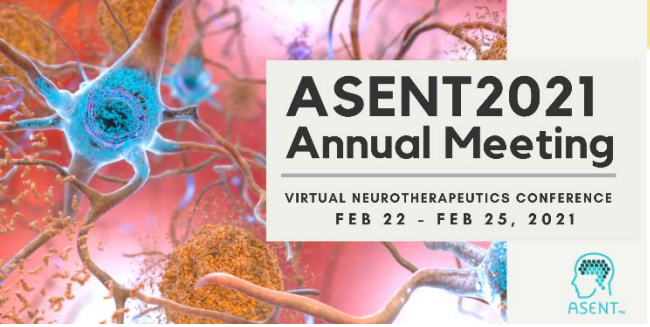


JOHNS HOPKINS
MEDICINE

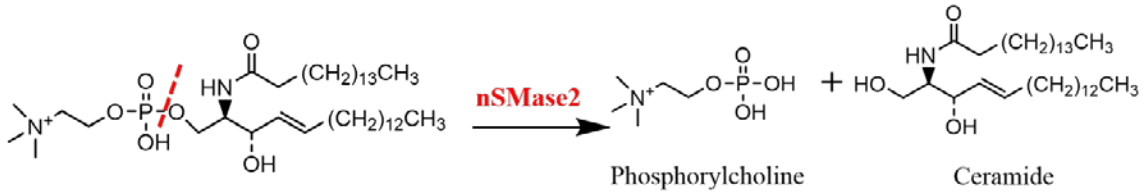
The neutral sphingomyelinase 2 inhibitor PDDC reduces tau burden in Alzheimer's disease mice

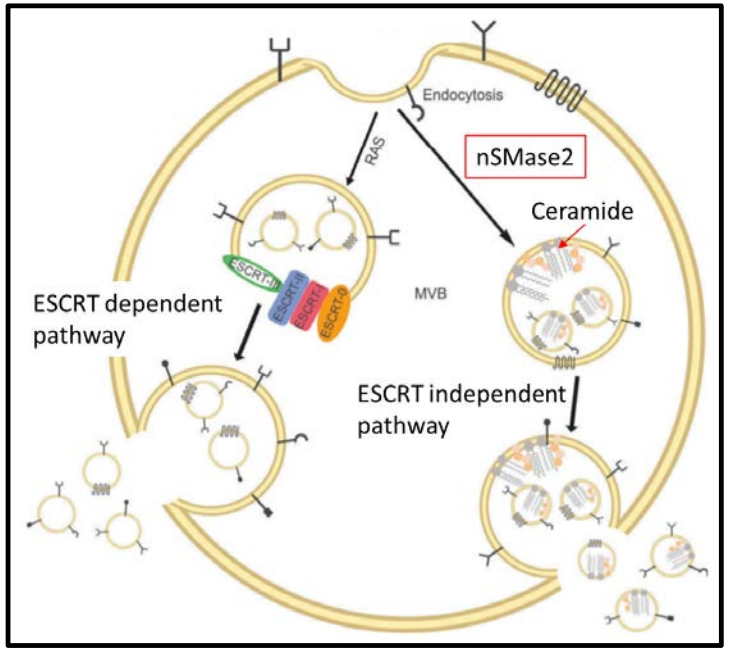
Carolyn Tallon
Johns Hopkins Drug Discovery
ASENT 2021 Meeting

