Mechanisms of Translocating an Intact Blood-Brain Barrier

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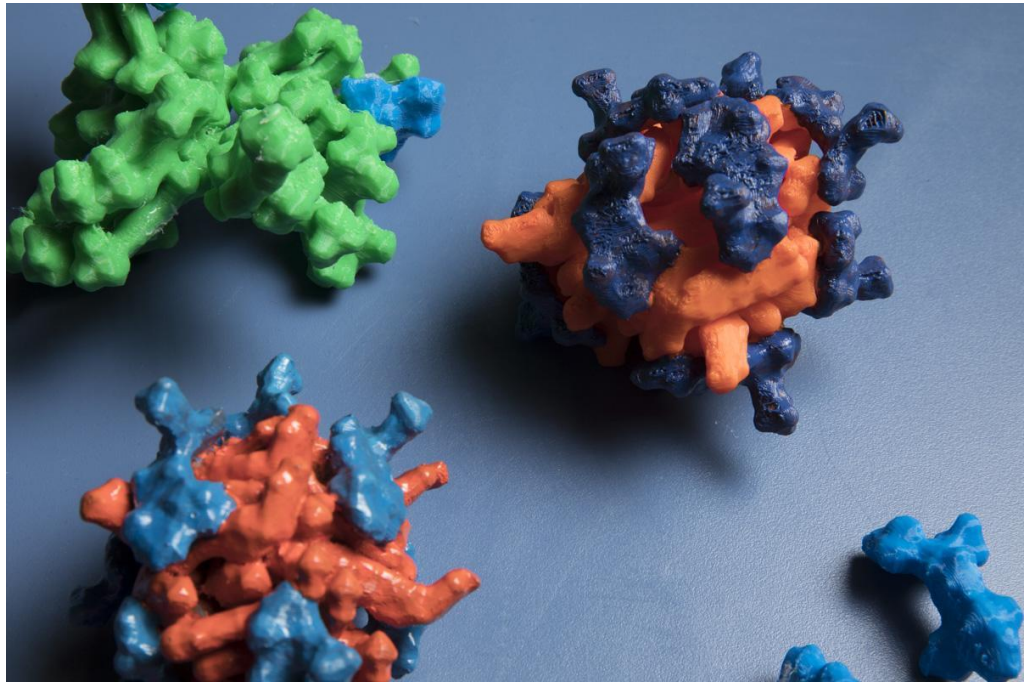


CRS 2022

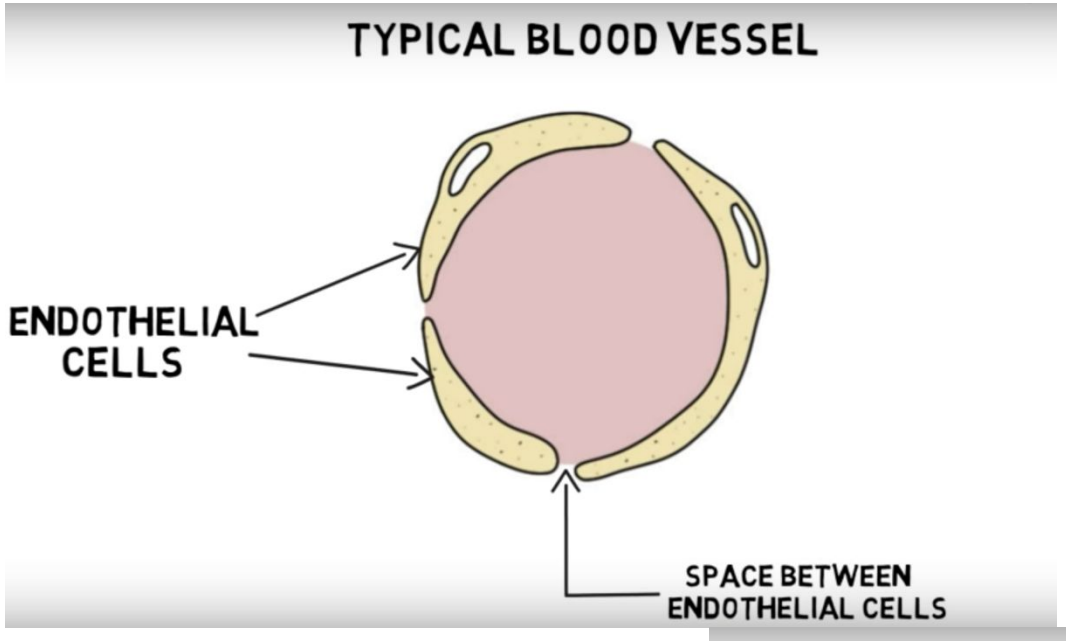
Memorial Sloan Kettering Cancer Center

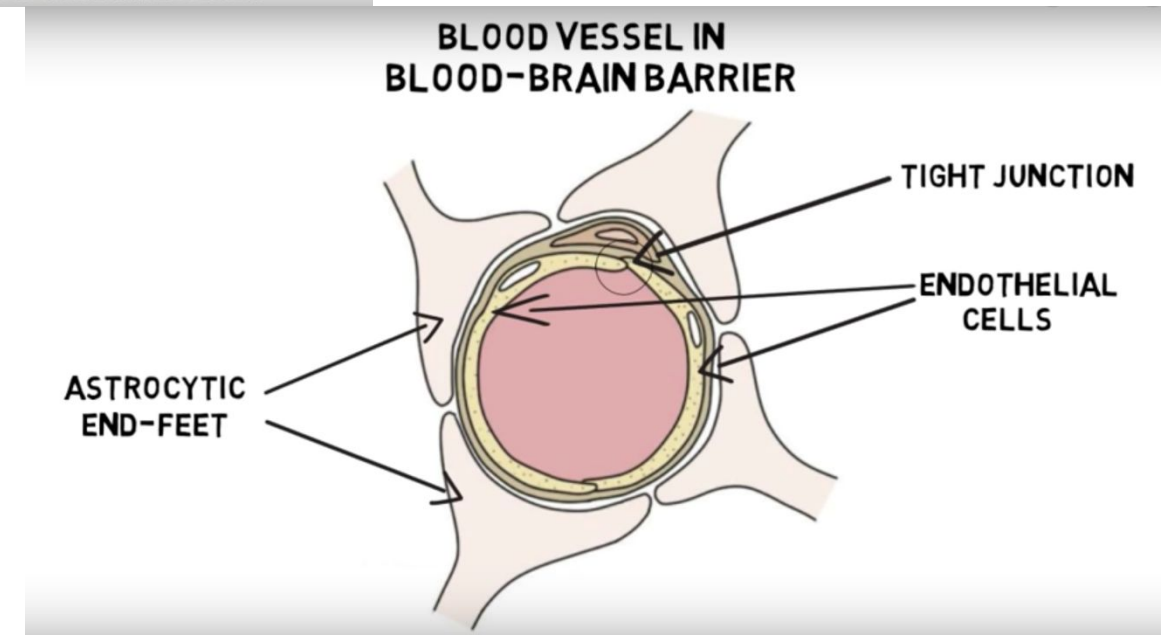
COI Disclosure Information

I have the following financial relationships to disclose:

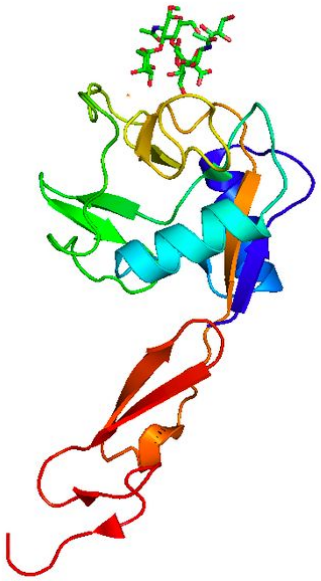
- Co-founder/SAB/Equity stake: Goldilocks Therapeutics, Inc., Lime Therapeutics, Inc., Nirova Biosense, Inc.
- SAB: Concarlo Holdings, LLC., Nanorobotics, Inc., Mediphage Bioceuticals, Inc.
- Inventor: “Fucoidan nanogels and methods of their use and manufacture” US patent #9,737,614 related to this work.

Can We Improve the Delivery of Drugs to CNS Tumors?

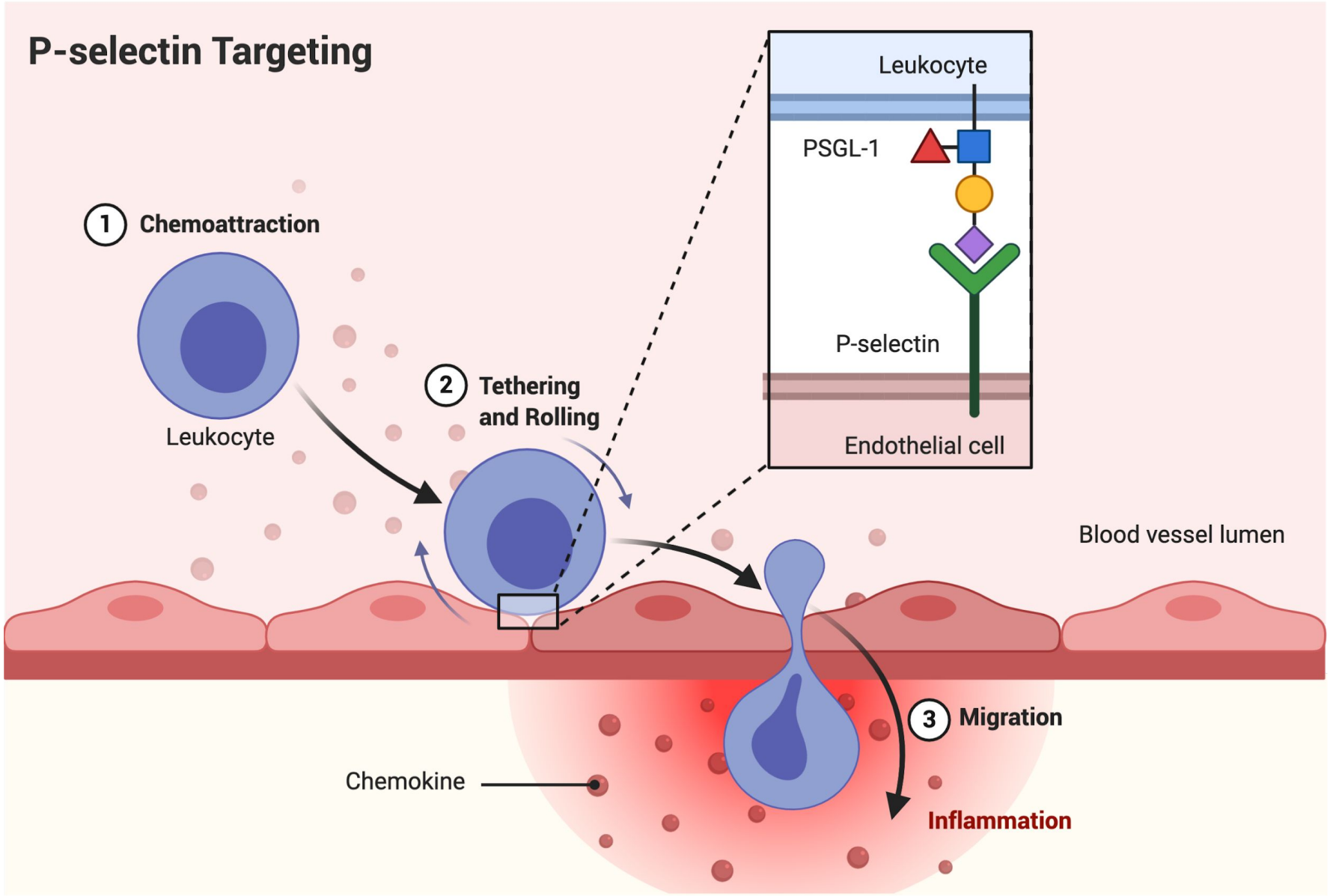




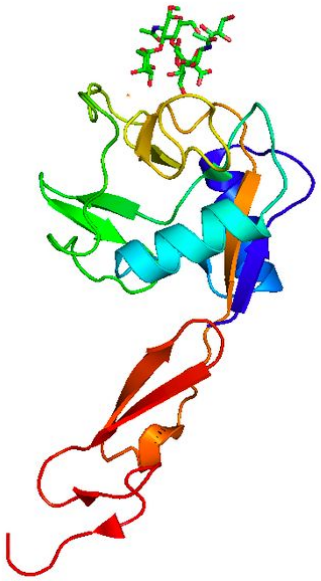
P-selectin is Released to Surface of Activated Endothelial Cells for Immune Cell Localization and Extravasation



