Vascular Pre-Treatment for Augmented Focused Ultrasound Mediated Drug Delivery

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University of Virginia

CRS 2025 Annual Meeting and Exposition
July 17th, 2025

UVA FOCUSED ULTRASOUND

Glioblastoma (GBM)

- Glioblastoma (GBM) is WHO classified **grade IV glioma**
- **40%** of primary brain tumors are GBM
- GBM takes more than **13,000 American lives** annually

UVA FOCUSED ULTRASOUND

Glioblastoma (GBM)

Current Standard of Care

Surgical Resection

Radiation Therapy

Temozolomide (TMZ)
Chemotherapy

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Surgical Resection

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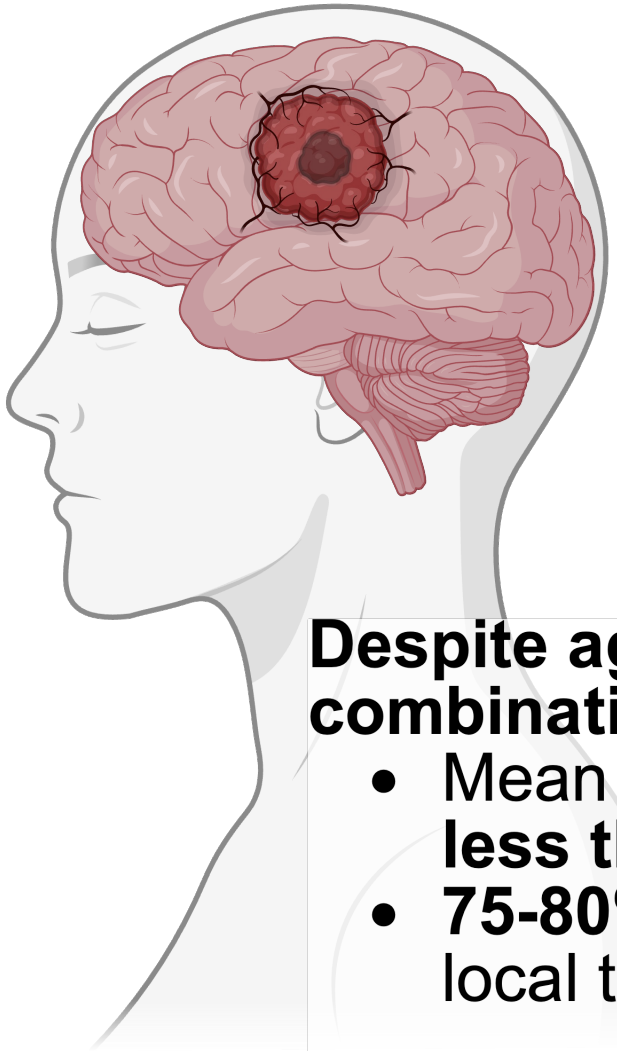
Temozolomide (TMZ) Chemotherapy



Despite aggressive combination therapy:

- Mean survival time of **less than 16 months**
- **75-80%** of patients have local tumor recurrence

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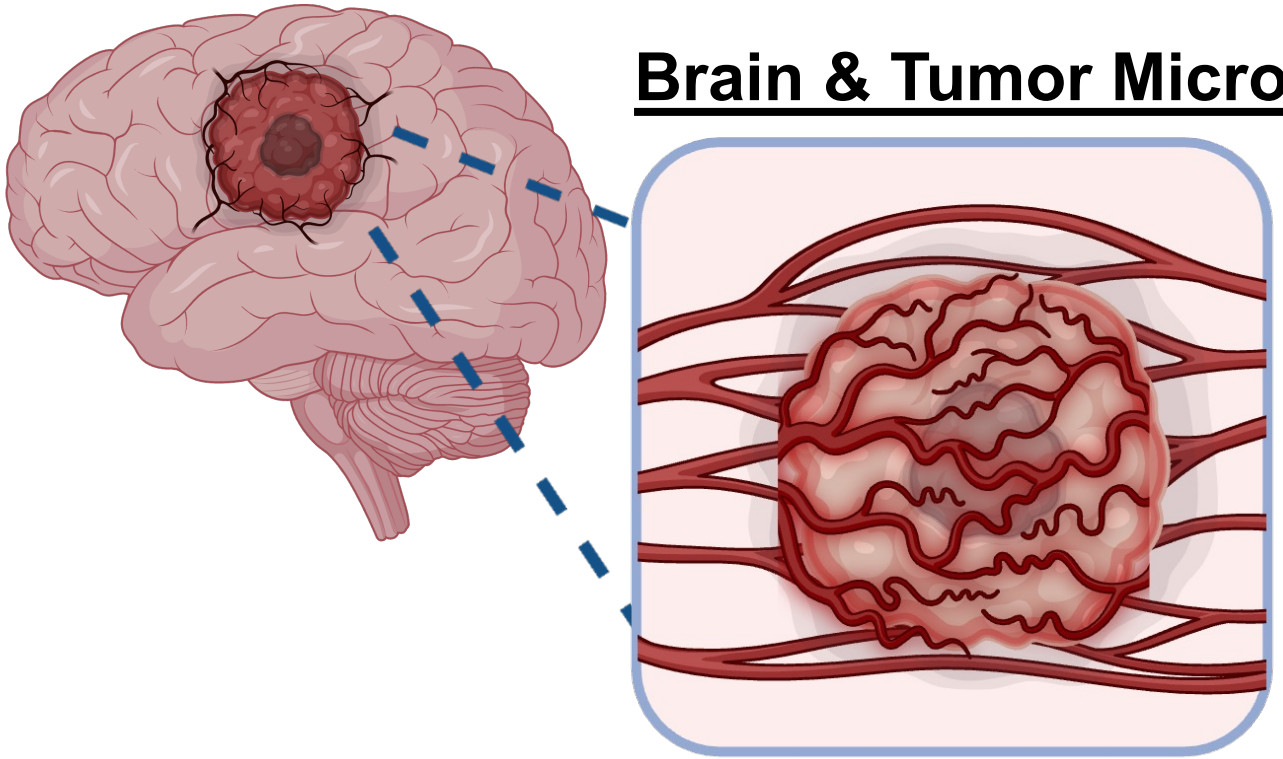
Brain & Tumor Microvasculature Impairs Drug Delivery



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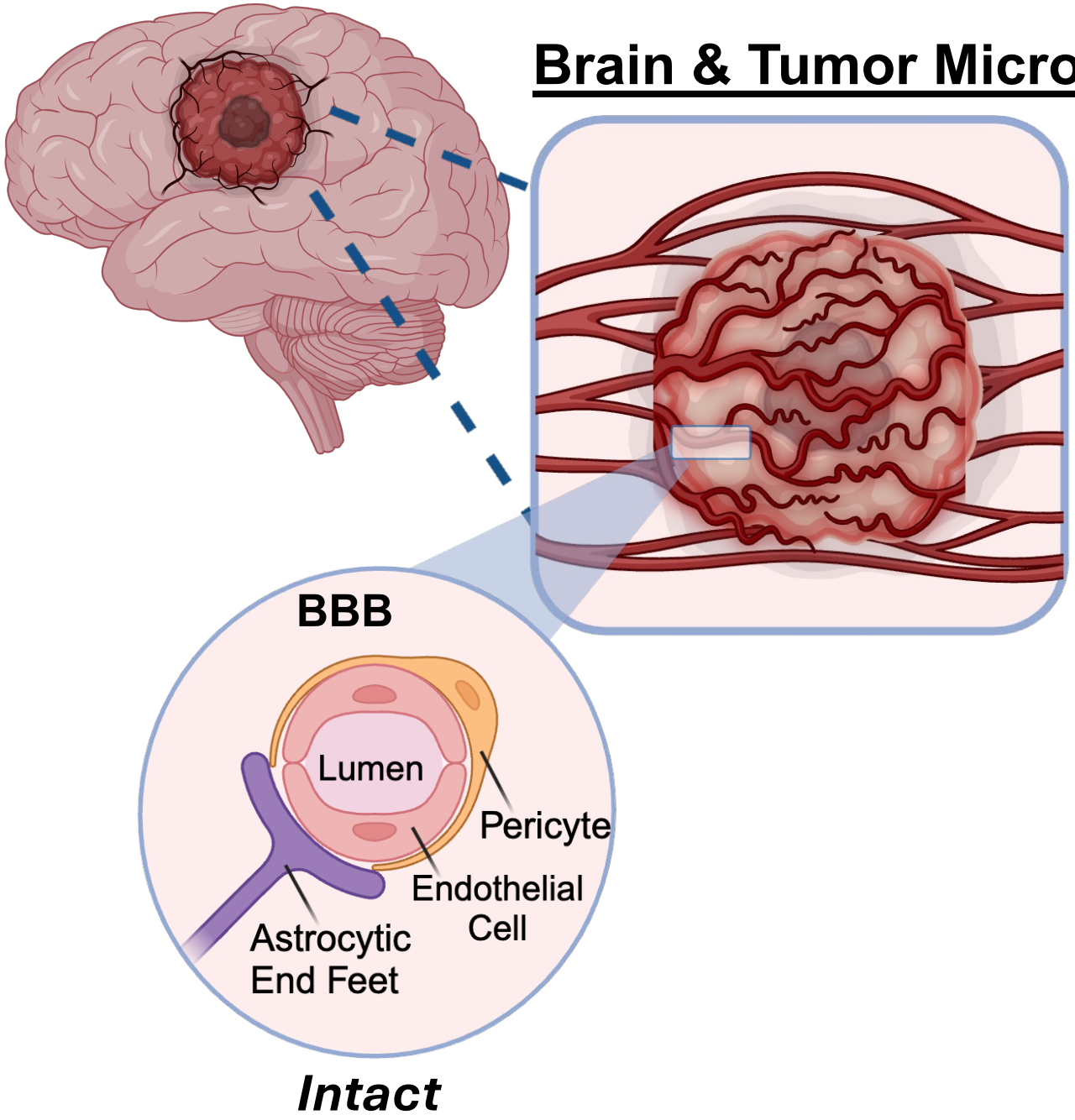

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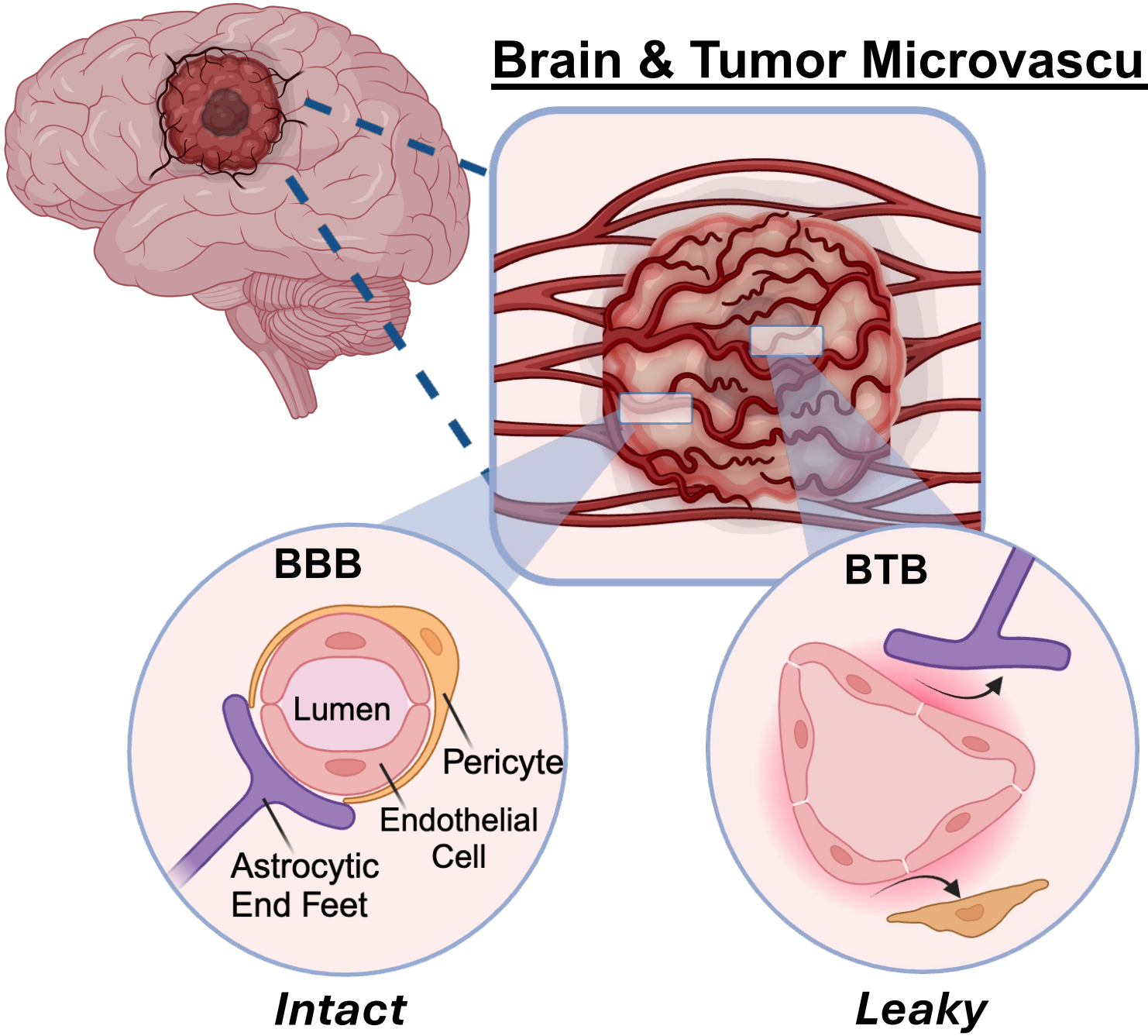

