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Tau Pathology Reduction with SM07883, a novel, potent, and selective oral DYRK1A inhibitor – a potential therapeutic for Alzheimer's Disease

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Objectives:

Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1a) is known to phosphorylate Tau proteins. Overexpression is correlated to Tau hyperphosphorylation and neurofibrillary tangle (NFT) formation in Alzheimer's Disease (AD). This study assessed the potential of SM07883, an oral DYRK1a inhibitor, to inhibit Tau hyperphosphorylation, aggregation, NFT formation, and associated phenotypes, in mouse models. Exploratory neuroinflammatory effects were also studied.

Methods:

SM07883 specificity was tested in a kinase panel screen and Tau phosphorylation (pTau) measured in cell-based assays. SM07883 was further tested in wild type (WT) mice and long-term efficacy assessed (3mg/kg, QD, for 3 months) in aged JNPL3 mice overexpressing P301L human Tau mutation. Motor coordination was evaluated biweekly using a wire hanging test. Brain stems and spinal cords were collected from mice and pTau, oligomeric and aggregated Tau were biochemically quantified. NFT-containing cells were detected by immunostaining, and astrocyte activation using glial fibrillary associated protein (GFAP) staining, and quantified by Western Blotting.

Results:

SM07883 inhibited DYRK1a kinase activity (IC_{50} = 2nM). In cells, SM07883 reduced pTau at the Threonine 212 site (EC_{50} = 16nM). Compared to vehicle, WT mice showed dose dependent reduction of transient brain pTau induction starting with a single, 1.25mg/kg SM07883 dose (47%, p=0.0002). Also compared to vehicle, JNPL3 mice treated with SM07883 experienced significant reductions in Tau hyperphosphorylation, oligomeric and aggregated Tau and significantly lower NFT staining. Reduced GFAP immunoreactivity was also confirmed by Western Blotting (37%, p=0.0010). SM07883 was well tolerated with improved general health, weight gain and significant wire hanging test task improvement noted 5 weeks after treatment initiation compared to vehicle (p=0.034).

Conclusion:

SM07883, a potent, oral, brain-penetrant, DYRK1a inhibitor significantly reduced effects of pathological Tau overexpression and neuroinflammation while functional endpoints were

improved compared to vehicle. Therefore, this molecule has potential as a treatment for chronic tauopathies such as AD.