Tech Session VII: Delivery to the Nervous System II

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CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

SPATT
SYSTEMS PHARMACOLOGY AND TRANSLATIONAL THERAPEUTICS

Penn
UNIVERSITY of PENNSYLVANIA

Empowering the Blood-Brain Barrier: VCAM Targeted Nanocarriers in Neuroinflammatory Diseases

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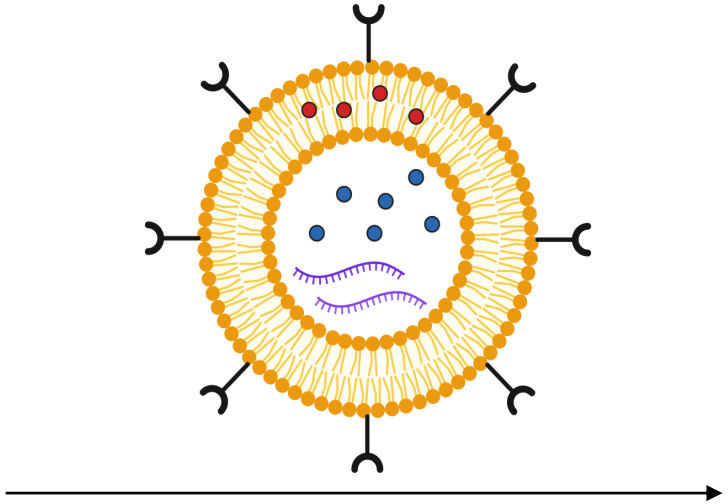
Systems Pharmacology and TranslationalTherapeutics (SPATT)
Neurology

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 (STTR: funded)	Co-founder

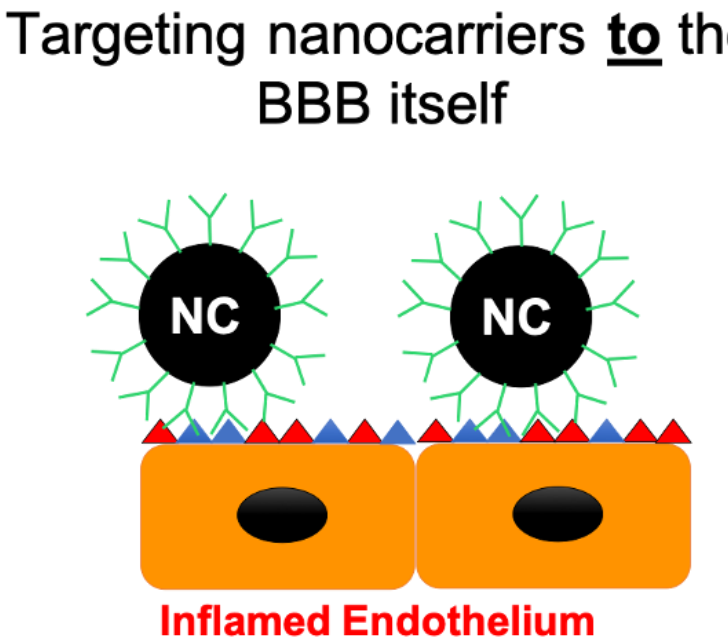
Research focus: Targeted Nanomedicine and neurovascular inflammation



NVI: **acute/chronic**
Stroke, TBI, MS, AD…

Outline:

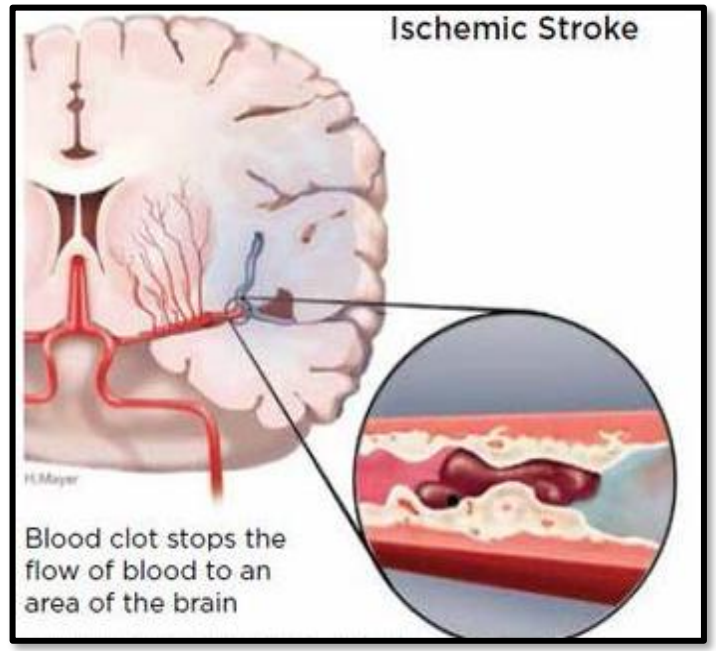
- Stroke and targeted nanomedicine
- Delivery approach: Targeting the inflamed BBB

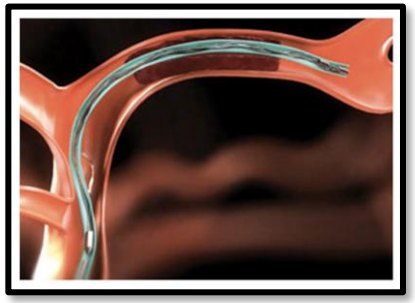


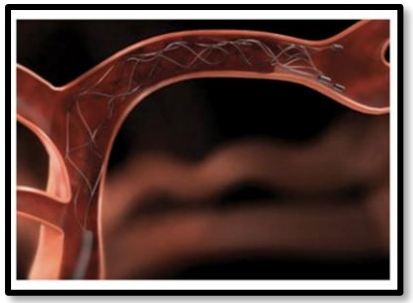
Stroke: facts

- 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

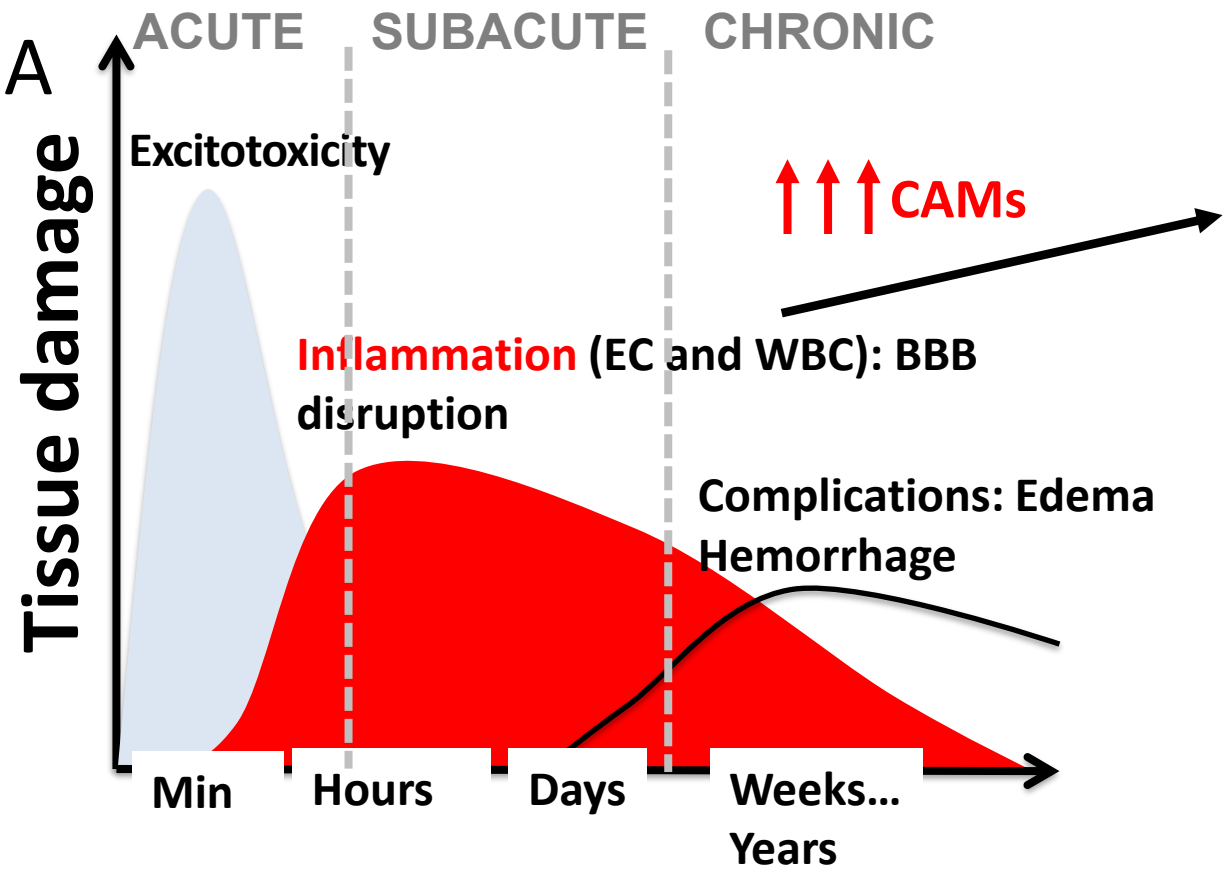
Still near 50% of patients after AIS are not functionally independent

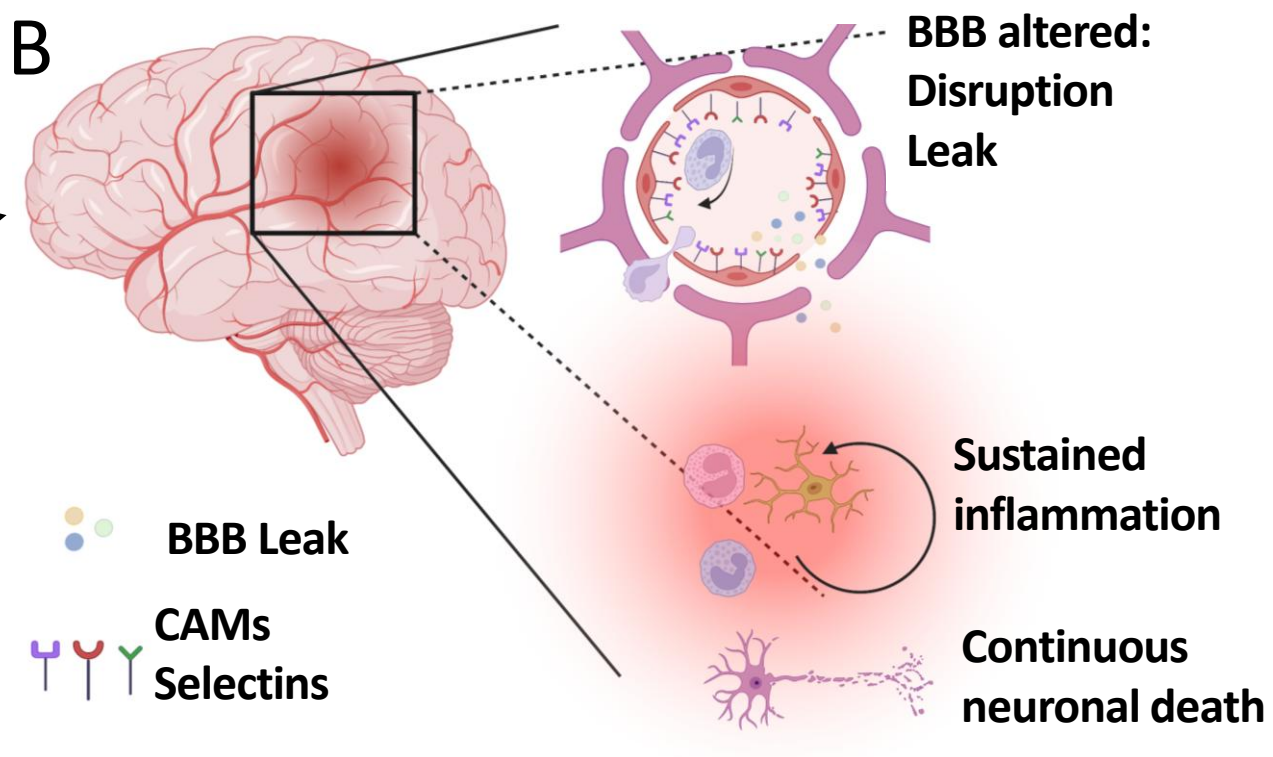






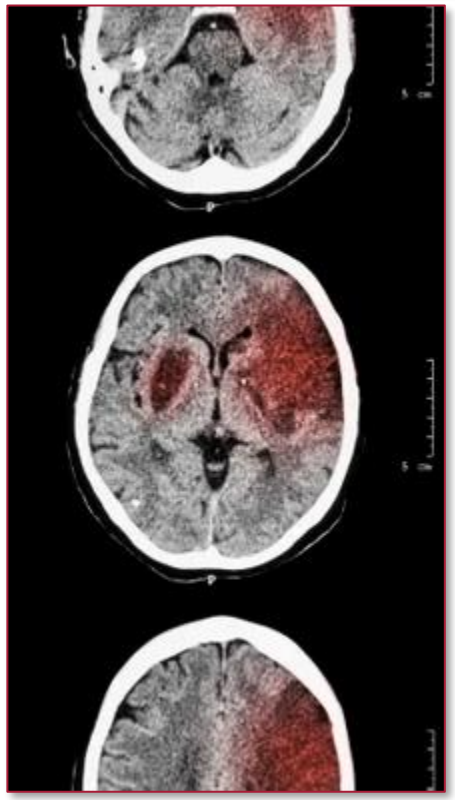
Acute ischemic stroke (AIS): pathophysiology





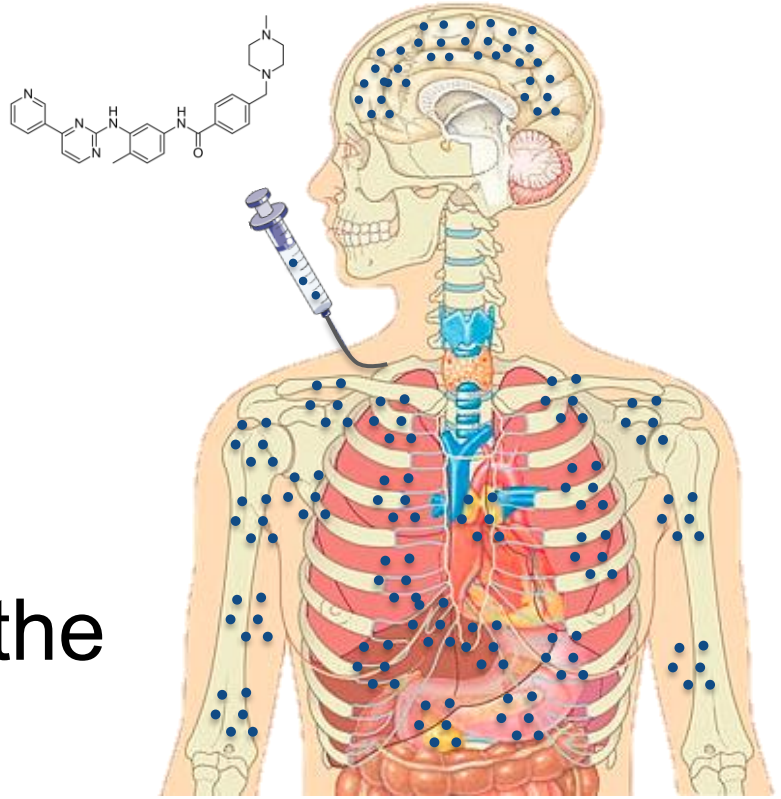
1,026 Experimental Treatments in Acute Stroke

Victoria E. O'Collins, B.Sci,[1] Malcolm R. Macleod, MRCP, PhD,[3] Geoffrey A. Donnan, MD, FRACP,[2] Laura L. Horky, MD, PhD,[2] Bart H. van der Worp, MD, PhD,[4] and David W. Howells, PhD[1]



Nihilism in acute ischemic stroke:

- 114 reached clinical trials and all failed. Why?
- Inability of concentrating the drug in the injured brain without off target toxicities

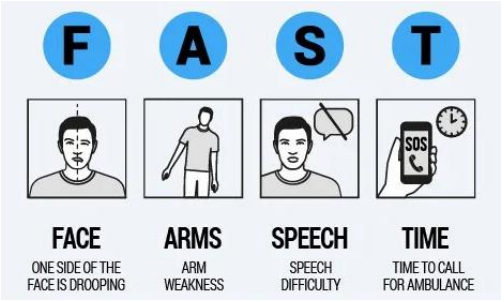


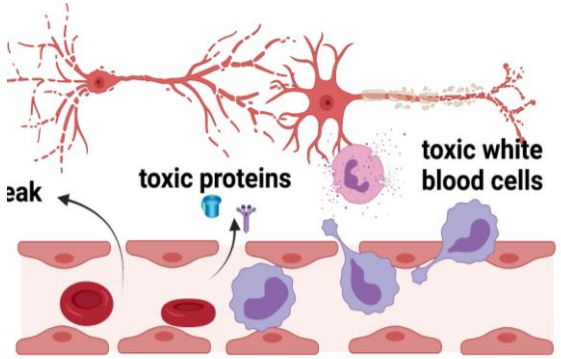
Neuroprotective drugs

<u>Need</u> :Targeted drug delivery better therapeutic index

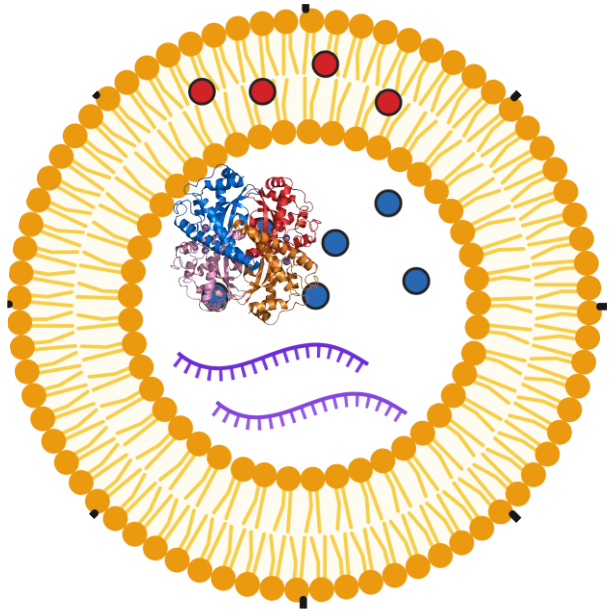
The patient and the pharmacological challenges

- Fragile patients: high blood pressure, arrhythmia, clotting, bleeding, multiorgan failure, pneumonia
  - ***Solution: Targeted therapeutics***
- Rapidly progressive disease
  - ***Solution: Multidrug loaded carriers***
- Challenging to reach the injured brain
  - ***Solution: Targeting specific cell types***





Nanomedicine: targeted nanocarriers (T-NC)

