SM07883, a novel, oral DYRK1A kinase inhibitor, reduced tau pathology and associated behavioral deficits in preclinical models

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Background

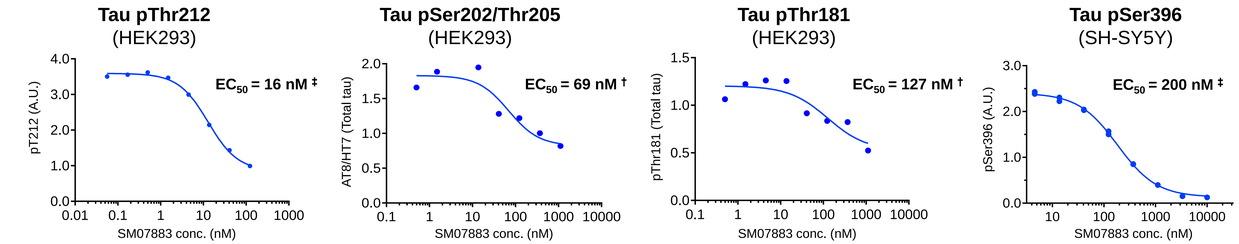
- In tau-associated neurodegenerative diseases, dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) is correlated with tau hyperphosphorylation, tau aggregates, and neurofibrillary tangles[1-4]
- SM07883 is a potent (1.6 nM), oral, brain-penetrant, small-molecule DYRK1A inhibitor[5]
- This study assessed SM07883 and its potential to inhibit tau phosphorylation and related pathology, decrease tau-induced neuroinflammation, and prevent associated functional phenotypes, including cognition and motor behaviors, in two transgenic mouse models

Conclusions

- **Daily administration of SM07883 reduced tau pathology, decreased neuroinflammation, and improved functional deficits compared to vehicle in tau transgenic mice (JNPL3 and 3xTg-AD)**
- **SM07883 may have therapeutic potential as a treatment for chronic tauopathies**
- **A Phase 1 human study is ongoing**
  - **ANZCTR.org.au registration #ACTRN12619000327189**

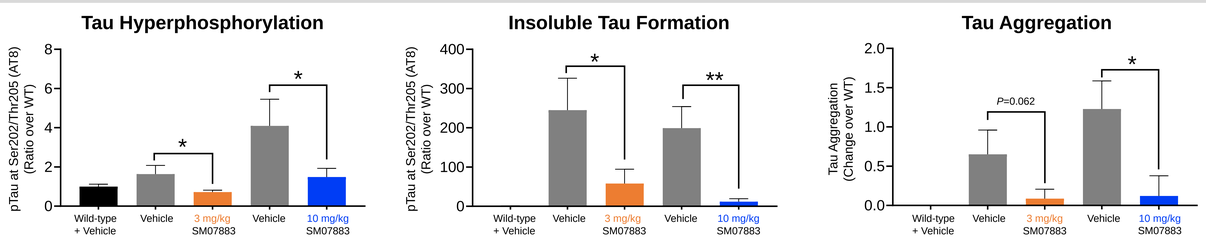
Results

Figure 1. SM07883 reduced pTau *in vitro*[5]



‡Measured by immunoassays; †Measured by Western blot; Note: EC_{50} = average across multiple assays

Figure 2. SM07883 reduced hyperphosphorylated tau and formation of tau aggregates in JNPL3 mouse brains[5]



Only 3 mg/kg normalized by β-actin; **3 mg/kg study**: WT + Veh. n=9, JNPL3: Veh. n=19, SM07883 n=19; **10 mg/kg study**: WT + Veh. n=10, JNPL3: Veh. n=15, SM07883 n=13; Mean ± SEM; **P*<0.05, ***P*<0.01 vs. vehicle

Figure 3. SM07883 inhibited tau pathology in JNPL3 mouse brains[5]

