HISTONE DEACEYLASE INHIBITOR, SUBEROYLANILIDE HYDROXAMIC ACID (SAHA) ATTENUATES CEREBRAL EDEMA AFTER TRAUMATIC BRAIN INJURY IN MICE.

S. Quaynor, D. Kimbler, J. Vender, S.Ramesh, and K. Dhandapani

Department of Neurosurgery, Medical College of Georgia Georgia Regents University, Augusta, GA

GRU

GEORGIA REGENTS UNIVERSITY

Introduction

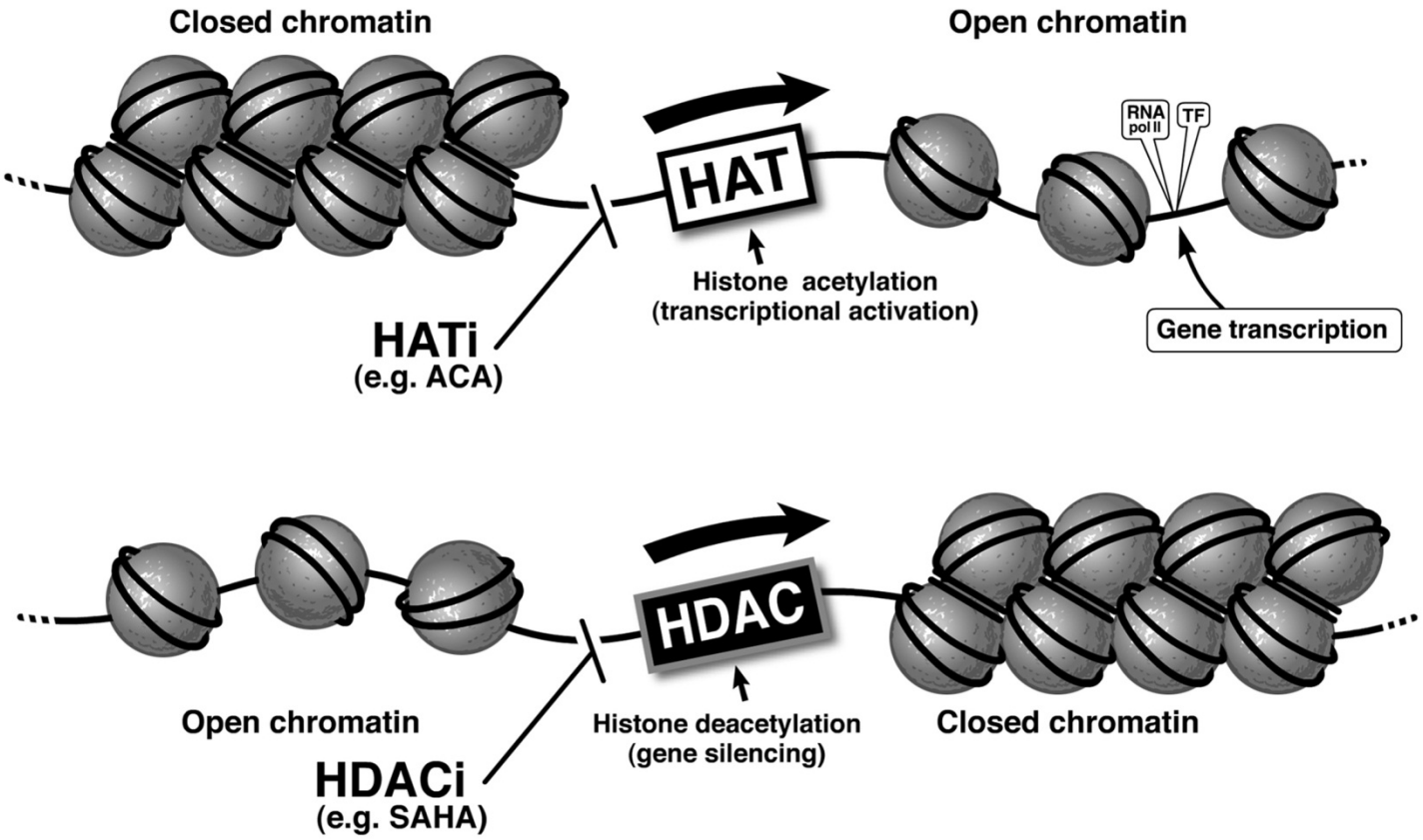
- **Traumatic brain injury (TBI) is a leading cause of death and disability worldwide.**
  - **Mortality rates remain at 25–35% with eighty percent of these deaths due to high intracranial pressure.**
  - **Cerebral edema increases intracranial pressure and contributes to a poor patient prognosis after TBI.**
  - **Unfortunately, surgical treatment options remain limited and medical treatment options are lacking.**
  - **Could HDACi be effective in reducing cerebral edema after TBI?**
    - **Mechanism: Alter the levels Anti-and pro inflammatory markers?**