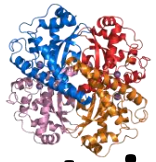


Dr. Muzykantov Dr. Brenner

Nucleic acids

Hydrophilic drugs

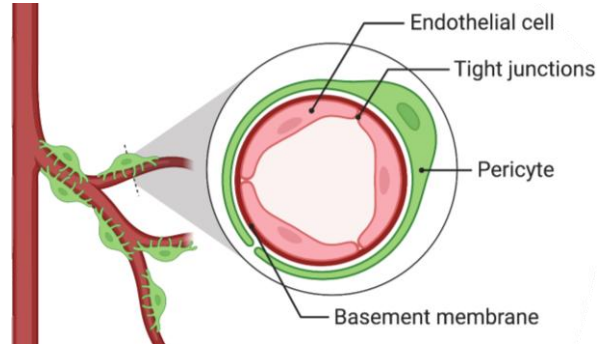
Lipophilic drugs



Proteins

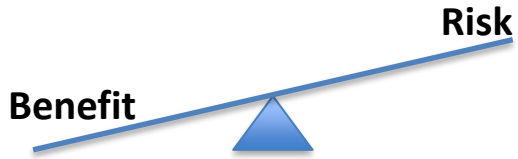
Targeted nanomedicine for CNS diseases

1. Delivery:
Current delivery of free drugs to brain
<<0.01%
Goal: 100-fold improvement

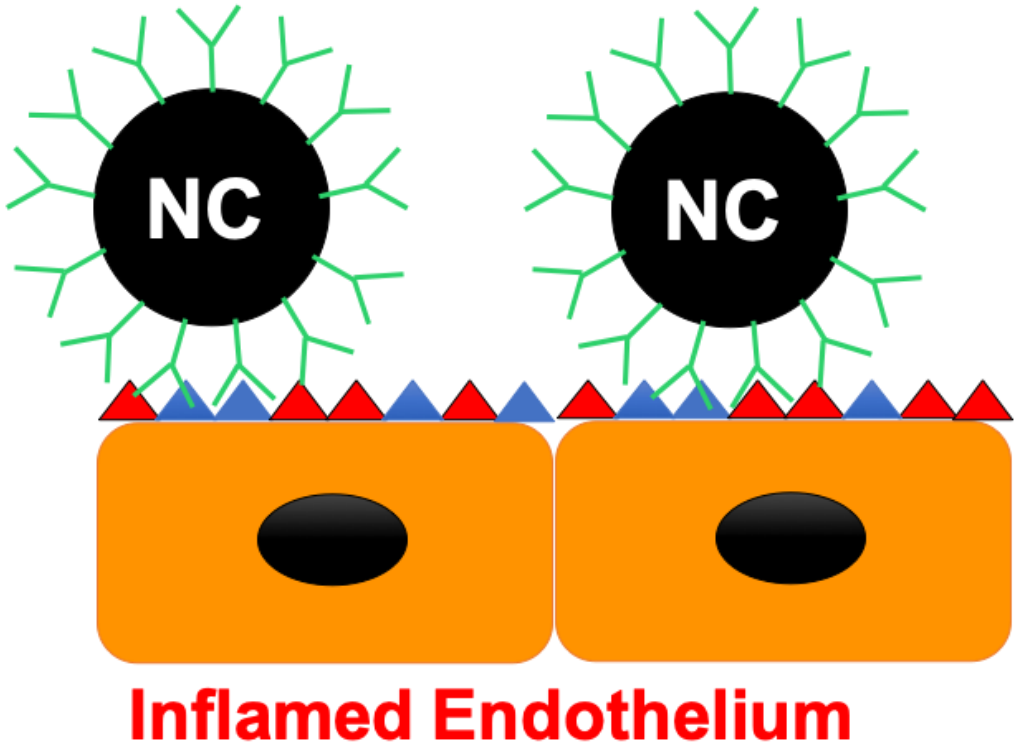


2. Therapeutic effects:
Biomarkers
Neurobehavior

3. Side effects:
Disease dependent inflammatory response
Protein corona effects/opsonization



Targeting nanocarriers **to** the BBB itself

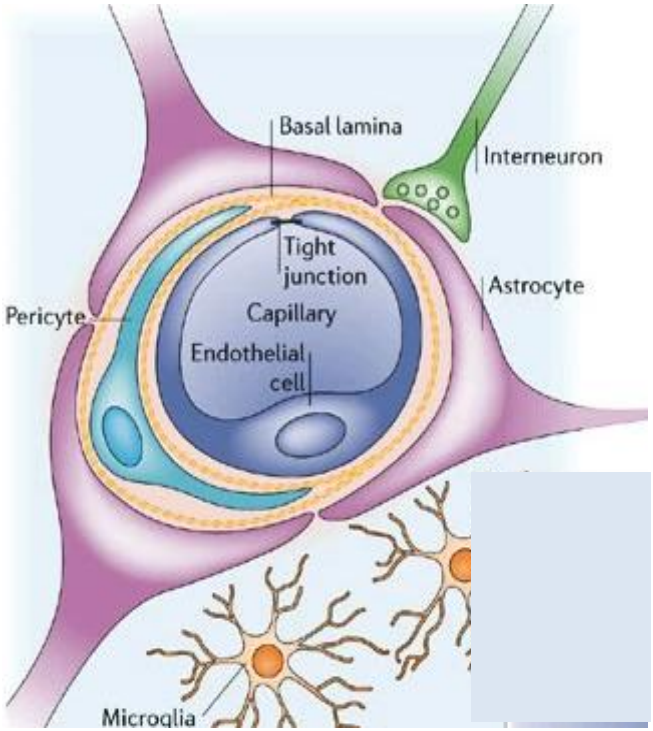


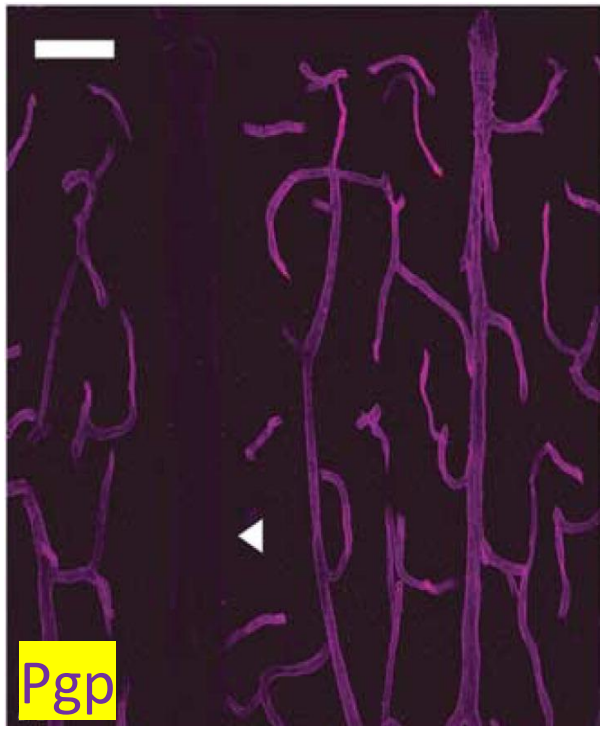
ICAM VCAM Anti-CAM Targeted NC

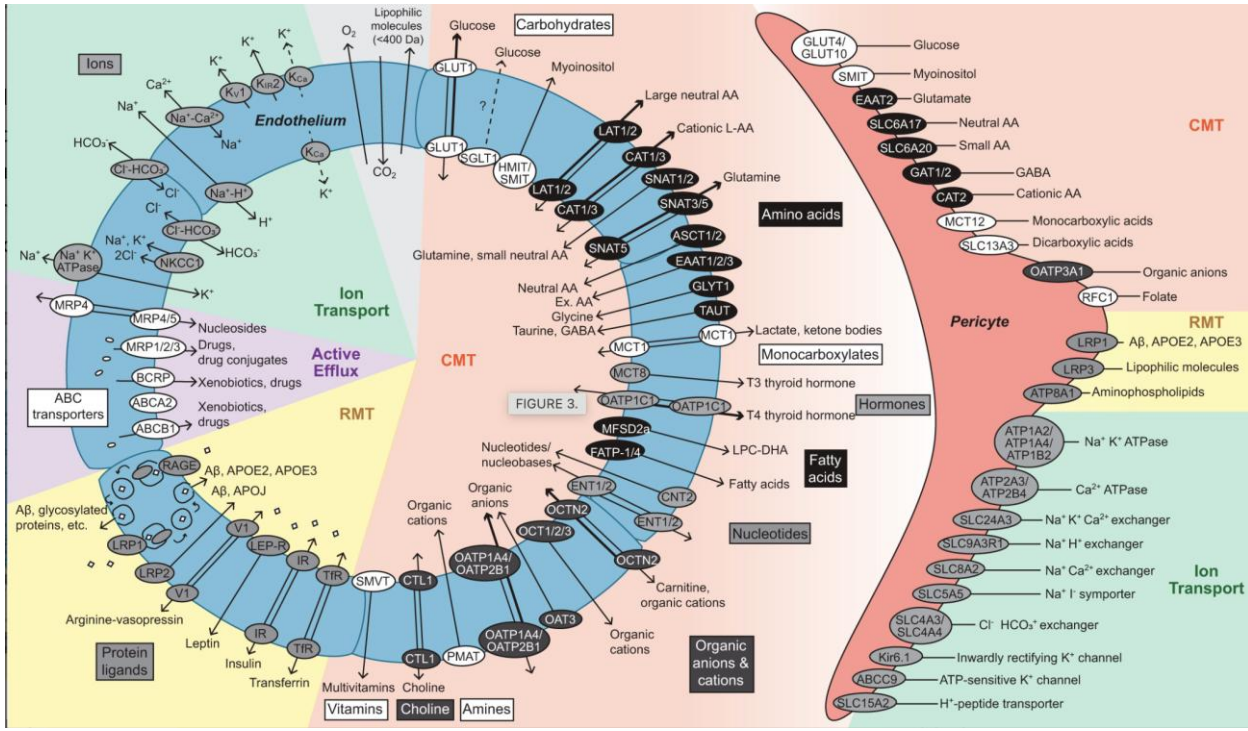
ICAM: intracellular adhesion molecule VCAM: vascular adhesion molecule NC: nanocarriers

Targeted nanomedicine for stroke: The BBB

- The BBB is a physical and metabolic barrier



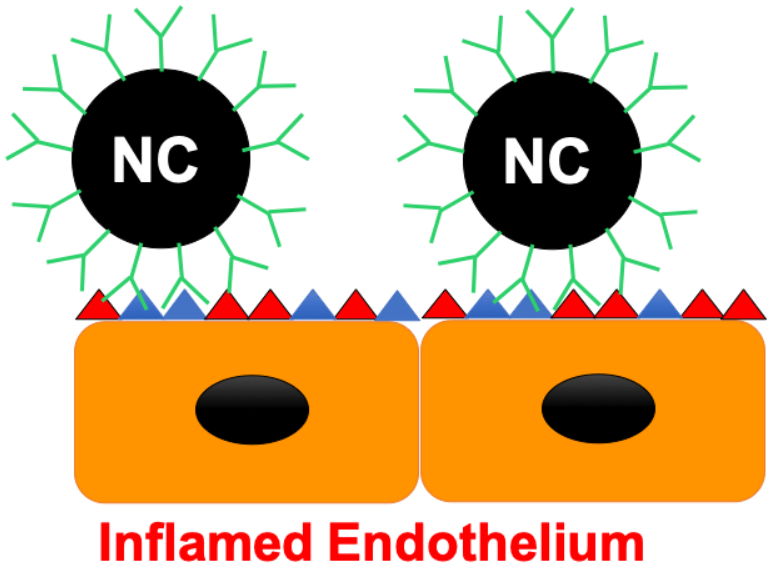




Abbott NJ *et al.* (2006) *Nat. Rev. Neuro*
Sweeney et al (2019). Physiol Rev
Saubaméa et al (2011) JCBM.
Smith Q (2008). HST

Delivery to the Brain: targeting the inflamed BBB

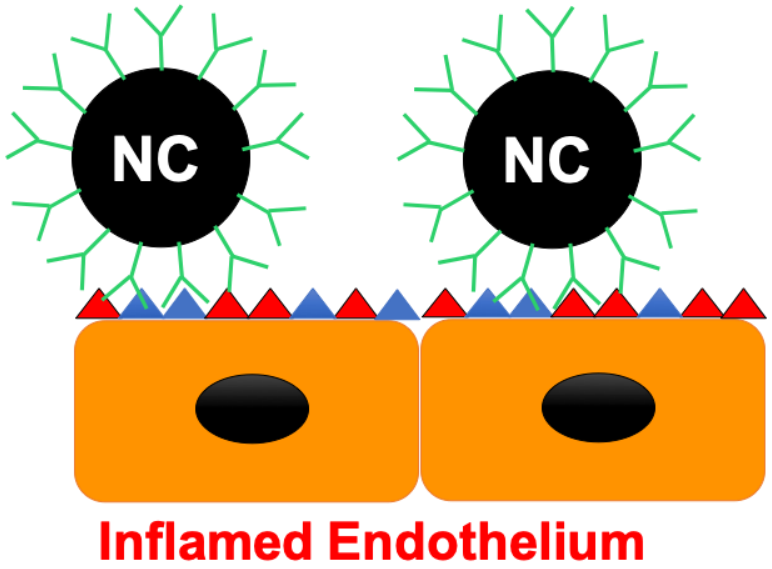
Targeting nanocarriers **to** the BBB itself



- High accessibility
  - Length: 600km
  - Surface area of ~15 m^2
  - 15% cardiac output
- Restoring the BBB
  - Protect against edema
  - Switch the proinflammatory environment to anti-inflammatory one

Delivery to the Brain: targeting the inflamed BBB

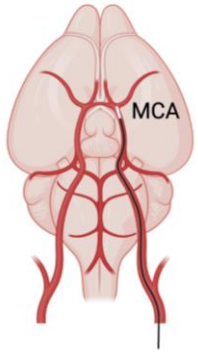
Targeting nanocarriers **to** the BBB itself

