Activation of the TWEAK/Fn14 Inflammatory Pathway in a Murine Model of Subarachnoid Hemorrhage

Brandon Miller, MD, PhD

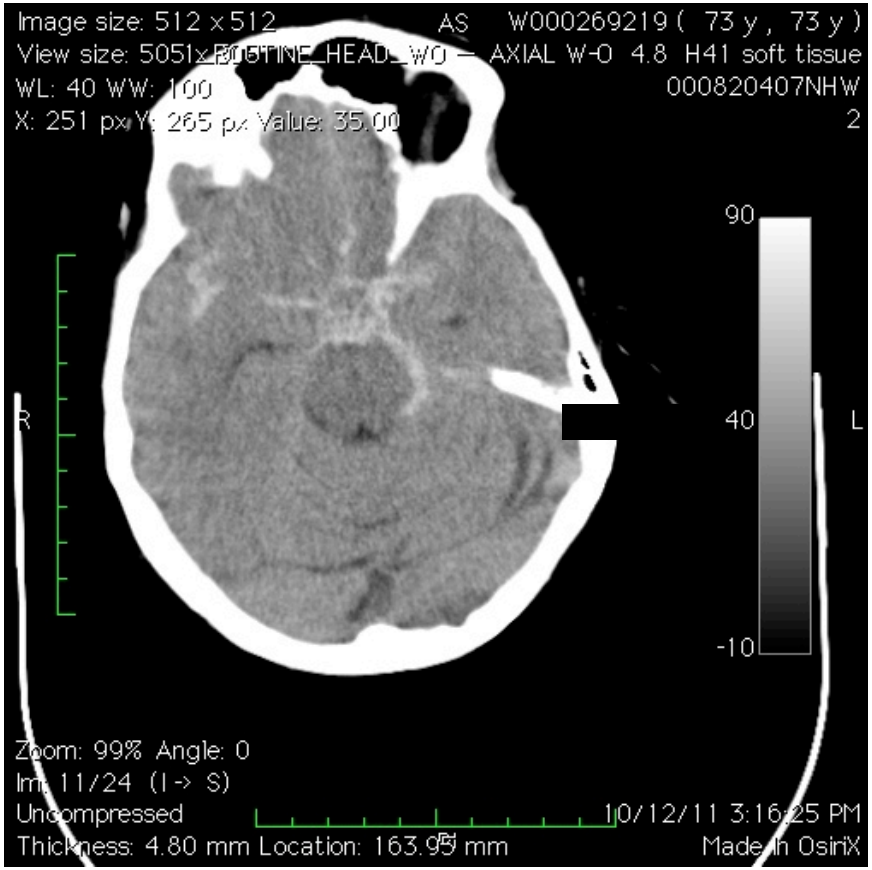
Department of Neurosurgery, Emory University

