# ADAPTAQUIN NEUROPROTECTION IN A MODEL OF SEVERE SUBARACHNOID HEMORRHAGE

**Nicolas K. Khattar, MD**

Mentors: Michal Hetman, MD, PhD, Scott R. Whittemore, PhD, Robert F. James, MD

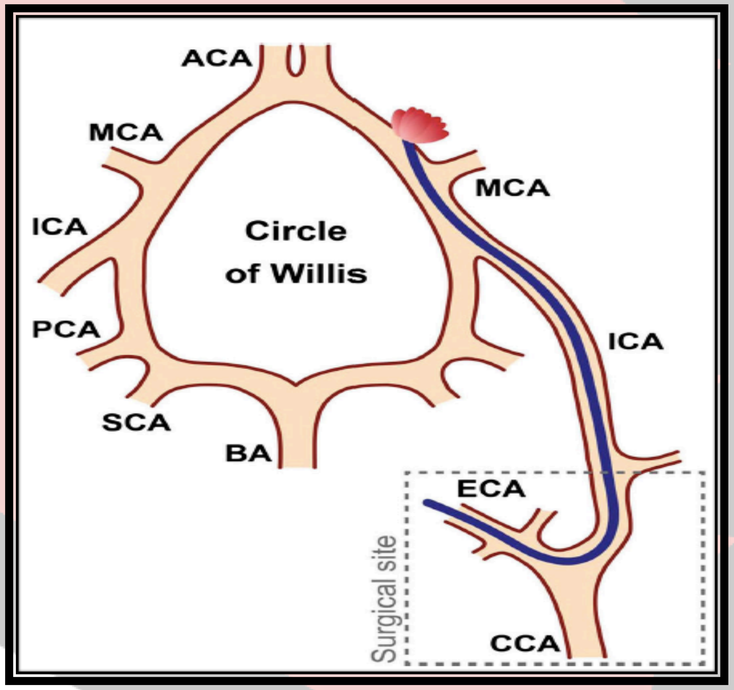
*Department of Neurological Surgery, University of Louisville, Louisville, KY*

## INTRODUCTION

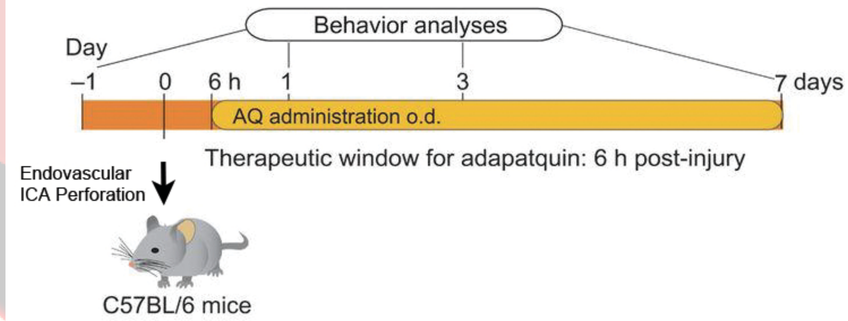
- Aneurysmal subarachnoid hemorrhage (aSAH) comprises 5–7% of all strokes and remains a cause of high mortality and morbidity
- Neurological injury secondary to intracerebral hemorrhage is associated with hemoglobin breakdown
- Hypoxia-inducing factor prolyl hydroxylase domain (HIF-PHD) metallo-enzymes prevent hemoglobin-induced brain injury
- HIF-PHD inhibition suppresses the Activating Transcription Factor 4 (ATF4) ferroptosis-mediated pathway

## HYPOTHESIS

**Adaptaquin could inhibit ferroptosis-mediated neurological injury secondary to aSAH**




*Endovascular perforation model of murine severe subarachnoid hemorrhage. Bühler et al. (2014)*




*Timeline of experiments and behavioral testing. Modified from Karuppagounder et al. (2016)*

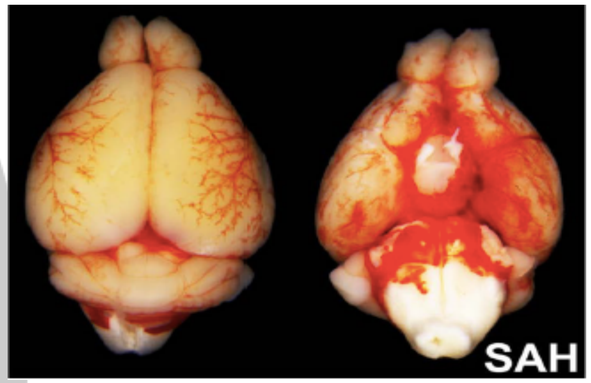
**Adaptaquin** has the potential to **prevent neurological injury** by **inhibiting** direct iron-mediated **ferroptosis**

## EXPERIMENTAL DESIGN

- Determine the efficacy of adaptaquin treatment in different cell types exposed to iron-based injury in subarachnoid hemorrhage including primary cortical neurons, endothelial cells, and smooth muscle cells.
- Determine the dosage, timing, and efficacy of adaptaquin therapy in a mouse model of severe subarachnoid hemorrhage. Adaptaquin treatment could be differentially protective at various times during the course of subarachnoid hemorrhage.
- We will determine the treatment effect observed in the mice at 1, 3 and 7 days with Rotarod and Adhesive removal behavioral tests.

## REFERENCES

1. Bühler D, Schüller K, Plesnila N. Protocol for the Induction of Subarachnoid Hemorrhage in Mice by Perforation of the Circle of Willis with an Endovascular Filament. Translational stroke research. 2014;5(6):653-9.
2. Karuppagounder SS, Alim I, Khim SJ, Bourassa MW, Sleiman SF, John R, et al. Therapeutic targeting of oxygen-sensing prolyl hydroxylases abrogates ATF4-dependent neuronal death and improves outcomes after brain hemorrhage in several rodent models. Sci Transl Med. 2016;8(328):328ra29
3. Karuppagounder SS, Ratan RR. Hypoxia-inducible factor prolyl hydroxylase inhibition: robust new target or another big bust for stroke therapeutics? Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 2012;32(7):1347-61.




*Gross specimen showing severe subarachnoid hemorrhage following ICA perforation. Bühler et al. (2014)*

Take a picture for more information