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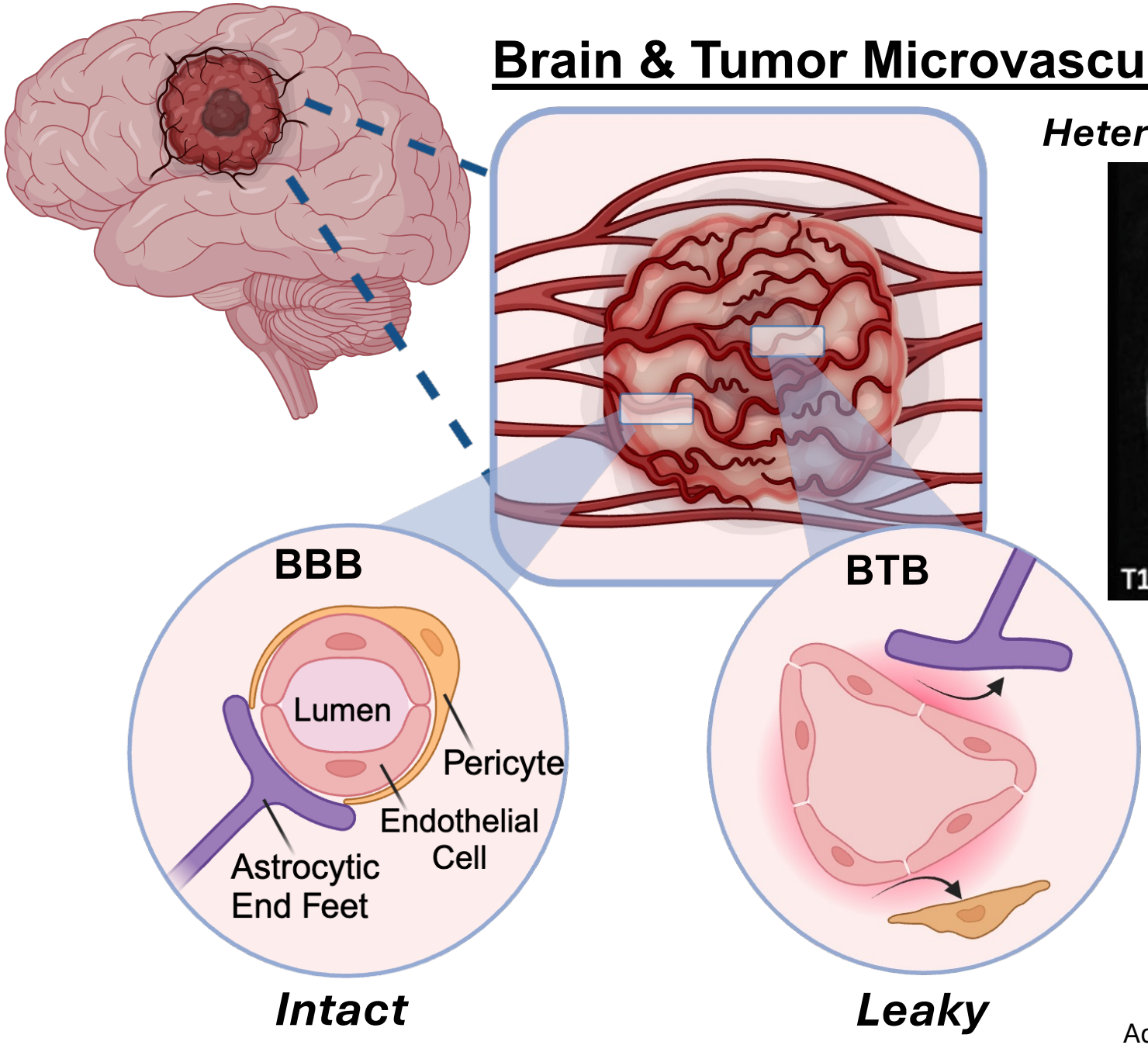
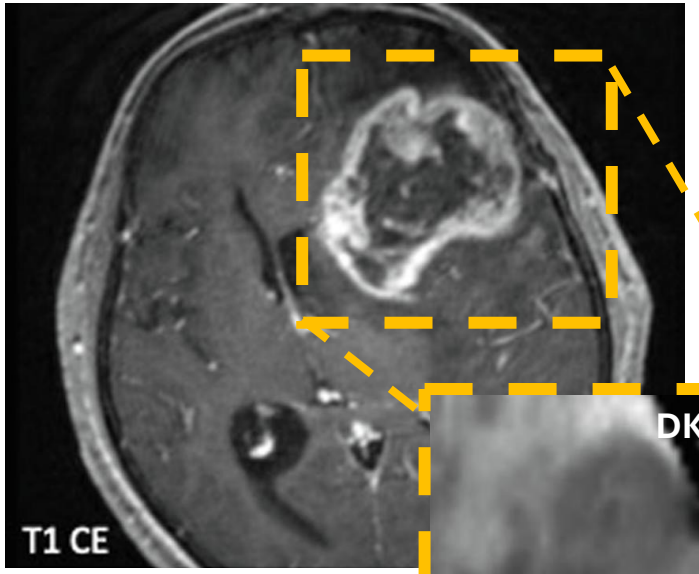
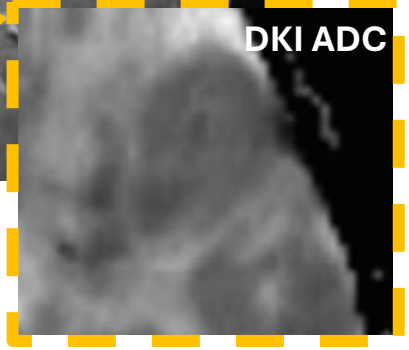


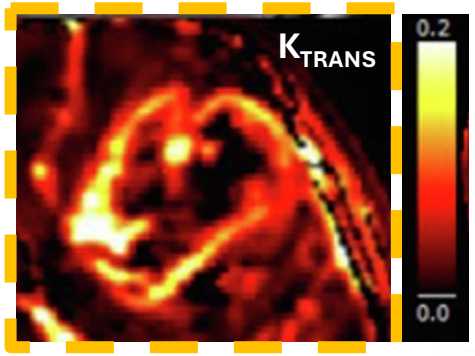
Heterogeneous Baseline Tumor Transport



Variable Contrast Enhancement



Variable ADC Restriction



Variable Tumor Permeability

Adapted from Richter, V., et.al., Eur. J. Radiol. (2024)

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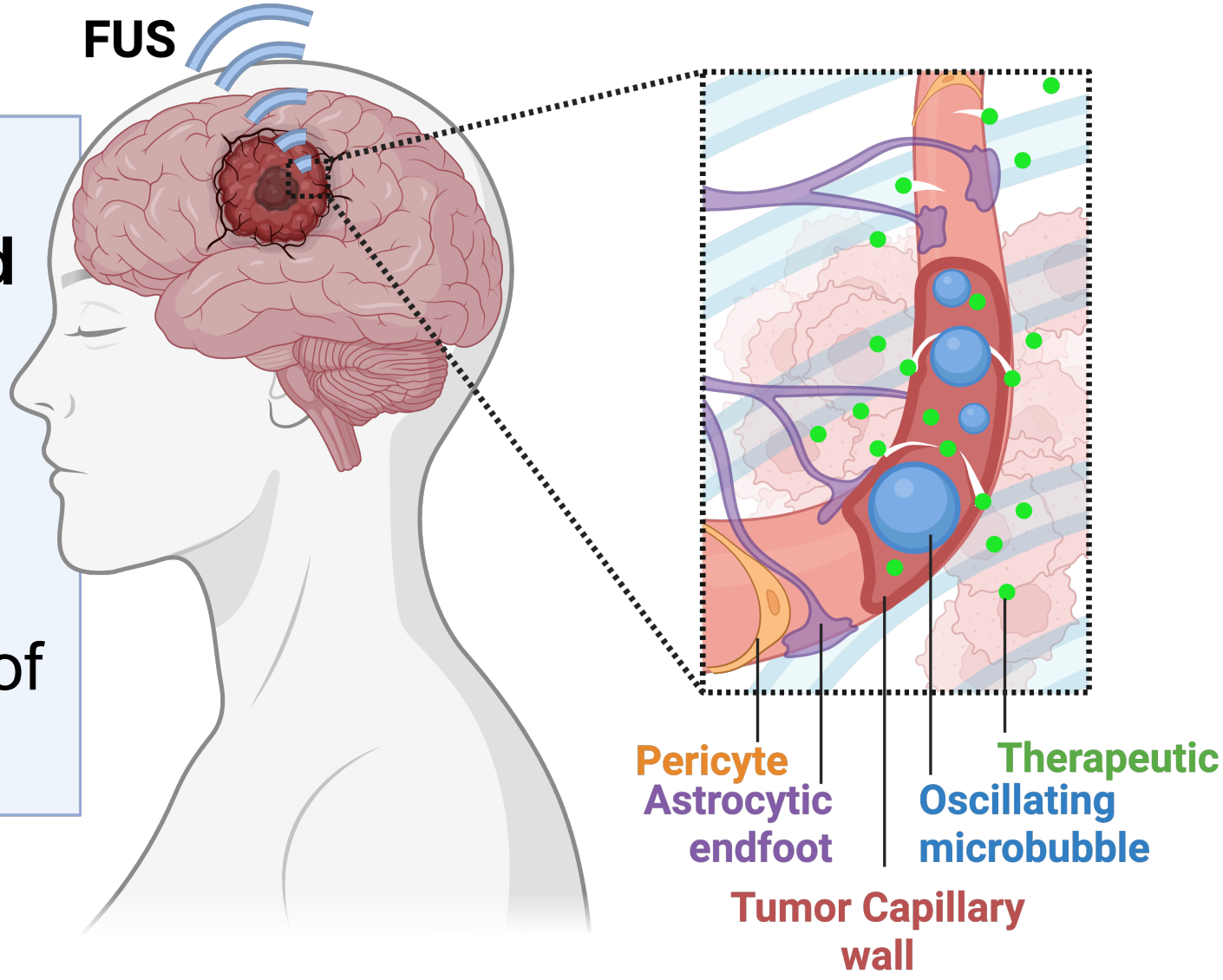
Brain & Tumor Microvasculature Impairs Drug Delivery

Magnetic resonance image-guided focused ultrasound (MRgFUS) has emerged as a targeted technique for BBB/BTB opening to **enhance the delivery** of anti-cancer therapies.

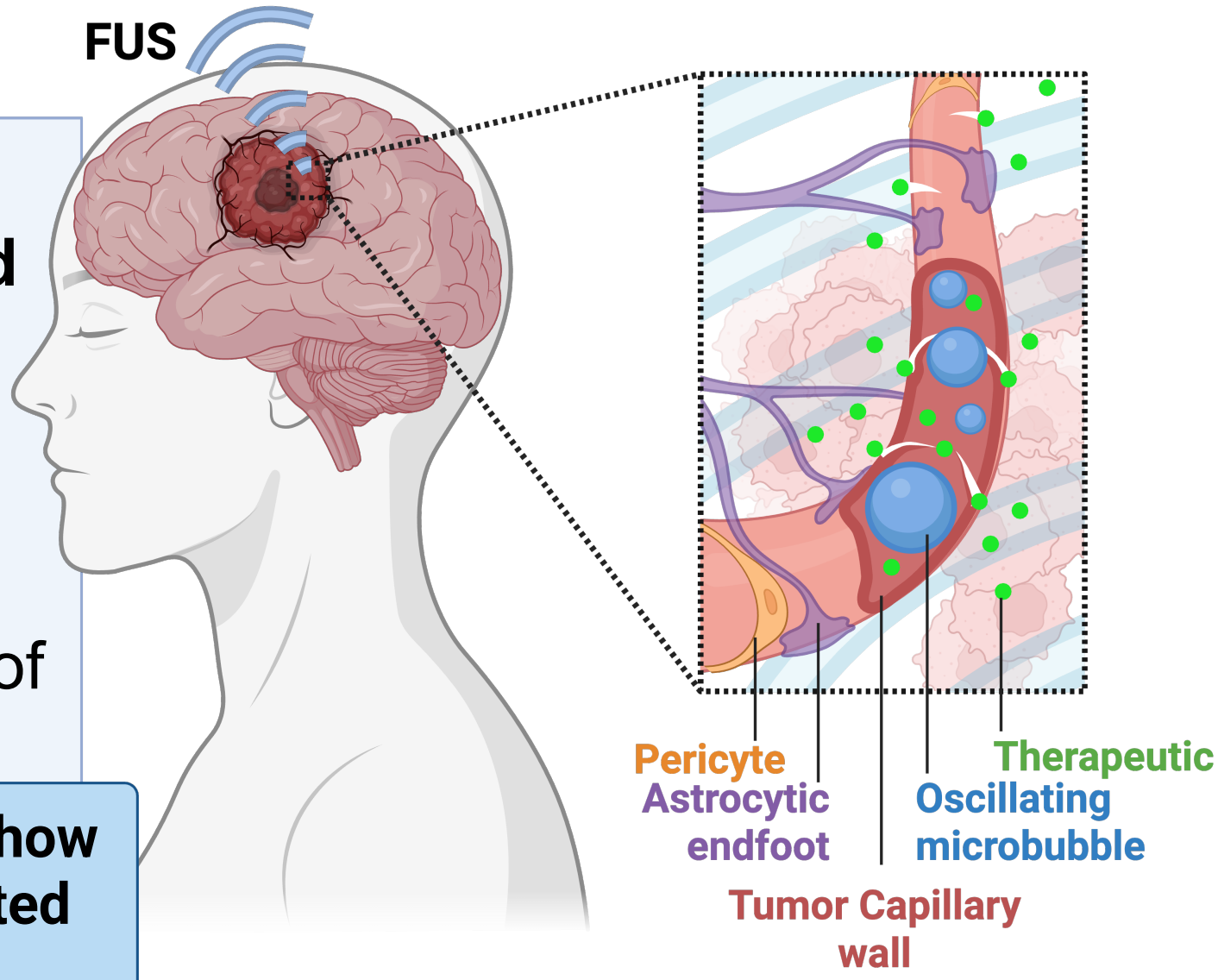


UVA FOCUSED ULTRASOUND

Brain & Tumor Microvasculature Impairs Drug Delivery

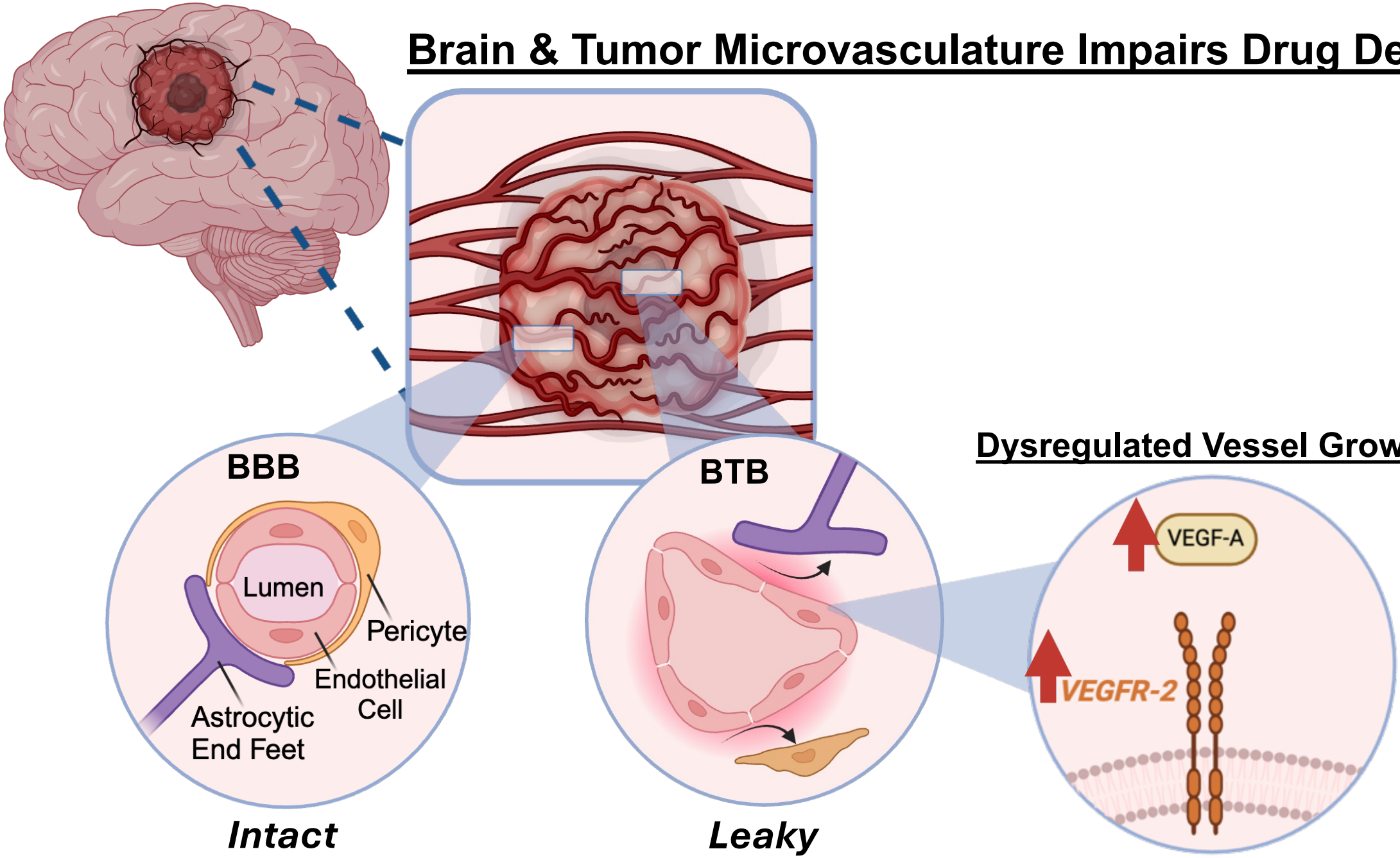
Magnetic resonance image-guided focused ultrasound (MRgFUS) has emerged as a targeted technique for BBB/BTB opening to **enhance the delivery** of anti-cancer therapies.

