MRI-Targeted Drug and Gene Delivery to the CNS with Focused Ultrasound

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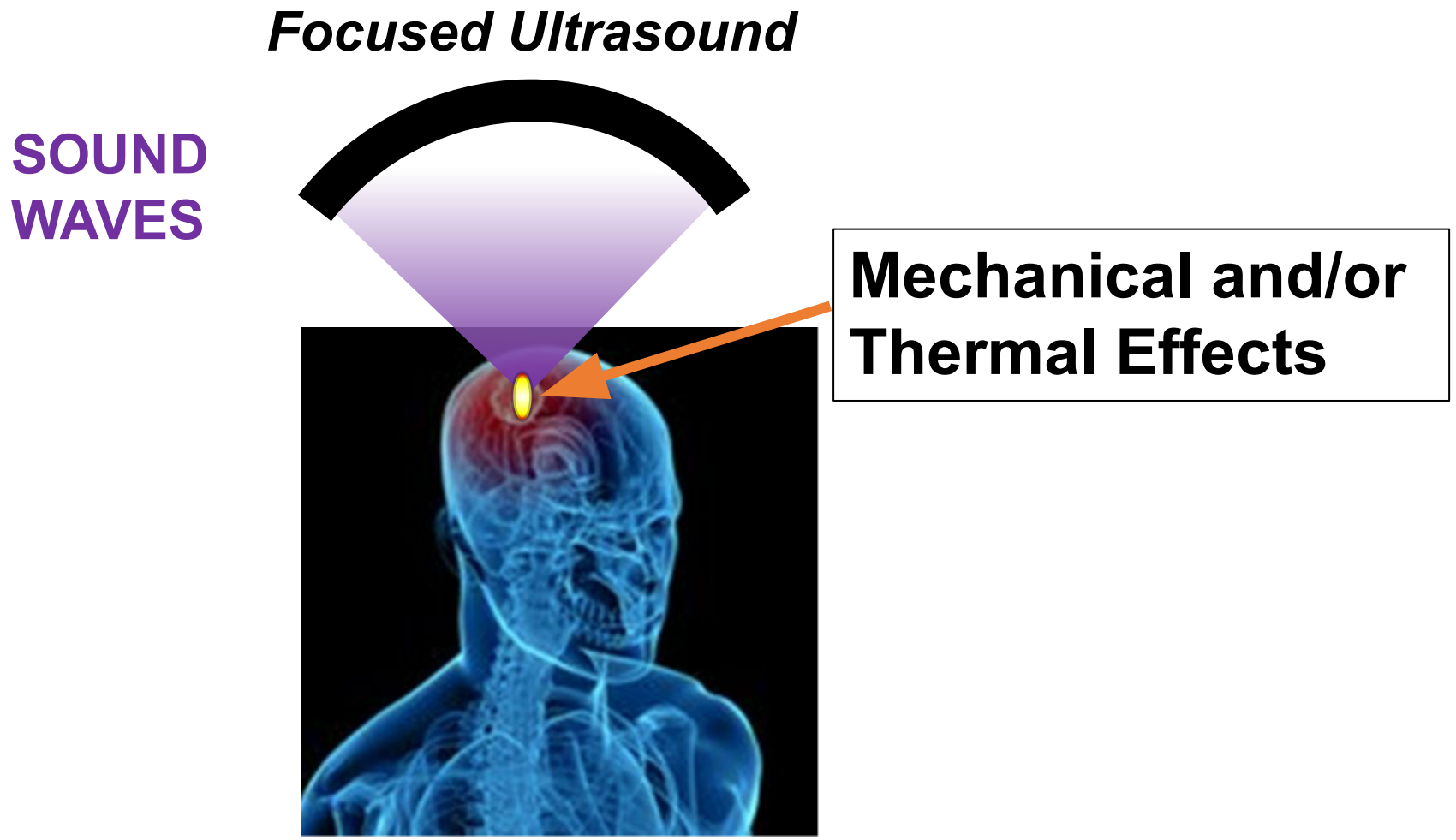
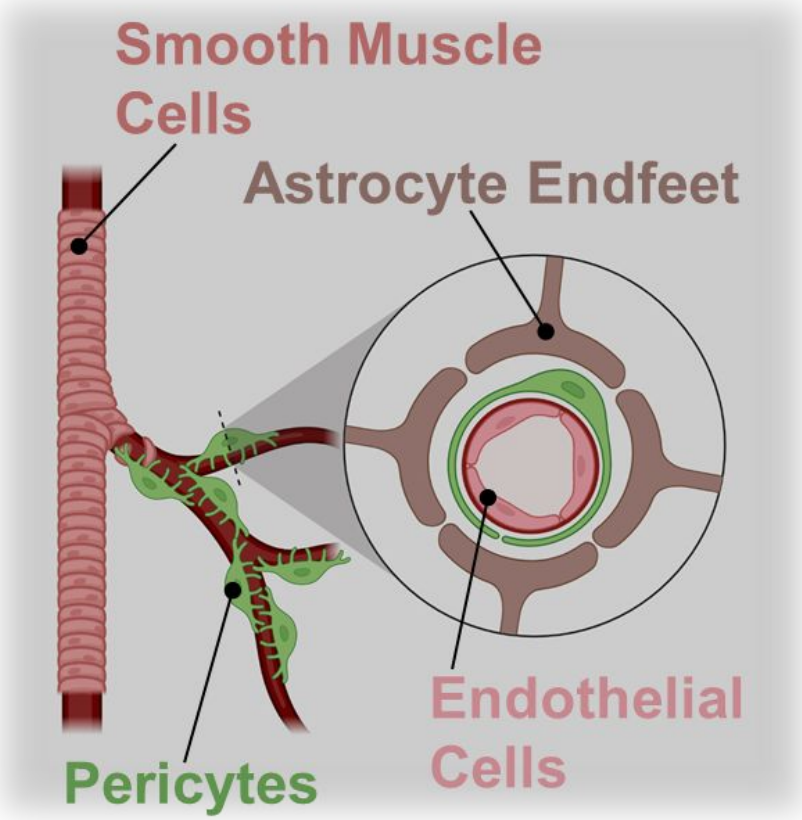
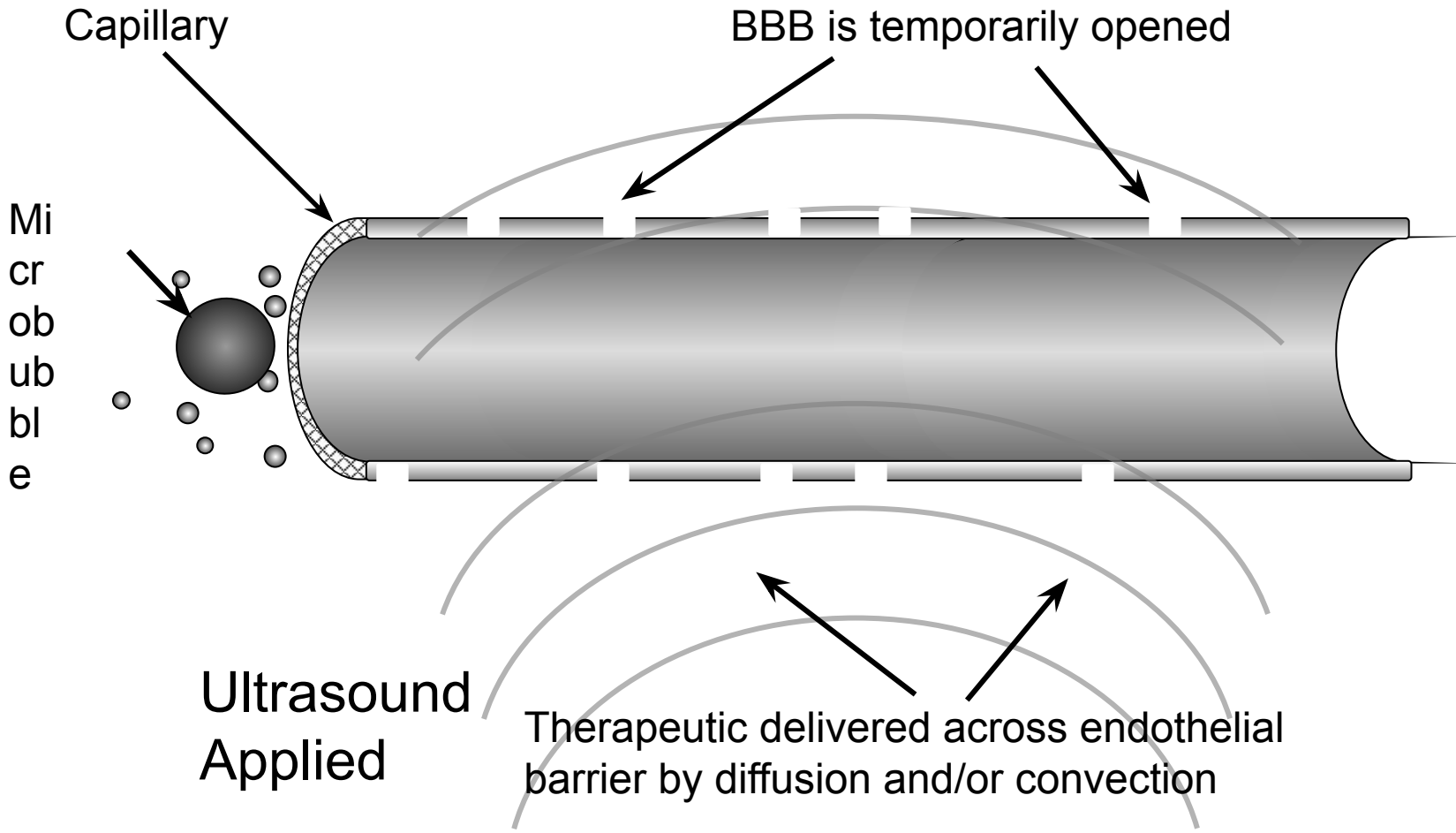
Focused Ultrasound (FUS): Ultrasonic Energy Concentrated into a Small Ellipsoidal Volume



Drug and Gene Delivery Across the Blood-Brain (BBB) & Blood-Tumor Barriers (BTB)





Timbie, Mead, Price *J Control Release* 219:61-75;2015

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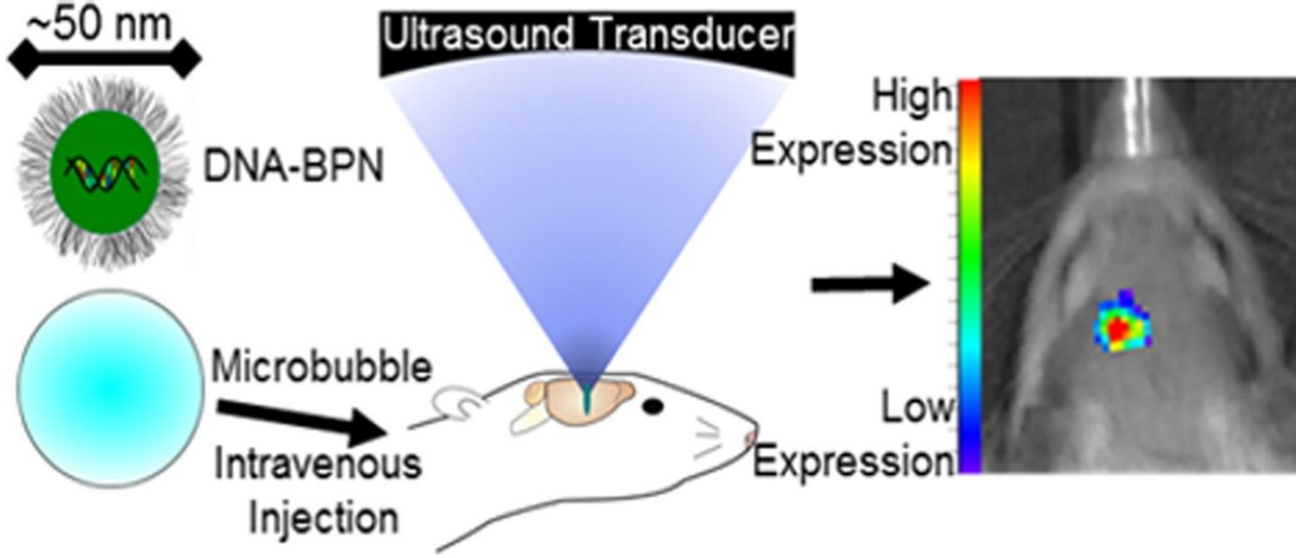
Specific Applications

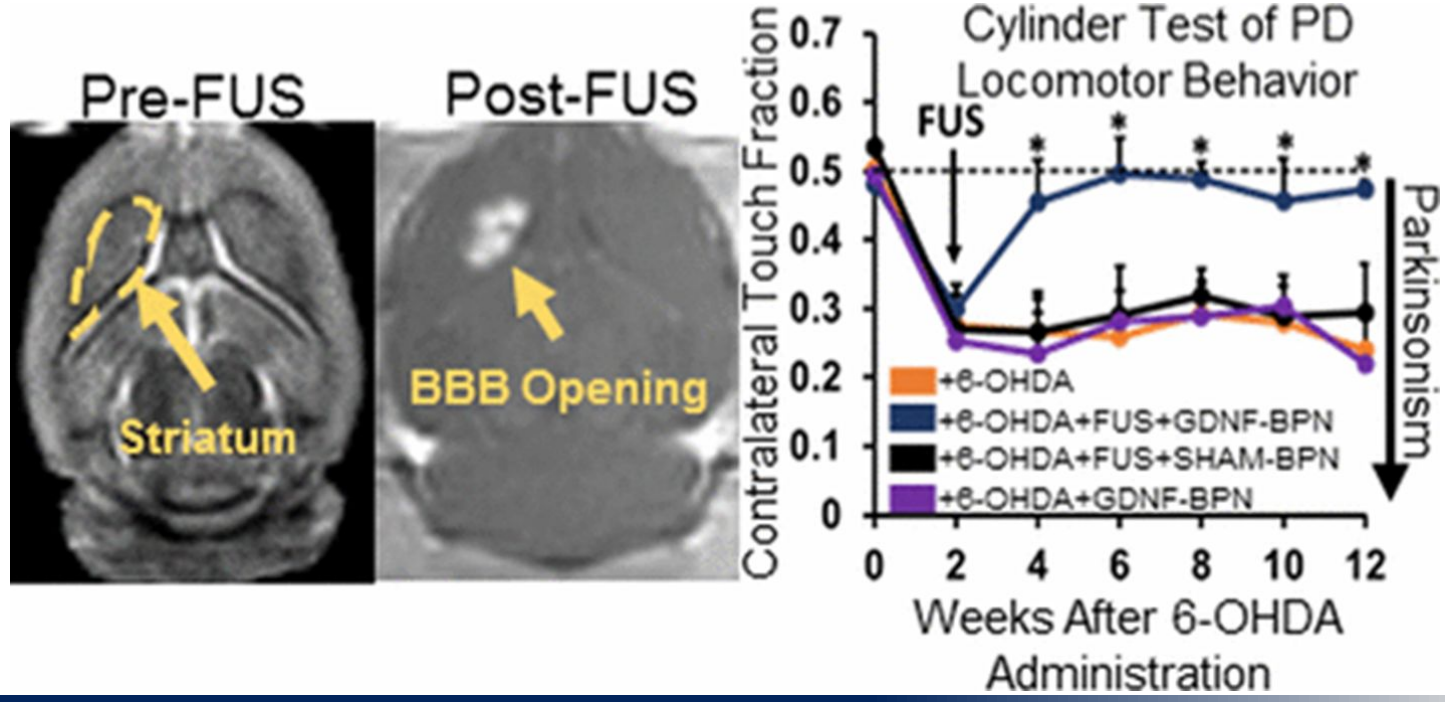
- Gene Delivery (“Toolkit” Overview)
- Immunotherapy Delivery to Brain Tumors
- Cerebral Cavernous Malformations

