

VCAM-targeted nanocarriers for the treatment of acute ischemic stroke

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Disclosure

Technology	Company/Stage	Disclosure
Therapeutic Targeting of Lipid Nanoparticles	Patent filings. Assigned to UPenn	Inventor
Targeted Therapeutic Lipid Nanoparticles and Methods of Use	Patent filings. Assigned to UPenn	Inventor
VCAM targeted LNP encapsulating mRNA for the treatment of acute ischemic stroke	Patent filings. Assigned to UPenn	Inventor
Targeted nanocarriers for acute critical illness	NanoMuse (Applying for STTR)	Co-founder



Dr. Jia Nong

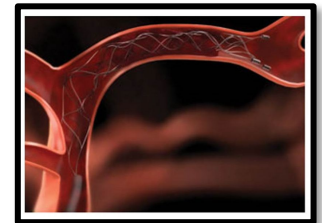
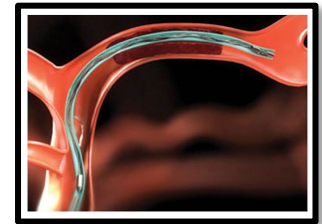
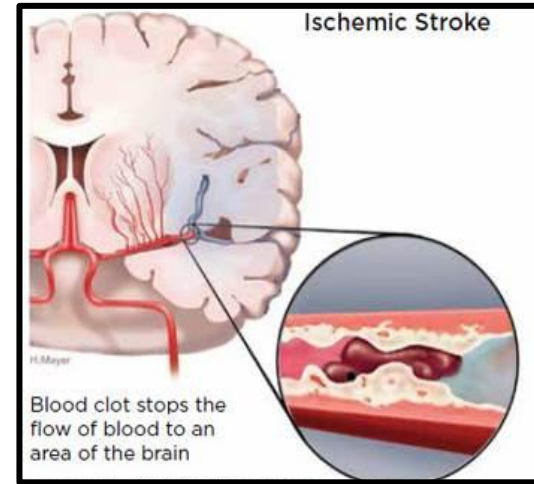
Poster: 229 (Wednesday and Thursday)

Targeted nanocarriers prevent drug partitioning to RBC and improve therapeutic efficacy in acute brain inflammation

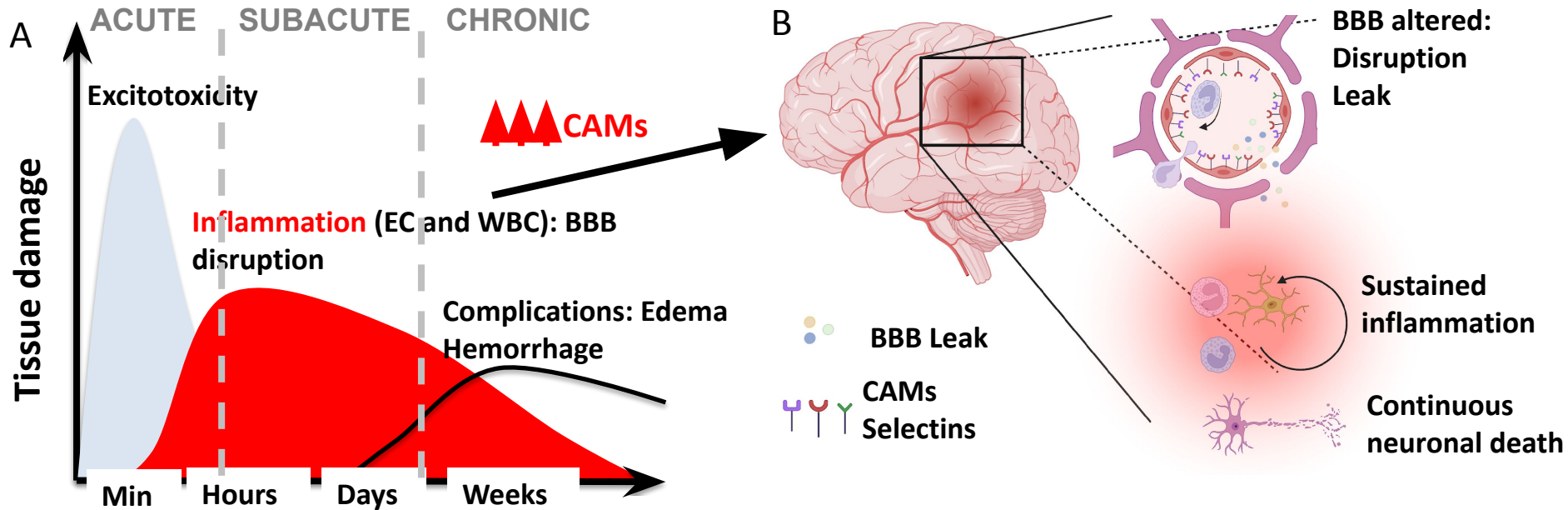
Stroke: facts

- 800,000 cases/year acute ischemic stroke (AIS, 87%), and hemorrhagic stroke (ICH, 13%)
- Second cause of death worldwide and main cause of long-term disability
- Urgent unmet need:
 - tPA, remains the only FDA approved treatment for acute ischemic stroke (since 90'). 19% functional independence
 - MR CLEAN (2015): mechanical thrombectomy. 33% functional independence

