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TAU PATHOLOGY REDUCTION WITH SM07883, A NOVEL, POTENT, AND SELECTIVE ORAL DYRK1A INHIBITOR - A POTENTIAL THERAPEUTIC FOR ALZHEIMER'S DISEASE

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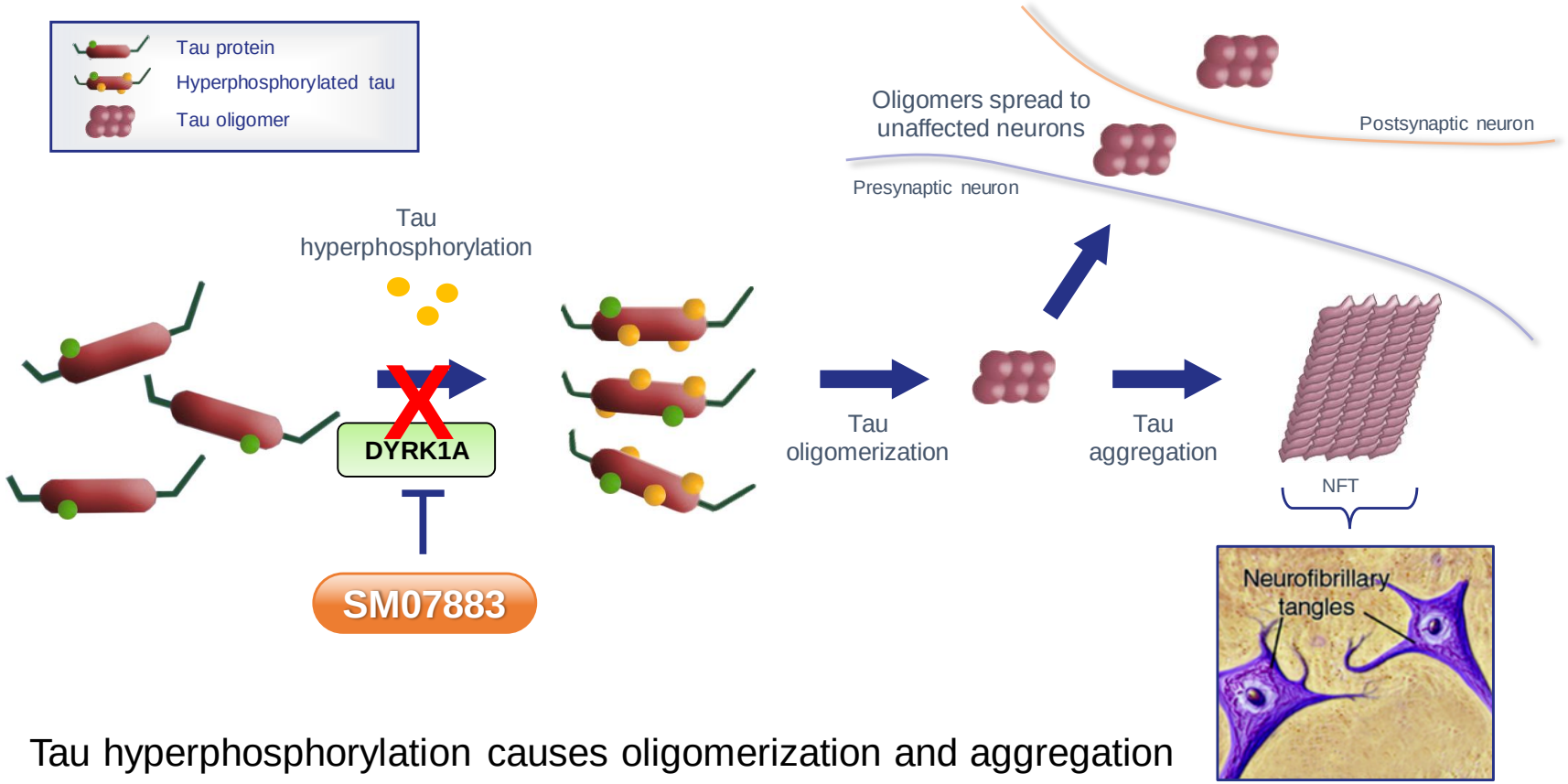
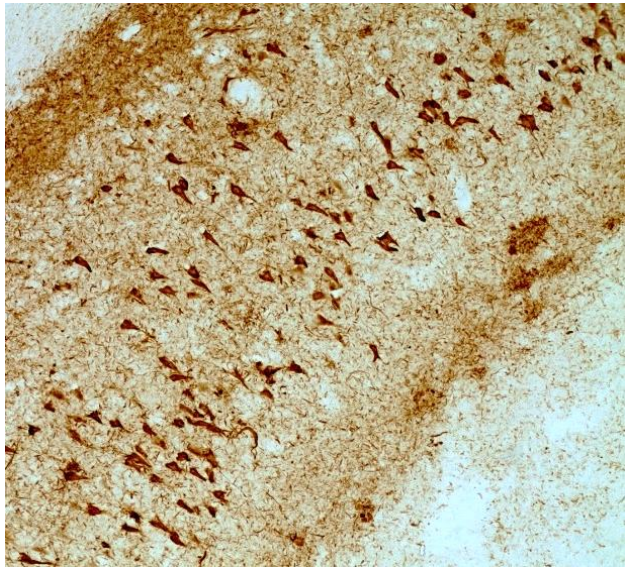
- All authors are employees and shareholders of Samumed LLC
- This presentation is not intended to provide a comprehensive overview of all studies using SM07883
- SM07883 is an investigational compound; SM07883 has not been approved by the US Food and Drug Administration (FDA) or any other pharmaceutical regulatory authority, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidate
- While the complete mechanism of action (MOA) for SM07883 is unknown, further investigation is being conducted. All of the MOA information is based on non-clinical data and the relationship to clinical benefit is unknown
- This presentation is intended as a scientific exchange of medical information, is provided for educational purposes only, and is not intended for any promotional purpose or to offer medical advice

Tau hyperphosphorylation and pathology





NFT staining in hippocampus of a 63 year old AD patient

- Tau hyperphosphorylation causes oligomerization and aggregation leading to neurofibrillary tangles (NFTs)[1]
- Tau oligomers are believed to spread across the synapse to unaffected neurons[2]
- **Inhibition of DYRK1A activity may reduce tau hyperphosphorylation and related inflammation thus reducing the pathogenesis of Alzheimer's Disease (AD) or other chronic tauopathies**

1. Selkoe, DJ *Nat Cell Biol* 2004
2. Walsh, DM & Selkoe, DJ. *Nat. Rev. Neurosci.* 2016

Tau Pathway figures adapted from Šimić, G. et al. *Biomolecules.* 2016
NFT Illustration adapted from Alzheimer's Disease Research, a program of the BrightFocus Foundation.