Non-Viral Nanoparticle Gene Delivery with FUS and MBs



MRI-Targeted Brain Transfection

Mead et al.
***J Control Release* 223:109-17;2016**



Neurotrophic Gene Delivery for PD

Mead et al.
***Nano Lett*. 17:3533-3542;2017**

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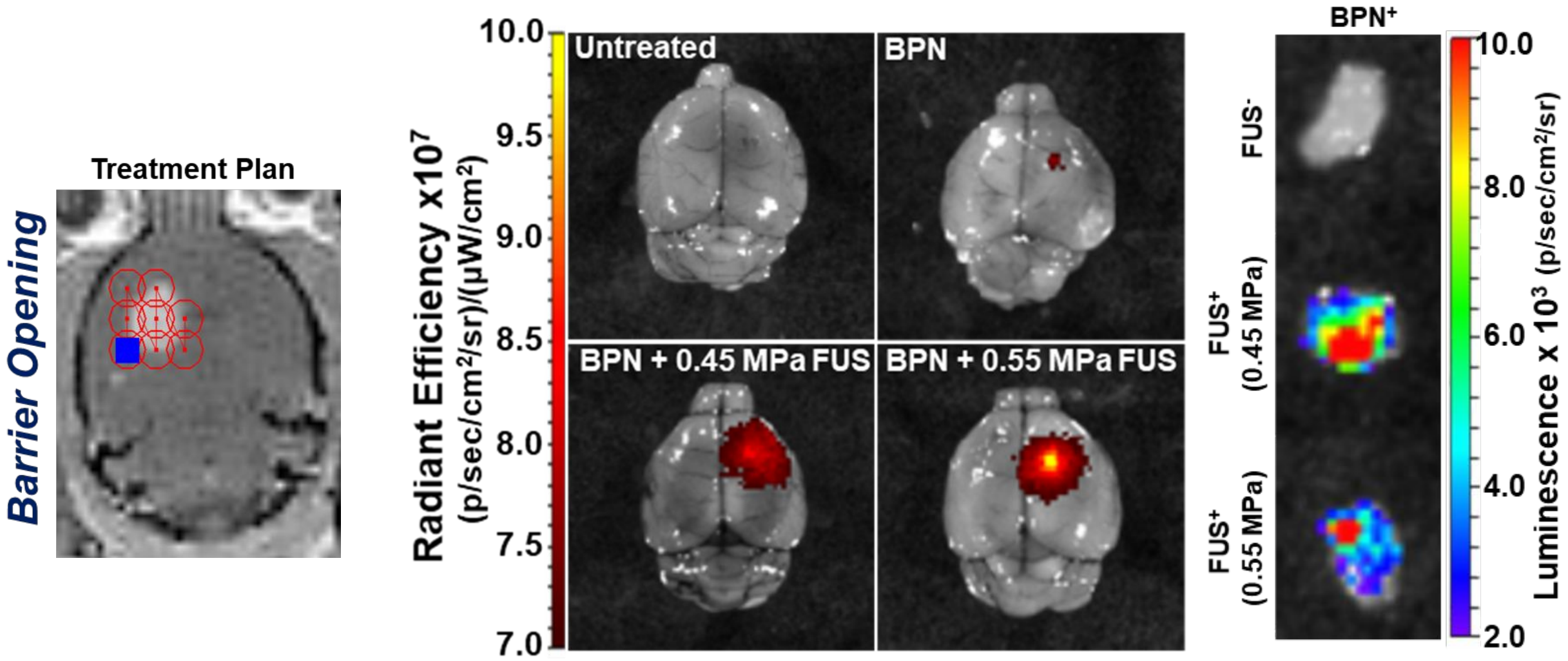
Nanoparticle (BPN) Delivery to Gliomas in Mice with MR Image-Guided Focused Ultrasound and Microbubbles (6h)



Curley et al. *Science Advances* DOI: 10.1126/sciadv.aay1344; 2020

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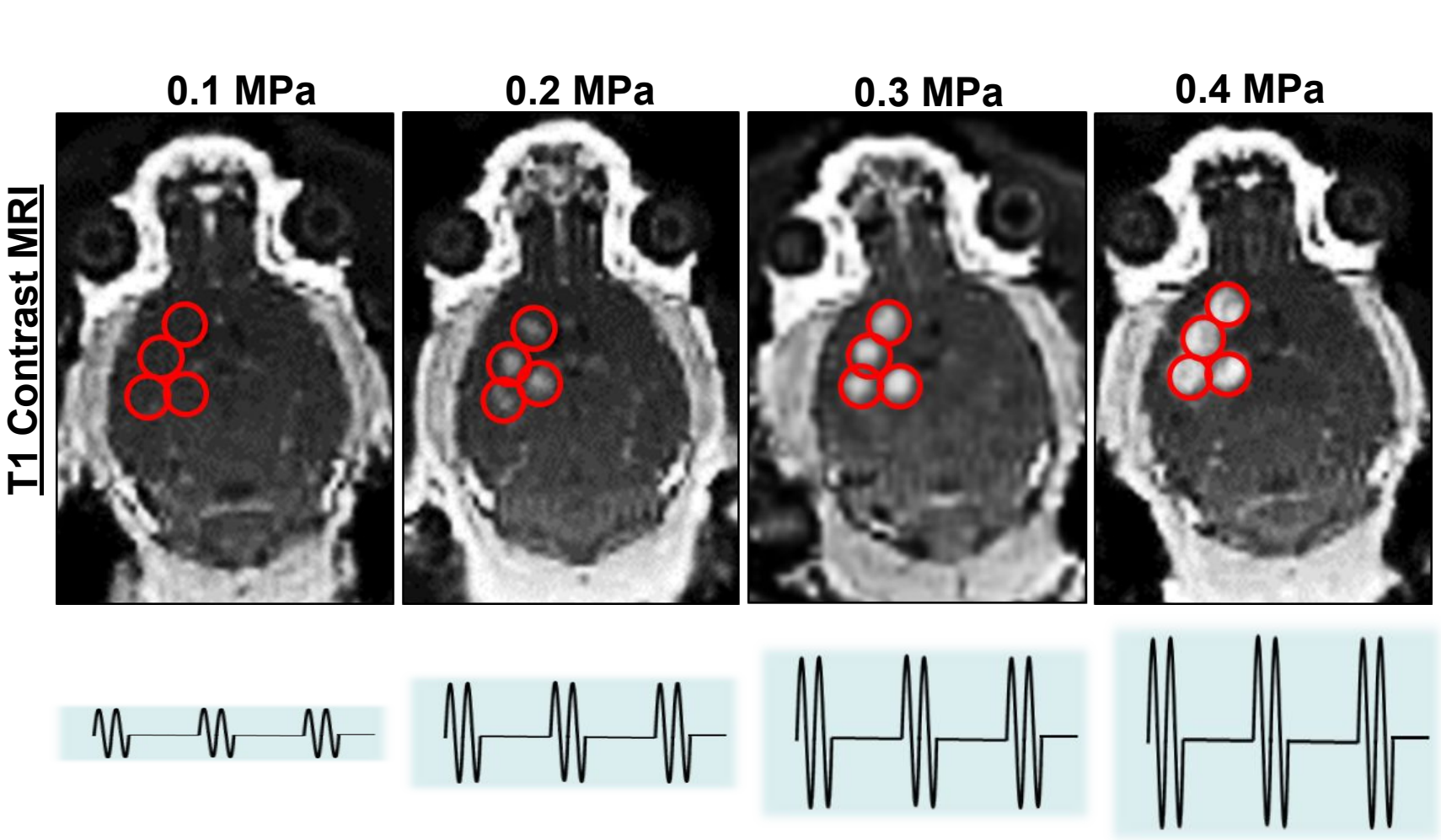
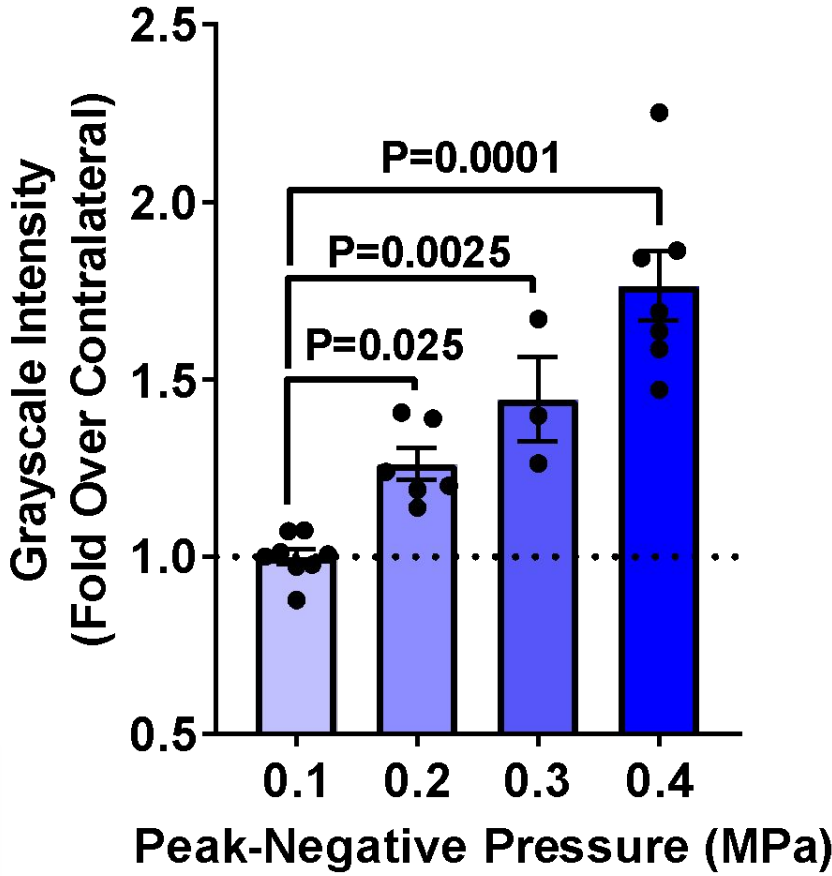
Relationships Between Focused Ultrasound Pressure and Transfected Cell Types





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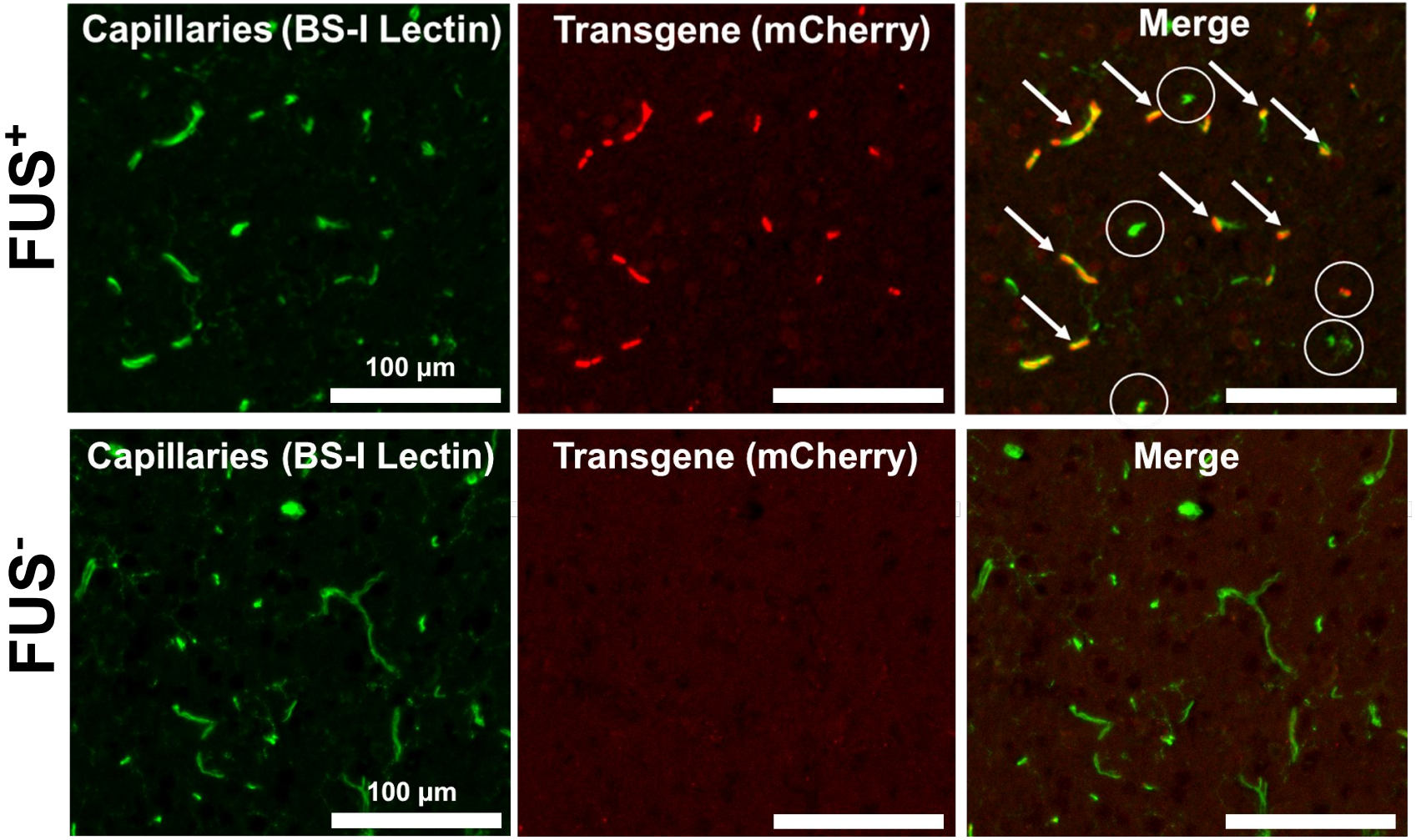
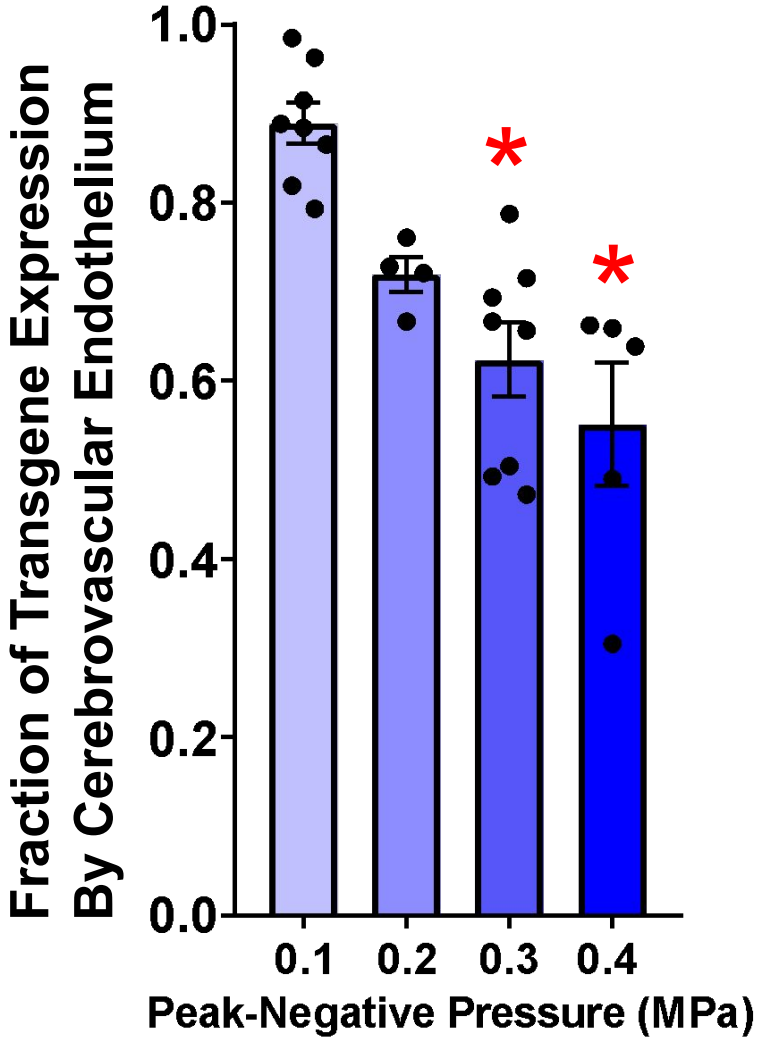
“Sonoselective” Endothelial Transfection At Low Pressures