Yepes Laboratory, Emory Dept. of Neurology

EMORY
NEUROSURGERY

“Early Brain Injury” after SAH

- Inflammation
- Cerebral Edema
- Cell Death

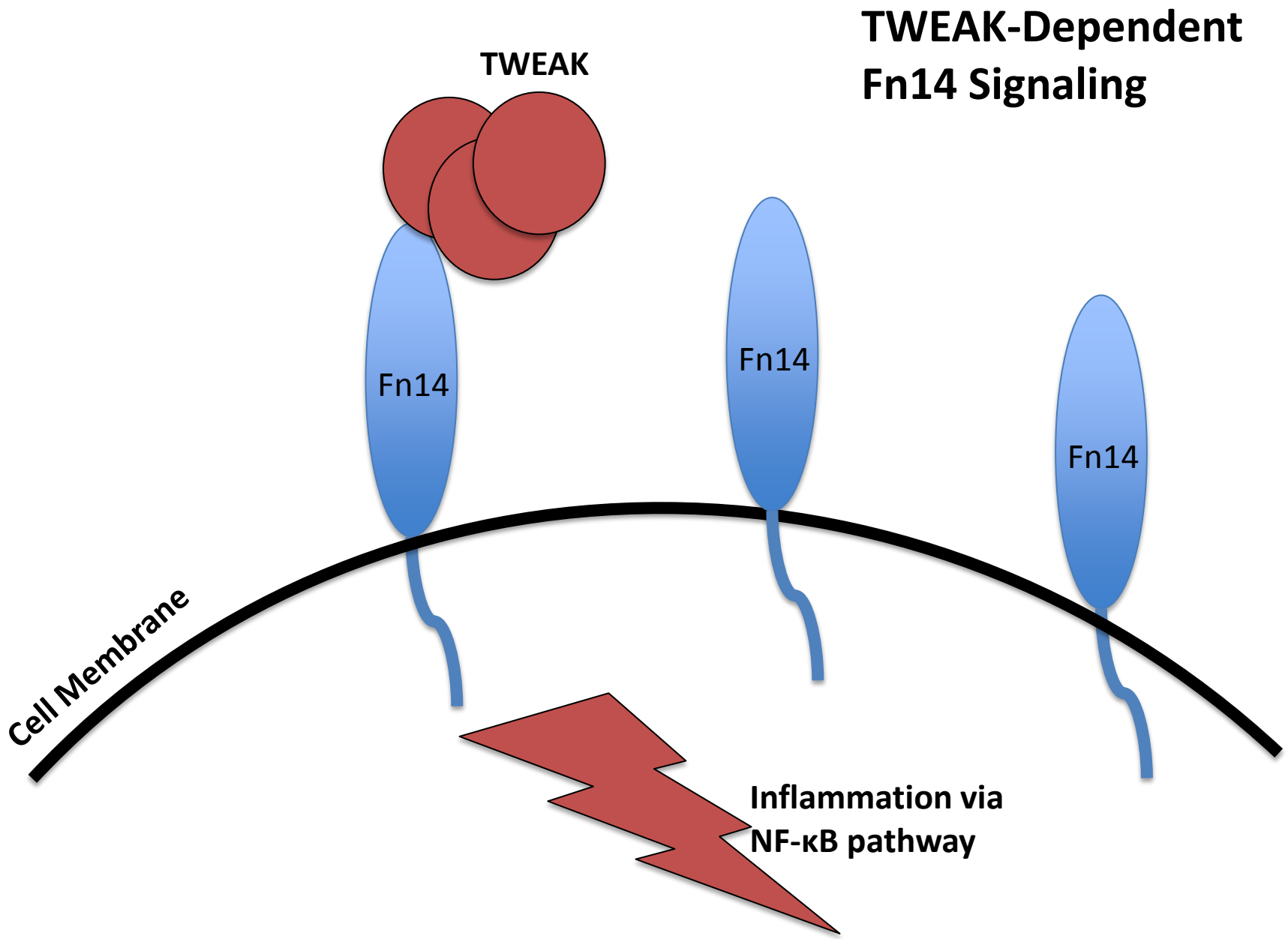


Inflammation after SAH

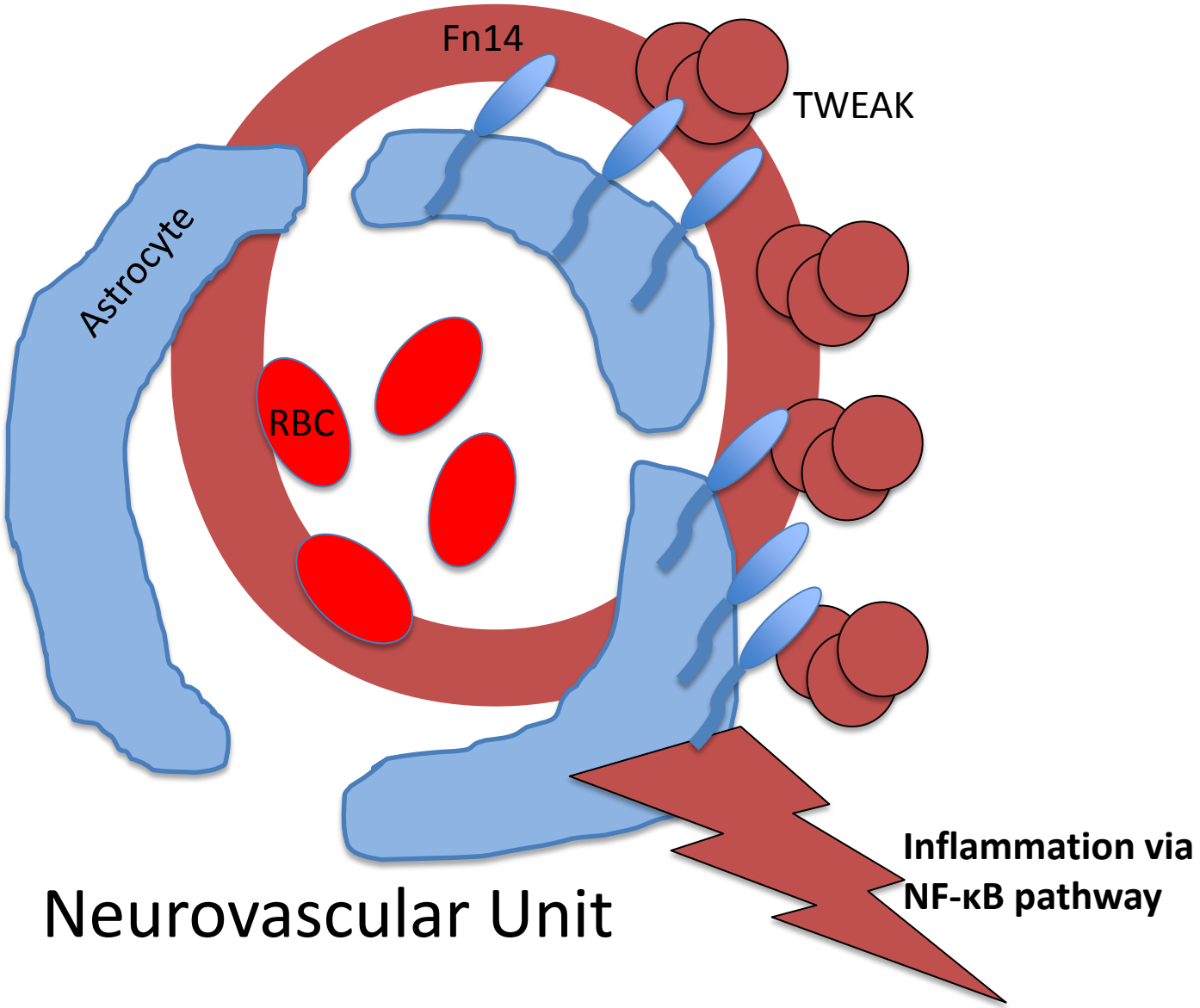
- Pro-inflammatory cytokines are found in the CSF after SAH
- There is a robust inflammatory response in animal models of SAH
- Inflammation may contribute to cerebral edema, cell death and vasospasm after SAH