Still near 50% of patients after AIS are not functionally independent

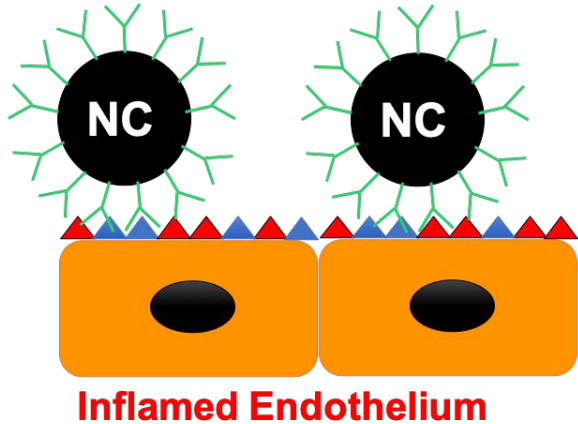


Acute ischemic stroke (AIS): pathophysiology



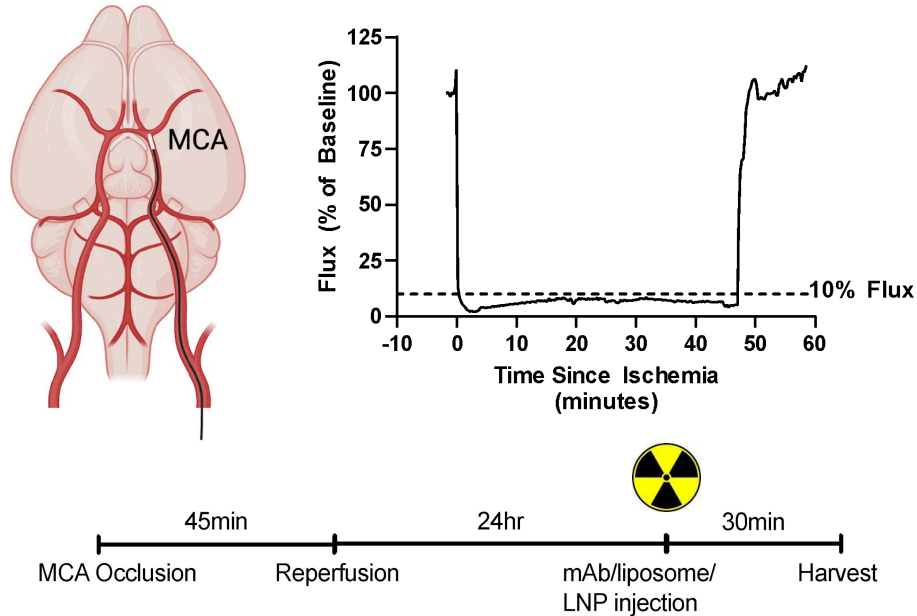
Delivery to the Brain: targeting the inflamed BBB

Targeting nanocarriers to the
BBB itself

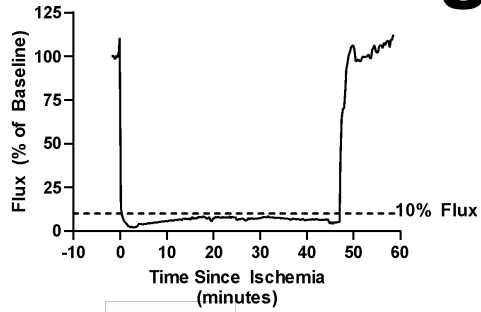
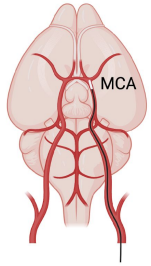


- High accessibility
 - Surface area of $\sim 20 \text{ m}^2$
 - Length: 600km
 - 15% Blood flow
- Seal the “gate”: Restoring the BBB
 - Protect against edema
 - Switch the proinflammatory environment to anti-inflammatory one

Transient Middle Cerebral Artery Occlusion (tMCAO) Model



Target selection



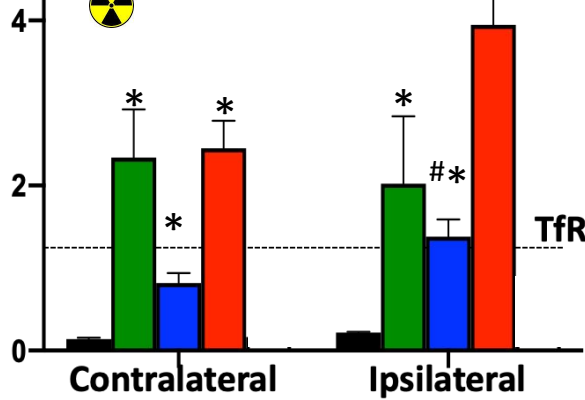
D

Brain uptake (%ID/g)



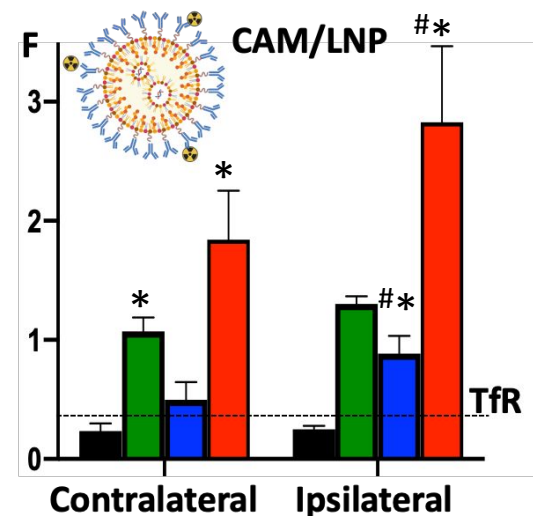
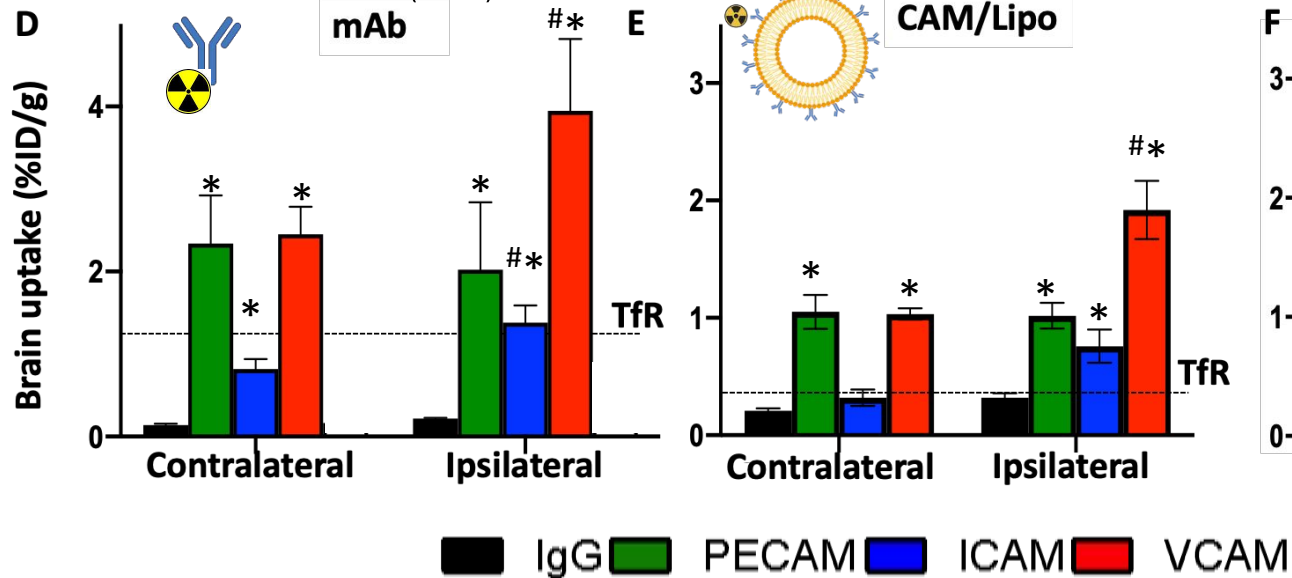
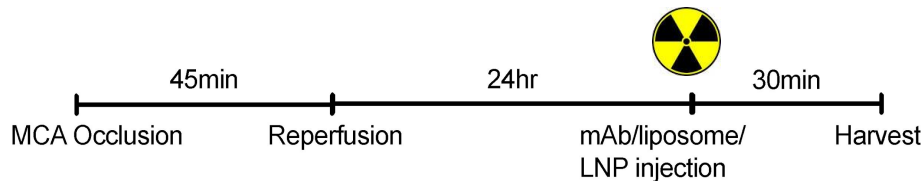
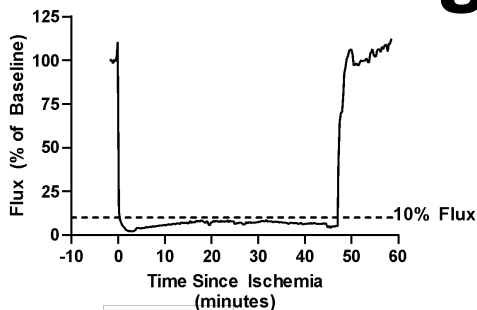
mAb