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Presentation Outline

- Gene Delivery ("Toolkit" Overview)
- **Immunotherapy Delivery to Brain Tumors**
- Cerebral Cavernous Malformations

FUS-Mediated BTB Opening Alone Does Not Markedly Alter Immune Landscape

Immunomodulation of intracranial melanoma in response to blood-tumor barrier opening with focused ultrasound

Colleen T. Curley[1], Aaron D. Stevens[2], Alexander S. Mathew[1], Katarzyna Stasiak[3], William J. Garrison[1], G. Wilson Miller[1,4], Natasha D. Sheybani[1]✉, Victor H. Engelhard[3], Timothy N.J. Bullock[2]✉, and Richard J. Price[1,4]✉

Theranostics

2020; 10(19): 8821-8833. doi: 10.7150/thno.47983

Profiling of the immune landscape in murine glioblastoma following blood brain/tumor barrier disruption with MR image-guided focused ultrasound

Natasha D. Sheybani[1] · Alexandra R. Witter[2] · William J. Garrison[1] · G. Wilson Miller[3] · Richard J. Price[1,3] · Timothy N. J. Bullock[2]

Journal of Neuro-Oncology (2022) 156:109–122
https://doi.org/10.1007/s11060-021-03887-4

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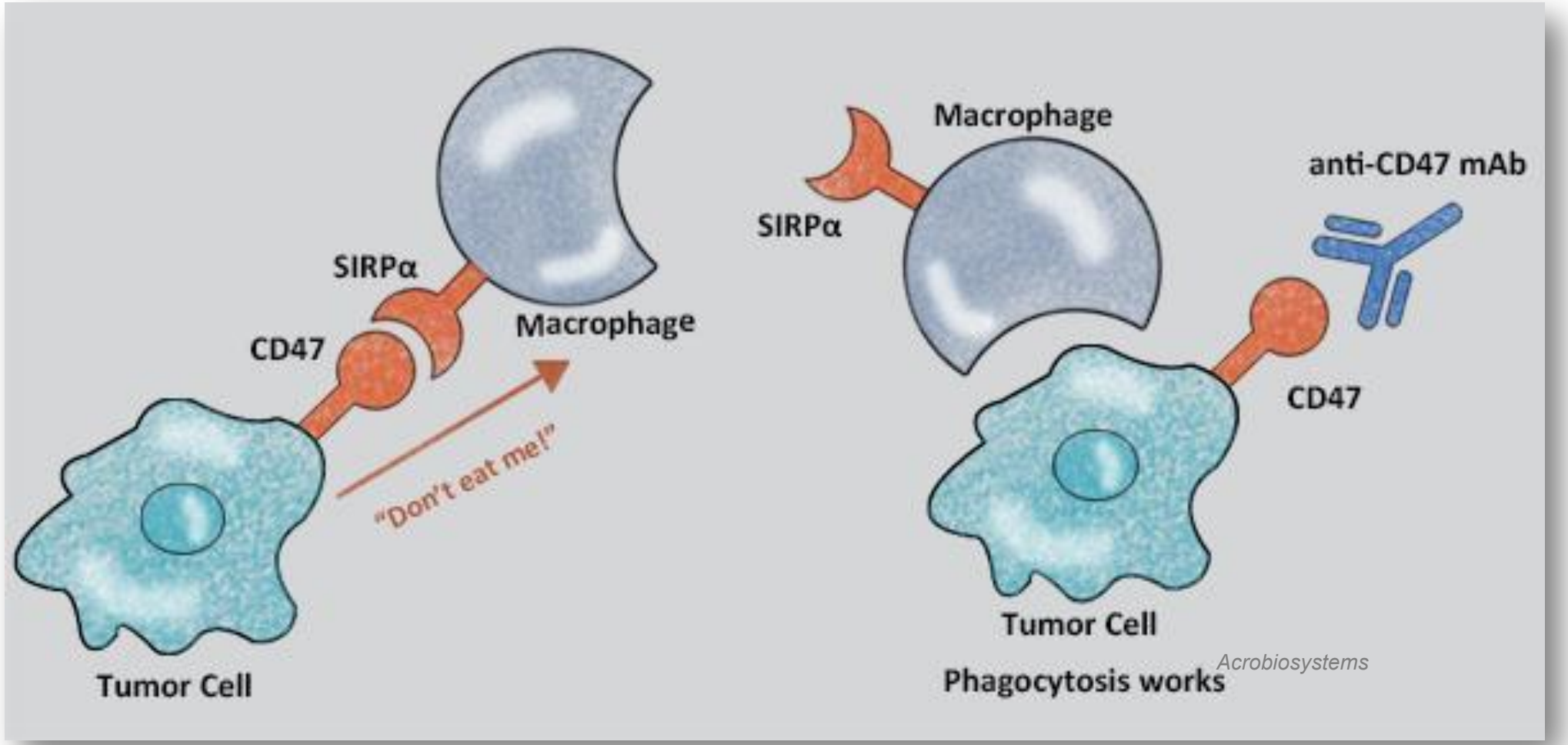
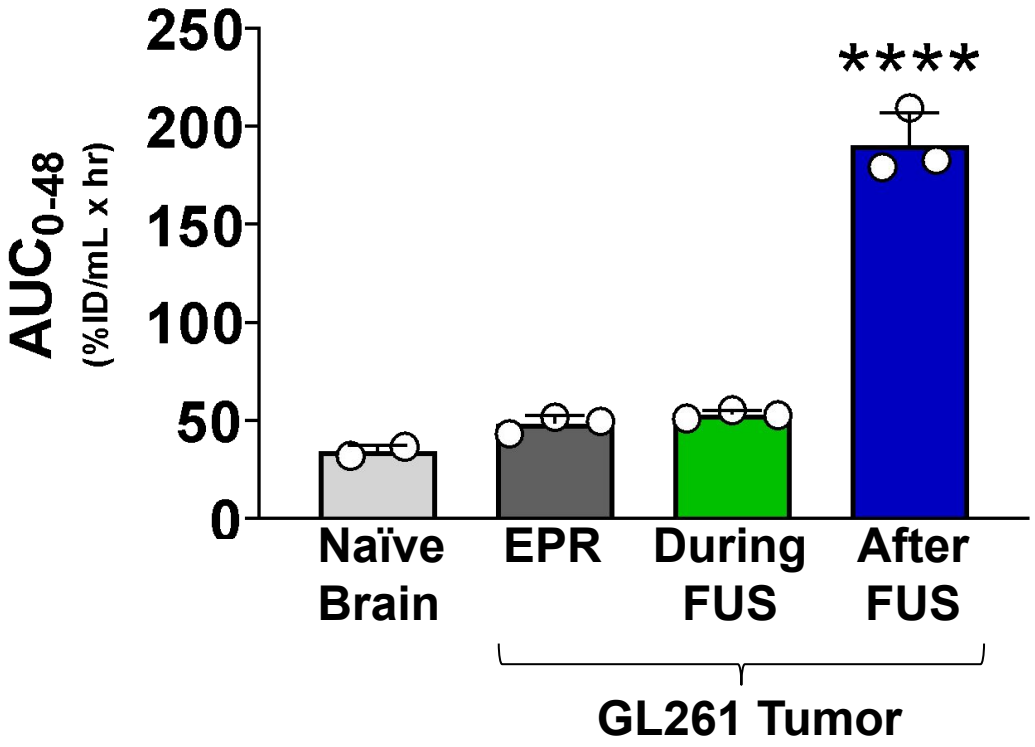
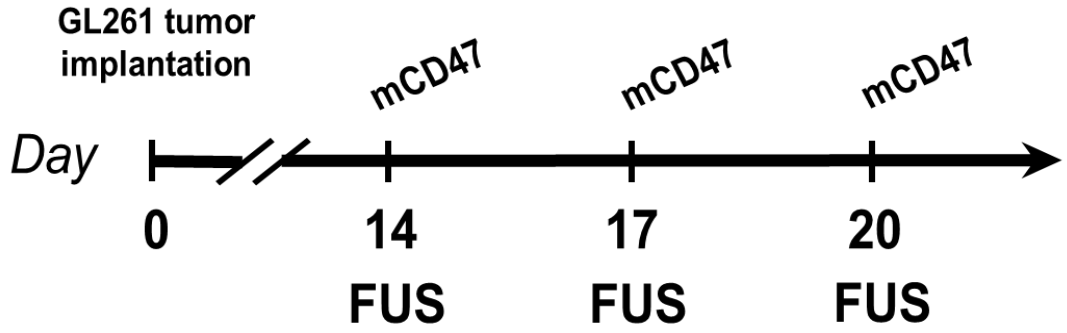
CD47 Blockade: An Immunotherapeutic Strategy for GBM

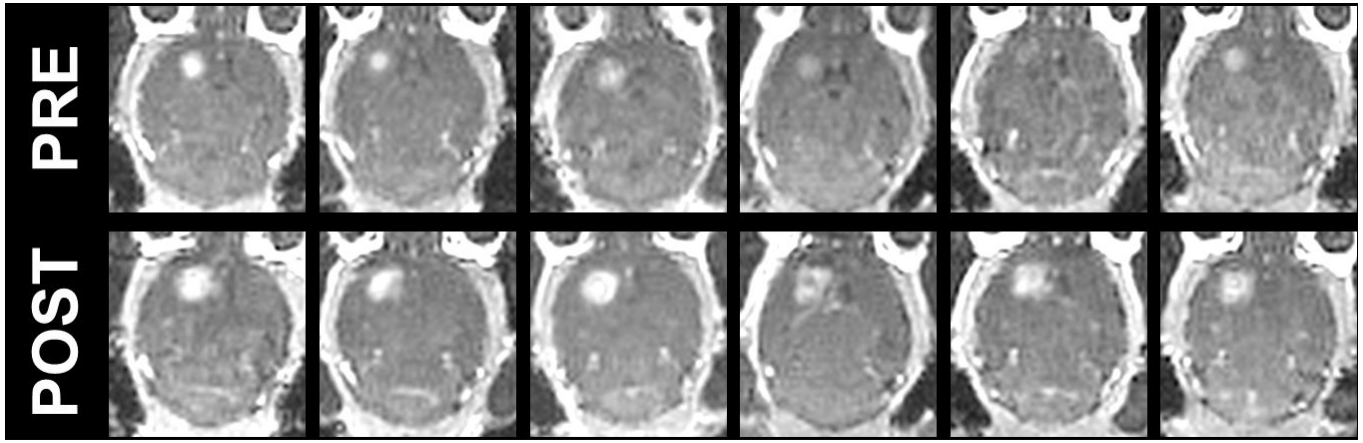


αCD47 Immunotherapy Delivery Protocol & Confirmation of BBB/BTB Opening

ImmunoPET Optimization of αCD47 Injection Timing







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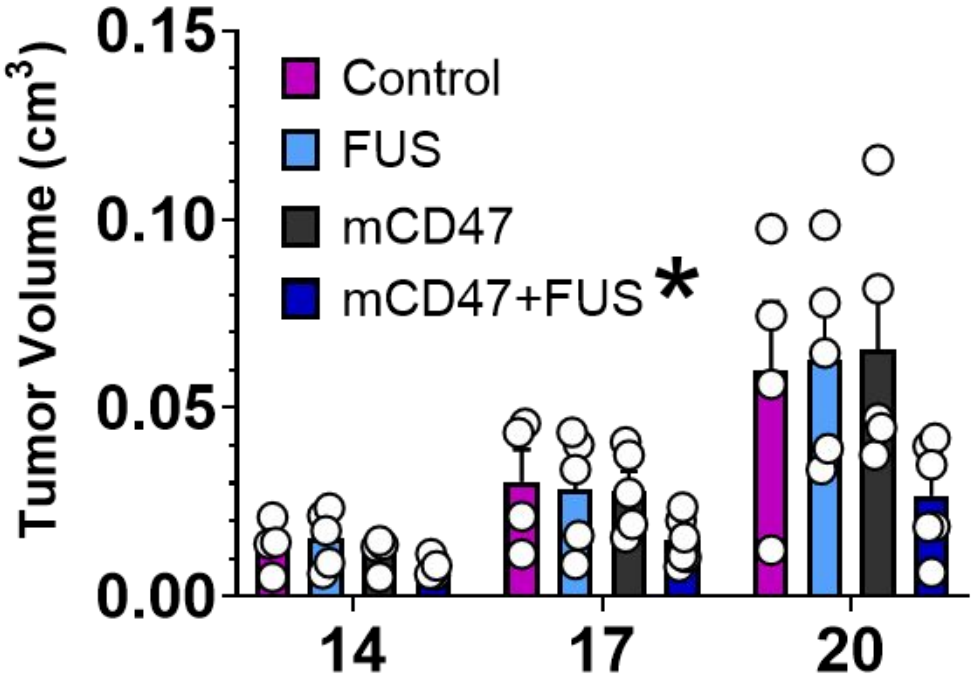
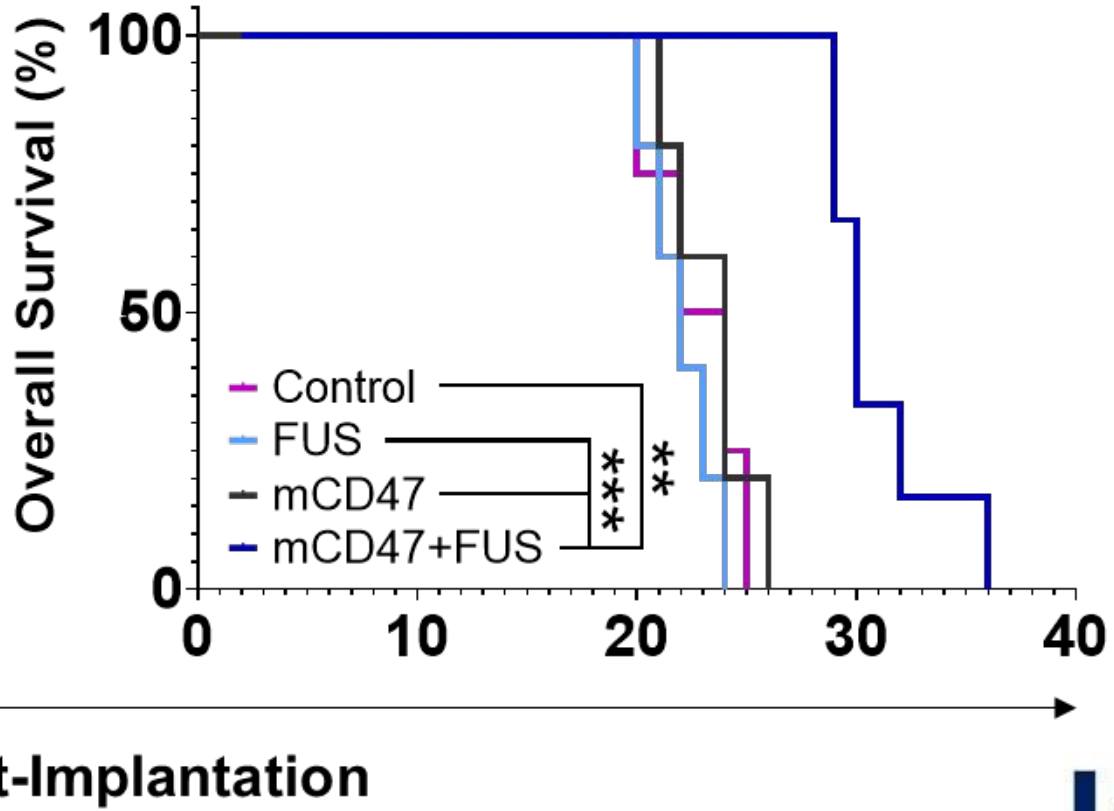
FUS-Mediated αCD47 Delivery Across the BBB/BTB Restricts GL261 Outgrowth and Improves Survival