Very few approaches explore how the uniformity of FUS-mediated delivery can be improved

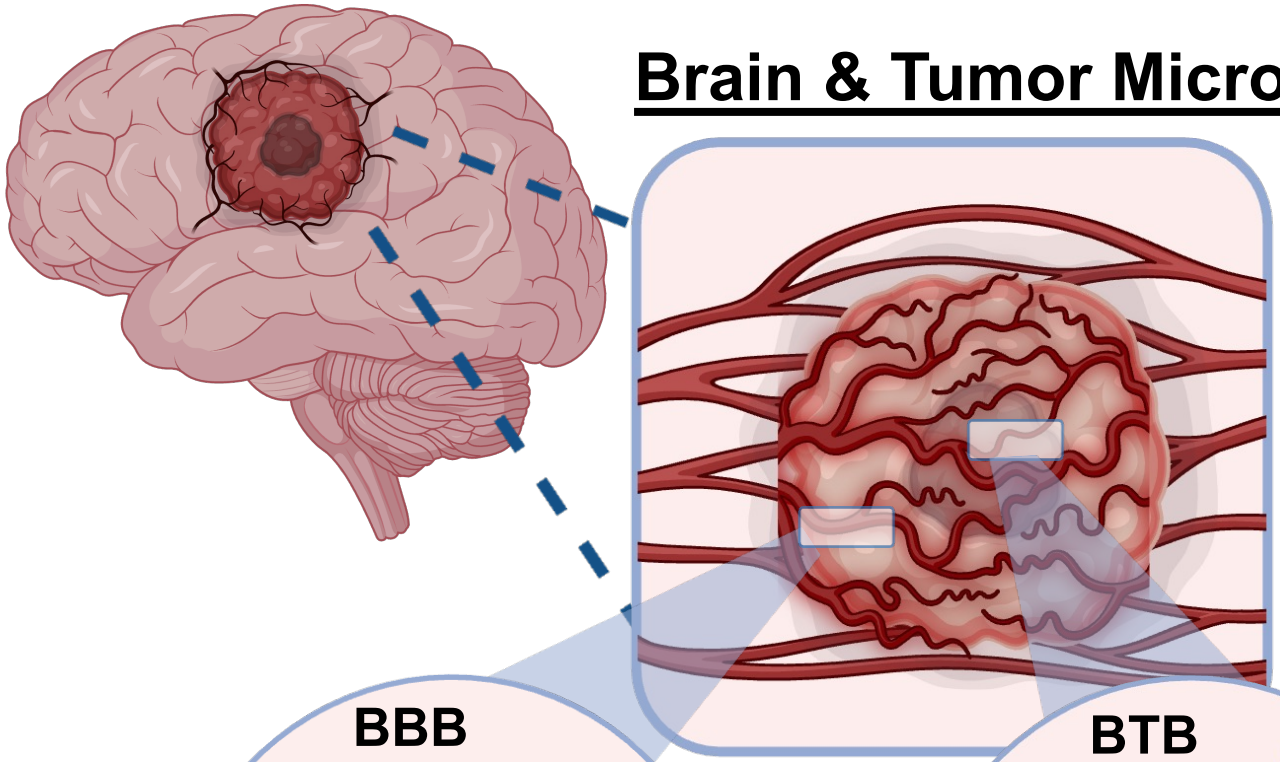


FOCUSED ULTRASOUND

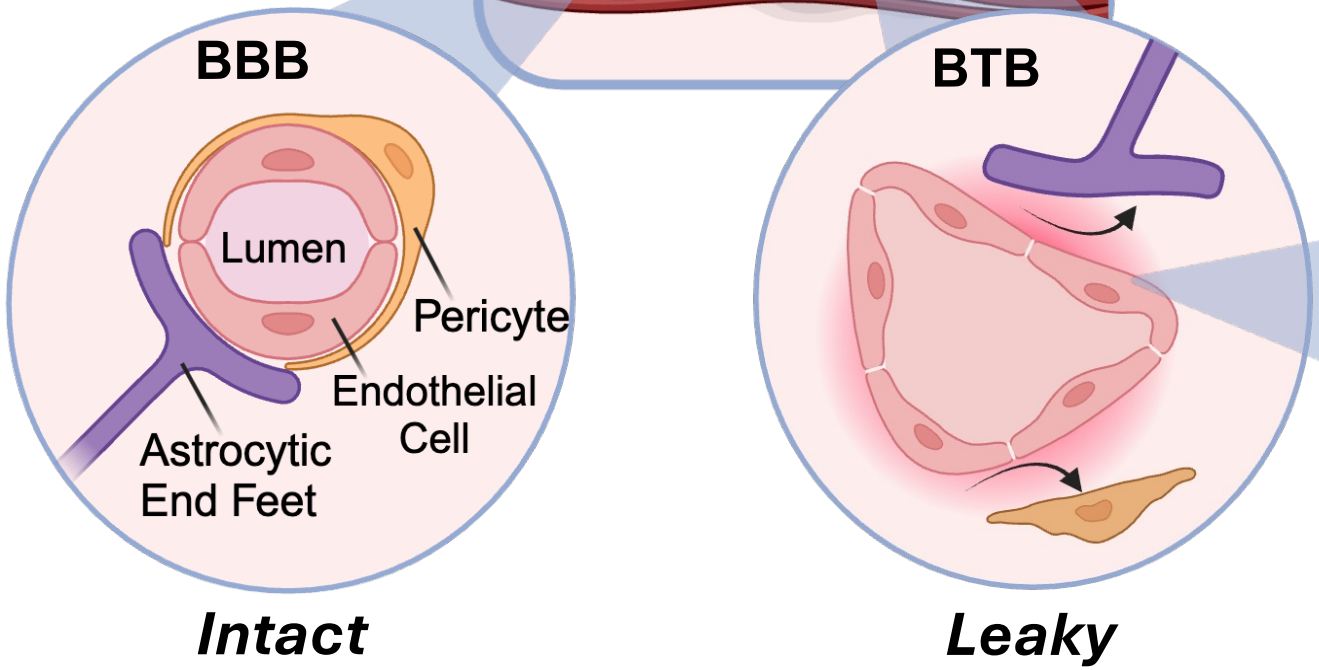
Brain & Tumor Microvasculature Impairs Drug Delivery



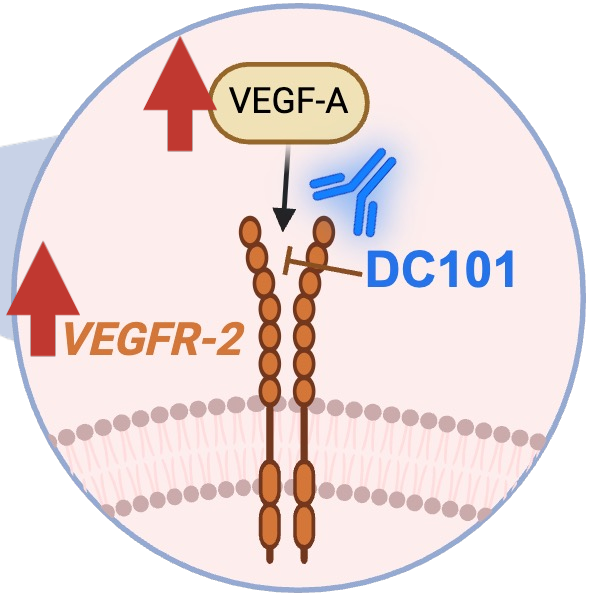
Brain & Tumor Microvasculature Impairs Drug Delivery



Goal: Test the hypothesis that **neoadjuvant VEGFR2 inhibition** can improve drug delivery and distribution with FUS.



Dysregulated Vessel Growth



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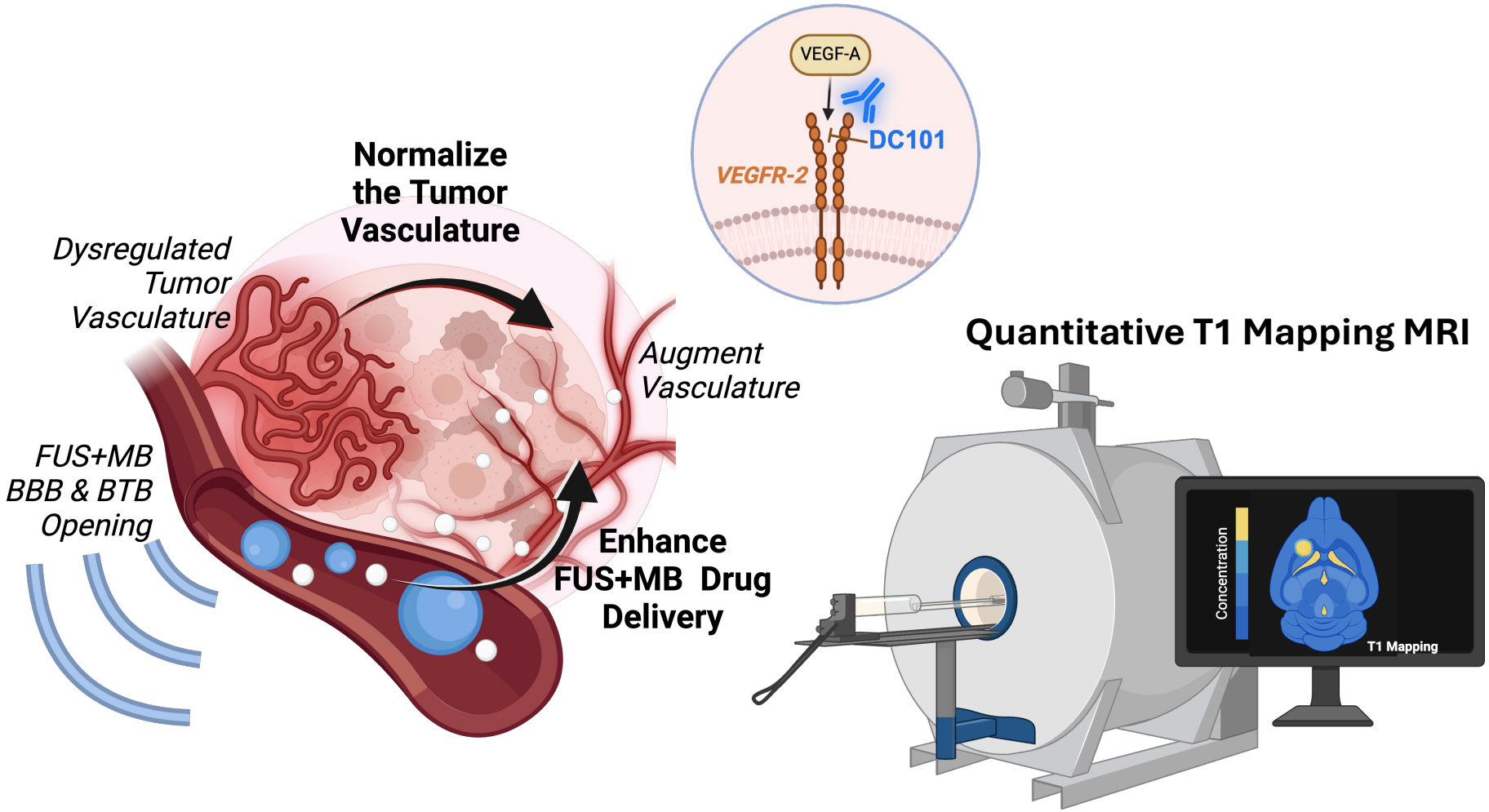
Investigate therapeutic strategy of neoadjuvant VEGFR2 inhibition-mediated vascular modulation to augment delivery of gadolinium-based model drugs with FUS.



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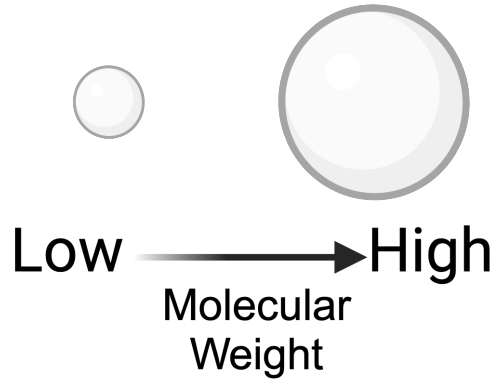
Gadolinium-Based Model Drugs

Investigate Drug Size Dependance



Low Molecular Weight Model Drug:

MultiHance™

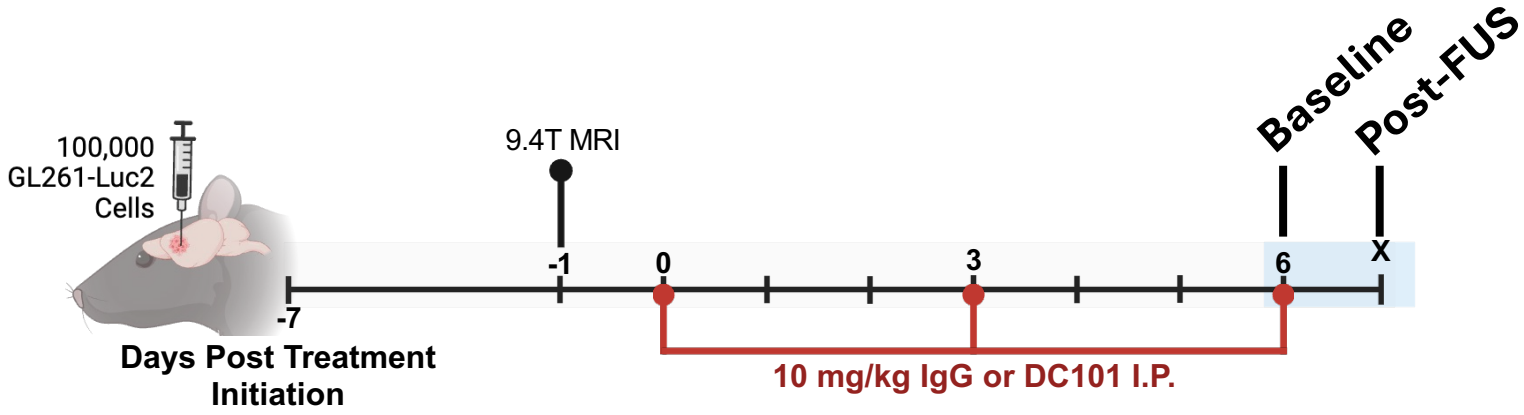
- ~1kDA Molecular Weight
- Commonly used in routine T1 Weighted MRI
- Similar in size to chemotherapies

High Molecular Weight Model Drug:

