

CitH3 inhibition attenuates acute ischemic stroke via targeted immune modulation

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Distinguished Majors Program in Neuroscience

Fozdar Symposium

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Division of Surgical Sciences

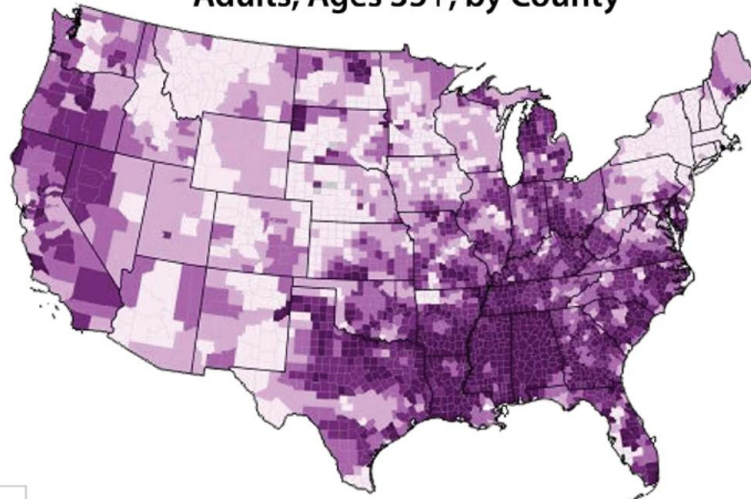
Department of Surgery

UVA School of Medicine

04/29/2026

Cerebral ischemia-reperfusion (I/R) injury in stroke

Stroke Death Rates, 2018-2020
Adults, Ages 35+, by County

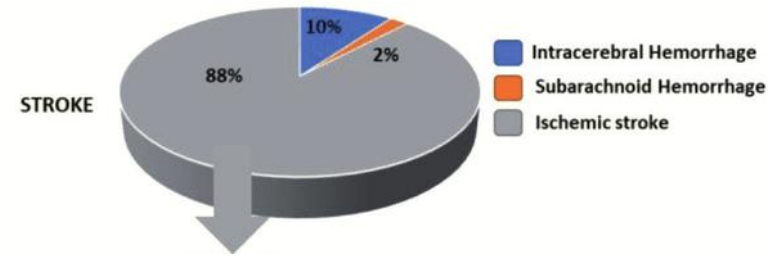


Age-Adjusted Prevalence (%)

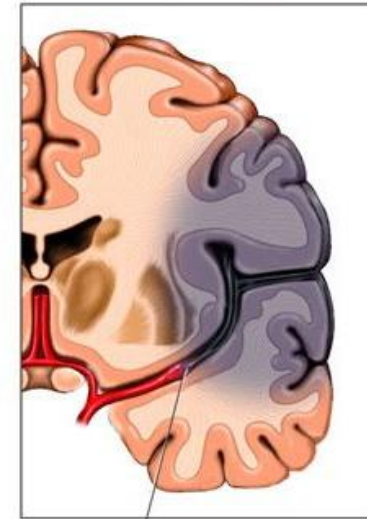
- 3.6-61.4
- 61.5-70.6
- 70.7-78.4
- 78.5-89.3
- 89.4-177.5
- Insufficient Data



Data source and methodology found at:
www.cdc.gov/dhisp/maps/atlas/statistical-methods