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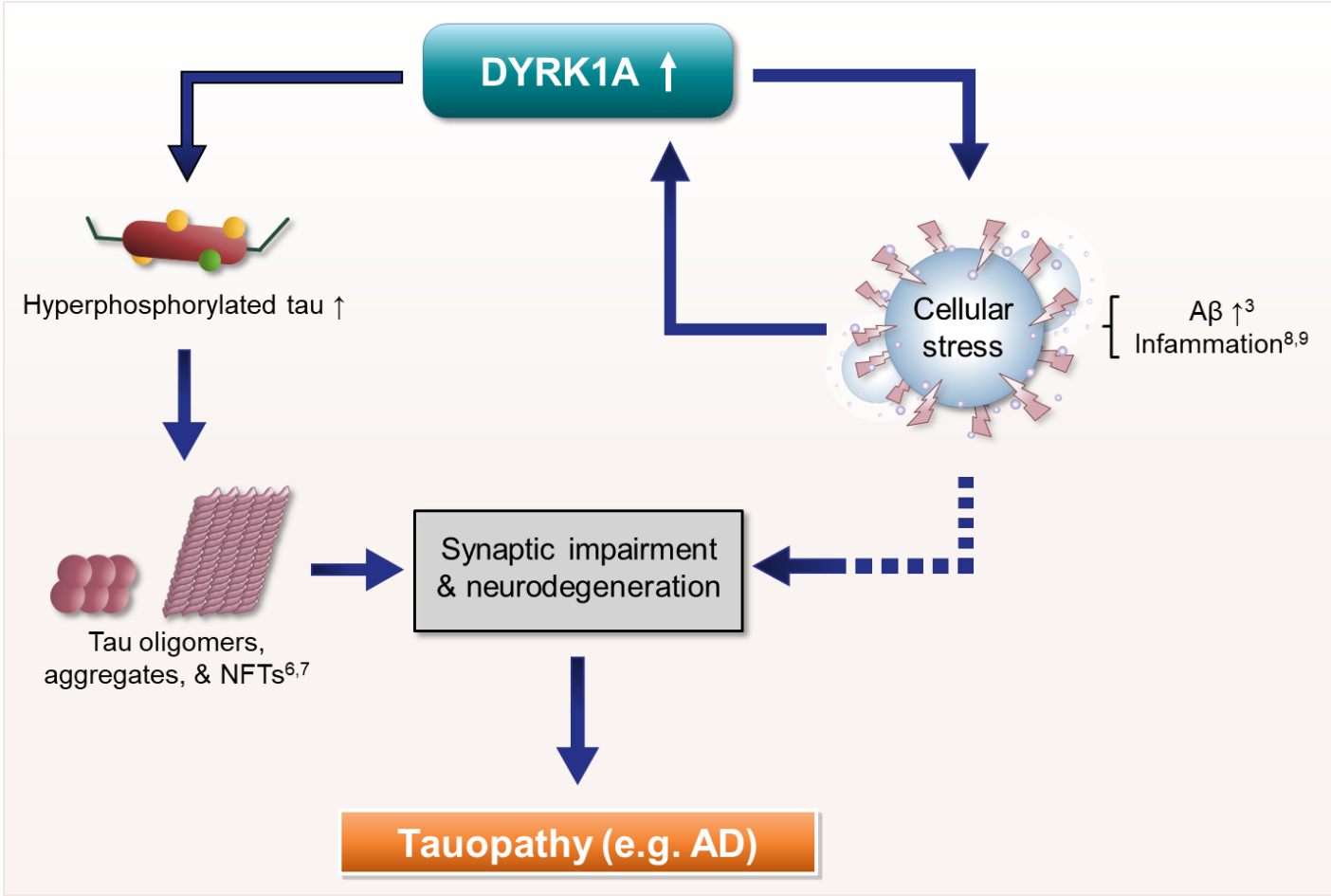
Mechanism of action of SM07883, a potent DYRK1A kinase inhibitor with a novel target profile

- DYRK1A is a novel target found overexpressed in AD, Pick's disease and Down syndrome brains[1,2]
  - Regulates phosphorylation of tau[1,2], APP (Aβ)[3], and presenilin[4]
  - Primes tau for further phosphorylation (hyperphosphorylation) and regulates GSK-3β (also involved in phosphorylation of tau)[5]
- SM07883 inhibited DYRK1A-mediated tau phosphorylation thereby preventing tau oligomerization, aggregation, and NFT formation



1. Ferrer, et al., *Neurobiol. Dis.* 2005
2. Ryoo SR, et al. *J. Neurochem.* 2008
3. Branca C et al. *Aging Cell* 2017
4. Ryu, Y. S. et al. *J. Neurochem.* 2010
5. Kay LJ et al. *Adv Protein Chem Struct Biol* 2016
6. Choi SH, et al. *Nature.* 2014
7. Selkoe DJ. *Nat Cell Biol.* 2004
8. Khor, B. et al. *Elife* 2015
9. Choi and Chung *Exp Neurobiol.* 2011

SM07883 Drug Discovery

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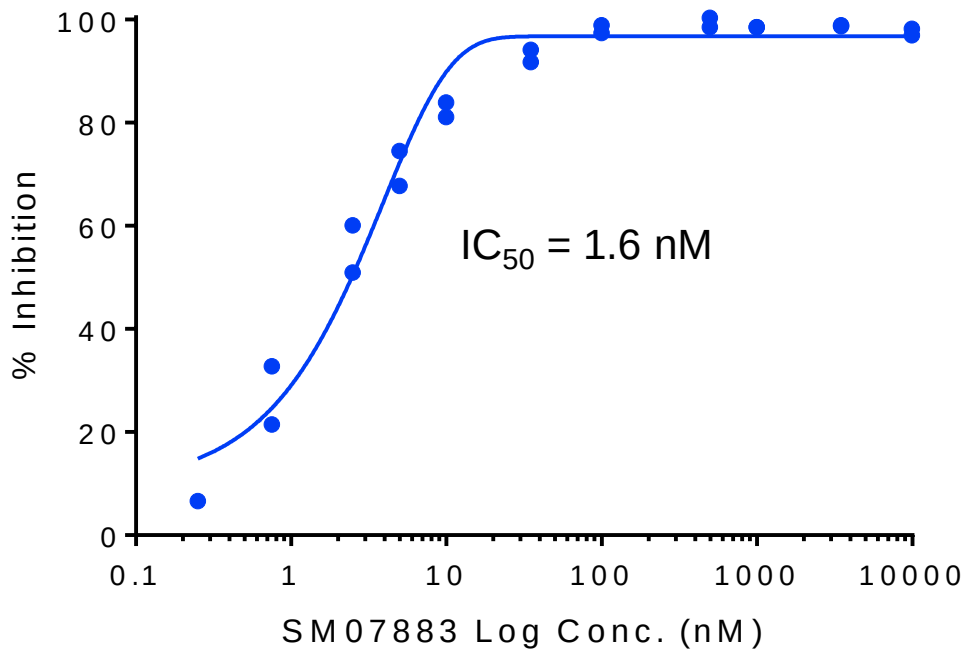
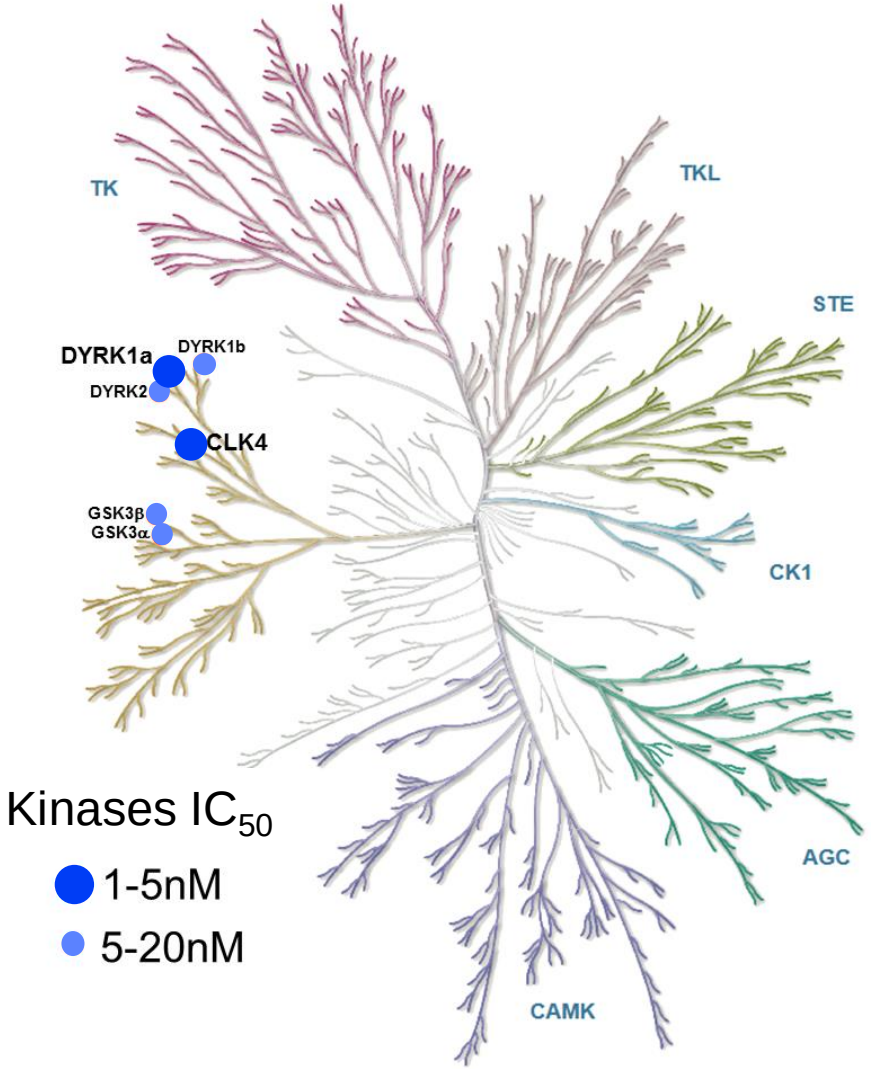
SM07883, a potent DYRK1A kinase inhibitor with a novel selectivity profile

