SM07883, a novel, oral DYRK1A inhibitor, improves cognition and protects against amyloid and tau pathologies in the 3xTg-AD mouse model of Alzheimer's disease

Karen Duong-Polk, Bora Güner, Stacy Habroun, Scott Anderson, Carolyn Lai, Benoît Melchior, PhD
Samumed, LLC, San Diego, CA

Poster #H28

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, DYRK1A inhibition may have therapeutic potential[1-4]
- DYRK1A inhibition has been shown to reduce phospho-APP (pAPP) and amyloid pathology[1,5]
- SM07883 is a potent (IC_{50} = 1.6 nM), oral, small-molecule DYRK1A inhibitor that reduced tau pathology in JNPL3 (human P301L tau mutation) transgenic mice[4]
- This study assessed the effects of SM07883 *in vitro* and *in vivo* on amyloid, tau, and neuroinflammation pathologies together with cognitive performance in a triple transgenic (3xTg-AD) mouse AD model

Conclusions

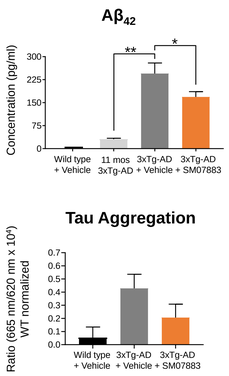
- **SM07883 (26-week daily oral dose) in 3xTg-AD mice, compared to vehicle, demonstrated**
  - **Reduction of AD hallmarks including hippocampal tau phosphorylation and amyloid burden**
  - **Reduction of hippocampal neuroinflammatory markers**
  - **Protection against cognitive deficits in behavioral tests**
- **SM07883, a small-molecule DYRK1A inhibitor, may have therapeutic potential in neurodegenerative diseases**
- **A Phase 1 human study is ongoing**
  - **ANZCTR.org.au registration #ACTRN12619000327189**

Results

Figure 1. SM07883 potently inhibited pTau, pAPP, and $A\beta_{40}$ *in vitro*

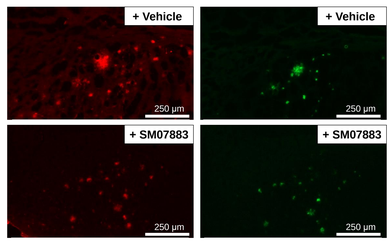
SM07883 *in vitro*	EC_{50}
Inhibited DYRK1A-mediated tau phosphorylation at pThr212	16 nM
Reduced DYRK1A-mediated pAPP at Thr668	187 nM
Reduced $A\beta_{40}$ secretion	798 nM

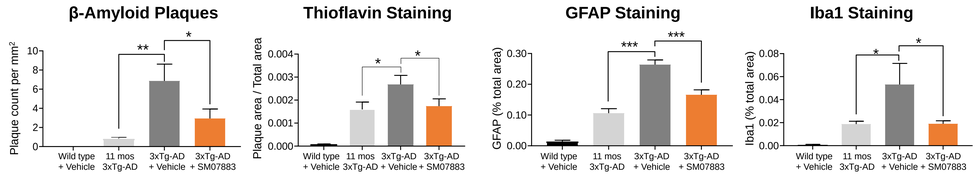
Figure 2. SM07883 reduced amyloid and tau fragments



Quantification of 3xTg-AD mouse hippocampal lysate amyloid (top) and tau fragments (bottom); wild type + vehicle n=9, 11 mos 3xTg-AD n=8, 3xTg-AD + vehicle n=9, 3xTg-AD + SM07883 n=11; mean ± SEM; *p<0.05, **p<0.01
Premature deaths have been removed from analysis

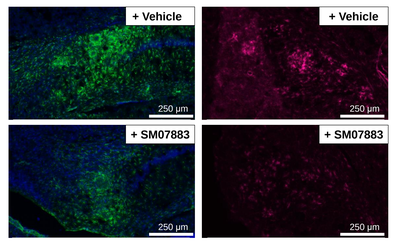
Figure 3. SM07883 reduced amyloid burden in 3xTg-AD brains





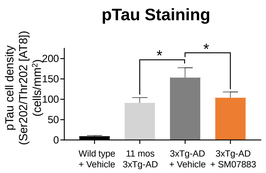
Top: 3xTg-AD mouse hippocampal staining (CA1 region magnified to illustrate detail) for amyloid plaques with 6E10 (amyloid, red; left) or thioflavin-s (protein aggregation, green; right). Bottom: Quantification of hippocampal staining in wild type + vehicle n=9, 11 mos 3xTg-AD n=8, 3xTg-AD + vehicle n=12, and 3xTg-AD + SM07883 n=13; mean ± SEM; *p<0.05, **p<0.01

Figure 4. SM07883 reduced neuroinflammation (gliosis)

