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[1-4]
- DYRK1A inhibition reduced phospho-APP (pAPP) and amyloid pathology[5,6]
- SM07883 is an oral small-molecule DYRK1A inhibitor that reduced tau pathology in JNPL3 (human P301L tau mutation) transgenic mice[3]
- 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

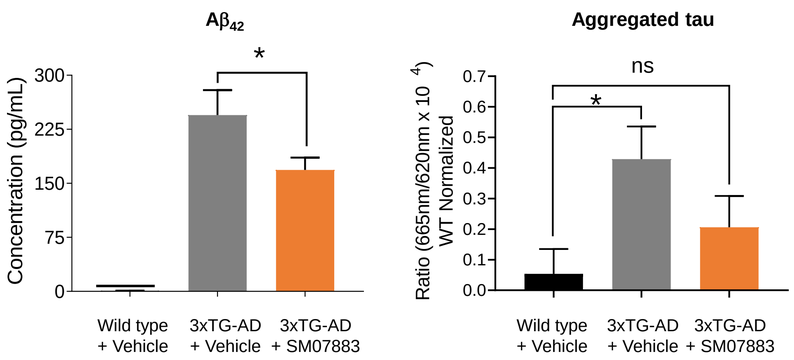
- SM07883, oral daily for 26 weeks, compared to vehicle, demonstrated:
  - Reduction of AD hallmarks (amyloid and tau) in triple-transgenic mice
  - Reduction of hippocampal neuroinflammatory markers
  - Protected against cognitive deficits in behavioral tests
- SM07883, a small-molecule DYRK1A inhibitor, may have therapeutic potential in neurodegenerative diseases
- Phase 1 human study is ongoing
  - ANZCTR.org.au registration # ACTRN12619000327189

Results

Figure 1. SM07883 inhibited DYRK1A activity and pTau, pAPP, and $A\beta_{40}$ production *in vitro*

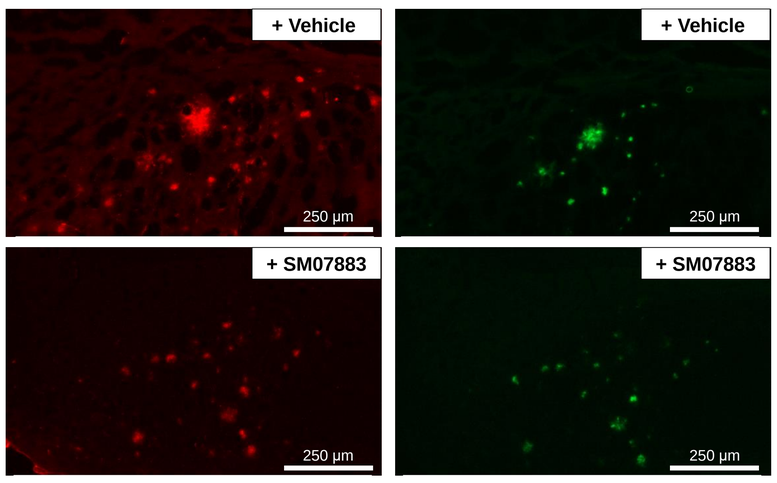
SM07883 *in vitro*	
Potently inhibited DYRK1A kinase activity[3]	IC_{50} 1.6 nM
Inhibited DYRK1A-mediated tau phosphorylation at pThr212	EC_{50} 16 nM
Reduced DYRK1A-mediated pAPP at Thr668	EC_{50} 187 nM
Reduced $A\beta_{40}$ secretion	EC_{50} 798 nM

Figure 2. SM07883 reduced amyloid and tau fragments



Quantification of 3xTG-AD mice hippocampal lysate amyloid (left) and tau (right) fragments; wild type + vehicle n=9, 3xTG-AD + vehicle=9, 3xTG-AD + SM07883 n=11, *p<0.05

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



Above: 3xTG-AD mouse hippocampal (magnification of CA1 region shown to illustrate detail) staining for amyloid plaques with 6E10 (amyloid, red; left) or thioflavin (protein aggregation, green; right). Below: Quantification of hippocampal staining in wild type + vehicle n=9, 3xTG-AD + vehicle n=12, and 3xTG-AD + SM07883 n=13, *p<0.05