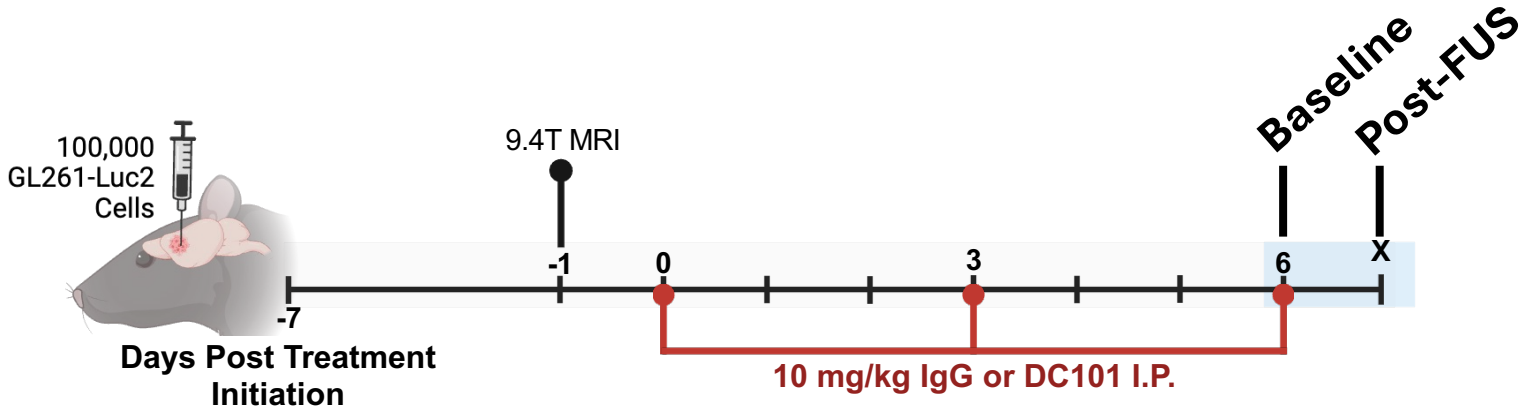
Gadospin-D

- ~35 kDA Molecular Weight
- Similar in size to small biologics

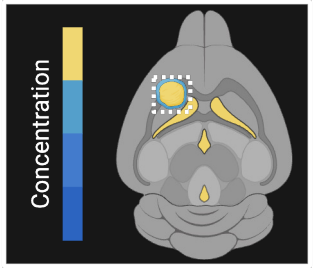
Treatment Strategy and Methods



Treatment Strategy and Methods

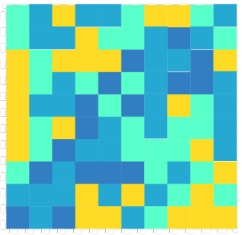


MRI Concentration Maps

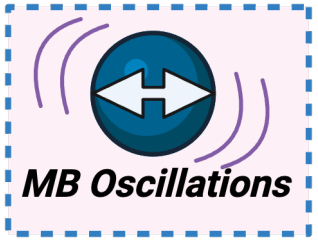


- Concentration
- Homogeneity
  - Skewness
  - Kurtosis

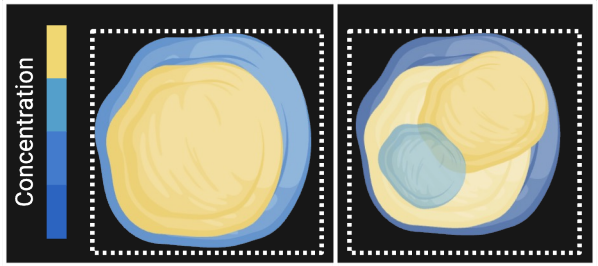
Radiomics Feature Extraction



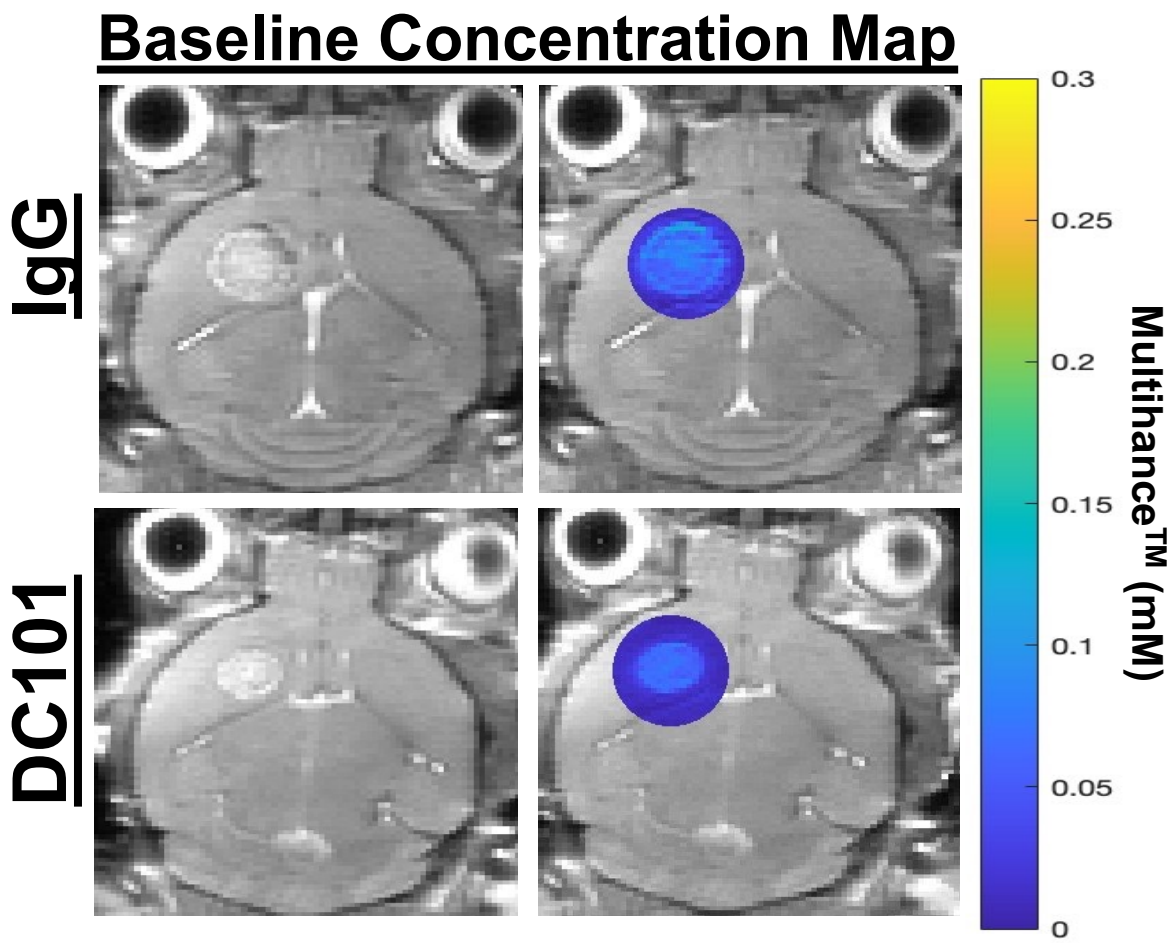
FUS Passive Cavitation Detection

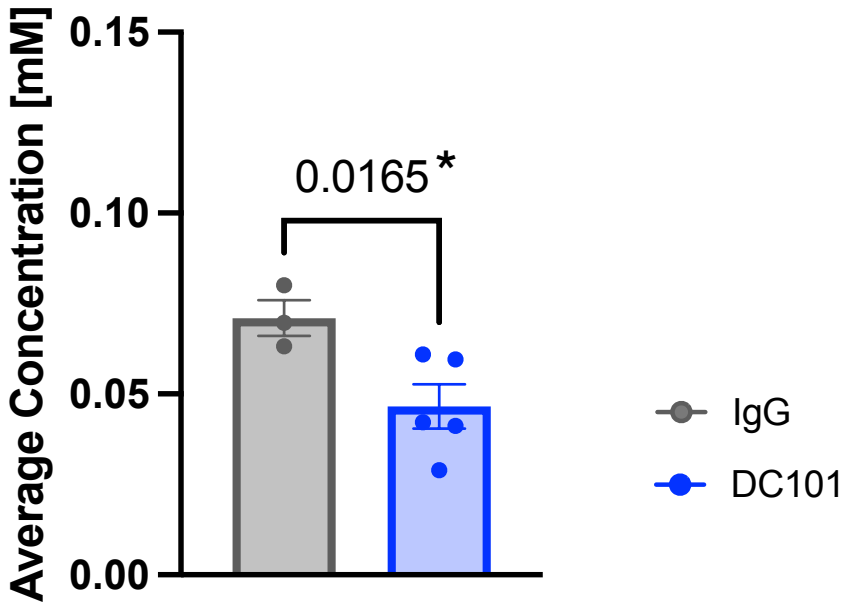


Reveal Delivery Differences Between Treatment Groups



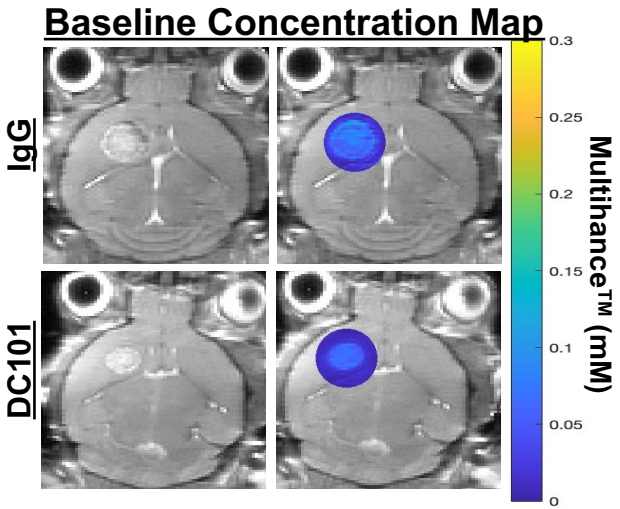
DC101 treatment reduces baseline permeability to MultiHance™ 6 days after treatment initiation.

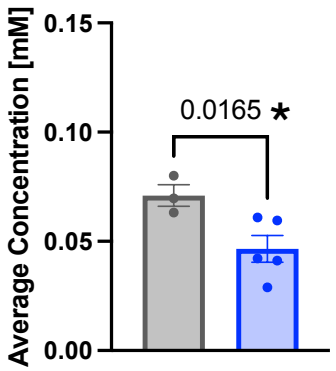


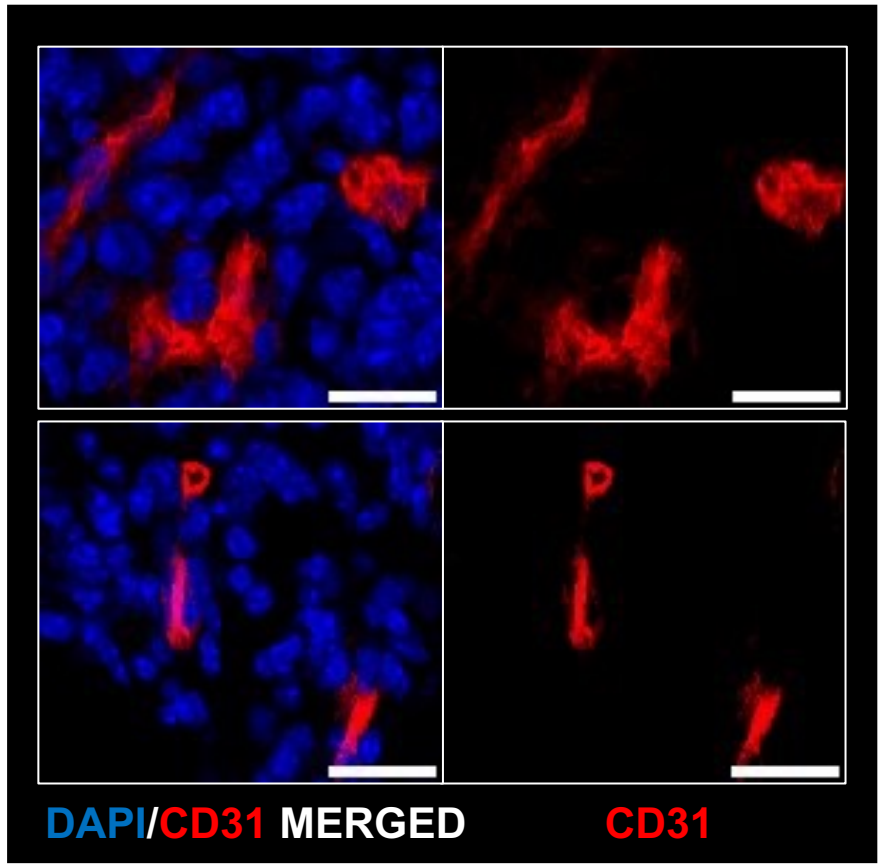


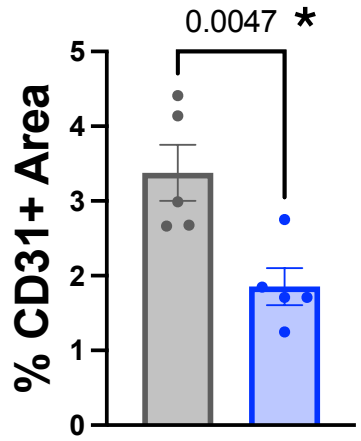
FOCUSED ULTRASOUND

Permeability changes due to VEGFR2 inhibition correspond with decreased vessel size.









IgG

DC101

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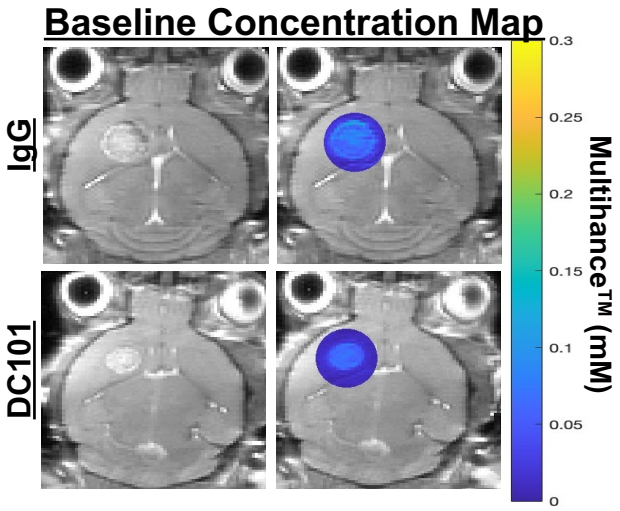
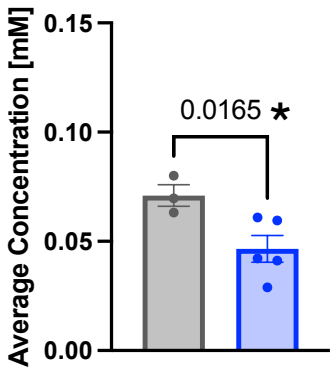
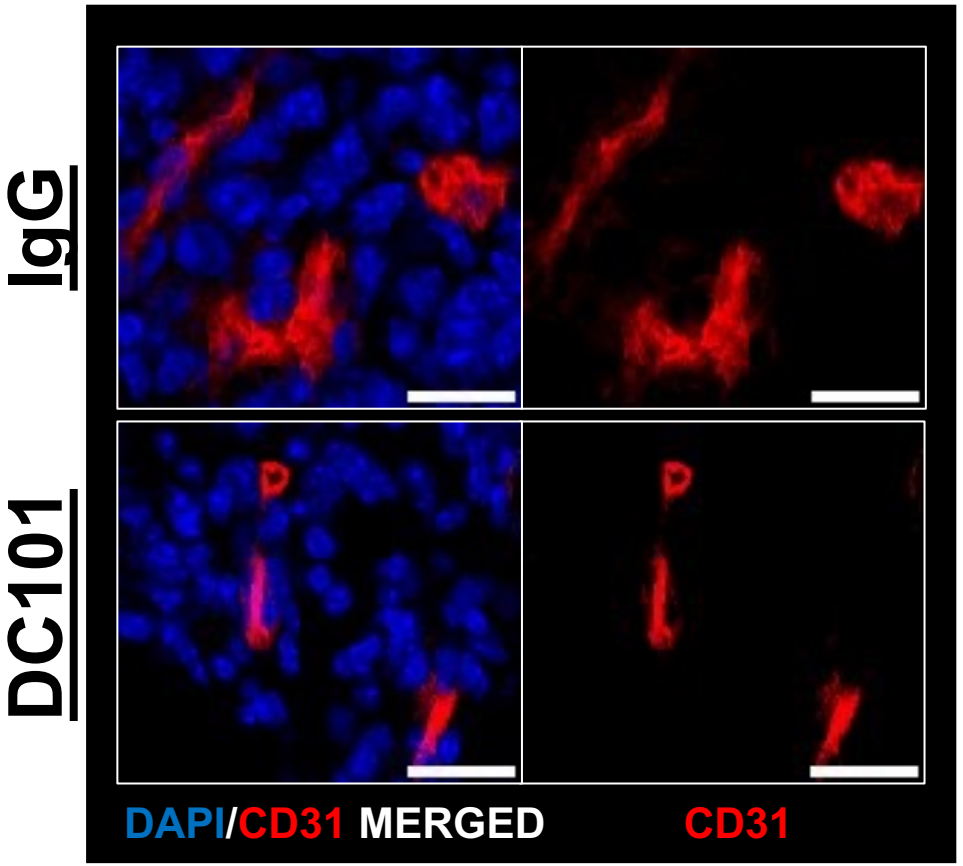
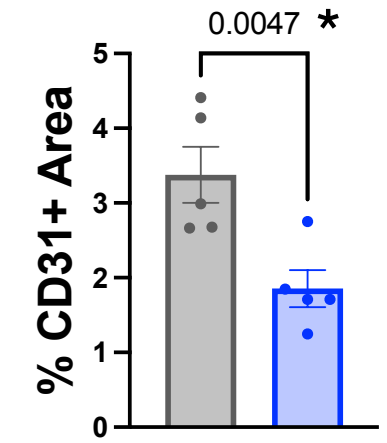
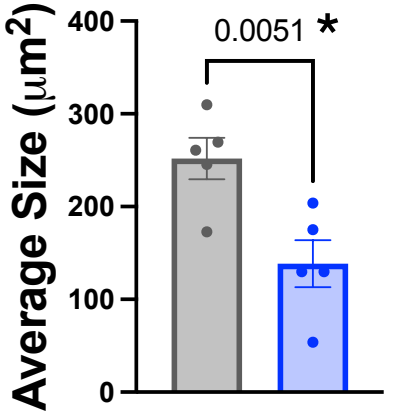
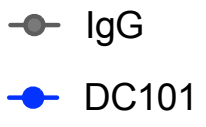






