Background

- Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) regulates amyloid precursor protein (APP) and tau phosphorylation (pTau). It is overexpressed in Alzheimer’s disease (AD) brains and correlates with pathology.
- DYRK1A inhibition reduces phospho-APP (pAPP) and amyloid pathology.
- A potential therapeutic for AD, SM07883 is an oral, small-molecule DYRK1A inhibitor.
- This study assessed the effects of SM07883 in vitro and in vivo on amyloid, tau, and neuroinflammation pathology together with function and cognition in two mouse AD models: human tau transgenic (JNPL3) and triple transgenic (3xTG-AD).

Results

- SM07883, a small-molecule DYRK1A inhibitor, may have therapeutic potential in neurodegenerative diseases.
  - SM07883 reduced tau pathology (pTau, aggregation, NFTs), reduced neuroinflammation, and improved functional deficits/health in tau transgenic mice (JNPL3).
  - SM07883 reduced AD hallmarks (amyloid and tau), hippocampal neuroinflammatory markers, and protected against cognitive deficits in behavioral tests in triple transgenic mice (3xTG-AD).
- Phase 1 human study is ongoing.

Conclusions

- SM07883, a novel oral DYRK1A kinase inhibitor, reduced tau, amyloid pathology, and related inflammation in preclinical models.

References


Methods

- Motor coordination was evaluated biweekly after treatment initiation using a wire hang test.
- Ten-month-old and twelve-month-old female 3xTG-AD mice (APPPS19/tau P301L) were orally administered SM07883 (5 mg/kg) or vehicle daily for 26 weeks.
- Cognitive behavior was assessed by Novel Object Recognition (NOR) discrimination index and time spent near novel object (10 min-trial) and 2 Y Maze spontaneous and percent alternations (5 min-trials) (Fig. 6).
- At termination, brains were analyzed for amyloid, tau, and inflammation.
- Hippocampal and surrounding cortical area brain sections from one hemisphere were analyzed for amyloid (MSD) and tau fragments (Fig. 5; IFTF assay).
- The other hemisphere was collected in formalin, sectioned, and stained for amyloid, tau, and glial markers. Immunoreactivity in the hippocampus was quantified (stain intensity; ImageJ) (Figs. 7 and 8).

Figure 1. SM07883 potently inhibited DYRK1A and reduced pTau, pAPP, Aβ42, and TNF-α production in vitro

Figure 2. SM07883 inhibited tau pathology in JNPL3 tau mouse brains

Figure 3. SM07883 reduced tau-induced glial activation (neuroinflammation) in JNPL3 tau mouse CNS

Figure 4. SM07883 improved motor function, weight, and general health of JNPL3 tau mice

Figure 5. SM07883 reduced tau pathology in 3xTG-AD mouse brains

Figure 6. SM07883 prevented cognitive deficit in NOR and in the Y Maze in 3xTG-AD mice

Figure 7. SM07883 reduced amyloid burden in 3xTG-AD mouse brains

Figure 8. SM07883 reduced neuroinflammation (glovis) in 3xTG-AD mouse brains

Figure 9. SM07883 Log Conc. (mM)