SANDERS-BROWN CENTER ON AGING

UNIVERSITY OF KENTUCKY

A Novel Class of CNS Drugs Administered Hours Post-Injury Alters Pathology Progression and Improves Neurologic Outcomes in Diffuse Axonal Injury Models

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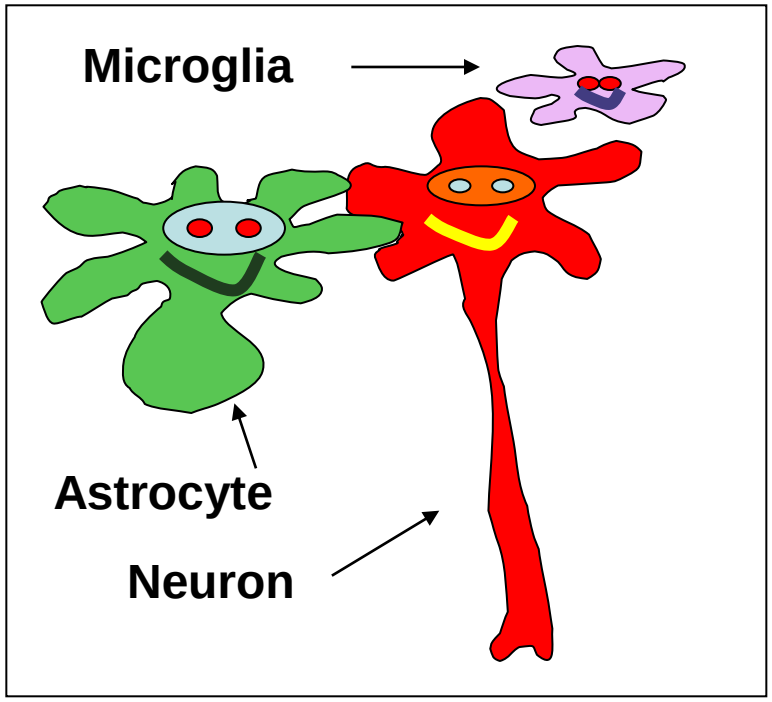
Financial Disclosures: P.I. on funded research in drug discovery for CNS disorders. Northwestern University has filed intellectual property protection and licensed to industry therapeutic candidates