Hypothesis

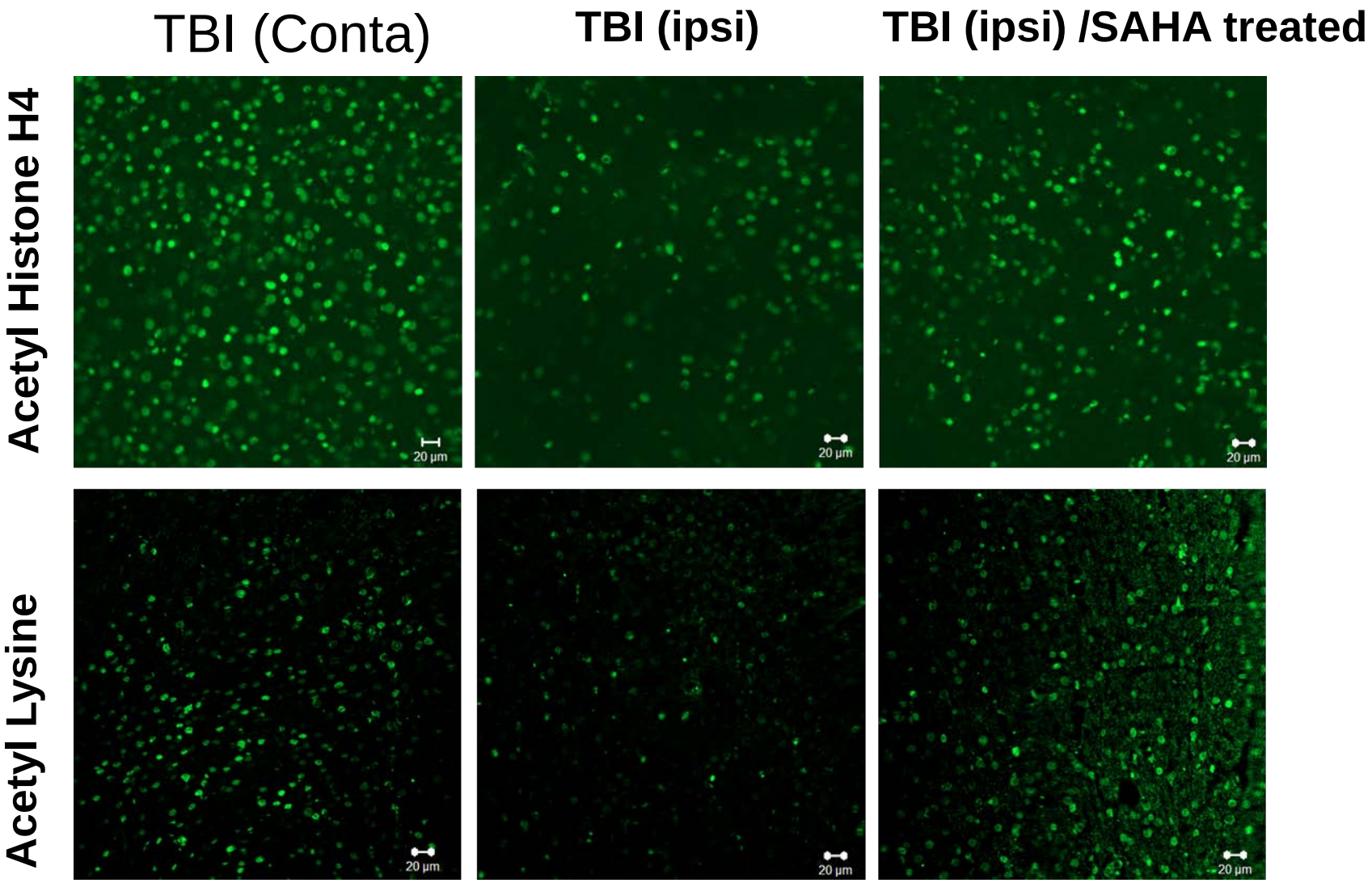
Suberoylanilide hydroxamic acid (SAHA), a FDA-approved pan-histone deacetylase inhibitor (HDACi) will attenuate immune activation and reduce cerebral edema after TBI.