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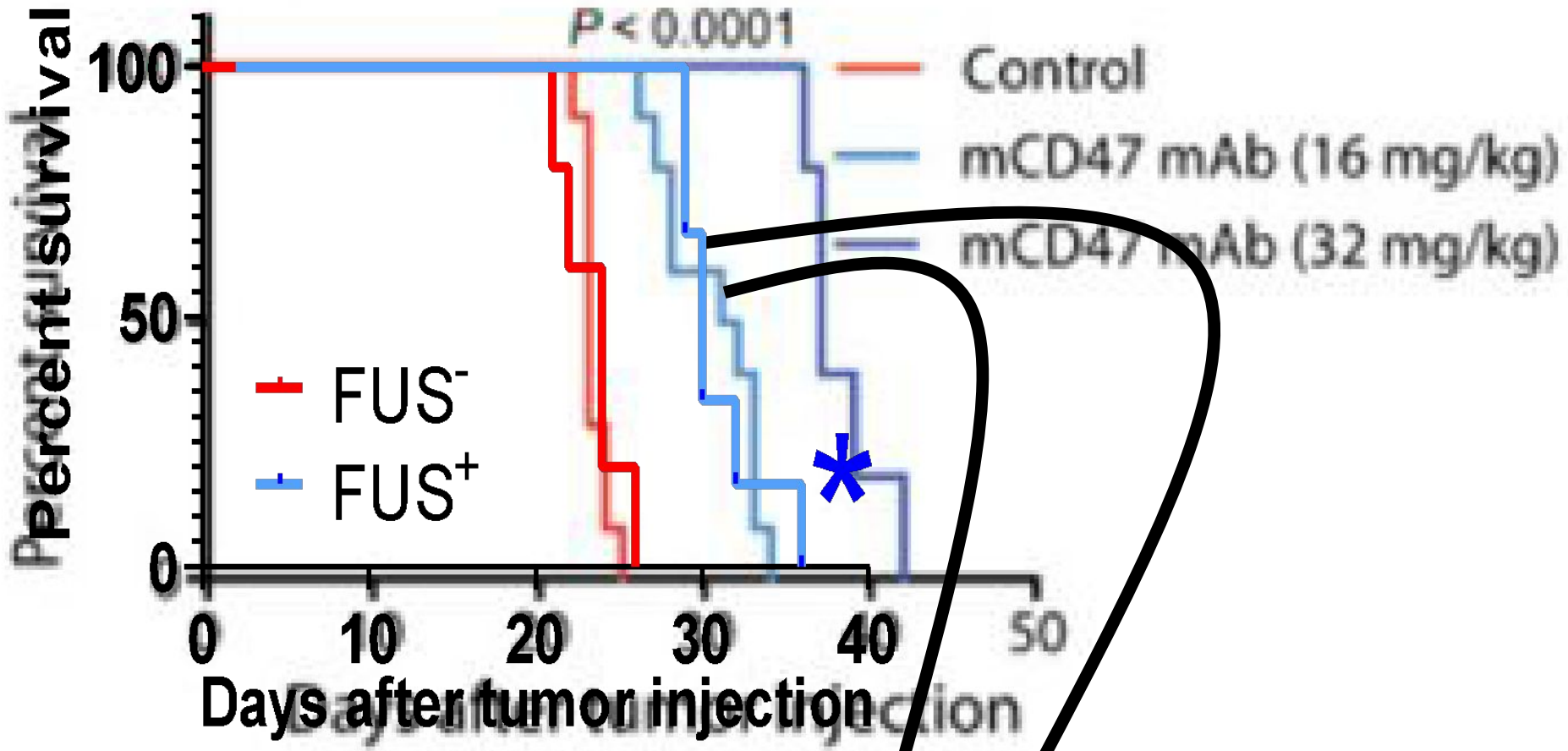
M-FUS BBB/BTB Opening Permits Tumor Cotrol with Markedly Lower Injected Mass of αCD47

Gholamin et al. *Sci Trans Med* 2017



3 injections x 8 mg/kg = 24 mg/kg

~27 injections x 16 mg/kg = 432 mg/kg

(An 18-fold decrease in administered drug!)

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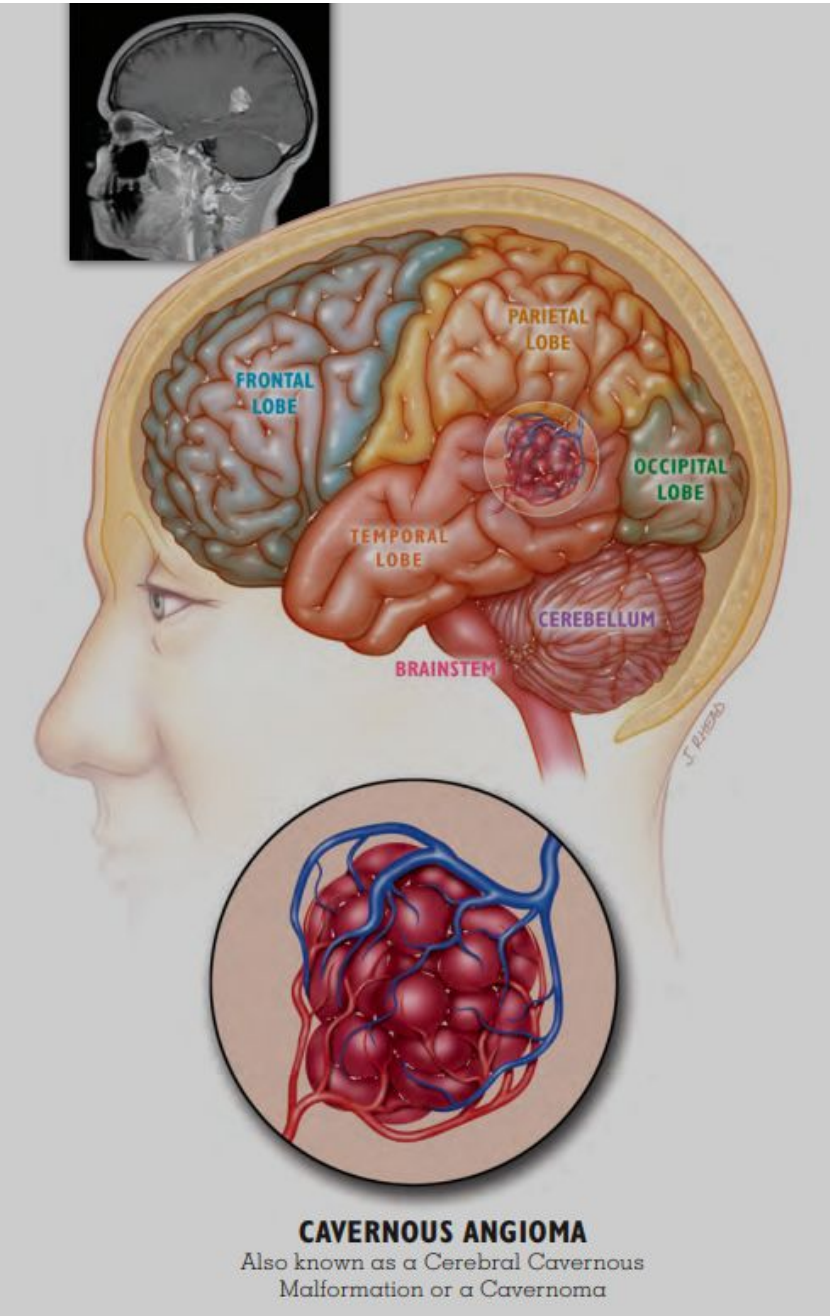
Presentation Outline

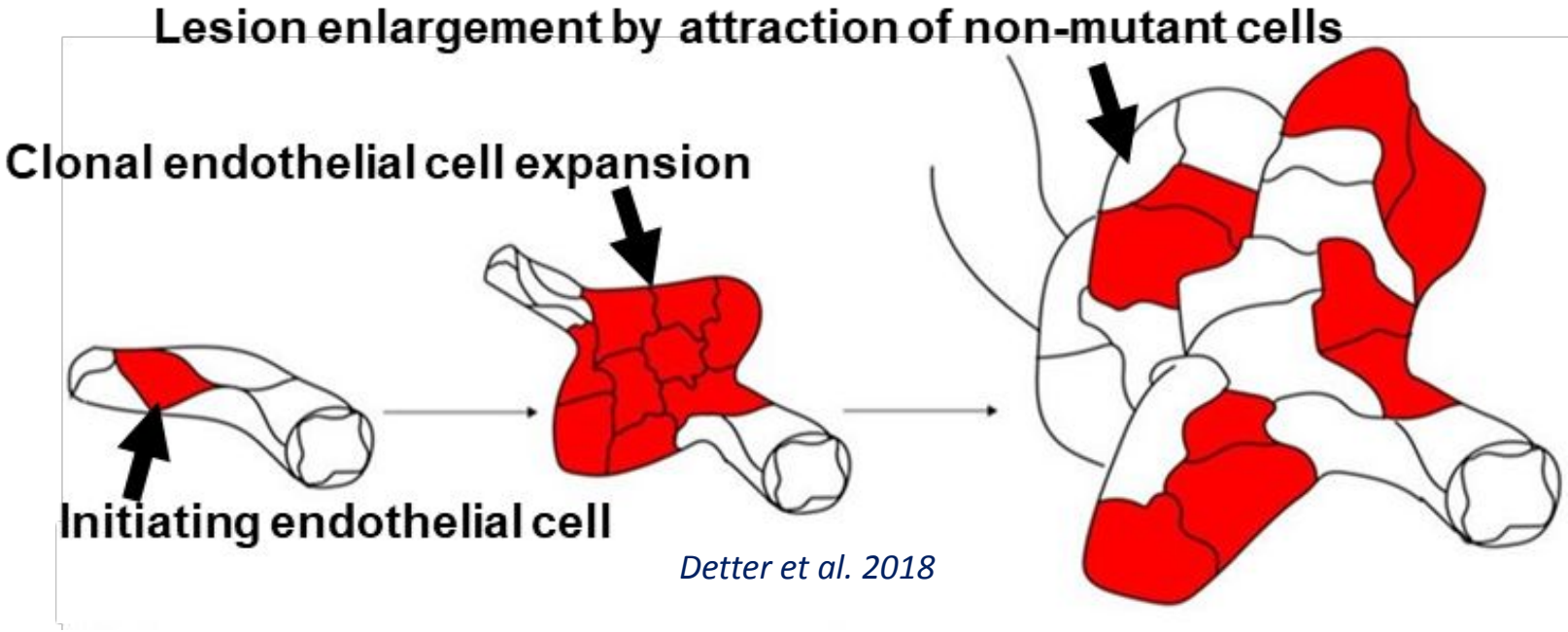
- Gene Delivery (“Toolkit” Overview)
- Immunotherapy Delivery to Brain Tumors
- **Cerebral Cavernous Malformations**

Cerebral Cavernous Malformation (CCM)



Angioma Alliance

- **Vascular lesions/neoplasms**
- **Biallelic loss-of-function mutation(s) in 1 of 3 CCM complex genes: KRIT1, CCM2, or PDCD10**



Detter et al. 2018

- **"Familial" and "Sporadic" forms of the disease**

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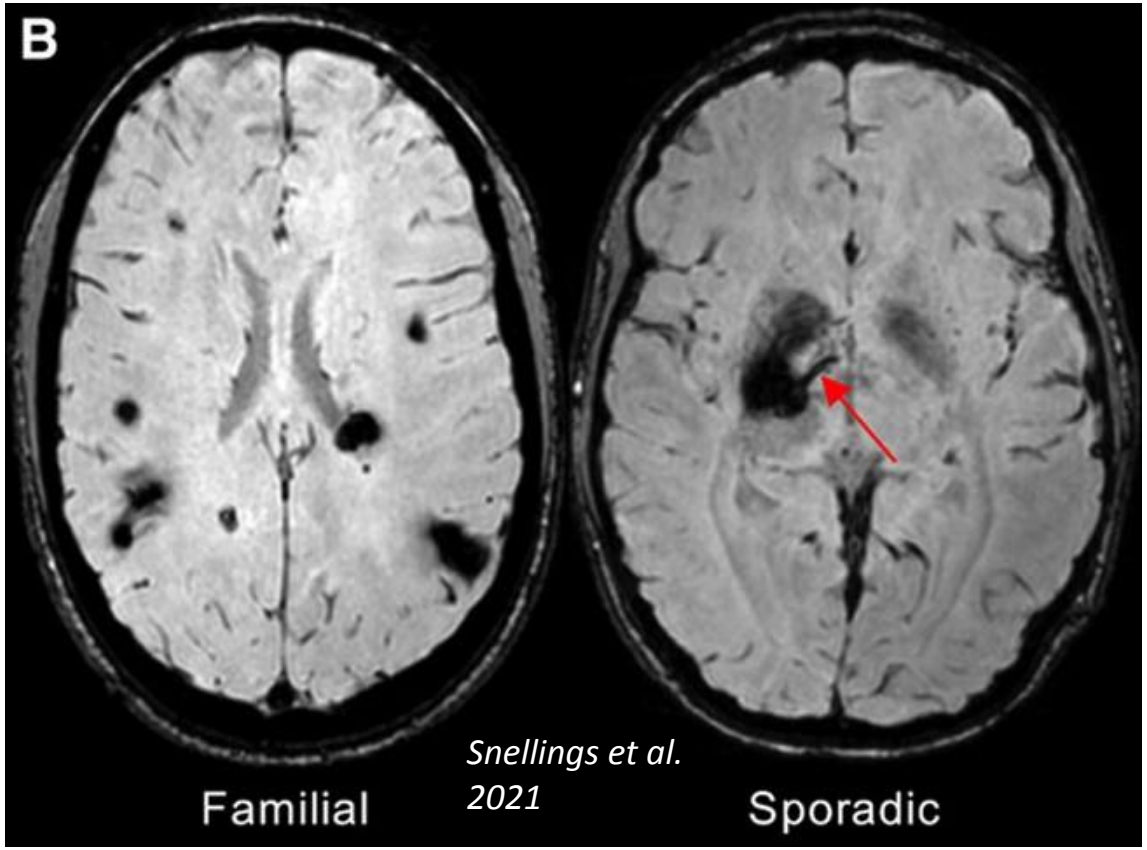
Rationale for Deploying FUS Against Cerebral Cavernous Malformations

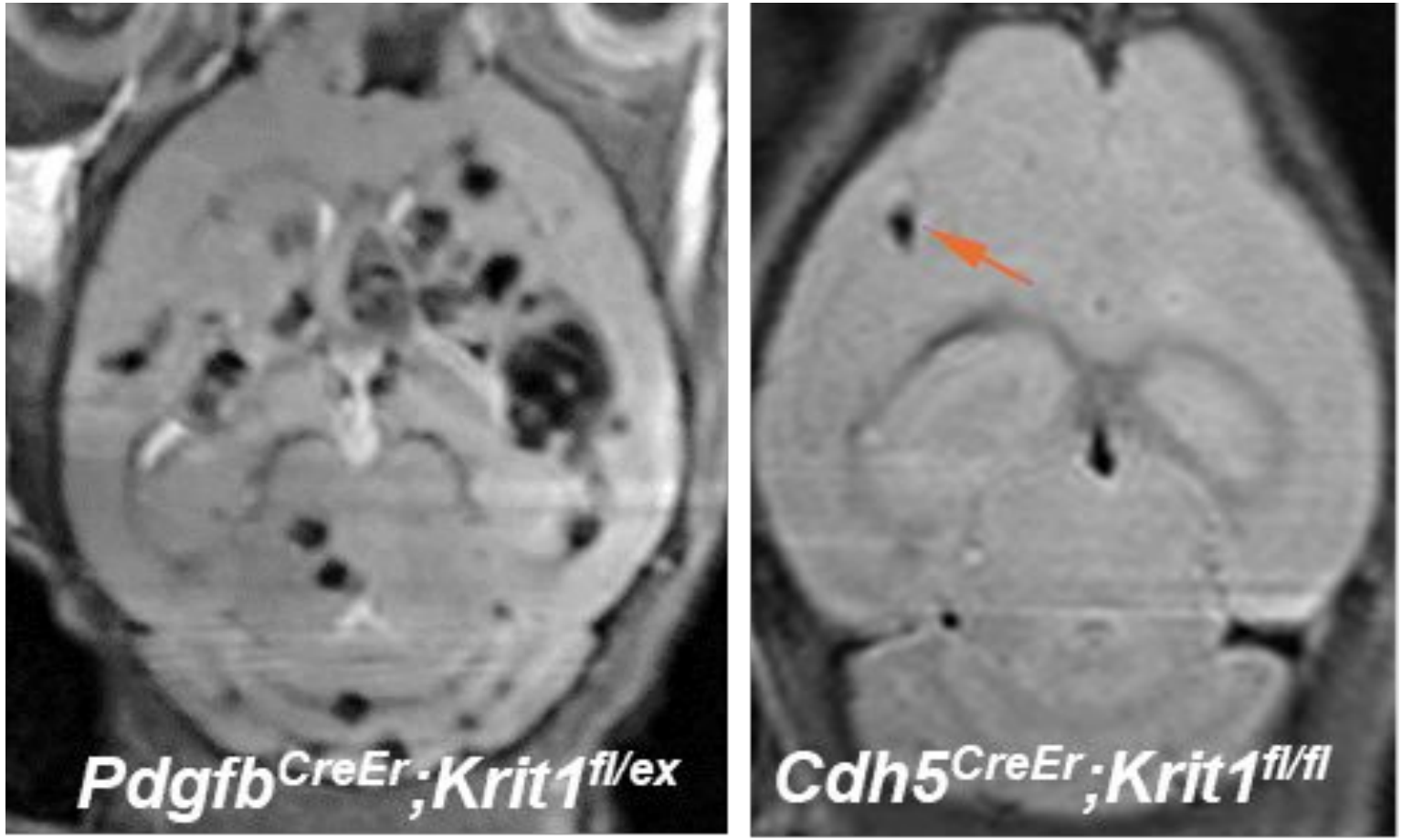
- **Surgical resection** only current therapeutic option
- Few attempts have been made to deploy **biologics** **(> 1KDa)** against CCM
- Lesions are **discrete** and identified with **MRI (iron rich)**