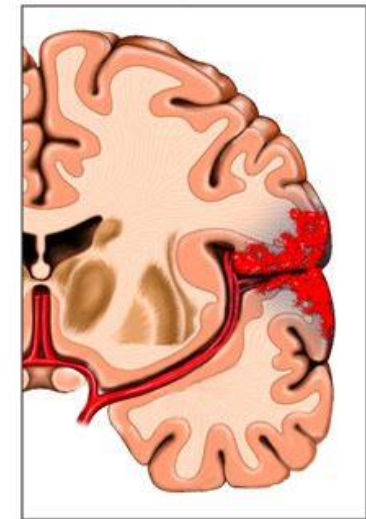


Ischemic Stroke



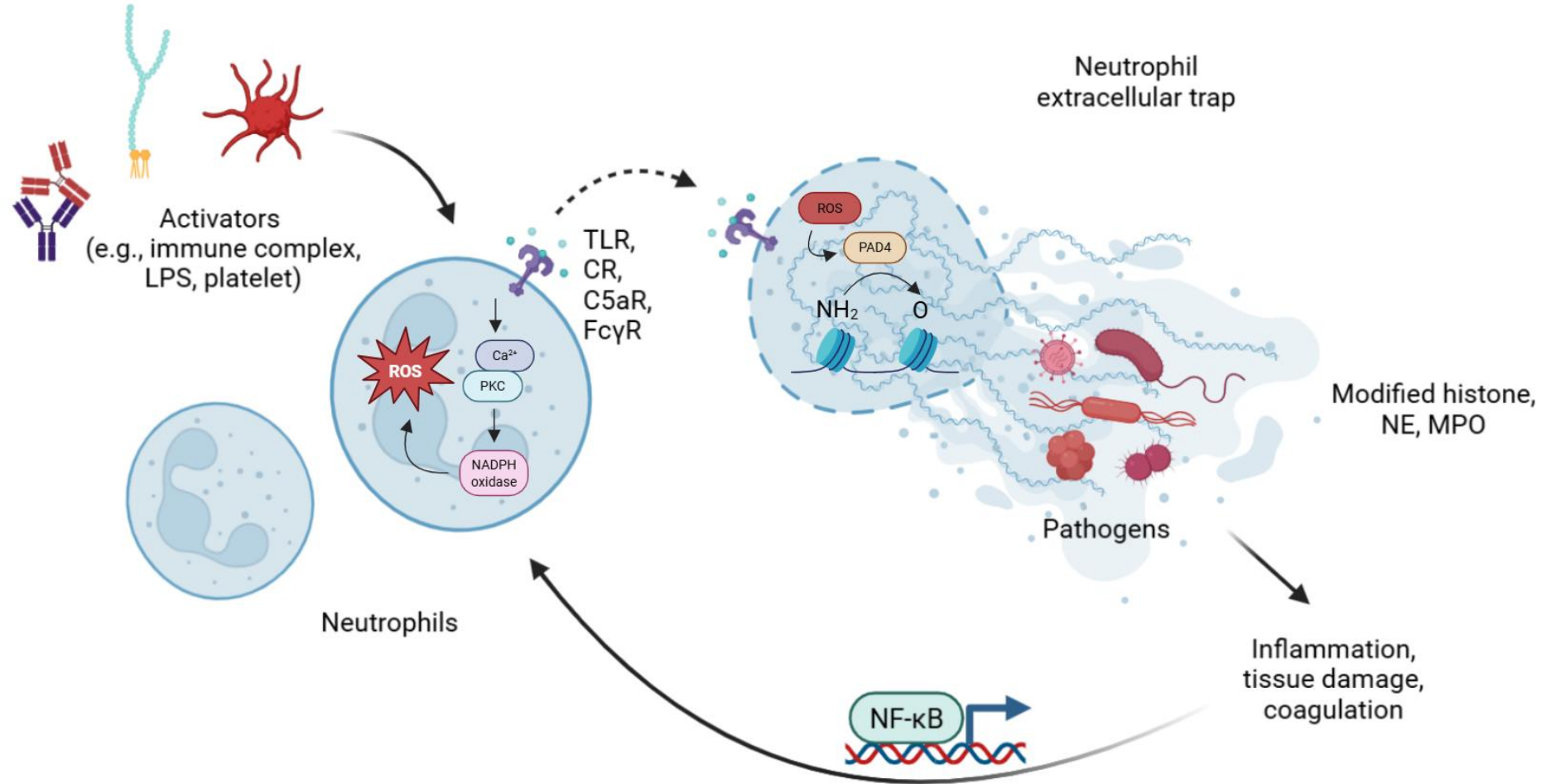
Clot stops blood supply to an area of the brain

Hemorrhagic Stroke

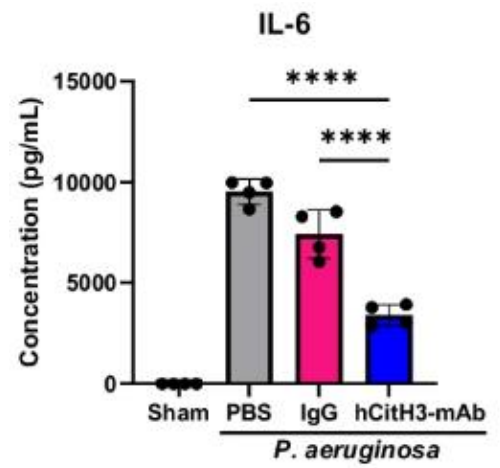
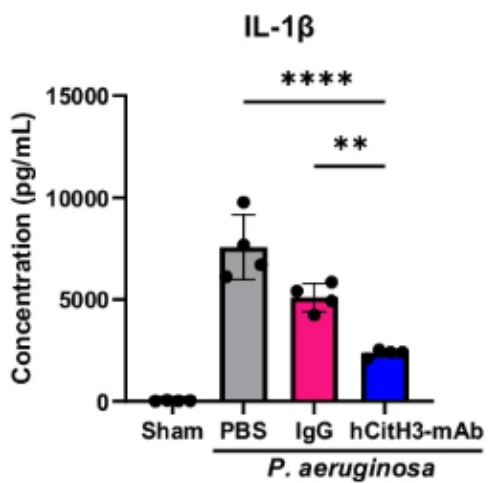
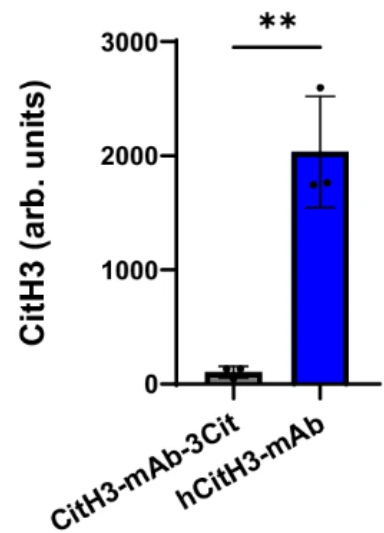
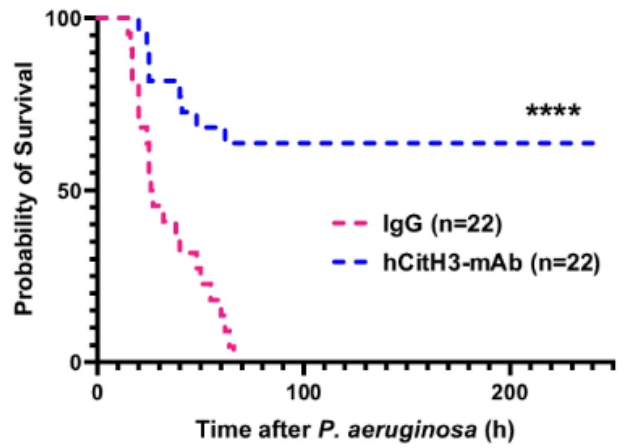
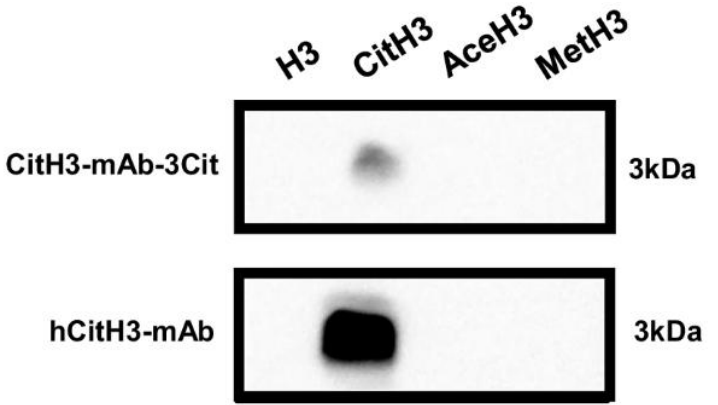