E

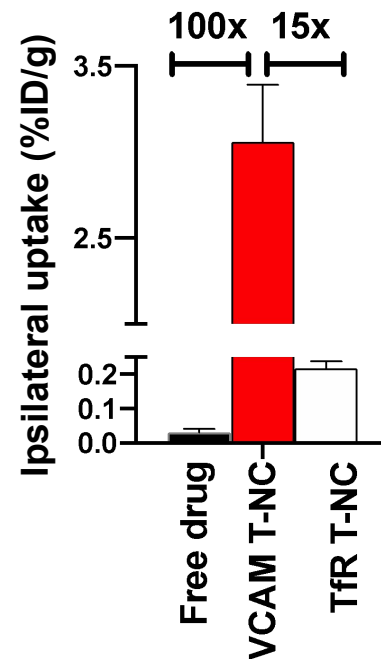
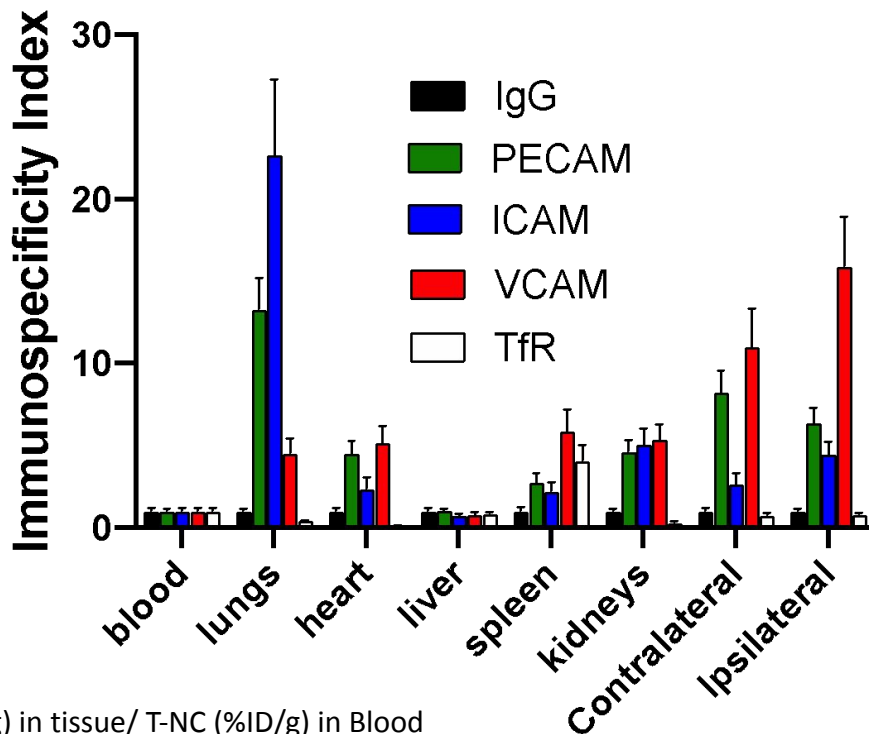
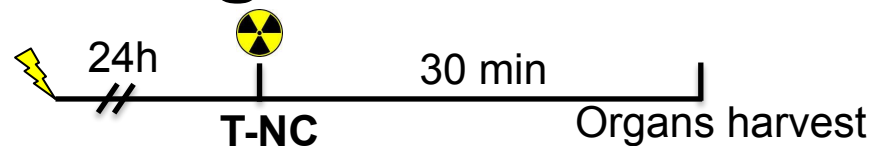


IgG
 PECAM
 ICAM
 VCAM

A diagram of the brain showing the territory of the middle cerebral artery (MCA). The MCA is labeled on the right side of the brain. The territory is shaded in light red and covers the lateral surface of the brain, including the frontal, parietal, and temporal lobes, and the lateral surface of the brainstem.

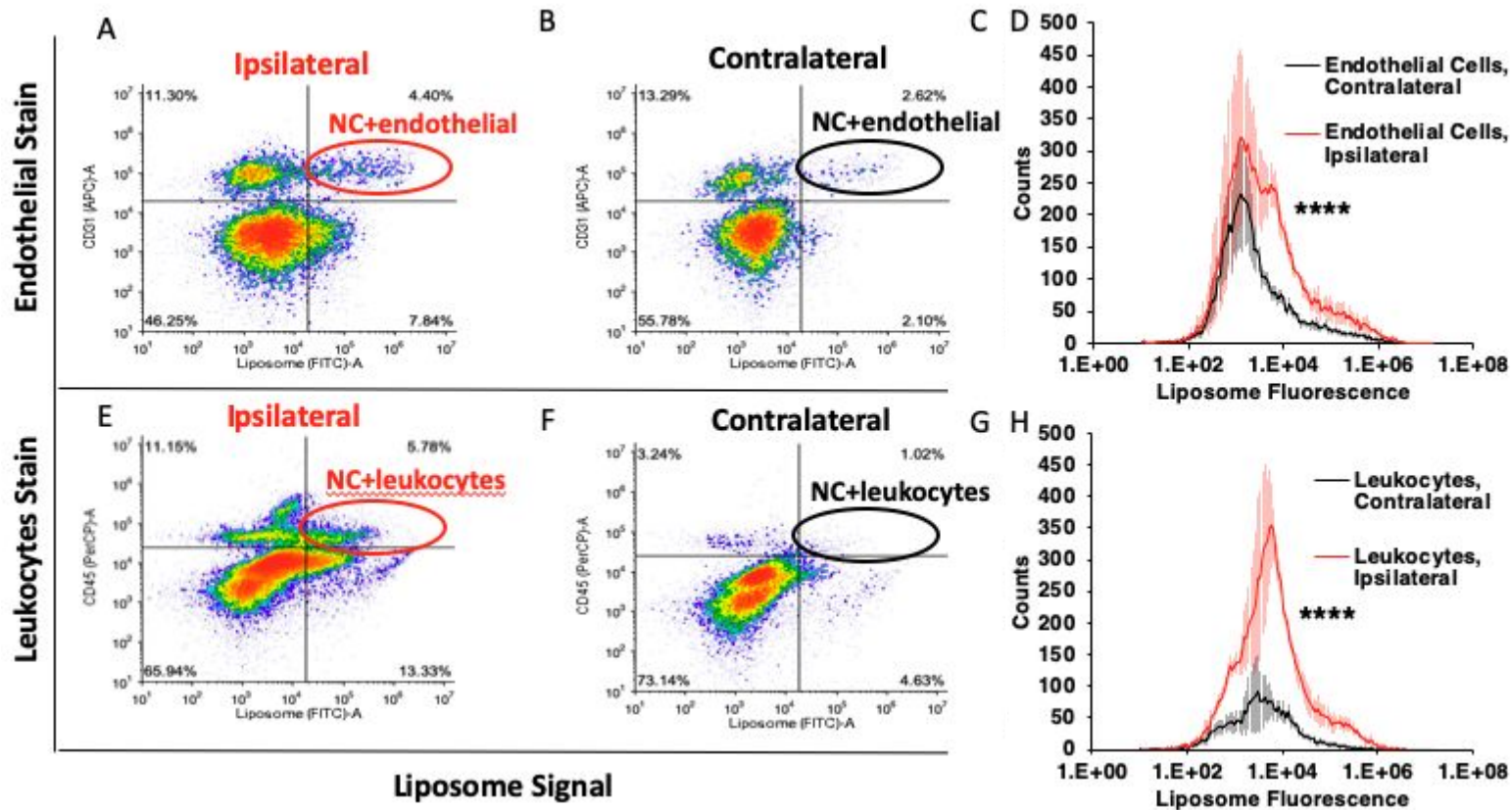
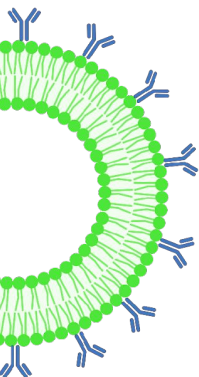