Tumor Necrosis Factor-like Weak Inducer of Apoptosis (TWEAK)

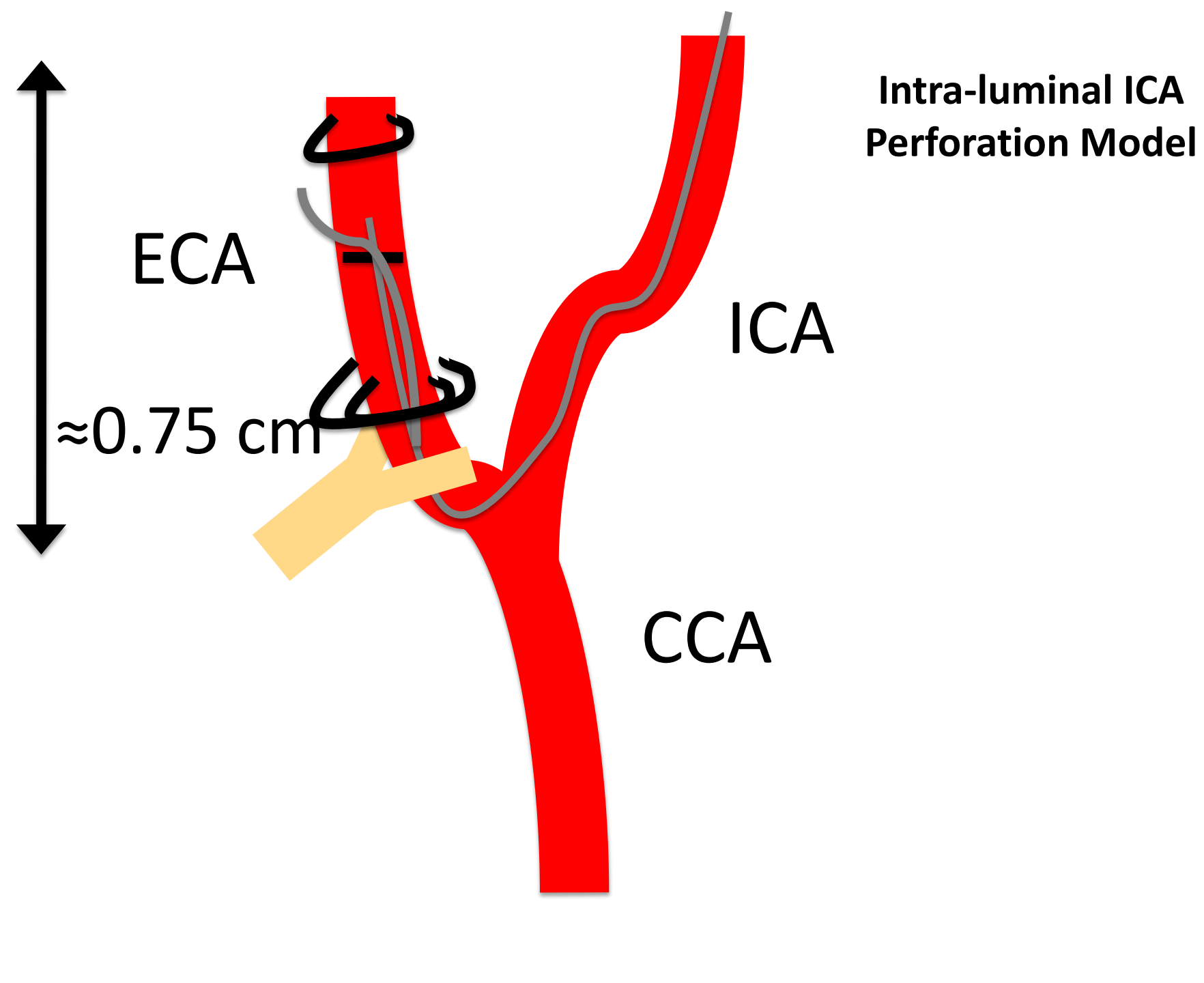
- Member of the TNF superfamily
- Binds to the receptor fibroblast growth factor-inducible 14 (Fn14)
- Both TWEAK and Fn14 are expressed by perivascular astrocytes, endothelial cells and microglia
- TWEAK and Fn14 expression increase after injury


TWEAK-Dependent
Fn14 Signaling
TWEAK
Fn14
Fn14
Fn14
Cell Membrane
Inflammation via
NF-κB pathway