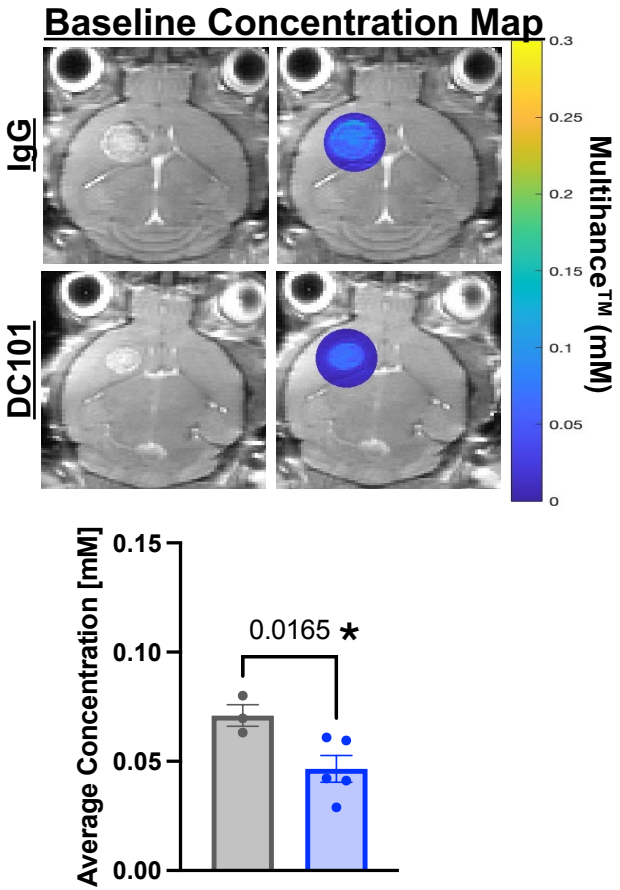


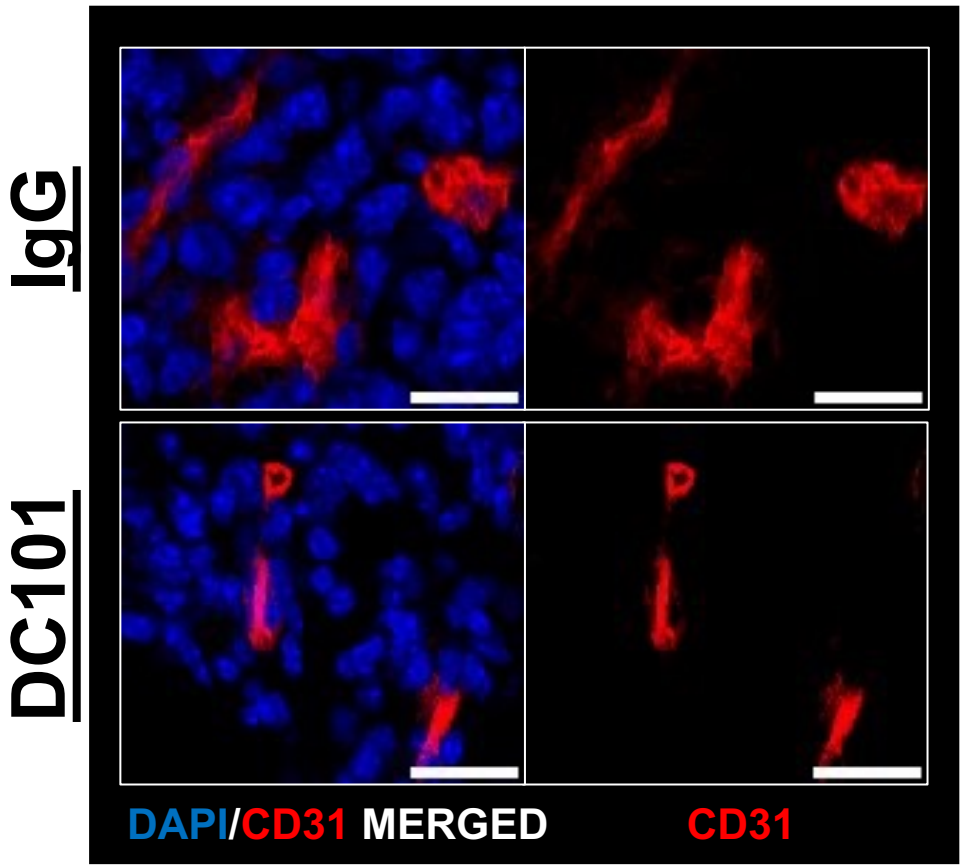


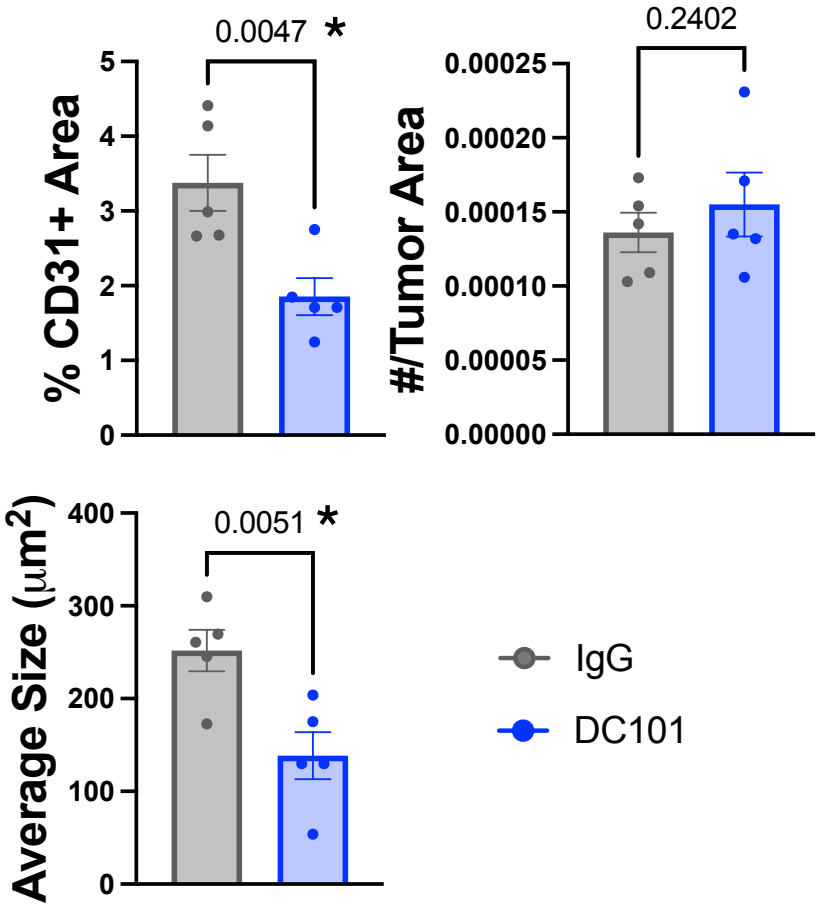


UVA FOCUSED ULTRASOUND

Permeability changes due to VEGFR2 inhibition correspond with decreased vessel size.







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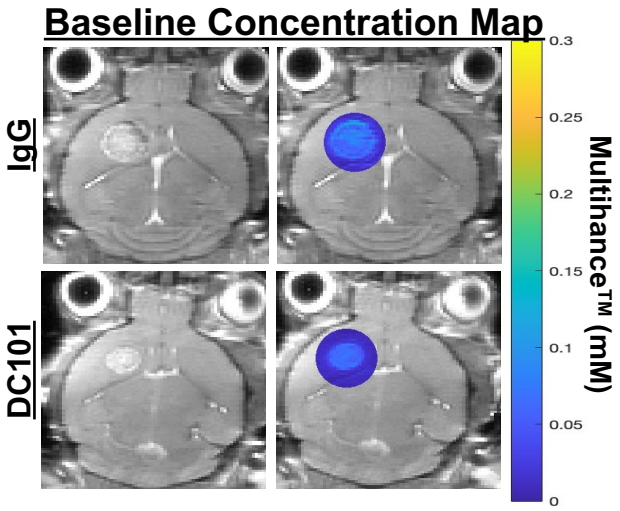
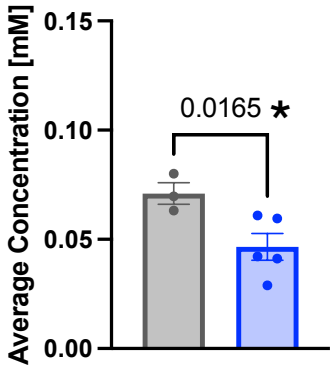
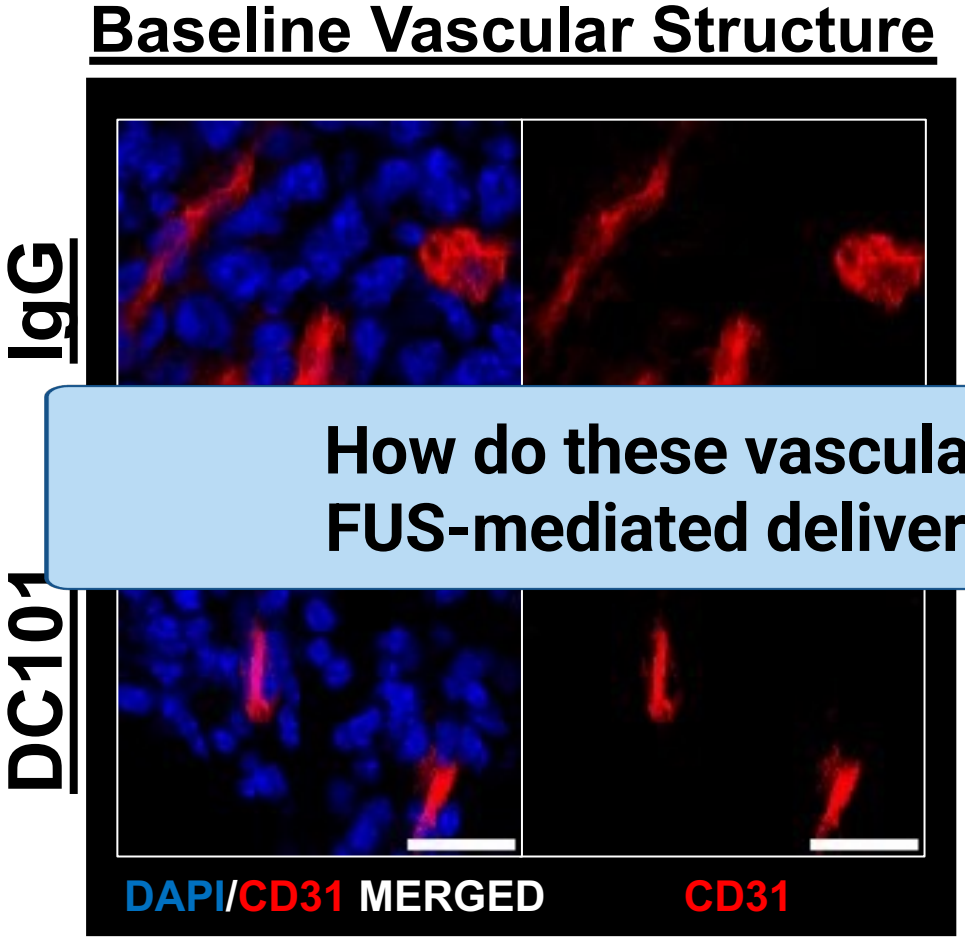
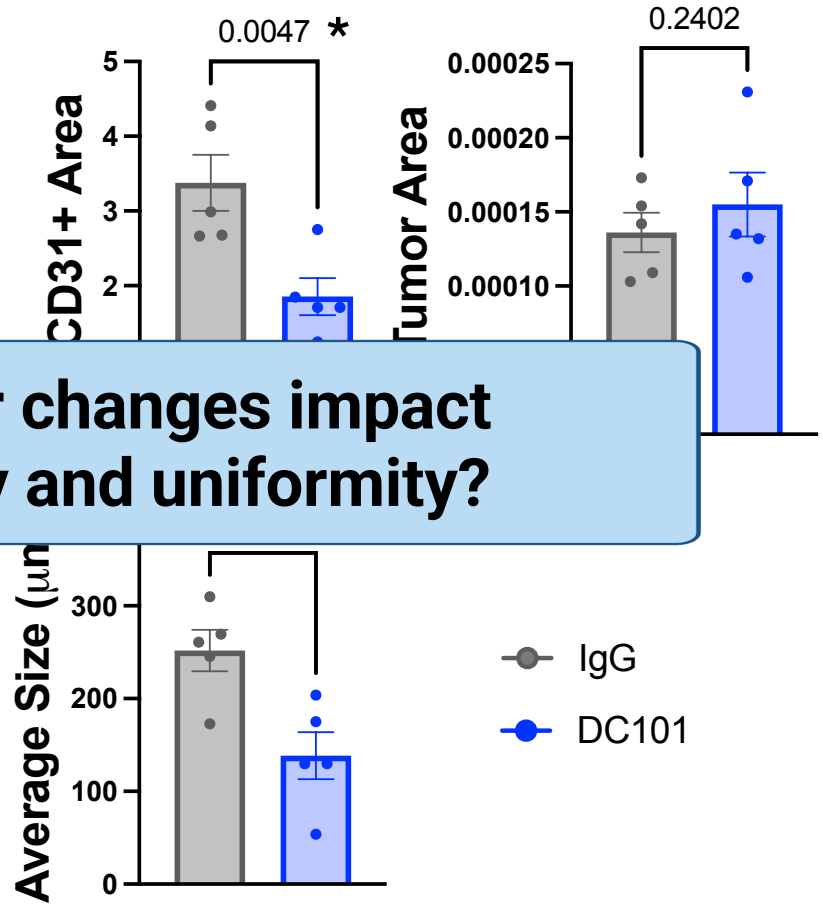




