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SM07883, a Novel, Potent, and Selective Oral DYRK1A Inhibitor Reduced Tau Pathology in Preclinical Models

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Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) overexpression is correlated with tau hyperphosphorylation, formation of oligomers, and neurofibrillary tangle (NFT) formation. SM07883, an oral DYRK1A inhibitor, was studied as a potential drug for chronic tauopathies in preclinical models. SM07883 selectively and potently inhibited DYRK1A activity (IC50 = 2nM) in kinase panels *in vitro*. Overexpression of both DYRK1A and the tau gene (HEK293T cells) increased tau phosphorylation, and treatment with SM07883 reduced pTau at multiple sites including Thr212, AT8, Thr181, and Ser396 (EC50 16, 69, 127 and 200 nM, respectively). In pharmacokinetic studies, SM07883 demonstrated brain exposure across multiple species (mouse brain to plasma ratio >2). Wild type mice showed dose-dependent reduction of transient, induced-brain pTau starting with a single, 1.25 mg/kg SM07883 dose (47%, $p<0.001$) compared to vehicle. To assess long-term effects *in vivo*, pTau and oligomeric and aggregated tau were biochemically quantified in brain stems and spinal cords of 10-month old JNPL3 mice (P301L human tau overexpression mutation). Significant reductions in pTau and oligomeric and aggregated tau, and fewer tau-positive inclusions (AT8 staining) in brain stems, were observed between SM07883 (3 mg/kg, QD) and vehicle-treated mice ($p<0.05$) at 14 weeks. Glial fibrillary associated protein (GFAP) and Iba1 immunoreactivity was reduced, and decrease in GFAP staining was confirmed by Western Blotting (37%, $p=0.001$). Motor function (wire-hang test) was significantly improved in SM07883-treated JNPL3 mice compared to vehicle ($p=0.034$) at 5 weeks after the start of treatment. SM07883 was well-tolerated with weight gain ($p<0.001$) and reduced morbidity/mortality observed in treated animals versus vehicle. SM07883, a selective and potent, oral, brain-penetrant, DYRK1A inhibitor, significantly reduced the effects of tau overexpression, neuroinflammation, and improved functional endpoints compared to vehicle. SM07883 is a potential treatment for chronic tauopathies.