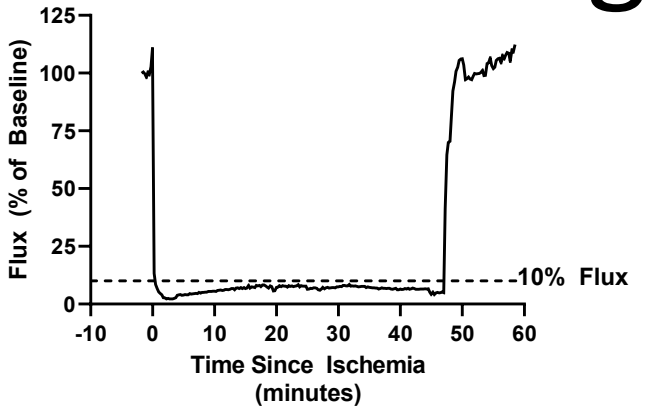


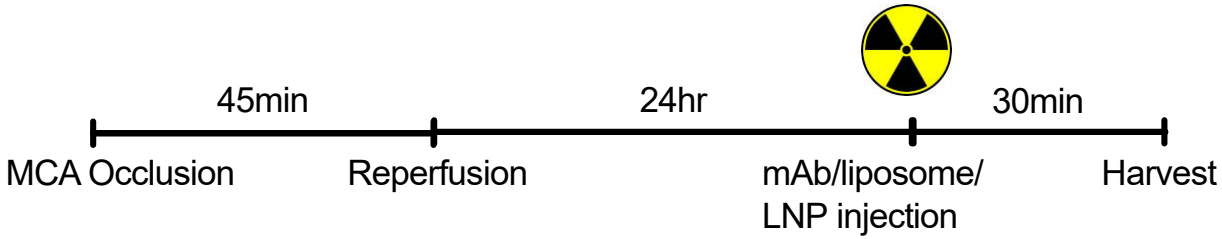
Dr. Nong

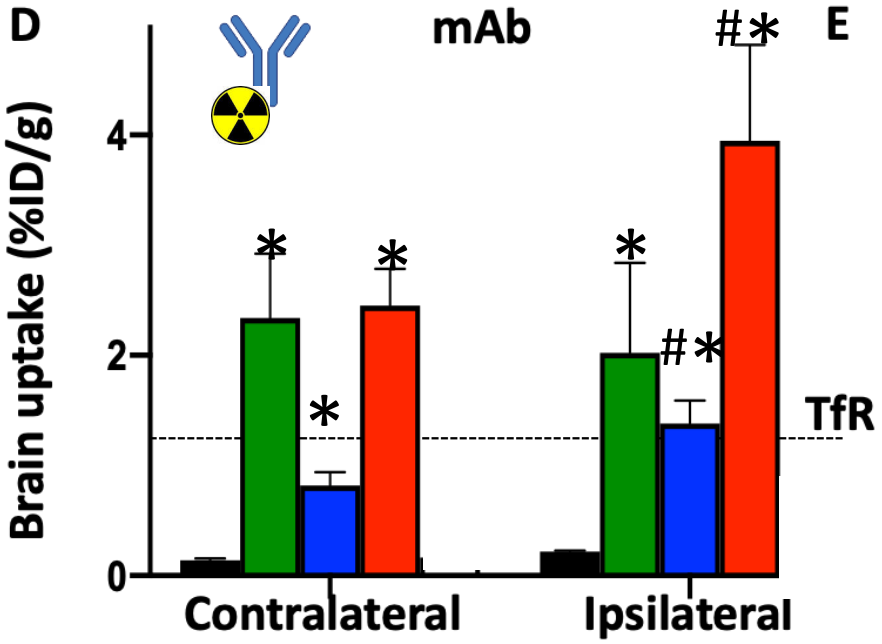
Dr. Jeong

Target selection





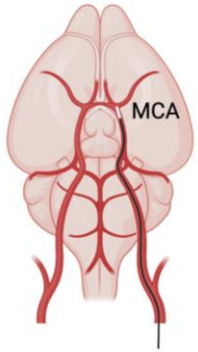


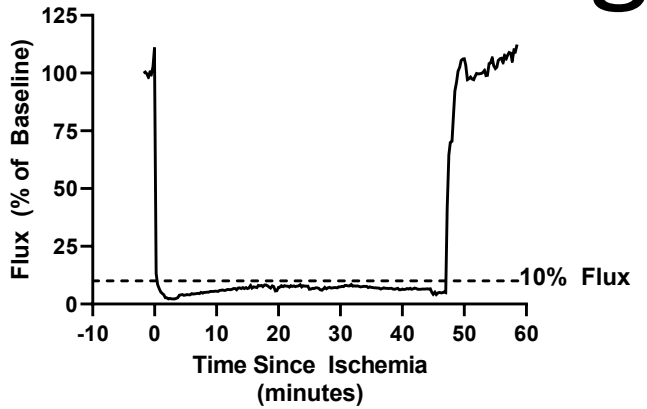


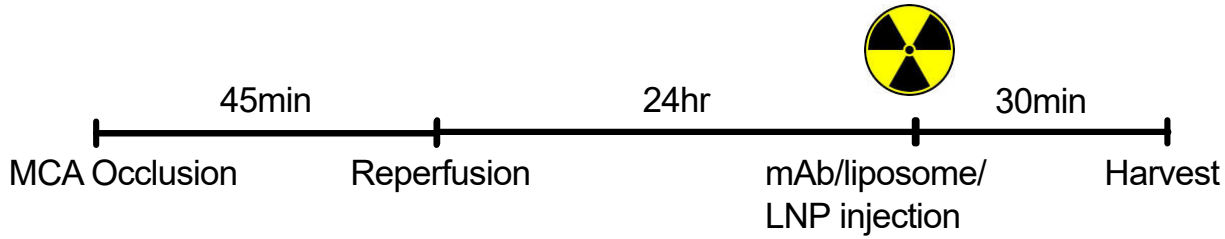
IgG PECAM ICAM VCAM

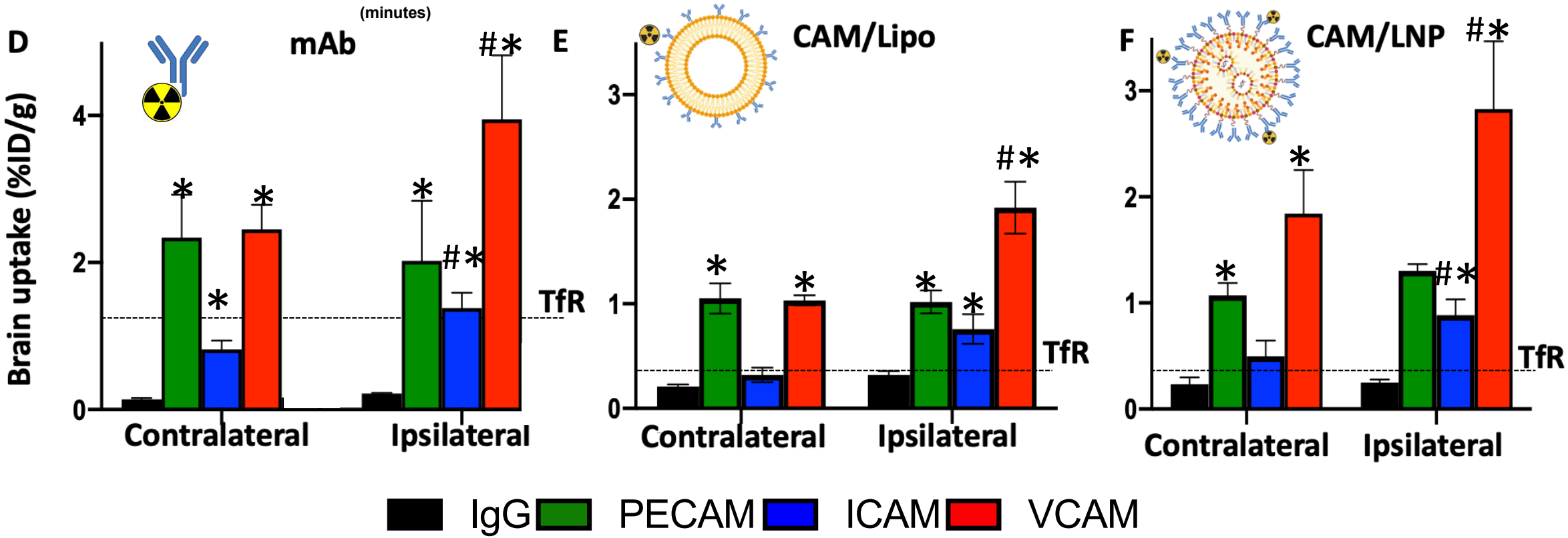
Nong et al. Mol therapy 2024. Corresponding: Marcos -Contreras

Target selection









Nong et al. Corresponding: Marcos -Contreras

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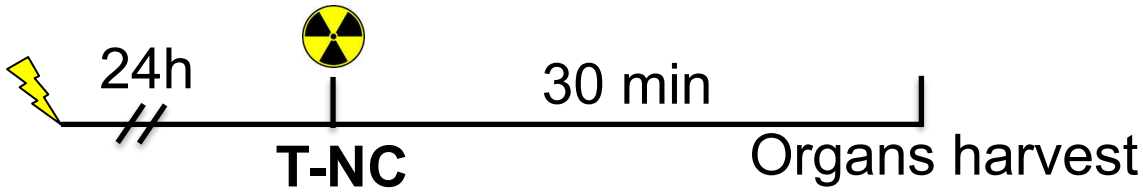
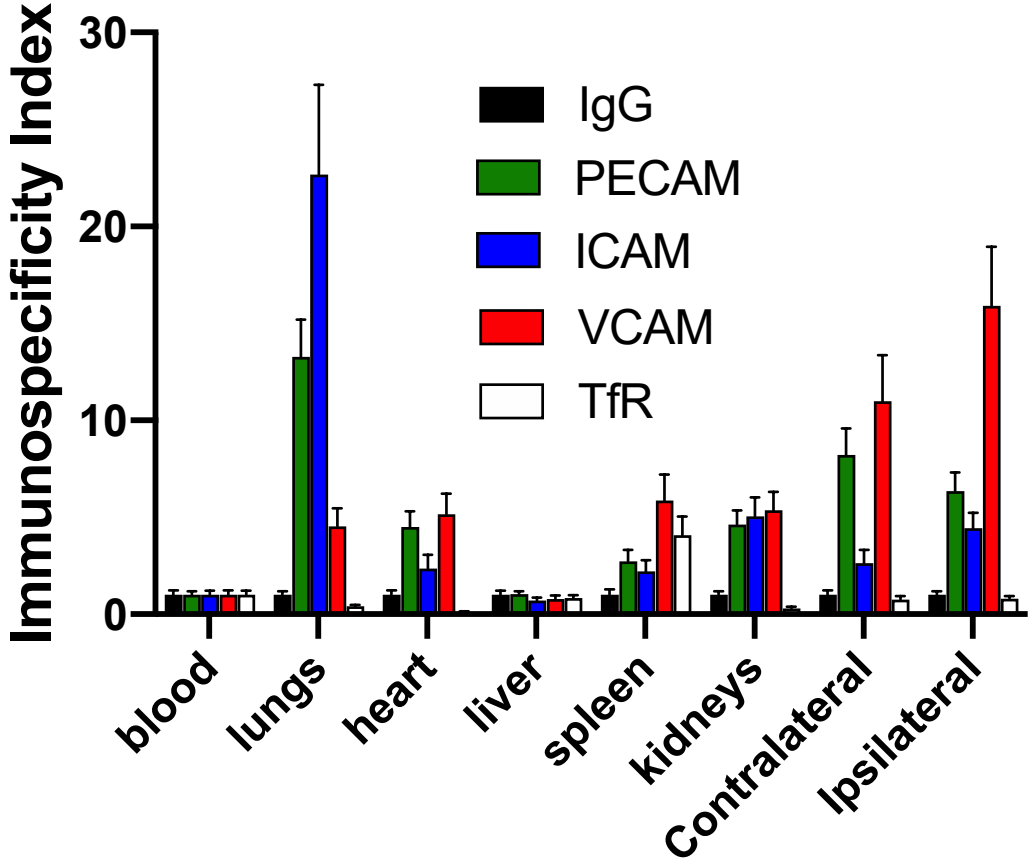
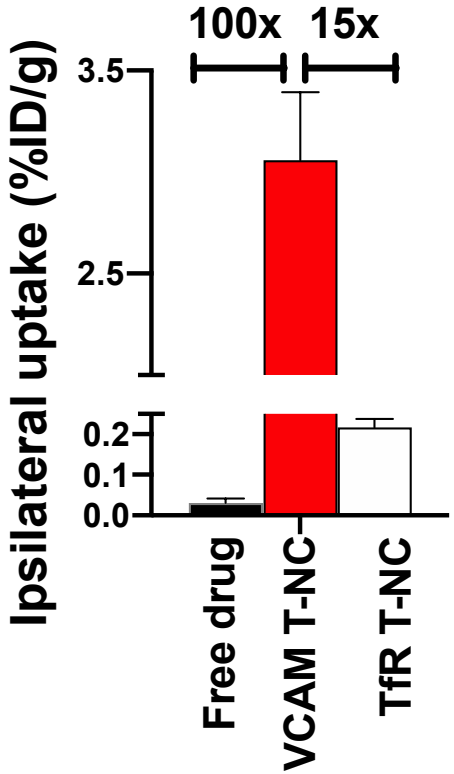
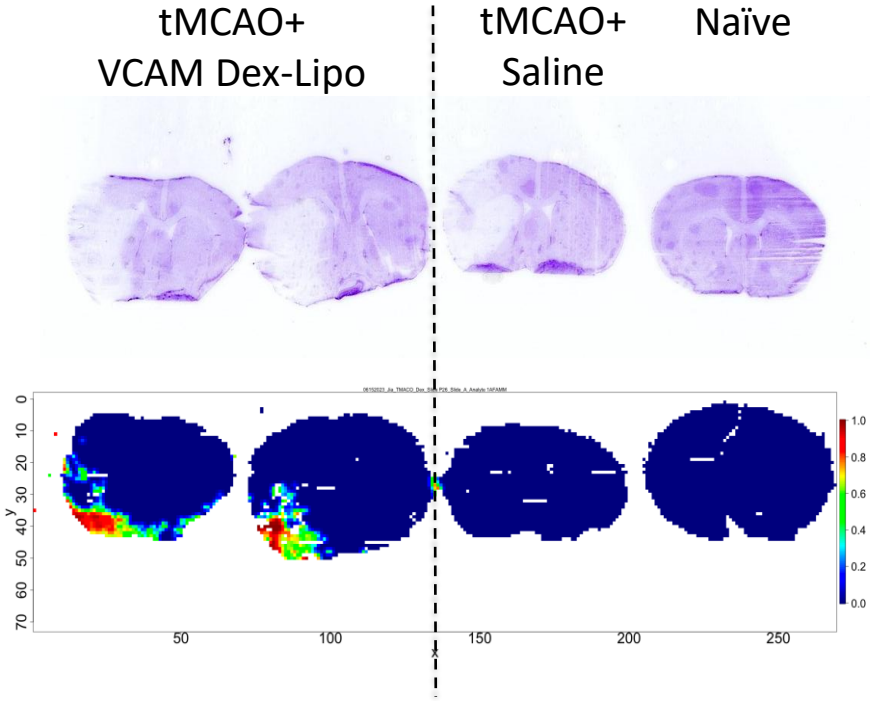






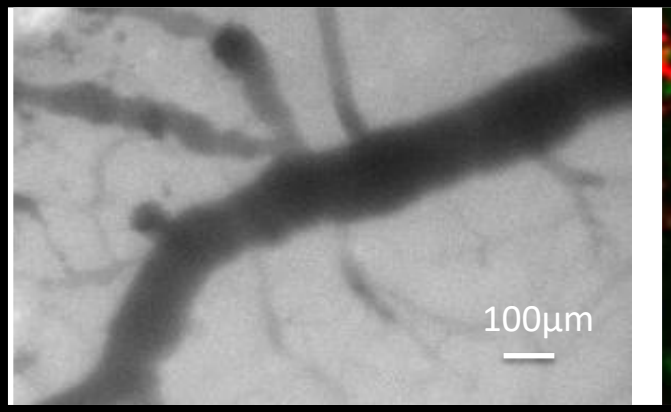


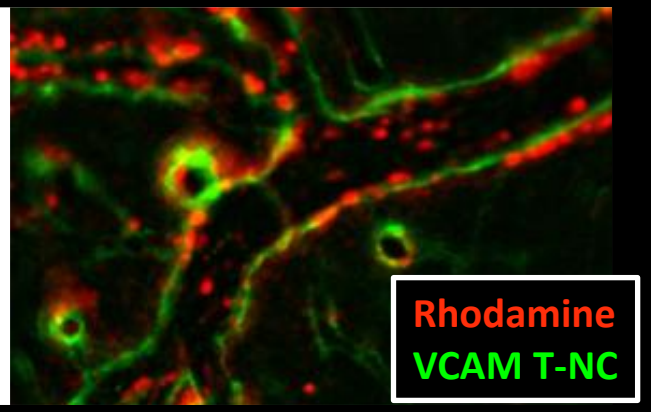
T-NC (%ID/g) in tissue/ T-NC (%ID/g) in Blood

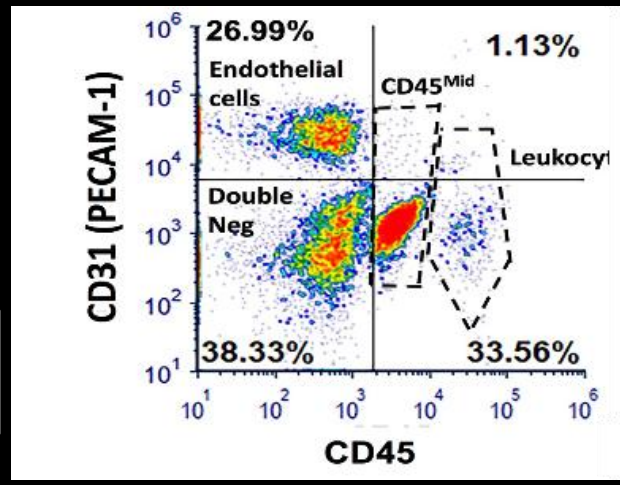
gG-NC (%ID/g) in tissue/ IgG-NC (%ID/g) in Blood

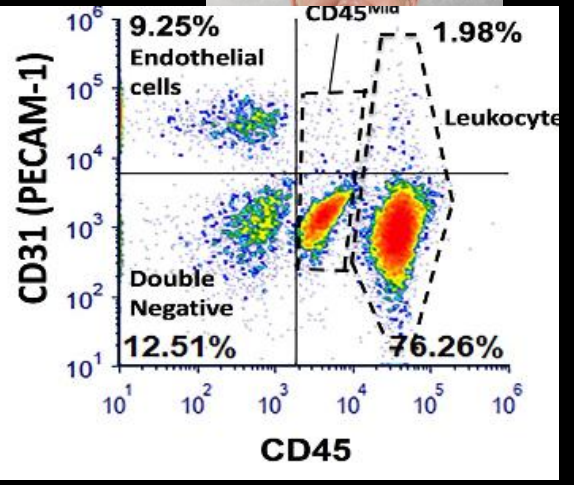
VCAM T-NC targets the inflamed BBB

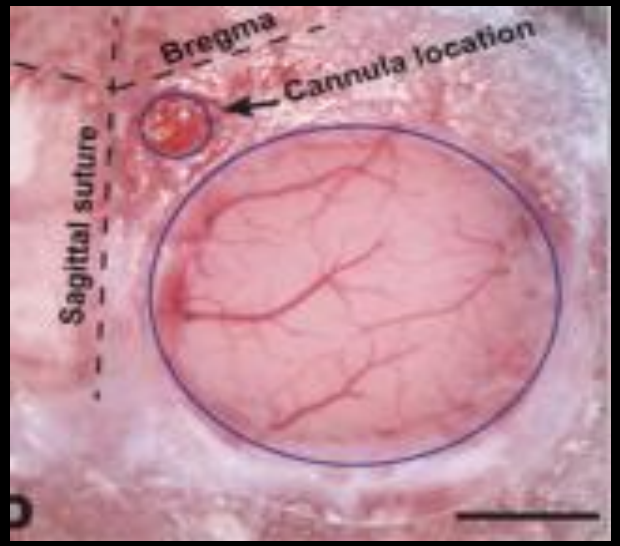
Anti-VCAM-Nanocarrier



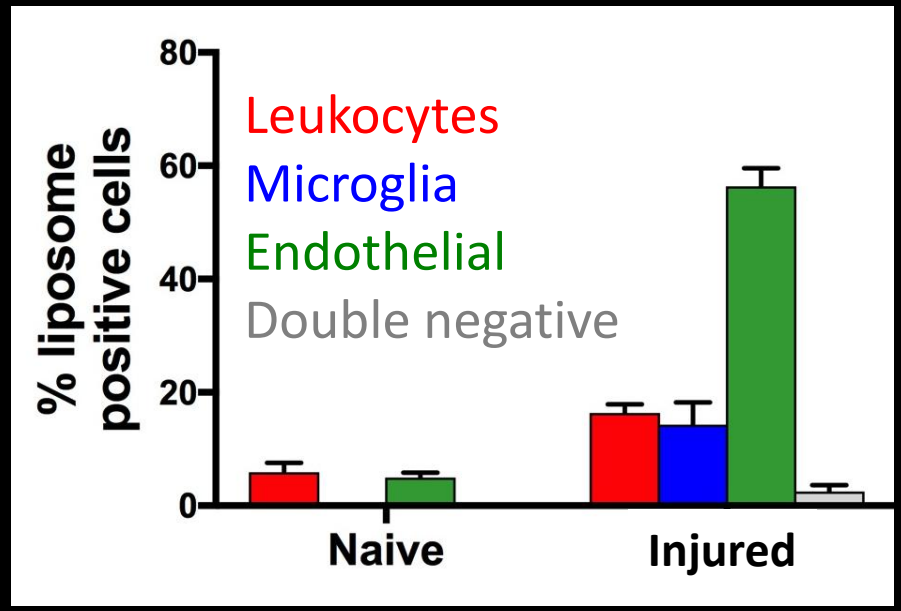








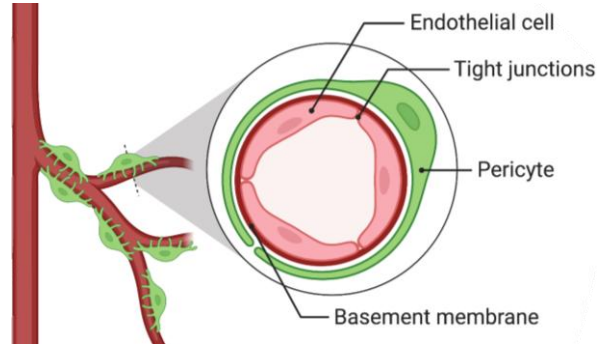
Zuluaga-Ramirez et al. 2015



Marcos-Contreras et al. PNAS 2020. Corresponding: Marcos-Contreras

Targeted nanomedicine for CNS diseases

1. Delivery:
Current delivery of free drugs to brain
<<0.01%
Goal: 100-fold improvement



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Biomarkers
Neurobehavior

3. Side effects:
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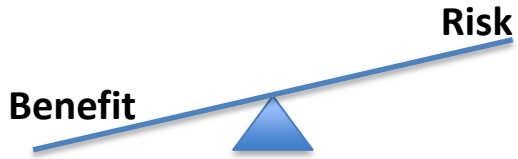
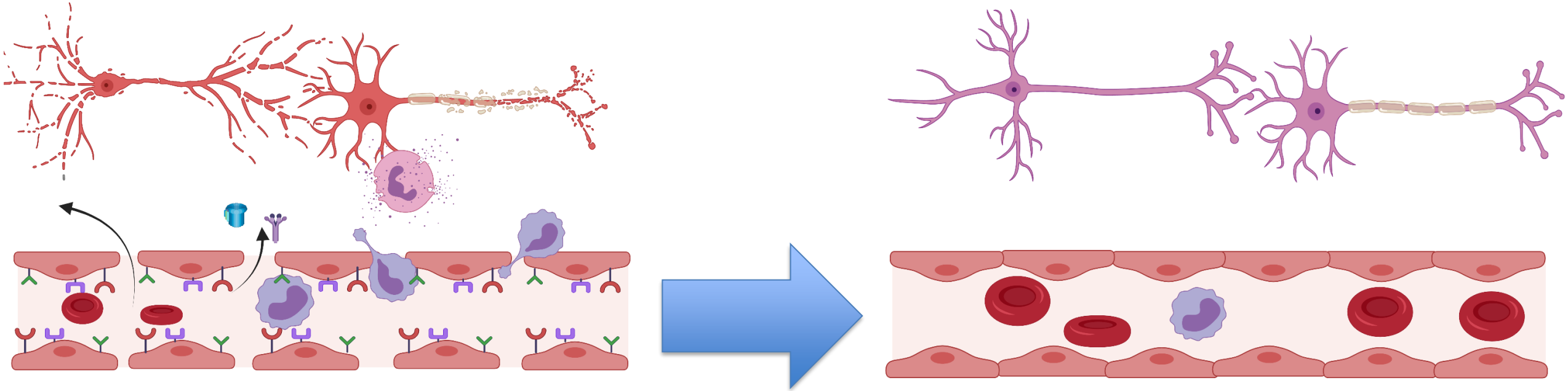
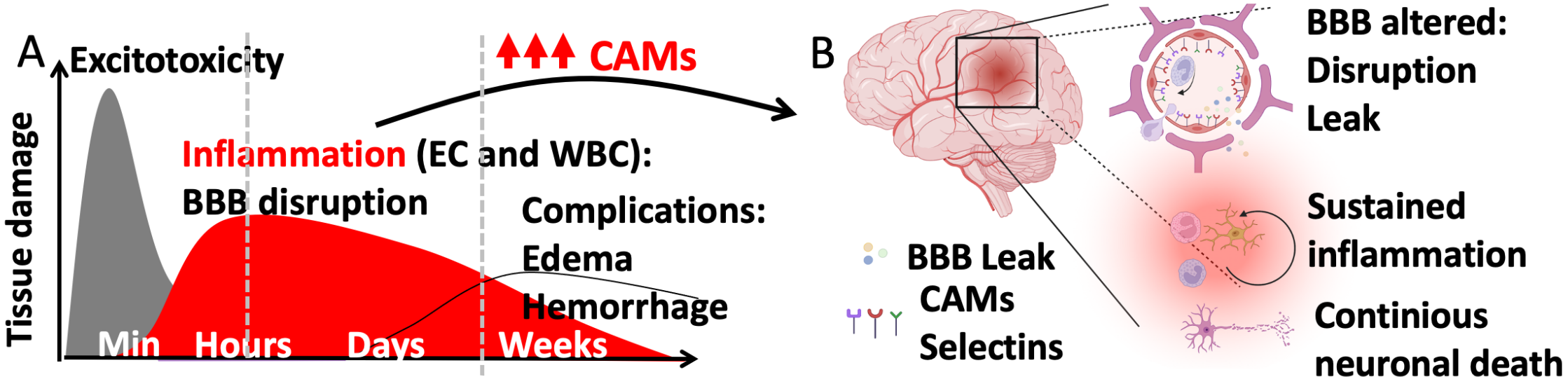