Hypothesis

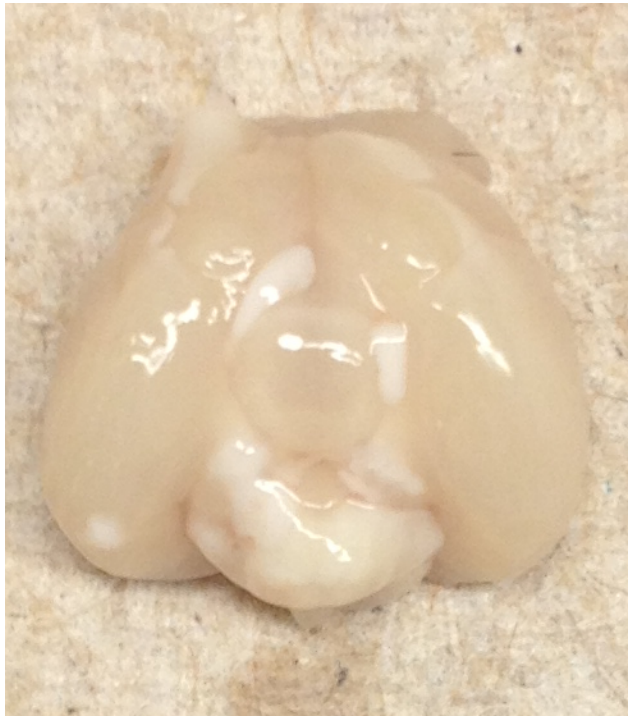


Neurovascular Unit

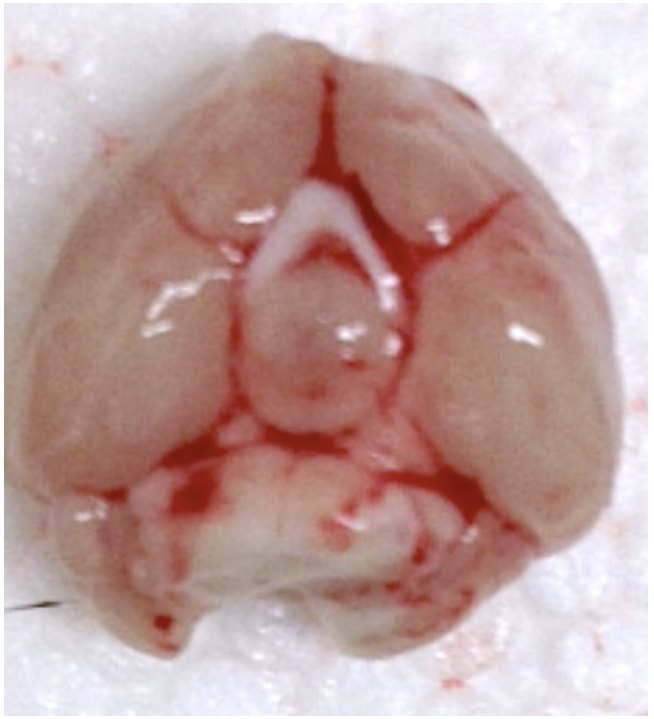


Intra-luminal ICA Perforation Model

After Transcardiac Perfusion