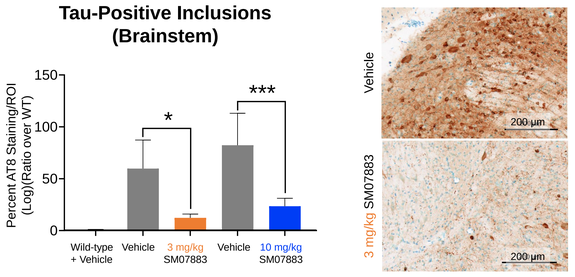
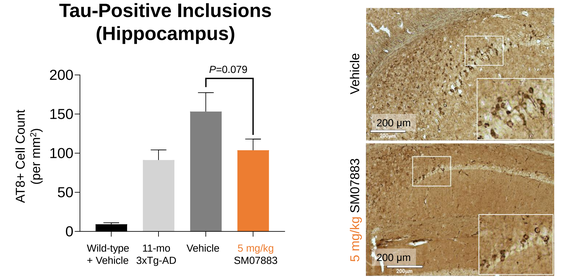


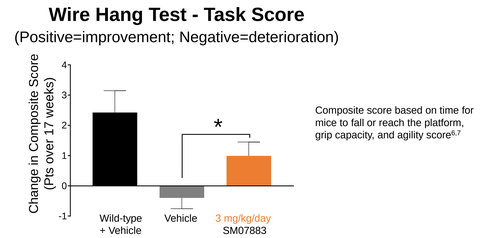
Figure 4. SM07883 inhibited tau pathology in 3xTg-AD mouse brains



Only 3 mg/kg normalized by β-actin; **3 mg/kg study**: WT + Veh. n=9, JNPL3: Veh. n=19, SM07883 n=19
10 mg/kg study: WT + Veh. n=10, JNPL3: Veh. n=15, SM07883 n=13; Mean ± SEM; **P*<0.05, ****P*<0.001 vs. vehicle

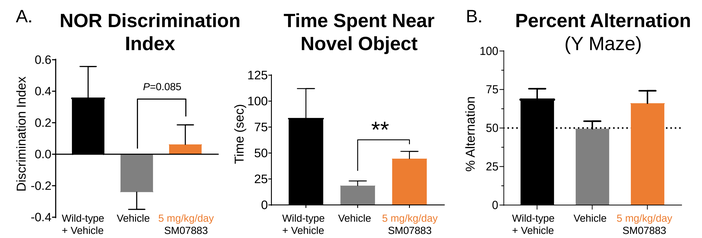
Quantification of 3xTg-AD mice hippocampal CA1 region AT8 staining in WT + Veh. n=9
3xTg-AD: 11-mo n=8, Veh. n=8, SM07883 n=11; Mean ± SEM; *P*=0.079 vs. vehicle

Figure 5. SM07883 significantly improved motor coordination in the wire hang test in JNPL3 mice[5]



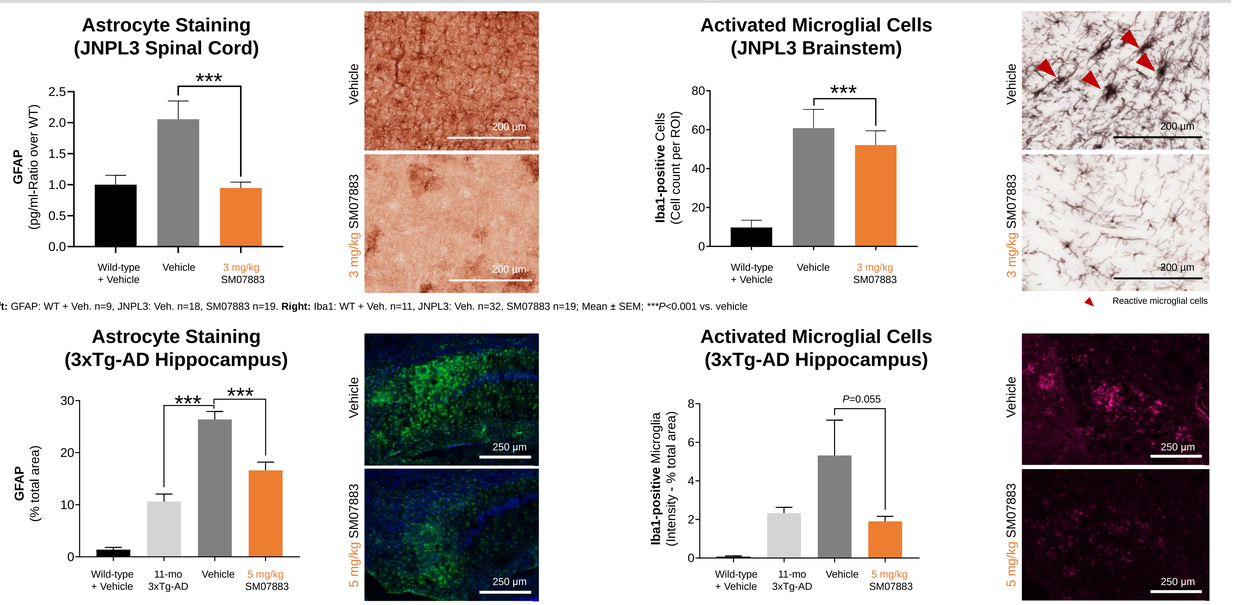
WT + Veh. n=10, JNPL3: Veh. n=19, SM07883 n=19; Mean ± SEM; **P*<0.05 vs. vehicle