Pharmacological working hypothesis

Restoring blood-brain barrier homeostasis will promote an anti-inflammatory environment resulting in neuroprotection

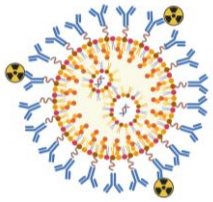


Pharmacological working hypothesis



Functional activity of VCAM targeted nanocarriers

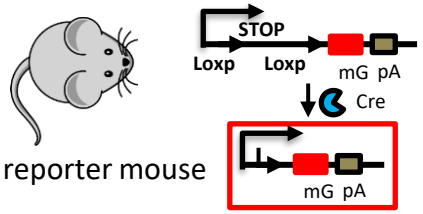
Dr. Weissman

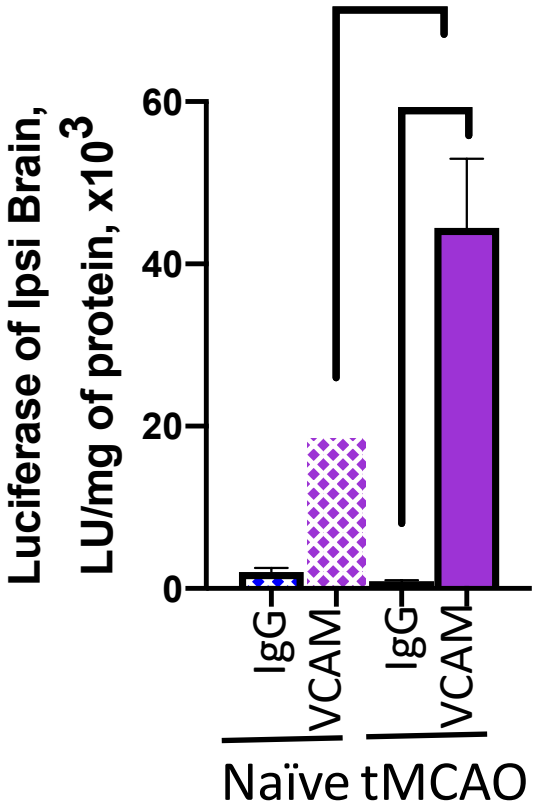


Reporter mRNA

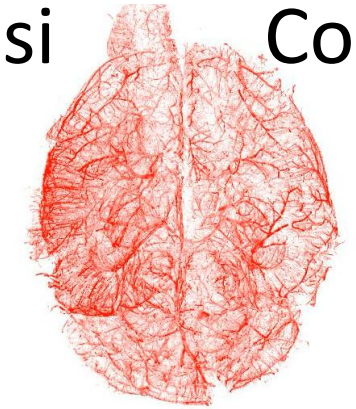
Luciferase

Cre-recombinase





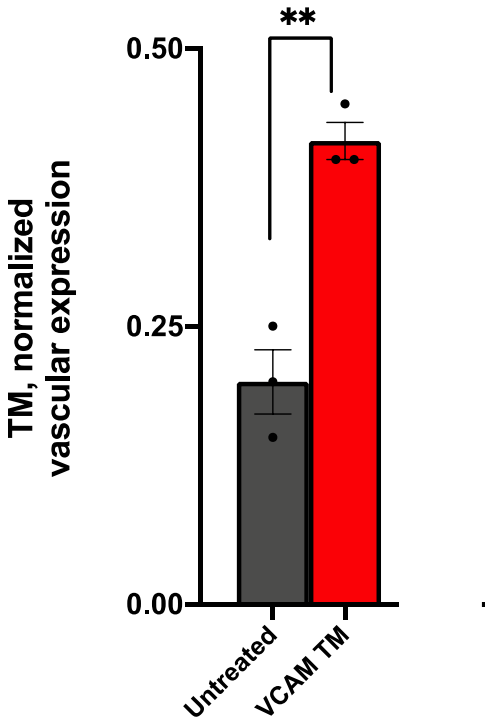
Ipsi Contra

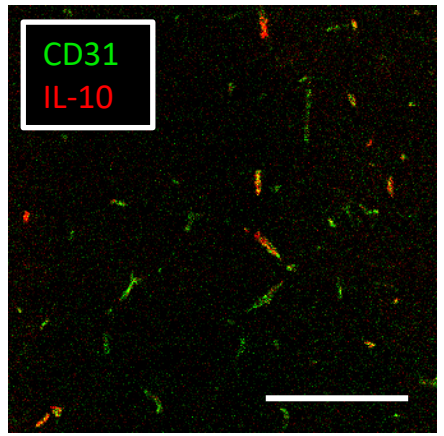


VCAM-LNP
mRNA Cre

Biotherapeutics mRNA

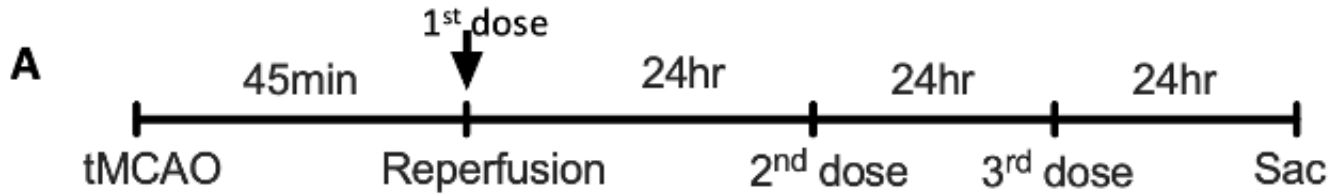
Thrombomodulin (TM) Interleukin 10 (IL-10)



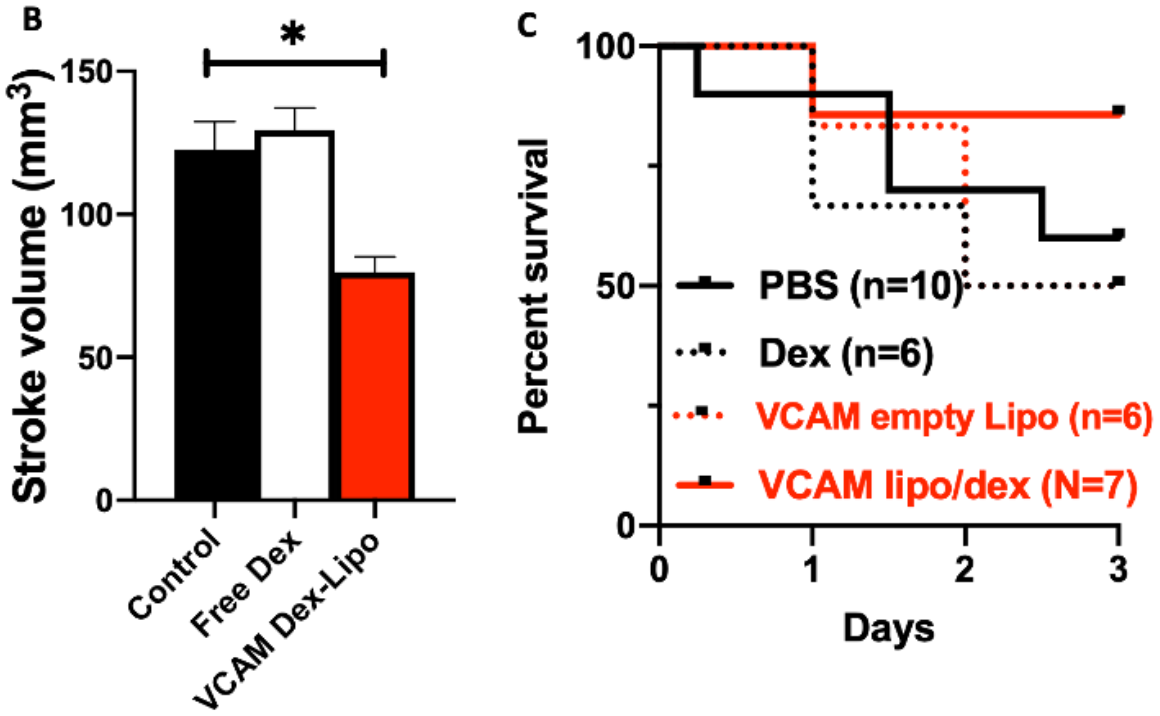


Marcos-Contreras et al. PNAS 2020. Corresponding: Marcos-Contreras
Nong et al. Molecular Therapy 2024. Corresponding: Marcos-Contreras

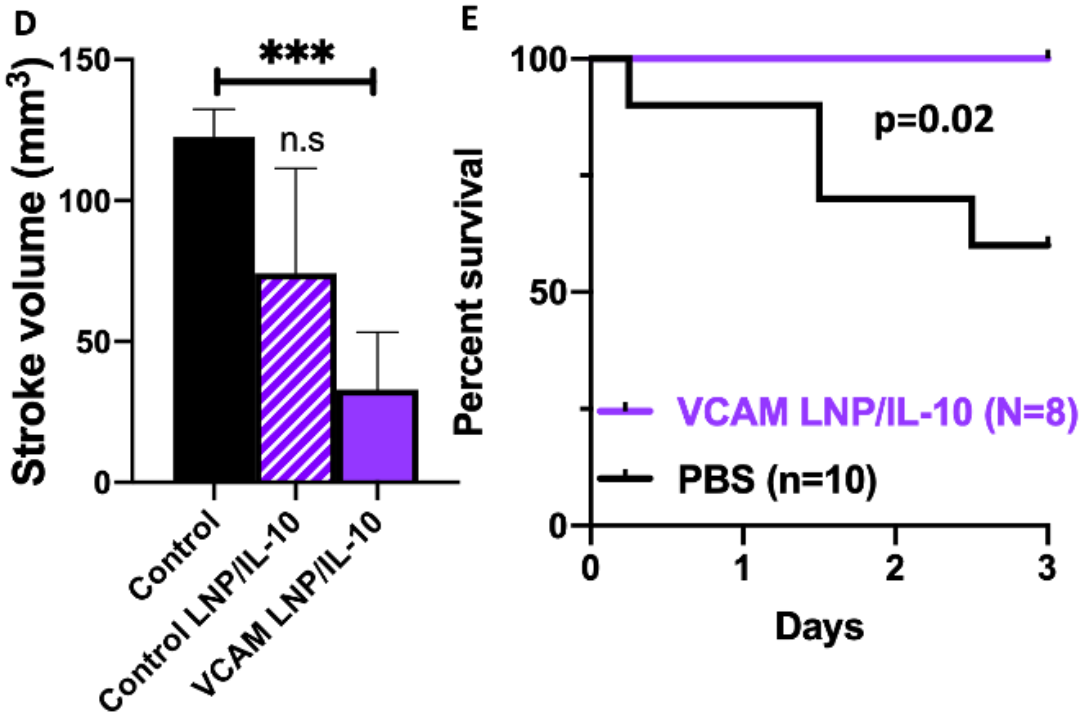
VCAM targeted nanocarriers improve AIS



Dexamethasone (Dex)

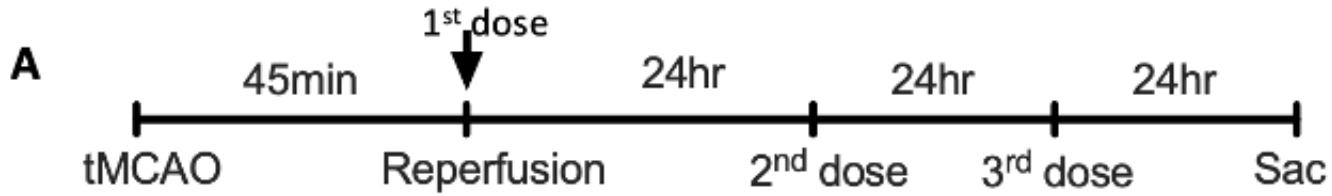


Interleukin 10 (IL-10)



Nong et al. Mol Therapy 2024. Corresponding: Marcos-Contreras

VCAM targeted nanocarriers improve AIS



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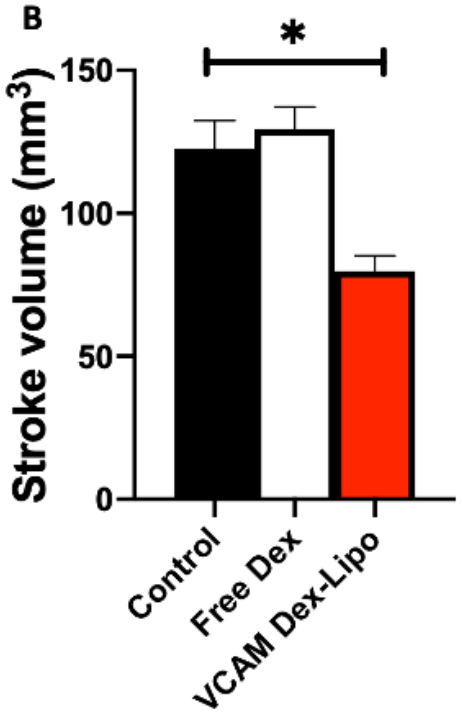