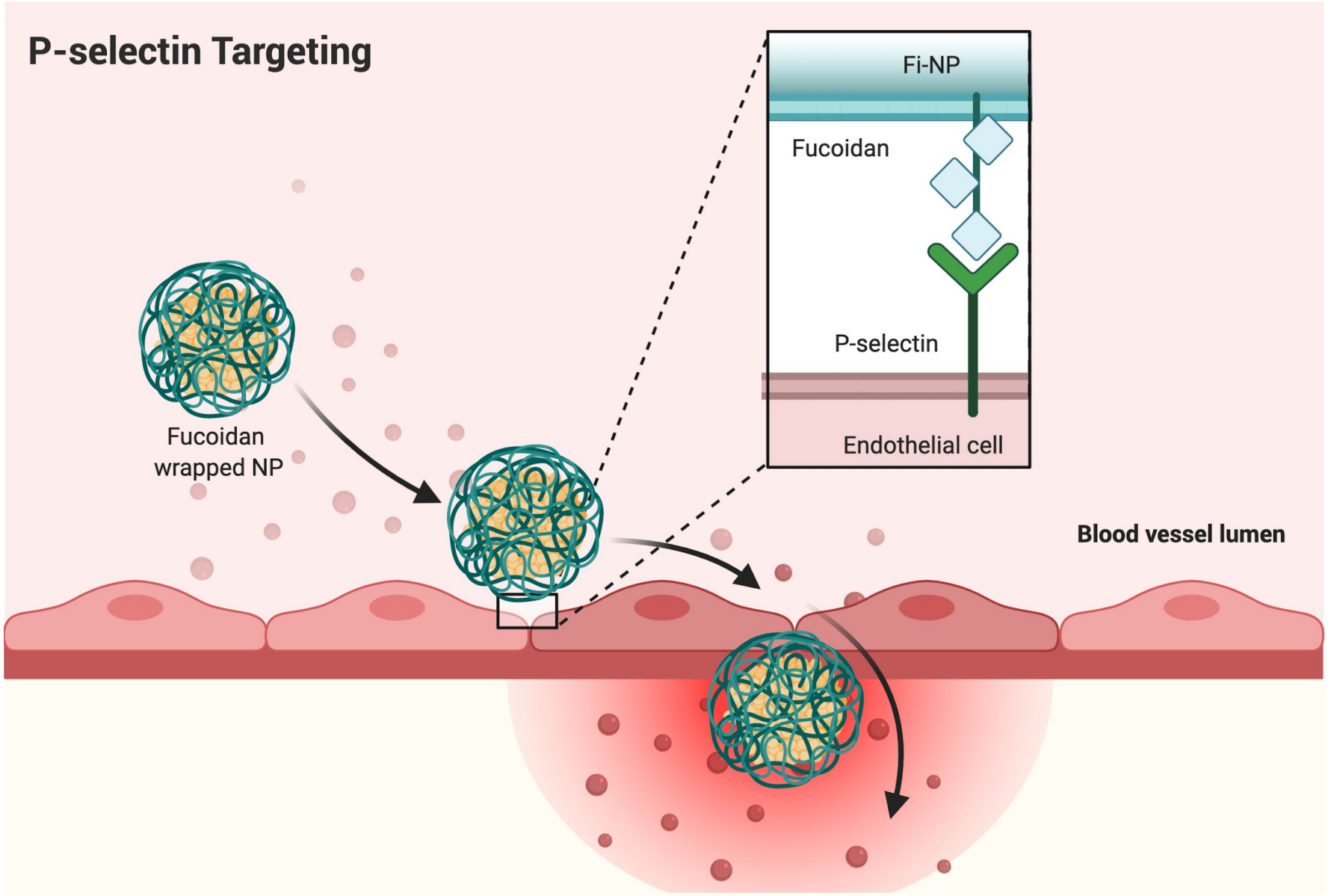
P-selectin



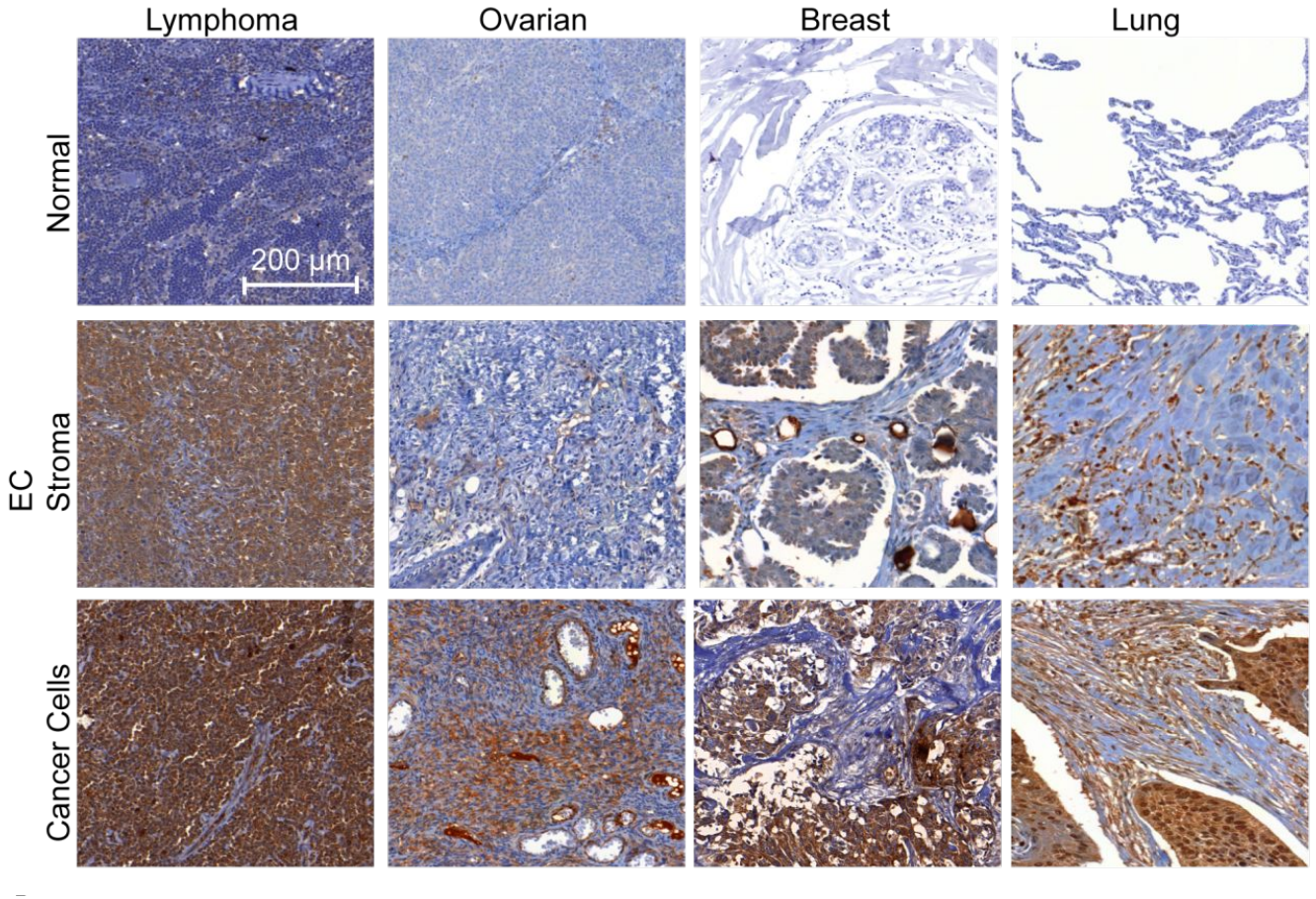
Can P-selectin-Targeting Facilitate Extravasation at Tumor Sites?

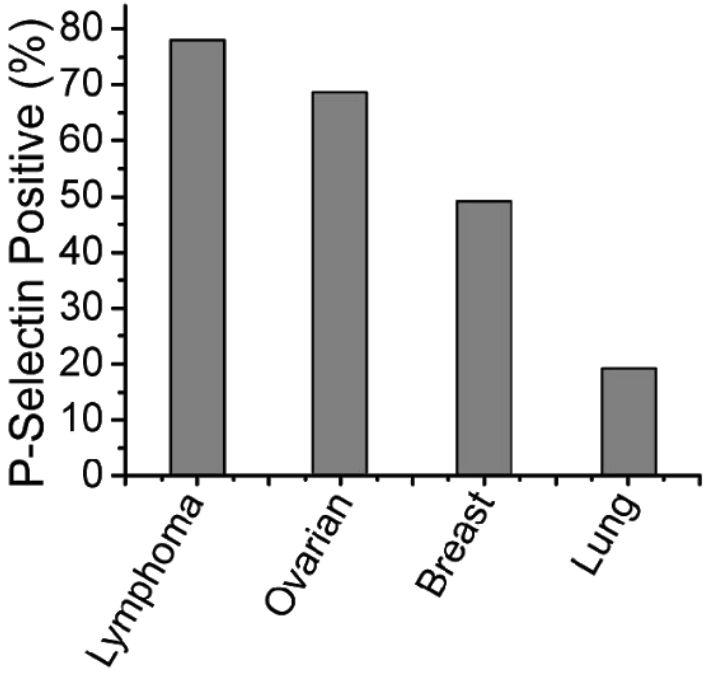


P-selectin



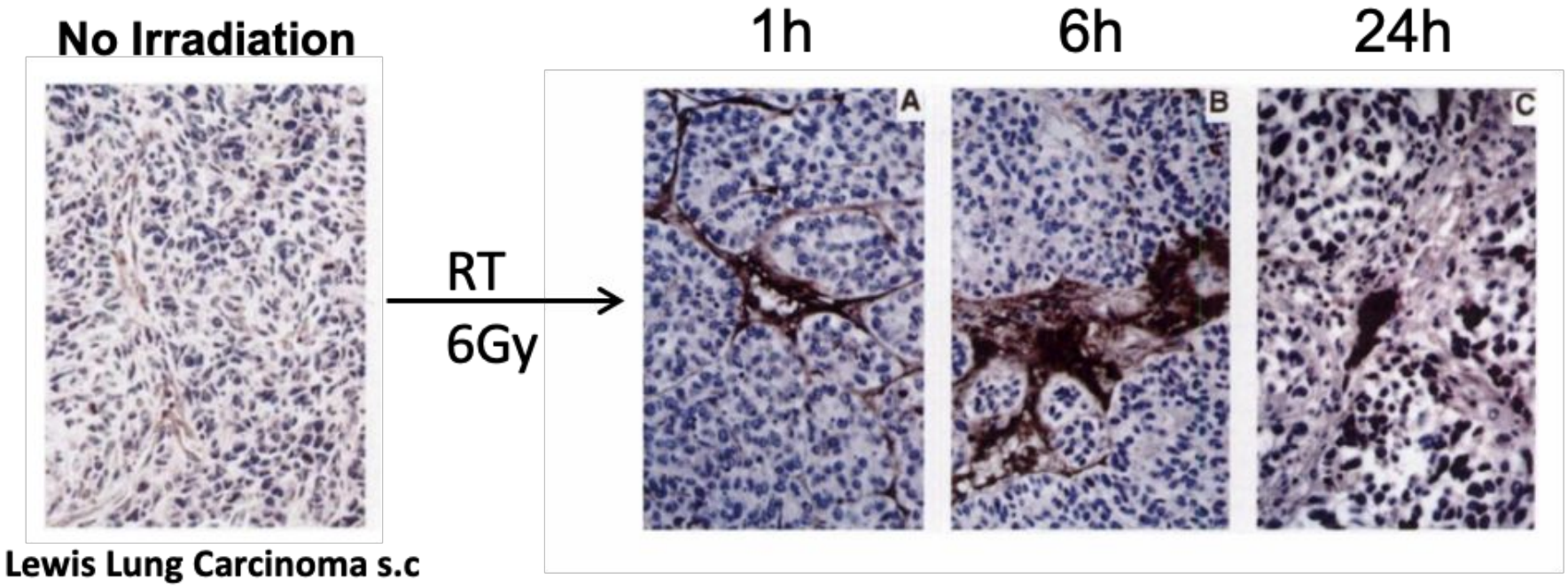
P-selectin is Expressed in Human Cancers on Blood Vessels, Stroma, and Cancer Cells





Shamay, *Science Translational Medicine* 2016

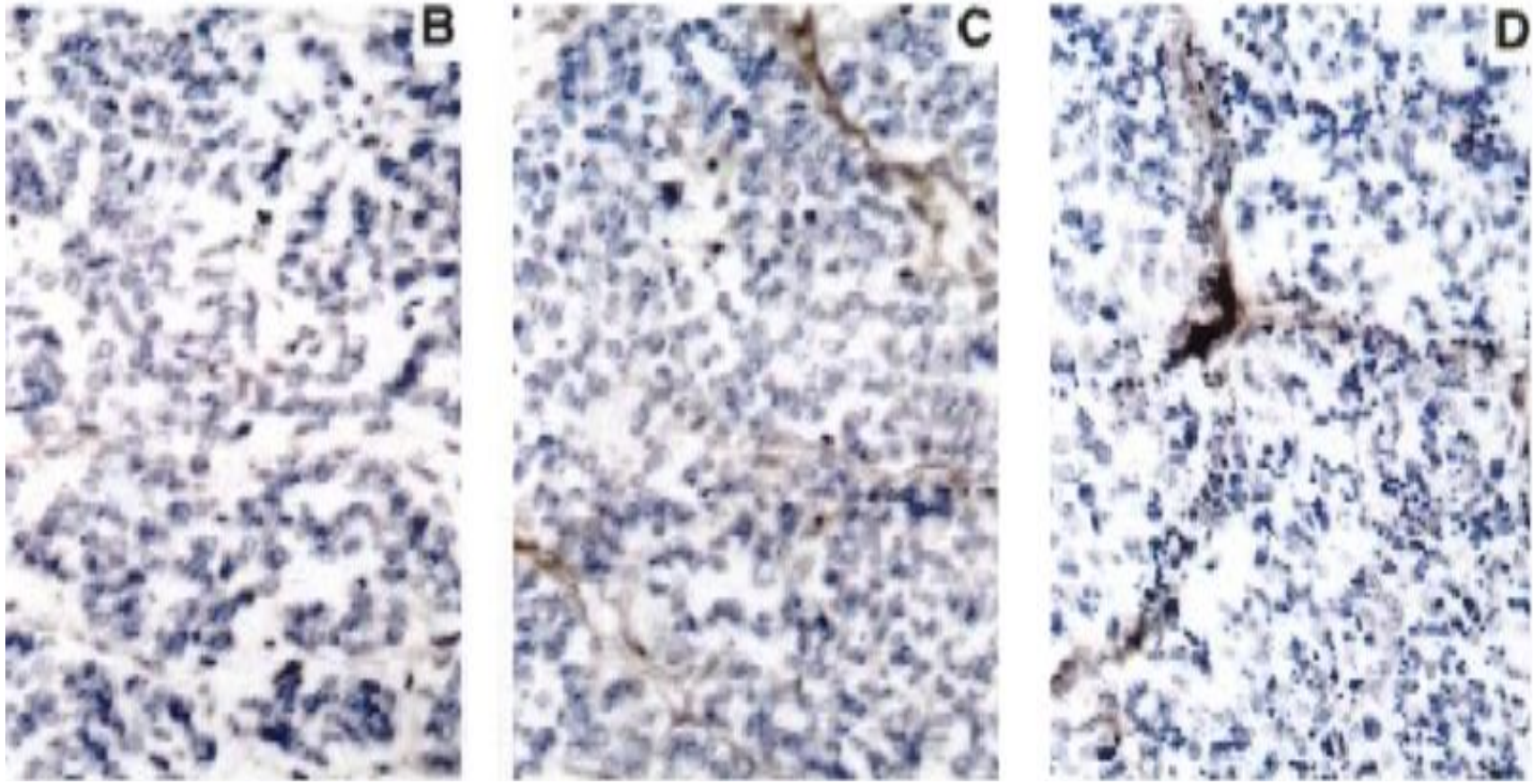
Radiotherapy Induces P-selectin Expression in Vasculature