Figure 6. SM07883 reduced cognitive deficits in the NOR test and the Y maze in 3xTg-AD mice



Treatment Week 21; Mean ± SEM; ***P*<0.01 vs. vehicle; --- 50% random level represented by dashed line in Y Maze
A. WT+ Veh. n=9, 3xTg-AD: Veh. n=10, SM07883 n=11 **B.** WT + Veh. n=9, 3xTg-AD: Veh. n=7, SM07883 n=8

Figure 7. SM07883 reduced tau-induced glial activation (neuroinflammation) in the CNS of JNPL3[5] and 3xTg-AD mice



Left: GFAP: WT + Veh. n=9, JNPL3: Veh. n=18, SM07883 n=19. **Right:** Iba1: WT + Veh. n=11, JNPL3: Veh. n=32, SM07883 n=19; Mean ± SEM; ****P*<0.001 vs. vehicle

Left: 3xTg-AD mouse hippocampal CA1 stained with GFAP (astrocytes, green, left) or Iba1 (activated microglia, magenta, right). **Right:** Quantification of staining in WT + Veh. n=9, 3xTg-AD: Veh. n=9 and SM07883 n=11; ****P*<0.001 vs. vehicle

Methods

- SM07883 inhibition of tau phosphorylation (pTau) was measured in human tau/DYRK1A-transfected HEK-293T cells and human neuroblastoma cells (SH-SY5Y) (**Fig. 1**)
- Ten-month-old JNPL3 mice (P301L human tau overexpression mutation) were orally administered vehicle or SM07883 (3 or 10 mg/kg, QD, 3 months)
  - pTau, sarkosyl-insoluble fraction, and aggregated tau were biochemically quantified in brainstems and spinal cords (**Fig. 2**)
  - Tau-positive inclusions were detected and quantified by immunostaining with a Ser202/Thr205 tau antibody (AT8 clone) at termination (13 months) (**Fig. 3**)
  - Motor coordination was evaluated biweekly after treatment initiation using a wire hang test[6,7] (**Fig. 5**)
  - Glial activation was assessed in brainstems using glial fibrillary acidic protein (GFAP) staining and ELISA quantification. Activated microglia were identified by Iba1-positive hindbrain staining at termination (**Fig. 7, top**)
- Eleven-month-old 3xTg-AD mice (APP, PSEN, P301L tau) were orally administered vehicle or SM07783 (5 mg/kg, QD, 6 months)
  - At termination (17 months), brains were collected in formalin, sectioned, and stained for tau-positive inclusions (**Fig. 4**), GFAP, and Iba1 (**Fig. 6, bottom**). Immunoreactivity in the hippocampus was quantified (stain intensity; ImageJ)
  - Cognitive behavior was assessed by Novel Object Recognition (NOR) discrimination index and time spent near novel object (10-min trial) (**Fig. 5A**) and Y Maze spontaneous and percent alternation (5-min trials) (**Fig. 5B**) at Week 21 of treatment

References

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All authors are employees, shareholders, or consultants of Samumed, LLC. Other disclosures are listed in the published abstract.

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