N-acetyl cysteine targets nuclear envelope-derived, toxic lipids to improve outcomes following hemorrhagic stroke in mice

Ratan Lab
Burke/Cornell Medical Research Institute
White Plains, NY

WICH 2017
N-acetyl cysteine

- FDA labeled indication
  - Acetaminophen overdose
RESEARCH ARTICLE

N-Acetyl Cysteine May Support Dopamine Neurons in Parkinson's Disease: Preliminary Clinical and Cell Line Data

Daniel A. Monti¹, George Zabrecky¹, Daniel Kremens², Tsao-Wei Liang², Nancy A. Wintering¹, Jingli Cai³, Xiantao Wei³, Anthony J. Bazzan¹, Li Zhong¹, Brendan Bowen¹, Charles M. Intenzo⁴, Lorraine Iacovitti³, Andrew B. Newberg¹,³*

¹ Myrna Brind Center of Integrative Medicine, Thomas Jefferson University, Philadelphia, PA, United States of America, ² Movement Disorders Center, Department of Neurology, Thomas Jefferson University, Philadelphia, PA, United States of America, ³ Department of Neuroscience, Thomas Jefferson University, Philadelphia, PA, United States of America, ⁴ Division of Nuclear Medicine, Department of Radiology, Thomas Jefferson University, Philadelphia, PA, United States of America

* Andrew.newberg@jefferson.edu
NAC to mediate its beneficial effects in CNS in preclinical models are variable.

- Lack of understanding of its efficacy in clinically relevant models
- Molecular target of action in mediating these salutary effects
Objective

- To examine the efficacy and mechanism of action of NAC in a mouse model of hemorrhagic stroke.
N-acetyl cysteine protects in in vitro and in vivo models of hemorrhagic stroke.
N-acetyl cysteine protection is independent of bulk iron chelation
N-acetyl cysteine prevents hemin induced death by neutralizing toxic lipids generated via 5-LOX
N-acetyl cysteine alters protein modified by oxidized lipid species
N-acetyl cysteine synergizes with protective prostaglandin, PGE2
Brain hemorrhage

**Arachidonic acid**

- PLA\(_2\)
- Hemin

**Cyclooxygenase pathway**
- Prostaglandins
  - PGE\(_2\)
  - Pro-survival

**Lipoxygenase pathway**
- Leukotrienes
  - LTB\(_4\)
  - Pro-death

**5-LOX**
- Reactive lipid species
  - ATF4
  - Chac1
  - Degradation of GSH
  - Cell death

**N-acetyl cysteine**

- FLAP
- Hemin
Acknowledgements

- Rajiv Ratan
- Lauren Alin
- Yingxin Chen
- David Brand
- Megan Bourassa (Burke/Cornell Medical Research)
- Ginger Milne (Vanderbilt University)
- Victor Darley-Usmar (University of Alabama)
- John Pinto (NYMC)

Support: The Burke Foundation, Sperling Center for Hemorrhagic Stroke Recovery at the Burke Medical Research Institute.