Mechanism of action of SAHA

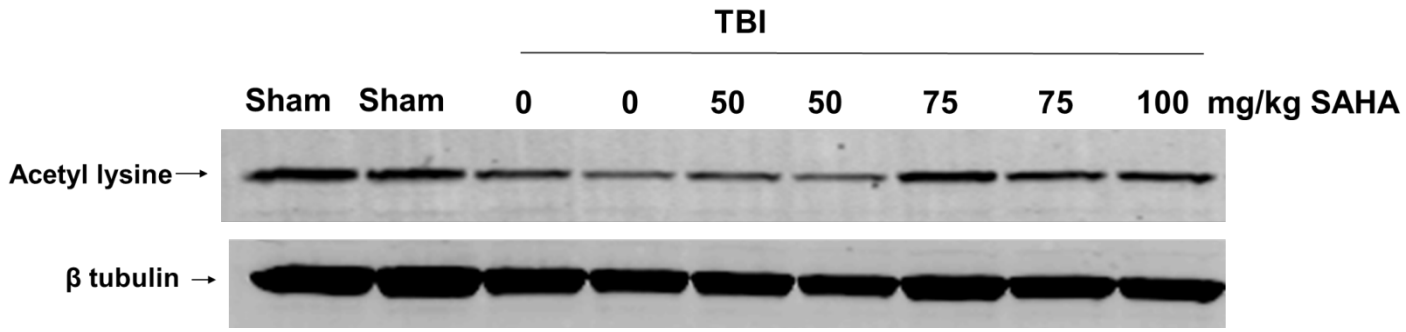
Suberoylanilide hydroxamic acid (SAHA)



SAHA prevented TBI induced hypoacetylation.



Cerebral edema attenuation paralleled prevention of hypoacetylation



After TBI, increasing concentration of SAHA causes increase in Acetyl Lysine expression

Role of inflammatory markers?

- **After brain injuries anti- and pro inflammatory markers are upregulated.**
  - **Normally barely detectable in healthy tissues.**
  - **Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-10 (IL-10), Granulocyte Stimulating Colony Factor (GC-SF) and Tumor Necrosis Factor.**