Hallahan, Cancer Research, 1999

Radiotherapy Induces P-selectin Expression in Brain Tumor Vasculature

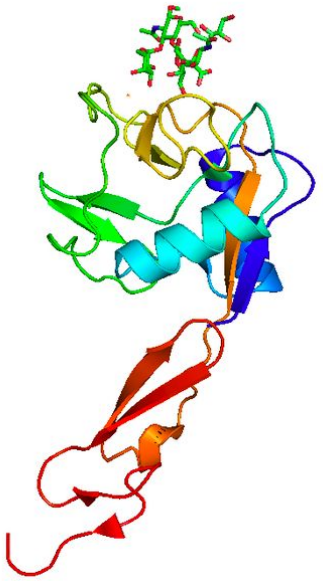
Rat C6 glioma



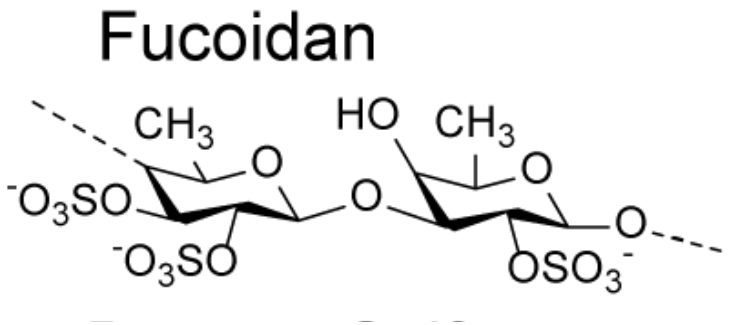
No XRT | 6Gy (1hr) | 6Gy (6hr)

Hallahan D et al. Cancer Res 1998

Polysaccharide Fucoidan Mimics Glycoprotein Binding Interactions to P-selectin



P-selectin



Structural similarity to PSGL-1

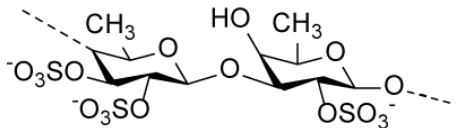
-High affinity to P-selectin (~20nM)

-Structural element for nanoformulation strategy

Nanoformulation Approach

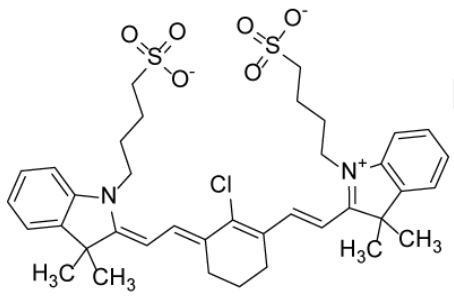
Drug +

Fucoidan



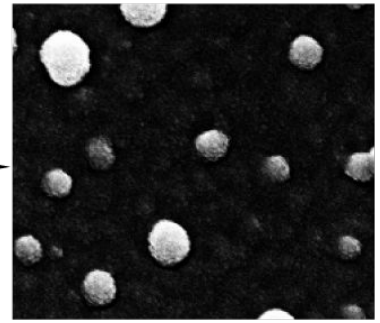
+

Indocyanine

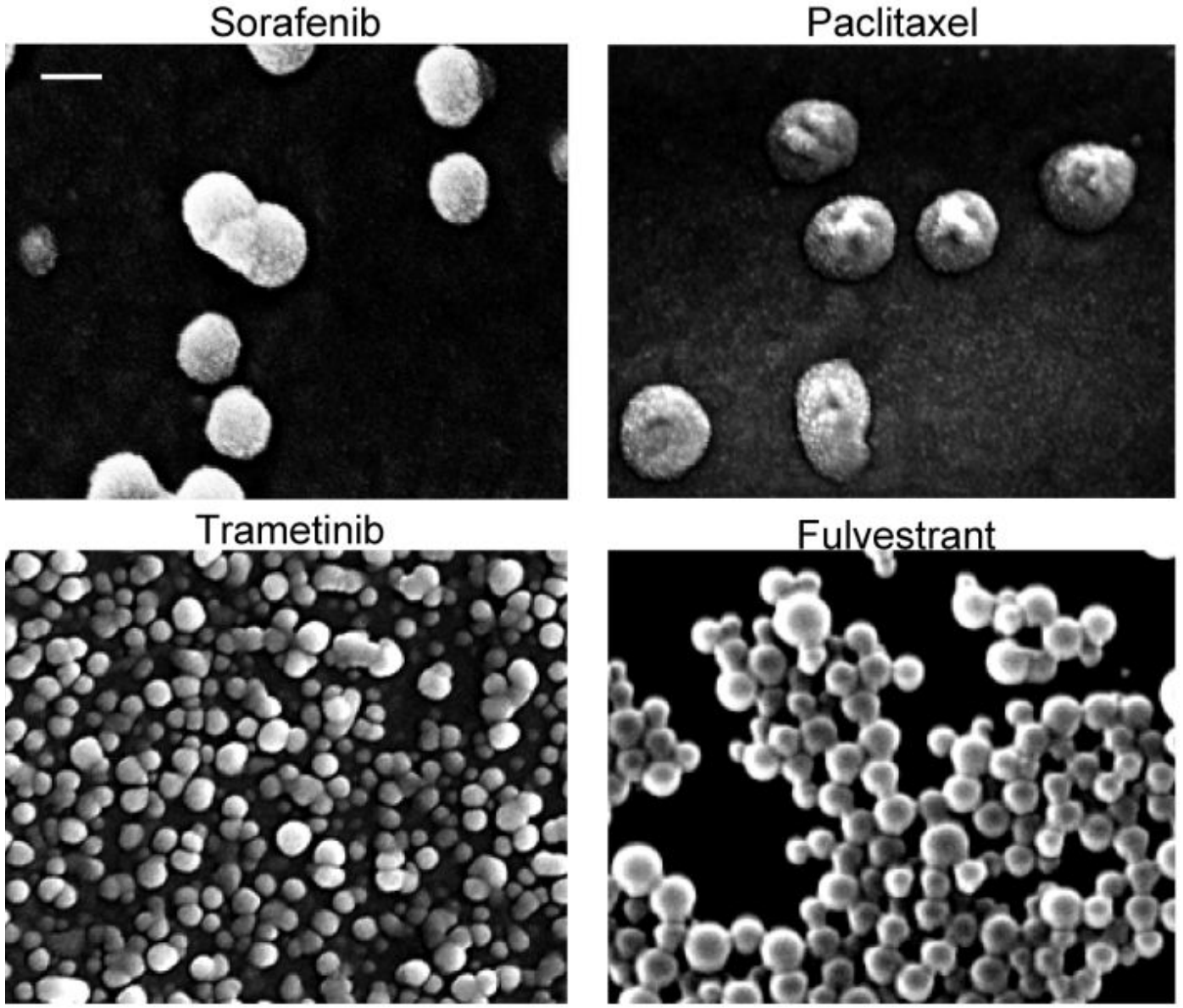


Nano-Precipitation

Nanoformulation

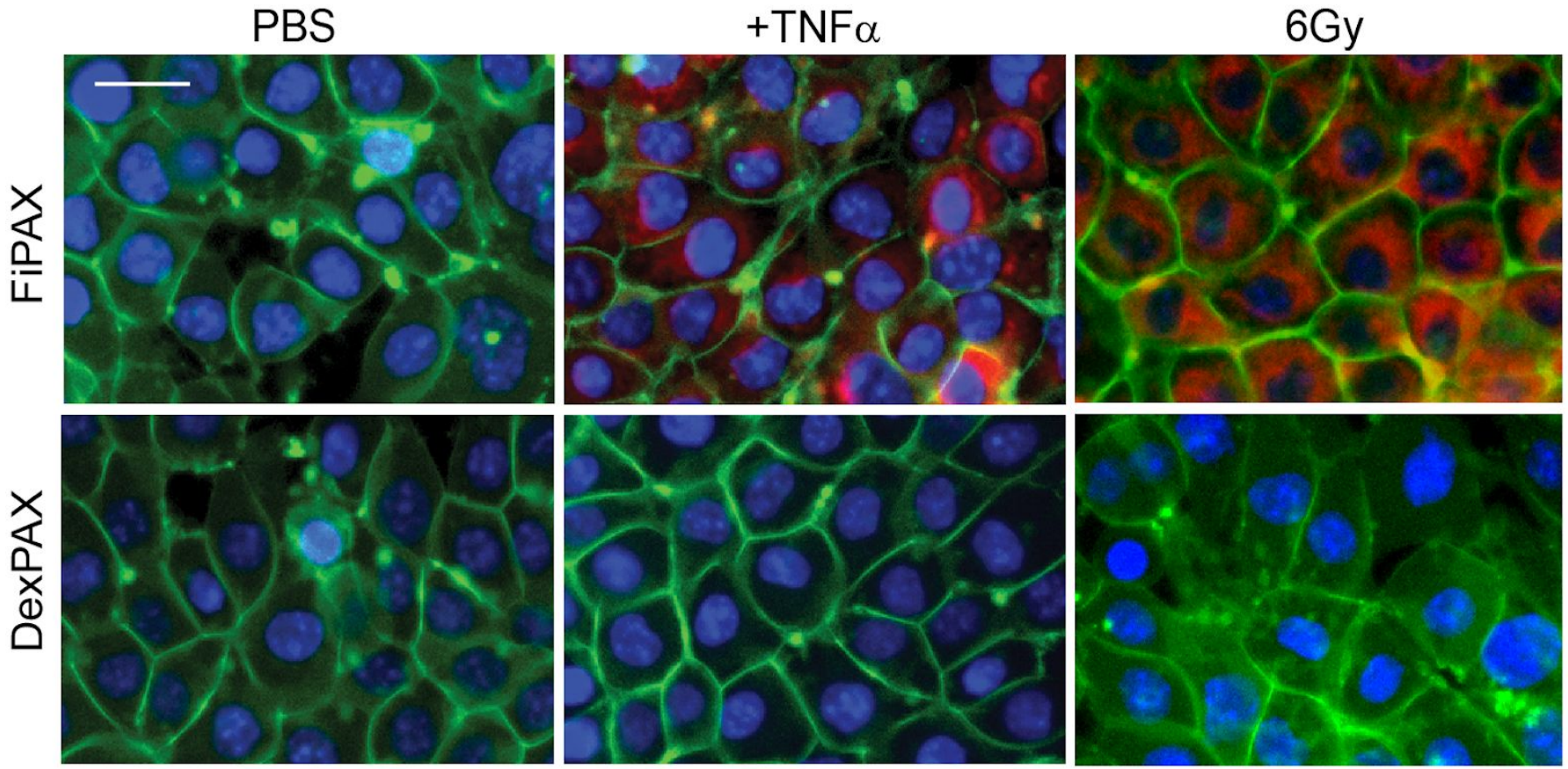


Indocyanine-Drug Suspensions Form Nanoparticles



Shamay, et al., *Nat Mater*, 2018

Nanoparticles Bind to Irradiated (or Inflamed) Endothelial Cells

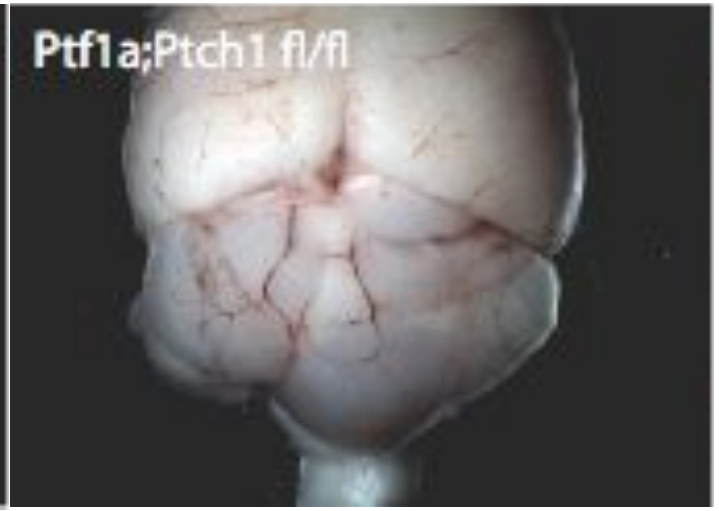


Novel Mouse Model of Sporadic SHH-Driven MB

Ptf1a$^{cre/+}$;*Ptch1*$^{fl/fl}$ mice develop Sonic hedgehog (SHH)-driven medulloblastoma (MB)

