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## **SM07883, a Novel, Potent, and Selective Oral DYRK1A Inhibitor, Reduces Neuroinflammatory Responses in Mouse Models**

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**Background:** Neuroinflammation is a hallmark of many neurological disorders, including Alzheimer's disease. SM07883, an oral, brain-penetrant DYRK1A inhibitor, reduced tau and amyloid pathology and gliosis in neurodegenerative mouse models. This study assessed the potential of SM07883 to modulate innate immunity *in vitro* and *in vivo*.

**Methods:** Cytokine secretion and NO<sub>2</sub><sup>-</sup> production were measured in LPS-activated BV2 microglial cells by electrochemiluminescence/multiplex assays and the Griess reaction, respectively. Cell phenotype was evaluated by flow cytometry. STAT3 phosphorylation and translocation were analyzed by Western blot and imaging. *In vivo*, inflammation was examined in brains from balb/c mice administered SM07883 (10 mg/kg, QD) or vehicle and acutely (single intracerebral injection) or chronically (low-dose intraperitoneal injection) challenged with LPS. Gliosis was analyzed by immunohistochemistry in brains and spinal cords from SM07883- and vehicle-treated 3xTg-AD (5 mg/kg, QD, 6 months) and JNPL3 (3 mg/kg, QD, 3 months) mice.

**Results:** *In vitro*, SM07883 inhibited production of pro-inflammatory mediators, such as TNF- $\alpha$  (EC<sub>50</sub>=71 nM) and NO<sub>2</sub><sup>-</sup>, and downregulated microglial activation markers in BV2 cells compared with control. Also, dose-dependent STAT3 phosphorylation reduction and nuclear translocation were observed with SM07883 treatment versus control. *In vivo*, SM07883 treatment reduced LPS-induced acute and chronic neuroinflammation, as illustrated by significantly reduced pro-inflammatory mediators in brains from mice treated with SM07883 versus vehicle. Similarly, SM07883 treatment reduced CNS gliosis in 3xTg-AD and JNPL3 mice compared with vehicle.

**Conclusion:** SM07883 potently reduced glial activation and inflammatory mediator production in preclinical models. SM07883 represents a potential treatment for neurodegenerative disorders; a clinical trial is ongoing.