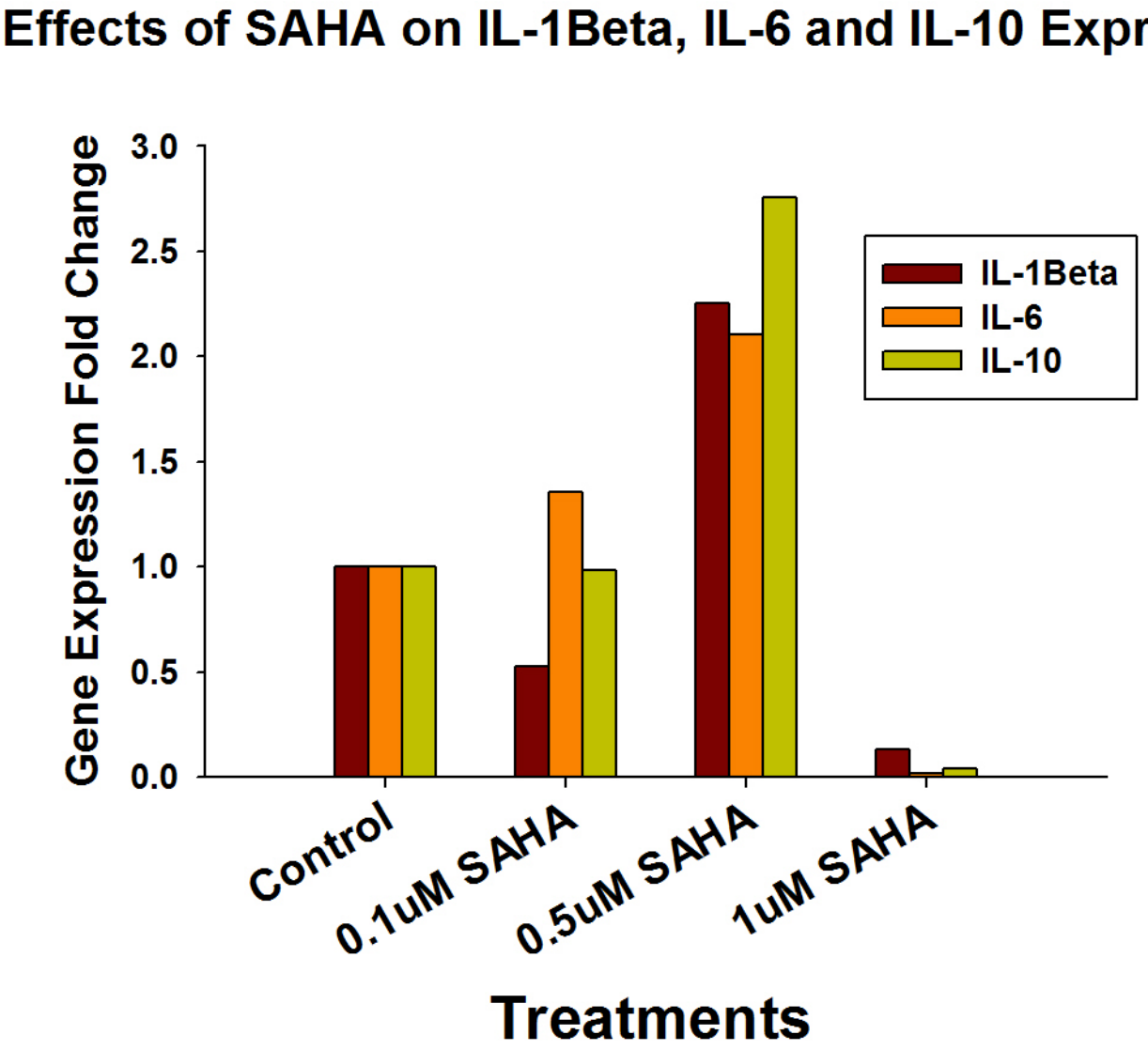
Ziebell et al., Neurotherapeutics, Vol. 7, No. 1, 2010