SM07883 – DYRK1A kinase inhibition



Kinases within 15 fold of DYRK1A IC_{50}



- In kinase inhibition screen assays of 414 kinases, SM07883 showed relatively specific and potent inhibition of DYRK1A
  - 5 additional kinases within the 15-fold range of DYRK1A IC_{50}

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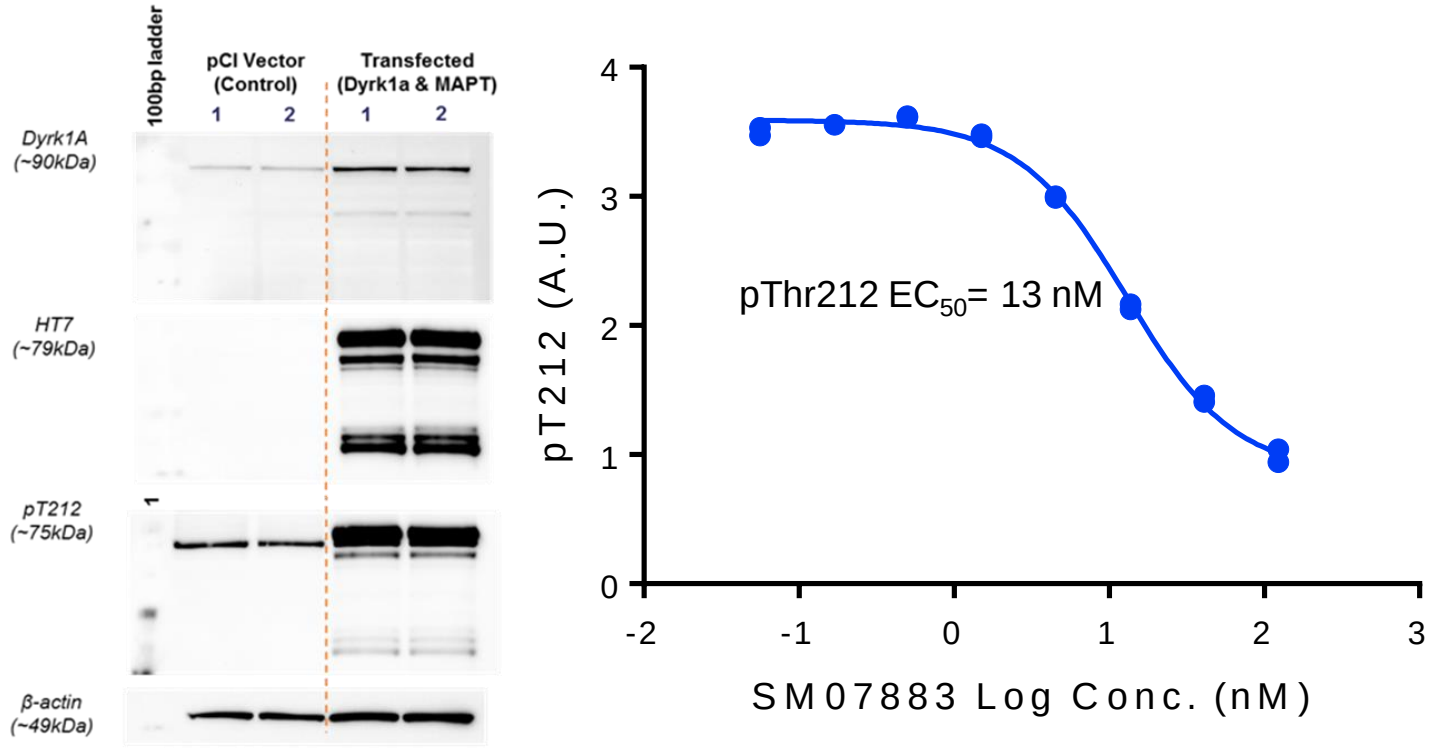
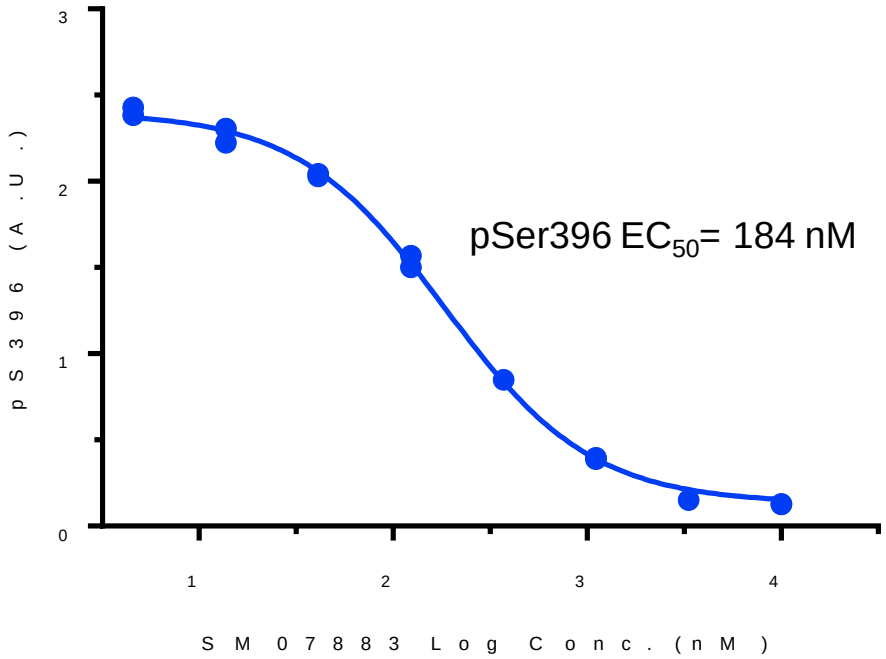
SM07883 inhibited tau phosphorylation *in vitro*

DYRK1A-induced tau hyperphosphorylation
in Tau/DYRK1A HEK293T cells



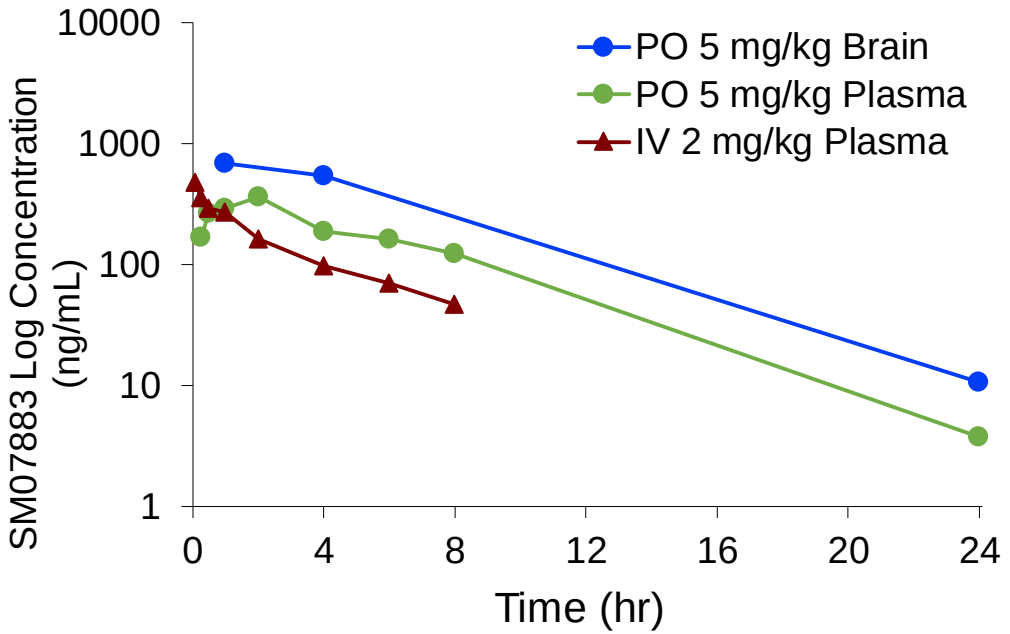
Tau phosphorylation in a human neuroblastoma cell line (SH-SY5Y)