JOHNS HOPKINS
DRUG DISCOVERY

Neutral sphingomyelinase 2 regulates extracellular vesicle release

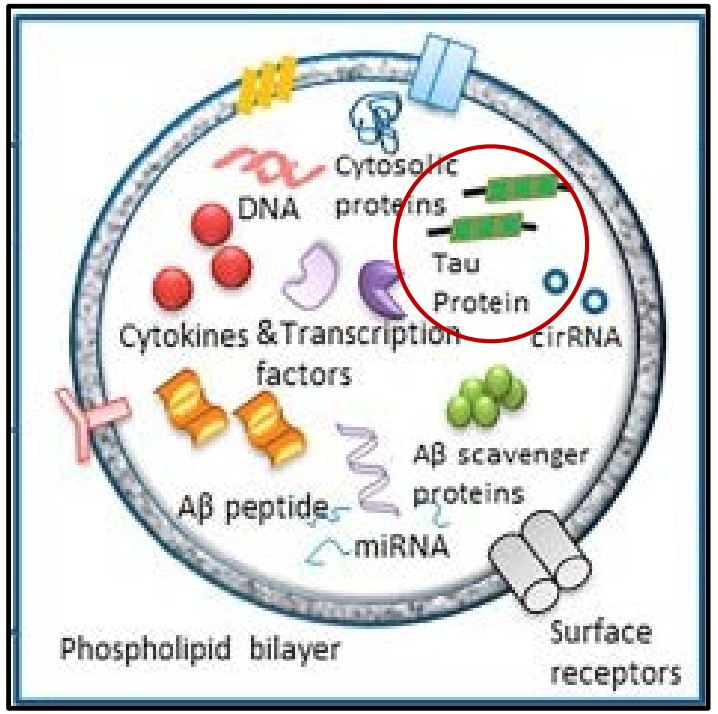
nSMase2 produces ceramide rich EVs





Modified from Catalano and O'Driscoll (2020) *Journal of Extracellular vesicles*

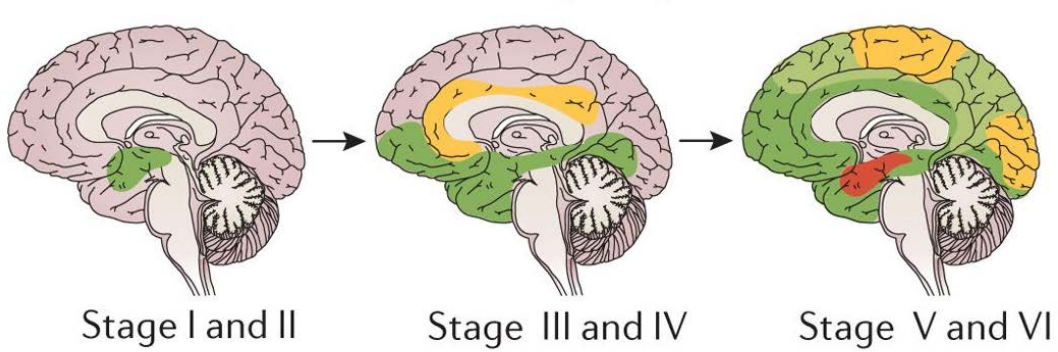
EVs package cargo and transport them



Modified from Trotta et al. (2018) *Biochemical Pharmacology*

AD pathological proteins propagate in the brain using EVs; plasma EVs can be used as a disease marker

Pathological tau spreads from a centralized region out to the cortex



Masters et al. (2015) *Nat Rev Dis Primers*

Content of neuronally-derived EVs in plasma can predict AD

Identification of preclinical Alzheimer's disease by a profile of pathogenic proteins in neurally derived blood exosomes: A case-control study

Massimo S. Fiandaca, Dimitrios Kapogiannis, Mark Mapstone, Adam Boxer, Erez Eitan, Janice B. Schwartz, Erin L. Abner, Ronald C. Petersen, Howard J. Federoff, Bruce L. Miller, Edward J. Goetzl

First published: 14 August 2014 | https://doi.org/10.1016/j.jalz.2014.06.008 | Citations: 32

Association of Extracellular Vesicle Biomarkers With Alzheimer Disease in the Baltimore Longitudinal Study of Aging

Dimitrios Kapogiannis, MD[1]; Maja Mustapic, PhD[1]; Michelle D. Shardell, PhD[2]; et al