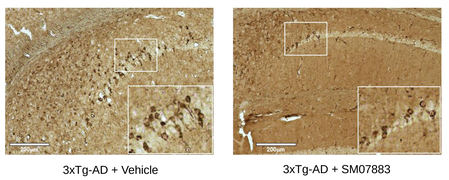


Top: 3xTg-AD mouse hippocampal CA1 stained with GFAP (astrocytes, green; left) or Iba1 (activated microglia, magenta; right). Bottom: Quantification of staining in wild type + vehicle n=9, 11 mos 3xTg-AD n=8, 3xTg-AD + vehicle n=9, and 3xTg-AD + SM07883 n=11; mean ± SEM; *p<0.05, ***p<0.001

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

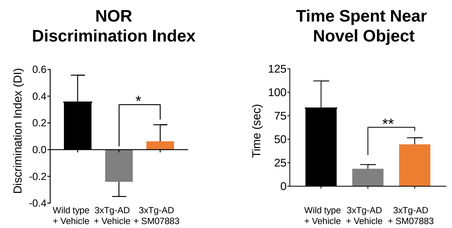


Quantification of 3xTg-AD mouse hippocampal CA1 region Ser202/Thr205 (AT8) staining in WT + vehicle n=9, 3xTg-AD + vehicle n=8, + SM07883 n=11; mean ± SEM; *p<0.05



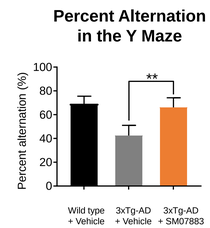
3xTg-AD + Vehicle | 3xTg-AD + SM07883

Figure 6. SM07883 reduced cognitive deficit in Novel Object Recognition (NOR)



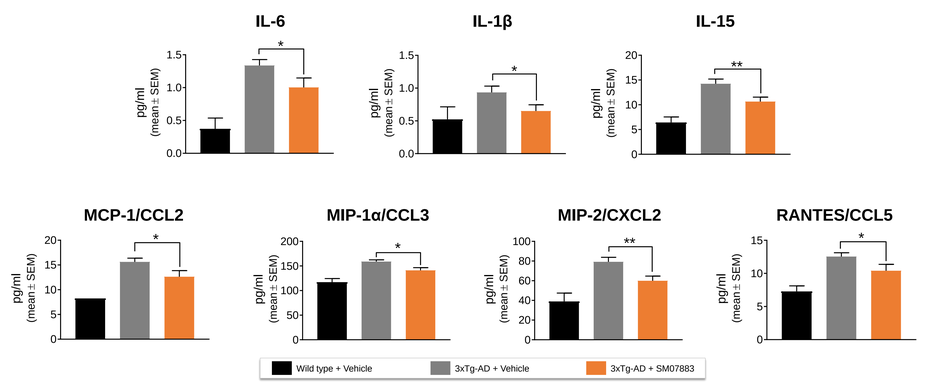
Novel Object Recognition at Week 21 of treatment; wild type + vehicle n=9, 3xTg-AD + vehicle n=10, 3xTg-AD + SM07883 n=11; mean ± SEM; *p<0.05, **p<0.01

Figure 7. SM07883 prevented cognitive deficit in the Y Maze



Y Maze alternation at Week 25 of treatment; wild type + vehicle n=9, 3xTg-AD + vehicle n=7, 3xTg-AD + SM07883 n=8; mean ± SEM; **p<0.01

Figure 8. SM07883 reduced proinflammatory mediators in 3xTg-AD hippocampal lysates



IL: interleukin, MCP: monocyte chemoattractant, Protein CCL: chemokine (C-C motif) ligand, MIP: macrophage inflammatory protein
CXCL: chemokine (C-X-C motif) ligand, RANTES: regulated on activation; normal T cell expressed and secreted
Wild type + vehicle n=3, 3xTg-AD + vehicle n=6, 3xTg-AD + SM07883 n=7; mean ± SEM; *p<0.05, **p<0.01

Methods

- SM07883 inhibition of tau phosphorylation (pTau) was measured in human tau/DYRK1A-transfected HEK293T cells and human neuroblastoma cells. SM07883 pAPP dose-response curves were measured in Western blots from unstimulated SH-SY5Y human neuroblastoma cells (densitometry, ImageJ). $A\beta_{40}$ secretion was measured by electrochemiluminescence/multiplex assays (Meso Scale Discovery [MSD]) in stably transfected SH-SY5Y cells overexpressing wild type human APP (hAPP[wt]) and treated with SM07883 (**Fig. 1**)
- Ten-month-old and twelve-month-old female 3xTg-AD (APP/PSEN/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 end of treatment (Week 26), animals were sacrificed; 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**; FRET-based assay) as well as proinflammatory mediators (**Fig. 8**; 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. 3-5**)

References

1. Branca C, et al. *Aging Cell.* 2017.
2. Ferrer I, et al. *Neurobiol. Dis.* 2005.
3. Wegiel J, et al. *FEBS J.* 2011.
4. Melchior B, et al. *Aging Cell.* 2019.
5. Ryoo SR, et al. *J. Neurochem.* 2008.

9381 Judicial Drive
San Diego, CA 92121
info@samumed.com