Target selection

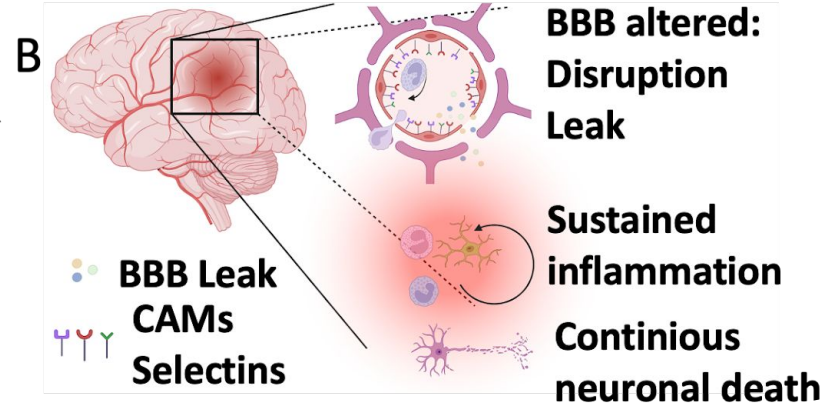
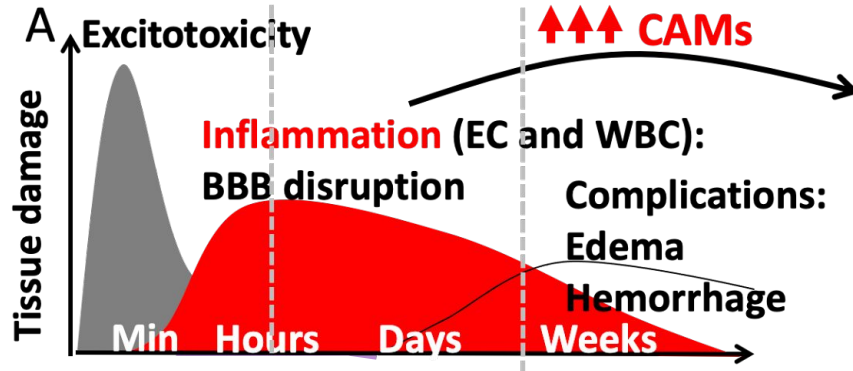


T-NC (%ID/g) in tissue/ T-NC (%ID/g) in Blood
IgG-NC (%ID/g) in tissue/ IgG-NC (%ID/g) in Blood

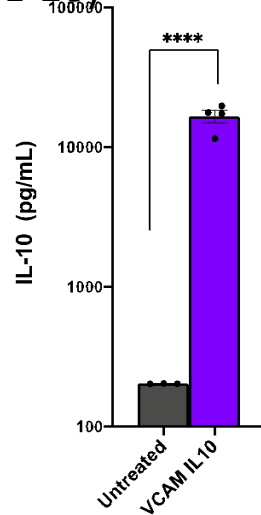
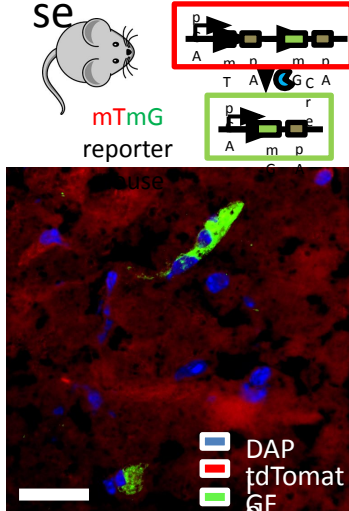
VCAM T-NC: cellular uptake



