# Novel Class of Small Molecule Protein Kinase Inhibitors

Published date: Nov. 3, 2014

## Technology description

A family of pyridazine compounds that modulate intracranial inflammatory responses following CNS insults such as diverse pathogenic stimuli, physical force trauma, brain hemorrhage, or complications of major surgeries. #therapeutics #CNS #smallmolecule

Northwestern researchers have developed a family of pyridazine compounds that modulate intracranial inflammatory responses following CNS insults such as diverse pathogenic stimuli, physical force trauma, brain hemorrhage, or complications of major surgeries. Proinflammatory mediators are known to contribute to pathologic processes including cerebral edema, long-term neuronal dysfunction and cognitive impairment. Therefore, preserving neurons during such proinflammatory processes would improve neurocognitive outcomes and enhance quality of life in affected individuals. The team of researchers have shown that these pyridazine compounds are able to suppress cytokine induction from activated microglia in culture like tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), monocyte-chemoattractant factor (MCP-1), and interleukin-6 (IL-6). These compounds were tested in three established rodent models of chronic neuroinflammatory diseases: (1) an amyloid beta infusion model of Alzheimer's Disease; (2) a closed-head injury model of traumatic brain injury; and (3) a clostridial collagenase-induced intracerebral hemorrhage model. In these models, they confirmed that treatment with the pyridazine compounds results in a significant reduction in cerebral edema and a remarkable improvement in both motor skills and neurocognitive outcomes. In addition, histological and biochemical studies show reduced hippocampal glial activation, strongly suggesting an in vivo reduction in neuroinflammation. These results serve as potential indications for these compounds. IND enablement studies showed no toxicology with a consistent pharmacokinetic profile across wide range of doses in different species and healthy humans.

## Publications

Hu W, Ralay Ranaivo H, Craft JM, Van Eldik LJ, Watterson DM (2005) Validation of the neuroinflammation cycle as a drug discovery target using integrative chemical biology and lead compound development with an Alzheimer's disease-related mouse model. Current Alzheimer Research. 2: 197-205.

Hu W, Ranaivo HR, Roy SM, Behanna HA, Wing LK, Munoz L, Guo L, Van Eldik LJ, and Watterson DM (2007) Development of a Novel Therapeutic Suppressor of Brain Proinflammatory Cytokine Up-

Regulation That Attenuates Synaptic Dysfunction and Behavioral Deficits. Bioorganic & Medicinal Chemistry Letters. 17: 414-418.

Ranaivo HR, Craft JM, Hu W, Guo L, Wing LK, Van Eldik LJ and Watterson DM (2006) Glia as a Therapeutic Target: Selective Suppression of Human Amyloid-beta-Induced Upregulation of Brain Proinflammatory Cytokine Production Attenuates Neurodegeneration. Journal of Neuroscience. 26: 662-670.

Lloyd E, Somera-Molina K, Van Eldik LJ, Watterson DM, Wainwright MS (2008) Suppression of acute proinflammatory cytokine and chemokine upregulation by post-injury administration of a novel small molecule improves long-term neurologic outcome in a mouse model of traumatic brain injury. Journal of Neuroinflammation. 5: 28.

## Application area

CNS Therapy (Alzheimer's Disease, Traumatic Brain Injury and Intracerebral Hermorrhage)

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