SM07883, a novel DYRK1A inhibitor, reduced Tau pathology – discovery and preclinical development of a potential therapeutic for Alzheimer’s disease

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Poster #P105

SM07883 is a potential DYRK1A inhibitor with a novel selectivity profile and therapeutic brain and CSF exposures after oral administration

In preclinical models compared to vehicle, SM07883:
- Reduced Tau pathology (pTau, aggregation, NFTs), improved functional deficits / health in Tau transgenic mouse
- Reduced neuroinflammation
- ‘No Observed Adverse Effect Level’ was 30x higher in AUC than the minimum efficacious dose in mice and >5x total exposure in monkeys, suggesting a broad therapeutic window for human dosing
- SM07883 may provide therapeutic, disease modifying effects in AD

Results

- Elevated cellular stress signals such as Aβ and TNFα have been shown to induce DYRK1A activity2−4 and DYRK1A activity contributes to Tau phosphorylation leading to Tau pathology1,5
- A potential therapeutic for AD, SM07883 (novel, small molecule, DYRK1A inhibitor) was evaluated, compared to controls as appropriate, for:
  - Inhibition of Tau hyperphosphorylation, aggregation, and NFT formation in a Tau transgenic mouse model
  - Effects on Tau-associated functional phenotypes
  - Effects on neuroinflammation
  - Pharmacokinetic and pharmacodynamic properties
  - Safety profile in toxicology studies

Figure 1. SM07883 potently inhibited DYRK1A kinase activity with a novel selectivity profile

Figure 2. SM07883 potently inhibited DYRK1A-mediated Tau hyperphosphorylation

Figure 3. SM07883 reduced LPS-stimulated proinflammatory cytokines

Figure 4. SM07883 inhibited Tau pathology in JNPL3 Tau mice

Figure 5. SM07883 improved motor function, weight, and general health of JNPL3 Tau mice

Figure 6. SM07883 reduced Tau-induced glial activation (neuroinflammation) in JNPL3 mice

Figure 7. SM07883 was orally bioavailable and brain penetrant in mice; apparent log-linear correlation between brain, plasma, and CSF absorption

Figure 8. SM07883 reduced Tau phosphorylation in the mouse brain

Figure 9. Toxicology studies suggested a broad therapeutic window

Methods

- SM07883 selectivity and potency were evaluated in an inhibition panel of 460 kinases
- Inhibition of Tau phosphorylation (pTau) was measured in human Tau/DYRK1A transfected HEK293T cells and human neuroblastoma cells
- Pharmacokinetics in brain, cerebrospinal fluid (CSF) and plasma were analyzed from wild-type (WT) mice following a single oral (PO) or intravenous (IV) administration of SM07883
- SM07883 pharmacodynamics were measured in WT mice in an anesthesia-induced transient Tau hyperphosphorylation model with brain lysates quantified using Western Blot for pTau
- The effects of SM07883 on LPS-induced TNFα secretion were measured in cultured BV-2 microglial cells
- Cytokines were measured in plasma and brain tissue by electrochemiluminescence (MesoScale Discovery) from WT mice after stereotactic injection of LPS/IFNγ

References