Control

Mutant

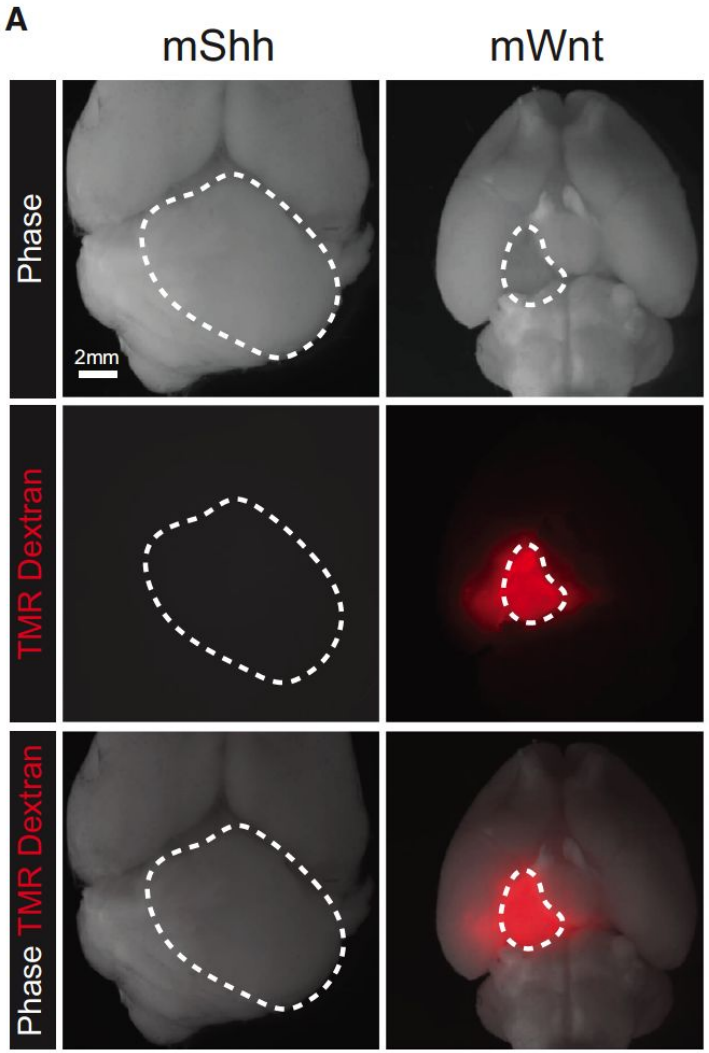


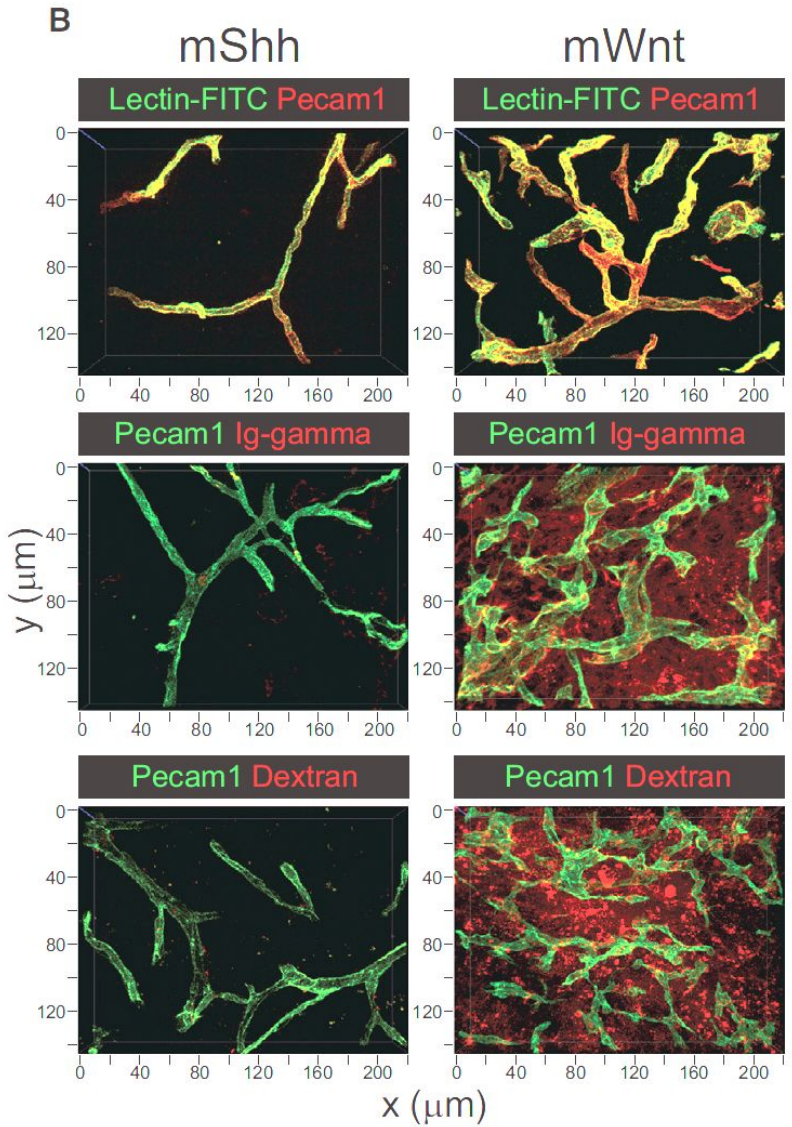
<u>High Penetrance ~ 85%</u>
(n=77/91 mice)

<u>Short Tumor Latency</u>
(mean 13.9 +/- 3.9 weeks)

w/Praveen Raju, Mount Sinai School of Medicine

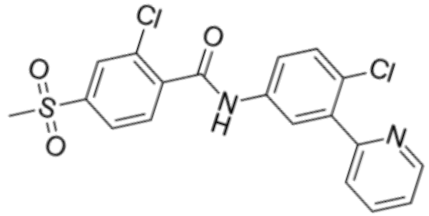
SHH Medulloblastoma Exhibits an Intact Blood-Brain Barrier



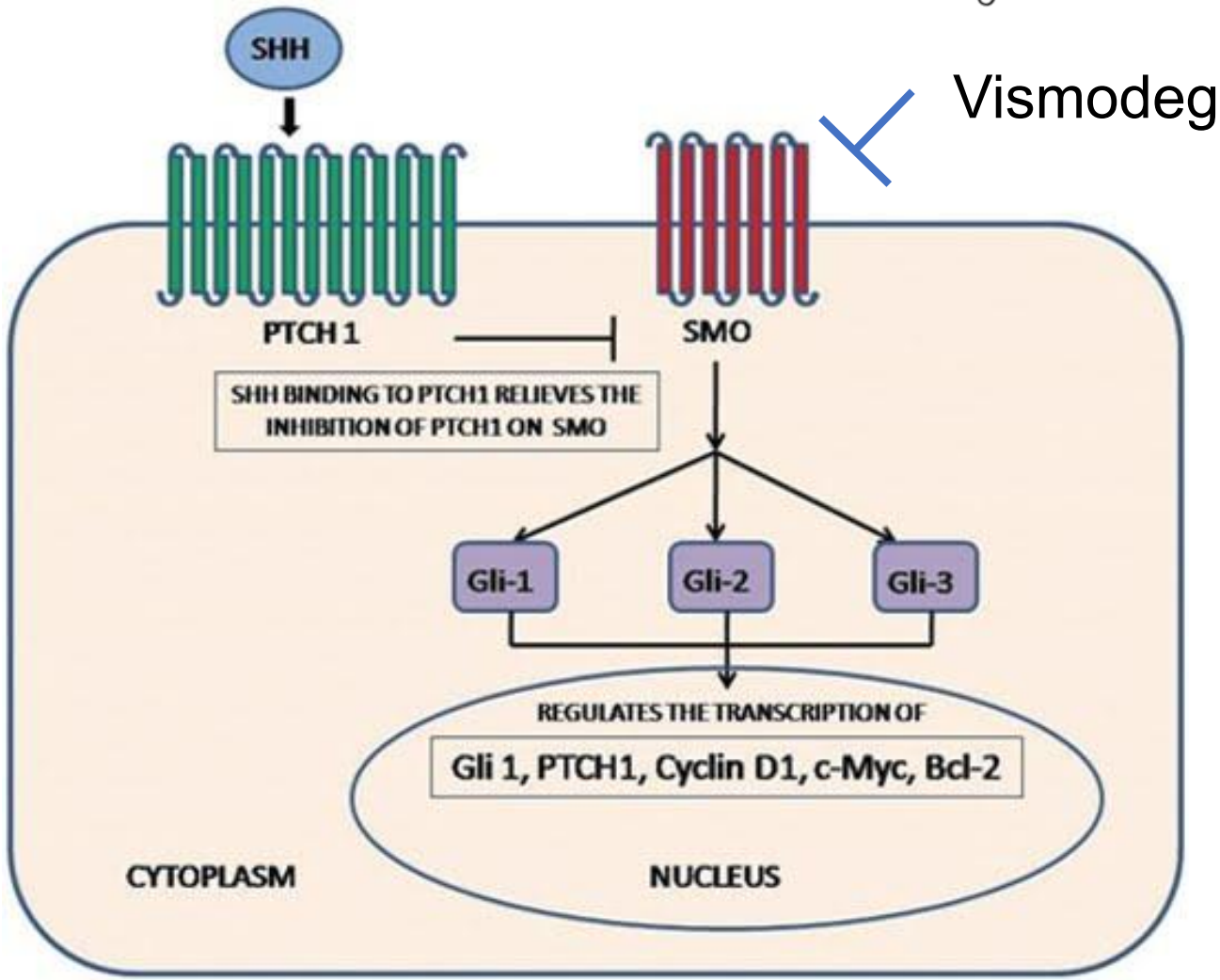


T. Phoenix et al, *Cancer Cell,* 2016

Sonic Hedgehog (SHH) Medulloblastoma

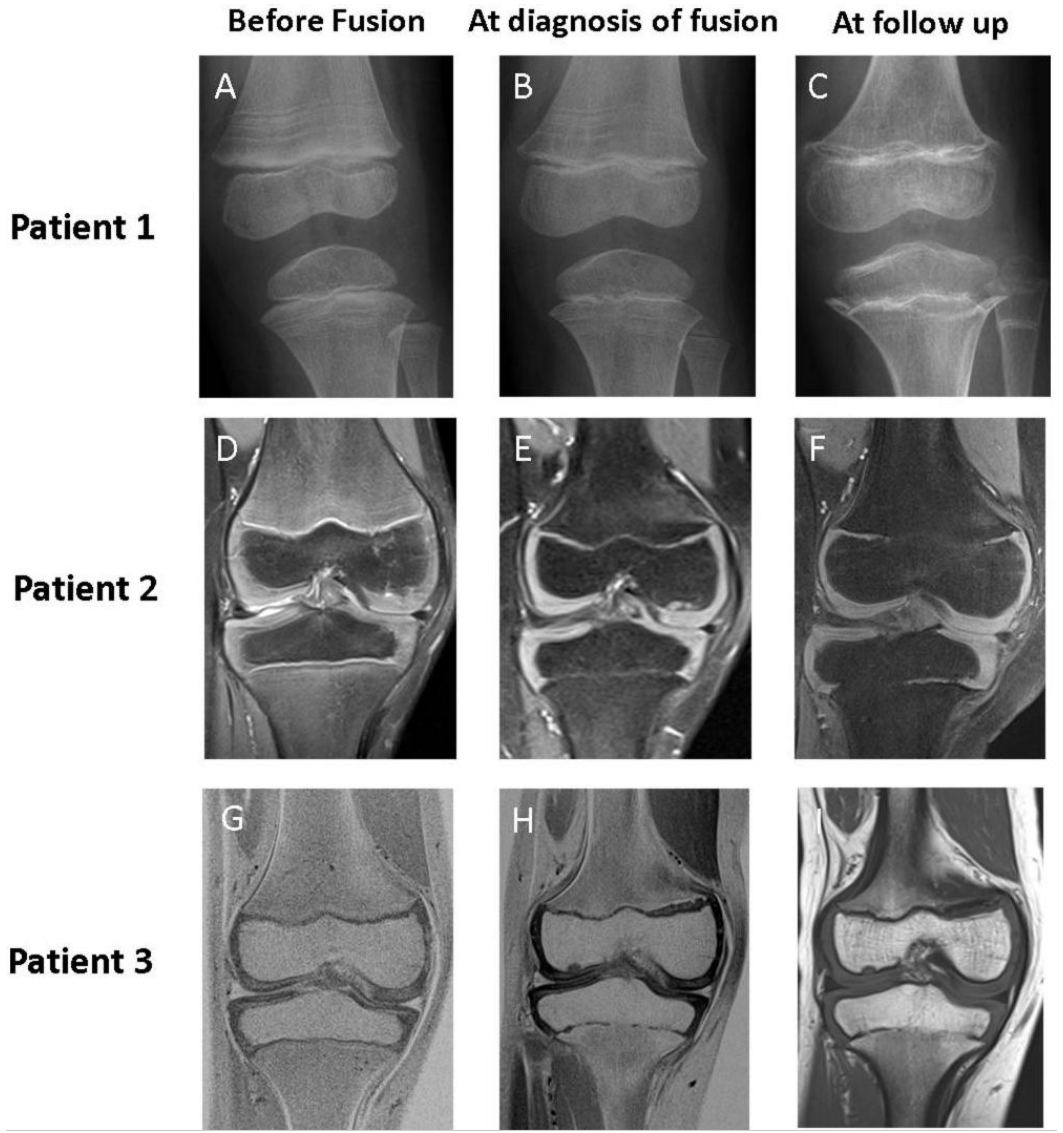


Vismodegib



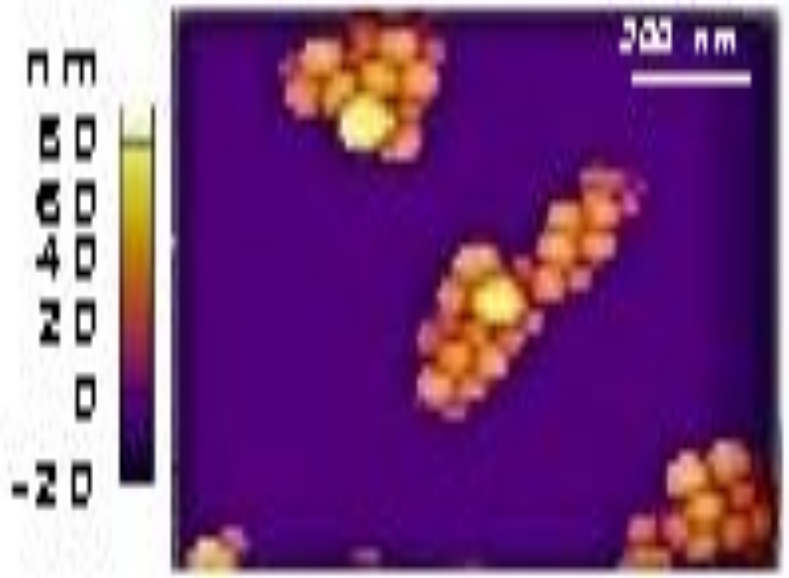
Mishra, P., et al. JCDR 2015. Nov 11. ZE10-ZE13.