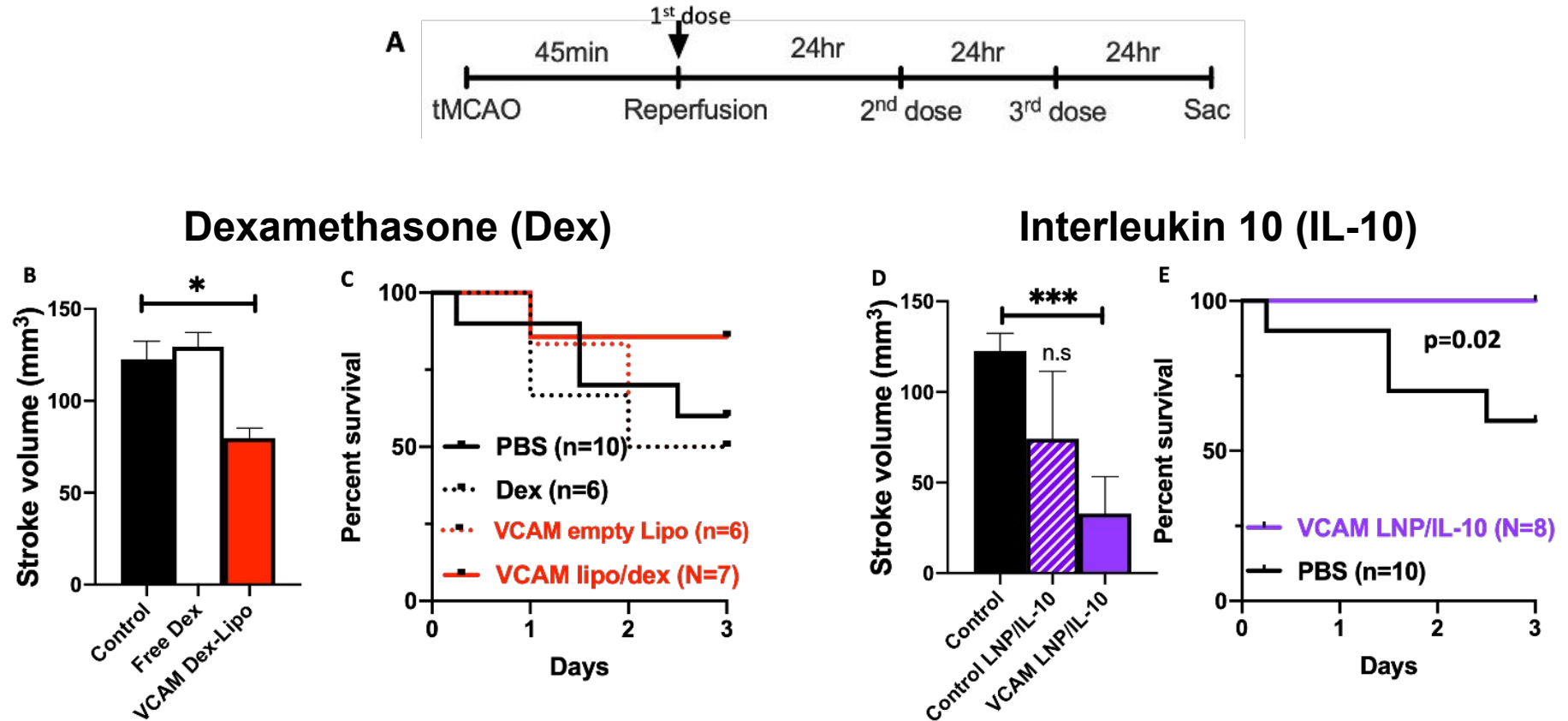
Pharmacological working hypothesis



A detailed diagram of a virus particle. It features a central core containing genetic material, surrounded by a capsid. The surface is covered with numerous blue Y-shaped proteins (antigens) and red spherical proteins (antibodies). Three black circular icons with yellow radiation symbols are positioned around the virus, indicating its potential for infection or harm.

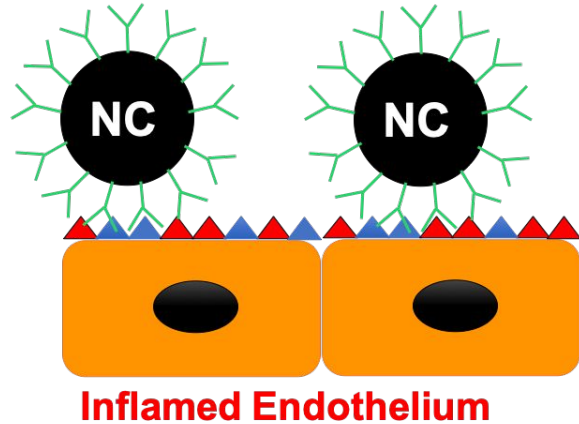


VCAM targeted nanocarriers improve AIS



Targeting the inflamed BBB: summary

Targeting nanocarriers to the
BBB itself



1. VCAM-targeted nanocarriers enhance delivery to the ischemic hemisphere in AIS vs. alternatives
2. VCAM-targeted nanocarriers containing small molecule and mRNA therapeutics effectively treat AIS

Acknowledgements

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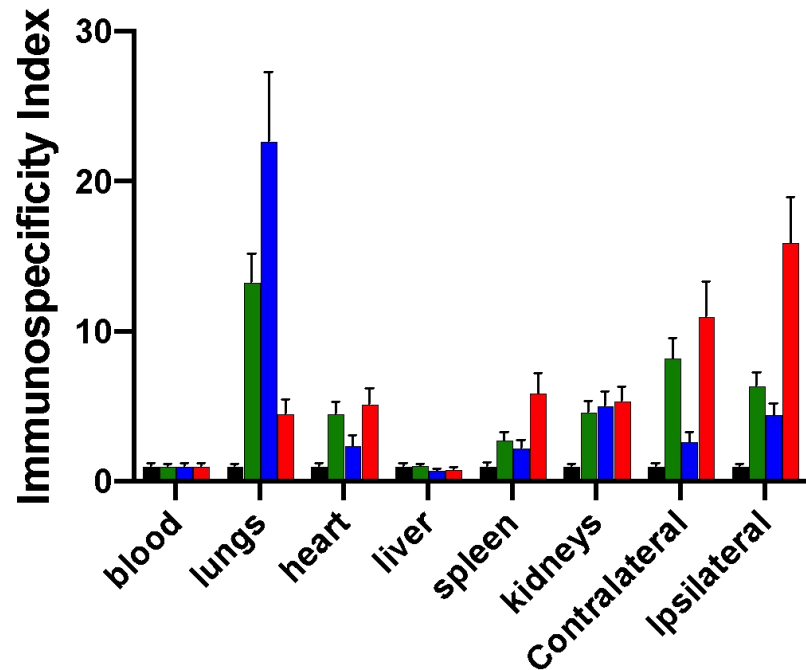
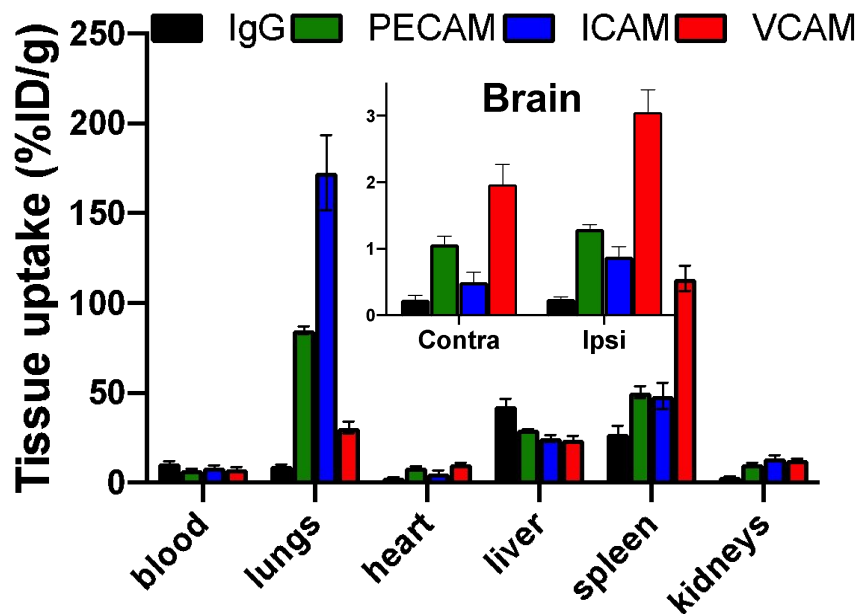
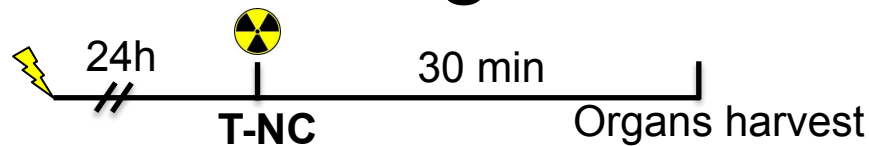
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H Parhiz
TE Papp