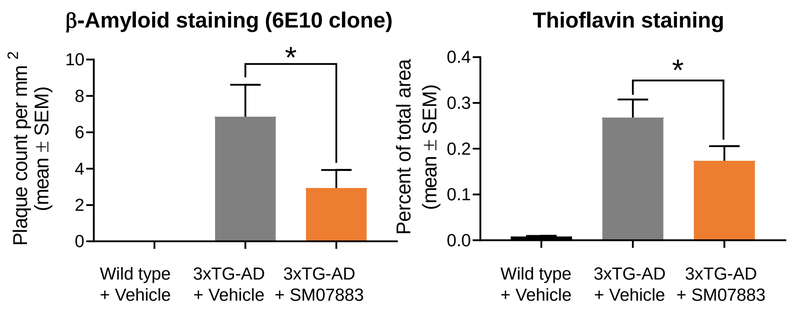
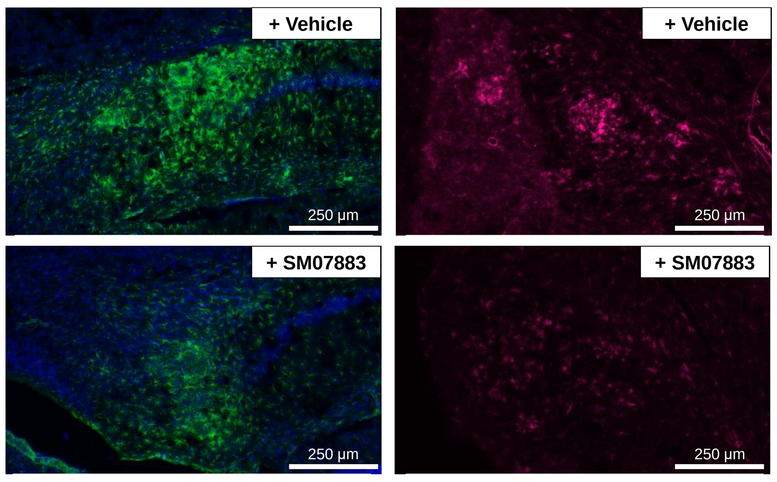


Figure 4. SM07883 reduced neuroinflammation (gliosis)



Above: 3xTG-AD mouse hippocampal CA1 stained with GFAP (astrocytes, green, left) or Iba1 (activated microglia, magenta, right). Below: Quantification of staining in wild type + vehicle n=9, 3xTG-AD + vehicle n=9, and 3XTG-AD + SM07883 n=11, *p<0.05, ***p<0.001

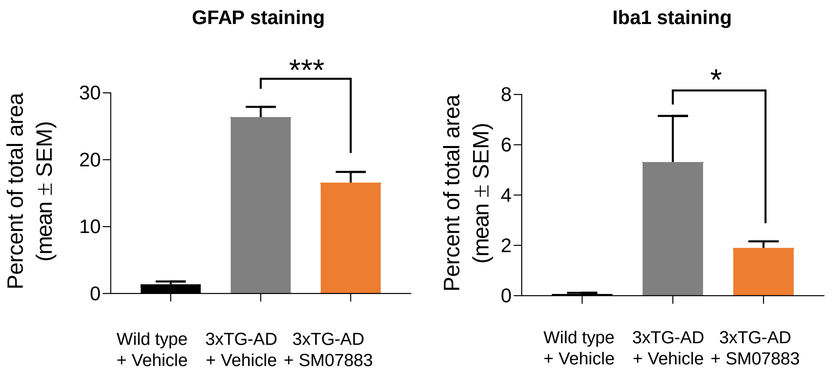
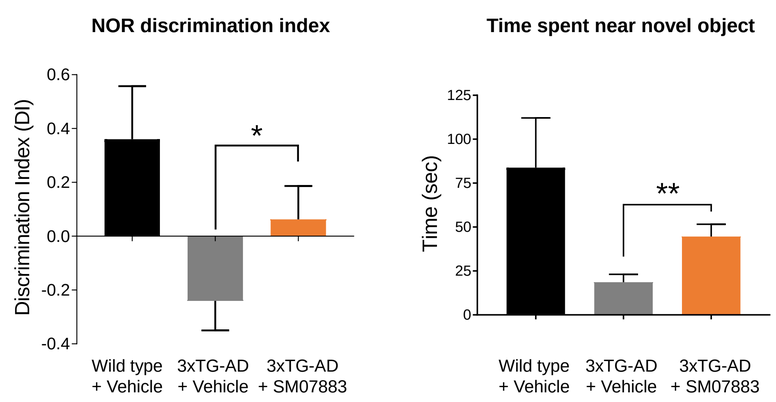


Figure 6. SM07883 prevented cognitive deficit in NOR



Novel Object Recognition at Week 21; wild type + vehicle n=9, 3xTG-AD + vehicle n=10, 3xTG-AD + SM07883 n=11, *p<0.05, **p<0.01