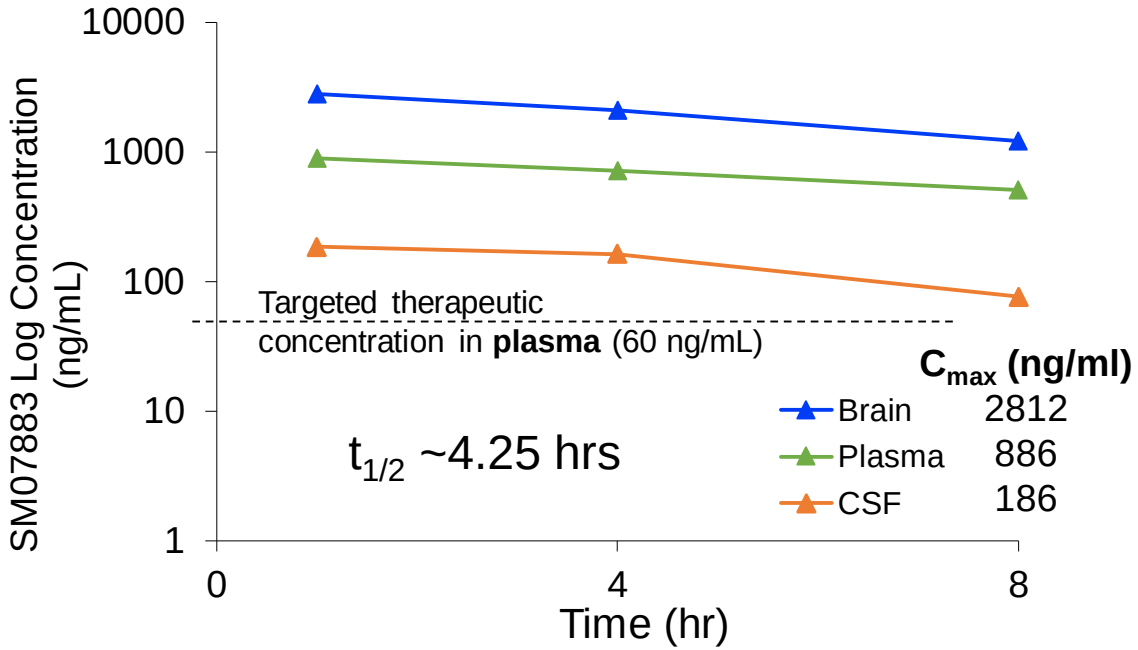
SM07883 potently inhibited tau hyperphosphorylation in two human cell lines

SM07883 was bioavailable and brain penetrant at therapeutic levels in mice

Mouse PK PO/IV administration



Mouse PK at 10mg/kg, PO administration



- **Good bioavailability** across species 35% – 100%
- **High permeability** and **limited efflux** (Caco-2 Efflux ratio: 0.283)
- **Brain / Plasma ratio: >3** in mice (F_{ub}/F_{up}=0.64); ~ 30% plasma free fraction across species; ~ 6% brain free fraction (rodent)
- **High correlation of PK between brain, CSF and plasma**; half life was consistent between plasma and brain
- **Plasma levels may be a surrogate for CNS exposure**
- Allometric projection >**11 hrs half life in human plasma** and potentially amenable to once a day dosing in human

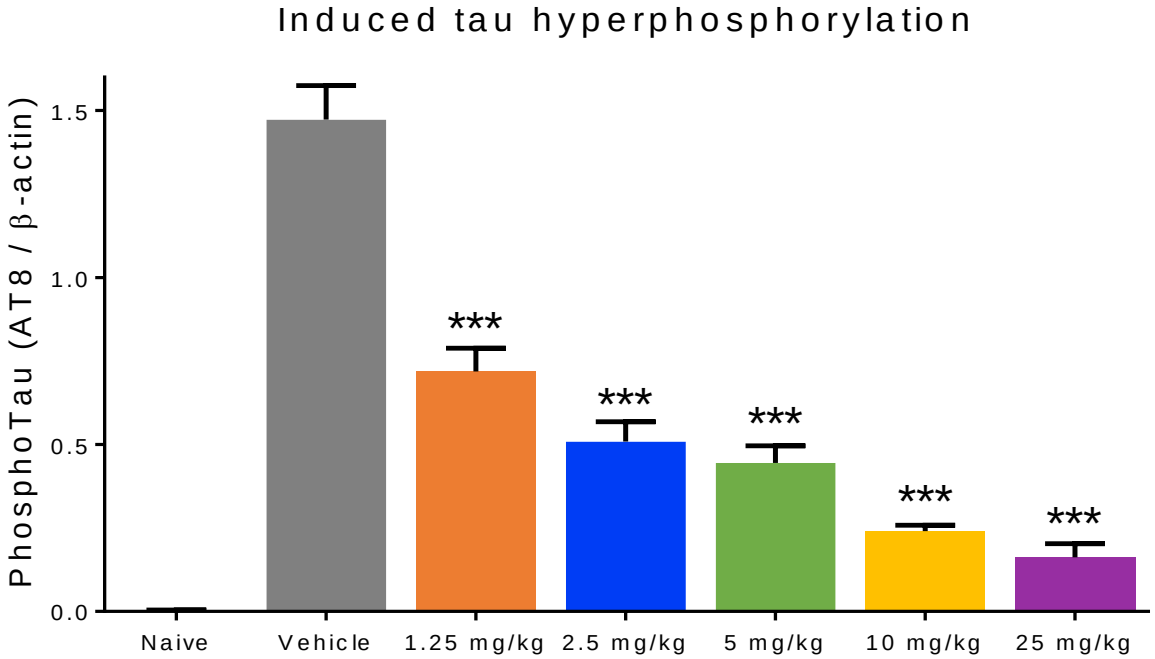
Animal toxicology and safety findings

- No Observed Adverse Effect Level' was 30x higher in AUC than the minimum efficacious dose (1.25 mg/kg/day) in mice
  - 8x total exposure in monkeys (GI intolerance was the dose-limiting factor, reversible)
- No cardiac abnormalities (e.g. QT prolongation, arrhythmia) were detected up to 50 mg/kg in monkey
  - hERG channel inhibition IC_{50} of 0.6 µM
- *In vitro* and *in vivo* studies demonstrated that SM07883 had low potential for genotoxicity in human
- Suggested a broad therapeutic window for human dosing

Preclinical tau efficacy studies

SM07883 reduced tau hyperphosphorylation in the mouse brain

- **Single oral dose** of SM07883 in wild type mice, followed (3 hr) by anesthesia-induced transient tau hyperphosphorylation[1] with brain collection at 4h and western blot for pTau
- SM07883 produced a **dose-dependent inhibition** of pTau
- Significant reduction of pTau after a single dose **as low as 1.25 mg/kg** compared to vehicle



	SM07883 Concentration				
Plasma (ng/ml)	60	145	256	360	1283
Brain (ng/ml)	92	226	451	655	2353

*** p<0.001 compared with vehicle

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1. Bretteville et al., *Scientific reports*, 2012

Tau transgenic mouse model for preclinical efficacy

- JNPL3 mice carry a mutated form of **human tau** from autosomal dominant tau FTD patients
- In this model, tau is primarily present in the **brain stem and spinal cord**
  - Decreased motor coordination, no cognitive deficit

