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

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Background: Neuroinflammation contributes to many neurodegenerative disorders, including Alzheimer's disease (AD). Inhibition of dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) activity with SM07883 reduced tau and amyloid pathology as well as gliosis in transgenic mice. This study assessed the potential of SM07883 to inhibit neuroinflammation *in vitro* and in four mouse models.

Methods: TNFα secretion was measured in vitro in supernatants from BV2 microglial cells challenged by lipopolysaccharide (LPS). In 3 repeat experiments, mouse balb/c splenocytes were sorted, stained with carboxyfluorescein succinimidyl ester, and stimulated for 5 days with anti-CD3/CD28 monoclonal antibodies. Cell division was analyzed by flow cytometry and cytokine concentrations were measured with the MesoScale Discovery platform. Similarly, brains from balb/c mice challenged with intracerebral or intraperitoneal LPS were analyzed after SM07883 (10mg/kg, QD, 5days) or vehicle administration. Brains and spinal cord samples were analyzed from SM07883-treated 3xTg-AD- (5mg/kg, QD, 6mos) and JNPL3- (3mg/kg, QD, 3mos) transgenic mice, respectively. C57bl/6 wild type mice with induced experimental autoimmune encephalomyelitis (EAE) after MOG_{35-55} immunization were treated with SM07883 (5-10mg/kg, QD, 35 days) or vehicle. Clinical scores were measured daily and cytokines and chemokines in spinal cord tissue were analyzed at termination using bead-based Milliplex assays.

Results: SM07883 potently inhibited TNFα secretion in BV2 cells (EC_{50}=71nM) and was accompanied by dose-dependent reduction in phosphorylation and translocation of STAT3 and NFATc1, analyzed by Western blot vs. control. Dose-dependent reduction of T cell proliferation was associated with decreased levels of proinflammatory cytokines (EC_{50}: IL-17a=15nM, IFNγ=41nM, TNFα=46nM) with SM07883 treatment vs. control. 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 vs. vehicle. Similar findings were observed in brains and spinal cords from 3xTg-AD and JNPL3 mice after treatment with SM07883. EAE mice treated with SM07883 demonstrated improved clinical scores correlated with a reduction in proinflammatory cytokines and a decrease in lymphocytes in spinal cord samples vs. vehicle.

Conclusion: SM07883, an oral DYRK1A inhibitor, significantly reduced proinflammatory mediators and associated inflammation in neurodegenerative models vs. vehicle. SM07883 may potentially modulate neuroinflammation in neurodegenerative diseases and has entered a clinical trial.