Figure 7. SM07883 prevented cognitive deficit in the Y Maze

Y Maze alternation at Week 25; wild type + vehicle n=9, 3xTG-AD + vehicle=7, 3xTG-AD + SM07883 n=8, **p<0.01

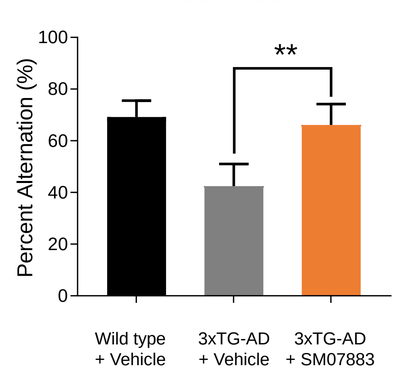
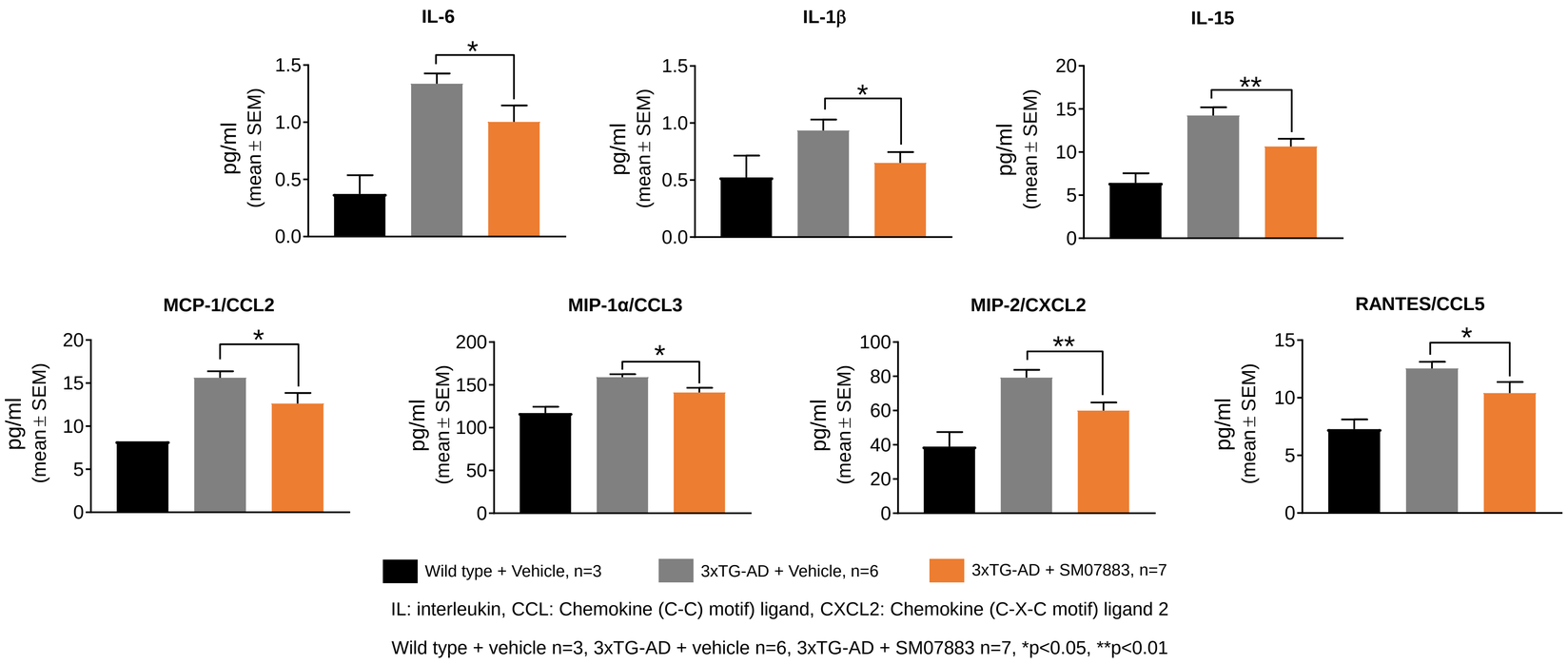


Figure 5. SM07883 reduced proinflammatory mediators in 3xTG-AD hippocampal lysates



IL: interleukin, CCL: Chemokine (C-C) motif) ligand, CXCL2: Chemokine (C-X-C motif) ligand 2

Wild type + vehicle n=3, 3xTG-AD + vehicle n=6, 3xTG-AD + SM07883 n=7, *p<0.05, **p<0.01

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)
- $A\beta_{40}$ secretion measured by MesoScale 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 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

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