Thaiss Lab

H Descamps

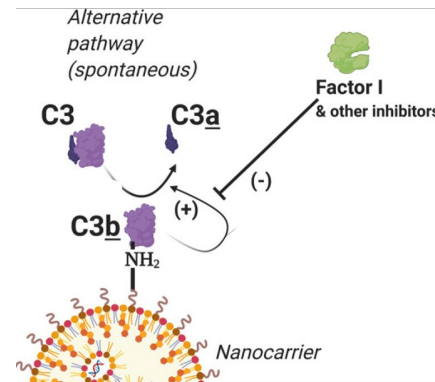
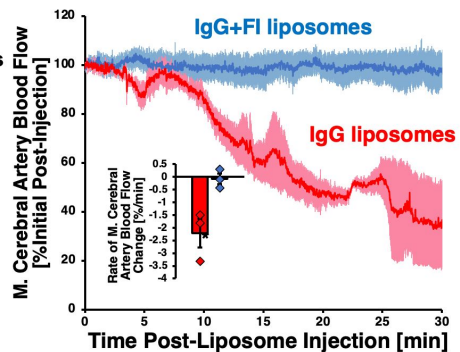
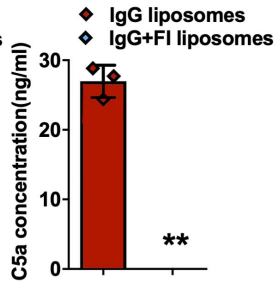


To the BBB: Target selection



$\frac{\text{T-NC (\%ID/g) in tissue}}{\text{IgG-NC (\%ID/g) in tissue}} \div \frac{\text{T-NC (\%ID/g) in Blood}}{\text{IgG-NC (\%ID/g) in Blood}}$

Group	C3a concentration (ng/ml)
IgG liposomes	~6800
IgG+FI liposomes	~3800*



Wang et al Adv Materials, 2021

Omo-Lamai et al. In preparation

Brain

Lungs

GI

Untargeted LNP-IL-10

25%

25%

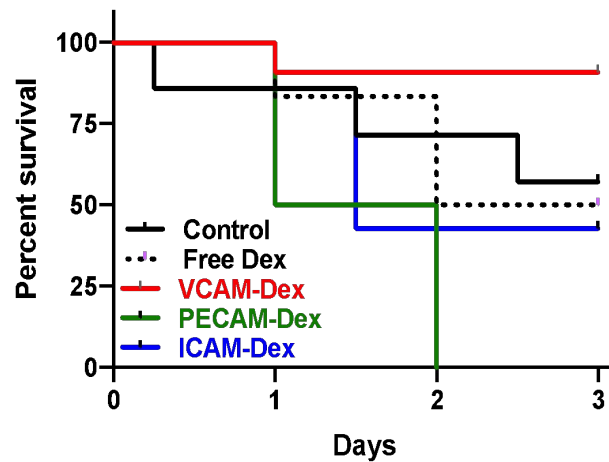
25%

Free dexamethasone

80%

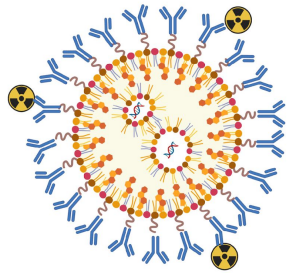
50

17%

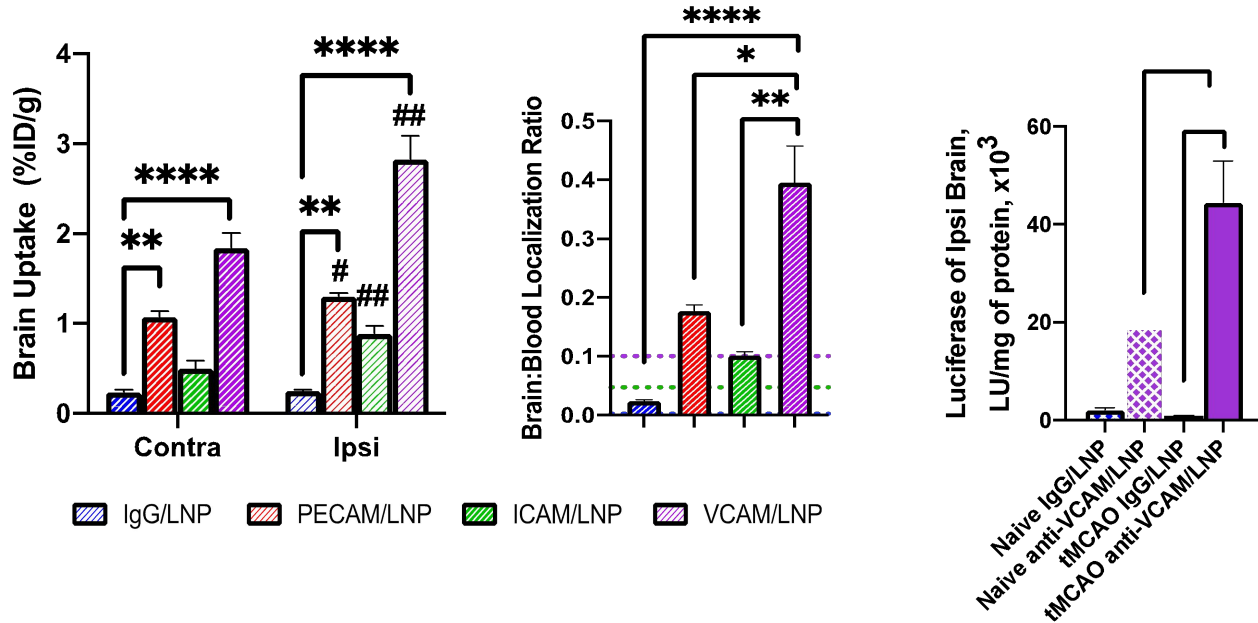


Nong et al. BioRxiv 2023

VCAM-targeted LNPs accumulate in tMCAO brain and produce significant luciferase activity