» Author Affiliations | Article Information

JAMA Neurol. 2019;76(11):1340-1351. doi:10.1001/jamaneurol.2019.2462

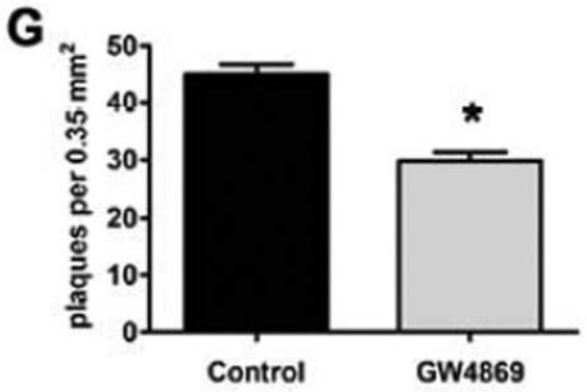
Extracellular vesicle biomarkers of Alzheimer's disease associated with sub-clinical cognitive decline in late middle age

Erden Eren, Jack F. V. Hunt, Michelle Shardell, Sahil Chawla, Joyce Tran, Jeffrey Gu, Nick M. Vogt, Sterling C. Johnson, Barbara B. Bendlin, Dimitrios Kapogiannis

First published: 26 June 2020 | https://doi.org/10.1002/alz.12130 | Citations: 5

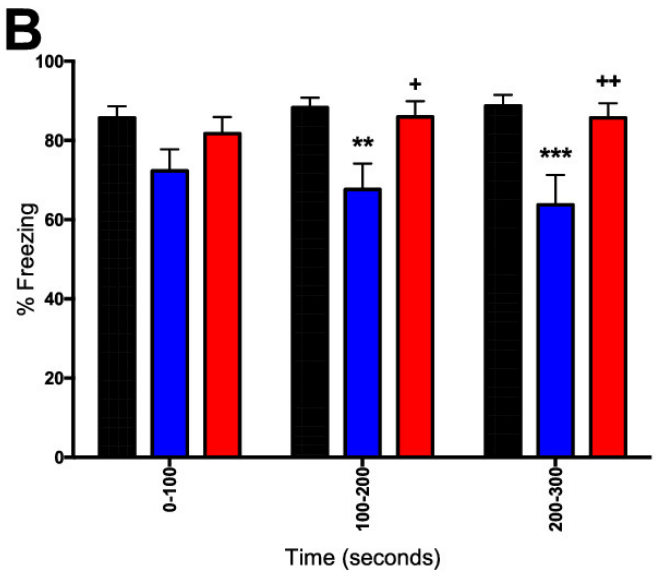
Reducing EV release through nSMase2 inhibition is efficacious in multiple murine AD models

Inhibiting nSMase2 reduced amyloid plaque numbers



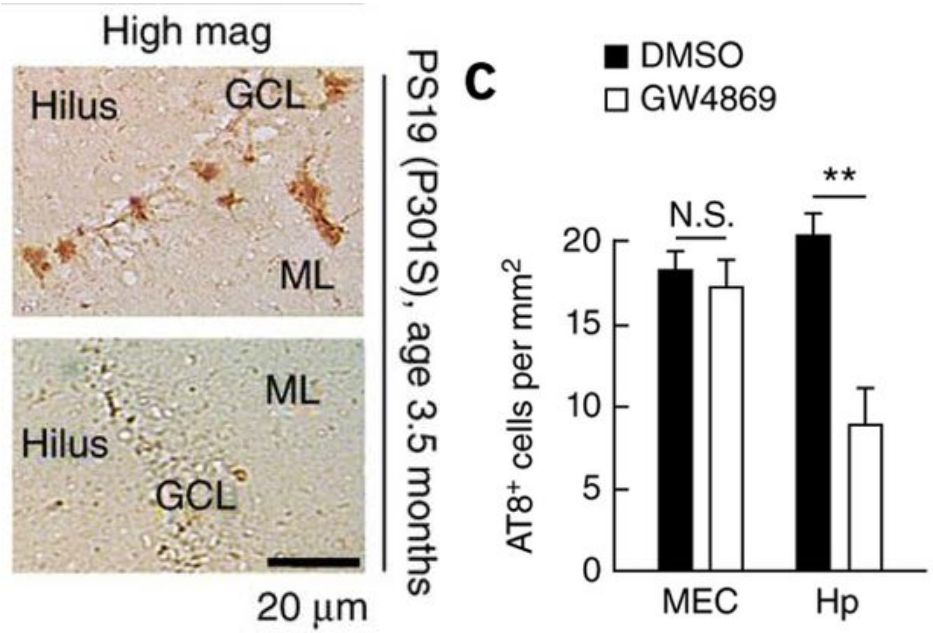
Dinkins et al. *Neurobiol Aging* (2014)