Pathological tau staining in the brain stem and spinal cord of JNPL3 mice (AT8 antibody, brown)

- The P301L mutation in JNPL3 mice results in **tau hyperphosphorylation at sites similar to AD brains** (Thr181, Ser202/Thr205 [AT8 epitope], Thr212, Thr231, Ser396)
- JNPL3 mice (10 months old) treated with QD SM07883 for 14 weeks and evaluated for:
  - Tau hyperphosphorylation
  - Formation of tau oligomers, aggregation, and NFTs
  - Neuroinflammation
  - Health and motor deficits

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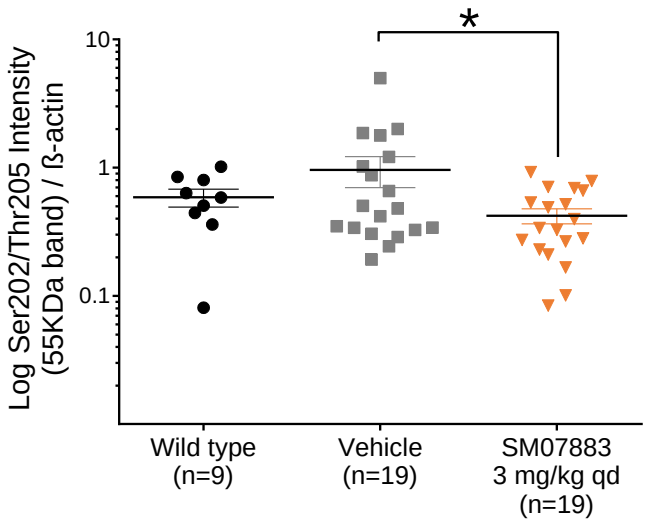
Lewis, J. *et al. Nat. Genet.* 2000

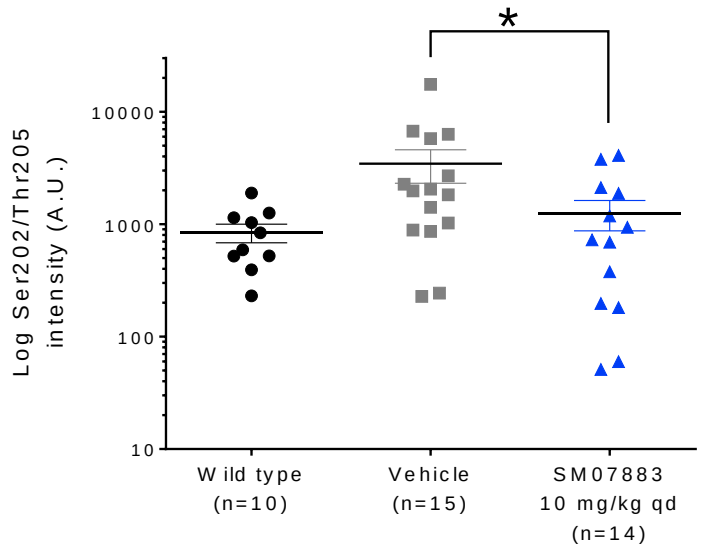
SM07883 reduced tau hyperphosphorylation in JNPL3 mice

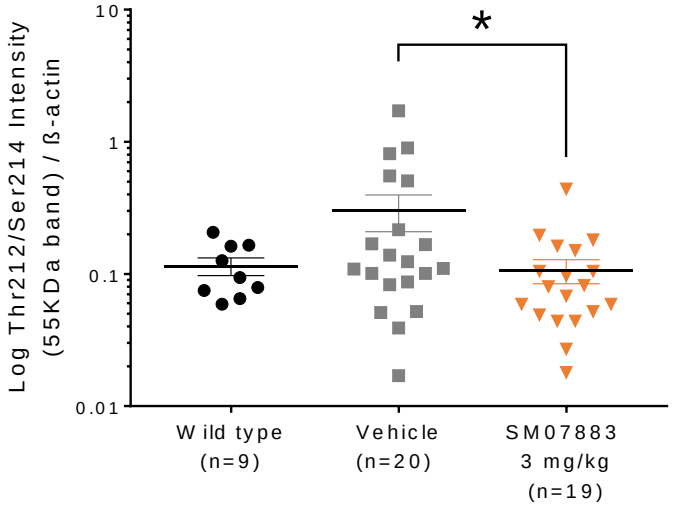
- Western blots of brainstem **Ser202/Thr205 (Top)** and **Thr212/Ser214 (Bottom)** levels
- SM07883 (3 mg/kg or 10 mg/kg SM07883 QD) **reduced tau hyperphosphorylation** at the AD pathogenic epitopes compared to vehicle

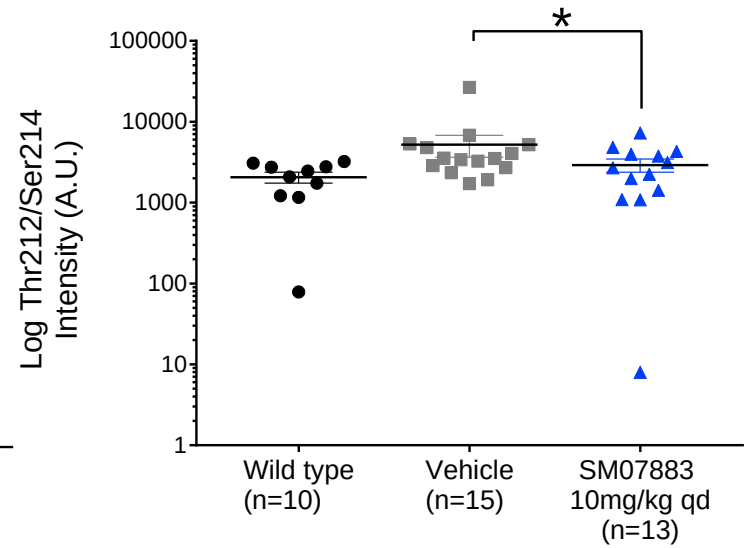
3 mg/kg



10 mg/kg







* p<0.05 compared to vehicle

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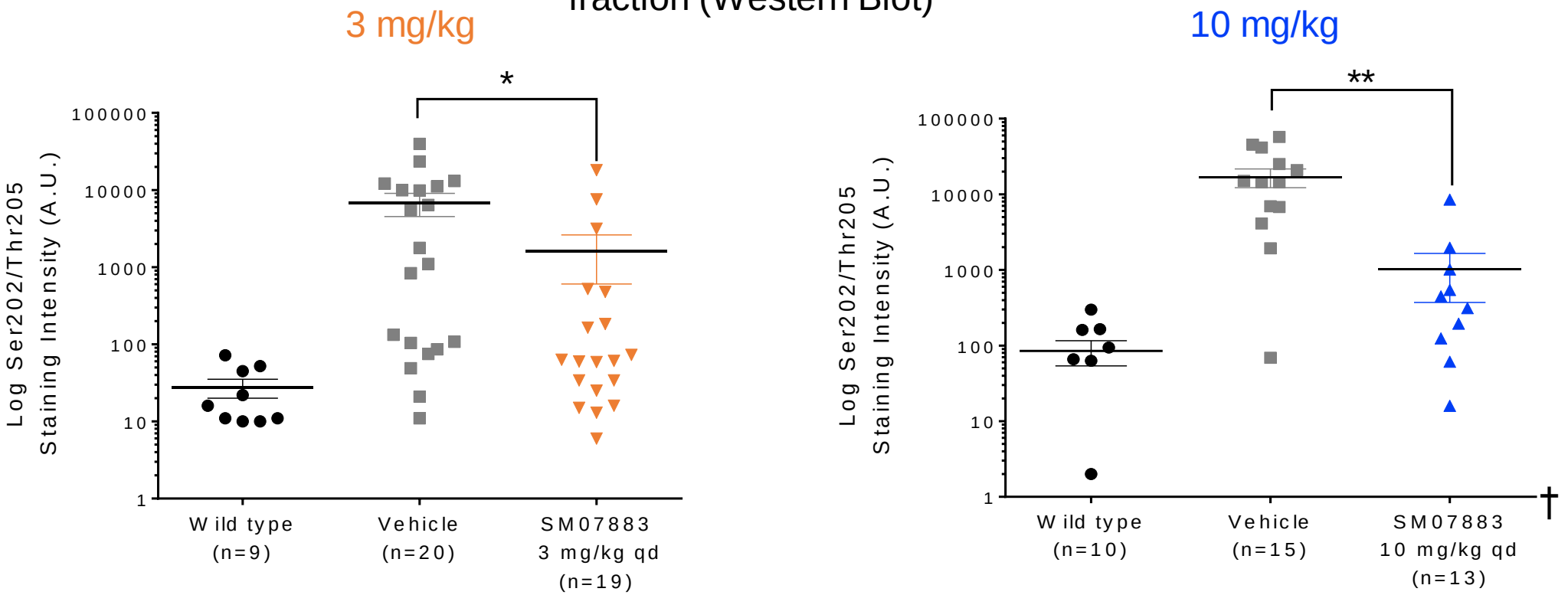
SM07883 prevented formation of insoluble tau in JNPL3 mice