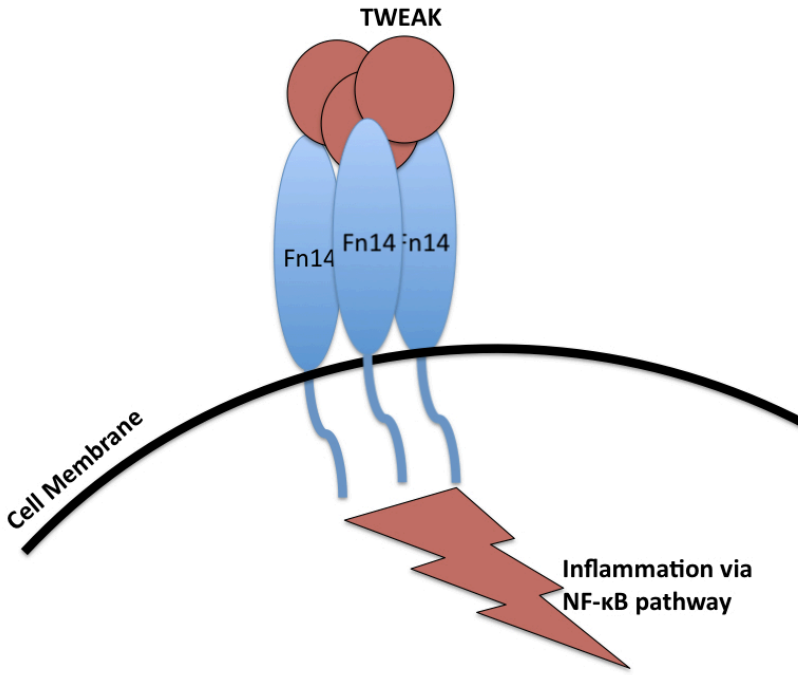


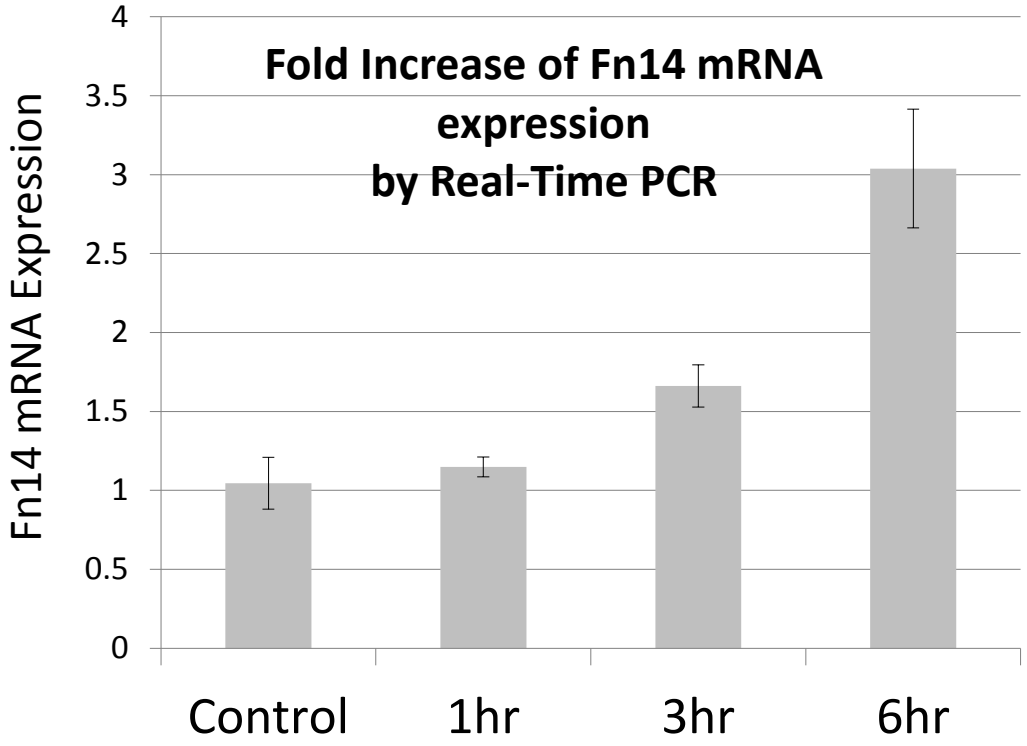
Sham-operated Control



Subarachnoid Hemorrhage

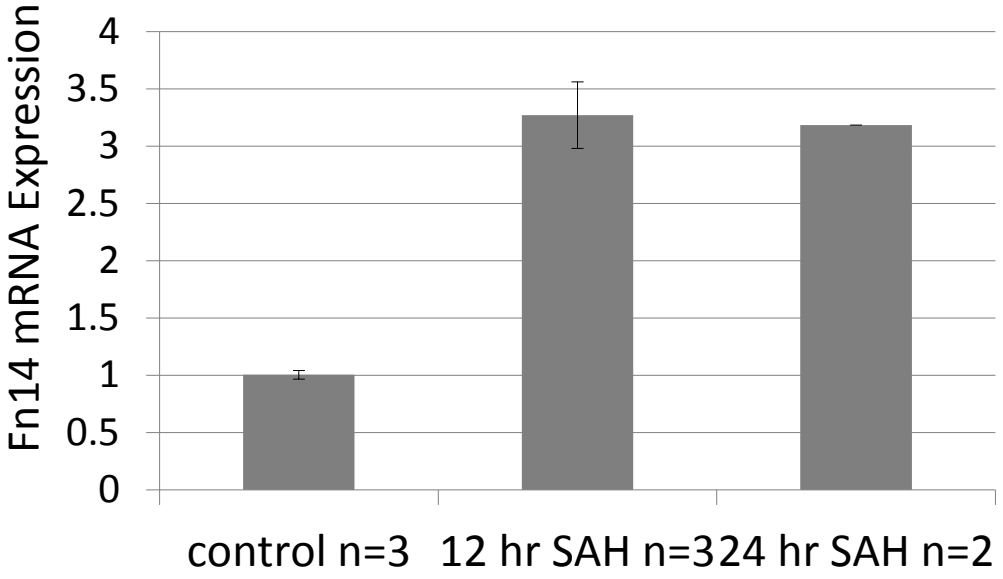
Fn14 Expression after SAH