Hemorrhage/blood leaks into brain tissue

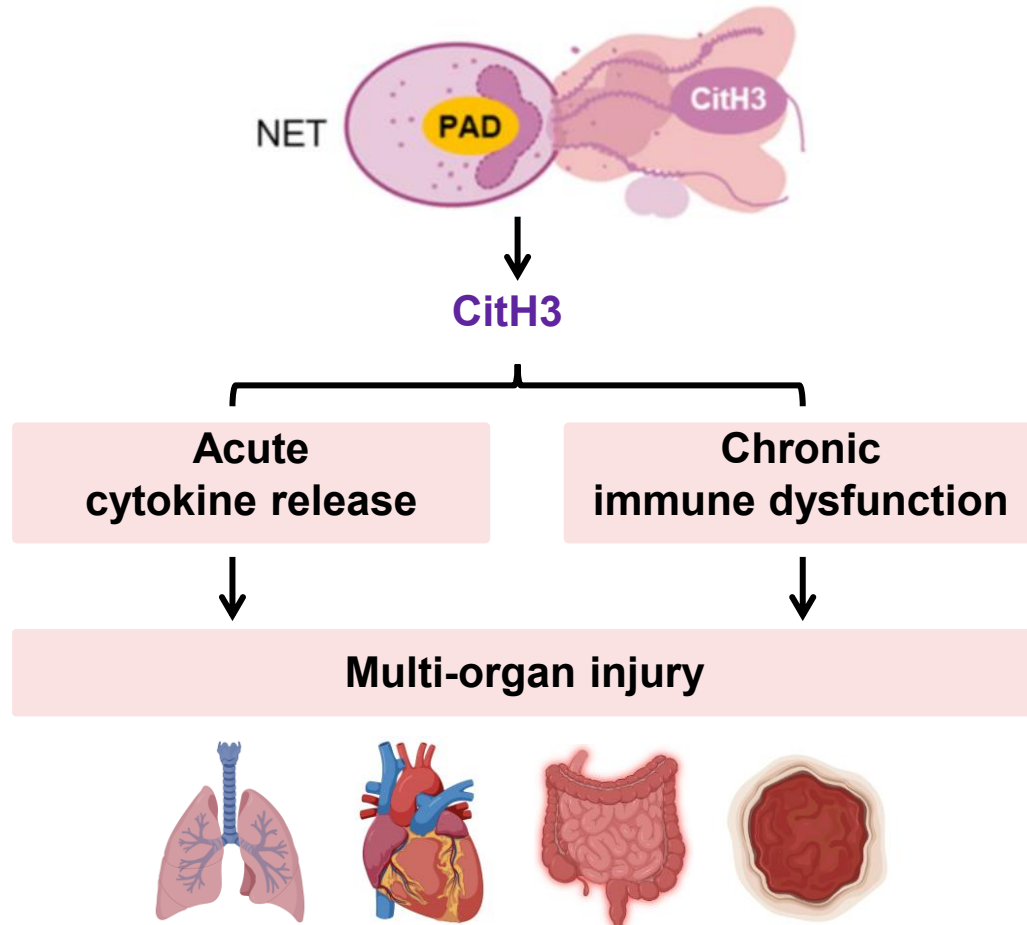
I/R-induced citrullination of histone H3 (CitH3) drives NETosis



Development of a humanized antibody (hCitH3-mAb) against CitH3-driven pro-inflammation