Ser202/Thr205 in the sarkosyl-insoluble fraction (Western Blot)



SM07883 (3 mg/kg or 10 mg/kg SM07883 QD) **inhibited insoluble tau formation** in the brainstem at the AD pathogenic Ser202/Thr205 (AT8) epitope compared to vehicle (sarkosyl insoluble fraction)

† Only positive values plotted (eight 0 or negative values not shown 3 WT, 2 Veh, 3 SM07883)

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

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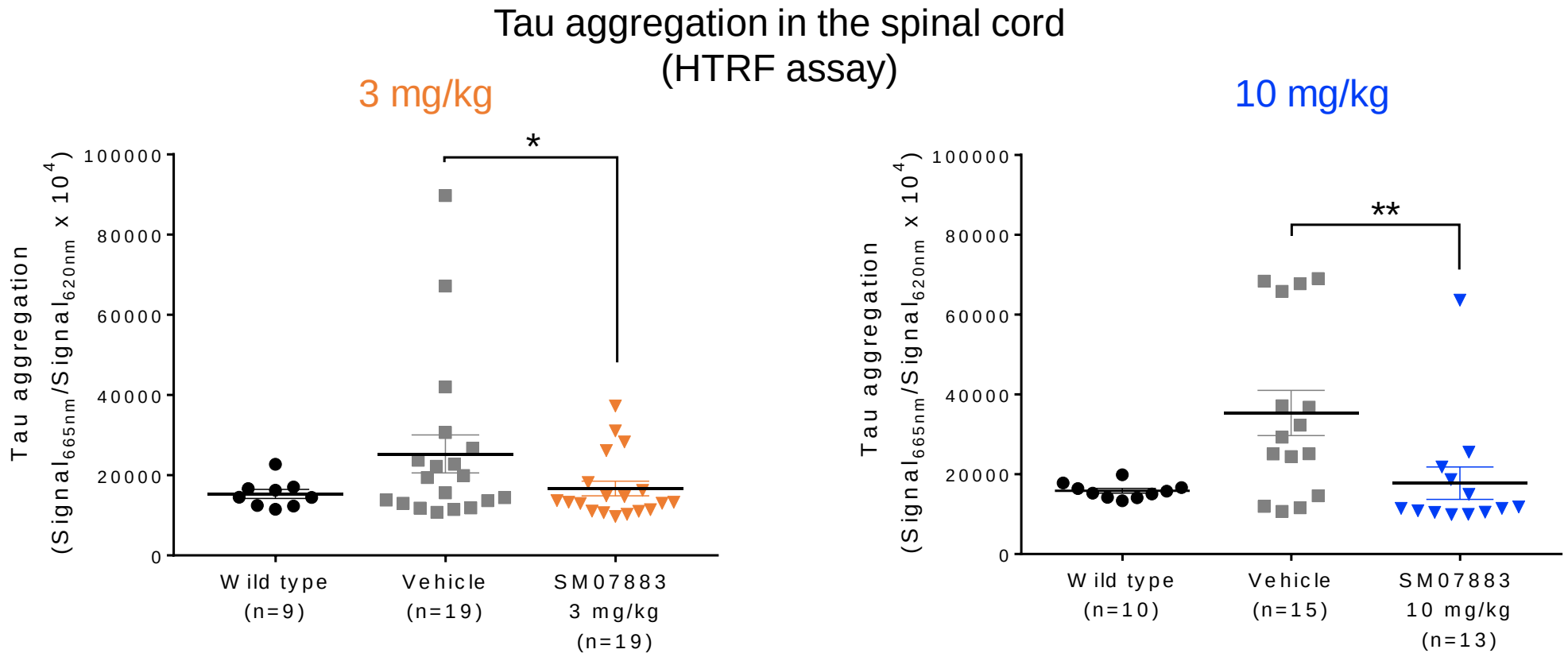
SM07883 prevented tau aggregation in JNPL3 mice



SM07883 (3 mg/kg or 10 mg/kg SM07883 QD) **inhibited tau aggregation** in the spinal cord compared to vehicle in a FRET (HTRF) based assay

HTRF: Homogeneous Time Resolved Fluorescence
* p<0.05, ** p<0.01 compared to vehicle