Vismodegib Causes Irreversible Growth Plate Fusions in Children

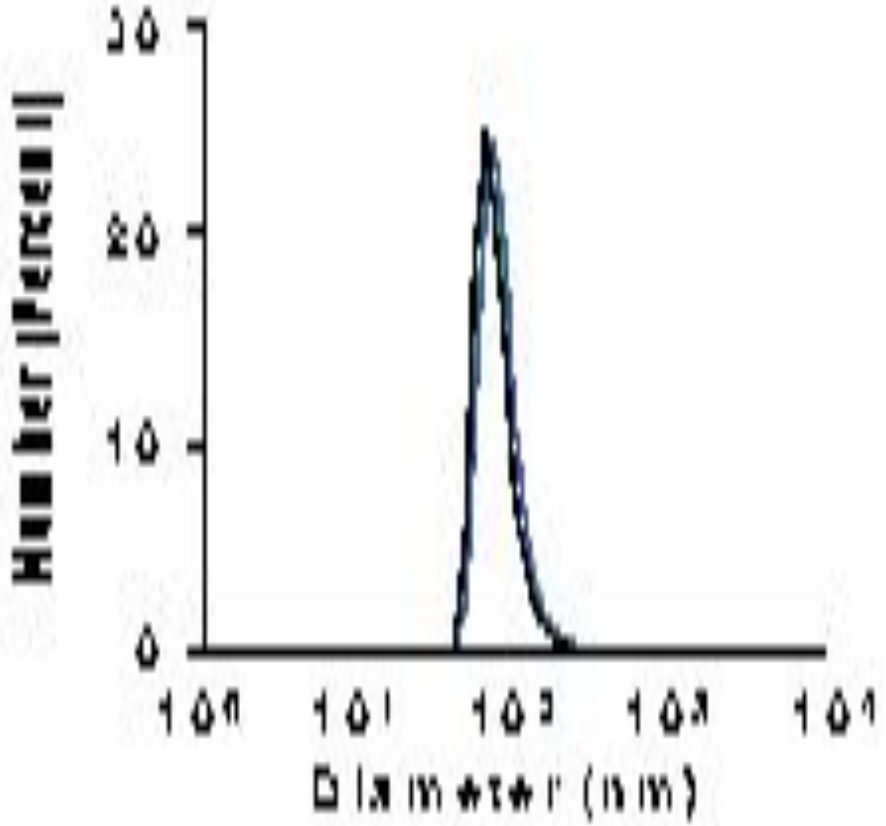


G. Robinson et al, *J Clin Oncology,* 2015

Fucoidan-Vismodegib Nanoparticles (Fi-Vis)

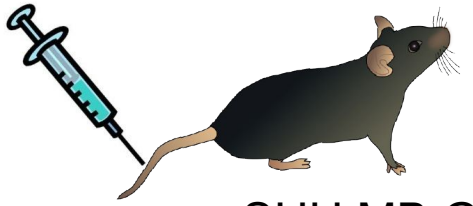


Atomic Force Microscopy

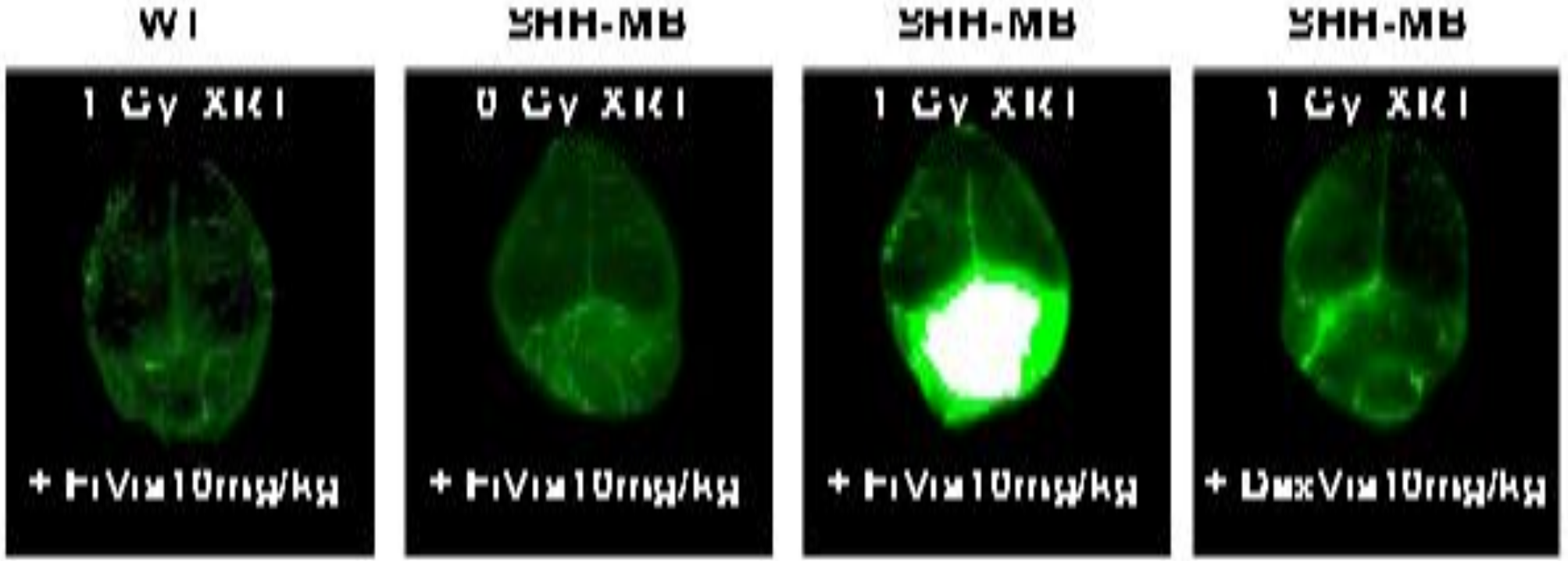


Dynamic Light Scattering

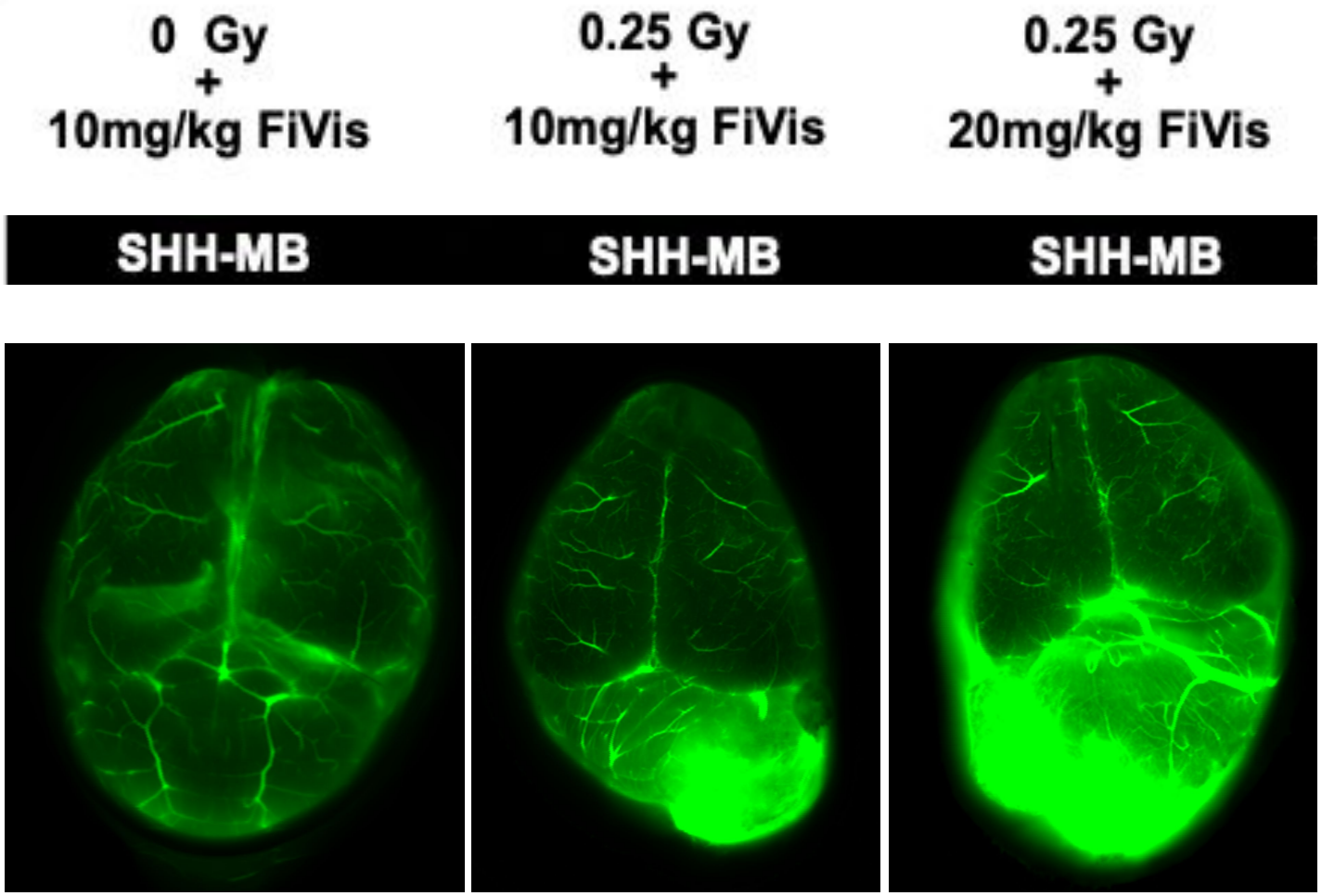
Enhanced Delivery Requires P-selectin-Targeting + Radiation



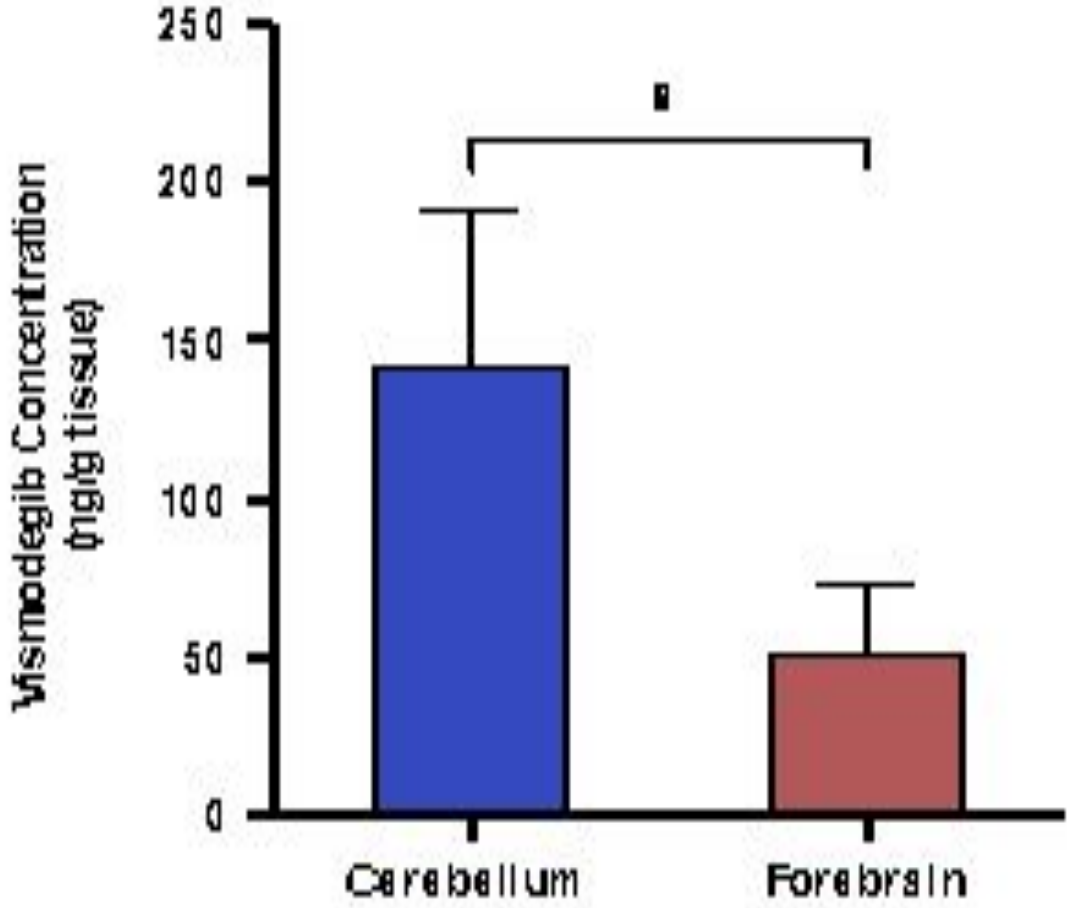
SHH MB GEM



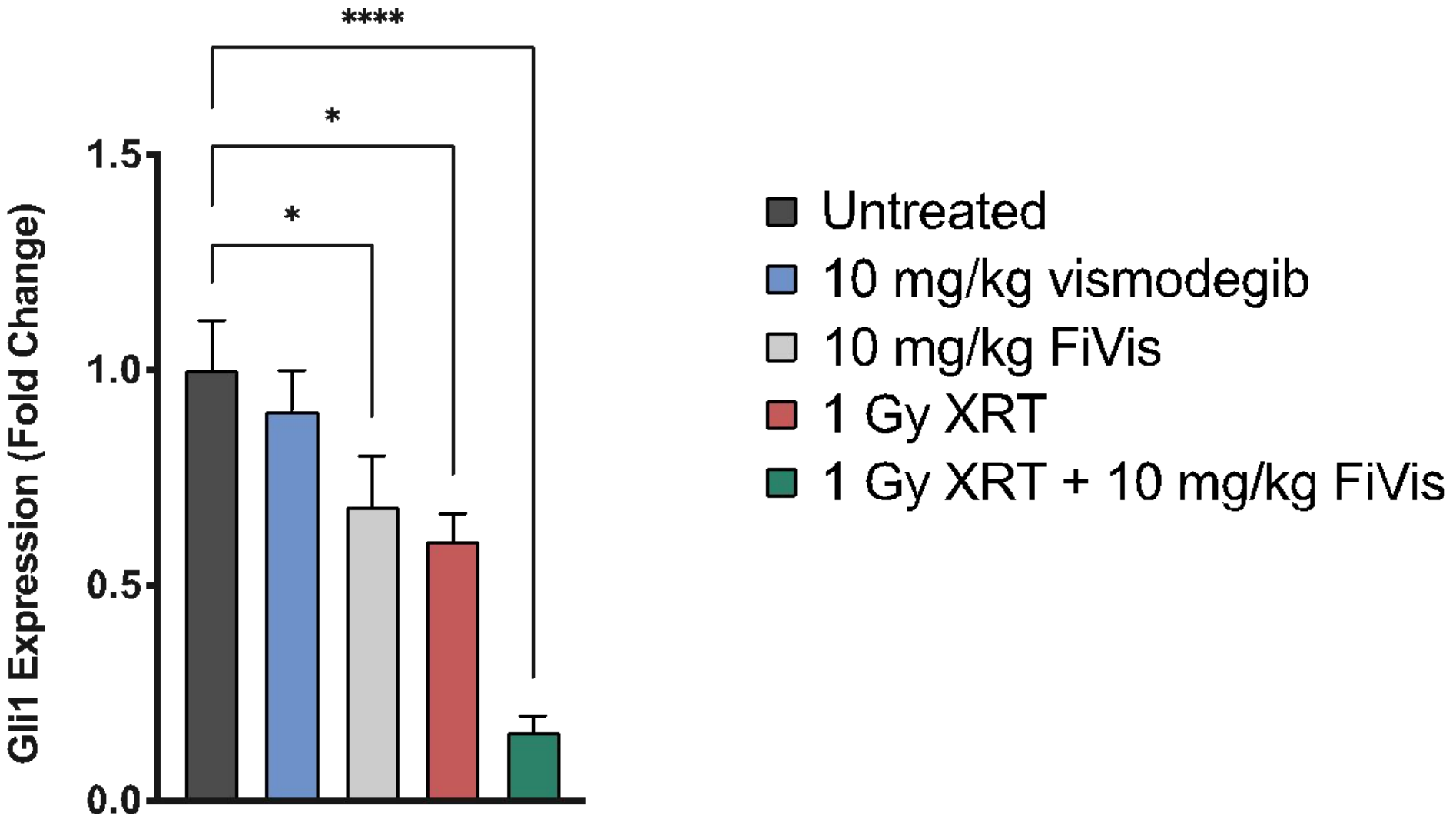
Tumor Localization is Radiation and P-selectin-Dependent