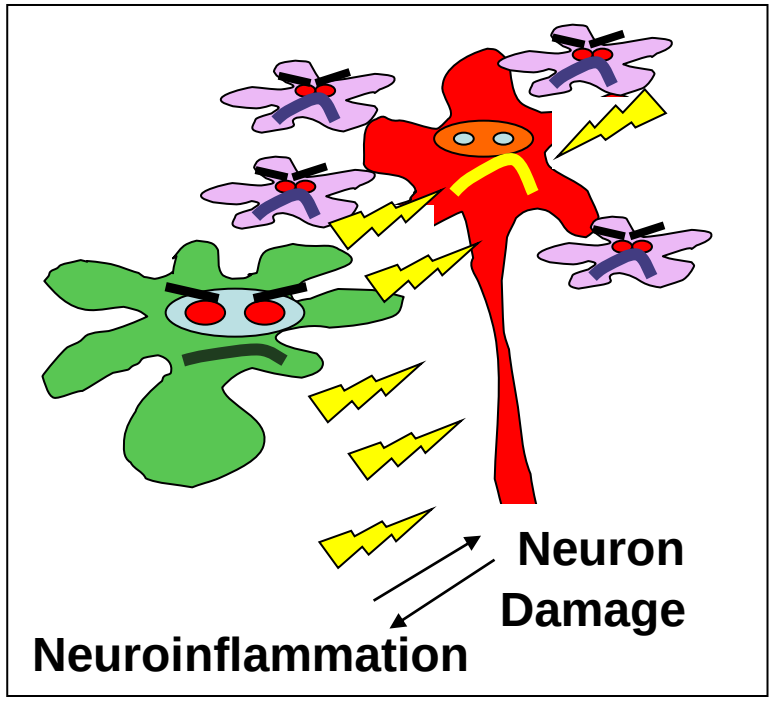
Keystone, Feb 2012

The Janus Face of Glial Activation

Healthy Brain



Neurodegenerative

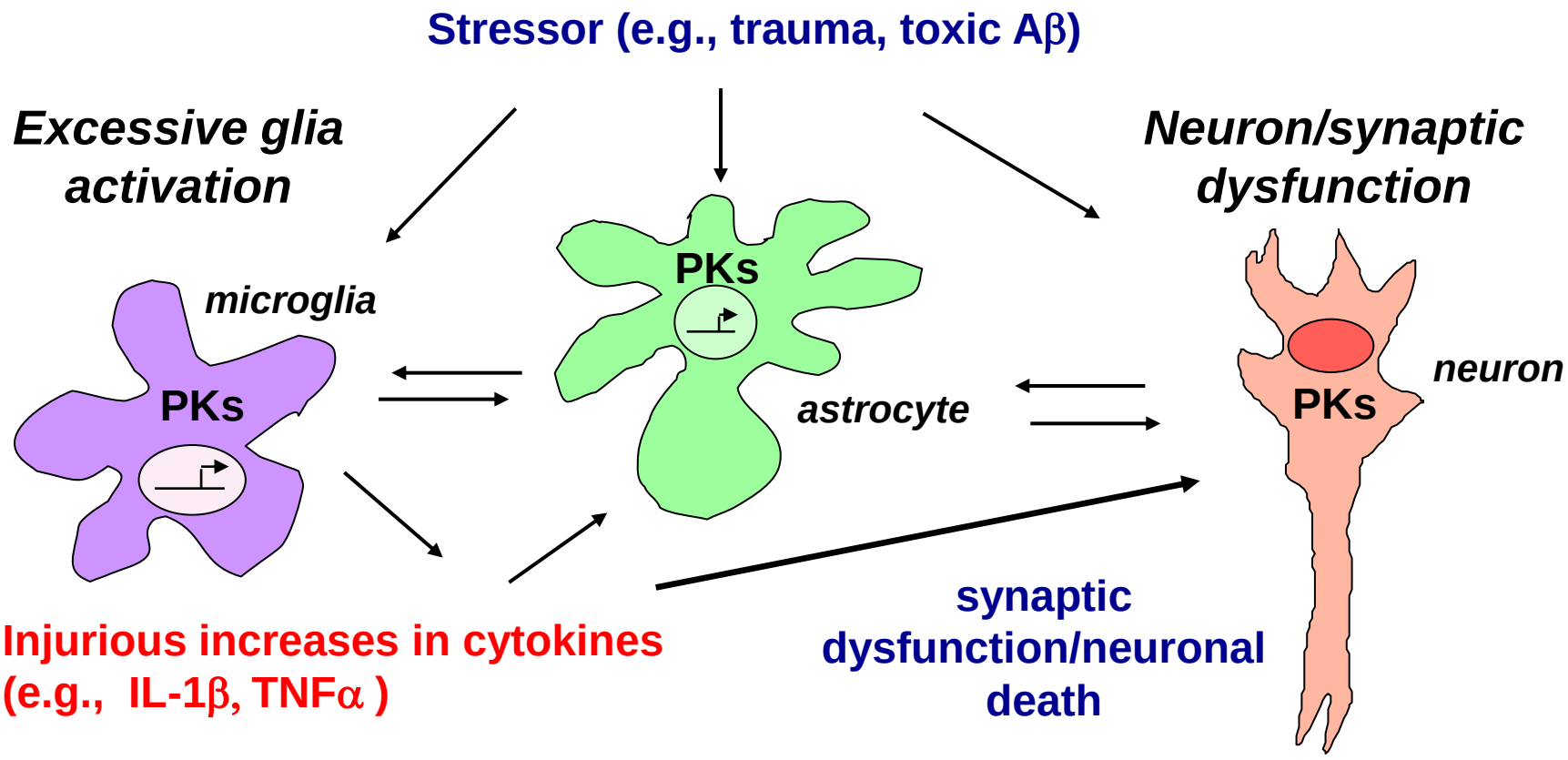


Glia respond to stimuli by undergoing activation ⇨ Normally beneficial

Chronic, unregulated glia activation ⇨ Detrimental neuroinflammation

Targeting the Up-Regulated Cytokine - Synaptic Dysfunction Cycle

Therapeutic Goal: attenuate pathology progression by appropriate dosing with intracellular signal transduction targeted small molecules



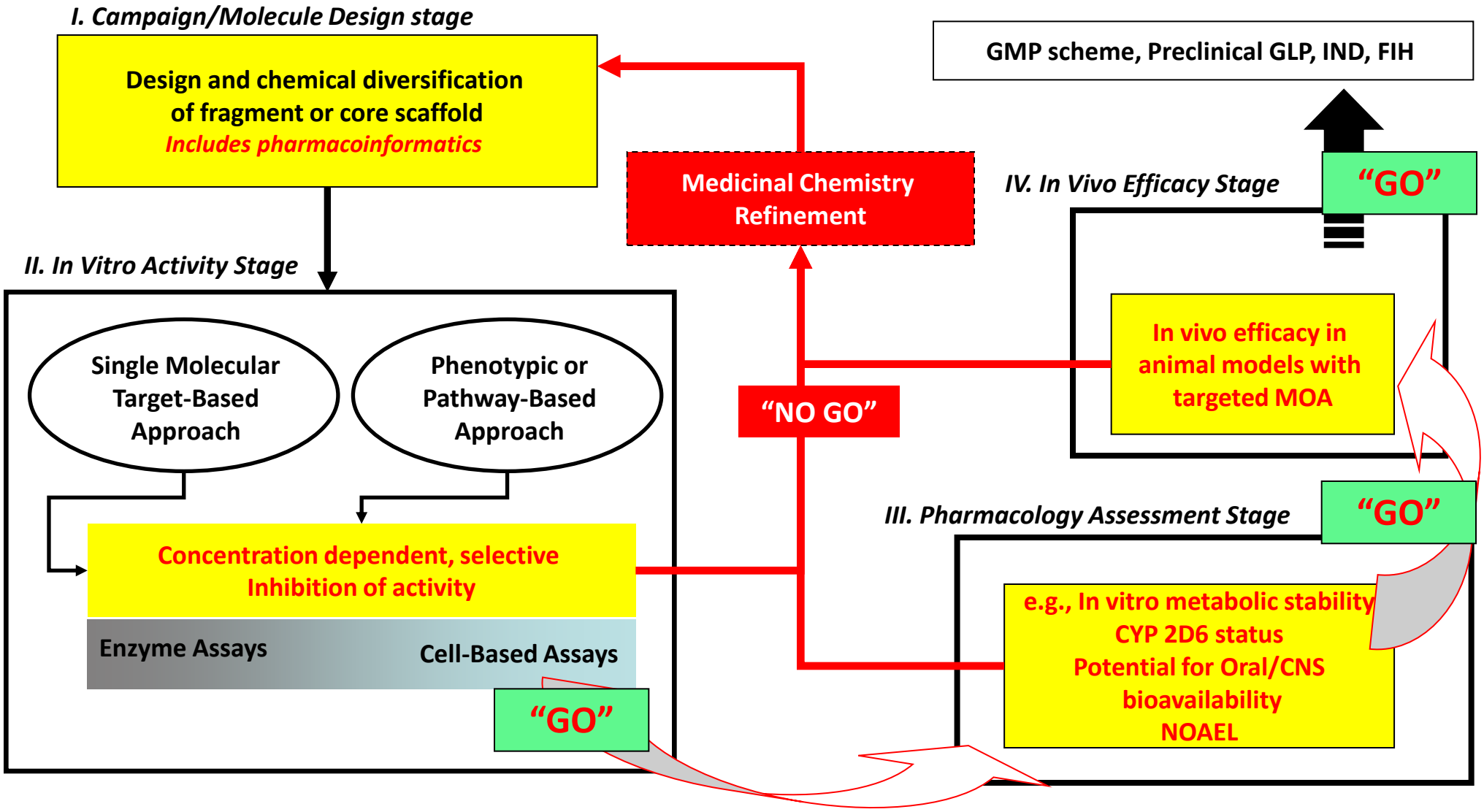
Minokine Class (p38)