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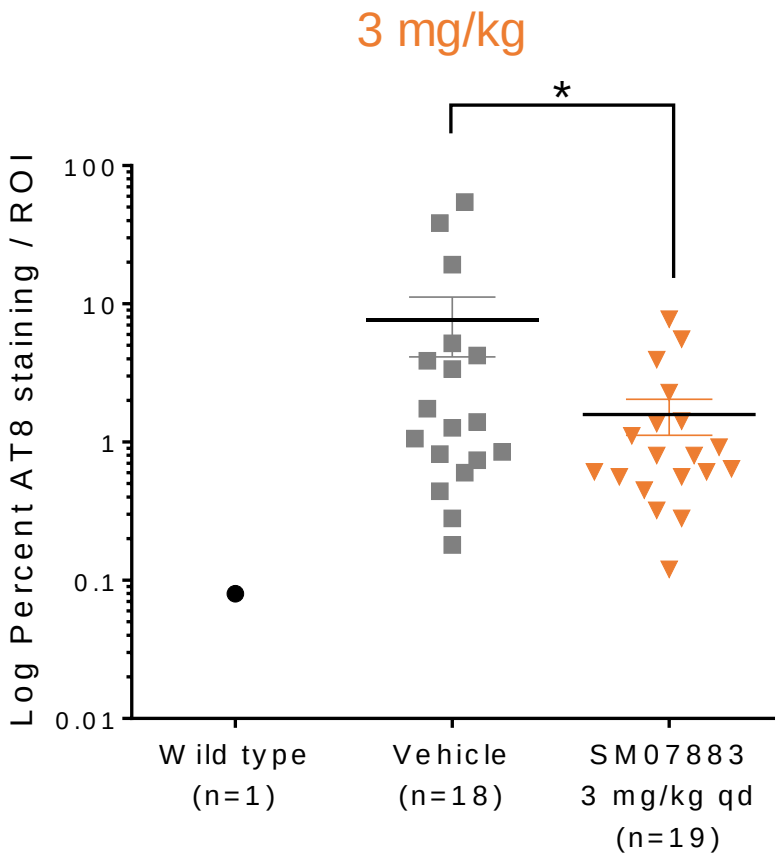
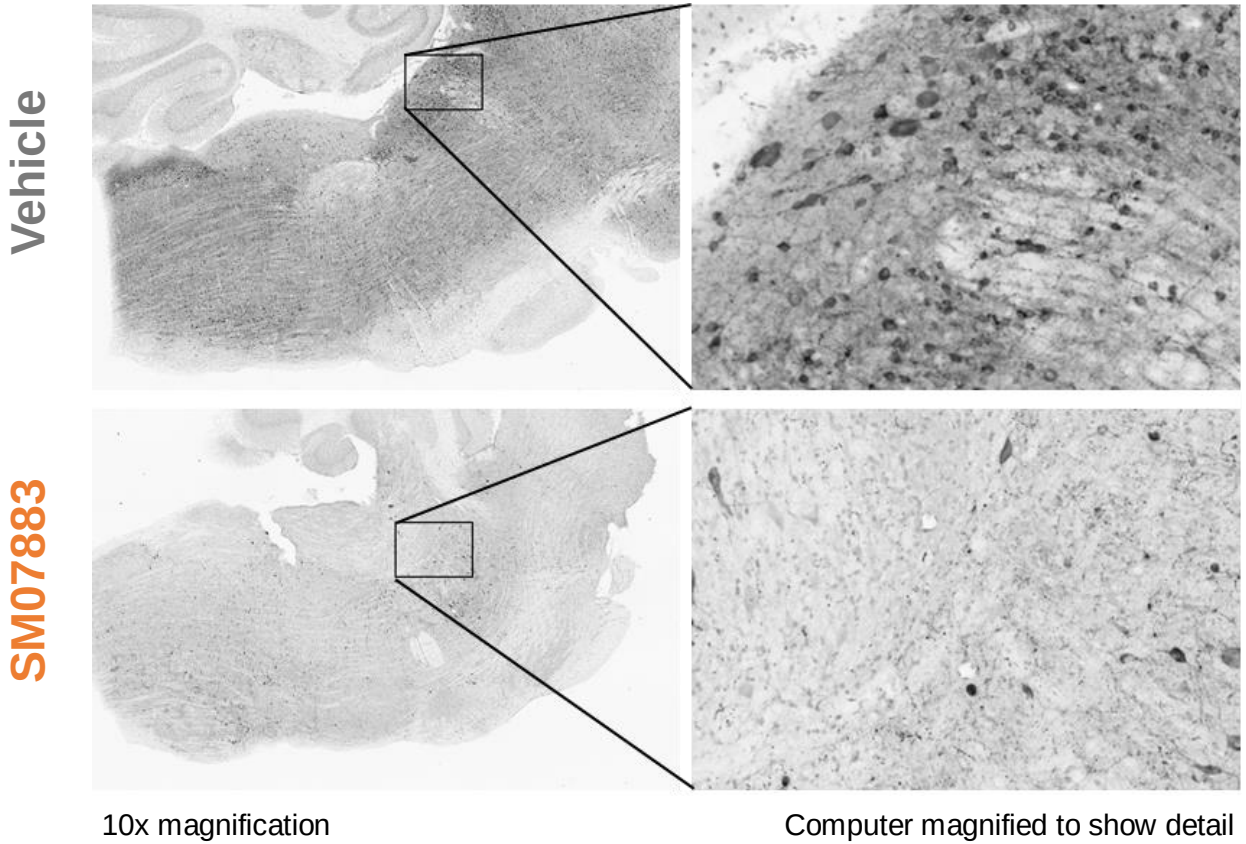
SM07883 reduced the formation of NFTs in JNPL3 mice

Brainstem NFTs
(AT8 immunostaining)





10x magnification

Computer magnified to show detail

SM07883 (3 mg/kg QD shown) significantly reduced the formation of brainstem NFTs compared to vehicle

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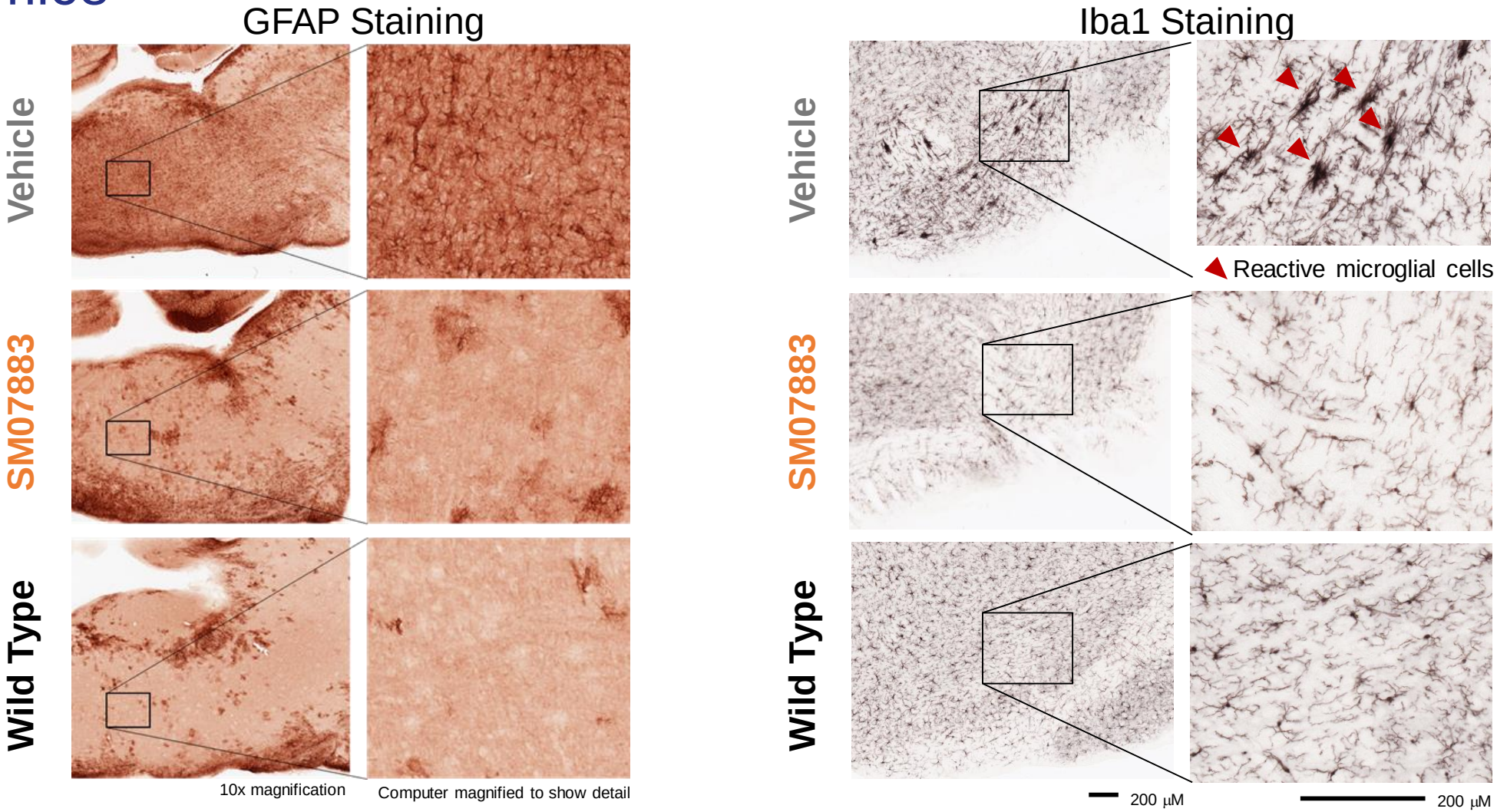
* p<0.05 compared to vehicle

SM07883 reduced tau-induced glial activation (neuroinflammation) in JNPL3 mice



SM07883 significantly **reduced GFAP** (astrocytes) **and Iba1** (activated microglia) **expression** compared to vehicle in the brainstems of JNPL3 mice (representative images shown)

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SM07883 reduced functional deficits in JNPL3 mice