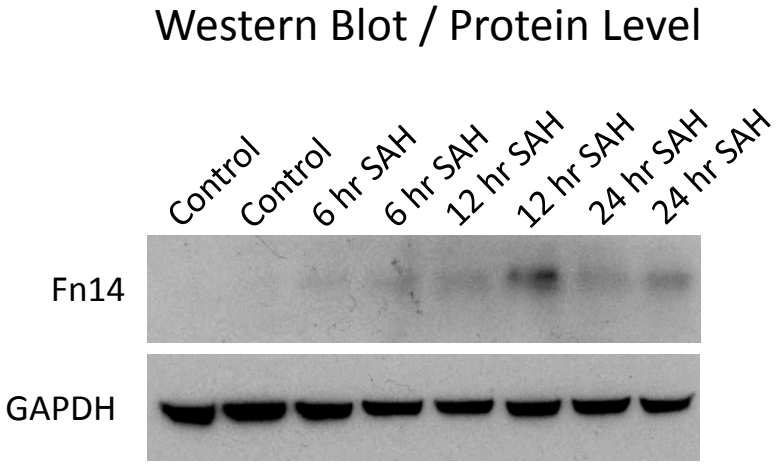




Tissue from ipsilateral parietal cortex was analyzed

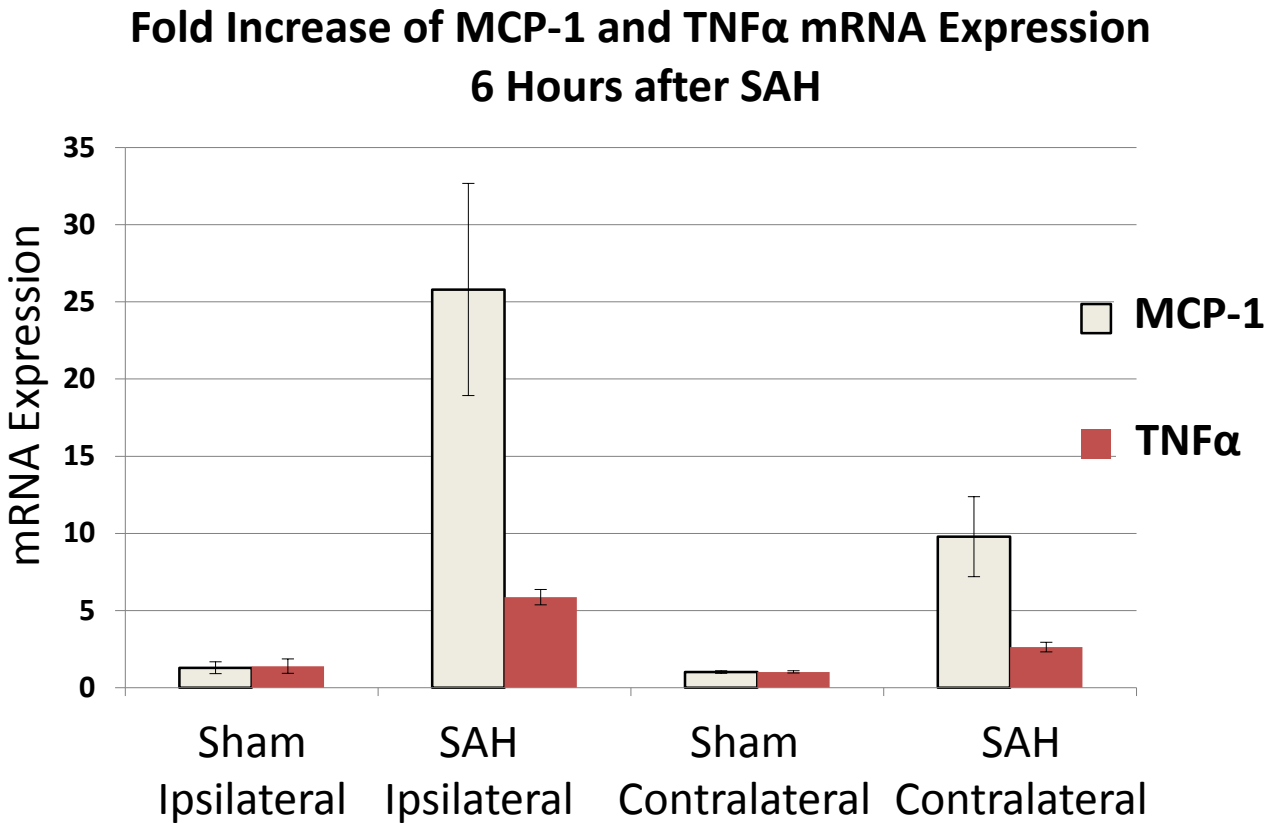
Increased Fn14 Expression is Sustained 12-24 Hours after SAH