Minozac Class

Minokine Class (p38)

DAPK inhibitors

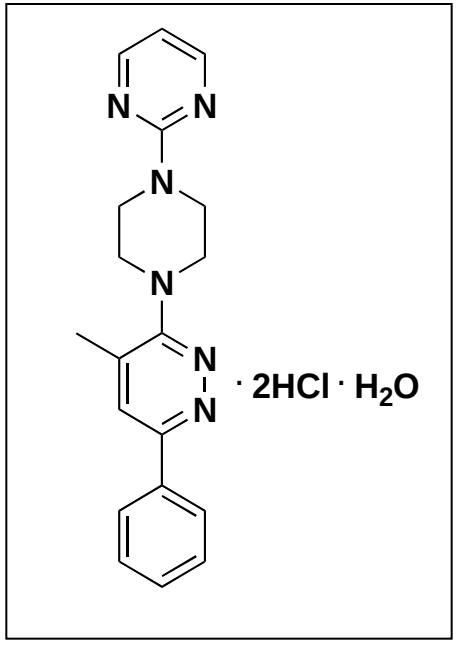
A Staged, Recursive Discovery Engine for Novel, Bioavailable, CNS-penetrant, Stable, Candidate Drugs



Example Novel Candidate with Desired Properties: MW151

Compound is within multi-property range characteristic of successful drugs with high potential for BBB penetration and low potential for key ADMET liabilities

Chico et al., 2009, Nature Rev Drug Discovery 8: 892; *Hu et al., 2007, Bioorg Med Chem Lett 17: 414*



- **MW = 423.34**
- **Aqueous solubility >332 mg/ml**
- **pKa (potentiometric titration): 3.75 ± 0.06**
- **Experimental lipophilicity (octanol/water), LogP = 2.3**
- **Melting point >215°C**
- **Oxidative chemical stability:**
  - **92% remaining-aqueous**
  - **100% remaining-acidic**
  - **74% remaining-basic**

Potential Indications for MW151

Observation:

- **Extensive animal studies and clinical observations suggest that up-regulated proinflammatory cytokine production contributes to neuropathological sequelae.**

Question:

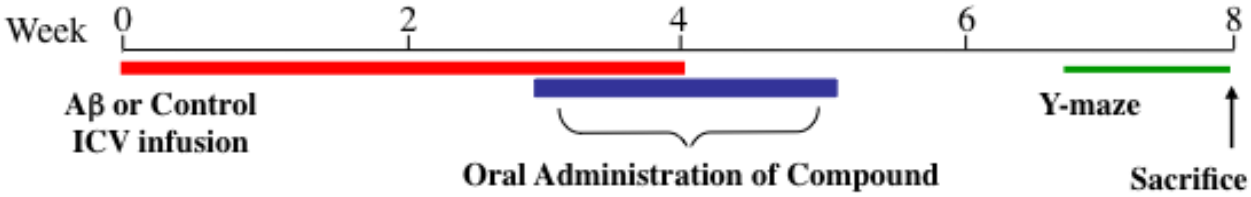
- **Is MW151 effective in animal models of CNS disorders where proinflammatory cytokine up-regulation is a characteristic of disease progression?**

Approach:

- **Test efficacy in animal models using consideration of therapeutic time windows.**

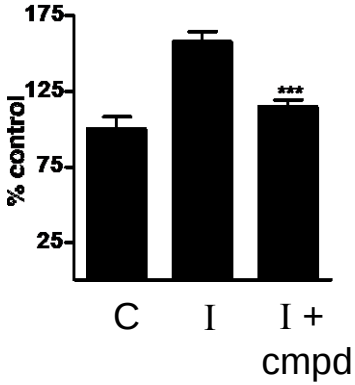
In vivo Efficacy Screen in AD Mouse Model

oral administration of MW151 attenuates human Aβ-induced brain injury

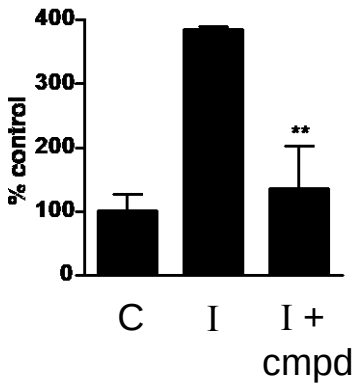


Compound is efficacious *in vivo* at low doses

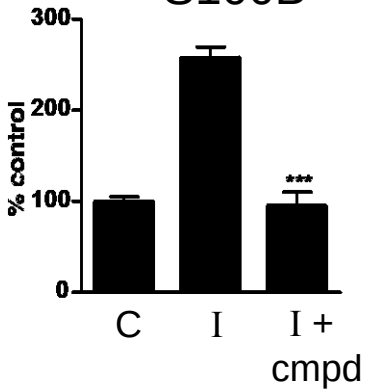
IL-1β



TNFα

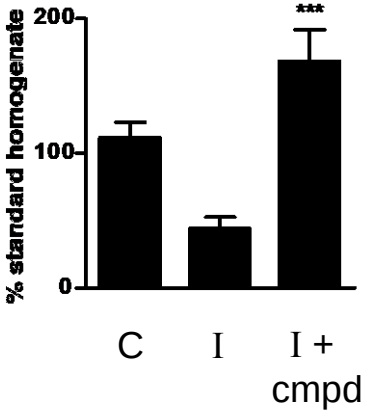


S100B

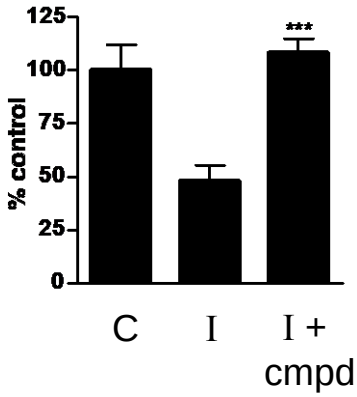


Attenuation of excessive proinflammatory cytokine production towards basal, and reduction of synaptic dysfunction and hippocampus-dependent behavior deficits

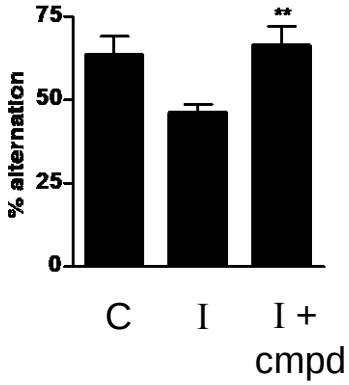
Synaptophysin



PSD-95



Y maze



MW151 (2.5 mg/kg/day) or saline vehicle administered by oral gavage once daily for 2 weeks, once daily Y-maze for 10 days prior to sacrifice at day 60; cytokines and synaptic proteins measured in hippocampal extracts.