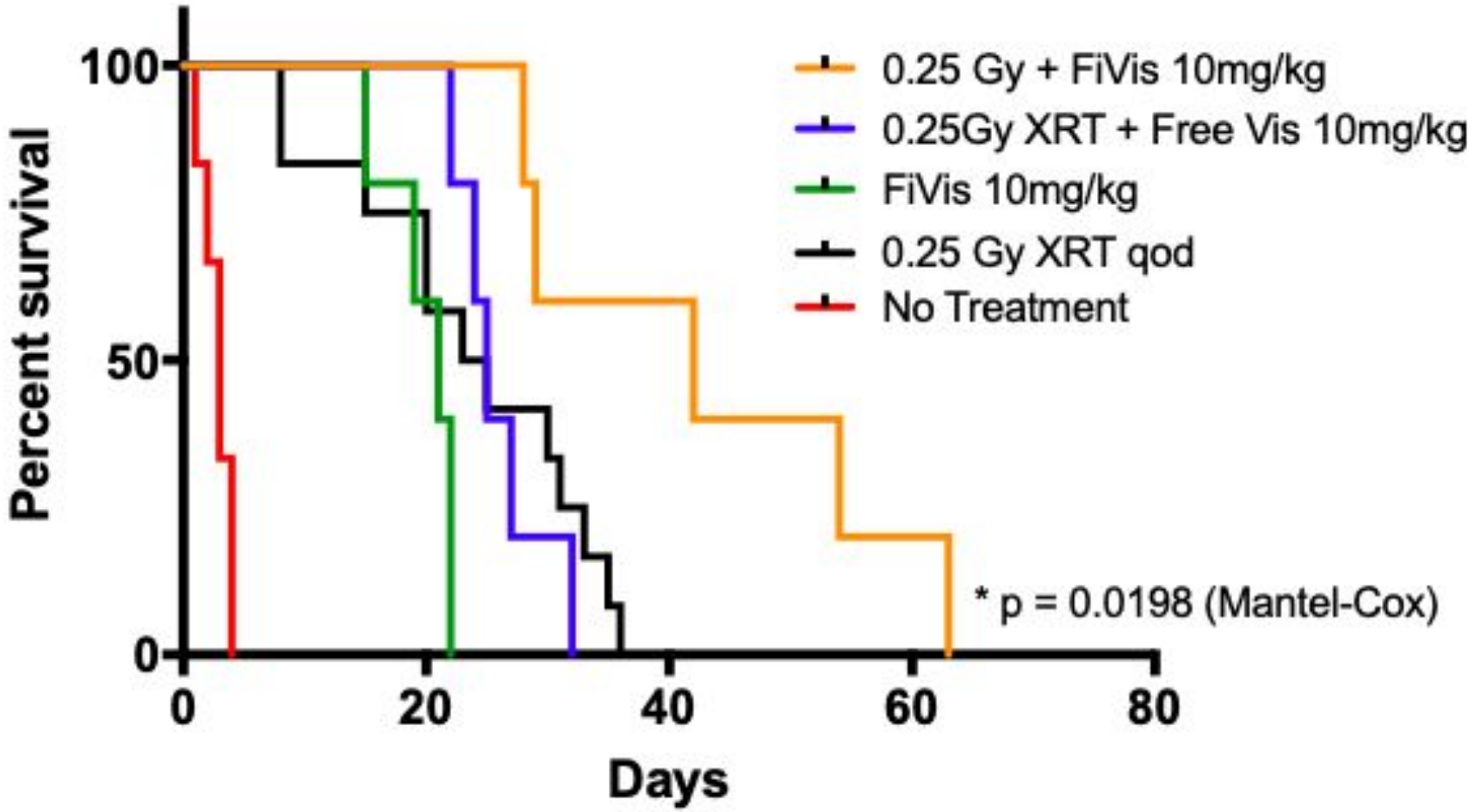
Drug Localizes to the Tumor Region



P-selectin-Targeted Vismodegib-Loaded Nanoparticles Inhibit SHH Effector Gli1 in MB Tumors

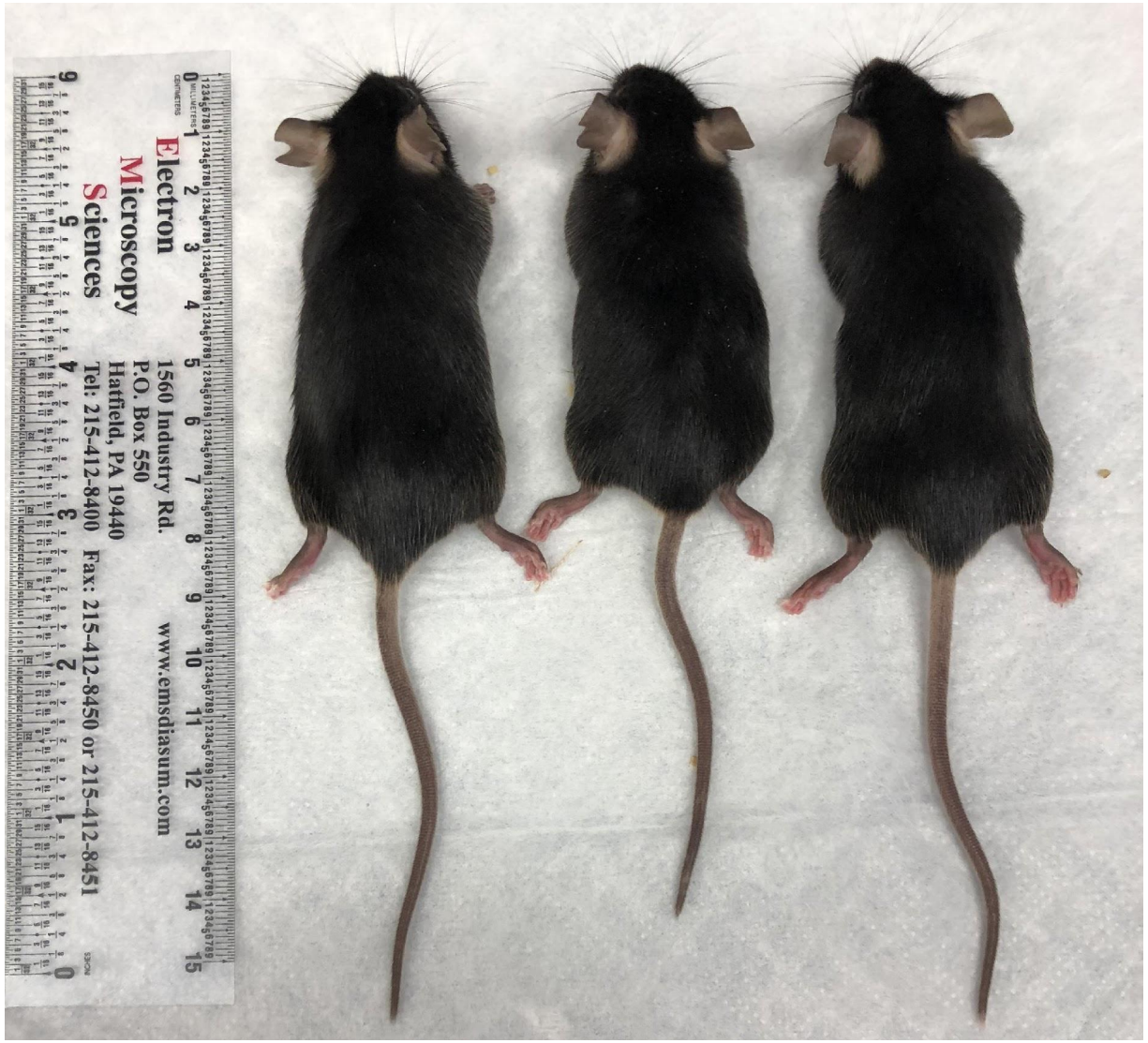


Low Dose RT (0.25 Gy x 8 qod) + Low Dose Vismodegib-Loaded Nanoparticles is Effective



Therapies until day 16

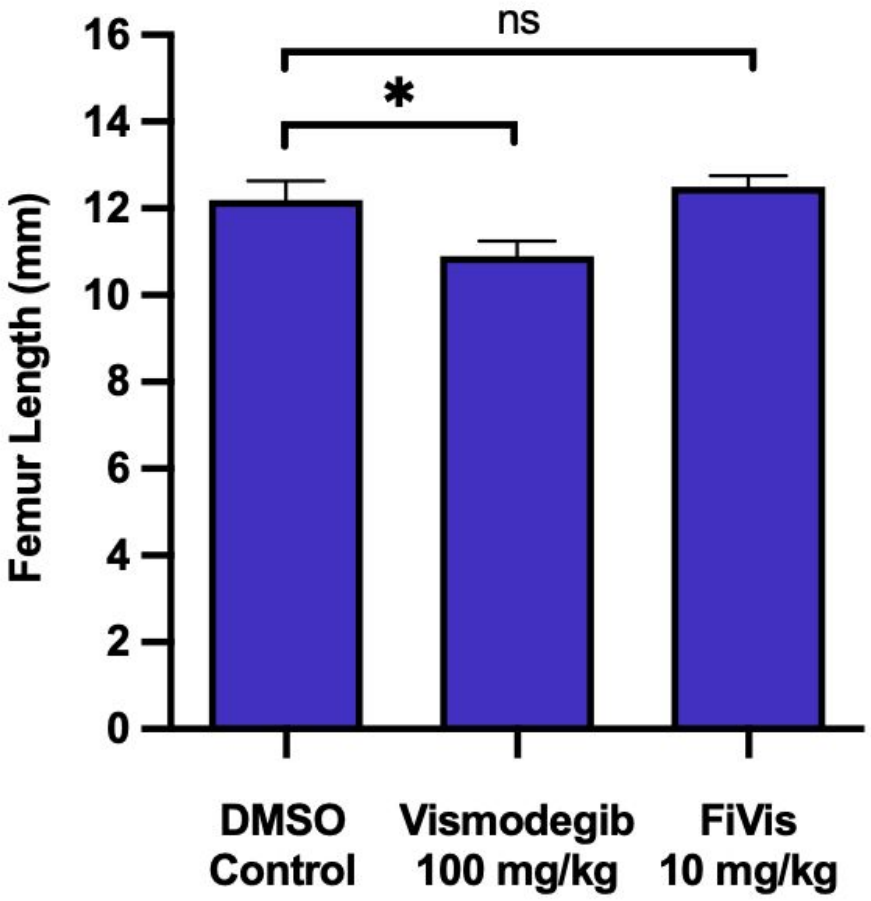
Nanoparticles Obviate Growth Defects



Control **Free Vis 100mg/kg** **FiVis NP 10mg/kg**

w/ Matthew Greenblatt & Praveen Raju

Nanoparticles Obviate Growth Defects

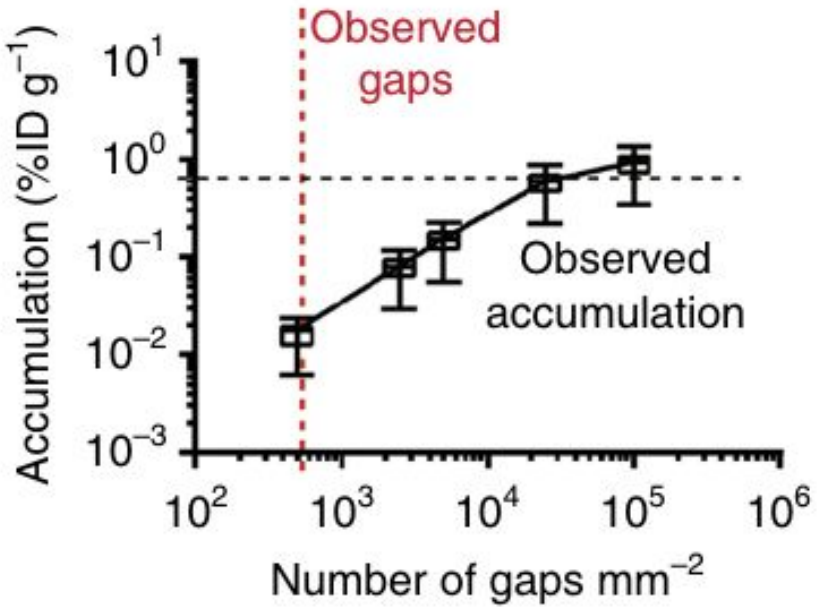


	DMSO Control	Vismodegib 100 mg/kg	FiVis 20 mg/kg
			
Avg. BV/TV	0.121	0.114	0.136
Avg. Tb. N (1/mm)	5.604	4.888	5.694
Avg. Tb. Th (mm)	0.031	0.033	0.034

w/ Matthew Greenblatt,
Weill Cornell Medicine

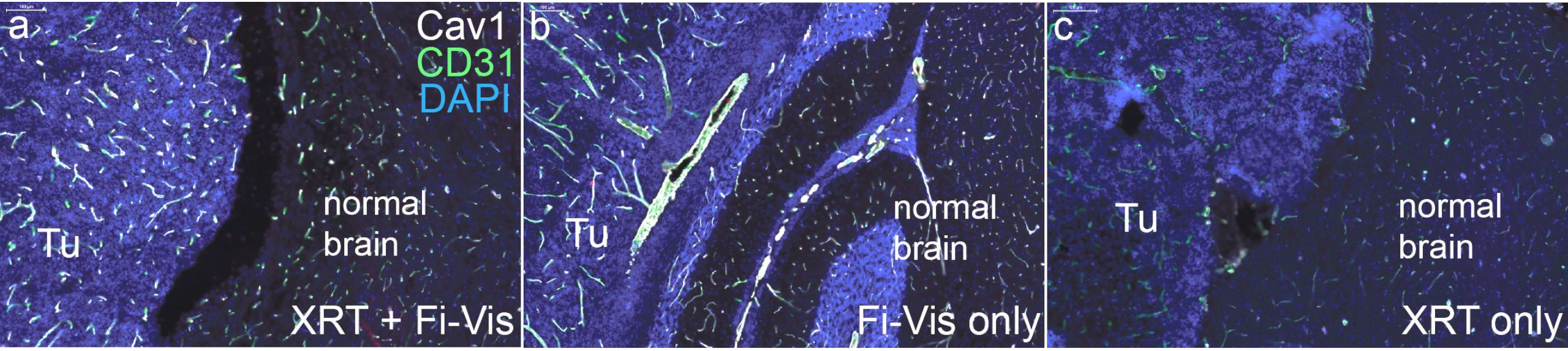
What is the mechanism of BBB Translocation?