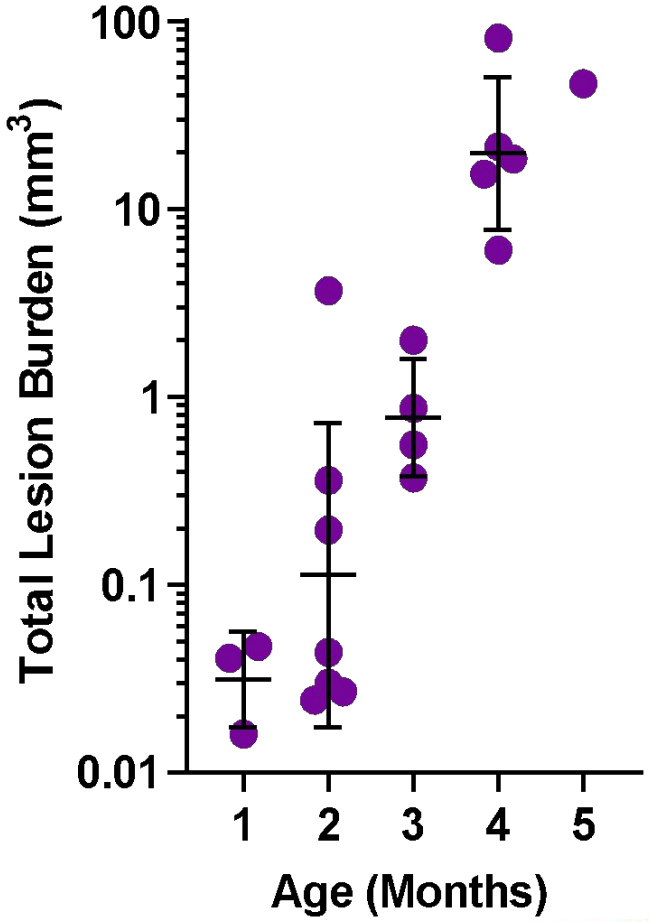
Snellings et al. 2021

Mouse Models Representative of "Familial" and "Sporadic" Disease

T2 SPACE MRI



Pdgfb^{CreEr};Krit1$^{fl/ex}$



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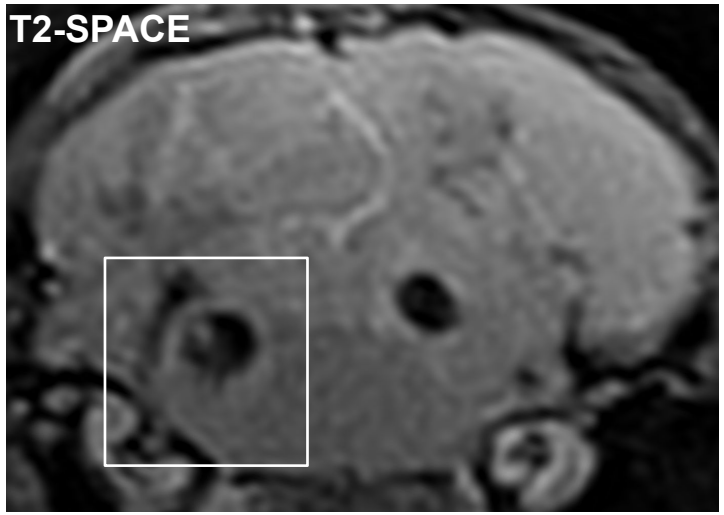
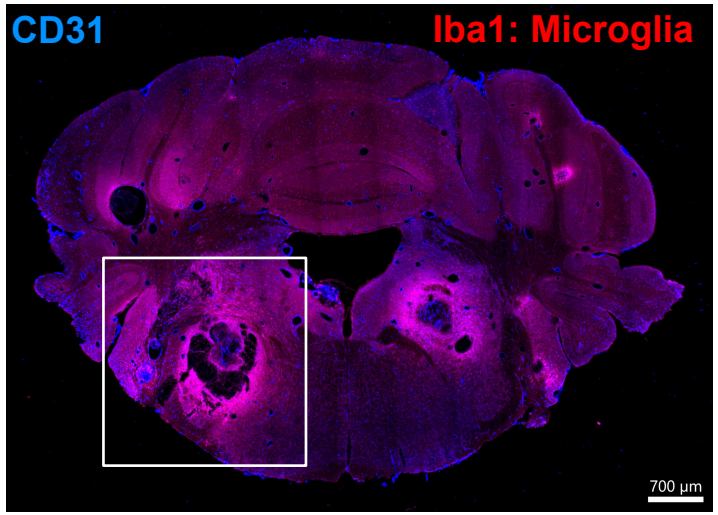
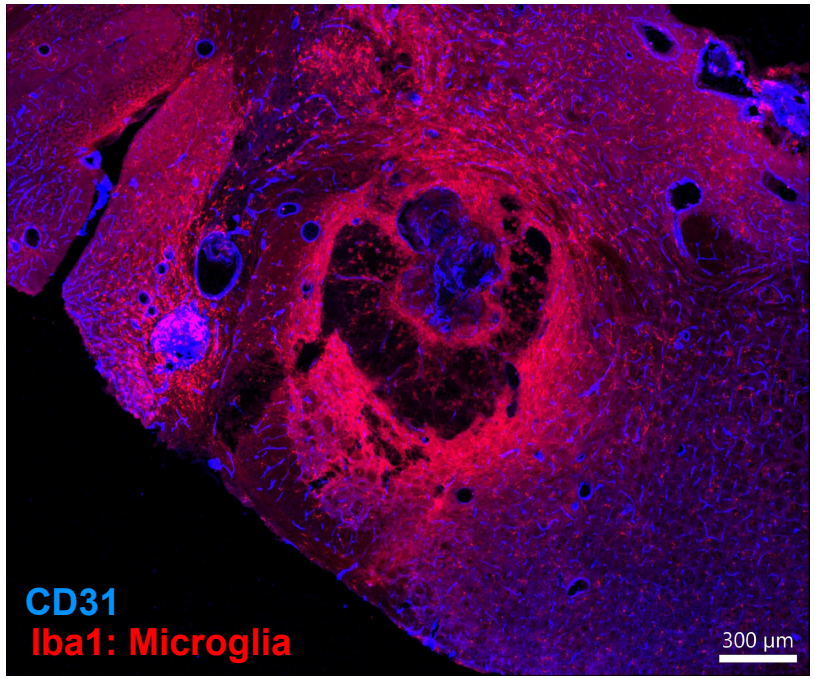
CCMs Cause Neuroinflammation and Oxidative Stress

Pdgfb^{CreEr};Krit1$^{fl/ex}$

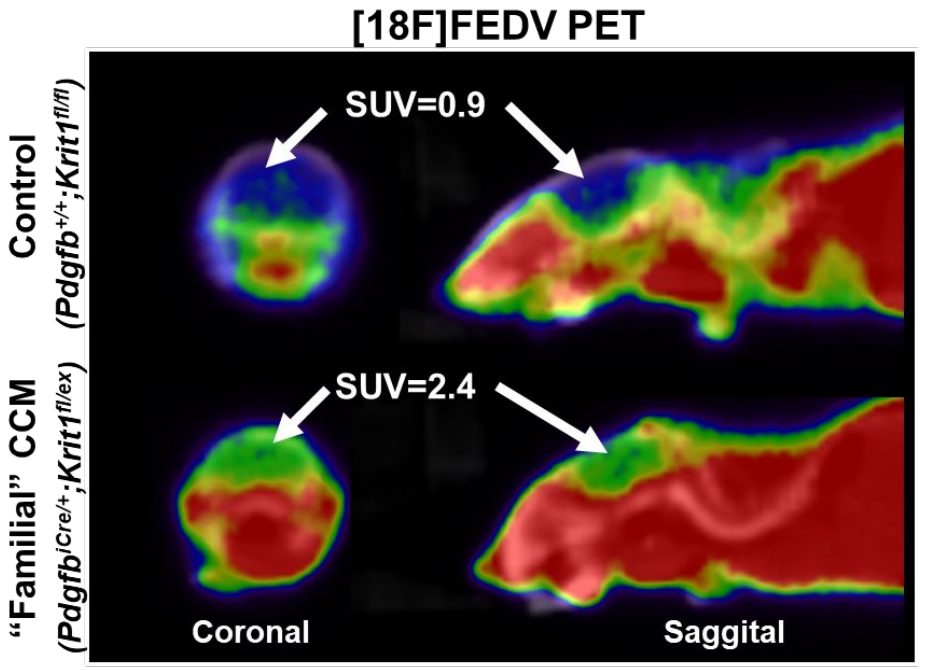




Neuro-inflammation



High Oxidative Stress



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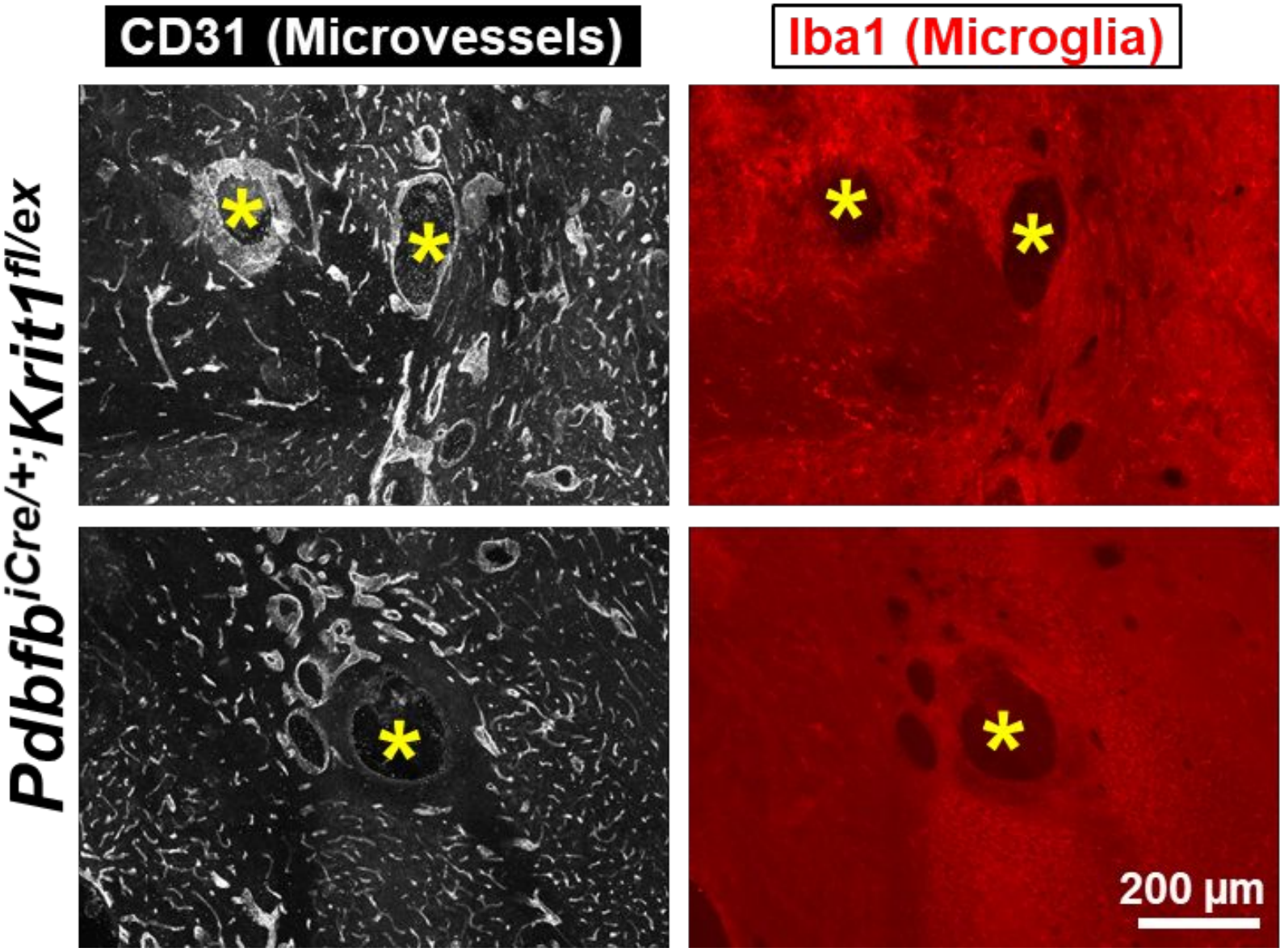
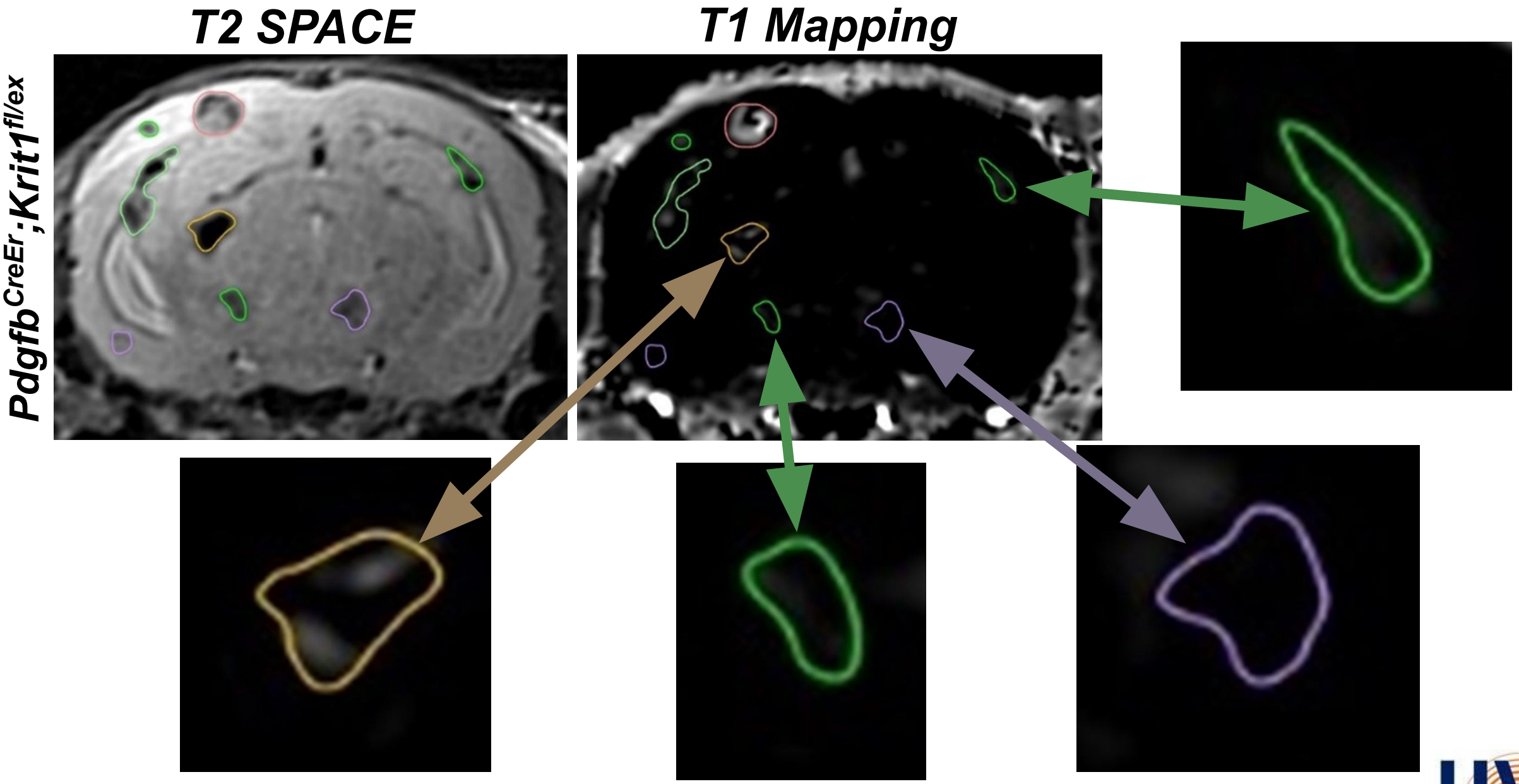
How might CCMs be accessed via the bloodstream?