Hu et al., 2007, Bioorg Med Chem Lett 17: 414

Potential Indications for MW151

Observation:

- **MW151 is efficacious in models of AD-relevant pathophysiology, when administered at a low dose (2.5 mg/kg/day) in a therapeutically relevant time window, after the start of injury.**

Question:

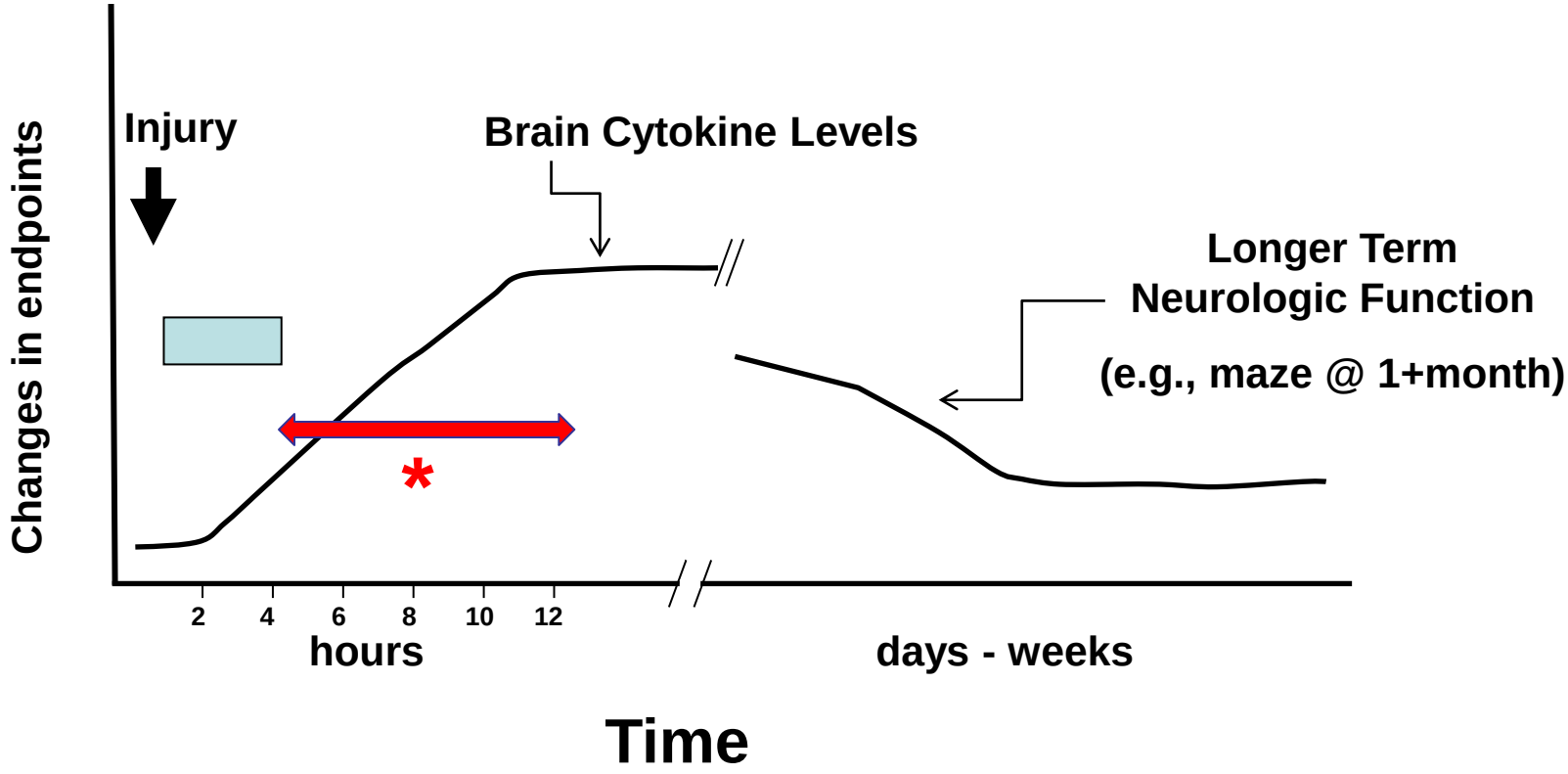
- **Is MW151 effective in an animal model of an acute CNS injury where proinflammatory cytokine up-regulation is a characteristic of pathology progression and later neurologic outcomes?**

Approach:

- **Test efficacy in a model of TBI using consideration of therapeutic time windows.**

In vivo Efficacy Screen:
rationale in closed head TBI model screening

***** *Does post-injury compound treatment within delayed window yield modulation of the targeted process and the desired morbidity outcomes?*

