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Tau Pathology Reduction with SM07883, A Novel, Potent, and Selective Oral DYRK1A Inhibitor - Potential Therapeutic for Alzheimer's Disease

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Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) overexpression is correlated to tau hyperphosphorylation and oligomer and neurofibrillary tangle formation. SM07883, an oral DYRK1A inhibitor, was studied in preclinical Alzheimer's Disease (AD) models. SM07883 selectively and potently inhibited DYRK1A activity (IC50 = 2 nM) in kinase panels. Overexpression of DYRK1A and tau genes (HEK293T cells) increased tau phosphorylation. SM07883 treatment reduced pTau at multiple sites including Thr212, AT8, Thr181, and Ser396 (EC50=16, 69, 127 and 200 nM, respectively). SM07883 had meaningful pharmacokinetic brain exposure across multiple species (mouse brain to plasma ratio >2). Wild-type mice showed dose-dependent reduction of transient, induced-brain pTau with SM07883 (47%, $p<0.001$) compared to vehicle. To assess long-term effects *in vivo*, 10-month old P301L human mutant tau overexpressing mice were treated daily with oral SM07883 or vehicle and pTau and tau aggregation were biochemically quantified in brain stems and spinal cords. SM07883 reduced pTau, oligomeric and aggregated tau, and tau-positive inclusions in brain stems at 14 weeks ($p<0.05$). Glial fibrillary associated protein (GFAP) and Iba1 immunoreactivity was reduced. Decreased GFAP was confirmed by Western Blotting (37%, $p=0.001$). Motor function (wire-hang test) was significantly improved in SM07883-treated mice ($p=0.034$) 5 weeks after the start of treatment. SM07883 was well-tolerated with weight gain ($p<0.001$) and reduced morbidity/mortality in treated animals. SM07883, a selective and potent, oral, brain-penetrant, DYRK1A inhibitor, showed reduction of AD pathology and improved functional endpoints compared to vehicle.