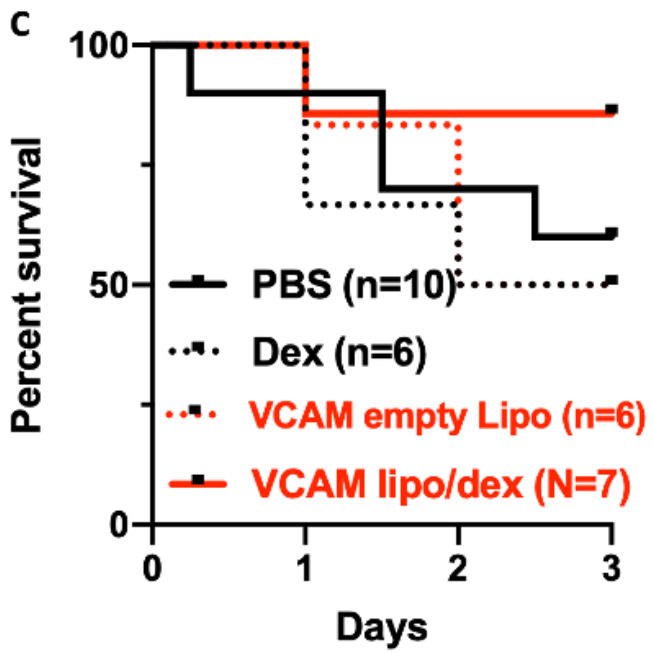

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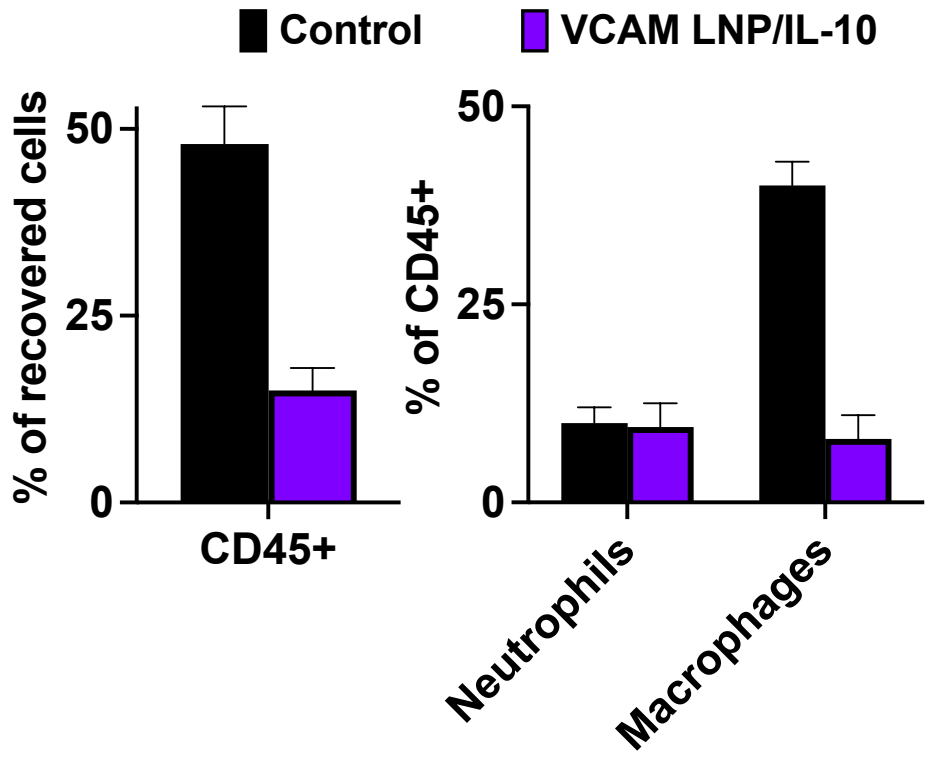
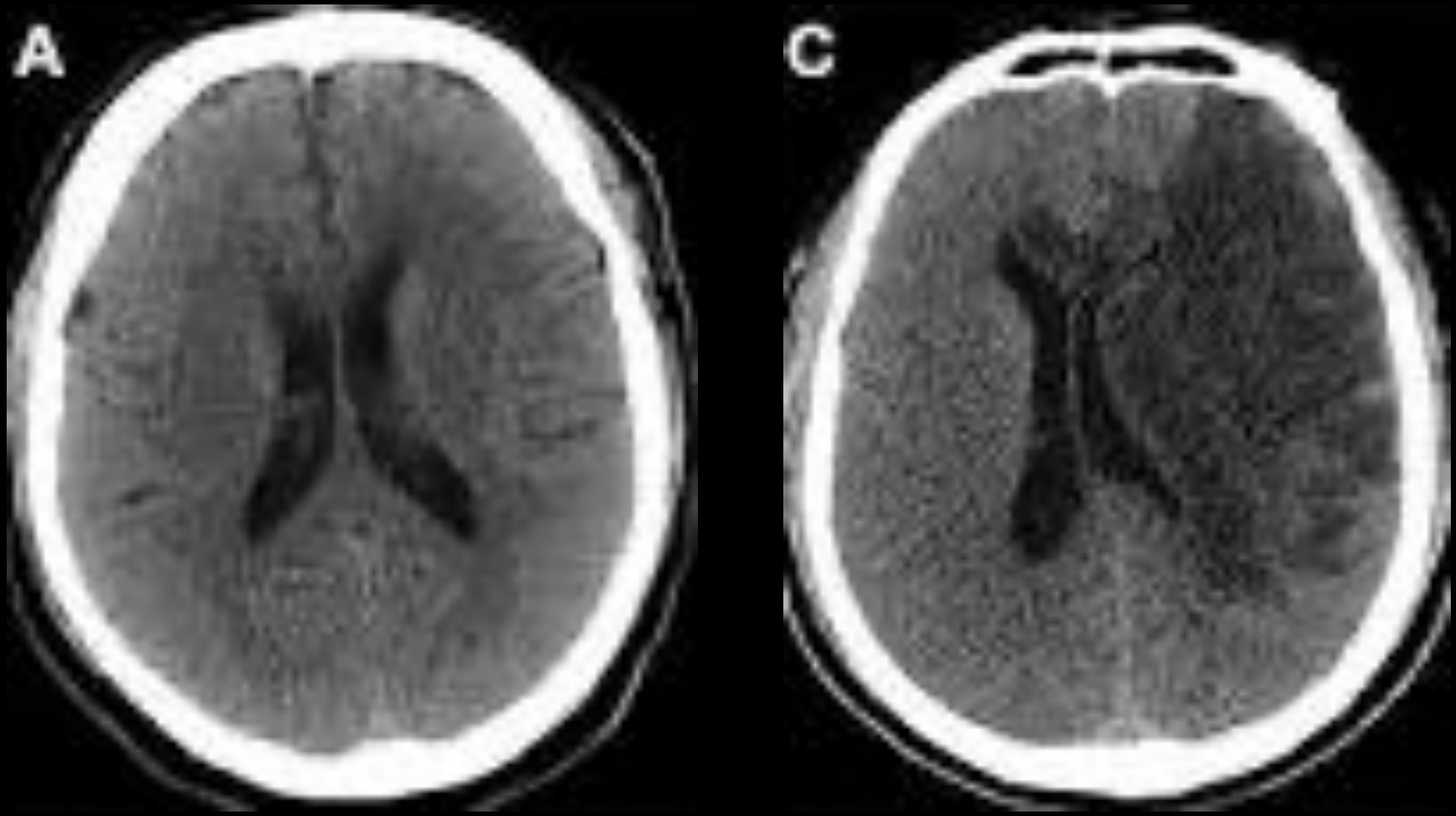


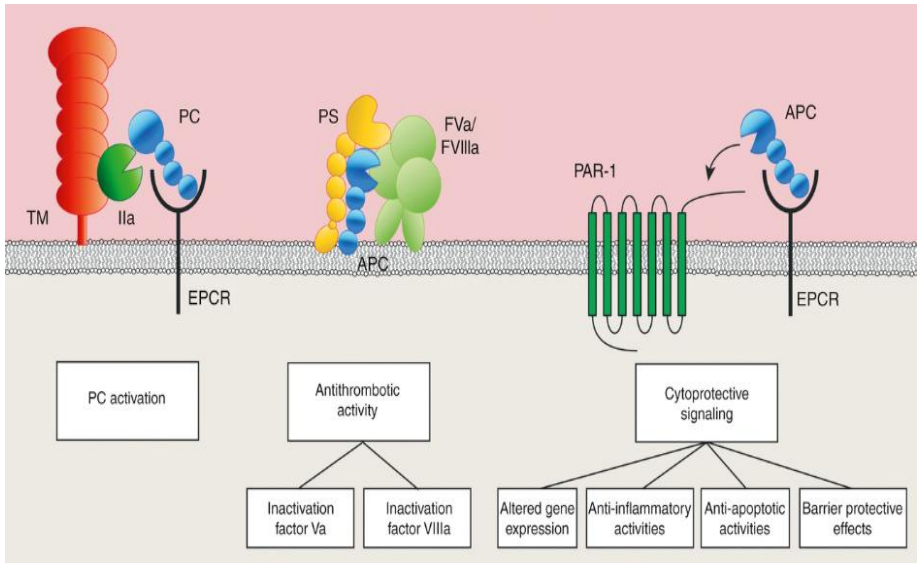
Nong et al. Mol Therapy 2024. Corresponding: Marcos-Contreras

VCAM targeted-nanocarriers reduces brain edema

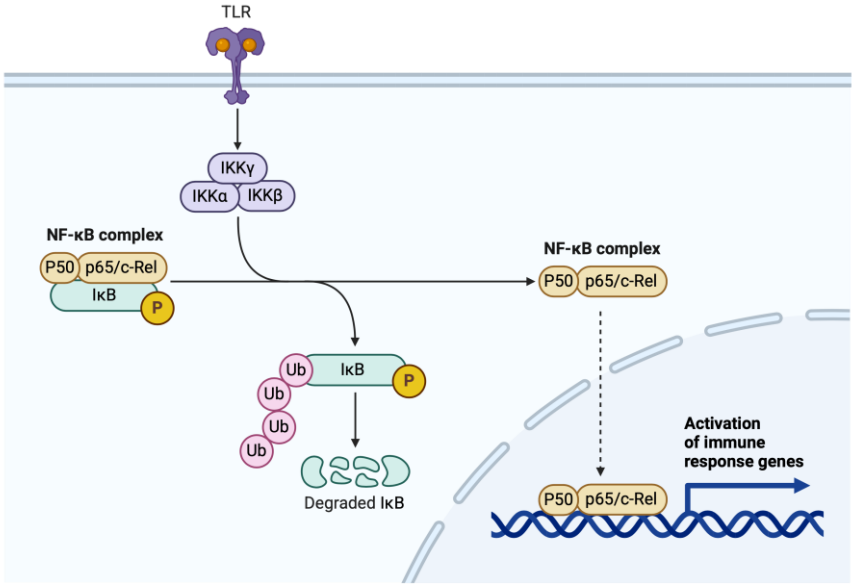


VCAM targeted-nanocarriers reduces brain edema

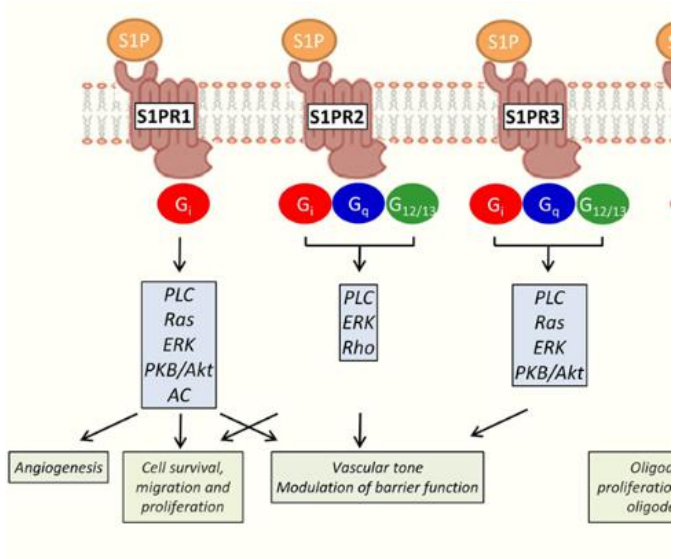
Thrombomodulin (TM)



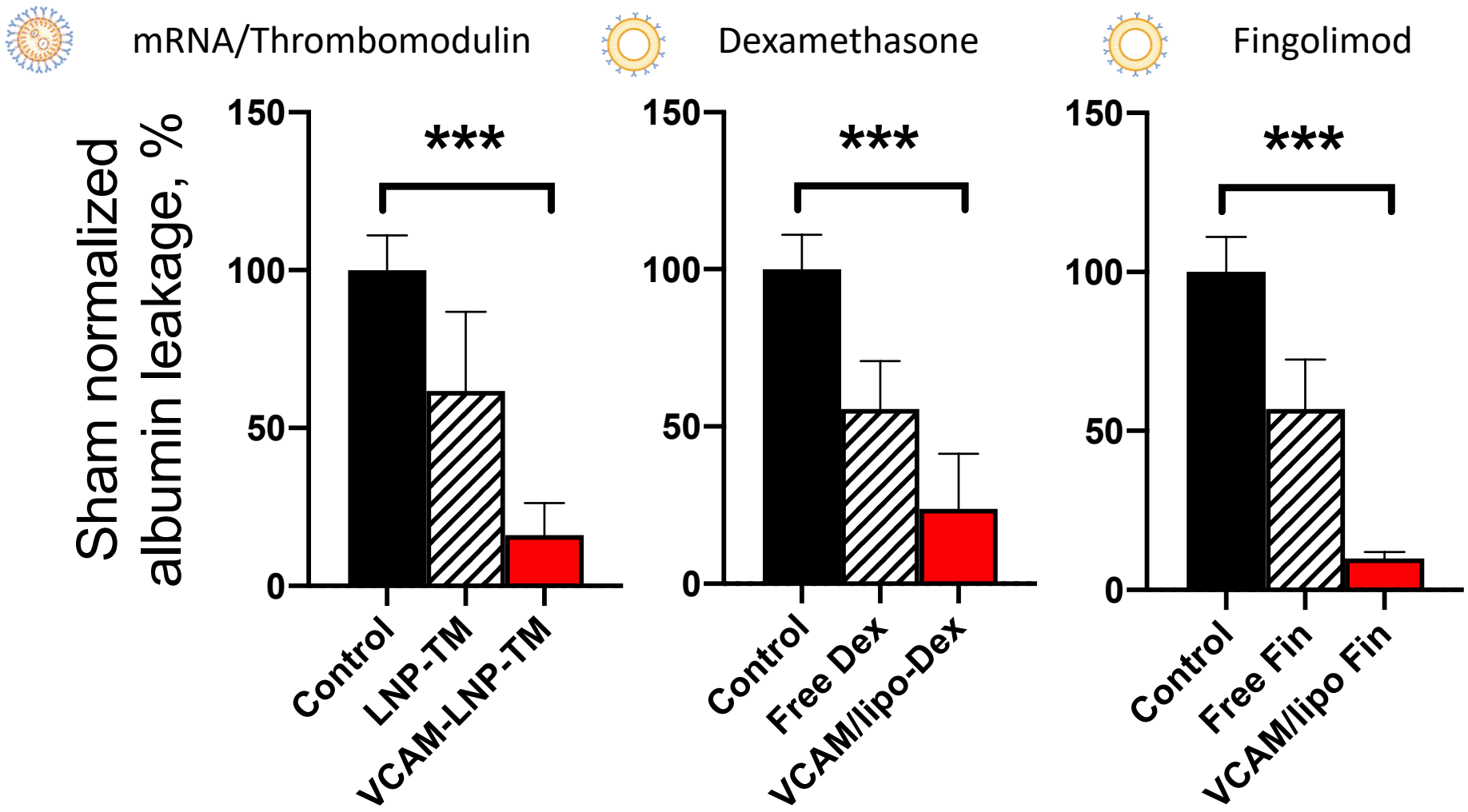
NF-kB



Sphingosine P-receptor

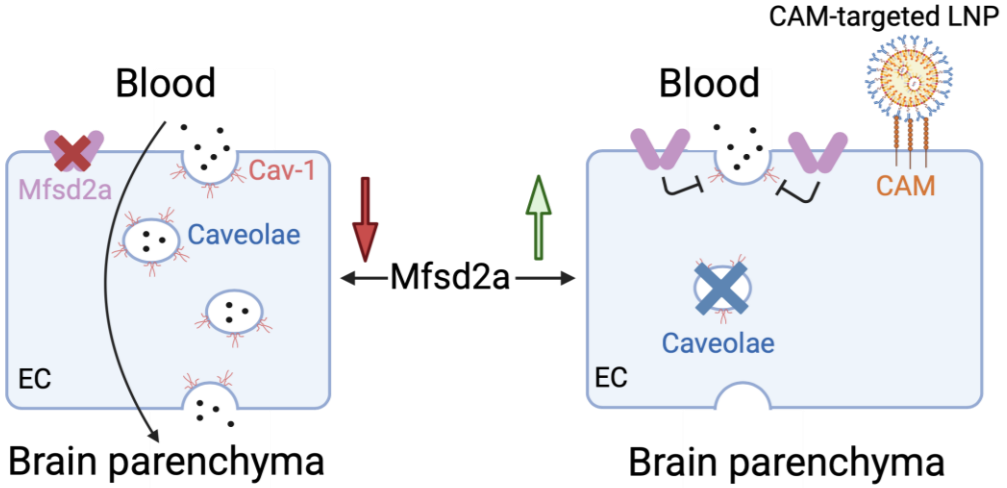


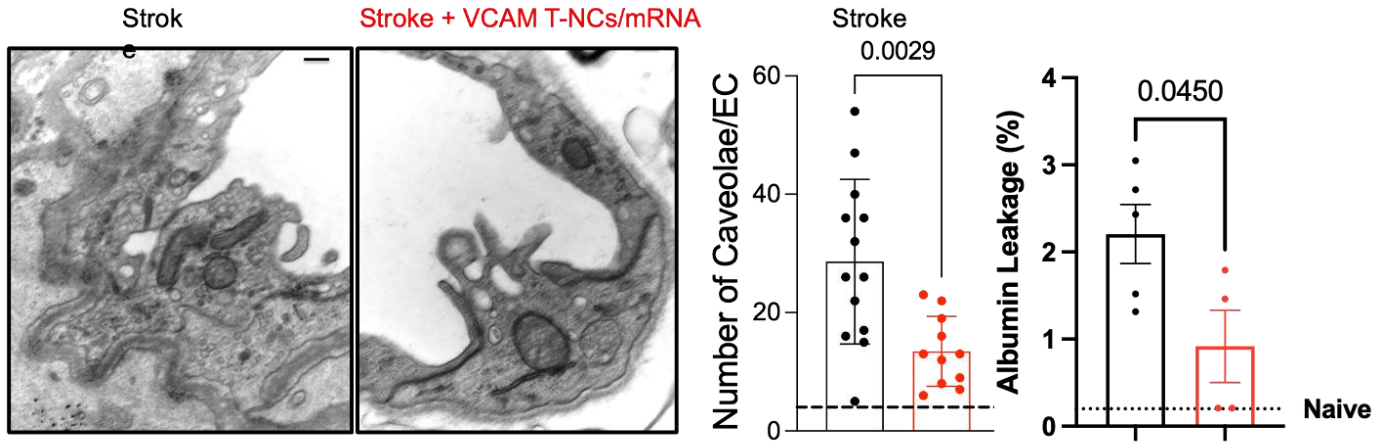
VCAM targeted-nanocarriers reduces brain edema

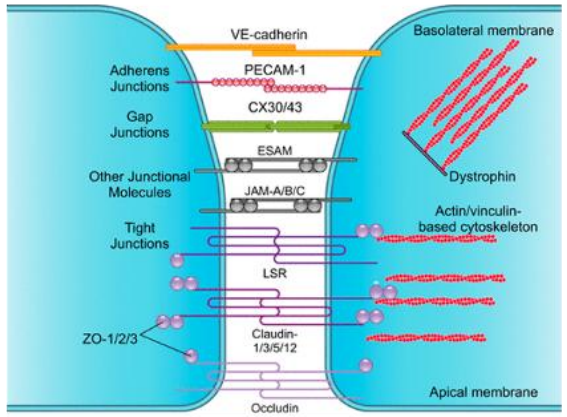


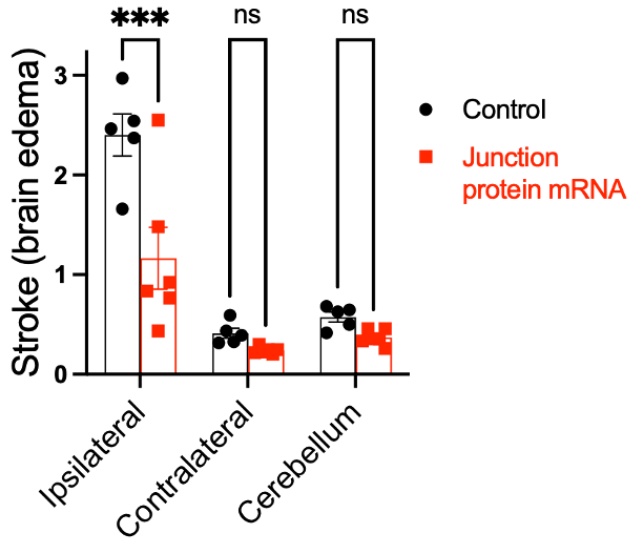
Zaleski et al. J Controlled Release 2024. Corresponding: Marcos Contreras
Marcos-Contreras et al. PNAS 2020. Corresponding: Marcos Contreras

