# SM07883, a novel DYRK1A inhibitor, reduced Tau pathology – discovery and preclinical development of a potential therapeutic for Alzheimer's disease

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**Poster #P105**

## Background

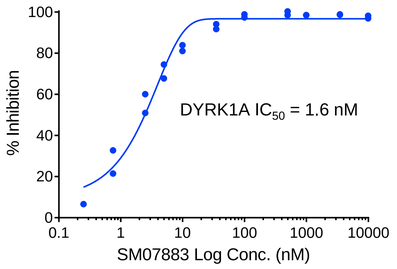
- Dual-specificity tyrosine phosphorylation-regulated kinase-1A (DYRK1A) overexpression in Alzheimer's disease (AD) is correlated to Tau hyperphosphorylation, oligomer, and neurofibrillary tangle (NFT) formation[1]
- Elevated cellular stress signals such as Aβ and TNFα have been shown to induce DYRK1A activity[2-4] and DYRK1A activity contributes to Tau phosphorylation leading to Tau pathology[1,5]
- A potential therapeutic for AD, SM07883 (novel, small molecule, DYRK1A inhibitor) was evaluated, compared to controls as appropriate, 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
  - Safety profile in toxicology studies

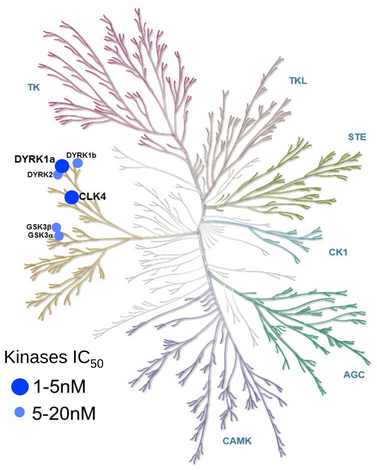
## Conclusions

- SM07883 is a potent DYRK1A inhibitor with a novel selectivity profile and therapeutic brain and CSF exposures after oral administration
- In preclinical models compared to vehicle, SM07883:
  - Reduced Tau pathology (pTau, aggregation, NFTs), improved functional deficits / health in Tau transgenic mice
  - Reduced neuroinflammation
- 'No Observed Adverse Effect Level' was 30x higher in AUC than the minimum efficacious dose in mice and >5x total exposure in monkeys, suggesting a broad therapeutic window for human dosing
- SM07883 may provide therapeutic, disease modifying effects in AD

## Results

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

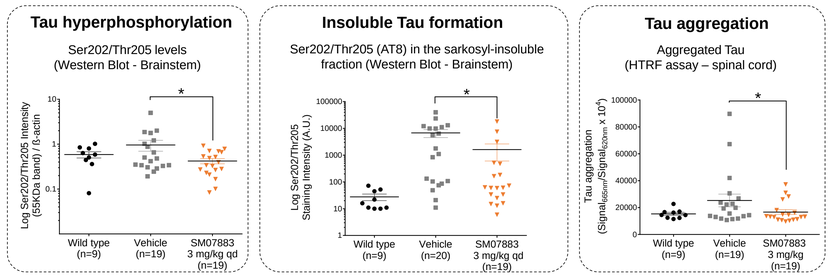


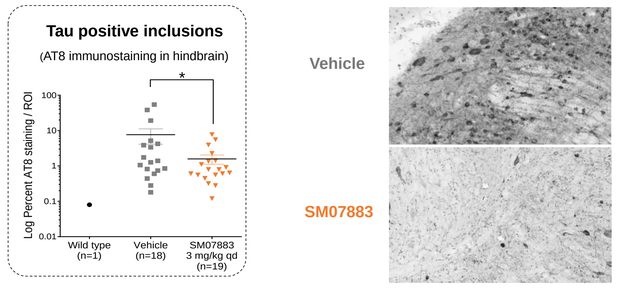




| | Full $IC_{50}$ (nM) | Fold over DYRK1A |
|---|---|---|
| DYRK1A | 1.6 | - |
| CLK4 | 2.8 | 2 |
| DYRK1B | 7.9 | 5 |
| GSK-3β | 11 | 7 |
| GSK-3α | 11 | 7 |
| DYRK2 | 16 | 10 |