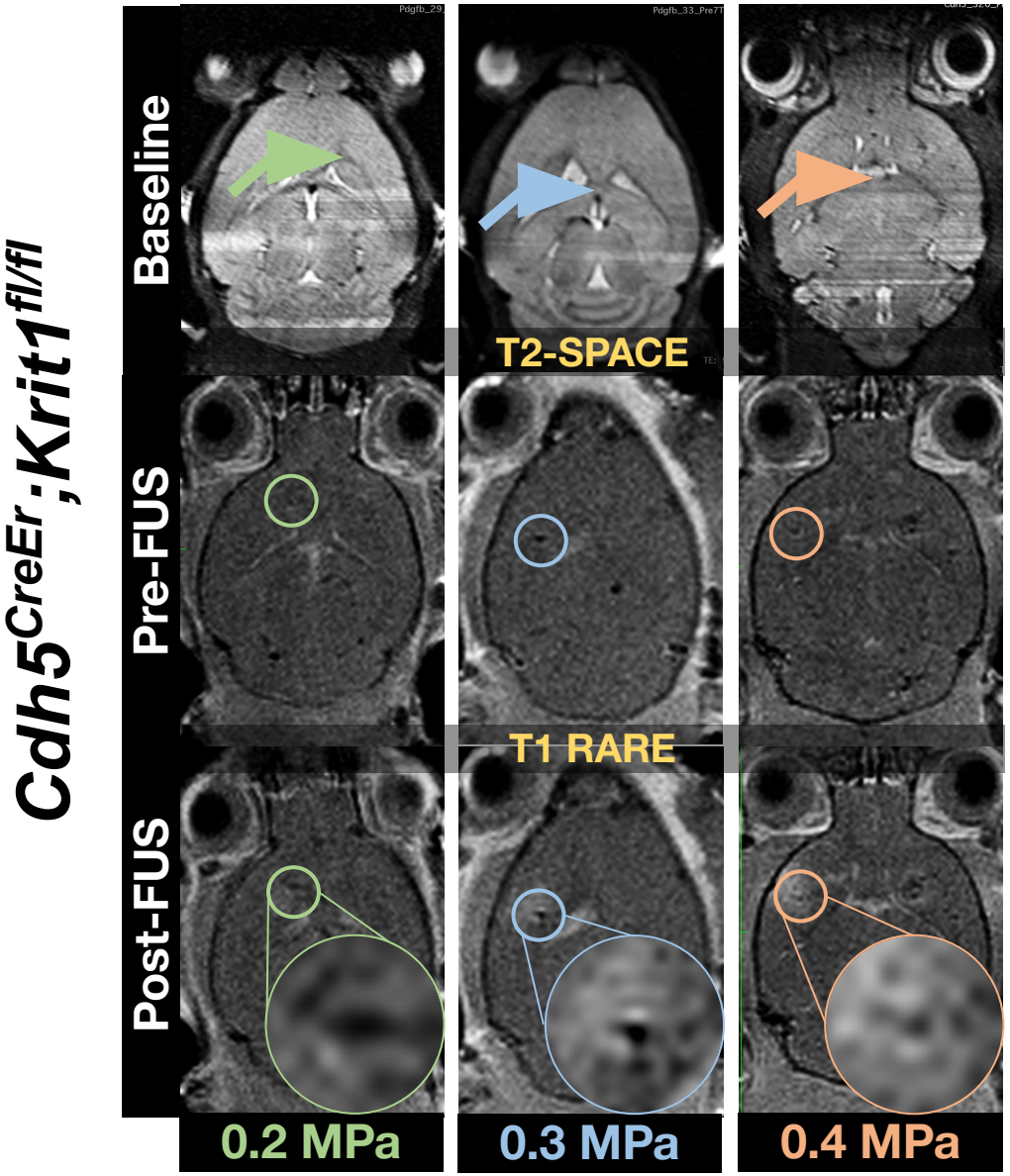


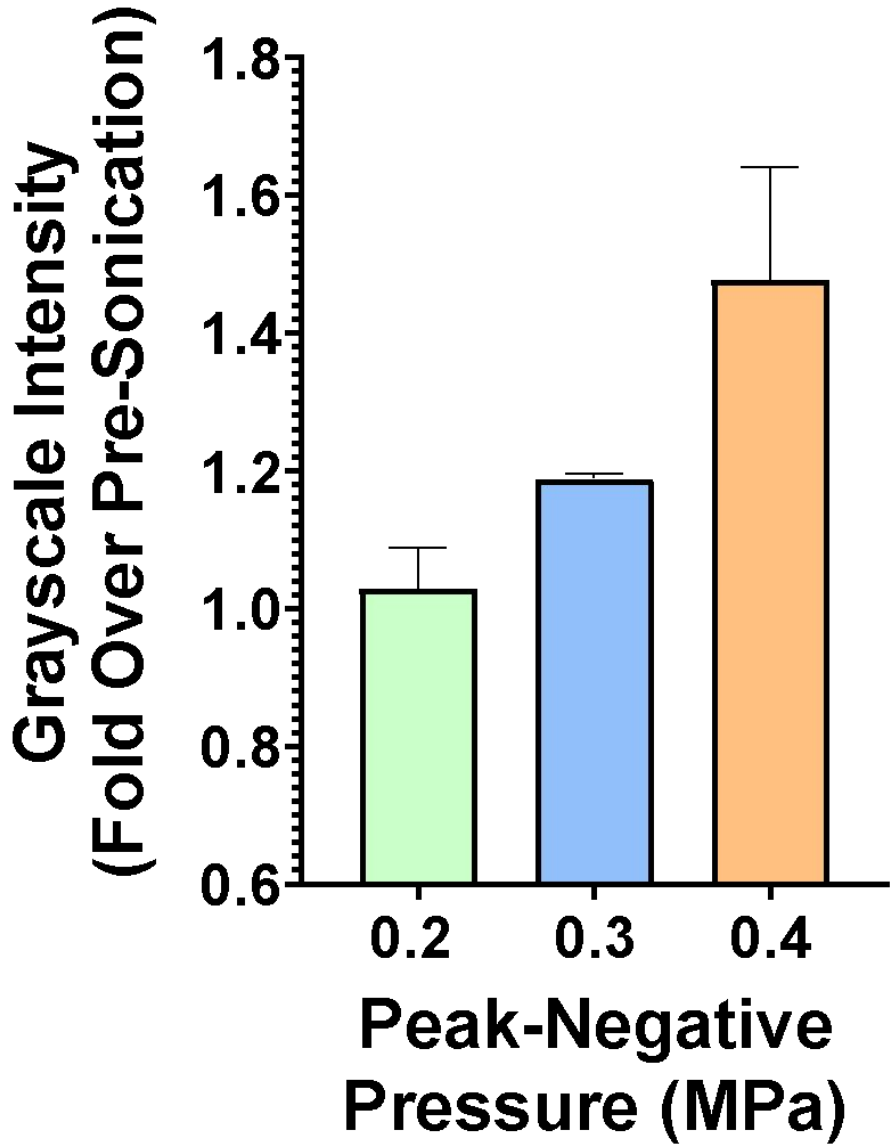
*CCM "Lumen"

Peri-CCM Microvessels Retain “BBB-Like” Function



FUS+MBs Permeabilizes Peri-CCM Microvasculature





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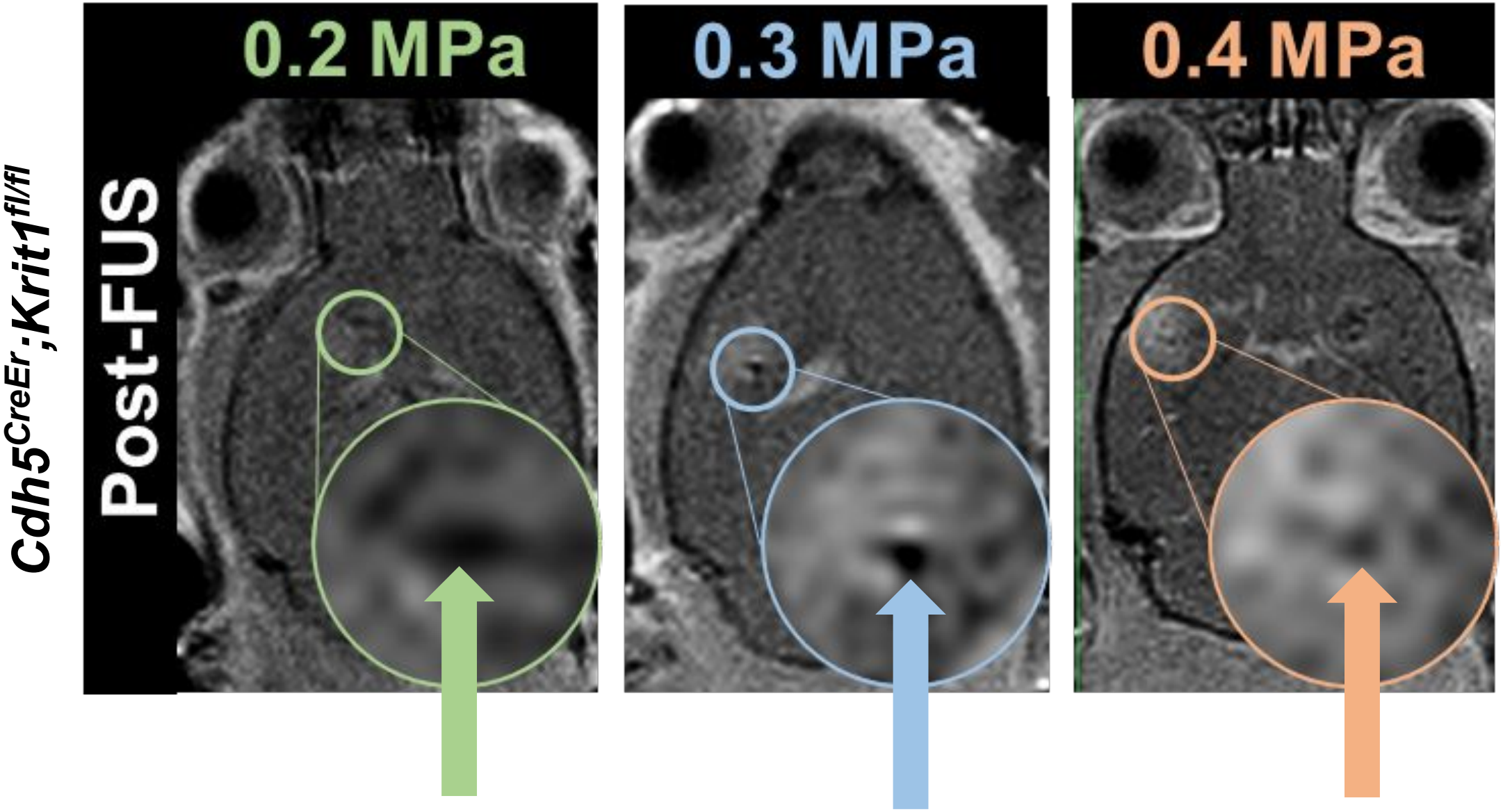
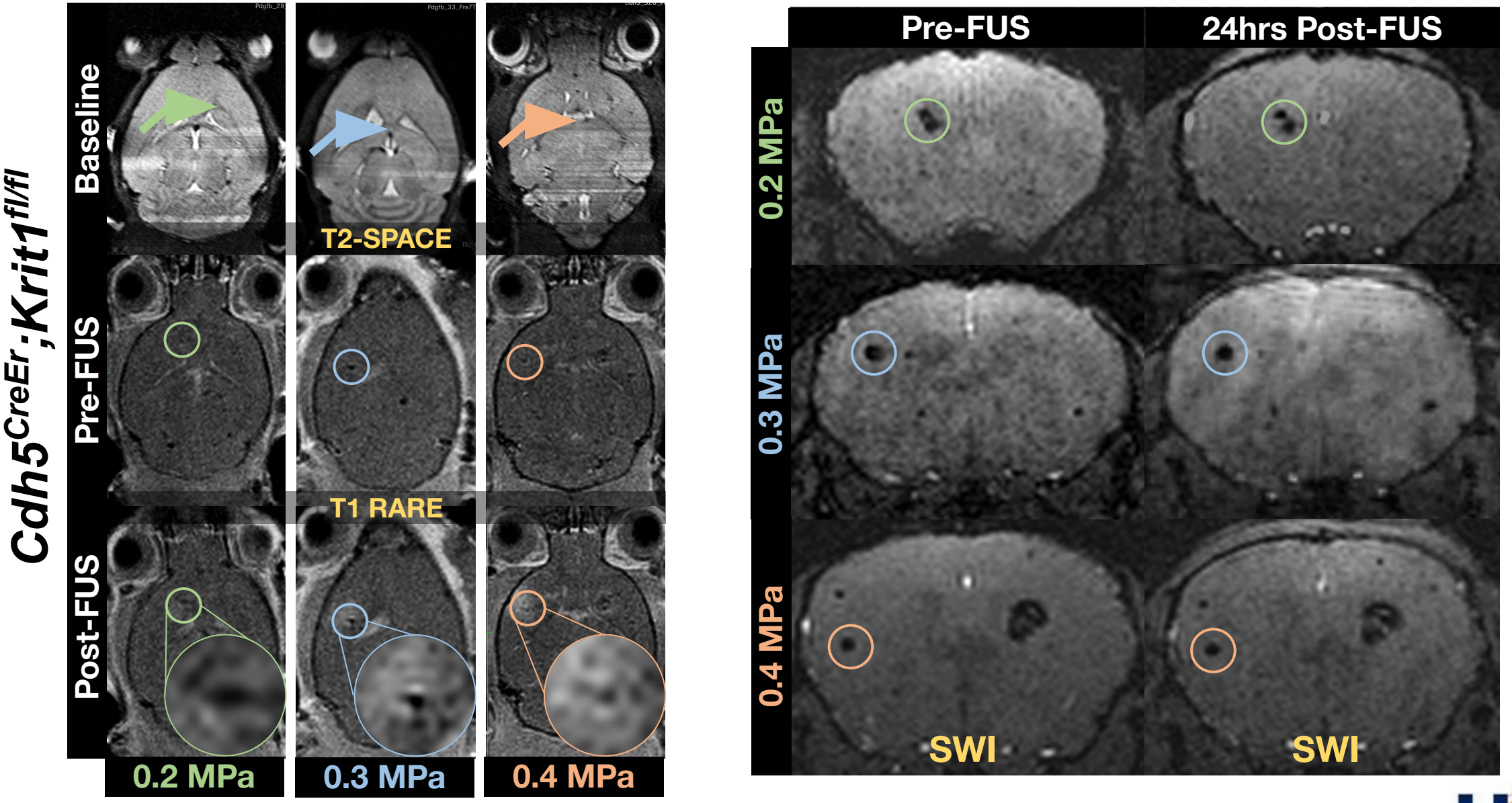
CCM “Lumens” Are Not Permeabilized by FUS



No Evidence of CCM Bleeding or Petechiae



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In Summary, FUS+MBs…..