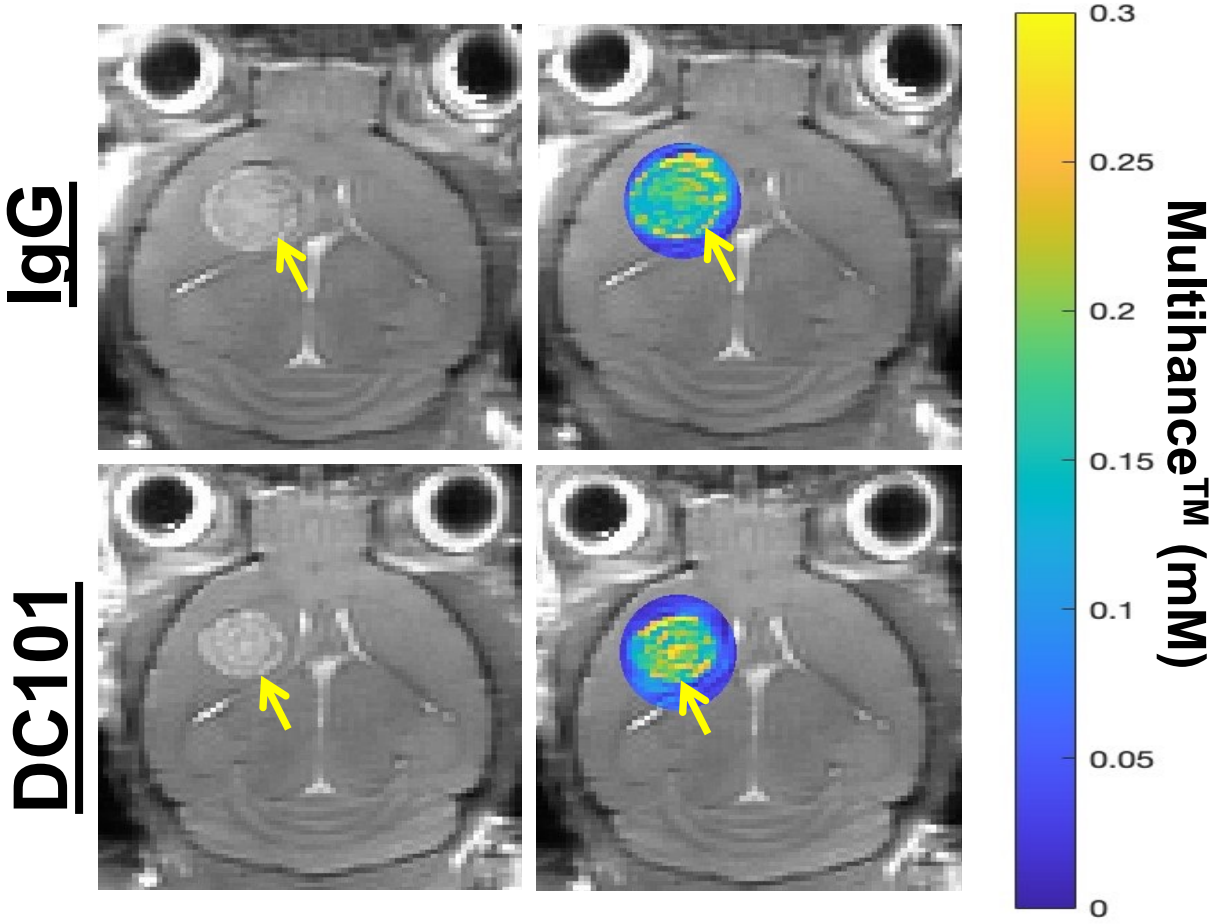


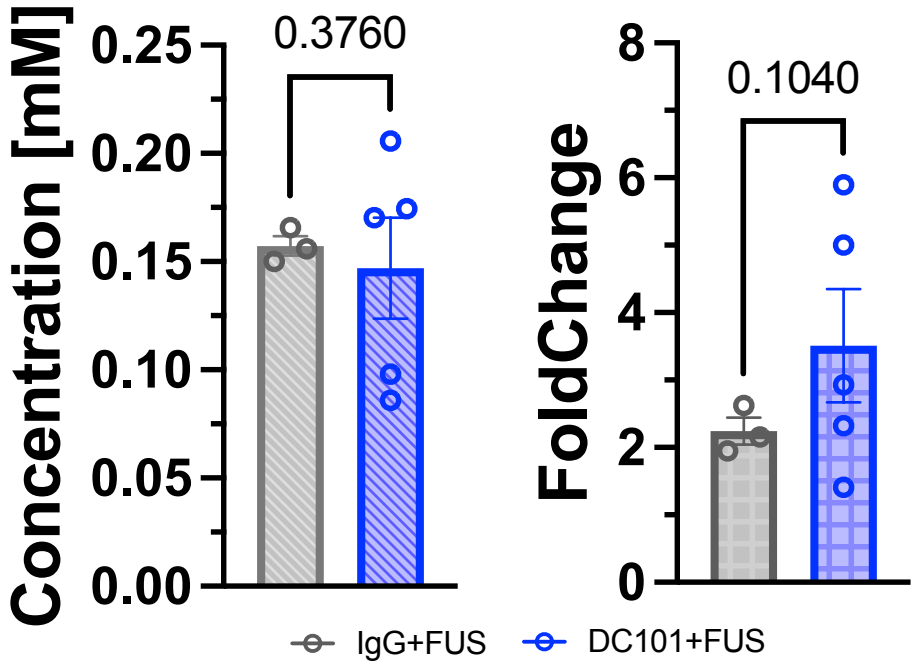
How do these vascular changes impact FUS-mediated delivery and uniformity?



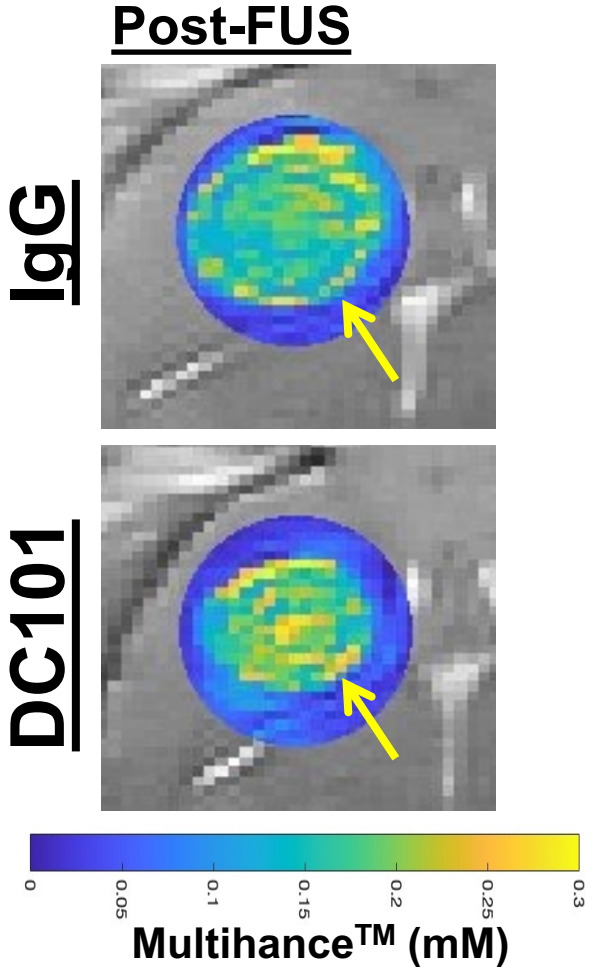
anti-VEGFR2 pre-treatment does not limit FUS-mediated low molecular weight model drug delivery.

Post-FUS Concentration Map





DC101 pre-treatment increases the uniformity of intratumoral MultiHance™ distribution.



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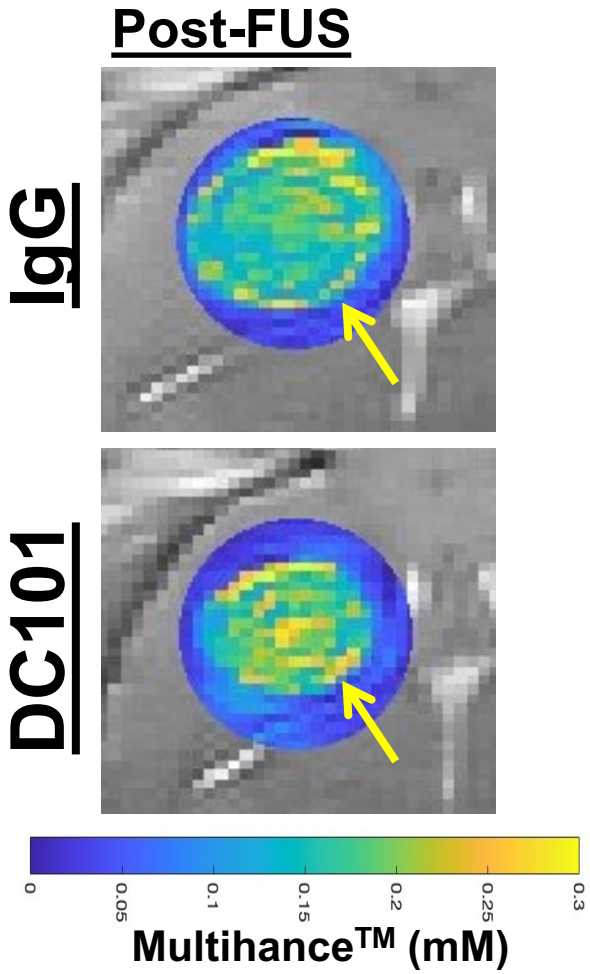

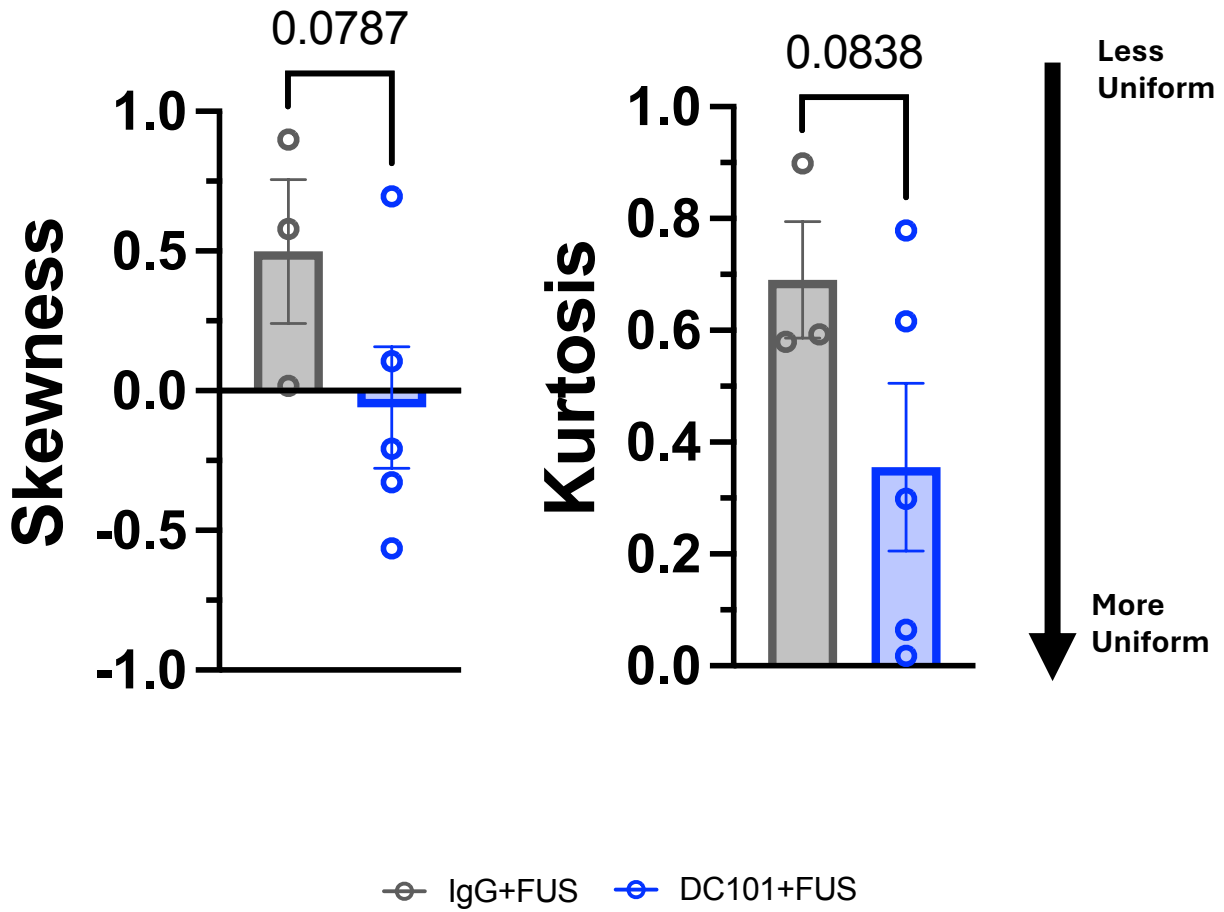

UVA FOCUSED ULTRASOUND

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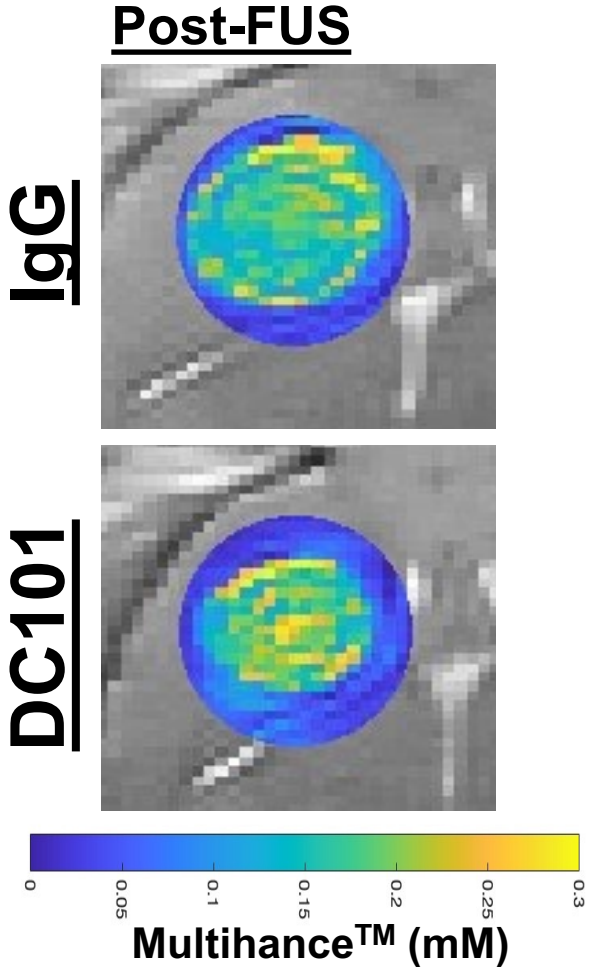
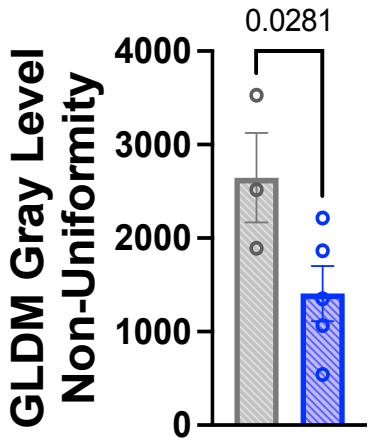
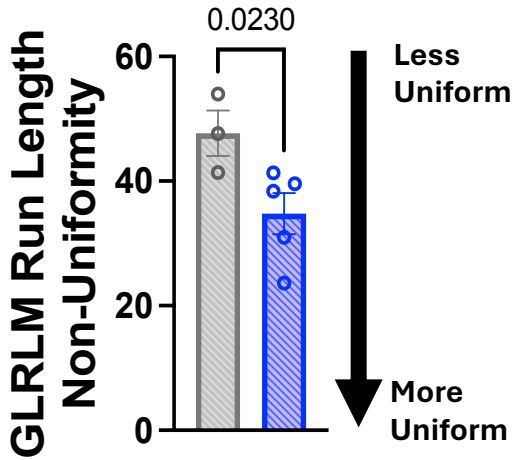
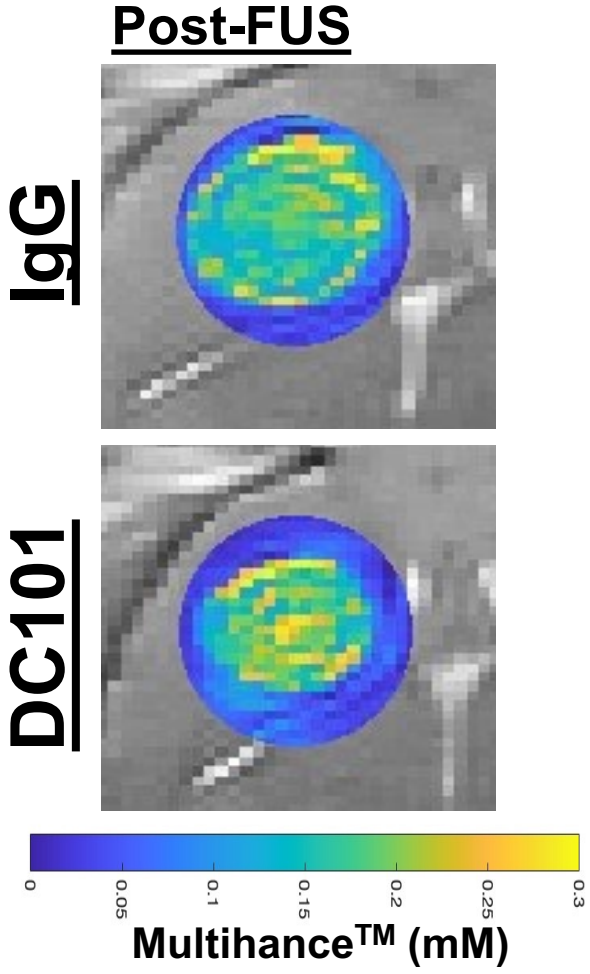