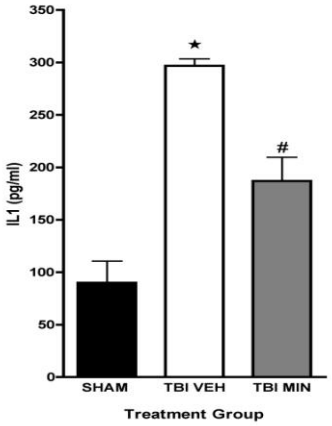


= time gap of injury-to-trauma center

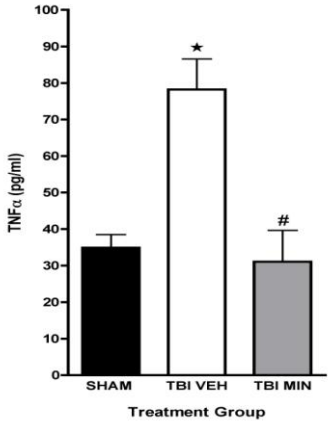
MW151 Post-Injury Treatment in Cortical Impact TBI Model of Diffuse Axonal Injury is Efficacious

addresses time window and yields pathology progression modification

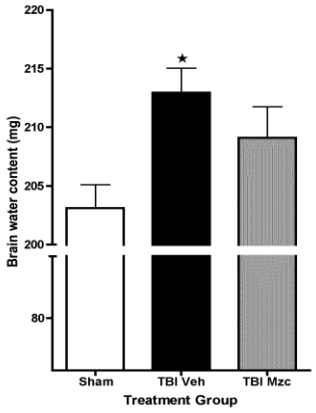
IL-1β



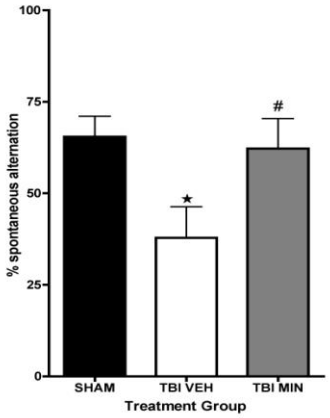
TNFα



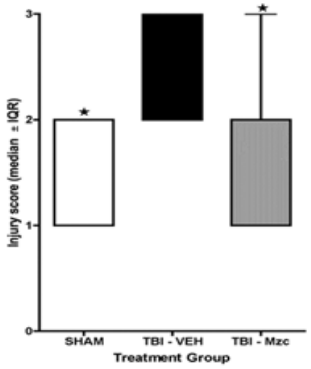
Edema

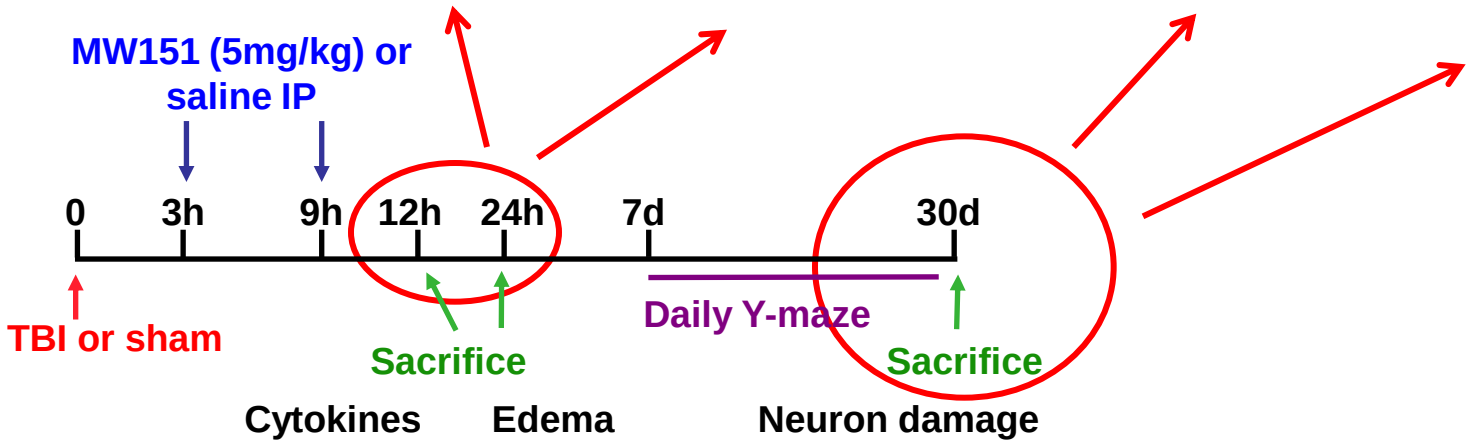


Y maze



Neuron damage

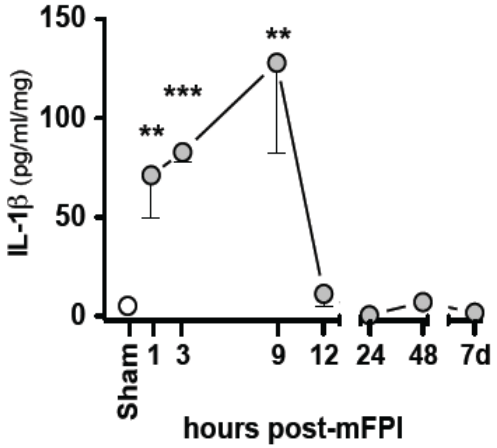




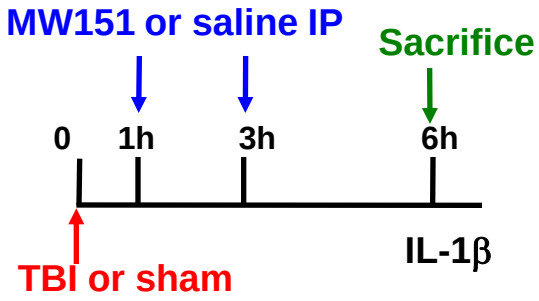
Lloyd et al., 2008, J Neuroinflammation 5:28

Post-Injury Treatment in a Midline Fluid Percussion TBI Model of Diffuse Axonal Injury is also Effective