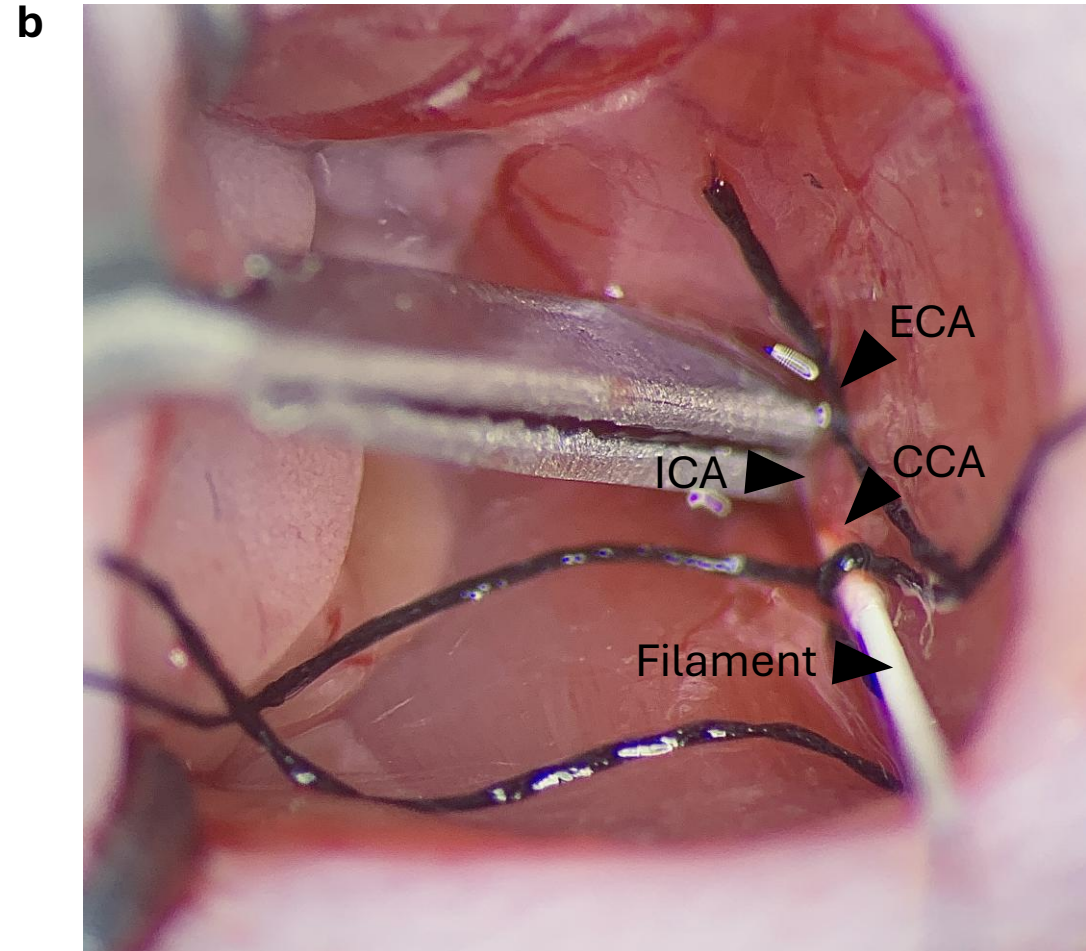
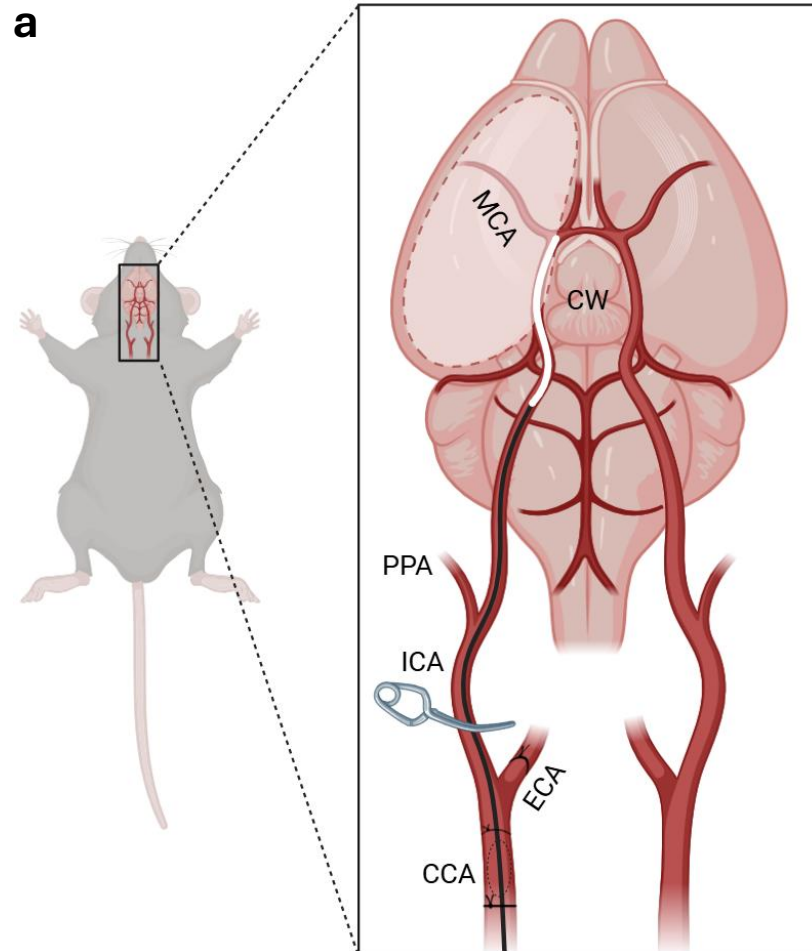
Targeting CitH3 suppresses multi-organ and immune dysfunctions