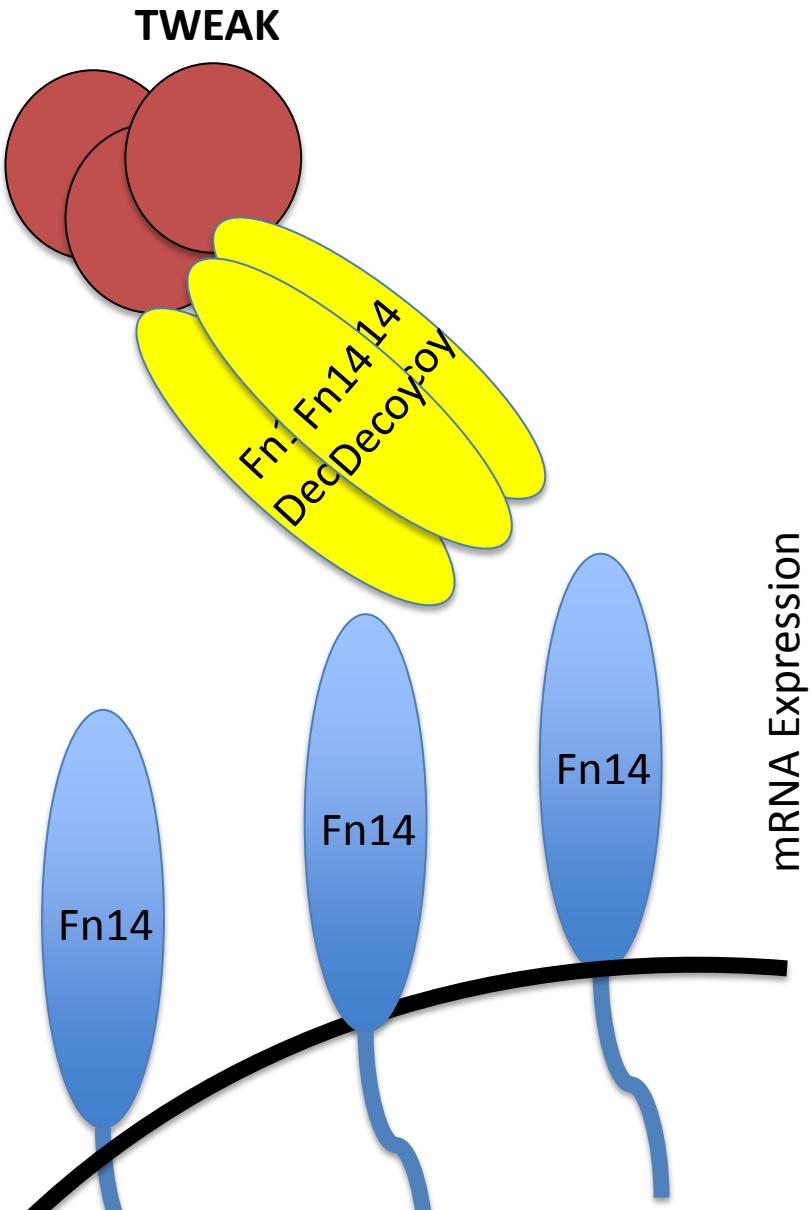


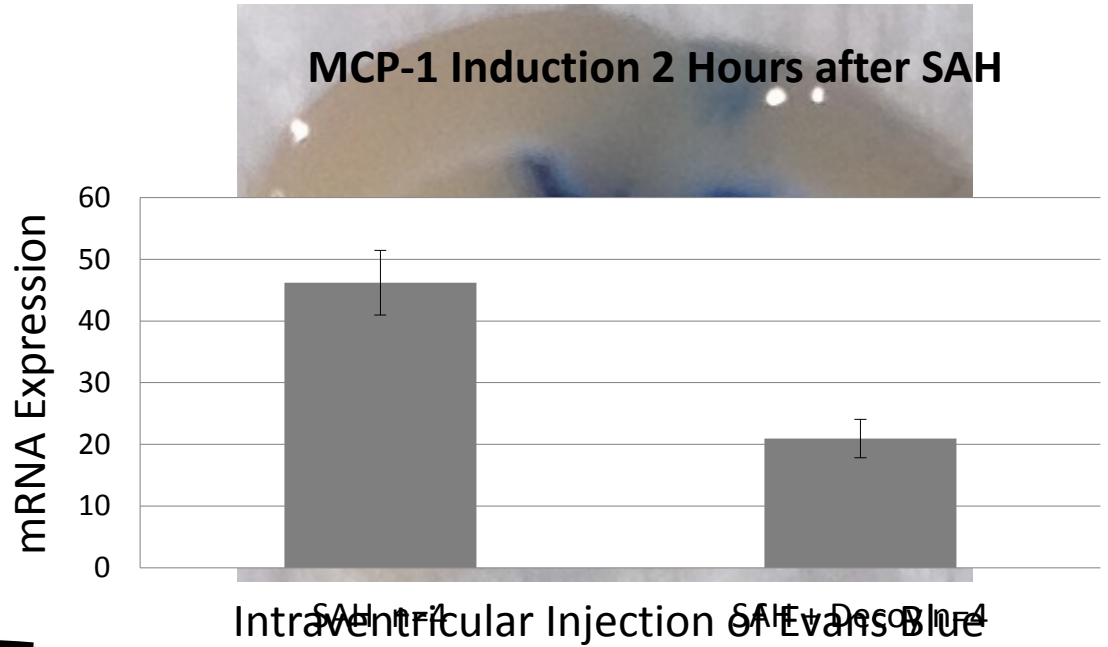
SAH Induces a NF-κB-mediated Inflammatory Reaction

- Monocyte chemorattractant protein-1 (MCP-1) is a proinflammatory chemokine
- MCP-1 and TNFα are NF-κB-mediated