VCAM targeted-nanocarriers reduces brain edema



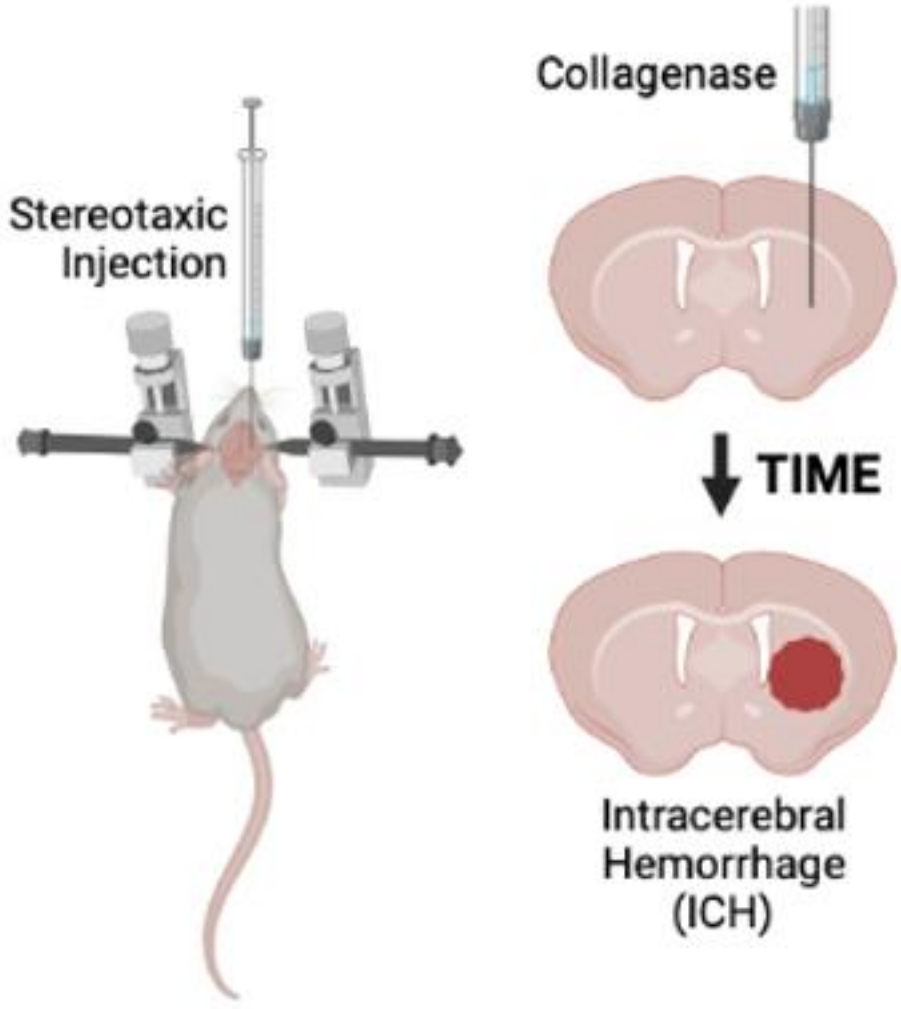






Unpublished

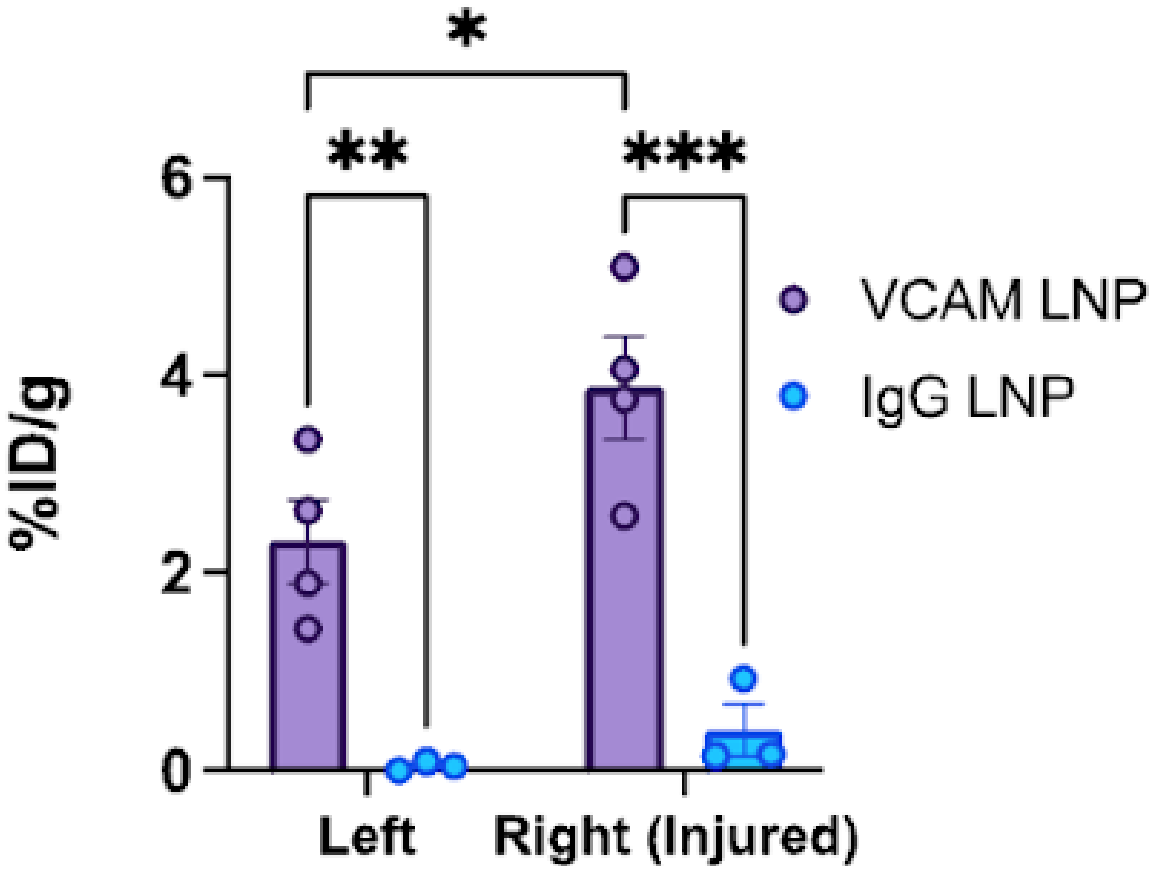
VCAM-targeted nanocarriers accumulate in ICH

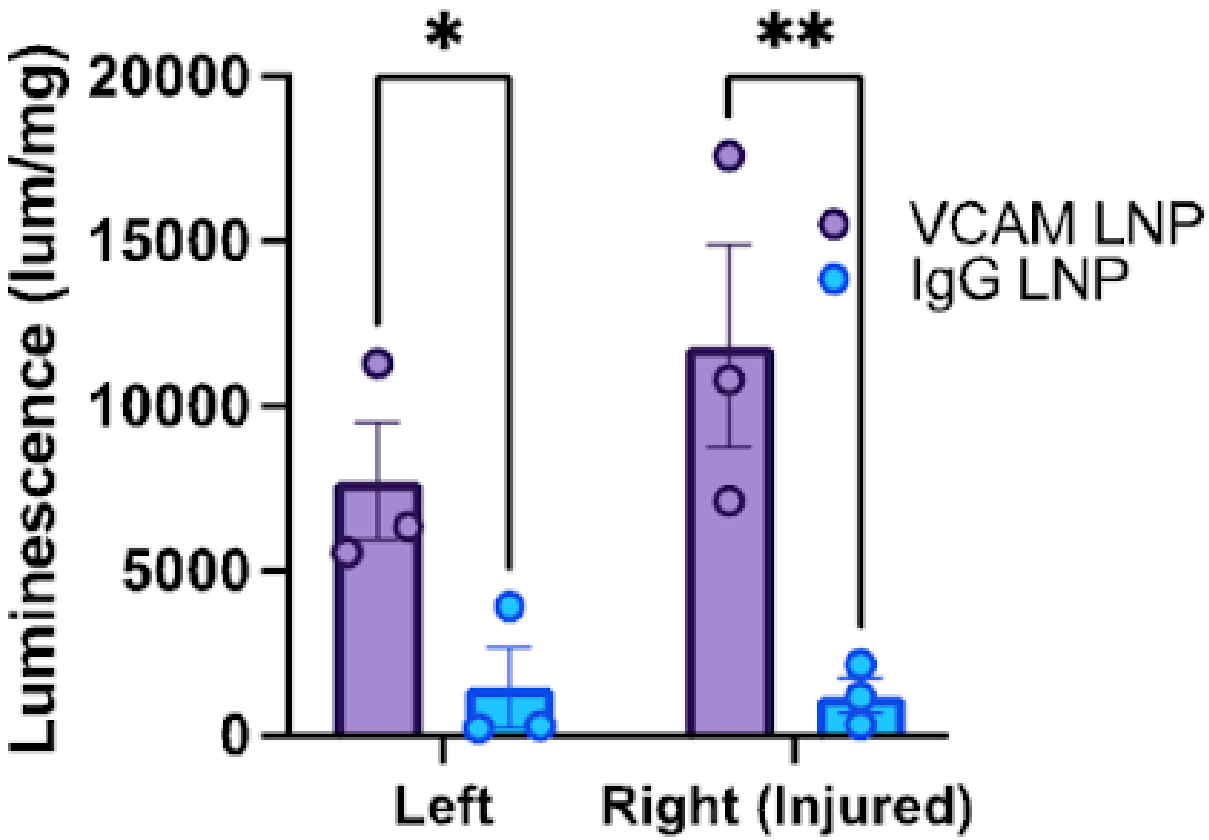


Reyes-Esteves
MD,PhD

Preprint: Res Sq .2025

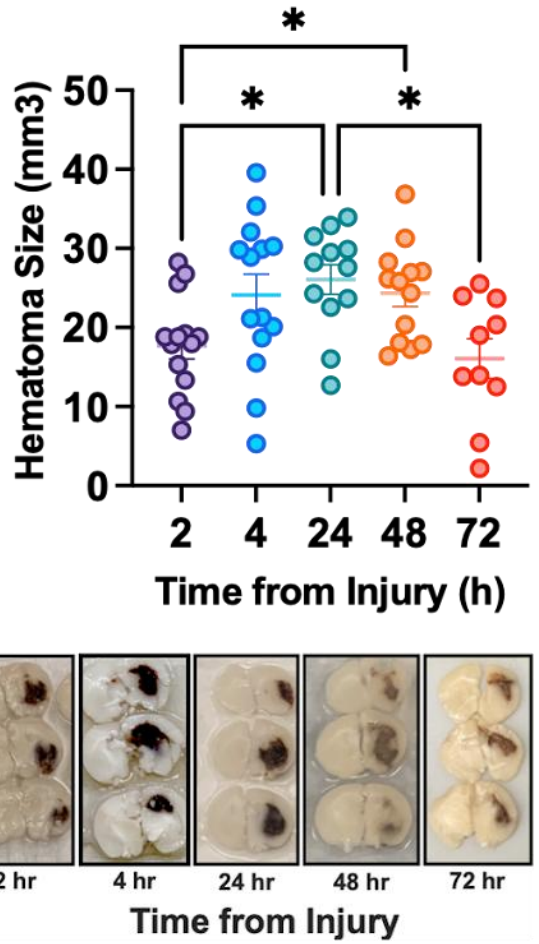
VCAM-targeted nanocarriers accumulate in ICH