Recent Findings Suggest Vascular Leakiness Does Not Account for Most Nanoparticle Extravasation in Tumor Models

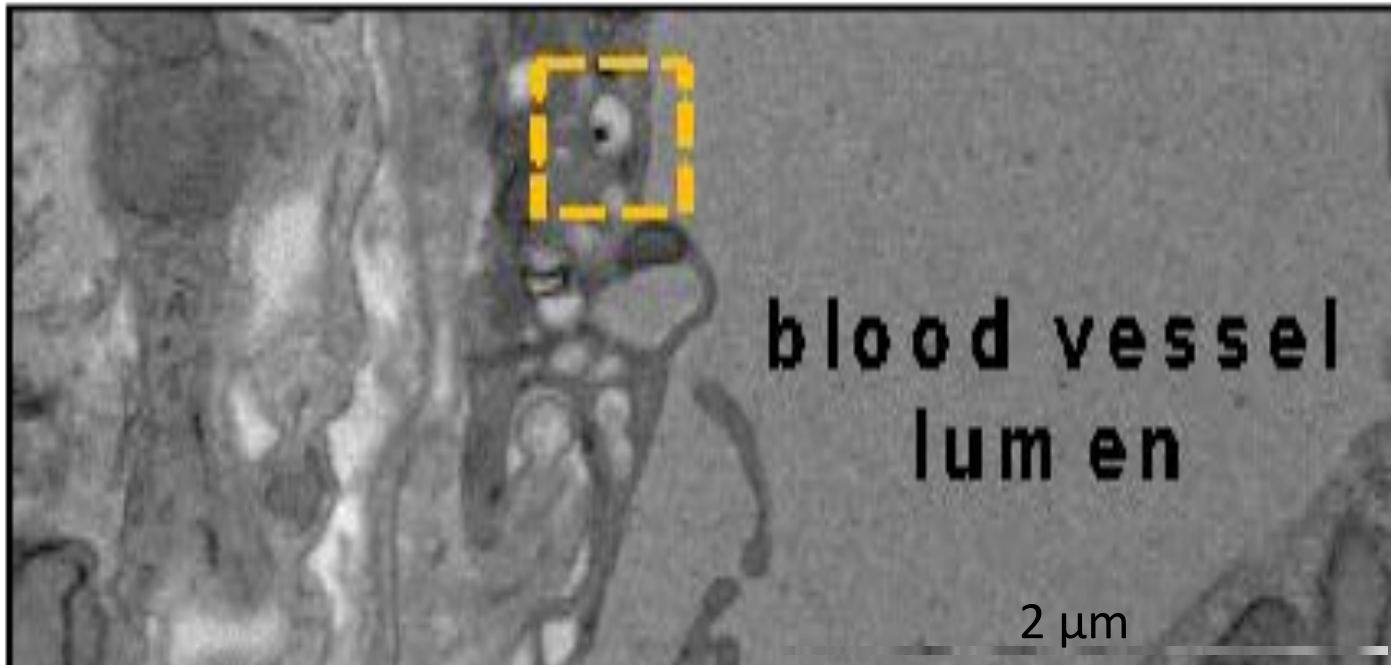


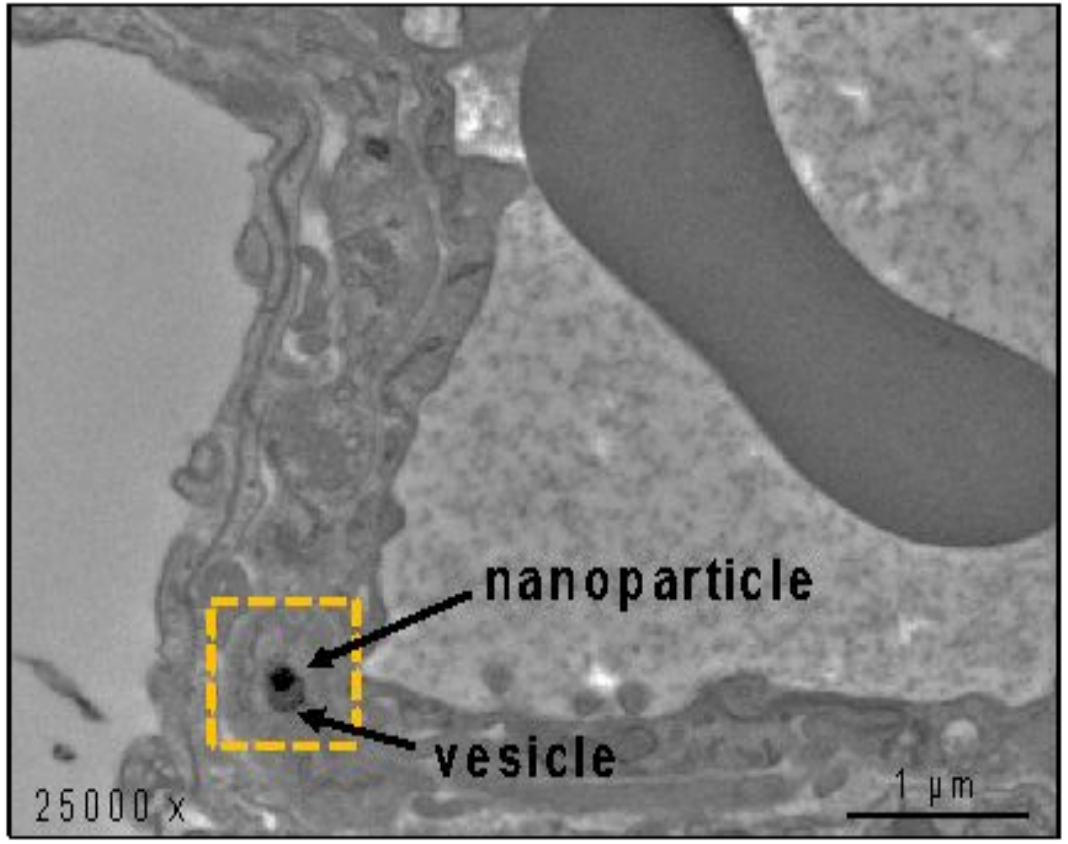
Sindhwani, *Nature Nanotechnology*, 2020

