Cognitive improvement and protection against amyloid and tau pathology with SM07883, an oral DYRK1A inhibitor, in the 3xTG-AD mouse model of Alzheimer’s disease

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Background

- Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) regulates amyloid precursor protein (APP) and tau phosphorylation (pTau), is overexpressed in Alzheimer’s disease (AD) brains, and correlates with pathology; therefore, inhibition may have therapeutic potential.
- DYRK1A inhibition reduced phospho-APP (pAPP) and amyloid pathology.
- SM07883 is an oral small-molecule DYRK1A inhibitor that reduced tau pathology in JNPL3 (human P301L tau mutation) transgenic mice.
- This study assessed the effects of SM07883 in vitro and in vivo on amyloid, tau, and neuroinflammation pathology together with cognition in a triple-transgenic (3xTG-AD) mouse AD model.

Conclusions

- SM07883, oral daily for 26 weeks, compared to vehicle, demonstrated:
  - Reduction of AD hallmarks (amyloid and tau) in triple-transgenic mice
  - Reduction of hippocampal neuroinflammatory markers
  - Protected against cognitive deficits in behavioral tests
- SM07883, a small-molecule DYRK1A inhibitor, may have therapeutic potential in neurodegenerative diseases
- Phase 1 human study is ongoing
  - ANZCTR.org.au registration # ACTRN12619003271889

Results

- SM07883 inhibited DYRK1A activity and pTau, pAPP, and Aβ0 production in vitro
- SM07883 reduced amyloid and tau fragments
- SM07883 reduced amyloid burden in 3xTG-AD brains
- SM07883 reduced proinflammatory mediators in 3xTG-AD hippocampal lysates
- SM07883 prevented cognitive deficit in NOR
- SM07883 prevented cognitive deficit in the Y Maze

Methods

- SM07883 potency evaluated in a DYRK1A kinase inhibition assay (Fig. 1)
- Inhibition of tau phosphorylation (pTau) was measured in human Tau-DYRK1A-transfected HEK293T cells and human neuroblastoma cells (Fig. 1)
- SM07883 PAPP dose-response curves were measured in Western blots from unstimulated SH-SY5Y human neuroblastoma cells (densitometry, ImageJ) (Fig. 1)
- Aβ0 secretion measured by MesoScale Discovery (MSD) in stably transfected SH-SY5Y cells overexpressing wild type human APP (hAPPwt) and treated with SM07883 (Fig. 1)
- Ten-month-old and twelve-month-old female 3xTG-AD (APP/PSEN1/Tau P301L) mice were orally administered SM07883 (5 mg/kg) or vehicle daily for 26 weeks. Wild type controls were age matched
- Mice were assessed for cognitive behavior:
  - Novel Object Recognition (NOR) discrimination index and time spent near novel object (10-min trial) (Fig. 6)
  - Y Maze spontaneous and percent alternations (5-min trials) (Fig. 7)
- At termination, brains were analyzed for amyloid, tau, and inflammation
  - Hippocampal and surrounding cortical area lysates from one hemisphere were analyzed for amyloid (MSD) and tau fragments (Fig. 2; HTRF assay) as well as proinflammatory mediators (Fig. 5; Milliplex beads)
  - The other hemisphere was collected in formalin, sectioned, and stained for amyloid, tau, and gliosis markers. Immunoreactivity in the hippocampus was quantified (stain intensity; ImageJ) (Figs. 3 and 4)

References


Figure 1. SM07883 inhibited DYRK1A activity and pTau, pAPP, and Aβ0 production in vitro

Figure 2. SM07883 reduced amyloid and tau fragments

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

Figure 4. SM07883 reduced neuroinflammation (gliosis)

Figure 5. SM07883 reduced proinflammatory mediators in 3xTG-AD hippocampal lysates

Figure 6. SM07883 prevented cognitive deficit in NOR

Figure 7. SM07883 prevented cognitive deficit in the Y Maze