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 MOG35-55 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 (EC50=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 (EC50: 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.

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