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

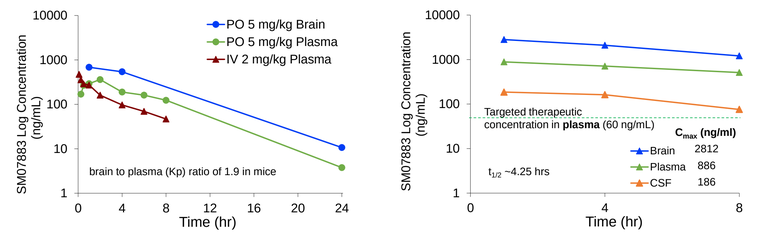
### Figure 4. SM07883 inhibited Tau pathology in JNPL3 Tau mice



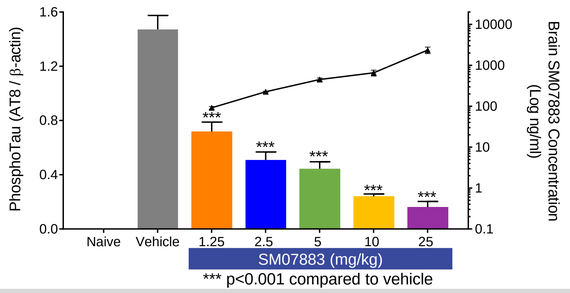




* p<0.05 compared to vehicle

### Figure 7. SM07883 was orally bioavailable and brain penetrant in mice; apparent log-linear correlation between brain, plasma, and CSF absorption

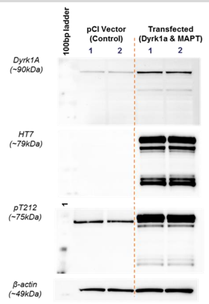


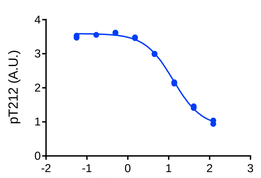

### Figure 8. SM07883 reduced Tau phosphorylation in the mouse brain




*** p<0.001 compared to vehicle

### Figure 2. SM07883 potently inhibited DYRK1A-mediated Tau hyperphosphorylation

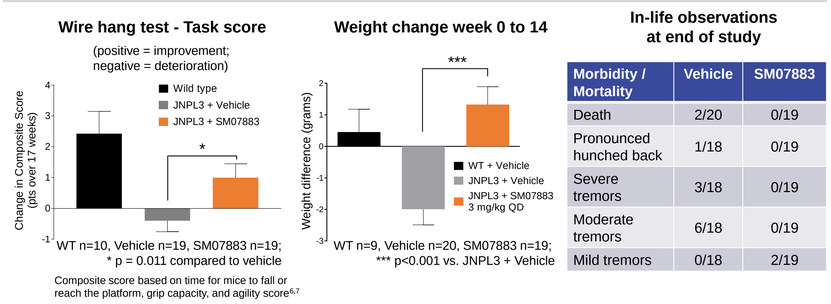



| Tau/DYRK1A HEK 293T cells | $EC_{50}$ |
|---|---|
| pThr212 | 16 nM* |
| pSer2-2/Thr205 (AT8) | 69 nM† |
| pThr181 | 127 nM† |
| **Human neuroblastoma cells (SH-SY5Y)** | |
| pSer396 | 200 nM* |

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

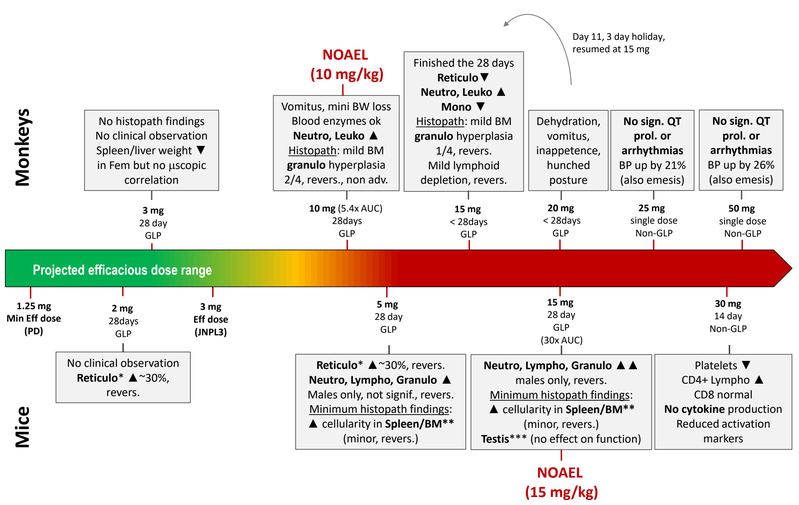
### Figure 5. SM07883 improved motor function, weight, and general health of JNPL3 Tau mice