Inhibition of TWEAK/Fn14 Reduces Inflammation after SAH





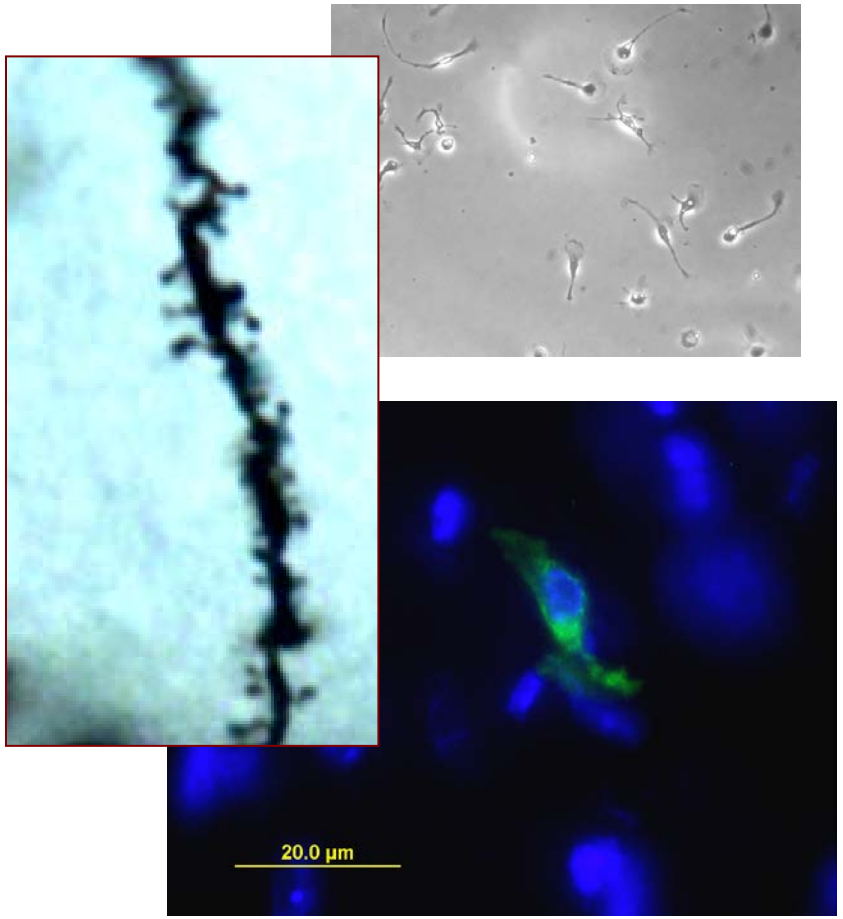
Conclusions

- SAH causes a widespread TWEAK/Fn14-mediated inflammatory reaction in the brain

- Inhibition of TWEAK/Fn14 axis may have a therapeutic effect on early brain injury after SAH

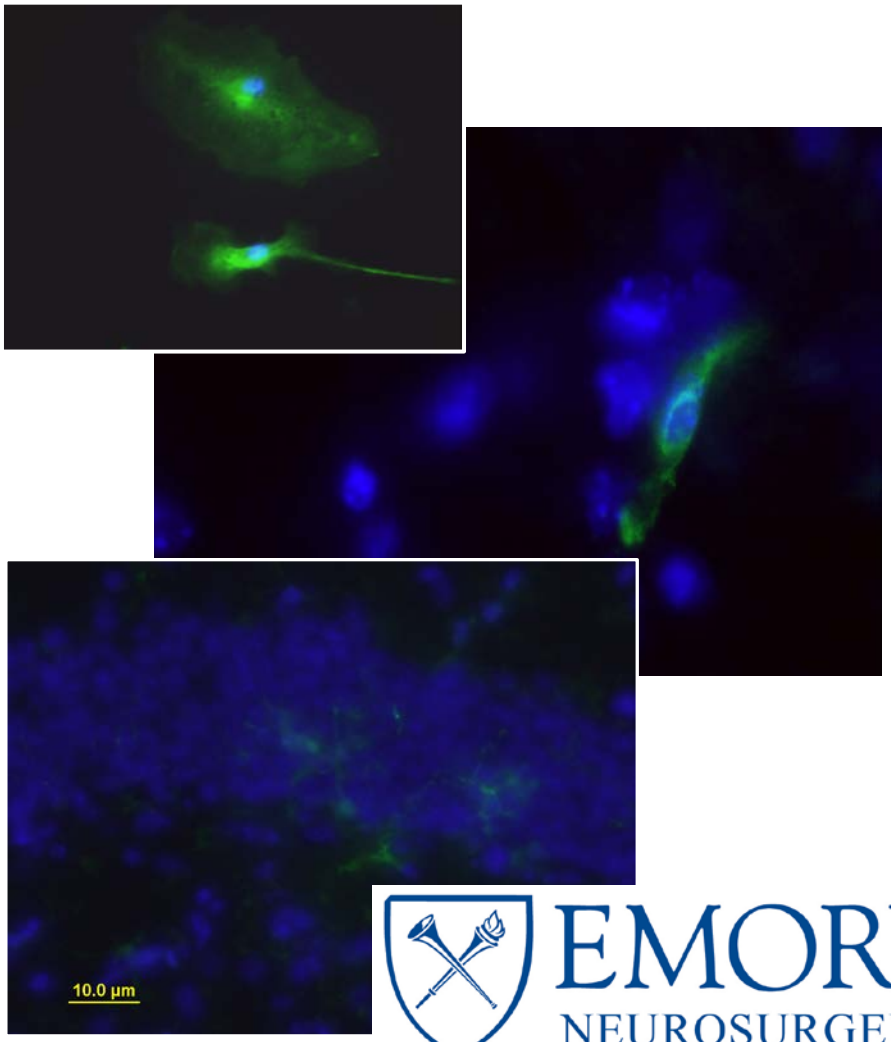
Future Experiments

- Determine the source of TWEAK after SAH
- Inhibition of TWEAK/Fn14 with intravenous inhibitors
- Long-term outcomes with behavioral studies and cell death markers



Acknowledgements

- Yepes Lab @ Emory
- Zipfel Lab @ WashU
- Winkles Lab @ Maryland
- Drs. Oyesiku & Sathian
- NIH & AANS/CNS Cerebrovascular Section



EMORY
NEUROSURGERY