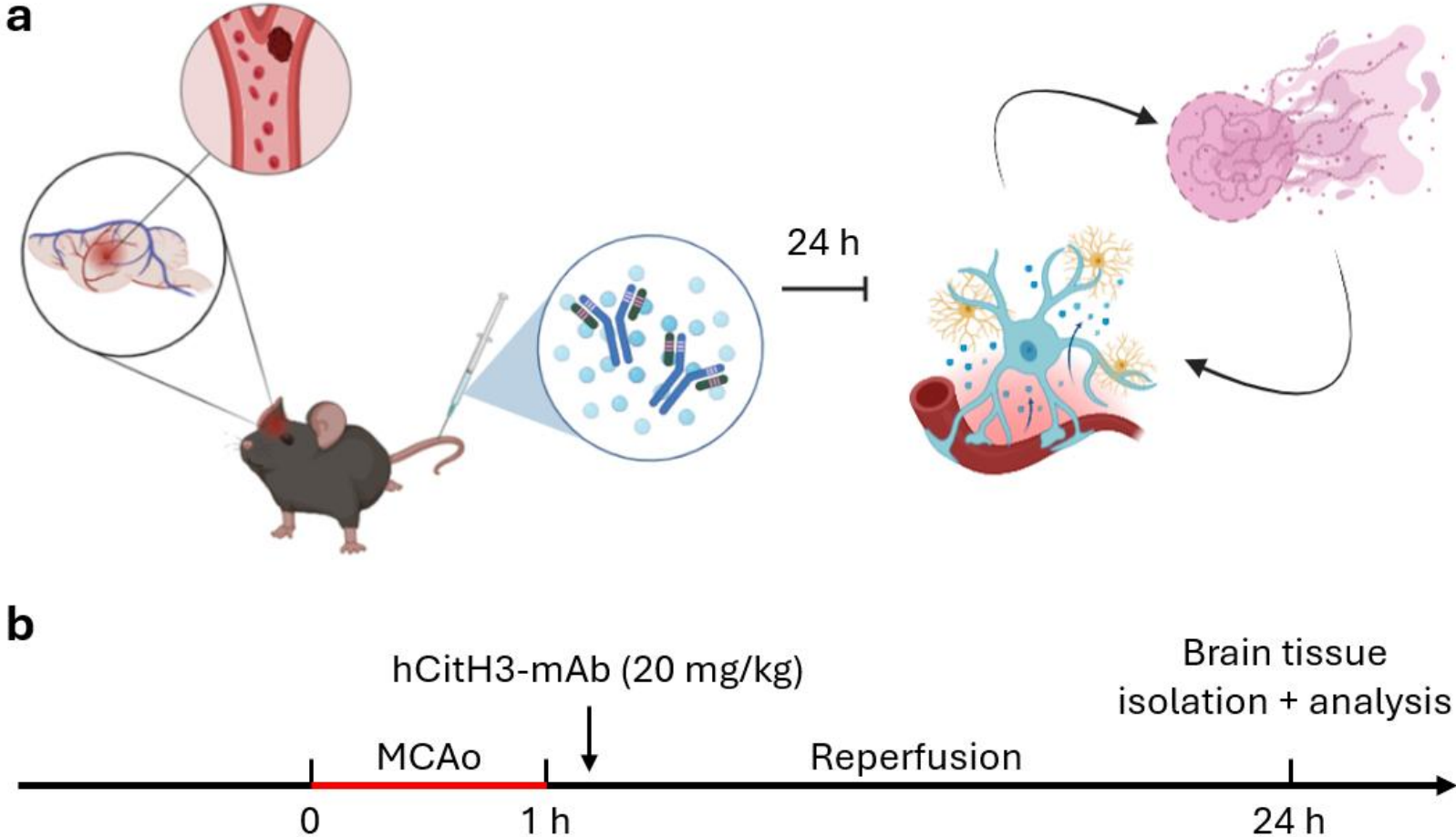
Hypothesis

hCitH3-mAb modulates immune cell polarization and inflammation, contributing to neuroprotection against I/R injury

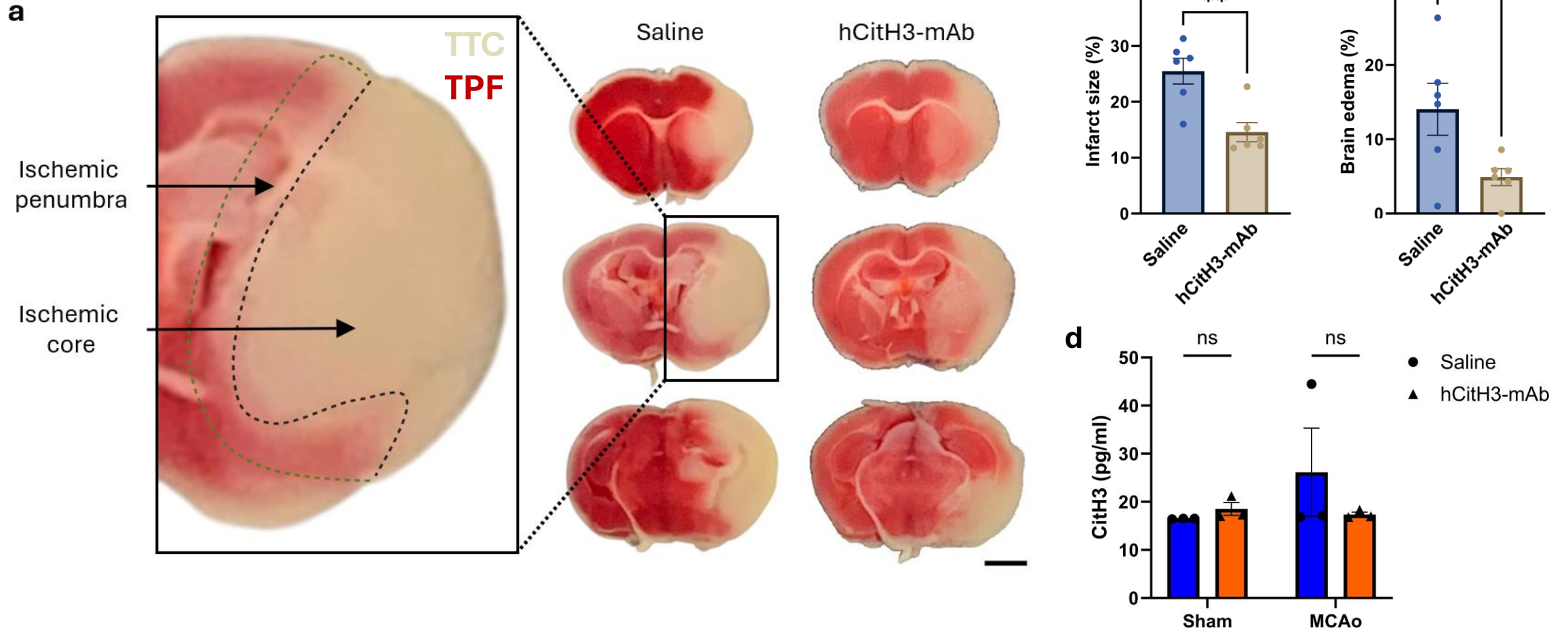
Intraluminal filament model of transient middle cerebral artery occlusion