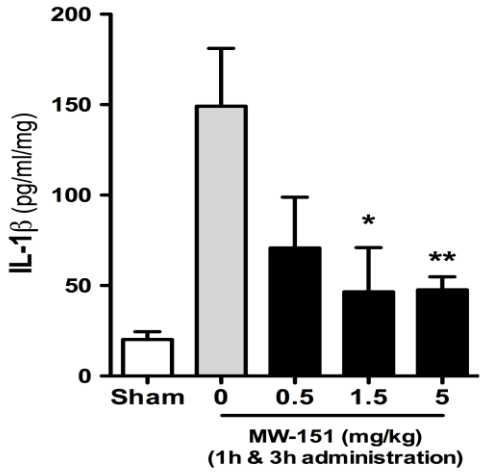
A. Cytokine surge after TBI

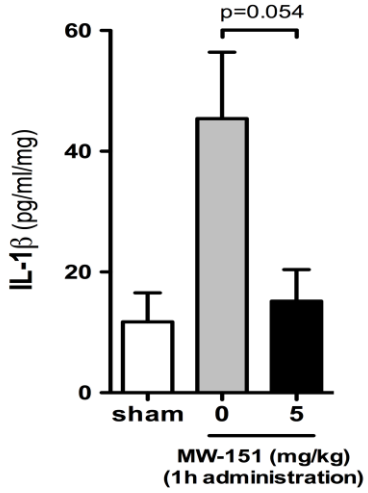


B. Therapeutic paradigm

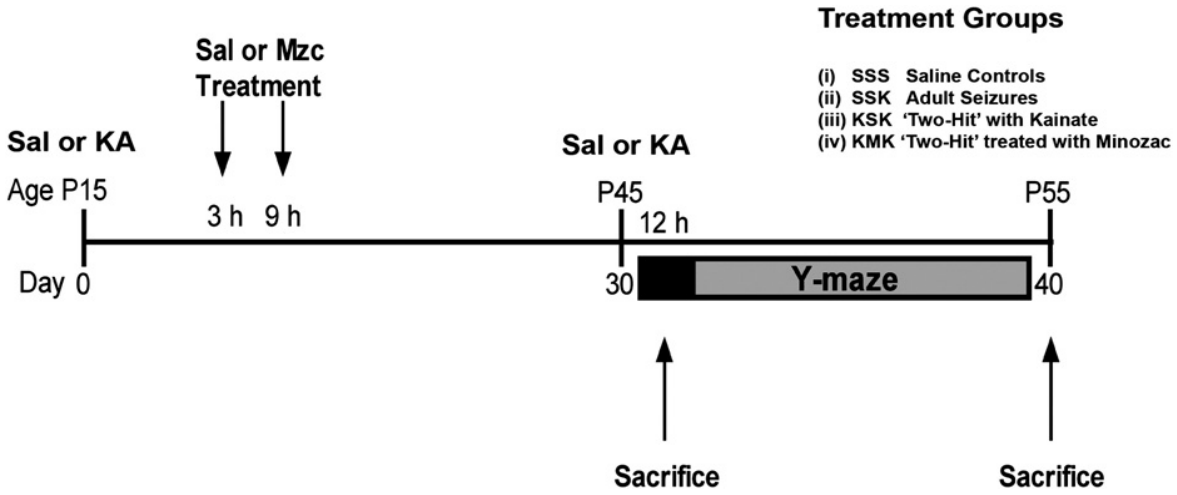


C. MW151 suppresses injury-induced brain IL-1β levels



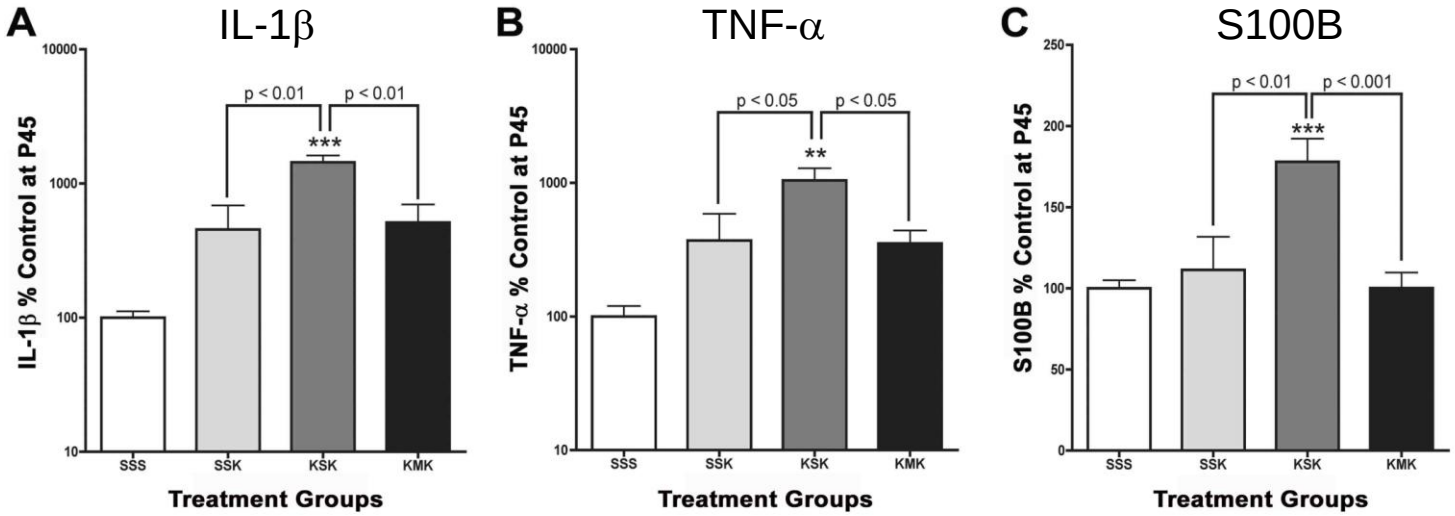


MW-151 is efficacious in “two-hit” seizure model



MW-151 treatment after the 1st hit prevented the enhanced increase in cytokine levels at P45.

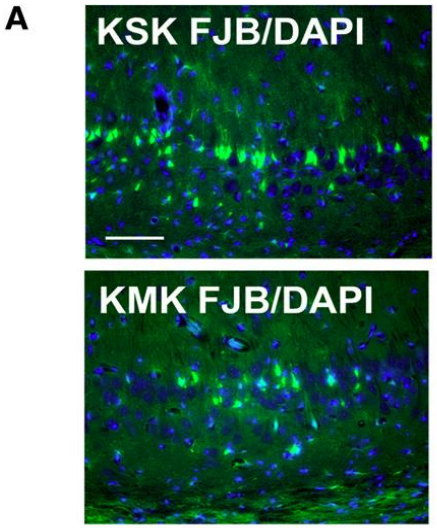
Treatment with saline or Mzc following early-life seizures (5 mg/kg i.p. at 3h & 9h after injury). Animals allowed to recover for 30d, then administered 2nd hit of KA or saline.