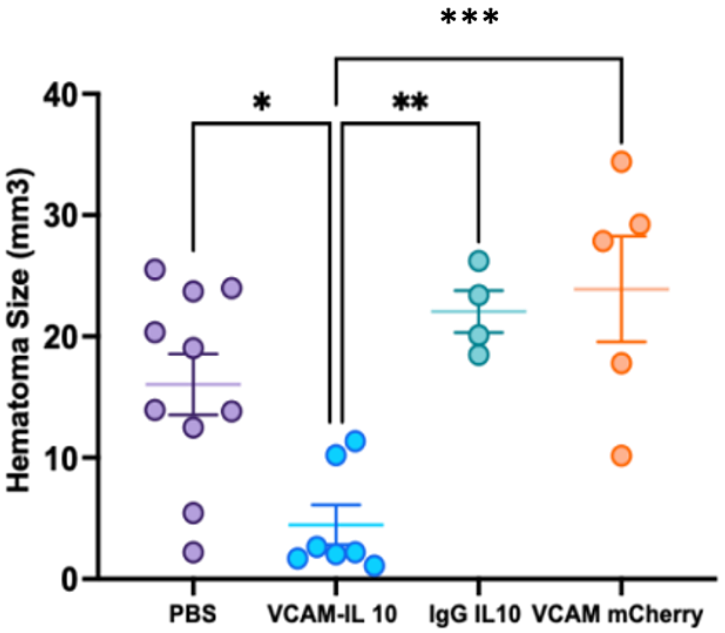




Preprint: Reyes-Esteves et al Res Sq .2025

VCAM targeted-nanocarriers improve ICH: mRNA IL-10

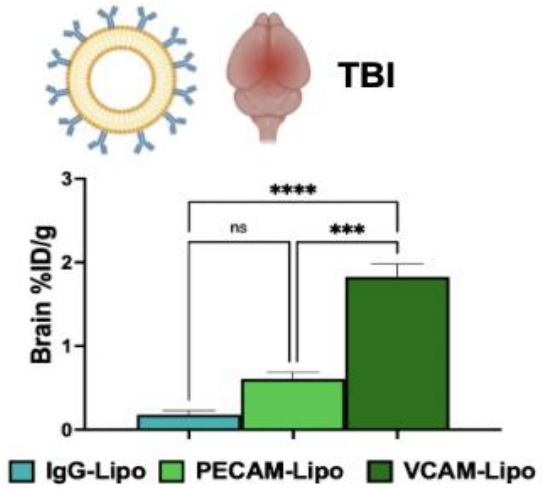


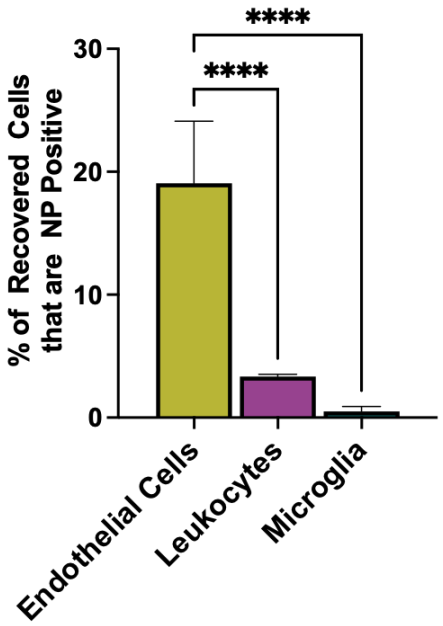


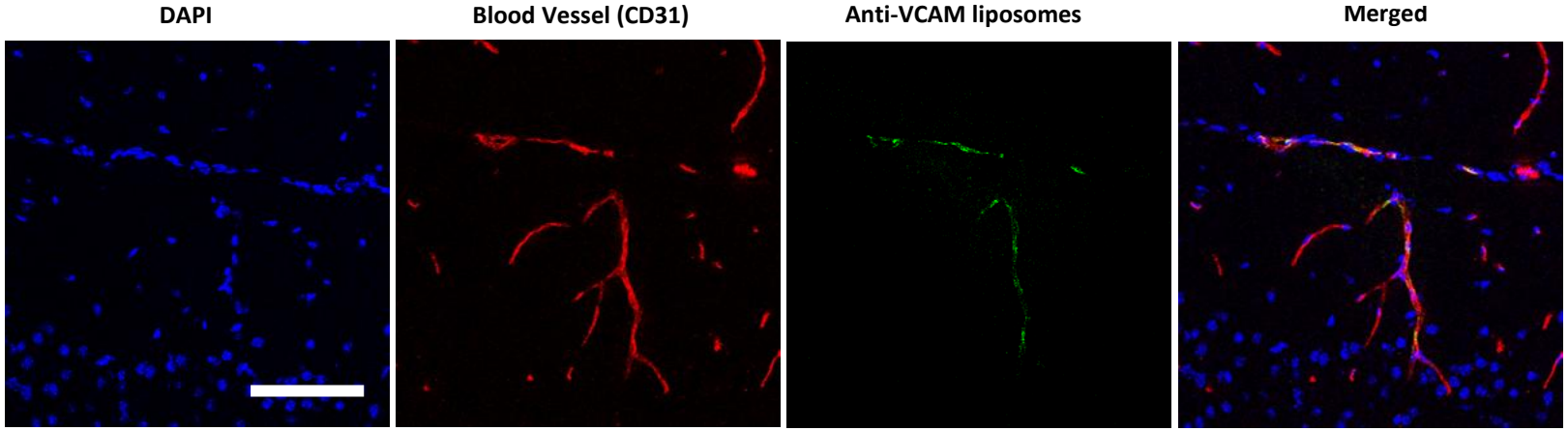
Hematoma

Preprint: Reyes-Esteves et al Res Sq .2025

VCAM-targeted nanocarriers accumulate in TBI



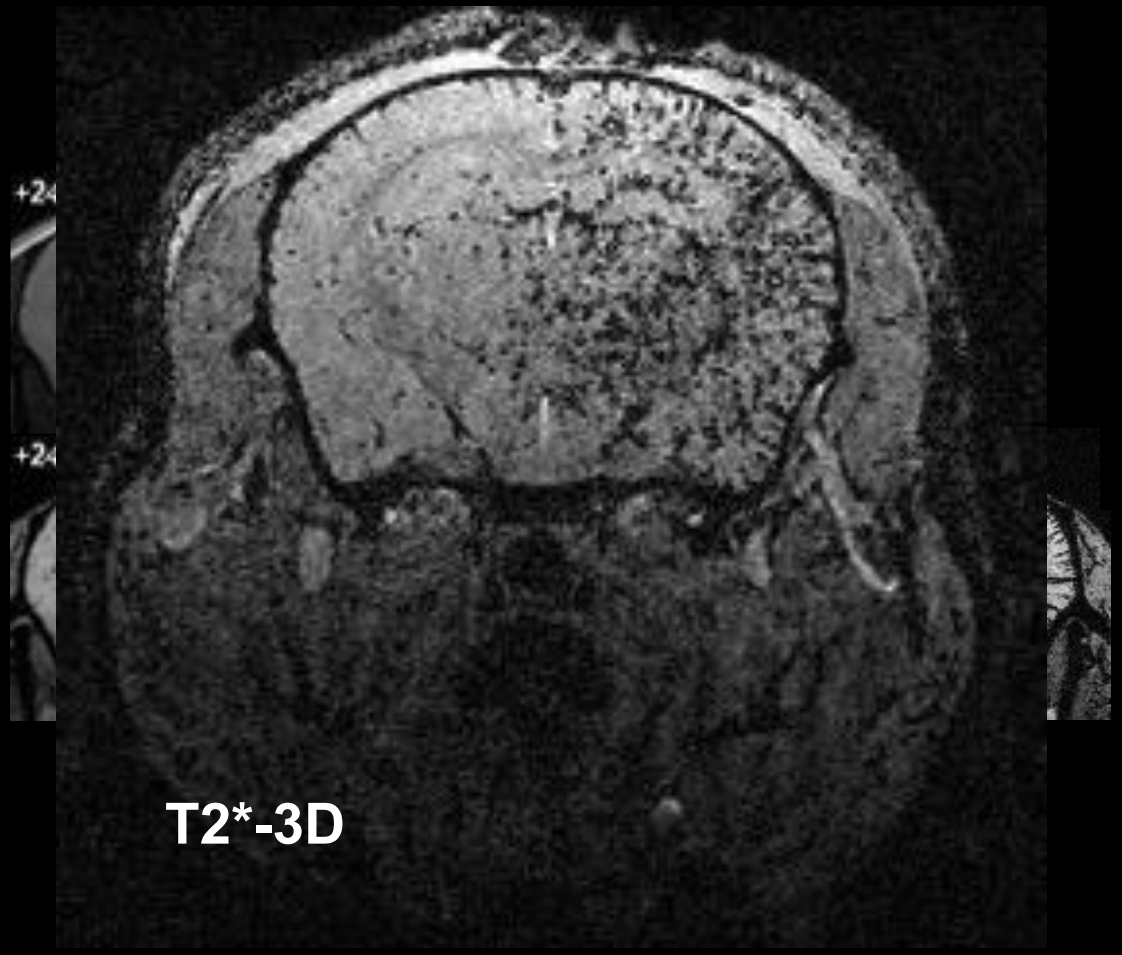




Omo-Lamai et al. Plosone 2024

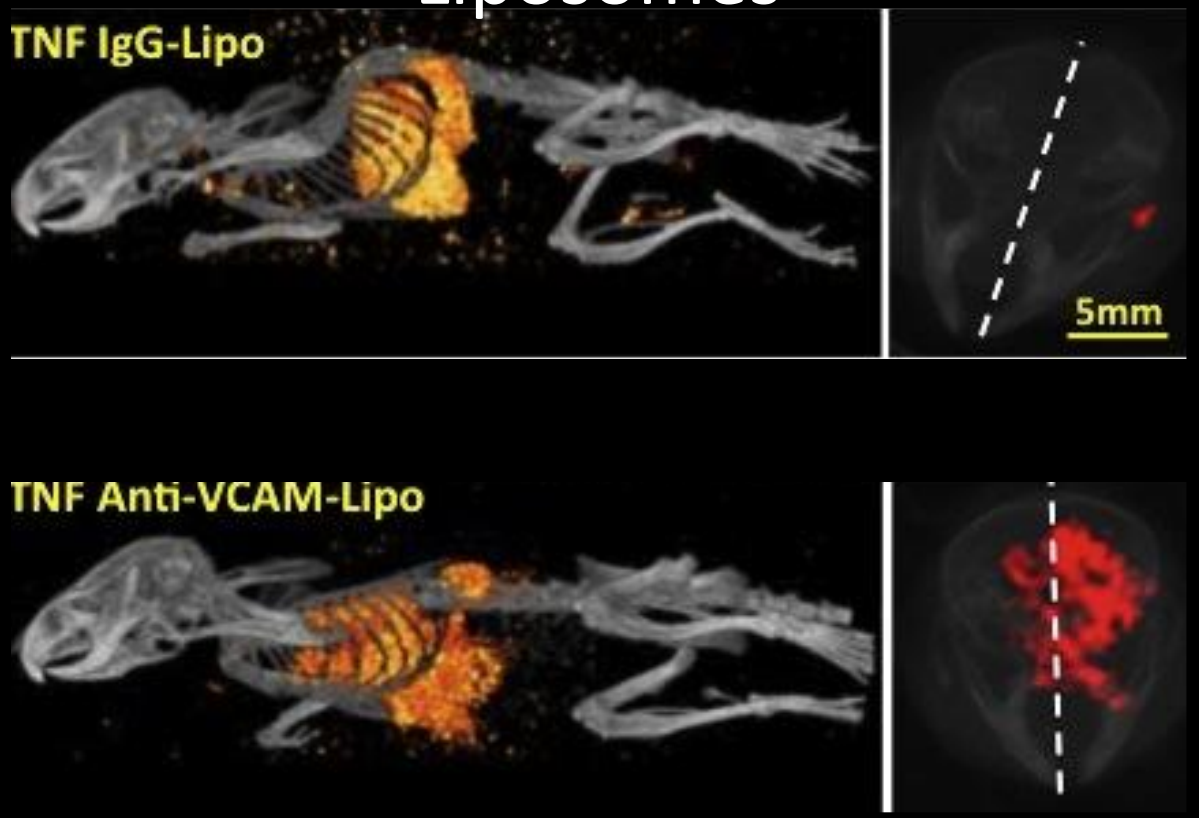
Molecular imaging: VCAM targeted nanocarriers

MRI: MPIO



Gauberti et al. Stroke 2013

SPECT: Liposomes

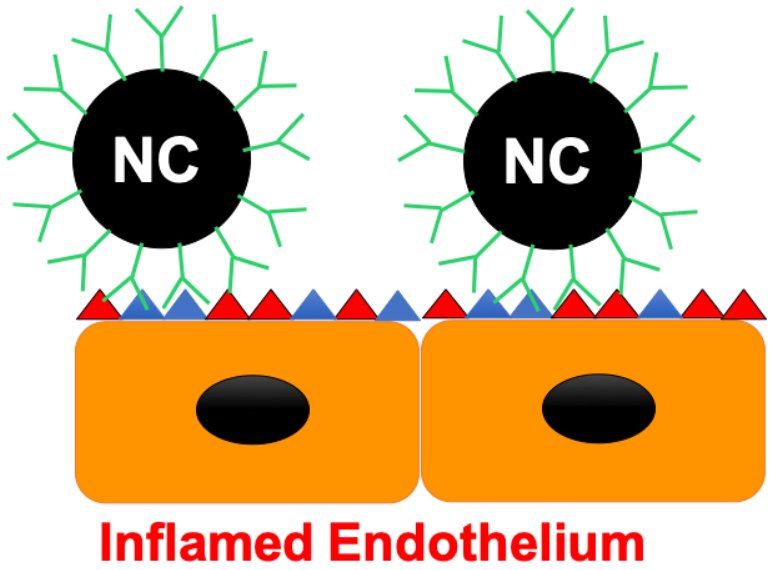


TNF

Marcos Contreras* et al. PNAS 2020. Corresponding: Marcos-Contreras

Targeting the inflamed BBB: summary

Targeting nanocarriers **to** the BBB itself



1. VCAM-targeted nanocarriers enhance delivery to the inflamed neurovasculature in acute and chronic CNS diseases.
2. VCAM-targeted nanocarriers can be used for molecular imaging.
3. VCAM-targeted nanocarriers containing small molecule and mRNA therapeutics effectively treat different neurological conditions.

Acknowledgements

Marcos-Contreras:
S Jeong
Muzykantov Lab:
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N Marzolini
A Majudmer
S Omo-Lamai
M Zamora
M Zaleski
Z Wang,

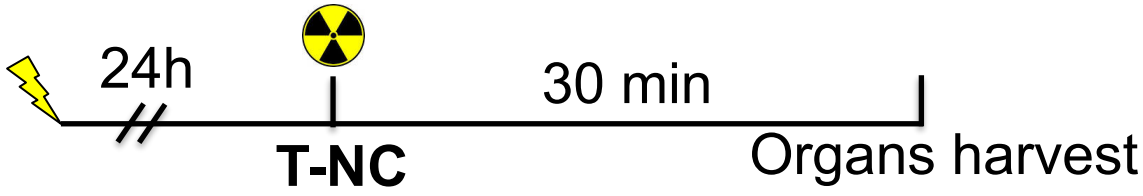
Weissman Lab:
H Parhiz
N Pardi

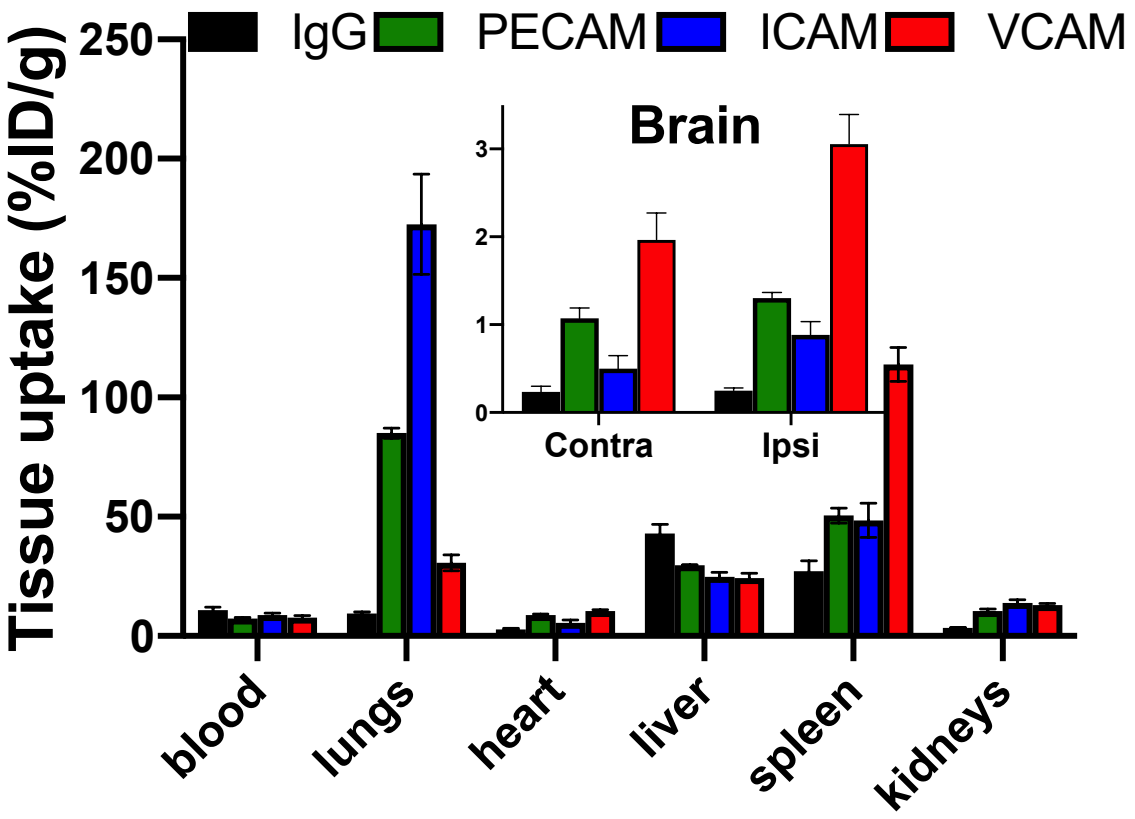
SE Kasner Smith Lab

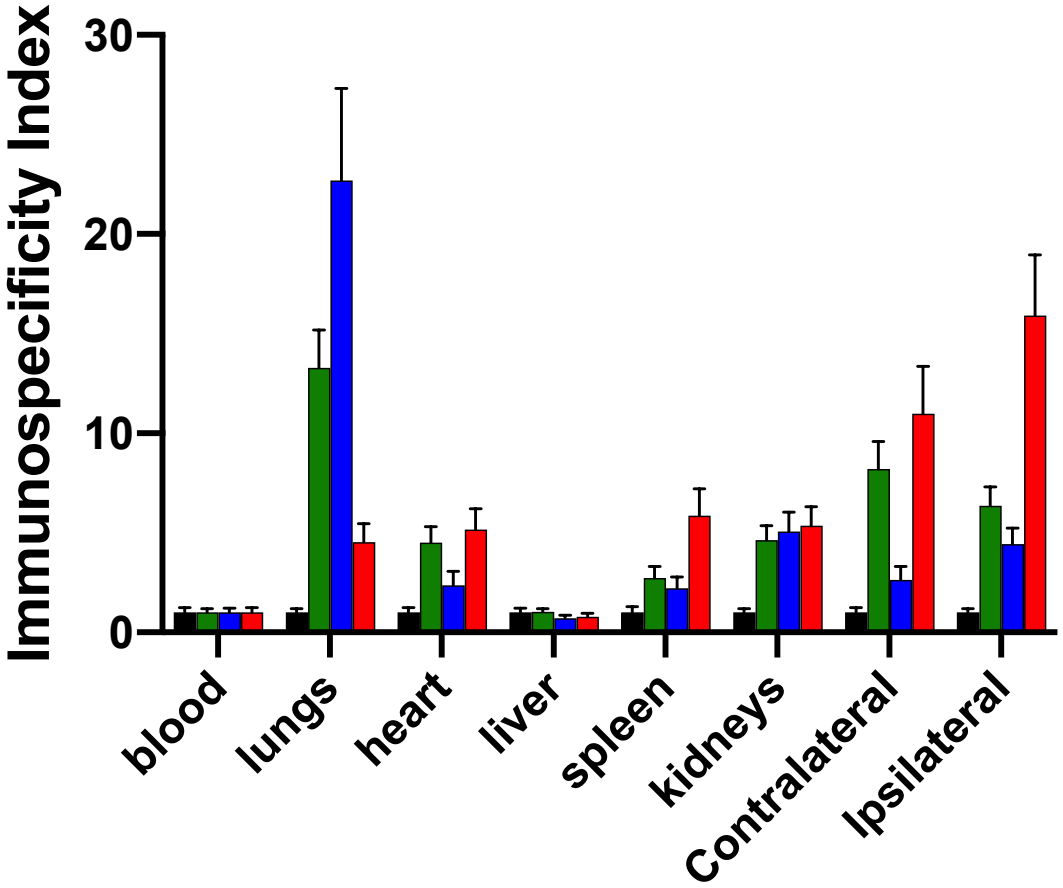
Persidsky Lab:
Zuluaga Ramirez

oscarmar@pennmedicine.upenn.edu

To the BBB: Target selection



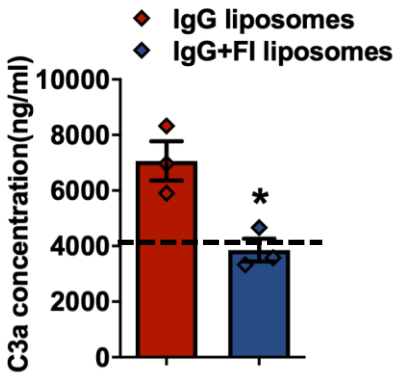


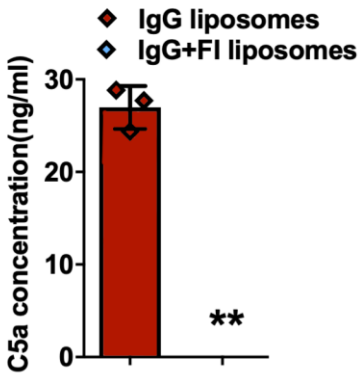


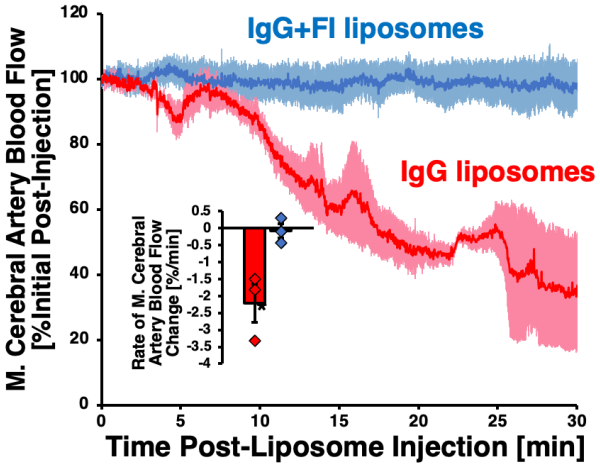
T-NC (%ID/g) in tissue/ T-NC (%ID/g) in Blood

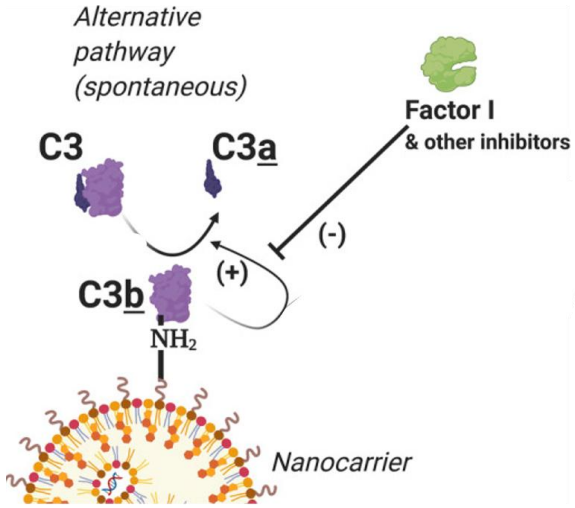
IgG-NC (%ID/g) in tissue/ IgG-NC (%ID/g) in Blood

Primum non nocere



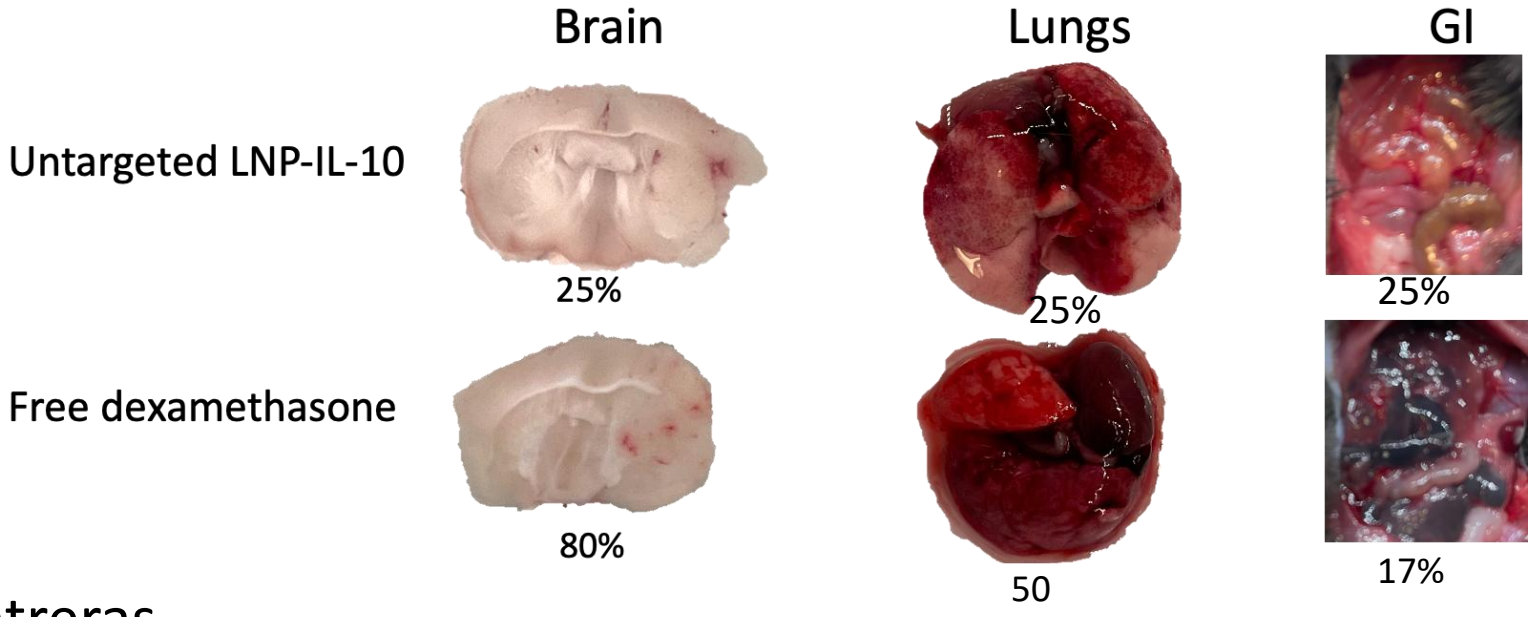






Dr. Brenner

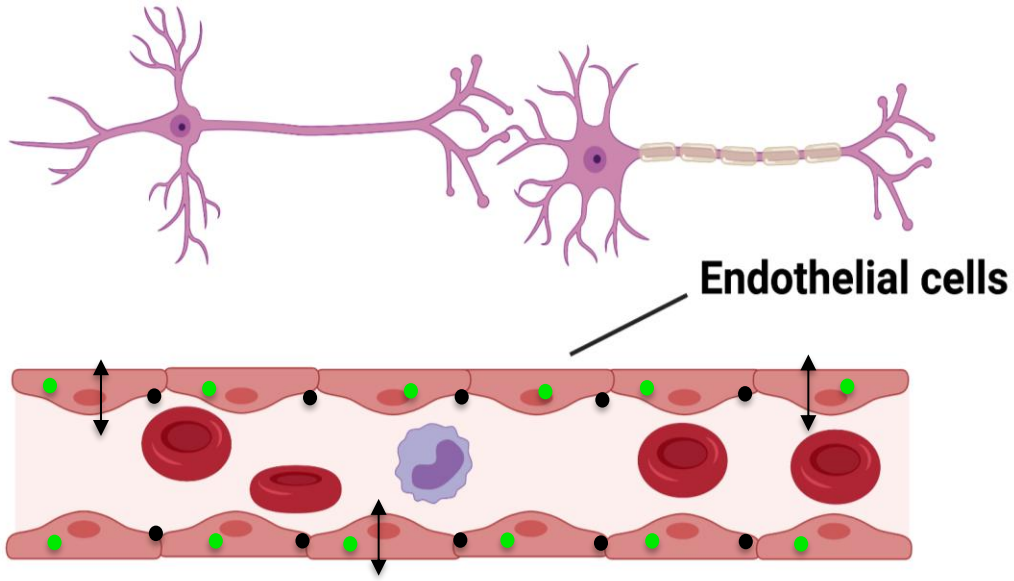
1. Wang et al. Cell, 2025
2. Omo-Lamai et al. Nat Nano, 2025 (accepted)
3. Omo-Lamai et al. Adv Materials, 2024.*
4. Zamora et al. Nano letters, 2024. *
5. Nong et al. Mol Therapy, 2024.*
6. Parhiz et al. JCR. 2022
7. Myerson et al Nat Nano, 2022
8. Wang et al Adv Materials, 2021