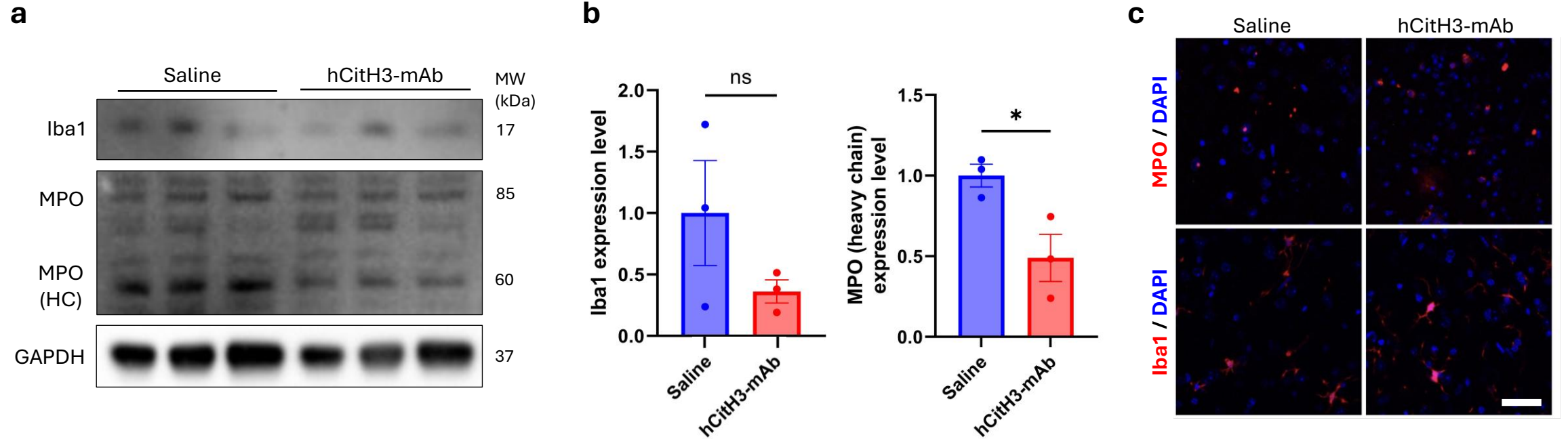
Acute treatment paradigm after experimental ischemic stroke



