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Anti-inflammatory Effects of SM07883, a Novel, Potent, and Selective Oral DYRK1A Inhibitor in Mouse Models of Neuroinflammation

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Background: Neuroinflammation contributes to many neurodegenerative disorders, including Alzheimer's disease and Multiple sclerosis. Inhibition of dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) activity reduced tau and amyloid pathology as well as associated gliosis in AD transgenic mice. This study dissected the mechanisms by which SM07883, an oral DYRK1A inhibitor, inhibited neuroinflammation *in vitro* and in mouse models with innate and adaptive CNS immune responses.

Methods: To measure inflammation *in vitro*, cytokine concentrations were measured with MSD platform in supernatants from BV2 microglial cells and primary mouse astrocytes challenged by lipopolysaccharide (LPS). STAT3 and NFATc1 phosphorylation and nuclear translocation were measured by Western blot, ELISA, and imaging. In 3 experiments, sorted BALB/C mouse splenocytes were stained with CFSE and stimulated for 5 days with anti-CD3/CD28 antibodies. Cell division was analyzed by flow cytometry. Brains from BALB/c mice challenged with intracerebral or intraperitoneal LPS were analyzed after SM07883 (10mg/kg, QD, 5 days, n=5) or vehicle administration. C57BL/6 wild type mice with induced experimental autoimmune encephalomyelitis (EAE) after MOG_{35-55} immunization were treated with SM07883 (5-10mg/kg, QD and 5mg/kg, BID, 35 days) or vehicle (n=15 for each group). Clinical scores were measured daily and cytokines in spinal cord tissue were analyzed by Milliplex assays.

Results: *In vitro*, SM07883 inhibited LPS-induced cytokine secretion compared to DMSO control in microglial cells (e.g., TNFα EC_{50}=71nM) and in primary astrocytes (EC_{50}: TNFα=932nM; IL-6=698nM; KC/GRO=2.1mM). These effects were associated with dose-dependent reductions in phosphorylation and nuclear translocation of NFATc1 and STAT3 ($p<0.05$). Potent reduction in T cell proliferation was associated with decrease in proinflammatory cytokines (EC_{50}=15nM, IFNγ=41nM, TNFα=46nM) with SM07883 compared to DMSO. Innate responses, measured by proinflammatory cytokines TNFα, IFN-γ, IL-1β, and IL-6 as well as the chemokine KC/GRO, were increased in brains from LPS-challenged mice and significantly reduced with SM07883 treatment compared to vehicle. EAE mice treated with SM07883 improved clinical scores with reduced adaptive immune responses measured by decreased cytokines ($p<0.05$) and lymphocyte count in spinal cord compared to vehicle.

Conclusion: SM07883, an oral DYRK1A inhibitor, significantly reduced proinflammatory mediators and associated inflammation in both innate and adaptive inflammatory mouse models compared to vehicle. SM07883 may potentially modulate neuroinflammation in neurodegenerative diseases.