SM07883, A NOVEL, POTENT, AND SELECTIVE ORAL DYRK1A INHIBITOR REDUCED TAU PATHOLOGY IN PRECLINICAL MODELS

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Poster # T2

Background

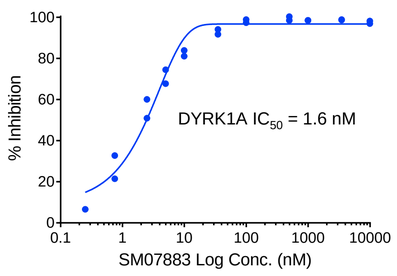
- Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) overexpression in Alzheimer's and Pick's Disease was correlated to Tau hyperphosphorylation, oligomer, and neurofibrillary tangle (NFT) formation[1]
- Elevated cellular stress signals (e.g. Aβ, TNFα) induce DYRK1A activity[2-6] which then contributes to Tau pathology[1,7]
- A potential therapeutic for tauopathies, SM07883 (novel, small molecule, DYRK1A inhibitor) was evaluated in preclinical models, compared to controls, for:
  - Inhibition of Tau hyperphosphorylation, aggregation, and NFT formation in a Tau transgenic mouse model
  - Effects on Tau-associated functional phenotypes
  - Effects on neuroinflammation
  - Pharmacokinetic and pharmacodynamic properties

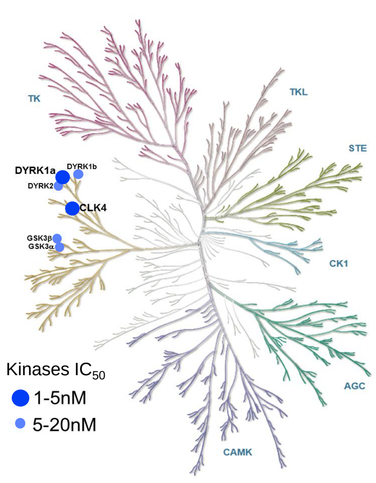
Conclusions

- SM07883 is a potent DYRK1A inhibitor with novel selectivity profile and therapeutic brain and CSF exposures after oral administration in mice
- In preclinical models compared with vehicle, SM07883:
  - Reduced Tau pathology (pTau, aggregation, NFTs)
  - Improved functional deficits and health of Tau transgenic mice
  - Reduced associated neuroinflammation
- SM07883 may provide therapeutic, disease modifying effects in tauopathies

Results

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

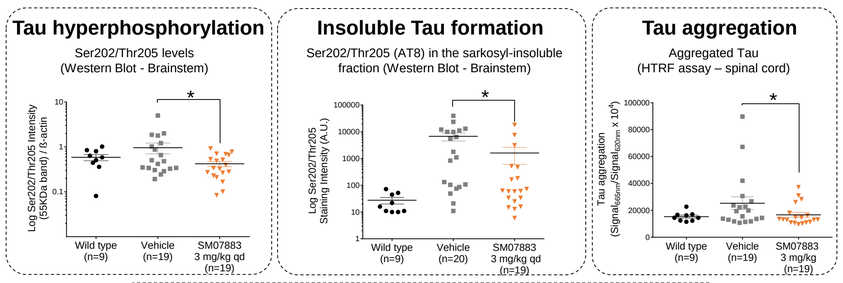




	Full IC_{50} (nM)	Fold over DYRK1A
DYRK1A	1.6	-
CLK4	2.8	2
DYRK1B	7.9	5
GSK-3β	11	7
GSK-3α	11	7
DYRK2	16	10