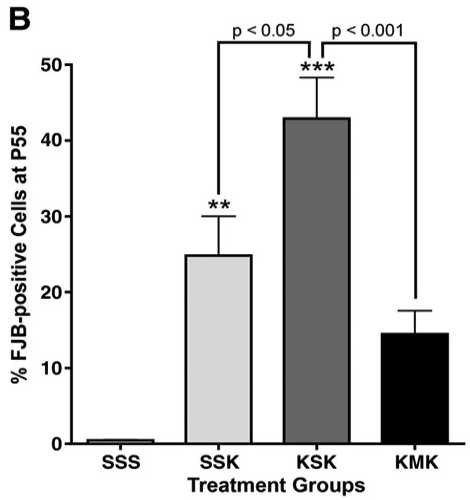
Somera-Molina et al., 2009, Brain Res. 1282: 162.

MW-151 is efficacious in “two-hit” seizure model

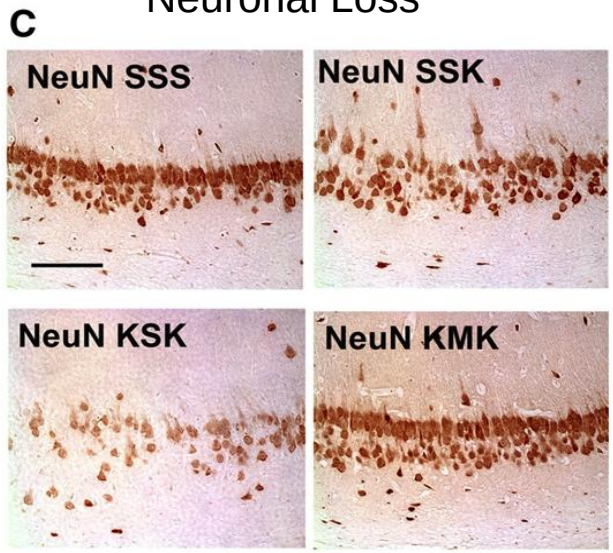
MW-151 treatment after early-life seizures prevents the increased neuronal injury, susceptibility to seizures, and neurobehavioral impairment induced by a second hit in adulthood.

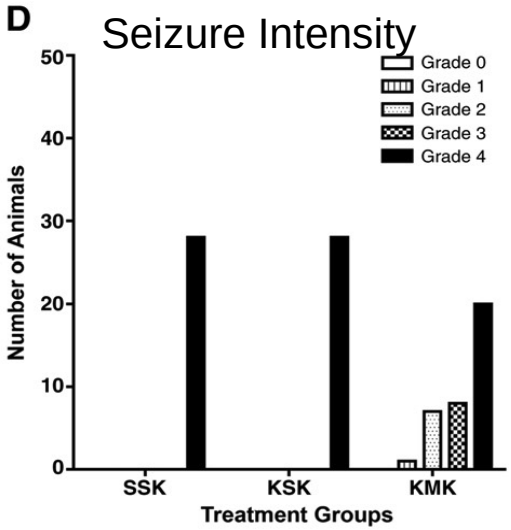


Neuronal Injury

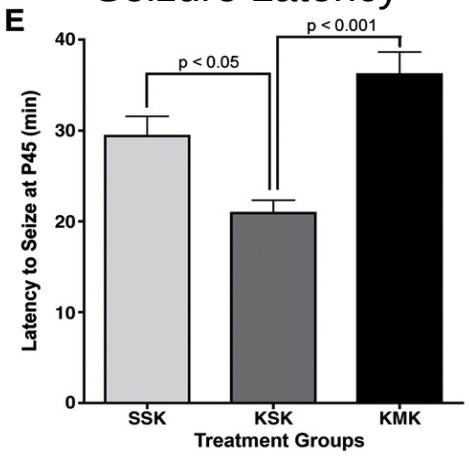


Neuronal Loss

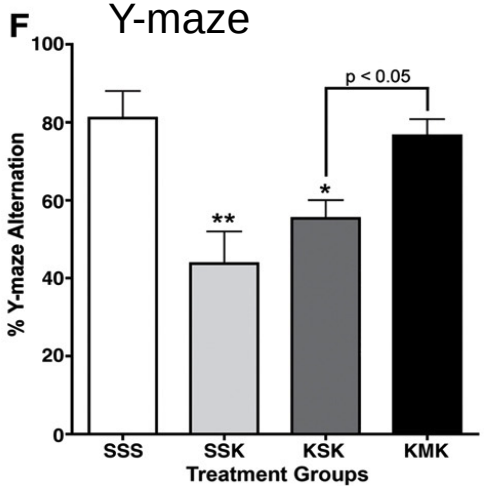




Seizure Latency



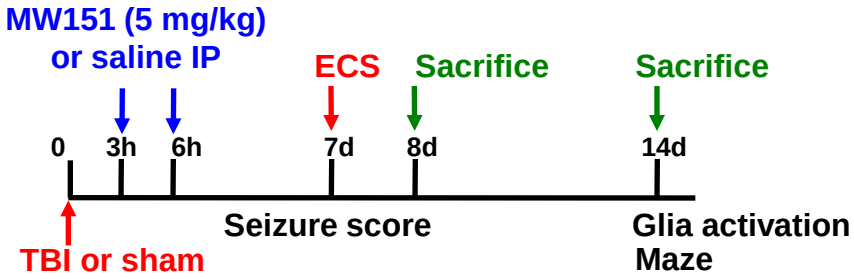
Y-maze



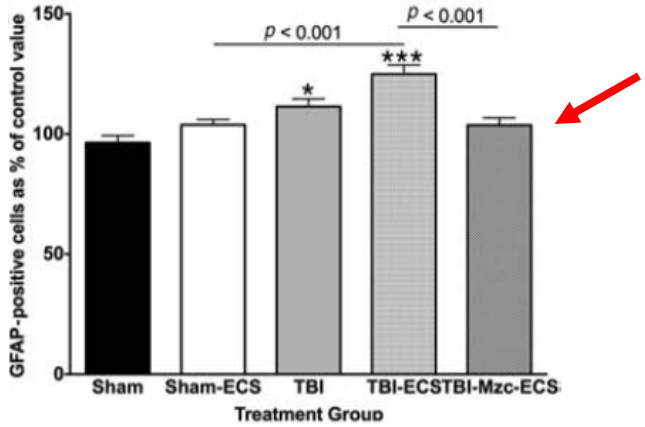
Somera-Molina et al., 2009, Brain Res. 1282: 162.