- Permits MRI-targeted gene delivery to the CNS
- Enhances αCD47 delivery to GBM, controlling growth and improving survival
  - Next Step – drive systemic immune responses
- May facilitate safe and effective deployment of biologics against CCM
  - Next Step – control CCMs with biologics

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Vinton Cheng

Lab Manager
Ji Song

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Natasha Sheybani
Aly Witter
Colleen Curley
Kelsie Timbie
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NIH National Cancer Institute — R21CA230088

Focused Ultrasound Foundation

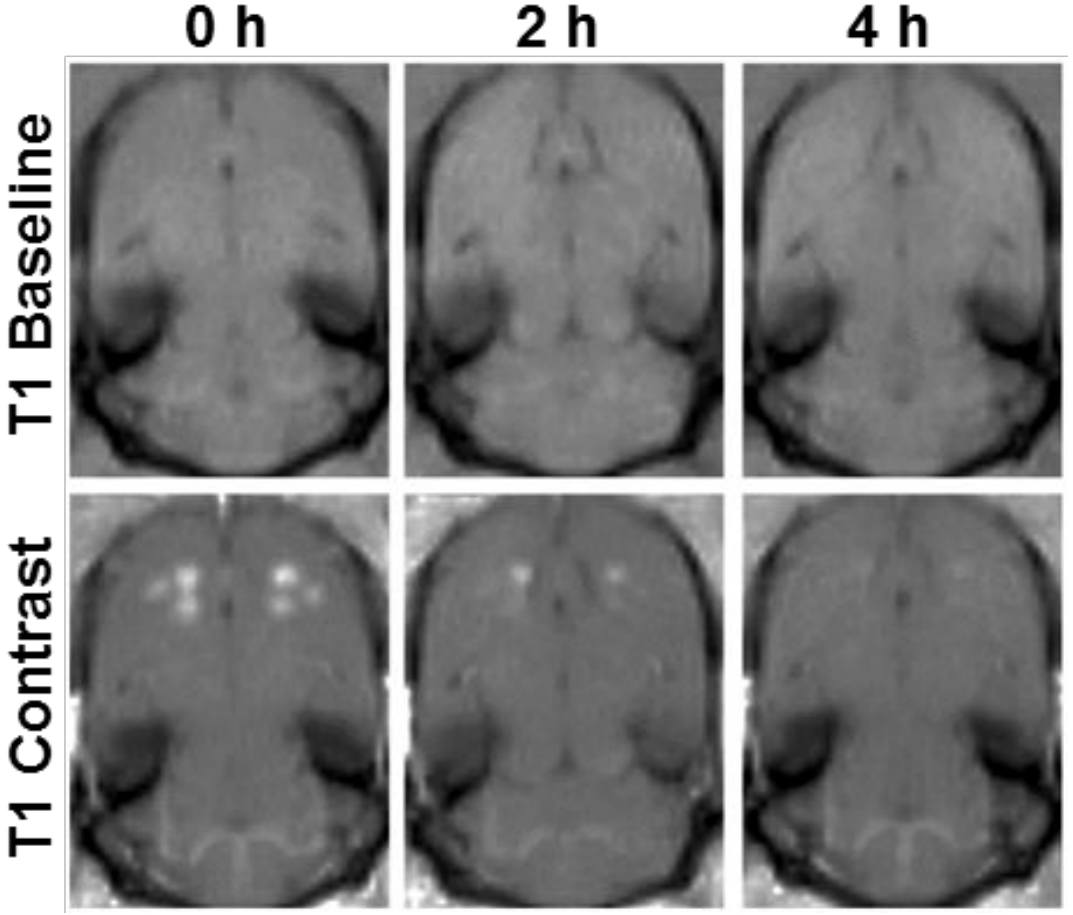
UVA Focused Ultrasound

@PriceLabUVaBME

price-lab.org

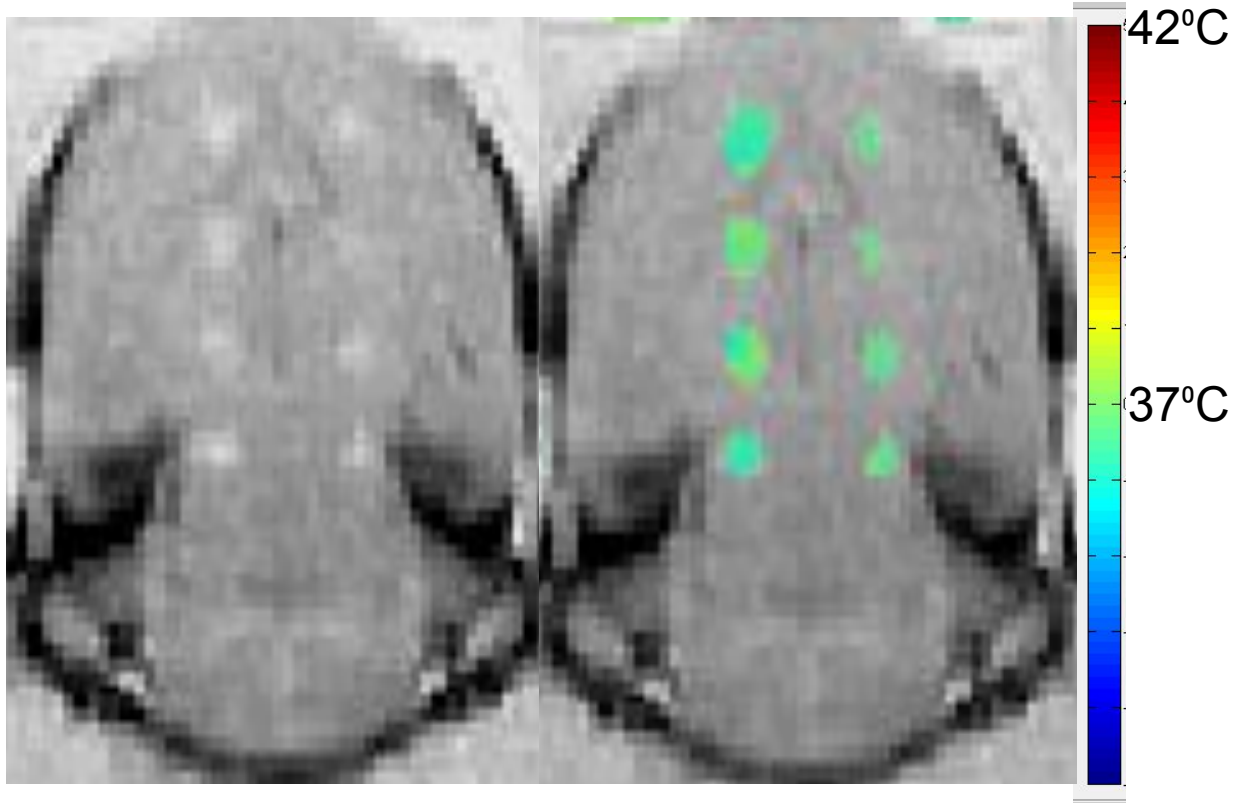
BBB Opening with Focused Ultrasound is Transient and Does not Elicit Significant Heating

Contrast Enhanced MRI



Mead, Curley et al. *Small* 15:e1903460;2019

MR Thermometry



Nance, Timbie et al. *J Control Release* 189:123-32; 2014

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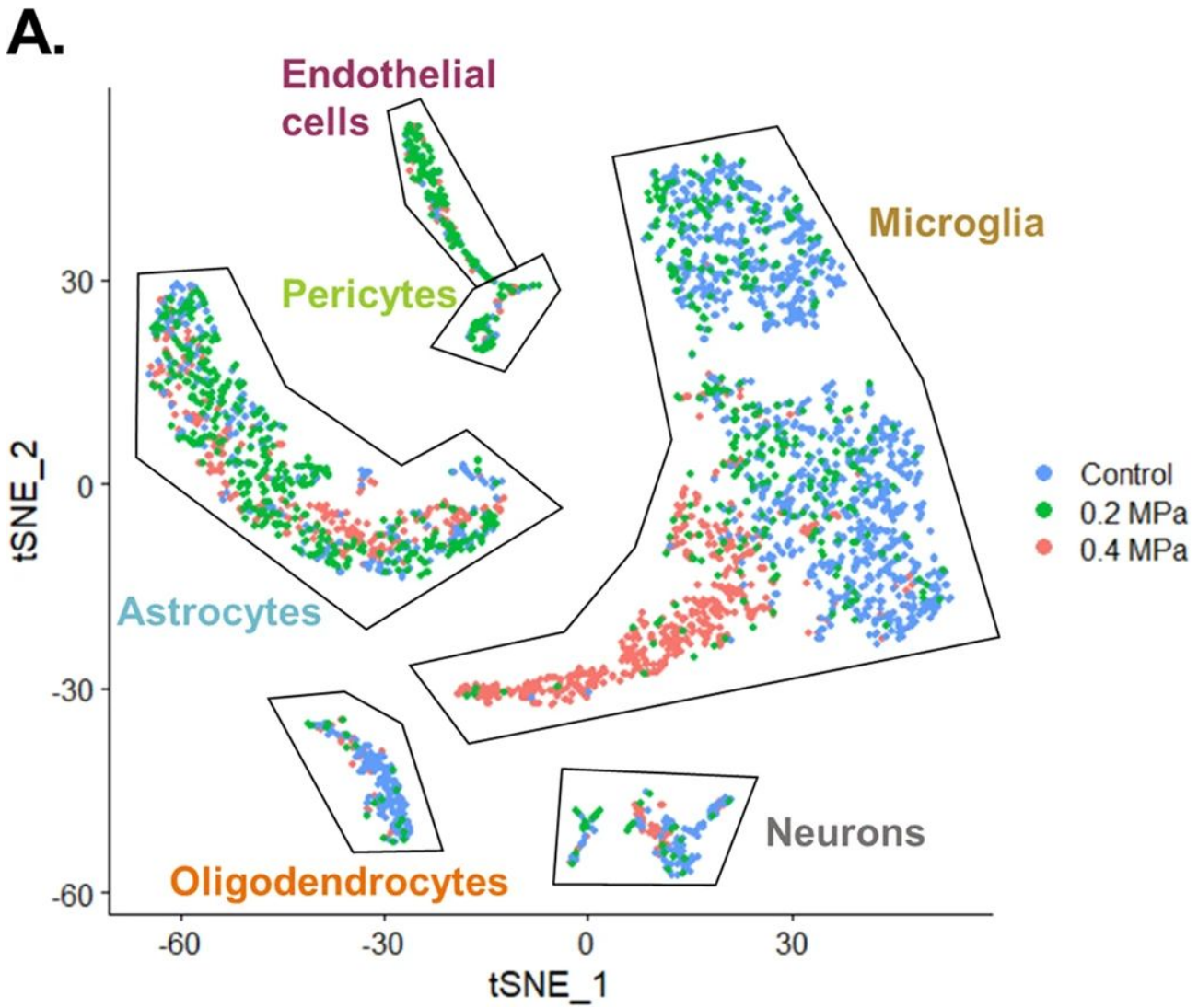
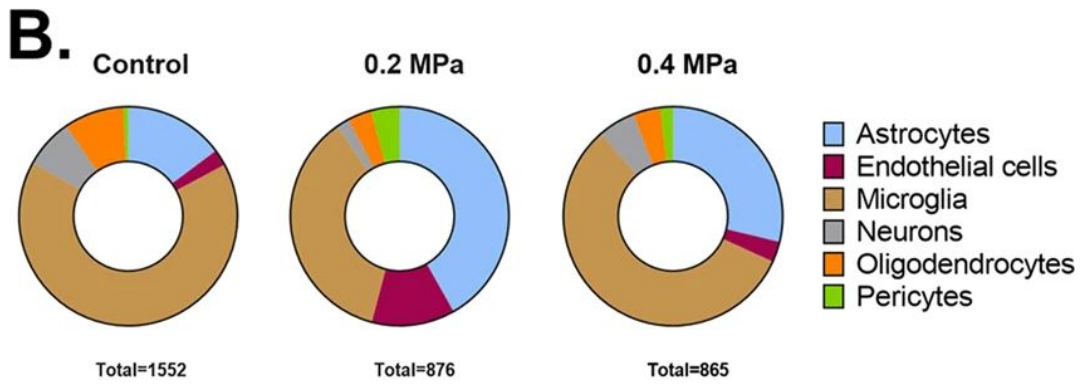
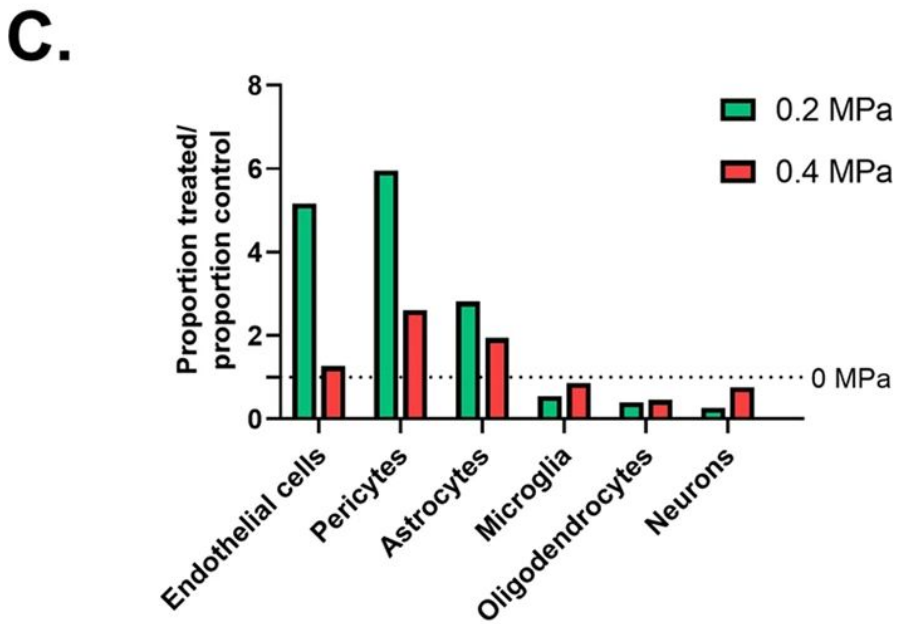
Enhanced Transfection Beyond Neurovascular Unit at High Pressures