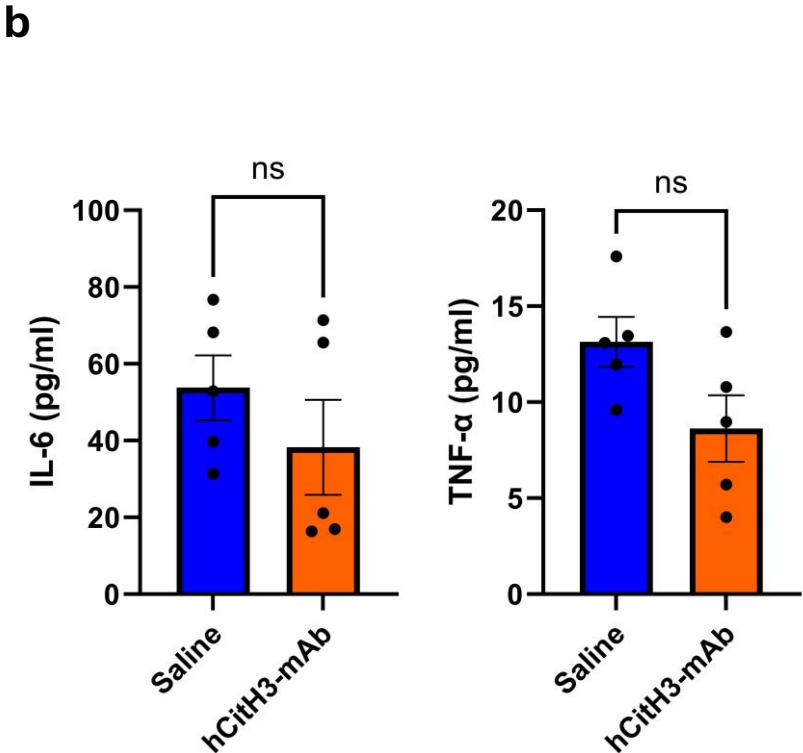
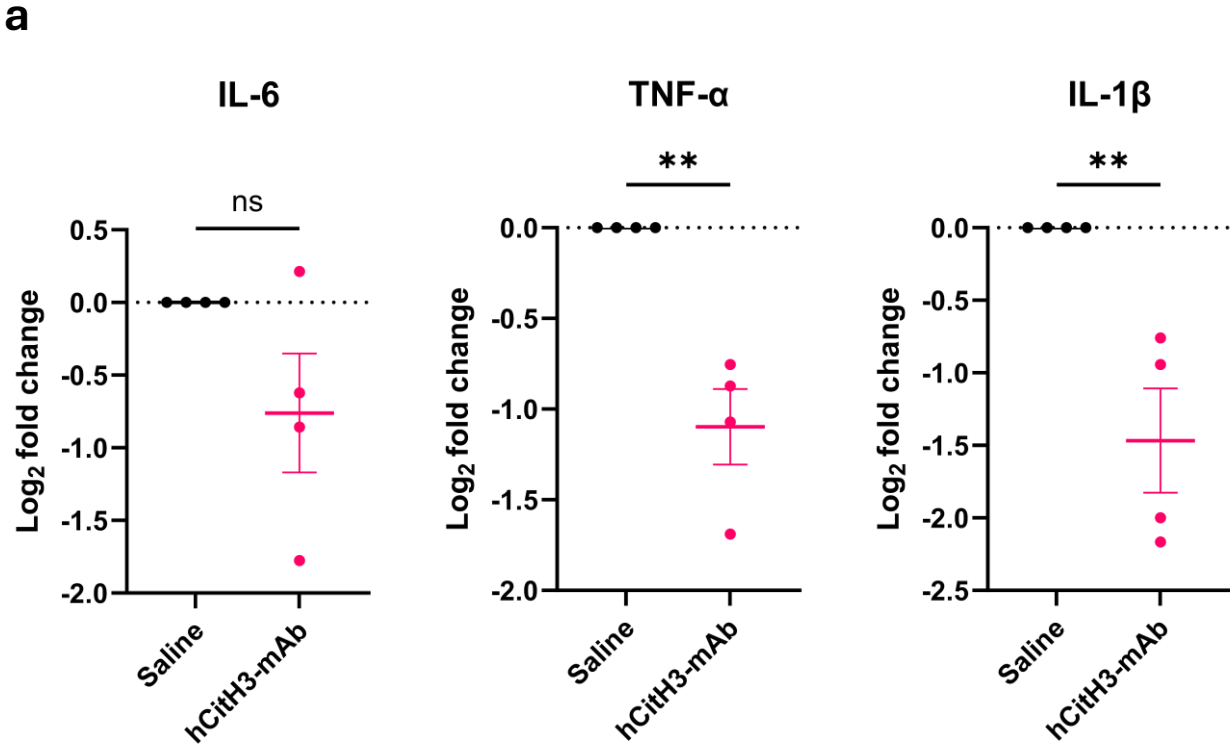
Intravenous delivery of hCitH3-mAb limits cerebral infarct growth



hCitH3-mAb reduces microglia activation and neutrophil infiltration

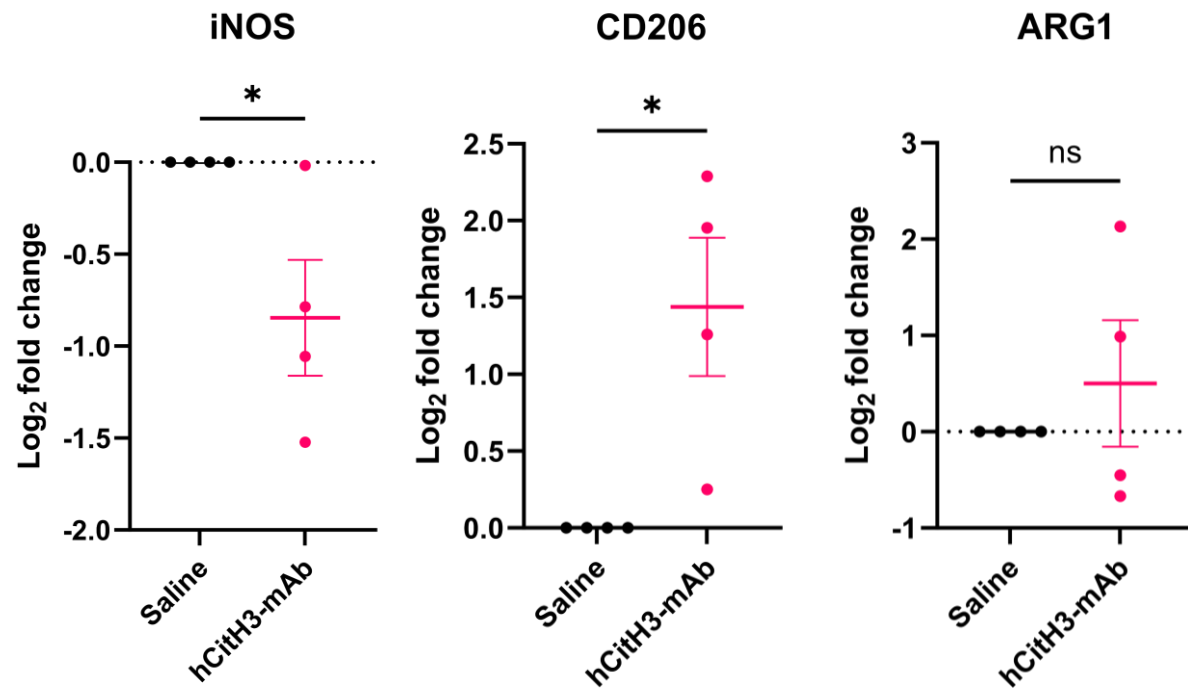


hCitH3-mAb protects against brain injury by mitigating pro-inflammatory cytokine release