MW151 is Efficacious in "Two-Hit" TBI-induced Epilepsy Susceptibility Model (Electroconvulsive Shock)

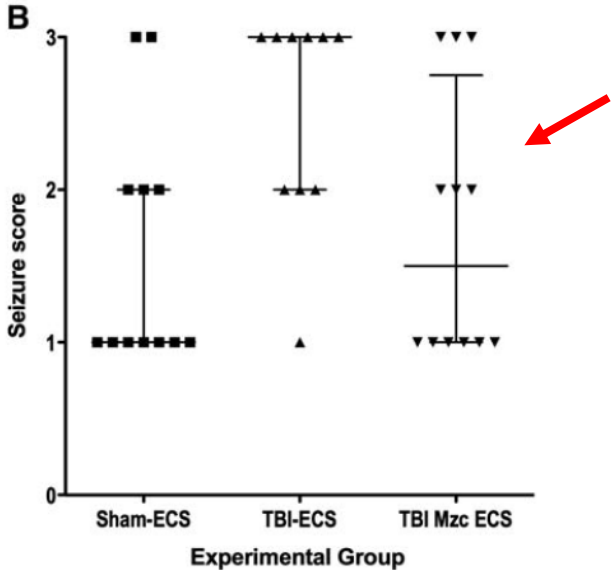
MW151 treatment after 1st hit (TBI) prevents increased seizure susceptibility after 2nd hit (ECS).



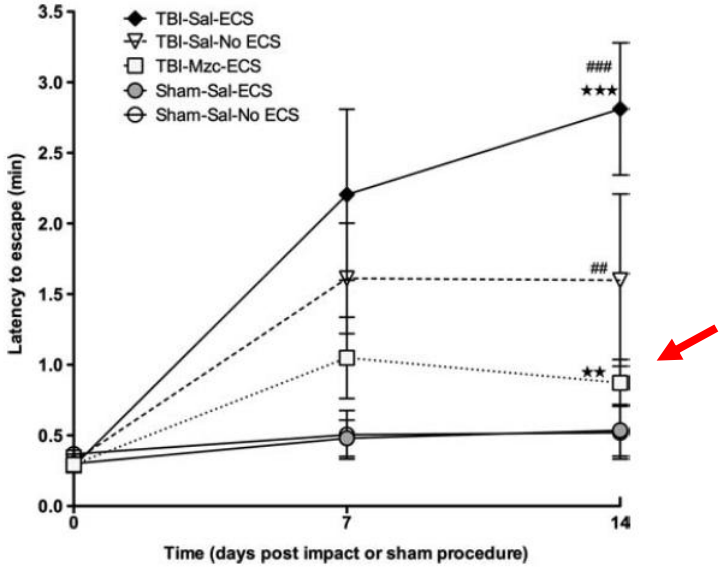
GFAP- 14d



Seizure score



Barnes maze



Chrzaszcz et al. (2010) J Neurotrauma 27: 1283-1295

MW151 Effective in Animal Models of Multiple CNS Disorders where Glia Activation/Inflammatory Cytokines Contribute to Pathophysiology

- **AD-relevant pathology models:**
  - Hu et al., 2007, Bioorg Med Chem Lett 17:414
  - AD Tg (APP/PS1 KI) unpublished
- **TBI models of diffuse axonal injury:**
  - Lloyd et al., 2008, J Neuroinflammation 5:28
  - mFPI unpublished
- **EAE model:**
  - Karpus et al., 2008, J Neuroimmunology 203:73
- **Seizure-induced neurologic sequelae:**
  - Somera-Molina et al., 2007, Epilepsia 48:1785
- **Two-hit models:**
  - Somera-Molina et al., 2009, Brain Res. 1282:162 (KA, KA)
  - Chrzaszcz et al., 2010 J. Neurotrauma 27:1283 (TBI, ECS)

Summary and Conclusions

- **Therapeutic intervention with MW151 in clinically relevant time windows attenuates the inflammatory cytokine up-regulation associated with synaptic dysfunction, with resultant improvement in neurologic and cognitive outcomes in diverse animal models of brain injury.**

- **Two-hit model data raise the possibility that intervention in with this new class of selective attenuators of glia activation might attenuate later in life susceptibility to other brain disorders.**

- **Novel, orally active, brain-penetrant drug candidates are available for clinical development into potential disease-modifying therapies for multiple CNS disorders.**

Acknowledgements

Current group members:

Aaron Bachstetter

Edgardo Dimayuga

Danielle Goulding

Bob Sompol

Bin Xing

Rachel Rowe

Former:

MaryAnn Chrzaszcz

Jeffrey Craft

Tina Dragisic

Eric Lloyd

Kathleen Somera-Molina

Charu Venkatesan

Collaborators:

D. Martin Watterson, NU

Mark Wainwright, NU

William Karpus, NU

Jonathan Lifshitz, UK

Sally Frautschy, UCLA

Funding:

NIH (NIA and NINDS), AHAF, ADDF, Alzheimer's Association Zenith Award, Lyndsey Whittingham Foundation

National Institute of Neurological Disorders and Stroke
National Institutes of Health

National Institute on Aging

AMERICAN HEALTH ASSISTANCE FOUNDATION

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