Accepted as an oral presentation at the Alzheimer's Solutions Conference (ASC) 2019, Philadelphia, Pennsylvania, June 2-3, 2019

Hitting 3 Birds with One Pill: How SM07883 May Prevent Tau, Amyloid, and Inflammation in Alzheimer's Disease

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There is an urgent need for treatments to prevent or slow progressive neurodegenerative diseases. In Alzheimer's disease (AD), hyperphosphorylation and misfolding of the tau protein appear to be enabled by amyloid-beta aggregation; thus far, therapeutics aimed at regulating the amyloid cascade have been insufficient in preventing disease progression in symptomatic patients.

A novel regulator of tau phosphorylation, dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A), has been found to be overexpressed in AD brains and is correlated to pathological hallmarks, including tau and amyloid aggregation. Elevated cellular stress signals may induce increased DYRK1A expression and activity, which contribute to AD pathology. Neuroinflammation has also been closely linked with multiple neurodegenerative disorders, including AD, and is similarly mediated by DYRK1A. Samumed is developing SM07883, a novel, selective, potent, orally bioavailable, small-molecule DYRK1A inhibitor as a potential therapeutic for AD.

In preclinical mouse models, daily oral administration of SM07883 significantly reduced tau and amyloid pathology compared to vehicle. Treatment also significantly reduced proinflammatory mediators and associated inflammation compared to vehicle. These effects ultimately corresponded with protection against cognitive and motor deficits compared to vehicle. Further pharmacology and toxicology studies in multiple species demonstrated acceptable safety profiles and enabled an ongoing Phase 1 clinical trial in healthy individuals. By both regulating tau and amyloid pathology as well as associated inflammation, SM07883 offers a novel approach to potentially treat AD.