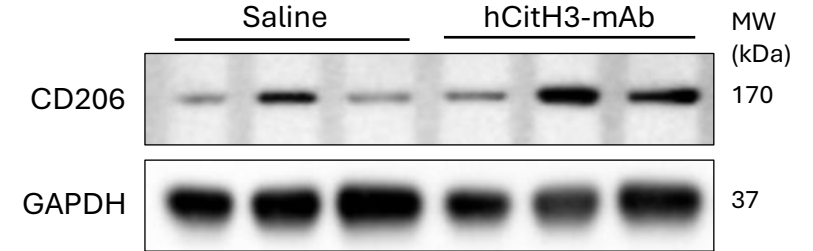


hCitH3-mAb shifts immune response toward an M2-like phenotype

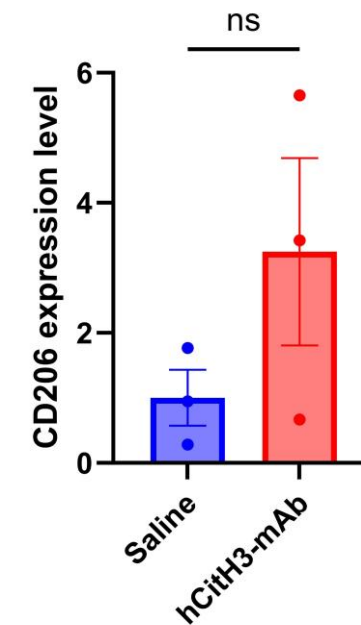
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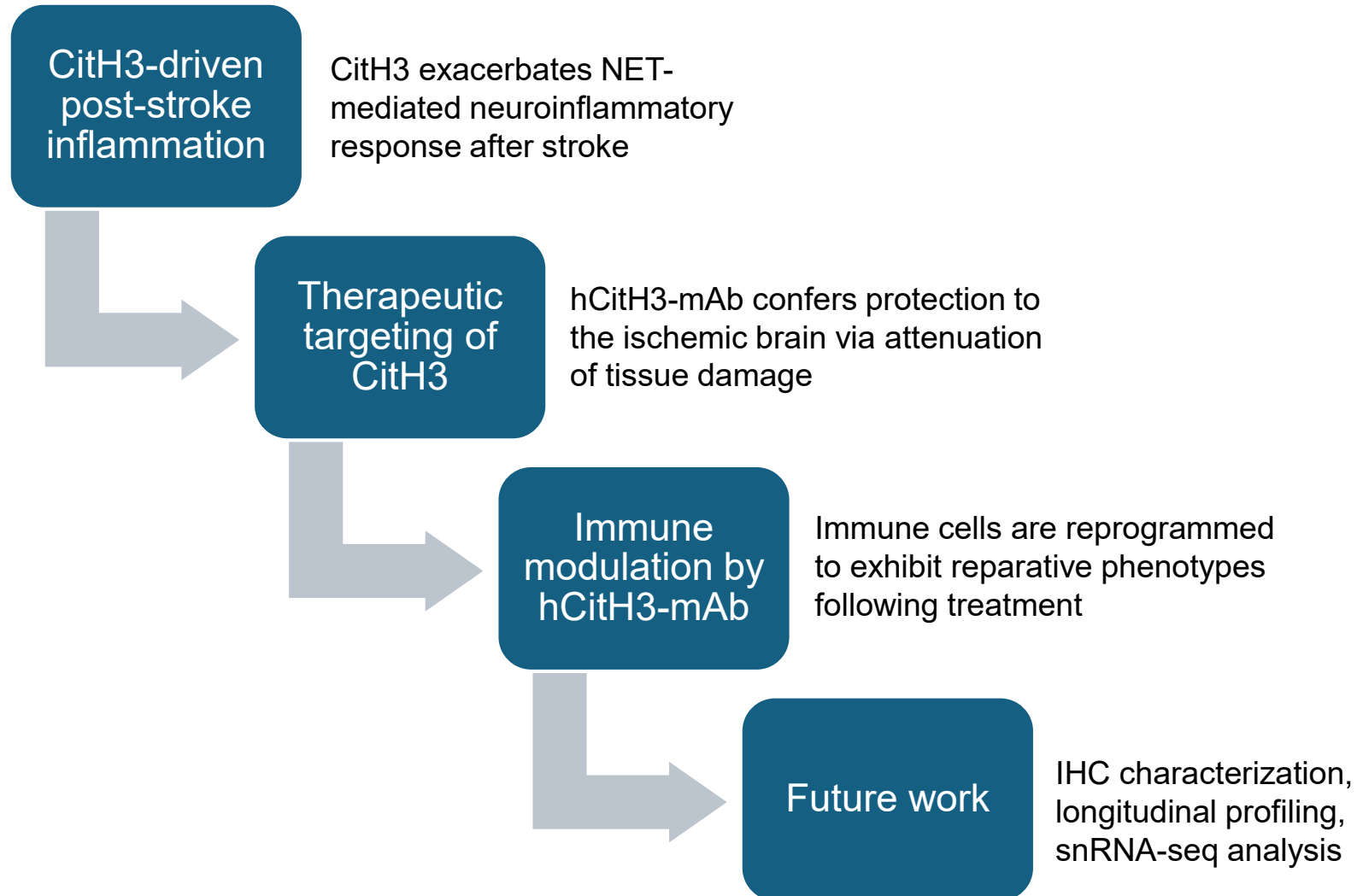
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Key summary



Acknowledgements

Ma Lab:

Jianjie Ma, PhD, Professor *

Chuanxi Cai, PhD, Associate Professor

Chengli Shen, MD, PhD, Research Associate Professor

Ki Ho Park, PhD, Assistant Professor

James Ko, Assistant Professor

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References

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