LNP



VCAM-targeted nanocarriers accumulate in ICH brain



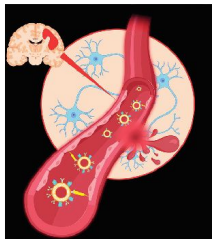
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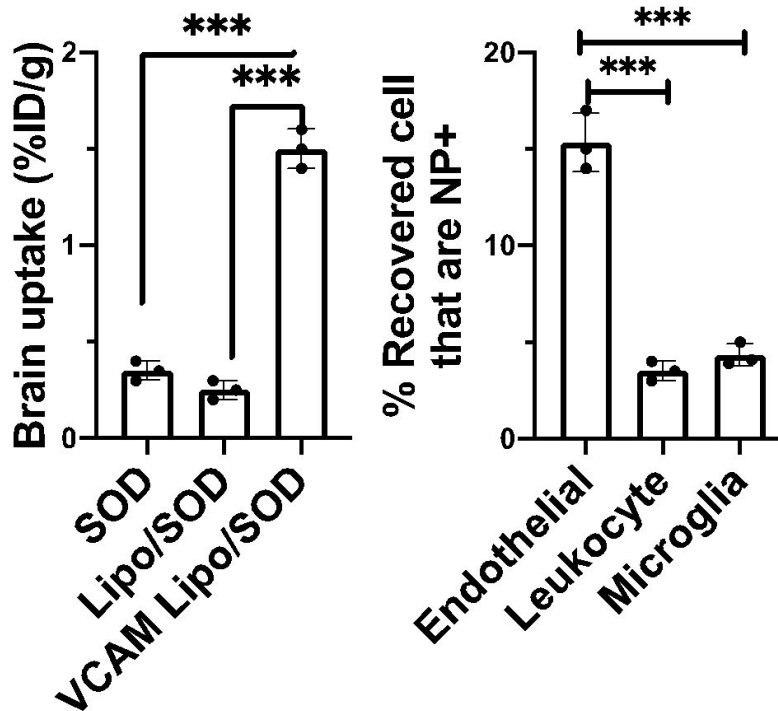


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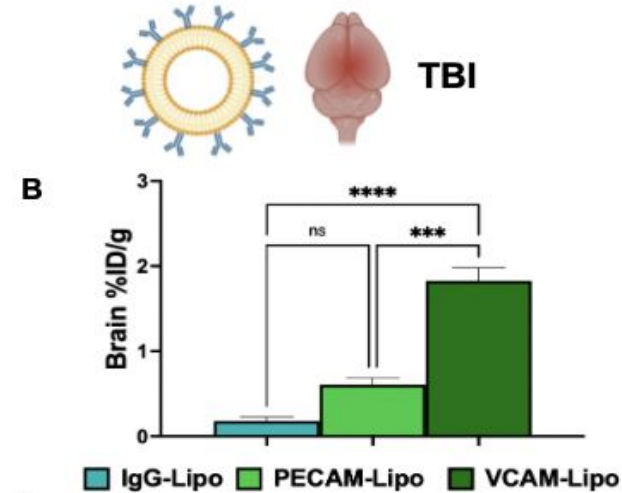
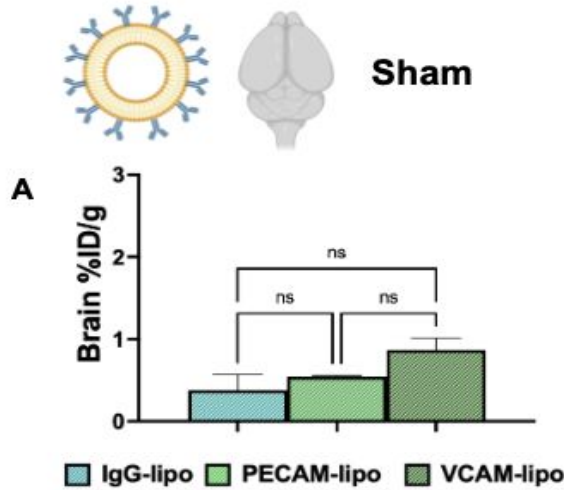
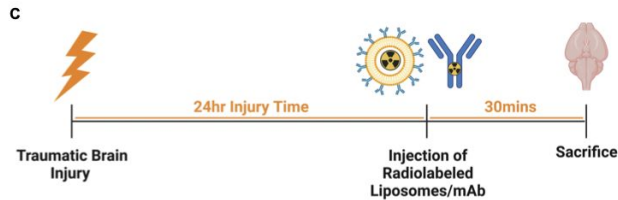
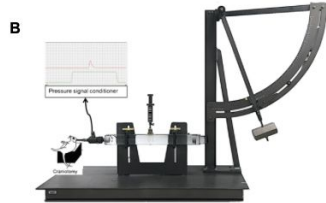
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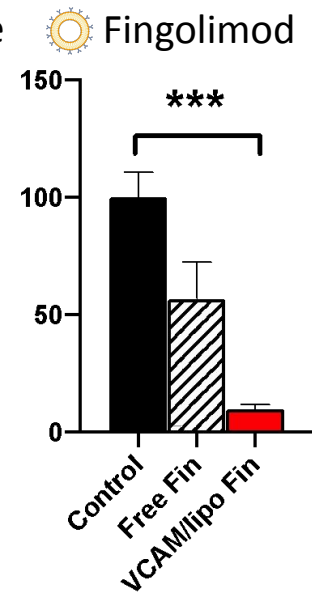
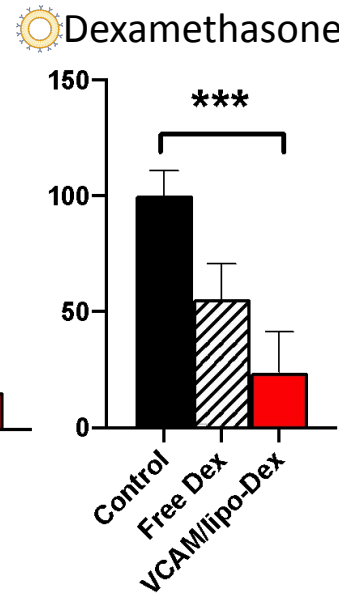
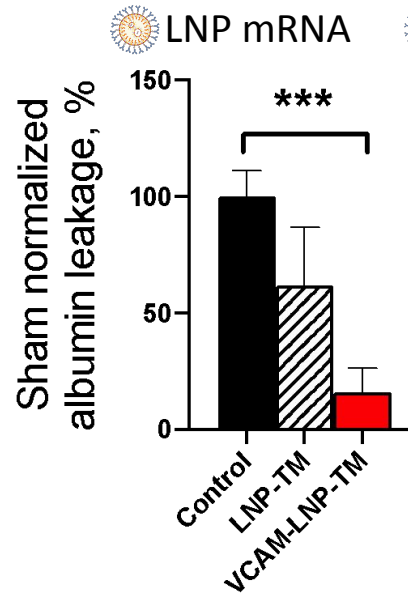
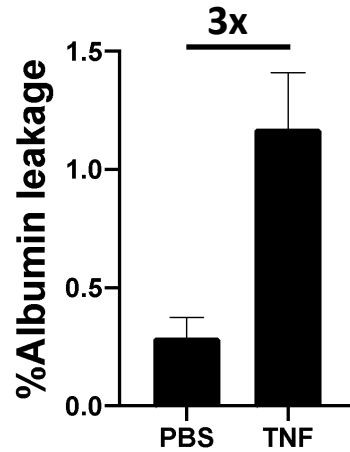
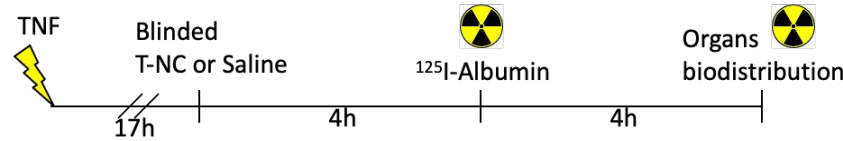
Targeted drug delivery to the brain endothelium dominates over passive delivery via vascular leak in experimental intracerebral hemorrhage