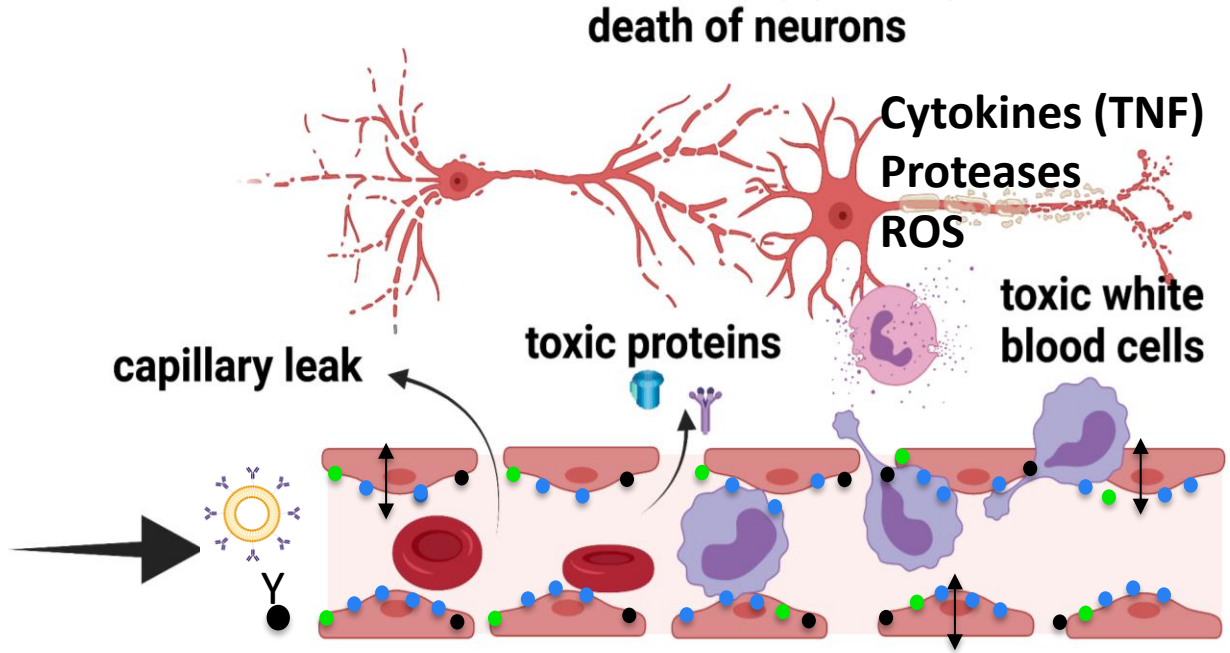
*Corresponding: Marcos-Contreras

Brain delivery

1. To the BBB



2. Across the BBB

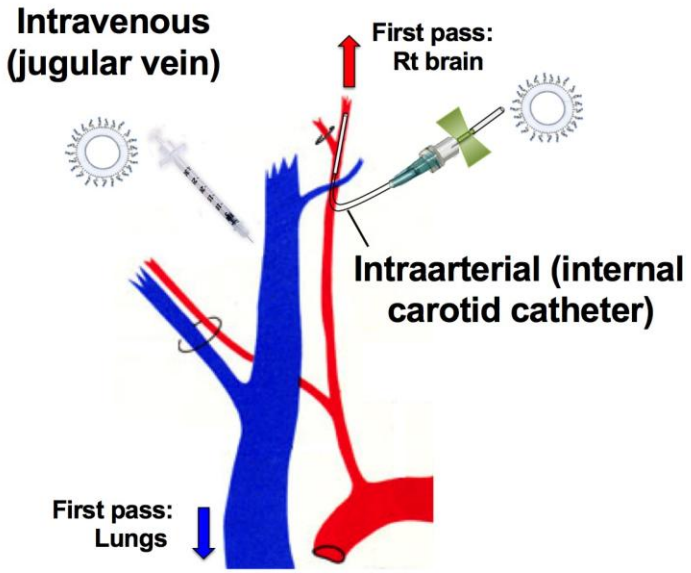


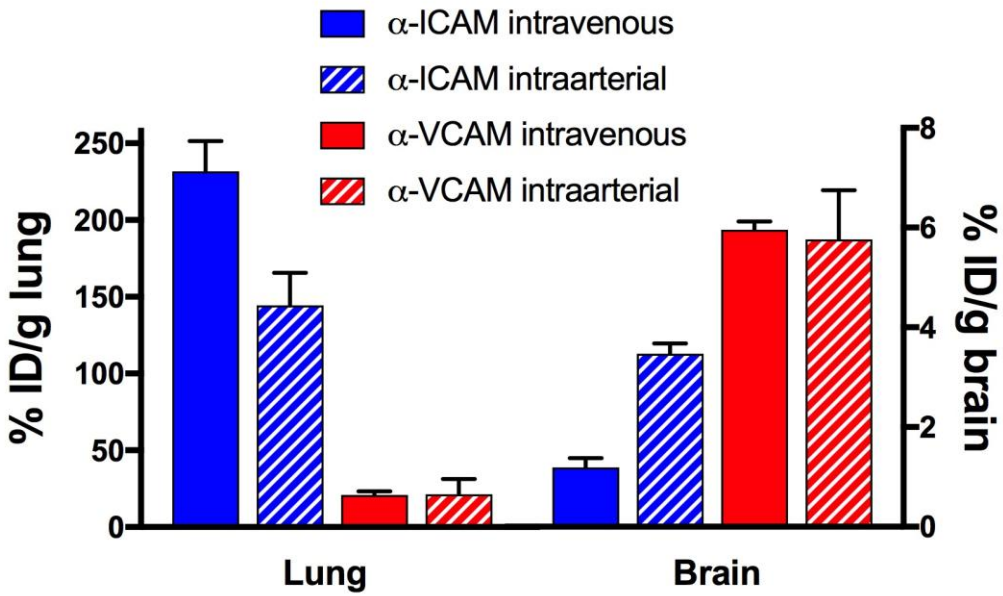
TfR; IR, LRP PECAM P-Selectin Inducible Cellular Adhesion Molecules (ICAM-1, VCAM-1)

Targeted nanocarrier Antibody delivery

Courtesy of JS Brenner (Edited)

IV vs IA





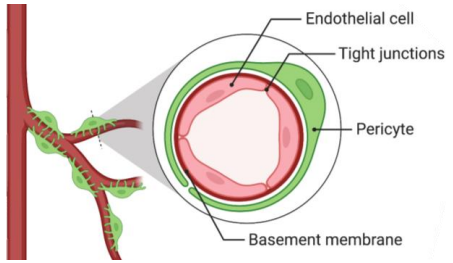
(Unpublished)

Nanomedicine for stroke

1. Delivery:

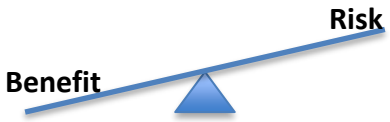
- Improve the delivery

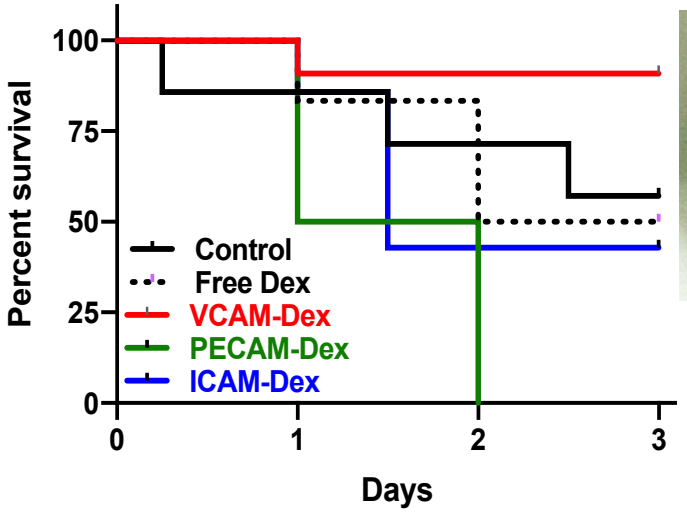
(free drugs <<0.1%)

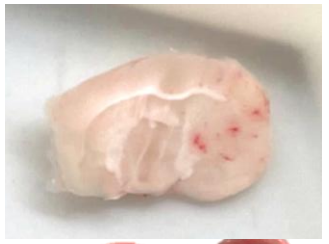


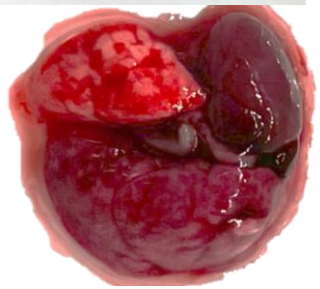
2. Side effects:

- Minimize drug and carrier side effects

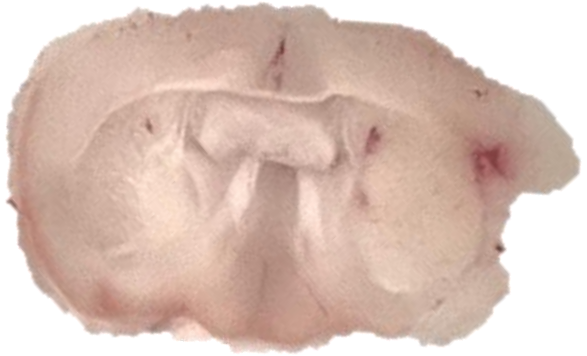
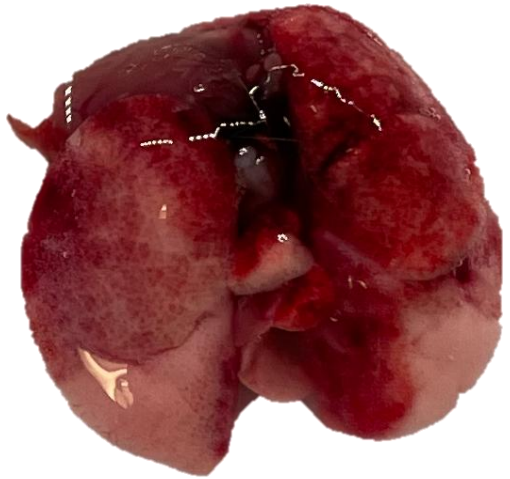






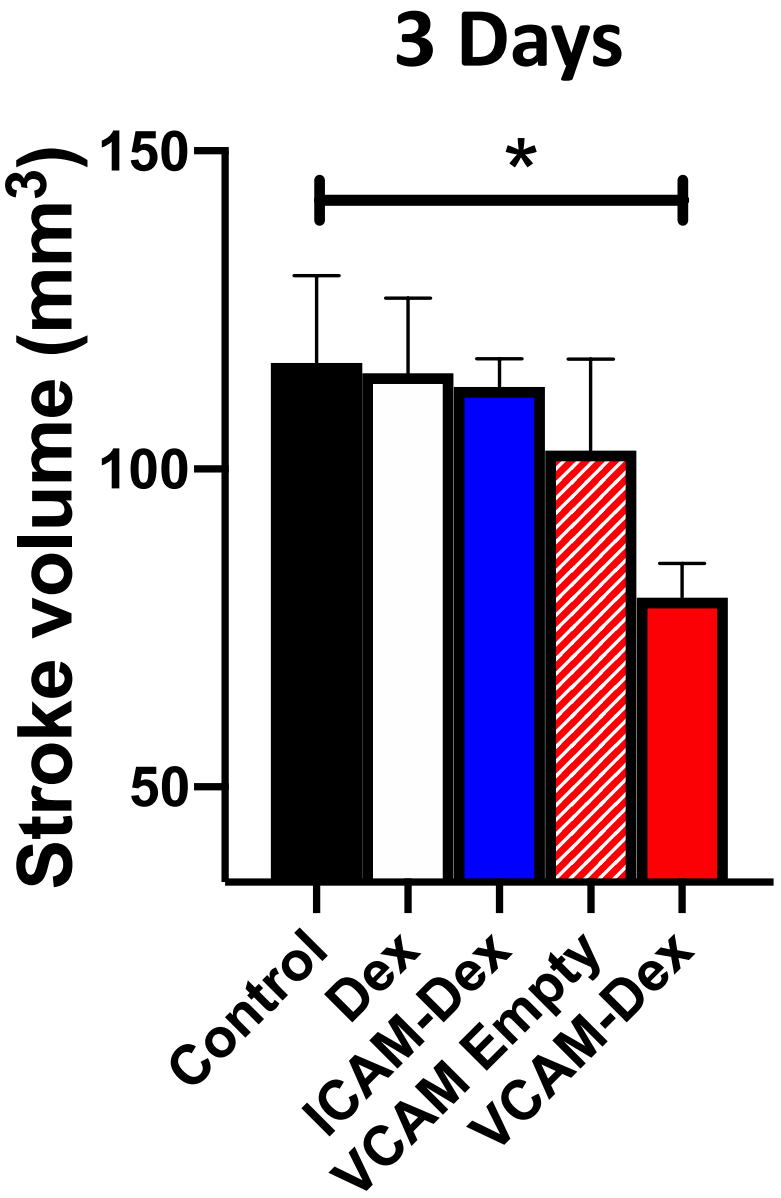


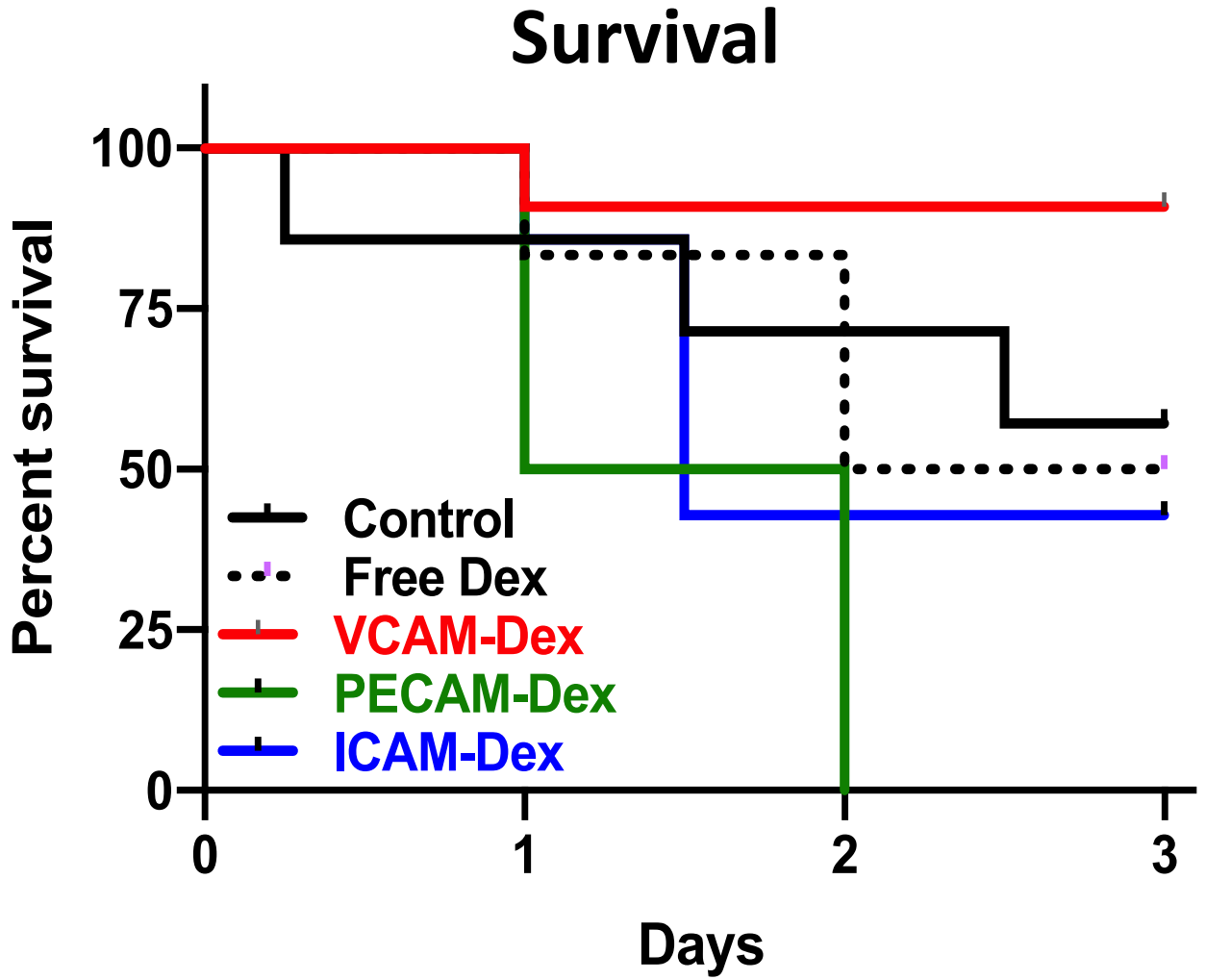
Primum non nocere

	Brain	Lungs	GI
Untargeted LNP-IL-10 (25%)			
Free dexamethasone (80%)			

Nong et al. Under review. (Corresponding: Marcos-Contreras)

Efficacy: VCAM liposomes-Dex improve stroke





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