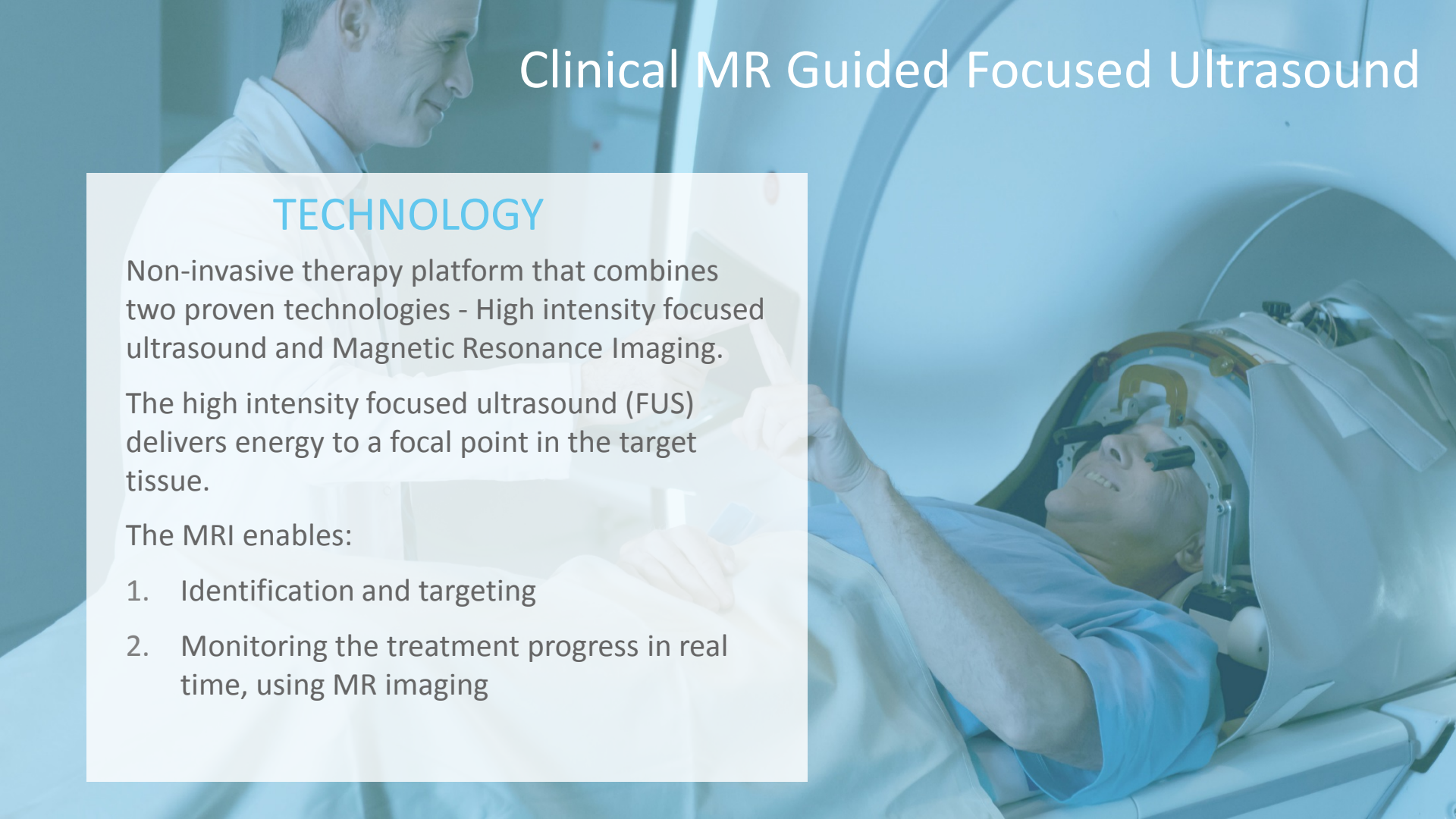
TECHNOLOGY

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

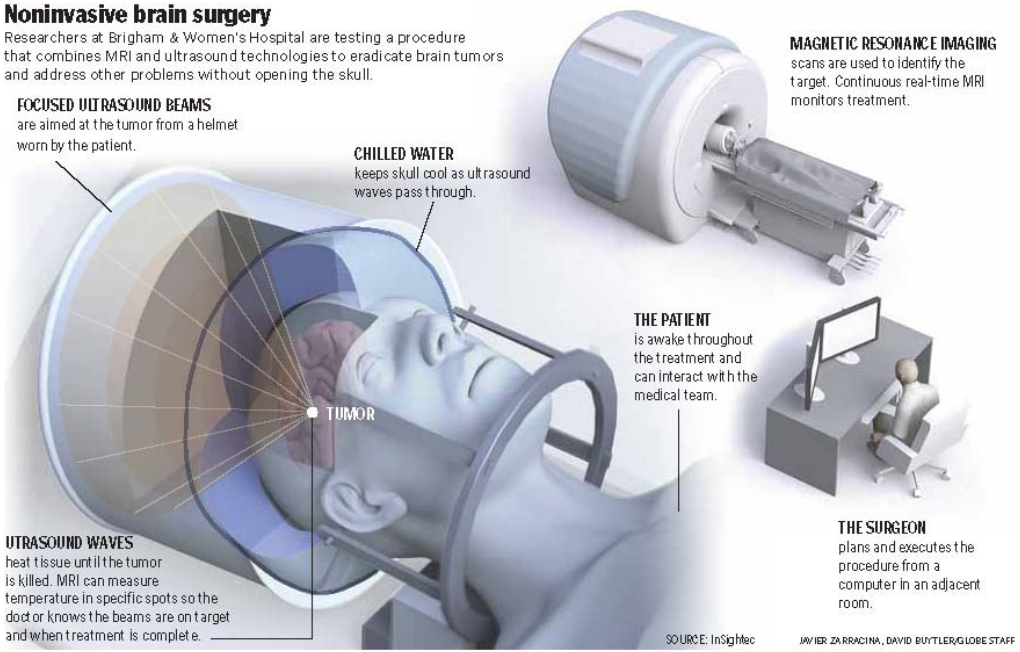
Phased array: beams individually corrected

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

TRANSCRANIAL MRI-GUIDED FOCUSED ULTRASOUND PHASE 1 IN HUMANS



Transcranial magnetic resonance imaging- guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. McDannold N, Clement GT, Black P, Jolesz F, Hynynen K.Neurosurgery. **2010**;66(2):323-32;

CLINICAL NEURO TREATMENTS TO DATE

TOTAL TREATMENTS PERFORMED > 1000 TREATMENTS