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

Figure 3. SM07883 inhibited Tau pathology in JNPL3 Tau mice



* p<0.05 compared to vehicle

Figure 6. SM07883 treatment of SH-SY5Y cells did not affect 3R/4R ratio

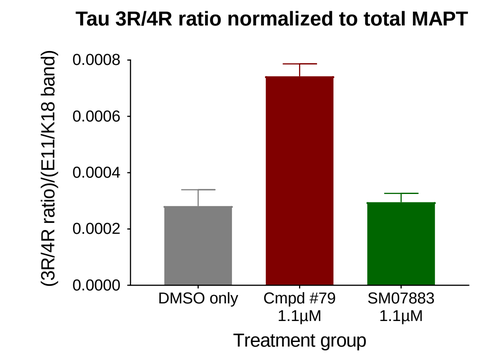
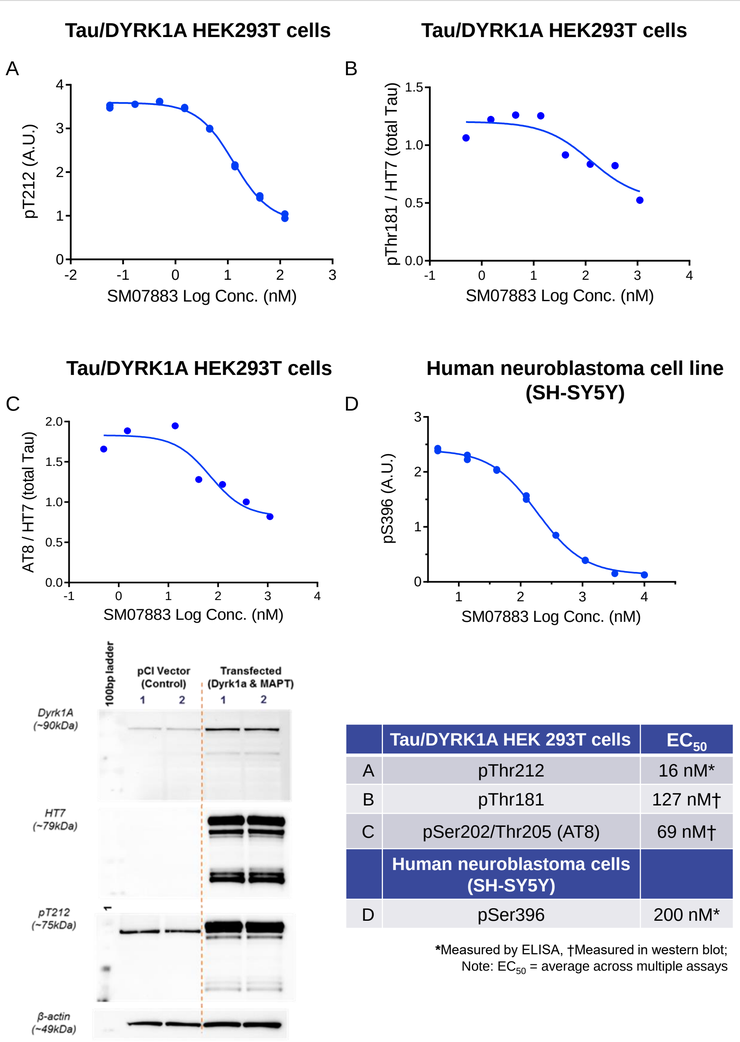


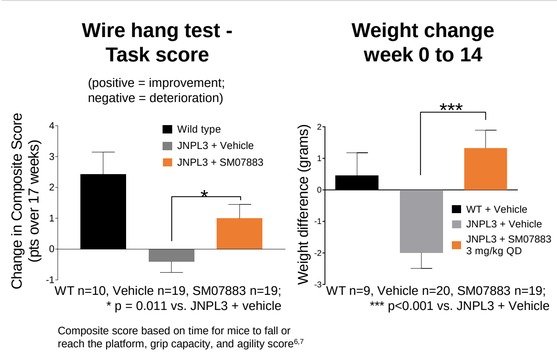
Figure 2. SM07883 potently inhibited DYRK1A-mediated Tau hyperphosphorylation *in vitro*



	Tau/DYRK1A HEK 293T cells	EC_{50}
A	pThr212	16 nM*
B	pThr181	127 nM†
C	pSer202/Thr205 (AT8)	69 nM†
	Human neuroblastoma cells (SH-SY5Y)	
D	pSer396	200 nM*

*Measured by ELISA, †Measured in western blot;
Note: EC_{50} = average across multiple assays

Figure 4. 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

Figure 7. SM07883 was orally bioavailable and brain penetrant in mice with an apparent linear correlation between brain, plasma, and CSF

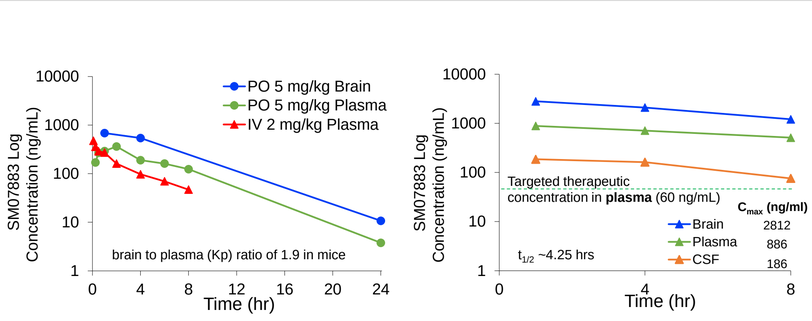


Figure 5. SM07883 reduced Tau-induced glial activation (neuroinflammation) in JNPL3 mice