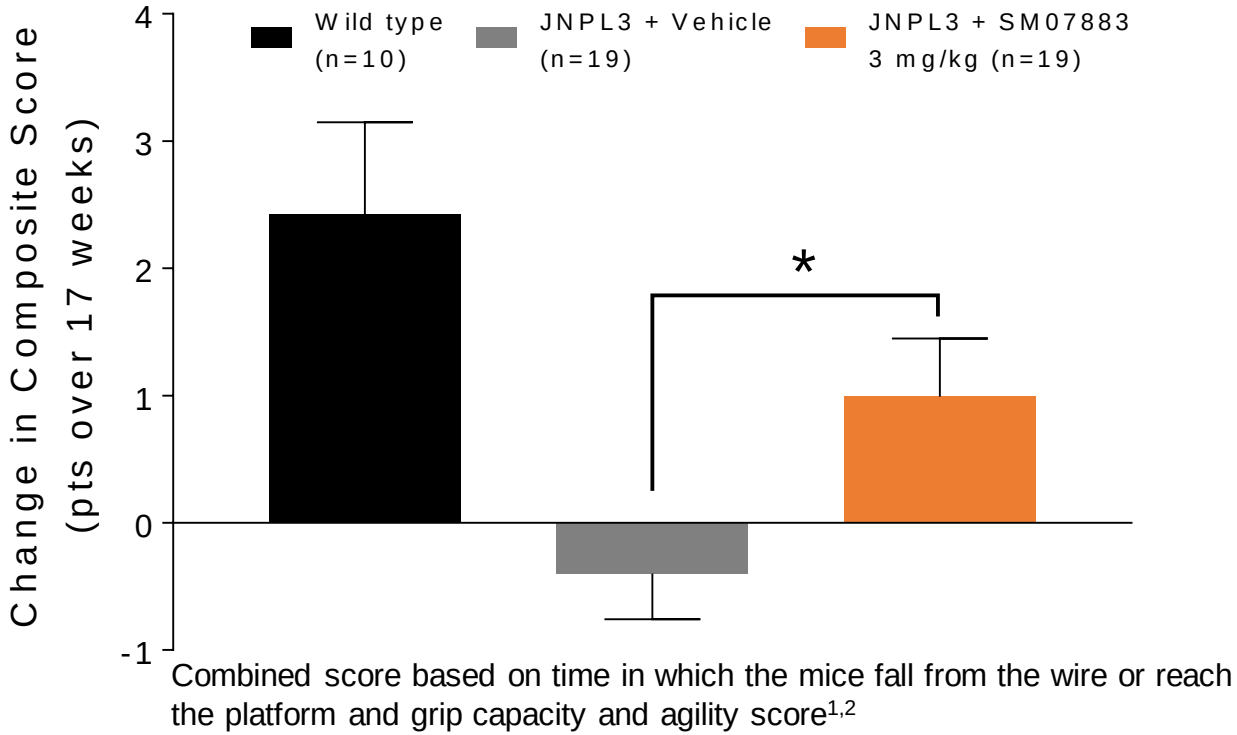
Motor Coordination
(Wire Hang Test Performance)

WT
+ vehicle

JNPL3
+ vehicle

JNPL3
+ SM07883

Task Score
(positive = improvement; negative = deterioration)



Combined score based on time in which the mice fall from the wire or reach the platform and grip capacity and agility score[1,2]

* P = 0.011 compared to vehicle

SM07883 improved motor coordination in JNPL3 mice compared to vehicle

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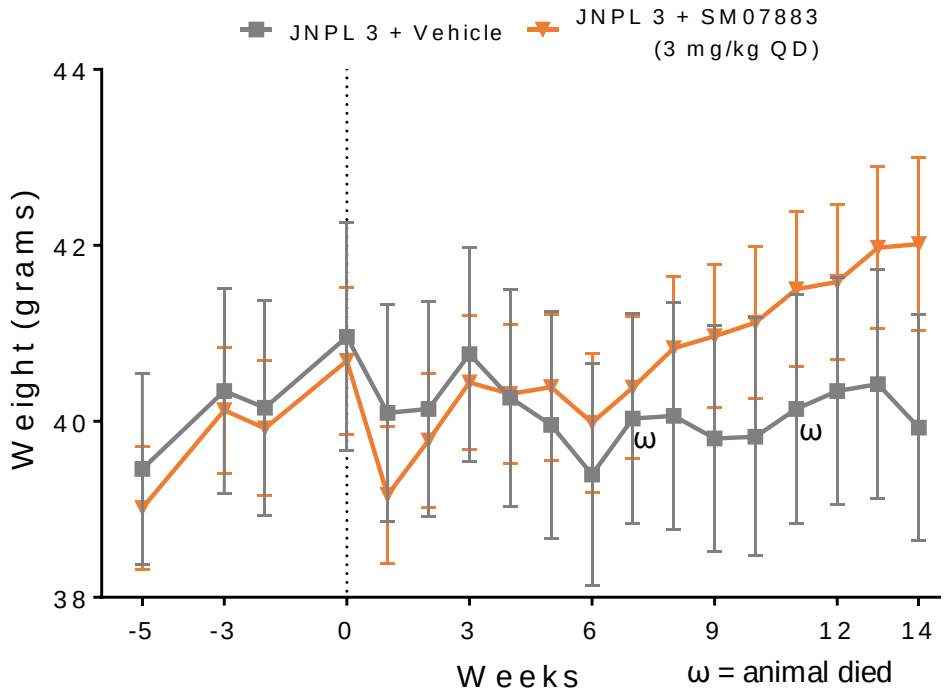
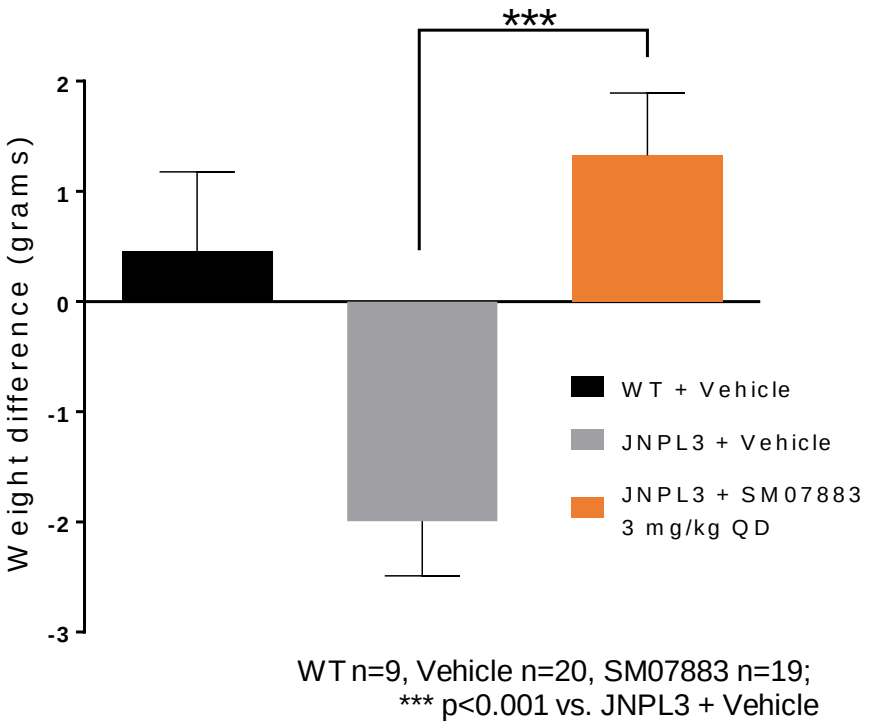
1. Morgan, D. *et al.* J. Alzheimer's Dis. 2008
2. Garcia, MF. *Scholar Commons USF* 2003

SM07883 improved weight & reduced morbidity / mortality of JNPL3 mice

Animal weight



Weight change week 0 to 14



WT n=9, Vehicle n=20, SM07883 n=19;
*** p<0.001 vs. JNPL3 + Vehicle

- JNPL3 mice have low body weight with incidence of morbidities and mortality
- SM07883 treatment **significantly improved body weight** and **empirically improved morbidity / mortality** compared to vehicle

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

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Summary

- SM07883 is a potent DYRK1A inhibitor with a novel selectivity profile that reduced tau hyperphosphorylation in mice
- In tau transgenic mice daily SM07883 compared to vehicle controls reduced:
  - Tau hyperphosphorylation
  - Formation of tau oligomers and aggregation
  - Formation of NFTs
  - Glial activation
- SM07883 demonstrated therapeutic brain and CSF exposures after oral administration in all species tested
  - Potentially amenable for once daily dosing in humans
- IND-enabling studies completed to allow 28 day multiple dose study in humans

➢ SM07883 may provide therapeutic, disease modifying effects in AD

➢ Phase 1 trial in healthy volunteers is planned

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Thank you