Various neurological disorders treated in commercial (750) and clinical research (~300)

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

Slide courtesy InSightec

FIRST HUMAN BBBD PROOF OF CONCEPT

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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Fiona Fennessy

Golby Lab
Prashin Unadkat
Walid Ibn Essayed
Daniel Orringer
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Lauren O'Donnell
Laura Rigolo
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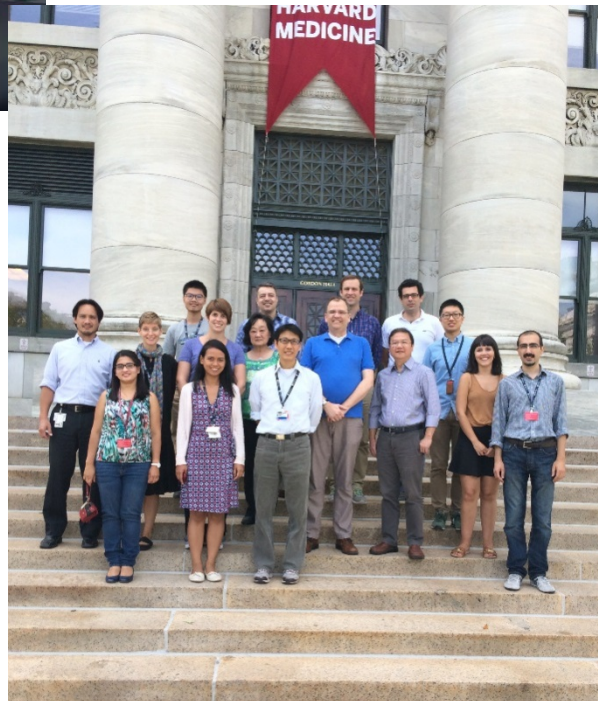
Zhenrui Chen



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