Tau pathology reduction with SM07883, a novel, potent, and selective oral DYRK1A inhibitor

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Poster #D46

Background

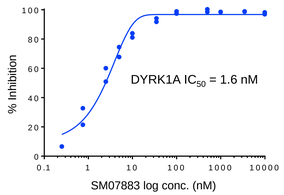
- Elevated cellular stress signals, such as amyloid beta (Aβ) and tumor necrosis factor alpha (TNF-α), have been shown to induce dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) activity[1-3]
- DYRK1A regulates amyloid precursor protein (APP) and tau phosphorylation (pTau), is overexpressed in Alzheimer's disease (AD) brains, and correlates with disease pathology[1-4]
- A potential therapeutic for AD, SM07883 (a novel small-molecule DYRK1A inhibitor), was compared *in vitro* and *in vivo* to controls for:
  - Pharmacokinetic and pharmacodynamic properties
  - Inhibition of tau hyperphosphorylation, aggregation, and neurofibrillary tangles (NFT) formation in a tau transgenic mouse model
  - Effects on tau-associated functional phenotypes
  - Effects on neuroinflammation

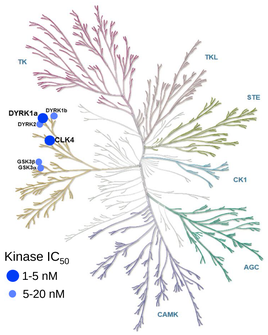
Conclusions

- **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 compared to vehicle in tau transgenic mice (JNPL3)**
- **Phase 1 human study is ongoing**
  - **ANZCTR.org.au registration #ACTRN12619000327189**

Results

Figure 1. SM07883 potently inhibited DYRK1A kinase activity with a novel selectivity profile

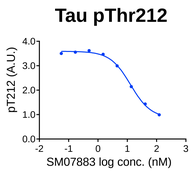


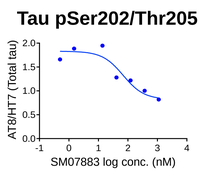


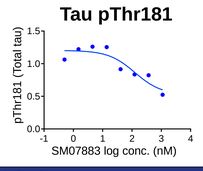
	Full IC_{50} (nM)	Fold over DYRK1A
DYRK1A	1.6	-
CLK4	2.8	2
DYRK1B	7.9	5
GSK-3β	11	7
GSK-3α	11	7
DYRK2	16	10

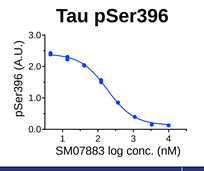
5 additional kinases within the 15-fold range of DYRK1A IC_{50}

Figure 2. SM07883 potently inhibited DYRK1A and reduced pTau *in vitro*





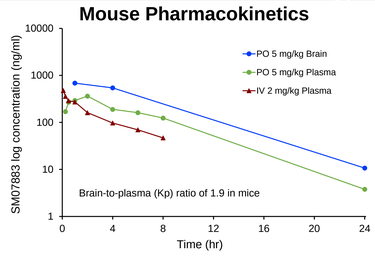




SM07883 *in vitro*	Cell Lines	EC_{50}
Tau phosphorylation at pThr212	Tau/DYRK1A in HEK293	16 nM ‡
Tau phosphorylation at pSer202/Thr205 (AT8)	Tau/DYRK1A in HEK293	69 nM †
Tau phosphorylation at pThr181	Tau/DYRK1A in HEK293	127 nM †
Tau phosphorylation at pSer396	Human neuroblastoma cells (SH-SY5Y)	200 nM ‡

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

Figure 3. SM07883 was orally bioavailable, brain penetrant, and dose-dependently reduced tau hyperphosphorylation in mice



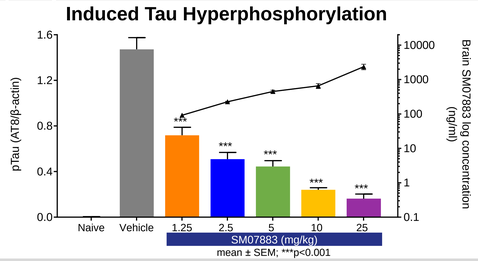


Figure 4. SM07883 distributed throughout the rat brain

Concentrations of SM07883 in rat plasma and brain regions after a single oral administration at 5 mg/kg									
Concentration (ng/ml)									
Plasma	OB	Pme	CER	PCx	OCCx	FCX	TCx	HYP	THA
383	785	455	516	991	928	946	763	737	650

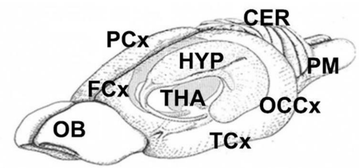
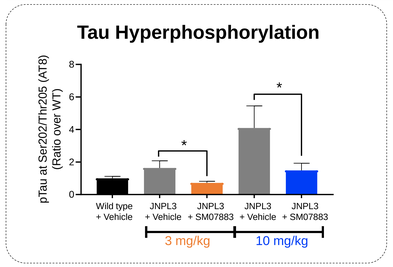
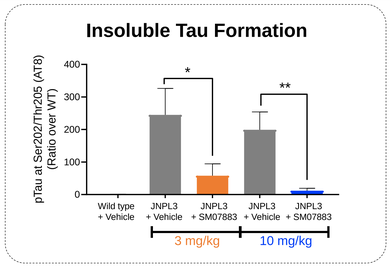
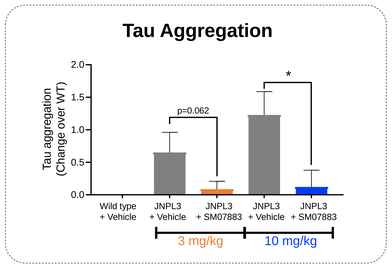
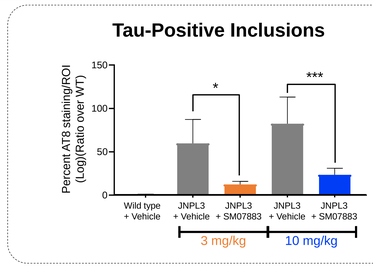