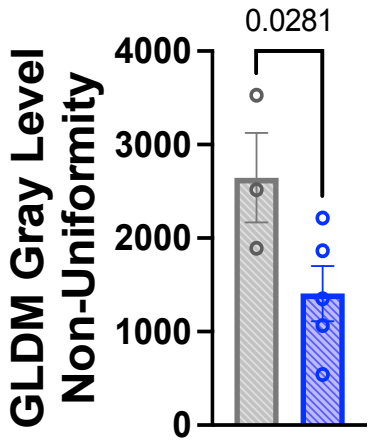


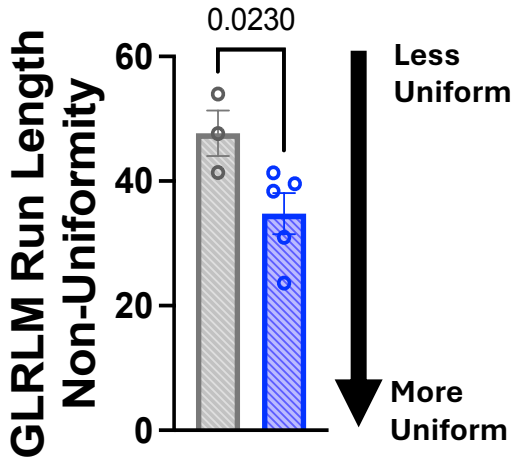


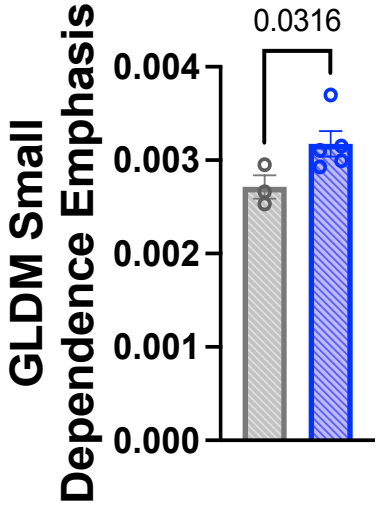
IgG+FUS DC101+FUS

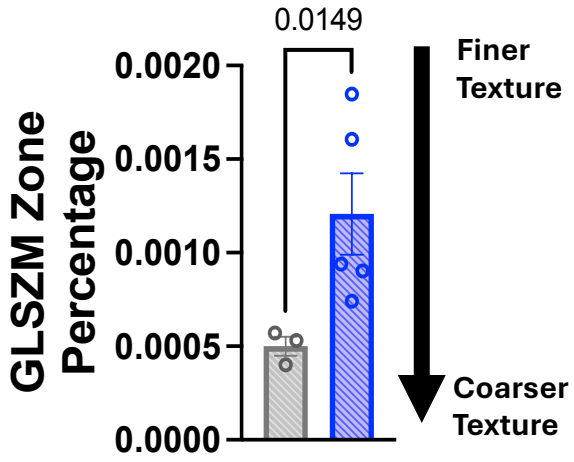
DC101 pre-treatment increases the uniformity of intratumoral MultiHance™ distribution.

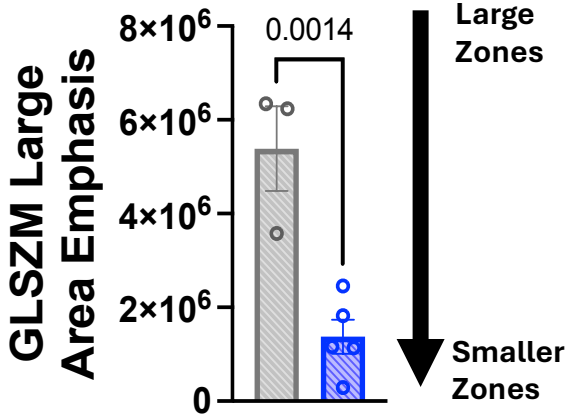








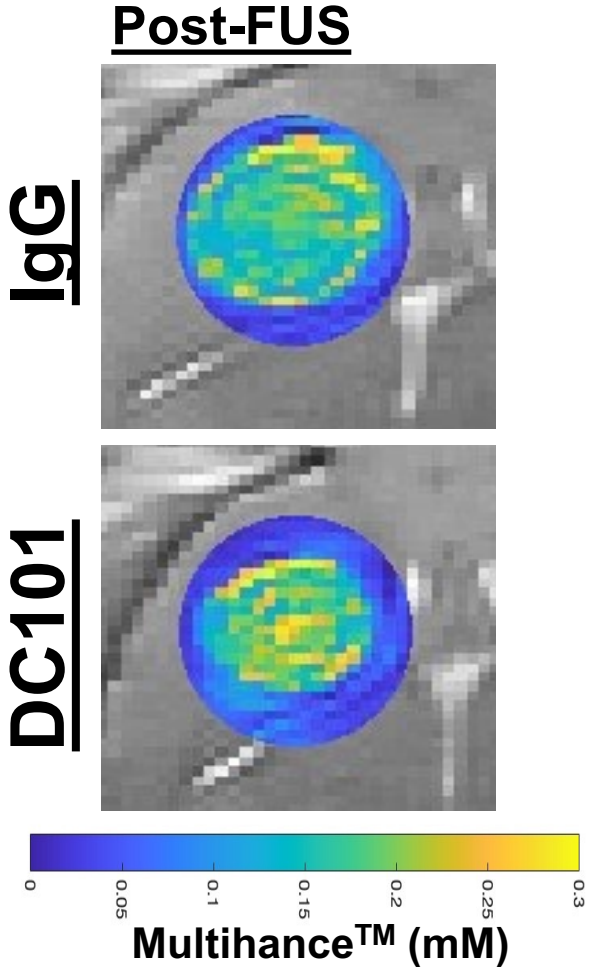


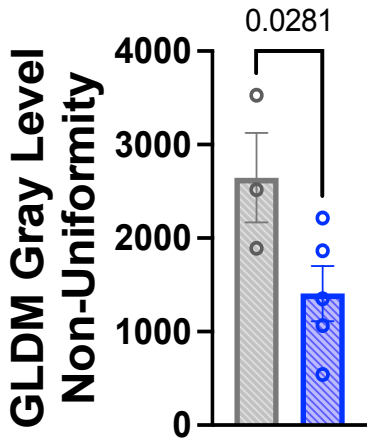


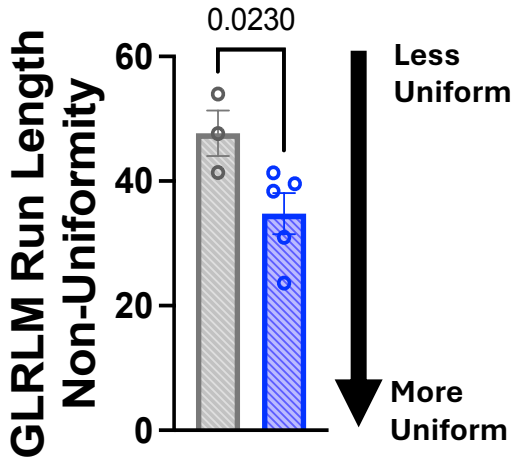
IgG+FUS DC101+FUS

FOCUSED ULTRASOUND

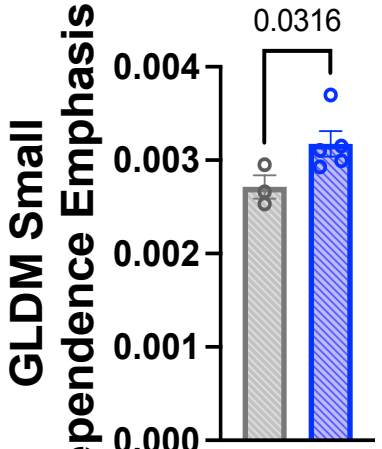
DC101 pre-treatment increases the uniformity of intratumoral MultiHance™ distribution.

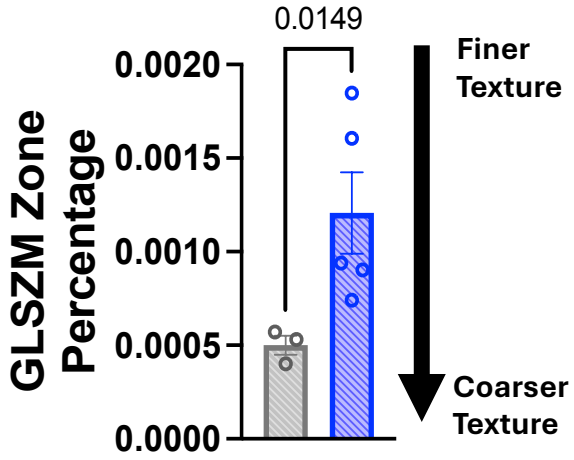


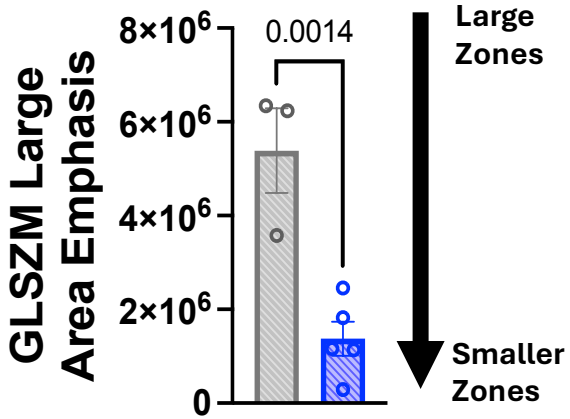




- **anti-VEGFR2**: many small homogenous delivery regions
- **IgG control**: larger, less homogenous delivery zones



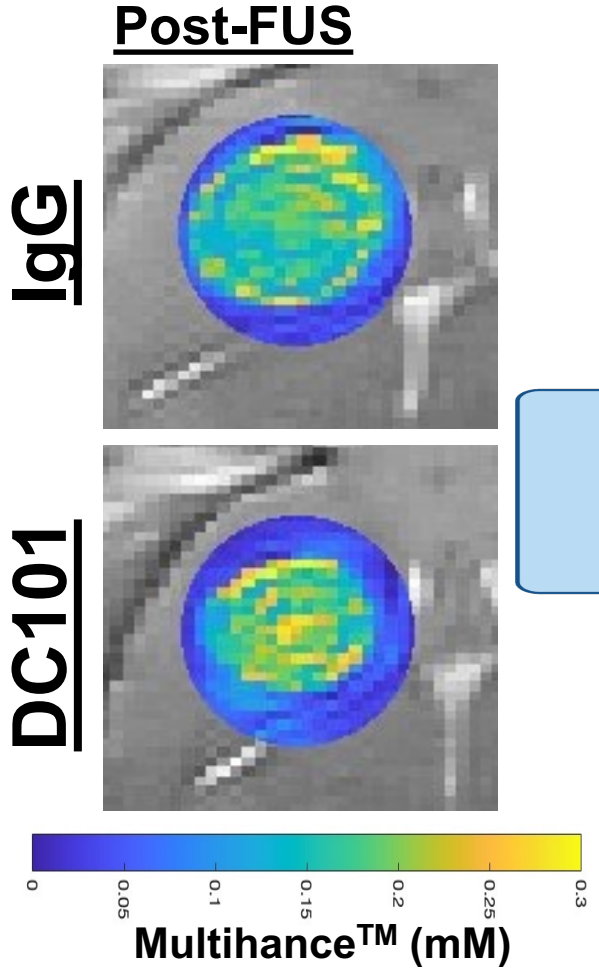


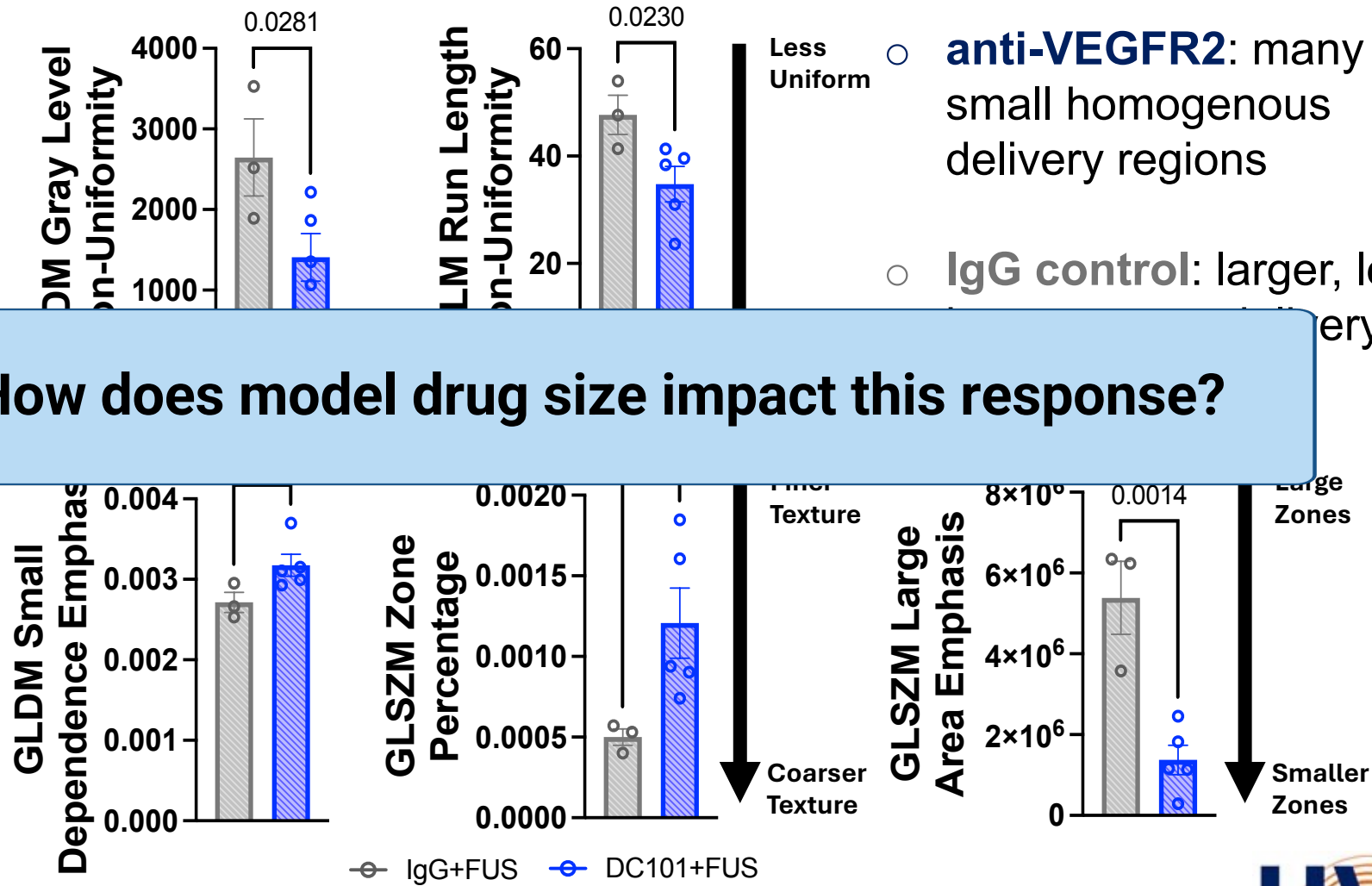


IgG+FUS DC101+FUS

UVA FOCUSED ULTRASOUND

DC101 pre-treatment increases the uniformity of intratumoral MultiHance™ distribution.