**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 9. Toxicology studies suggested a broad therapeutic window

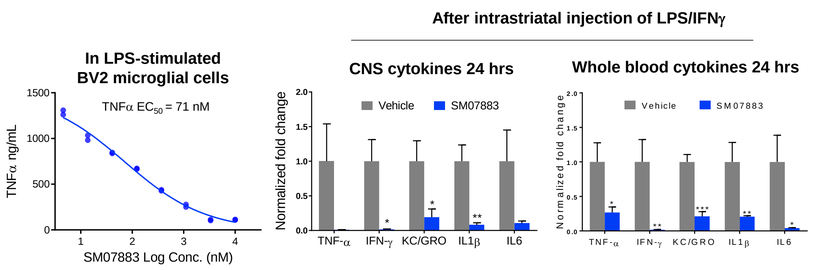



Fold AUC based on 550 h.ng/ml minimum efficacious dose in mice
* No correlative alterations in red cell mass
** Increase hematopoietic cellularity - not dose dependent
*** Normal spermatogenesis and abundance of sperm within the tubule

*In vitro* and *in vivo* studies demonstrated that SM07883 had **low potential for genotoxicity in human**

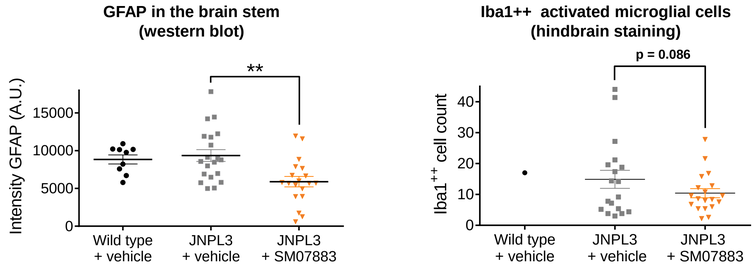
Adv: Adverse
BW: Body weight
BM: Bone marrow
Revers: Reversible (28 day recovery)
BP: Blood pressure
Signif: Significant
Prol: Prolongation
Fem: Females
Reticulo: Reticulocytes
Neutro: Neutrophils
Leuko: Leukocytes
Granulo: Granulocytes

### Figure 3. SM07883 reduced LPS-stimulated proinflammatory cytokines




* p<0.05, ** p<0.01, *** p<0.001 compared to vehicle

### Figure 6. SM07883 reduced Tau-induced glial activation (neuroinflammation) in JNPL3 mice




** p<0.01 compared to vehicle

## Methods

- SM07883 selectivity and potency were evaluated in an inhibition panel of 460 kinases
- Inhibition of Tau phosphorylation (pTau) was measured in human Tau/DYRK1A transfected HEK293T cells and human neuroblastoma cells
- 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-induced transient Tau hyperphosphorylation model[8] with brain lysates quantified using Western Blot for pTau
- The effects of SM07883 on LPS-induced TNF-α secretion were measured in cultured BV-2 microglial cells
- Cytokines were measured in plasma and brain tissue by electrochemiluminescence (MesoScale Discovery) from WT mice after stereotaxic injection of LPS/IFNγ
- 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 by monitoring weight, morbidity and mortality, and motor coordination was evaluated biweekly after treatment initiation using a wire hang test[6,7]
  - pTau, oligomeric and aggregated Tau were biochemically quantified in brain stems 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 the brainstems using glial fibrillary associated protein (GFAP) staining and Western Blot quantification, and activated microglia were identified by Iba1 staining at 13 months
- GLP-compliant, 28-day, repeat-dose oral toxicity studies (QD) in both mice and rhesus monkeys were conducted with in-life, recovery time, clinical pathology, histopathology, and toxicokinetic evaluations

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