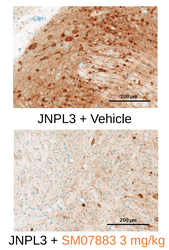
Figure 5. SM07883 inhibited tau pathology in JNPL3 tau mice brains











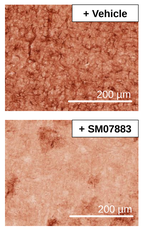
Only 3 mg/kg normalized by β-actin

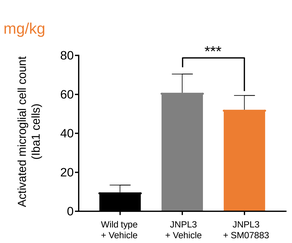
3 mg/kg study: WT + Veh. n=9, JNPL3 + Veh. n=19, + SM07883 n=19

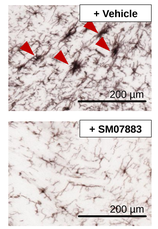
10 mg/kg study: WT + Veh. n=10, JNPL3 + Veh. n=15, + SM07883 n=13

mean ± SEM; *p<0.05, **p<0.01, ***p<0.001

Figure 6. SM07883 reduced tau-induced glial activation (neuroinflammation) in JNPL3 tau mice CNS

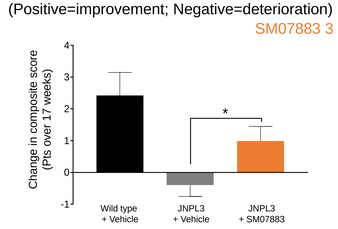




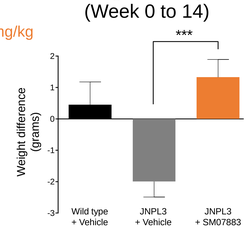


GFAP: WT + Veh. n=9, JNPL3 + Veh. n=18, +SM07883 n=19; **Iba1**: WT + Veh. n=11, JNPL3 + Veh. n=32, + SM07883 n=19; mean ± SEM; ***p<0.001

Figure 7. SM07883 improved motor function, weight, and general health of JNPL3 tau mice



Composite score based on time for mice to fall or reach the platform, grip capacity, and agility score[6,7]



In-Life Observations at End of Study

Morbidity / Mortality	Vehicle	SM07883
Death	2/20	0/19
Pronounced hunched back	1/18	0/19
Severe tremors	3/18	0/19
Moderate tremors	6/18	0/19
Mild tremors	0/18	2/19

WT + Veh. n=10, JNPL3 + Veh. n=19, + SM07883 n=19; mean ± SEM; *p=0.011, ***p<0.001

Methods

- SM07883 selectivity and potency were evaluated in an inhibition panel of 460 kinases (**Fig. 1**)
- SM07883 inhibition of tau phosphorylation (pTau) was measured in human tau/DYRK1A-transfected HEK-293T cells and human neuroblastoma cells (**Fig. 2**)
- Pharmacokinetics in brain, cerebral spinal fluid (CSF), and plasma were analyzed from wild type (WT) mice following a single oral (PO) or intravenous (IV) administration of SM07883. SM07883 pharmacodynamics were measured in WT mice in an anesthesia/hypothermia-induced transient tau hyperphosphorylation model[5]; Western blot was used to quantify pTau in brain lysates (**Fig. 3**)
- Brains from rats administered SM07883 (P.O., 5 mg/kg) 4 hrs prior were dissected and grossly separated into 9 regions (n=3 rats; OB: olfactory bulb, PM: pons and medulla, CER: cerebellum, PCx: parietal cortex, OCCx: occipital cortex, FCx: frontal cortex, TCx: temporal cortex, HYP: hippocampus, THA: thalamus). Plasma and brain tissue exposures are shown in the table above in ng/ml (**Fig. 4**)
- Ten-month-old JNPL3 mice (P301L human tau overexpression mutation) were orally administered vehicle or SM07883 (3 or 10 mg/kg, QD, 3 months) (**Fig. 5-7**)
  - pTau (Tau Ser202/Thr205 [AT8] levels) and sarkosyl-insoluble fraction (Tau AT8 in the sarkosyl-insoluble fraction) were biochemically quantified in brainstems (Western blot). Aggregated tau were biochemically quantified in spinal cords (FRET-based assay). Tau-positive inclusions (AT8 immunostaining with an AT8 clone antibody) were detected and quantified at termination in the hindbrain (13 months)
  - Glial activation was assessed in the brainstems using glial fibrillary acidic protein (GFAP) staining and ELISA quantification, and activated microglia were identified by Iba1 hindbrain staining at 13 months
  - General tolerability was assessed by monitoring weight, morbidity, and mortality
  - Motor coordination was evaluated biweekly after treatment initiation using a wire hang test[6,7]

References

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