- **anti-VEGFR2**: many small homogenous delivery regions
- **IgG control**: larger, less ery

How does model drug size impact this response?

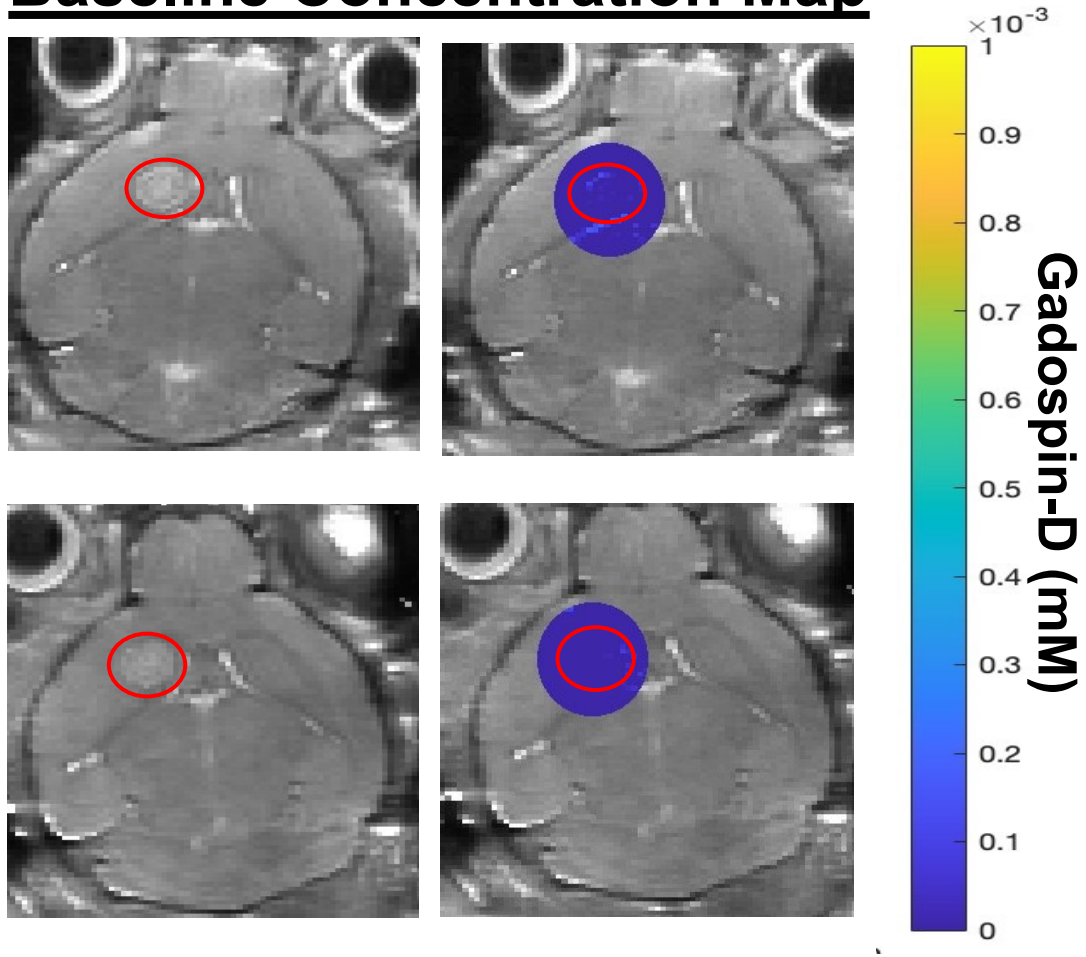
FOCUSED ULTRASOUND

At baseline, tumors are impermeable to high molecular weight model drug, Gadospin-D, independent of treatment.

Baseline Concentration Map

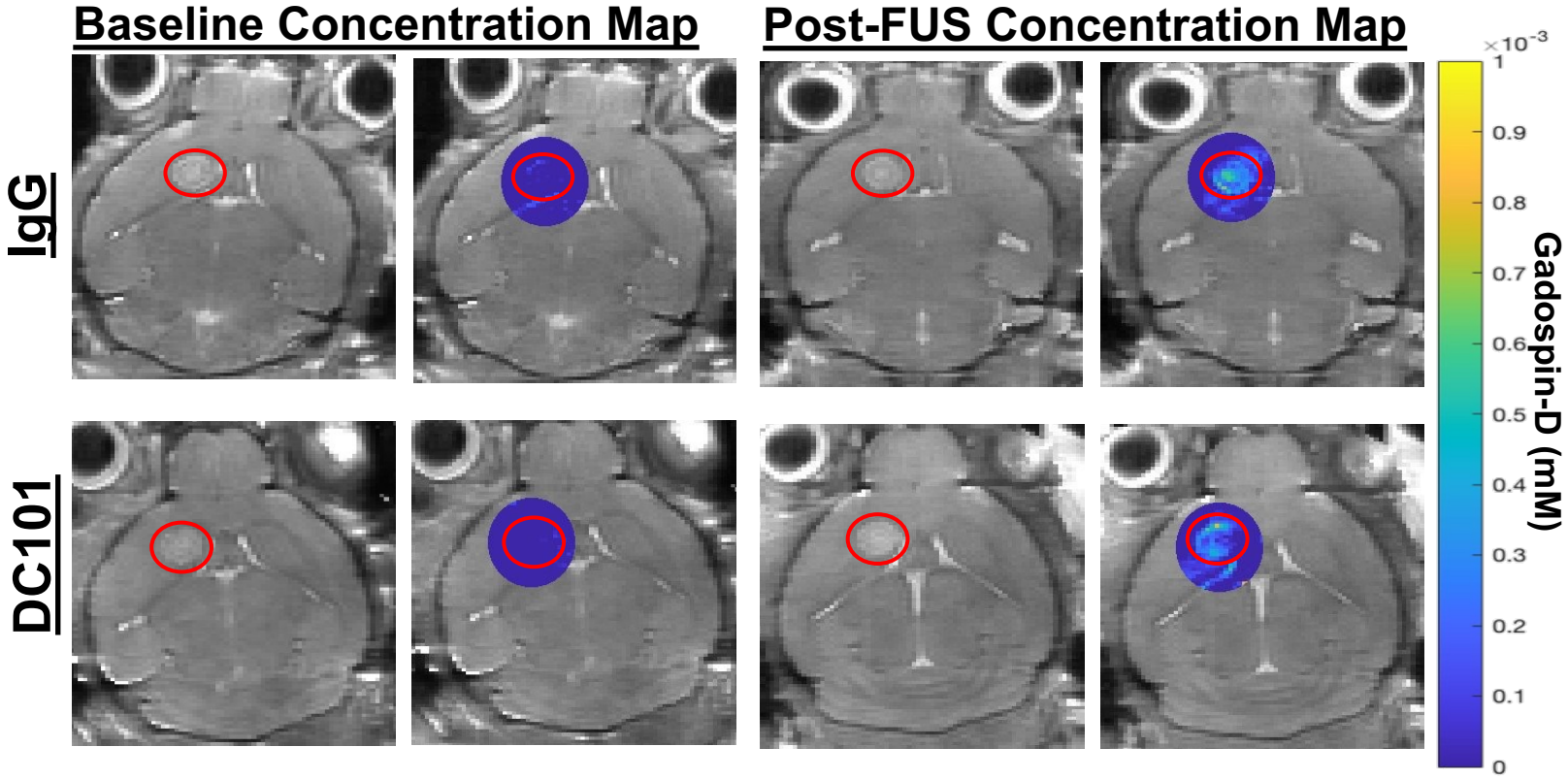
IgG

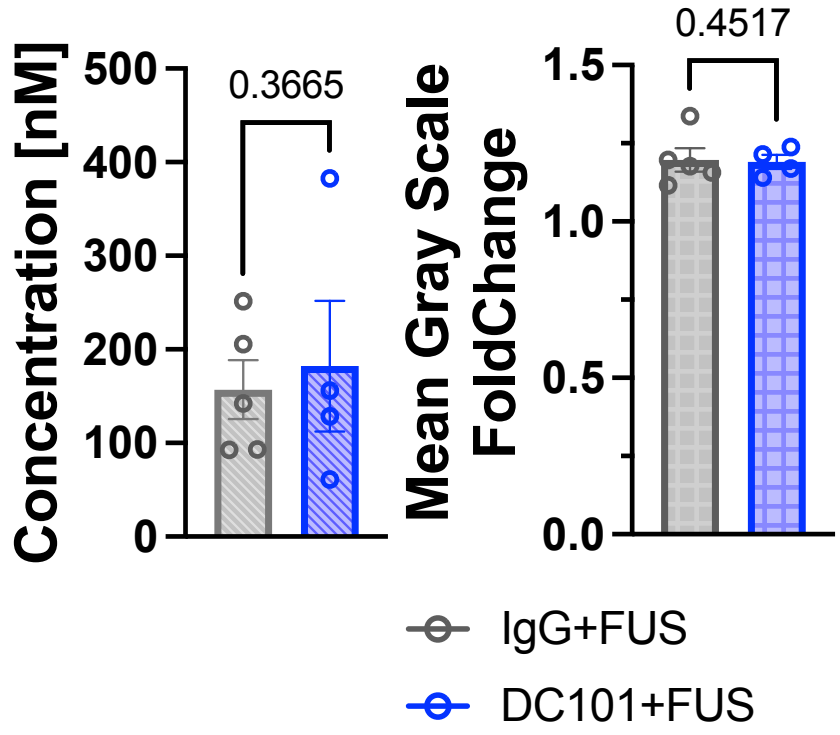
DC101



UVA FOCUSED ULTRASOUND

VEGFR2 inhibition did not augment larger MW model drug delivery.



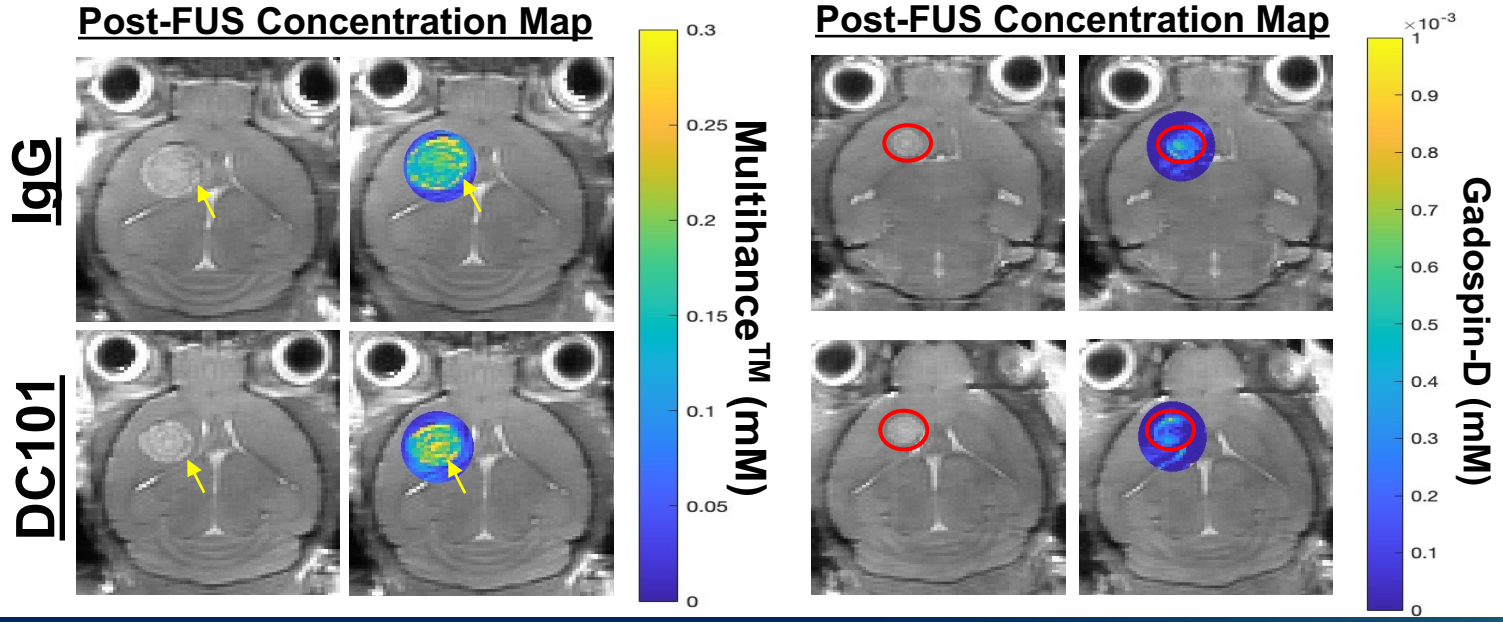


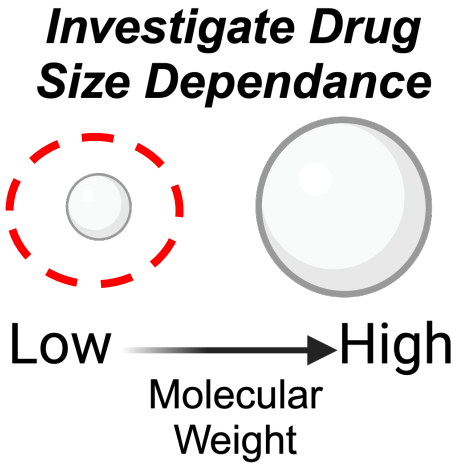
UVA FOCUSED ULTRASOUND

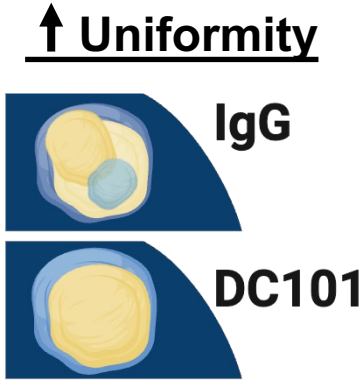
Conclusions

- Demonstrated the **utility of quantitative T1 Mapping MRI** for the tracking of two different sized gadolinium-based model drugs.

- Neoadjuvant VEGFR2 inhibition enhanced the uniformity of low molecular weight, but not high molecular weight, model drug delivery, **offering a promising approach to treat pockets of tumor that would otherwise go untreated to enhance therapeutic efficacy.**







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Acknowledgements

Supported By:

NIH National Institute of Biomedical Imaging and Bioengineering — R01EB030744, R01EB030409

NIH National Cancer Institute — R01CA279134, R21CA286367

NIH National Institute of Neurological Disorders and Stroke — R01NS111102

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