Mathew et al. *Gene Therapy.* DOI:10.1038/s41434-021-00226-0; 2020

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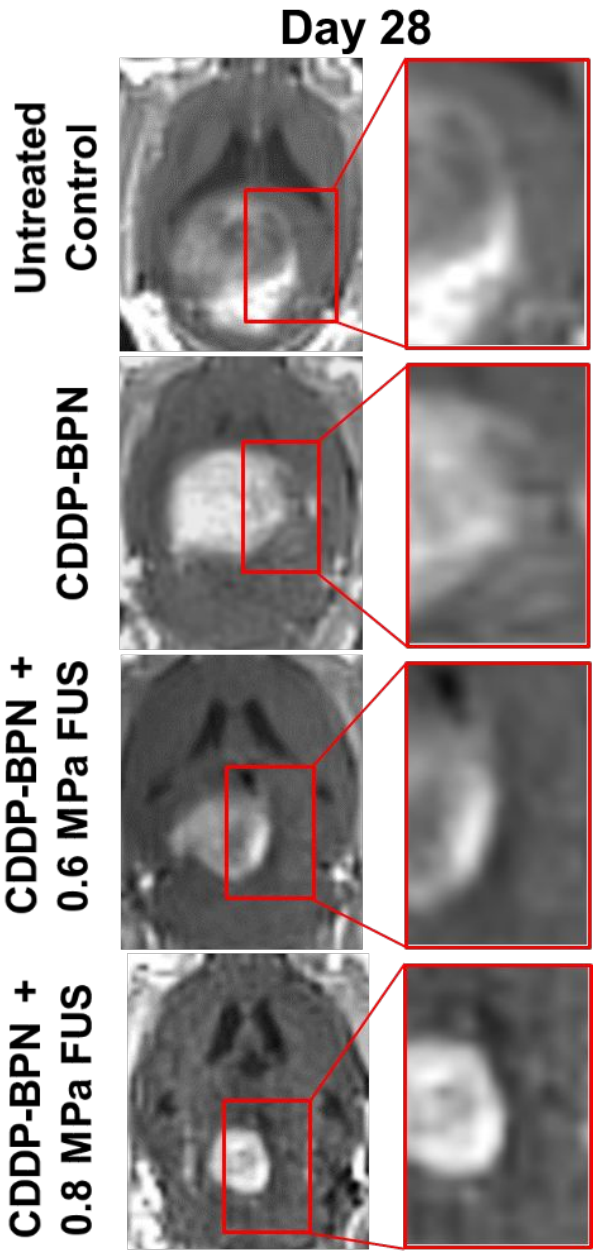
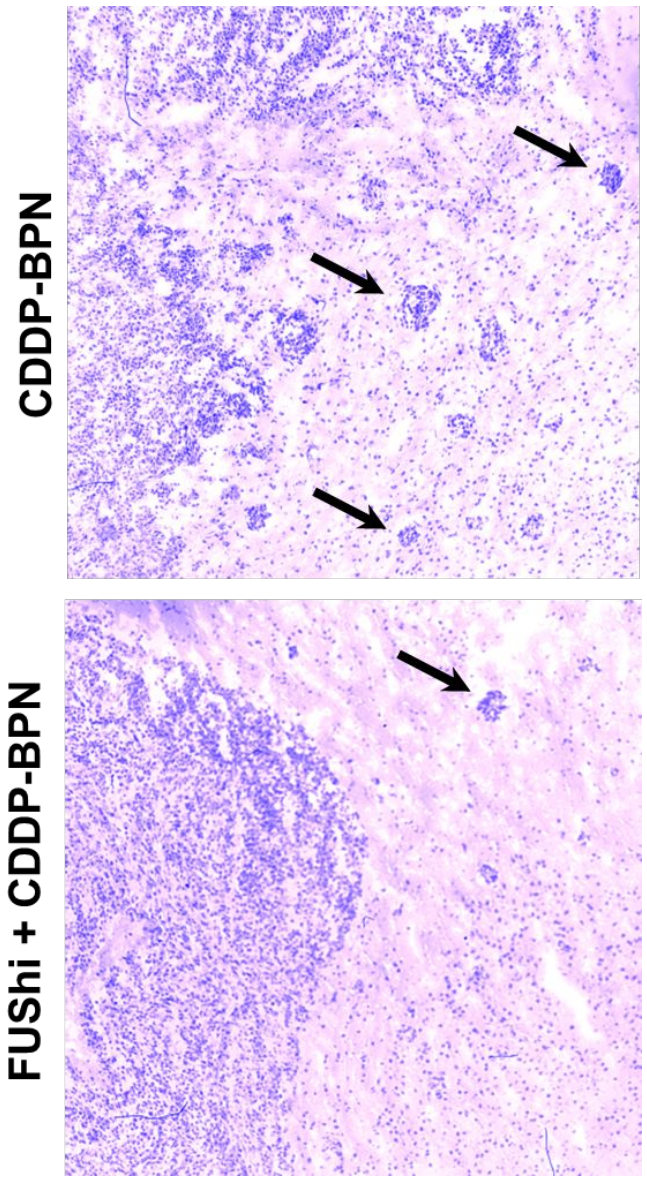
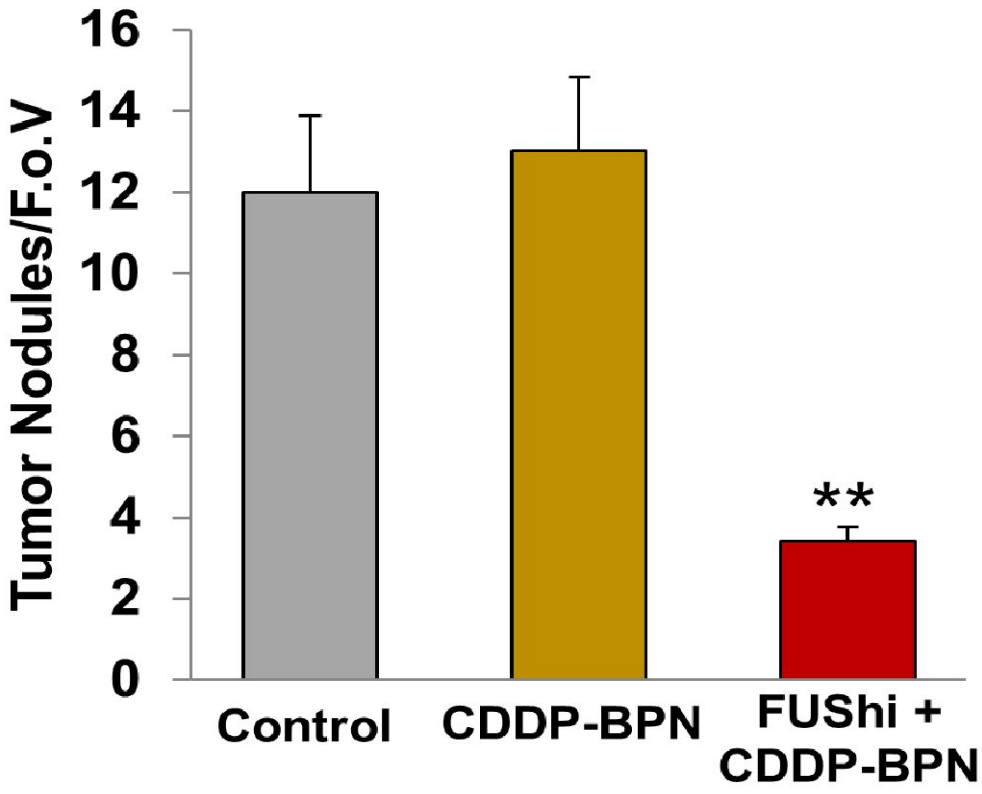
Cisplatin-Nanoparticle Delivery Inhibits Glioma Growth & Invasion







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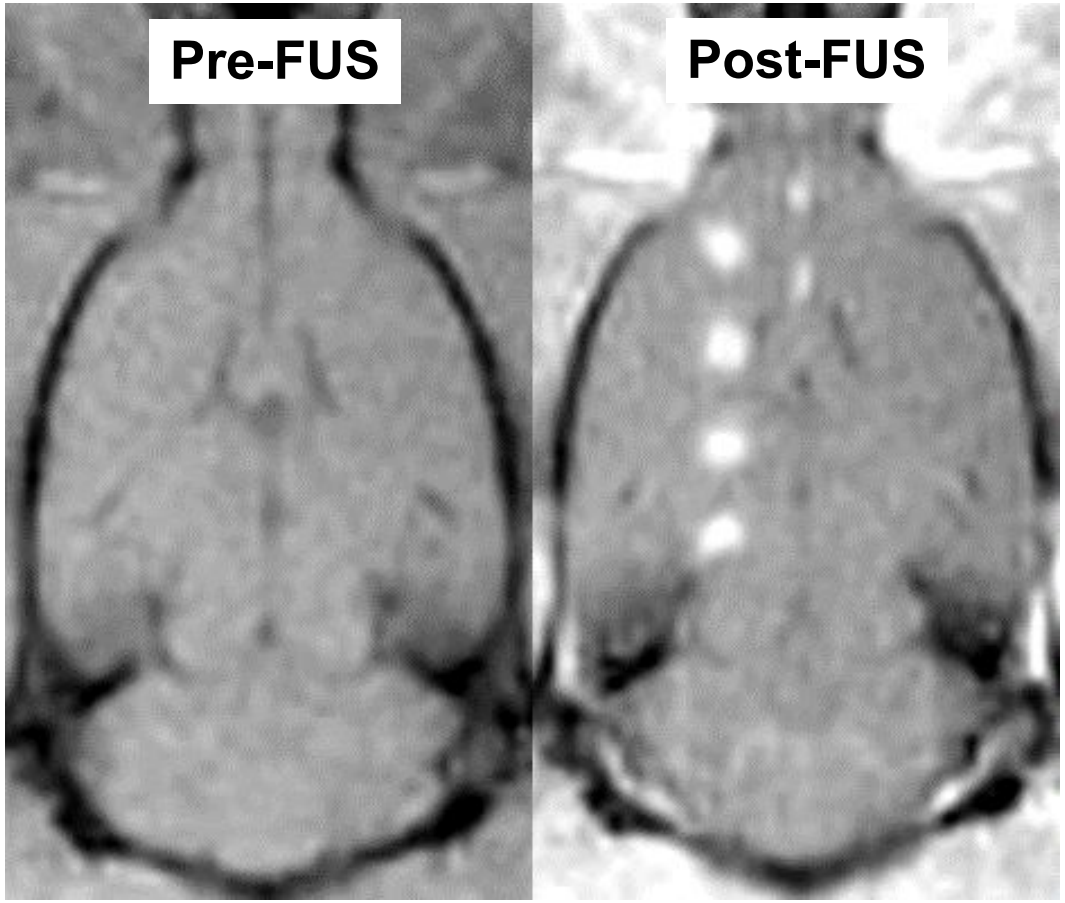
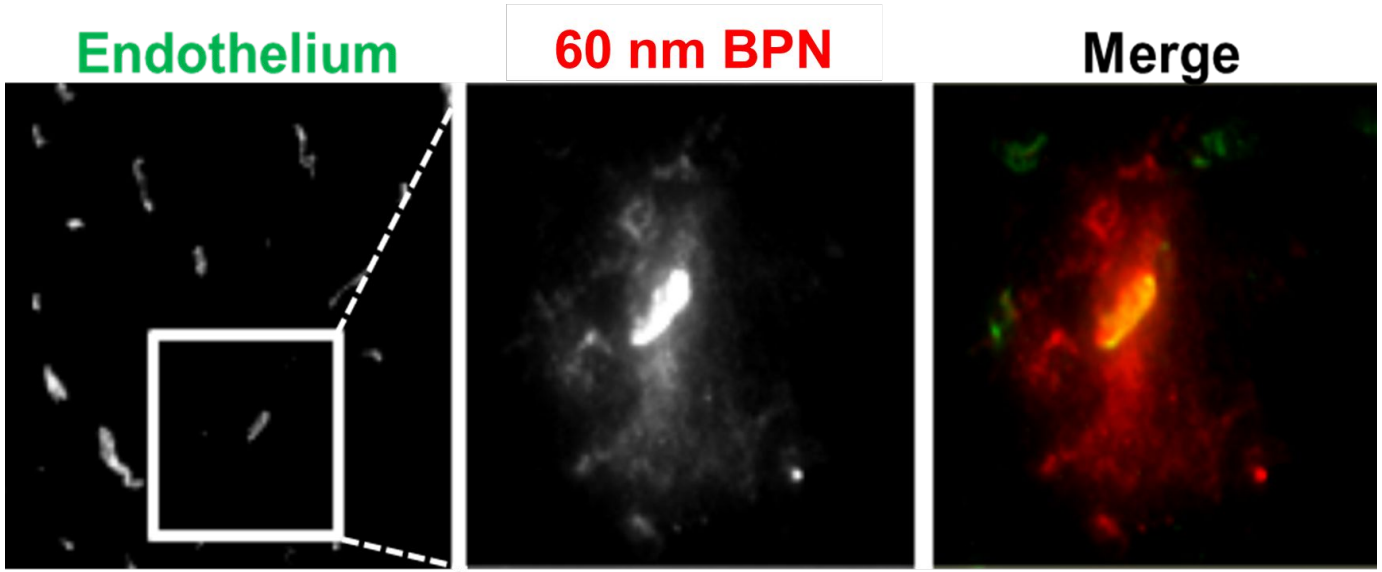
“Brain-Penetrating” Nanoparticle (BPN) Delivery Across the BBB via Microbubble Activation with Focused Ultrasound





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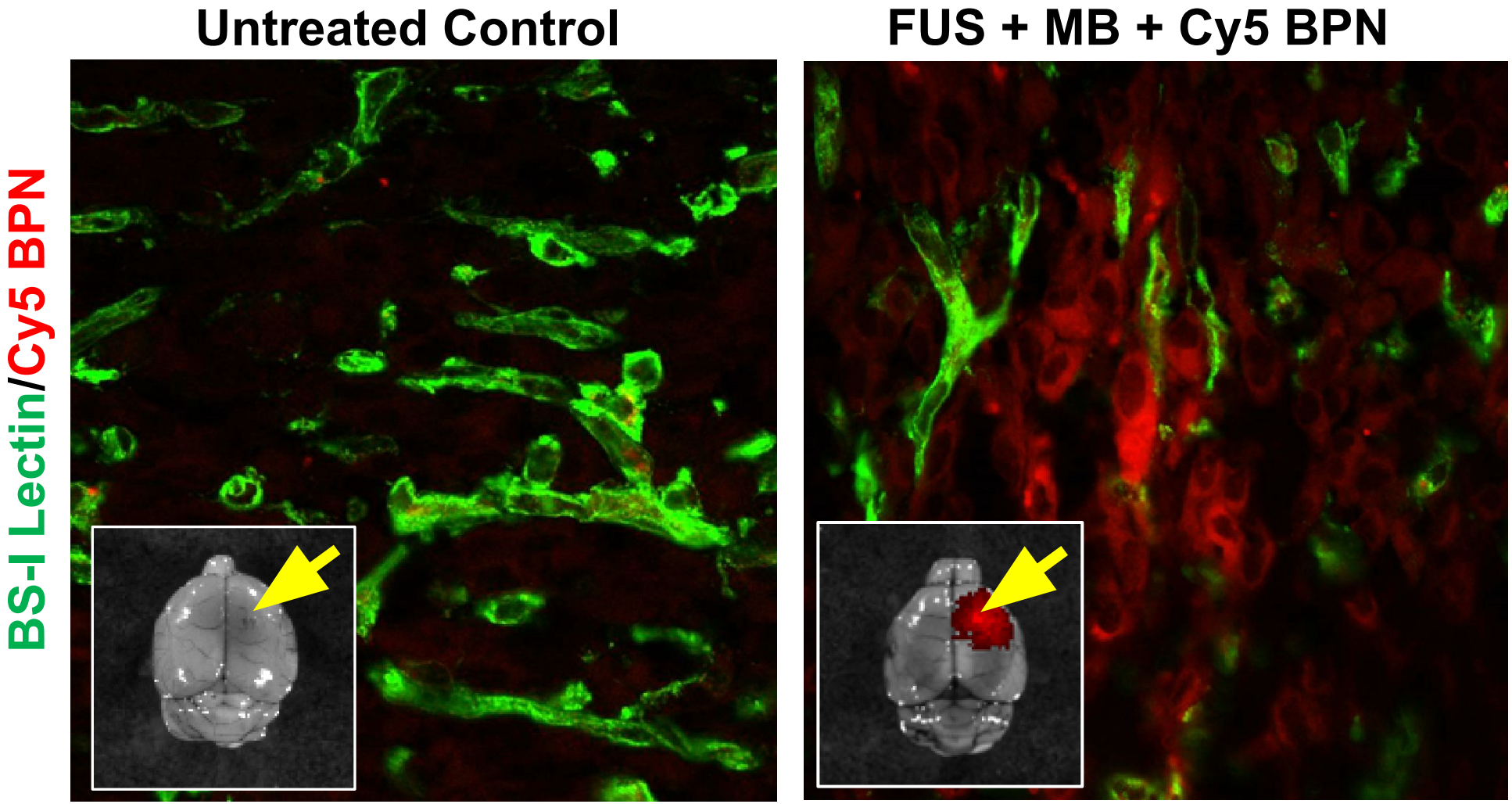
Nanoparticle (BPN) Delivery to Gliomas in Mice with MR Image-Guided Focused Ultrasound and Microbubbles (6h)



Curley et al. *Science Advances* DOI: 10.1126/sciadv.aay1344; 2020

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