VCAM-targeted nanocarriers accumulate in **TBI**

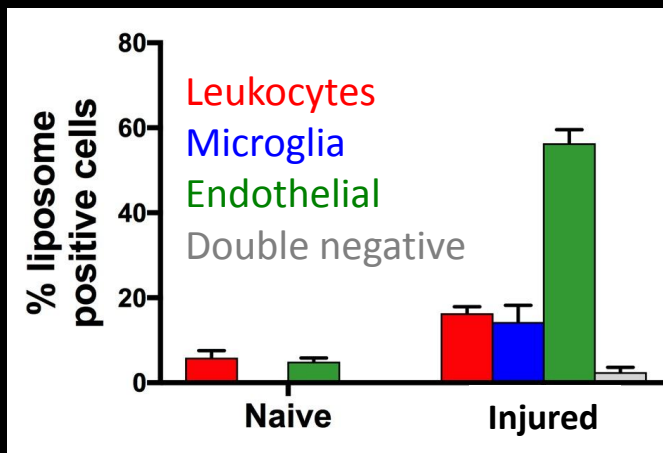
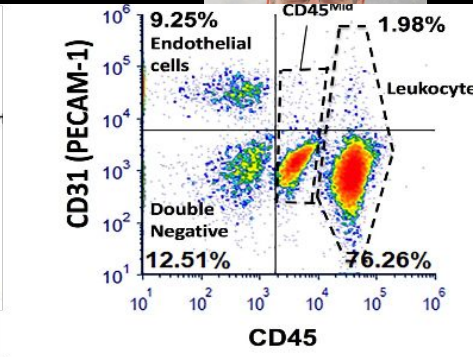
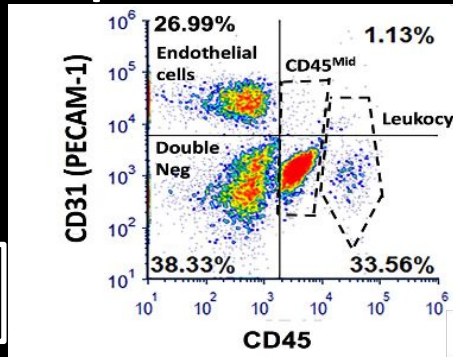
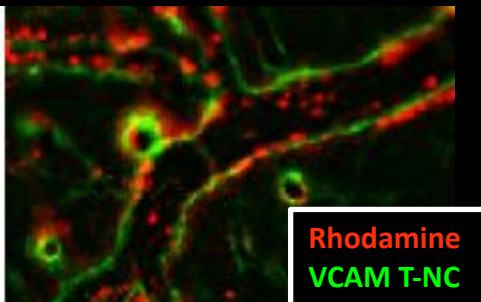
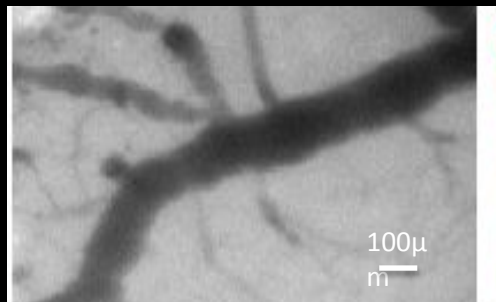


VCAM targeted-nanocarriers reduces brain edema



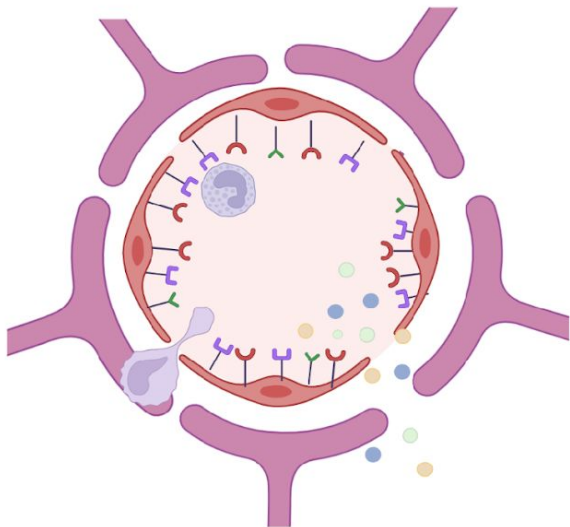
VCAM T-NC targets the inflamed BBB

Anti-VCAM-Liposome



Delivery To The Brain: What Are We Targeting?

Neurovascular Inflammation

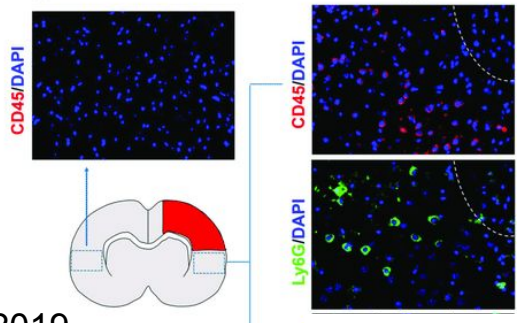


A

Endothelial Surface Protein	
Constitutively Expressed	Inducible
Platelet Endothelial Adhesion Molecule (PECAM) Transferrin Receptor Insulin Receptor Low Density Lipoprotein Receptor-related Protein	P-selectin Intercellular Adhesion molecule (ICAM) Vascular Adhesion Molecule (VCAM)

B

Leukocytes infiltration



VCAM targeted nanocarriers are uptaken by leukocytes and endothelial cells

