Accepted as poster #H28 at the Society for Neuroscience (SFN) Annual Meeting 2019, Chicago, Illinois, October 19-23, 2019

SM07883, a Novel, Oral DYRK1A Inhibitor, Improves Cognition and Protects Against Amyloid and Tau Pathologies in the 3xTg-AD Mouse Model of Alzheimer's Disease

Karen Duong-Polk, Bora Güner, Stacy Habroun, Scott Anderson, Carolyn Lai, and Benoît Melchior

Samumed, LLC, San Diego, CA

Background: Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) regulates Amyloid Precursor protein (APP) and tau phosphorylation. DYRK1A is overexpressed in Alzheimer's disease (AD) brains and correlates with disease pathology. We hypothesized that DYRK1A inhibition may reduce AD pathology. The effectiveness of SM07883, a small-molecule DYRK1A inhibitor currently being tested in a clinical trial, was assessed on amyloid, tau, and neuroinflammation pathology together with cognition in two independent studies using the 3xTg-AD mouse model.

Methods: To test the effect of SM07883 on amyloid processing *in vitro,* a serial dilution was tested on SH-SY5Y cells and APP phosphorylation at Threonine 668 was measured by Western blot. Stable transfected SH-SY5Y cells overexpressing wild type human APP were treated with SM07883 and Aβ40 secretion was measured by MSD. For *in vivo* assessment of amyloid and tau pathology, 10- and 12-month-old female 3xTg (APP/PSEN/Tau P301L) mice were orally administered SM07883 (QD, 5mg/kg) or vehicle for 6 months. Mice were evaluated for cognitive behavior in the Novel Object Recognition (NOR) and Y-maze spontaneous alternation tests. At termination (6 months), left hemispheres were stained for amyloid burden (6E10, thioflavin), astrocytes activation (GFAP), activated microglia (Iba1), and tau pathology (AT8) compared to vehicle. Hippocampal and surrounding cortical areas were analyzed for tau and APP phosphorylation by Western blot while amyloid, tau fragments, and proinflammatory mediators were analyzed by immunoassays.

Results: *In vitro* data showed that SM07883 reduced APP phosphorylation and Aβ40 production in cells compared to DMSO controls with EC_{50} of 187 nM and 798 nM, respectively. Transgenic 3xTg mice treated with vehicle had elevated tau, APP phosphorylation, gliosis, and activated microglia in the hippocampal area compared to age-matched wild type littermates ($p<0.05$). All SM07883 results showed significance ($p<0.05$) when compared to vehicle at termination. A reduction of elevated tau and APP phosphorylation as well as amyloid fragments were reduced in lysates. Immunostaining showed amyloid and tau pathology reduction in the hippocampal area while GFAP and Iba1 showed reduced gliosis, which was associated with a reduction in proinflammatory cytokines. SM07883-treated mice performed better in NOR and SM07883 prevented cognitive deficit in the Y-maze.

Conclusion: In two independent studies in triple transgenic mice, daily oral administration of SM07883, a DYRK1A inhibitor, showed reduction of pathological AD hallmarks (tau and

amyloid), associated neuroinflammation, and protected against cognitive deficits compared to vehicle.