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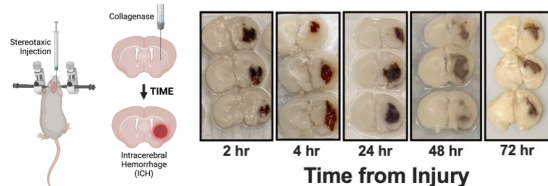
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Background

- Intracerebral hemorrhage (ICH) is a morbid and lethal form of stroke with no disease-modifying therapeutics
- Neuroinflammation after ICH worsens outcomes
- Endothelial targeting via highly expressed cell surface proteins is an attractive method to increase regional uptake of nanocarriers in the brain
- We developed a **platform technology** that targets lipid nanoparticles (LNPs) to inflamed brain vasculature by conjugating anti-VCAM antibodies to LNPs
- We test this platform by delivering mRNA encoding IL-10, a potent anti-inflammatory cytokine that has shown pre-clinical promise, in an experimental ICH model

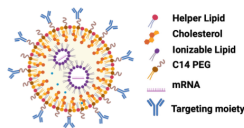
Methods

Disease Model: Intrastriatal Collagenase Injection

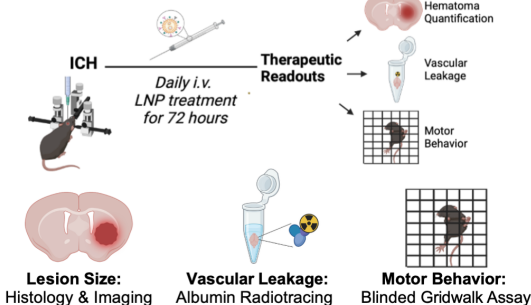


Vehicle: Targeted Lipid Nanoparticles against VCAM

- IL-10 mRNA

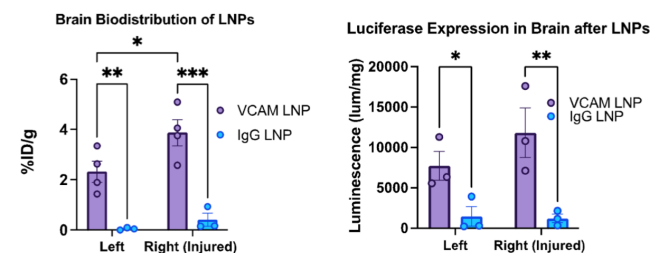


Outcome measures: Biodistribution, Cargo Expression, Brain Flow Cytometry, Lesion Size, Brain Vascular Leakage, Motor Behavior

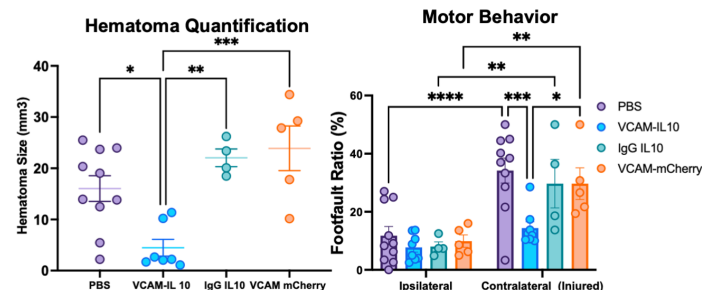


Results

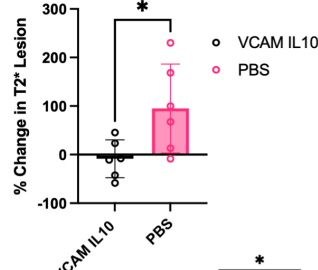
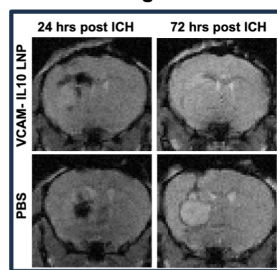
VCAM-LNPs have superior brain delivery and expression after ICH



VCAM-LNP-treated mice have significantly smaller hematoma size and improved motor behavior at 72h compared to PBS and vehicle controls

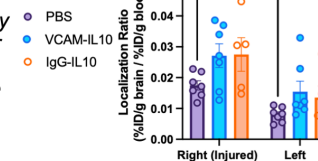


T2*-Weighted MRI



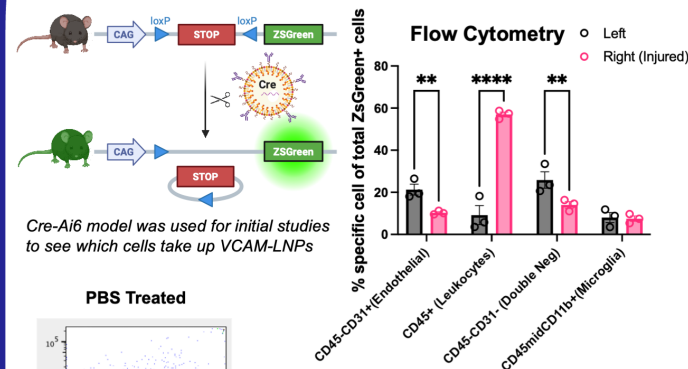
IL10-loaded VCAM-LNPs do not improve albumin leakage at 72h

IL-10 delivery in VCAM-LNPs greatly improves hematoma size and motor phenotype at 72h, but these phenomena are surprisingly not due to improvement in albumin leakage at this time point...

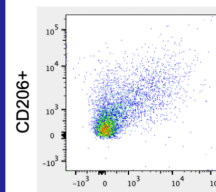


Results

VCAM-LNPs mostly transfect leukocytes in the injured region

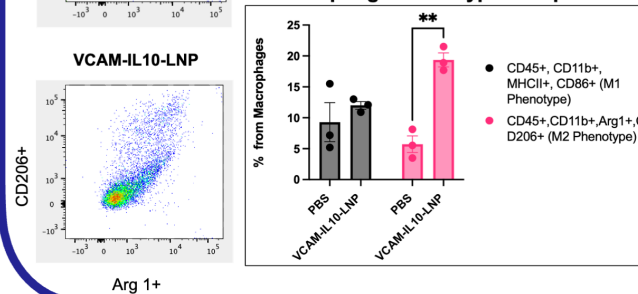


PBS Treated



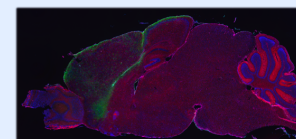
IL10-loaded VCAM-LNPs induce phenotype shift in infiltrated macrophages from M1 to M2

Macrophage Phenotype Comparison



Discussion & Future

- VCAM-LNPs lead to significantly higher brain expression of cargo when compared to untargeted IgG controls
- VCAM-LNPs containing IL-10 mRNA markedly improve hematoma size and motor behavior in ICH mice but do not impact albumin leakage at 72h
- IL-10-VCAM-LNPs switch macrophage phenotype from pro-inflammatory M1 to anti-inflammatory M2 phenotype, promoting hematoma clearance/precluding expansion



Brenner Bioengineering Lab