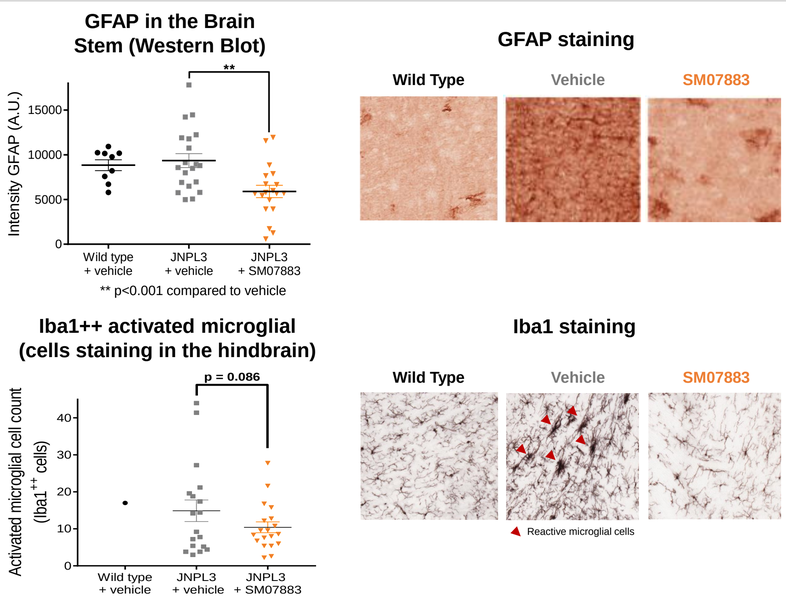
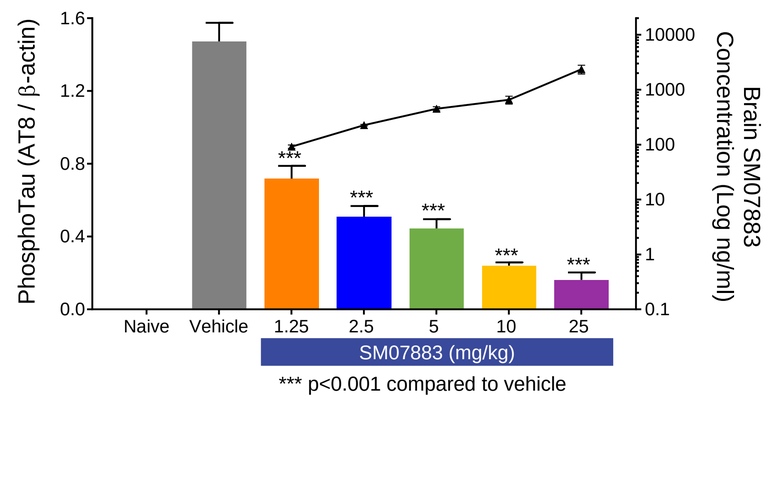


Figure 8. SM07883 reduced Tau phosphorylation in the mouse brain



Methods

- SM07883 selectivity/potency was evaluated in a 460 kinase inhibition panel
- Tau phosphorylation (pTau) inhibition was measured in human Tau/DYRK1A transfected HEK293T cells and human neuroblastoma cells
- Pharmacokinetics in brain, cerebral spinal fluid (CSF) and plasma were analyzed in wild-type (WT) mice after single administration of oral or intravenous SM07883
- Pharmacodynamics were measured in WT mice in an anesthesia-induced transient Tau hyperphosphorylation model[8] with brain lysates quantified using Western Blot for pTau
- Cytokines were measured in plasma and brain tissue by electrochemiluminescence (MesoScale Discovery) from WT mice after stereotaxic injection of LPS/IFNγ
- SH-SY5Y human neuroblastoma cells were treated for 16 hours with DMSO, 1.1µM of a potent CLK inhibitor (Cmpd #79, patent US20160008365A1; CLK2 IC50: 9nM) or 1.1µM of SM07883 and the respective cDNA was used to amplify specific regions of the MAPT gene. Reverse transcription polymerase chain reaction (RT-PCR) was used for identification of splicing (3R) or inclusion of exon 10 (4R). Quantification of 3R/4R was by densitometry for a ratio over total amount of Tau cDNA in the samples. N=2 per condition.
- Ten-month-old JNPL3 mice (P301L human Tau overexpression mutation) were orally administered SM07883 or vehicle (3 mg/kg, QD, 3 months)
  - General tolerability was assessed monitoring weight, morbidity and mortality. Motor coordination was evaluated after dosing using a wire hang test[9,10]
  - pTau, oligomeric and aggregated Tau were biochemically quantified in brainstems and spinal cords. Tau-positive inclusions were detected and quantified by immunostaining with a Ser202/Thr205 (AT8 clone) antibody at 13 months
  - Glial activation was assessed in brainstems using glial fibrillary associated protein (GFAP) staining and Western Blot quantification. Activated microglia were identified by Iba1 staining at 13 months

References

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