Brain Injuries: IL-1β, IL-6 and IL-10

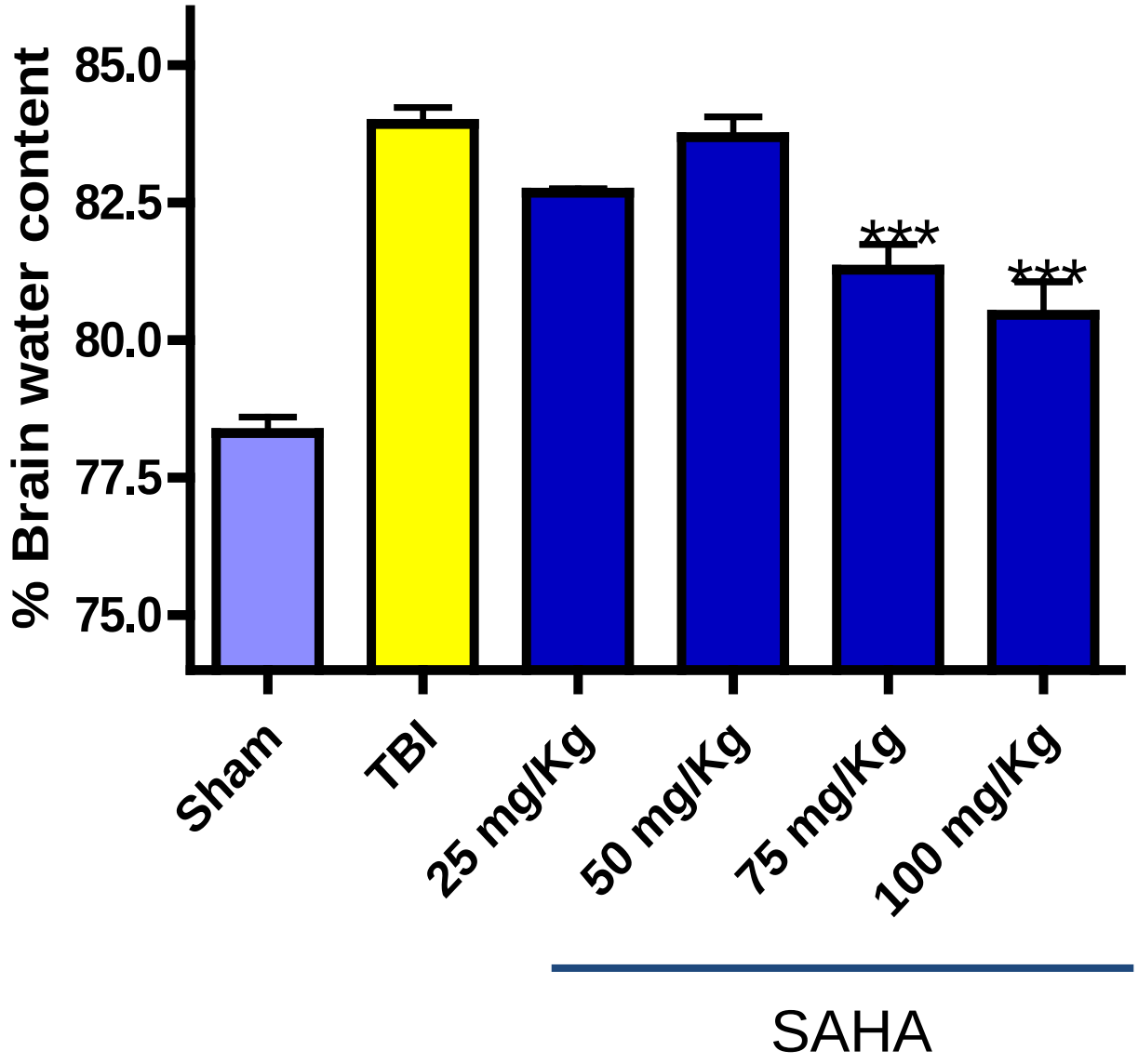
- **IL-1β**
  - **Elevated levels have been in CSF and brain parenchyma within early hours after brain injury**
  - **High levels clinically correlate with elevated ICP and neurological demise after brain injury**
- **IL-6**
  - **Highly elevated in CSF after brain injury**
  - **This increase causes severe blood brain barrier dysfunction**
- **IL-10**
  - **High levels measured in CSF of children with brain injury.**
  - **This increase has been correlated with adverse outcomes.**

Ziebell et al., Neurotherapeutics, Vol. 7, No. 1, 2010

Preliminary Data:



SAHA attenuated cerebral edema following TBI.



Conclusion

- **Preliminary data shows**
  - **At different concentrations, SAHA either increased or decreased the expression of classical inflammatory markers, such as IL1β, IL6 and IL10, in activated macrophage cells *in vitro.***
    - **1uM of SAHA decreases the expression of IL1β, IL6 and IL10.**
  - **HDACi may represent a novel class of drugs to reduce cerebral edema following TBI, in part, via the modulation of immune activation.**

Acknowledgements

- Donald E. Kimbler, Ph.D.
- John R. Vender, M.D.
- Sangeetha Sukumari Ramesh, Ph.D.
- Krishnan M. Dhandapani, Ph.D.
- Department of Neurosurgery, Medical College of Georgia, Georgia Regents University