Caveolin-1 is Upregulated Upon Nanoparticle Binding to the Tumor Endothelium

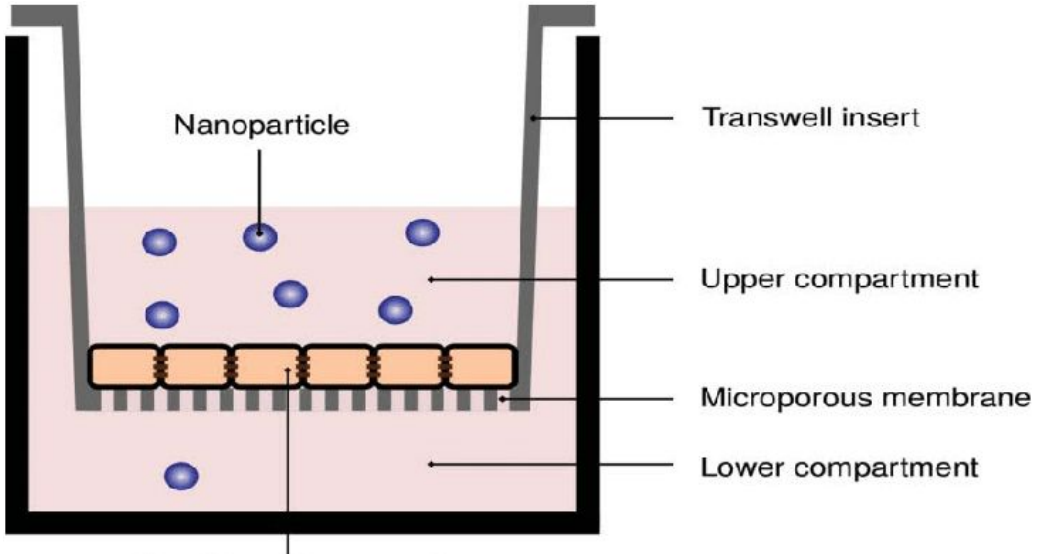


Gold-Coated Fucoidan Particles in Brain Endothelial Vesicles

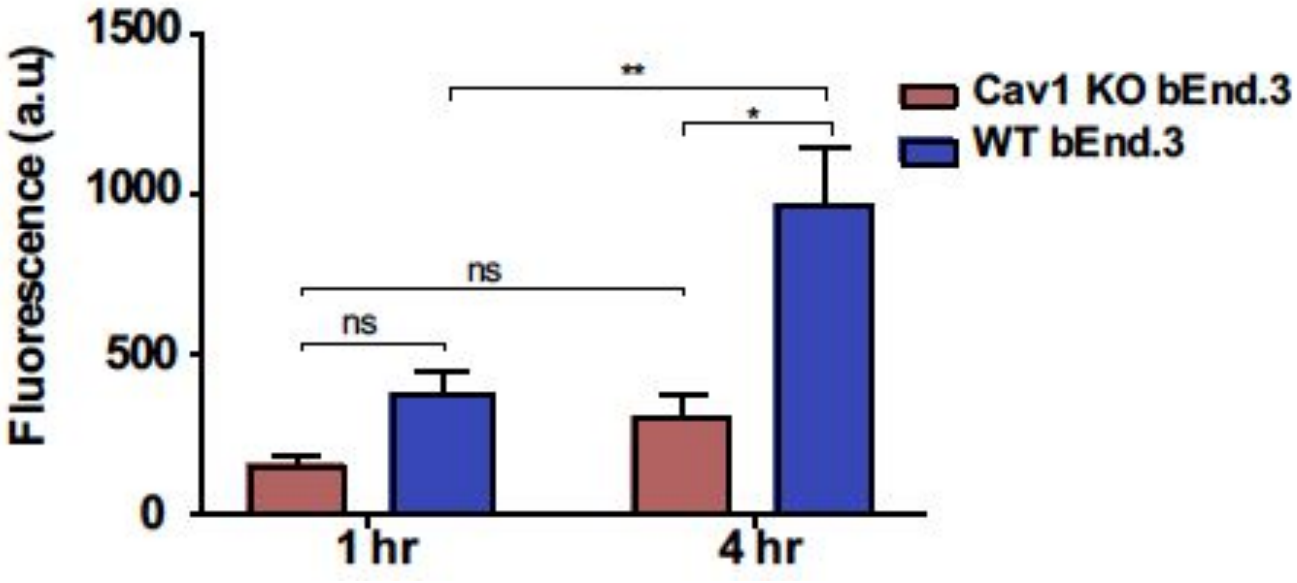




Transwell Migration Assay Shows CAV1 Dependence on Transendothelial Transport

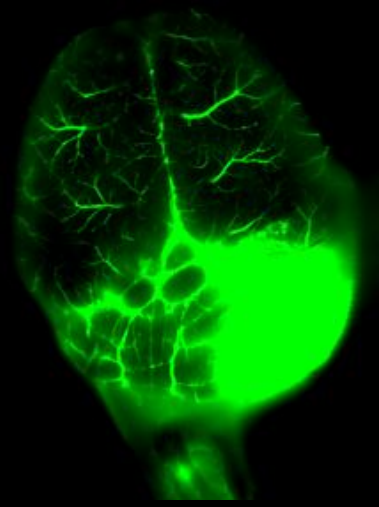


bEnd.3 Brain endothelial cells



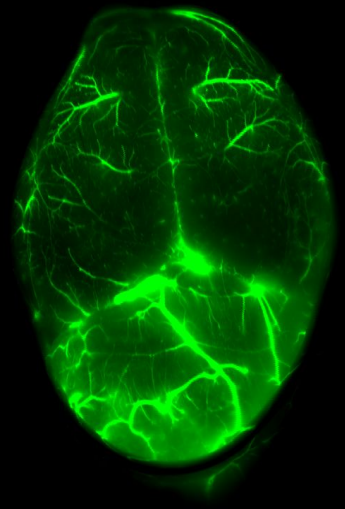
Cav-1 Knockout Prevents BBB Penetration

SHH-MB



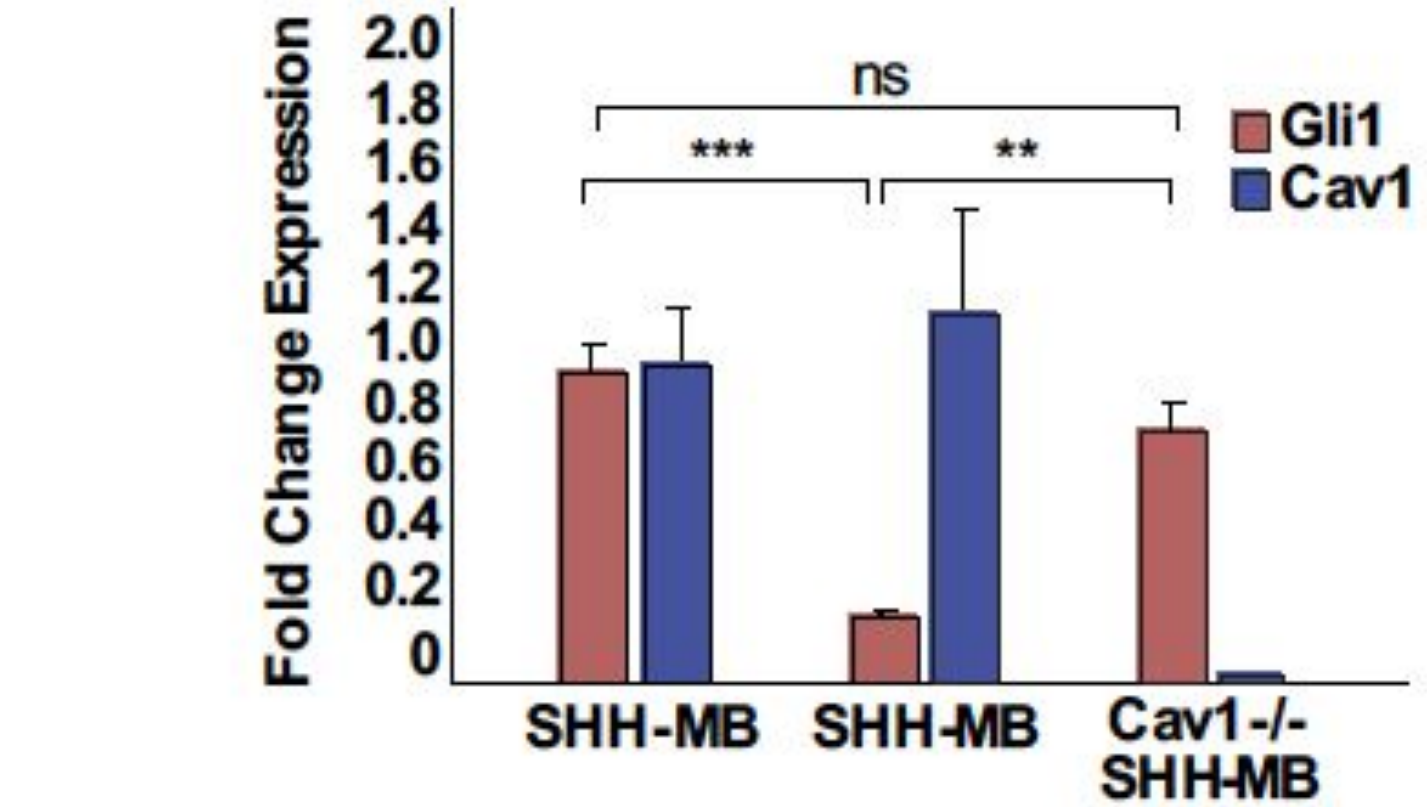
0.25 Gy XRT
+ 10mg/kg FiVis

Cav-1$^{-/-}$ SHH-MB

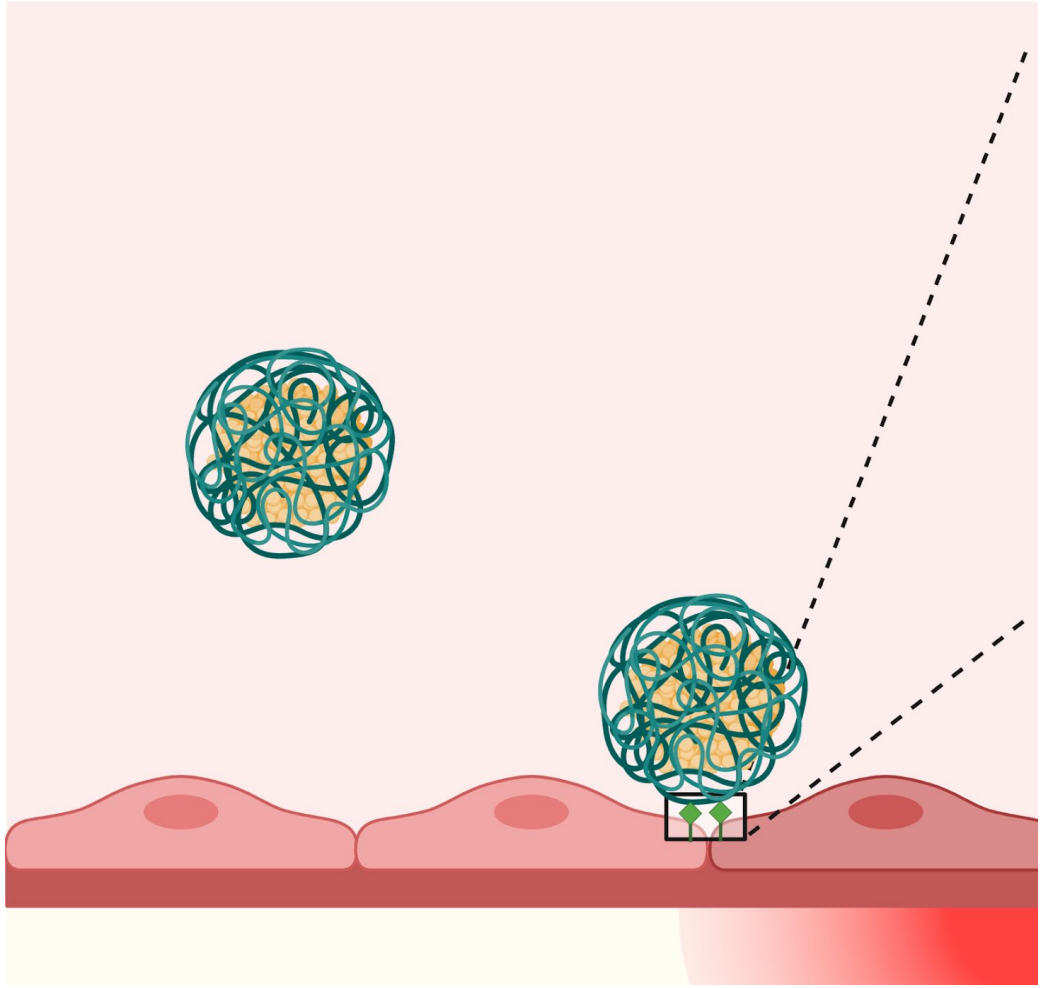


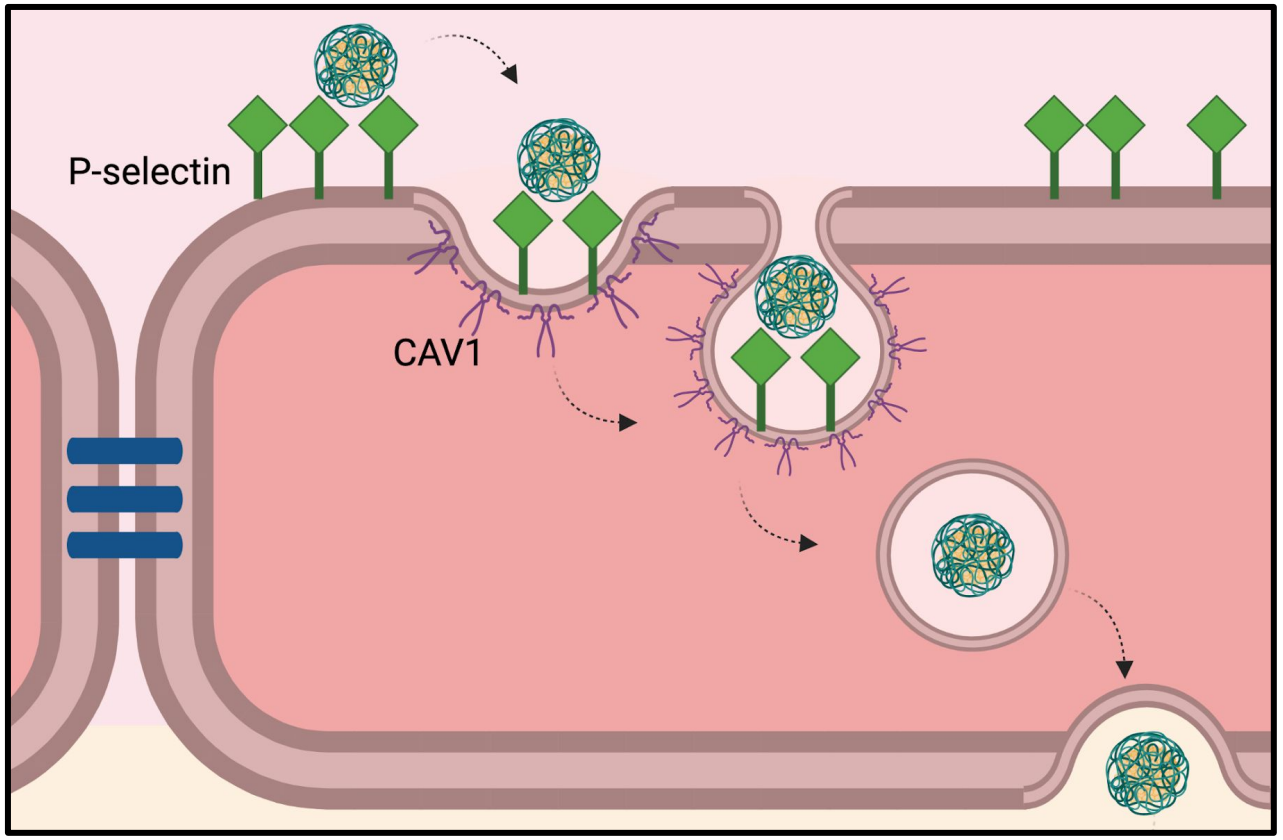
0.25 Gy XRT
+10mg/kg FiVis

CAV-1 Knockout Prevents Nanoparticle Delivery/Efficacy



P-selectin/Caveolae Mediate BBB Penetration

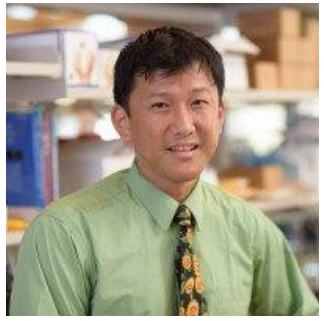




Summary & Next Questions

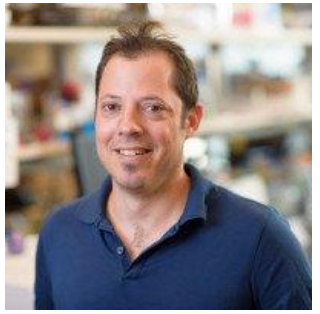
- P-selectin is a target that enables the targeting of drugs specifically to the sites of CNS disease tissue, via activated endothelium.
- P-selectin-targeted nanoparticles improve brain tumor drug localization, efficacy, and mitigation of toxicities in an intracranial GEM tumor with an intact BBB.
- **A P-selectin/caveolin axis facilitates transendothelial transport across an intact blood-brain barrier.**


Daniel Tylawsky


Hiro Kiguchi


Adriana Haimovitz-Friedman


Praveen Raju


Yosi Shamay

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Mizrachi, et al., *Nat Comms*, 2017
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Tannan et al., *Blood*, 2020
Tylawsky, et al., (Preprint) 2021
https://doi.org/10.21203/rs.3.rs-658944/v1

Acknowledgements

NIH NATIONAL CANCER INSTITUTE

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NIH National Institute of Neurological Disorders and Stroke

Tina's Wish® For the Early Detection of Ovarian Cancer Know Early. Know Hope.®

NIH National Institute of Diabetes and Digestive and Kidney Diseases

EXPECT MIRACLES FOUNDATION Financial Services Against Cancer

American Cancer Society®

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Experimental Therapeutics Center, MSKCC

Memorial Sloan Kettering Cancer Center

Cancer Nanomedicine Lab

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Ewelina Randall
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Raashed Raziuddin
Ramya Sridharan
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Neal Rosen
Adriana Haimovitz-Friedman
Charles Sawyers
David Spriggs
Maurizio Scaltriti
Raj Vinagolu
Leila Akkari
Johanna Joyce
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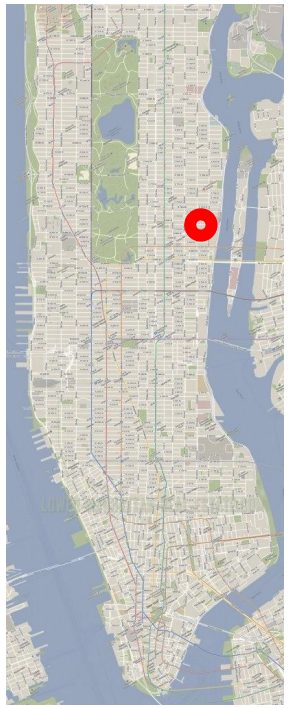
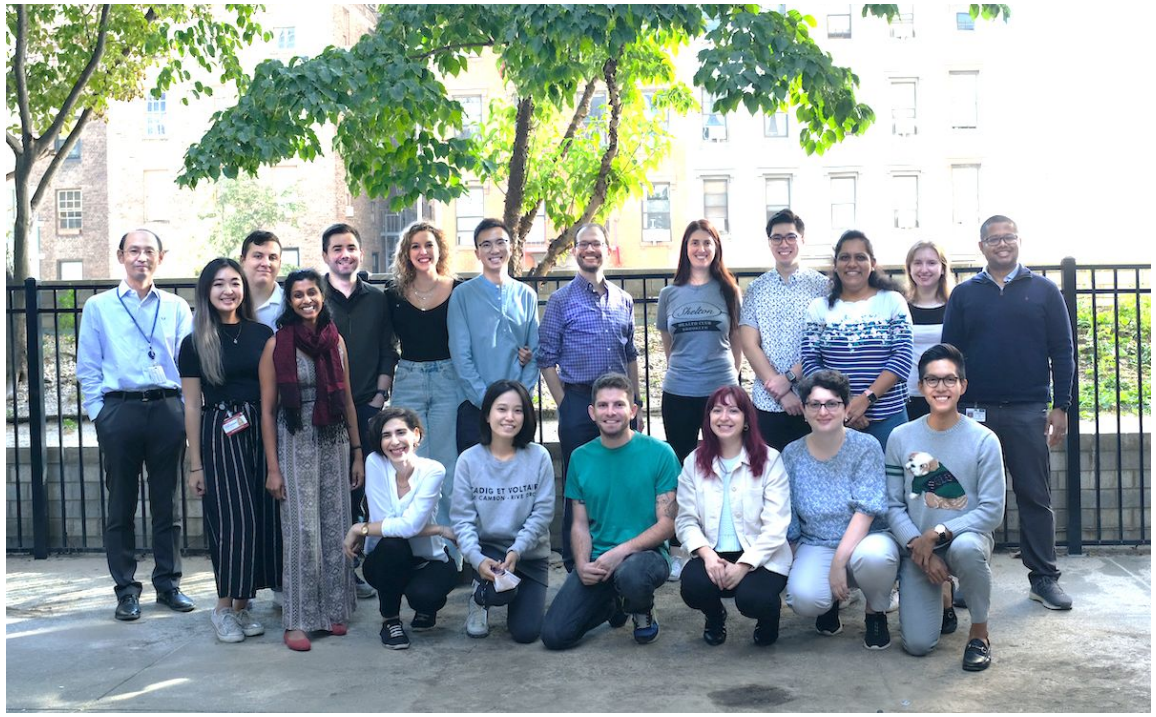
Daniel Roxbury

A Biomedical Engineering Lab at Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine





Memorial Sloan-Kettering Cancer Center

Weill Cornell Medicine
Graduate School of Medical Sciences
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Tri-Institutional PhD Program
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