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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The Janus Face of Glial Activation

Healthy Brain

Neurodegenerative

Glia respond to stimuli by undergoing activation

Chronic, unregulated glia activation

Normally beneficial

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

Stressor (e.g., trauma, toxic Aβ)

- Excessive glia activation
- Injurious increases in cytokines (e.g., IL-1β, TNFα)

PKs

- microglia
- astrocyte
- neuron

Neuron/synaptic dysfunction

- synaptic dysfunction/neuronal death

Minokine Class (p38)

Minozac Class

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

I. Campaign/Molecule Design stage
- Design and chemical diversification of fragment or core scaffold
  - Includes pharmacoinformatics

II. In Vitro Activity Stage
- Single Molecular Target-Based Approach
- Phenotypic or Pathway-Based Approach
  - Concentration dependent, selective inhibition of activity
    - Enzyme Assays
    - Cell-Based Assays

III. Pharmacology Assessment Stage
- GMP scheme, Preclinical GLP, IND, FIH
- In vivo efficacy in animal models with targeted MOA
  - e.g., In vitro metabolic stability
    - CYP 2D6 status
    - Potential for Oral/CNS bioavailability
    - NOAEL

IV. In Vivo Efficacy Stage
- "GO"
- "NO GO"
- "GO"
- "NO GO"
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): $3.75 \pm 0.06$
- 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

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

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

![Graph showing changes in endpoints over time.](image)

- Time gap of injury-to-trauma center
- Long-term neurologic function (e.g., maze @ 1+month)
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

MW151 (5mg/kg) or saline IP

TBI or sham

Sacrifice

Cytokines

Edema

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.
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).

MW151 (5 mg/kg) or saline IP

<table>
<thead>
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<th>Time</th>
<th>TBI or sham</th>
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<th>Sacrifice</th>
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Seizure score

GFAP- 14d

Barnes maze

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.
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