Inhibiting nSMase2 improves fear conditioning memory



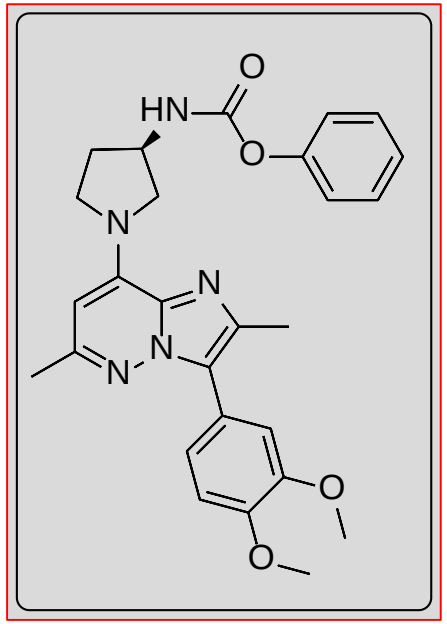
Sala et al. *J Med Chem* (2020)

Inhibiting nSMase2 reduced hippocampal tau staining



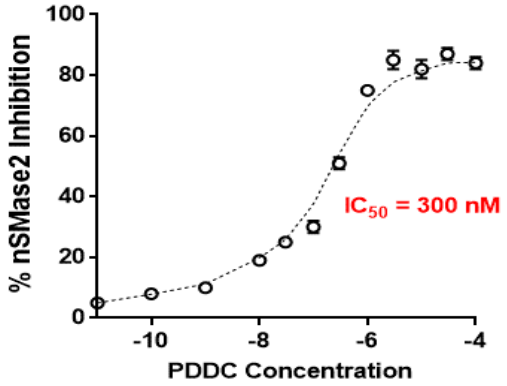
Asai et al. *Nat Neurosci* (2015)

HTS of >365,000 compounds and extensive SAR led to PDDC



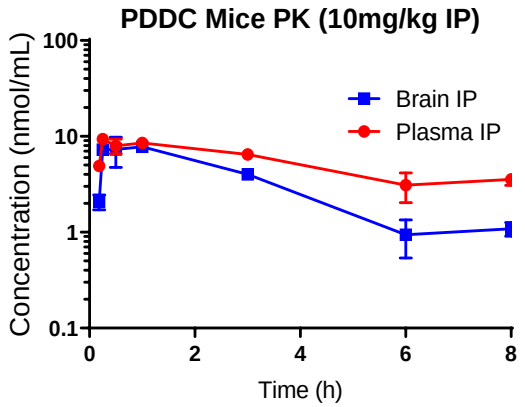
Phenyl (R)-(1-(3-(3,4-Dimethoxyphenyl)-2,6-Dimethylimidazo[1,2-b]pyridazin-8-yl)pyrrolidin-3-yl)Carbamate

nM POTENCY



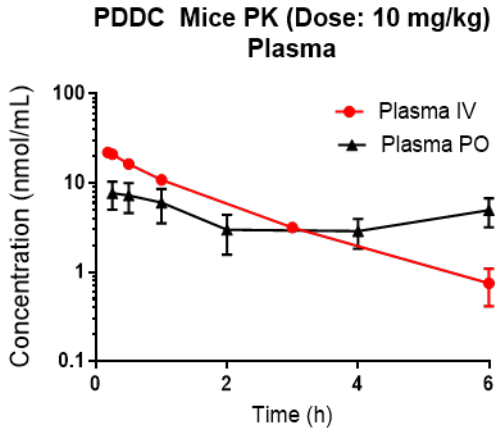
BRAIN PENETRABLE

AUC_{brain}/AUC_{plasma}=0.6

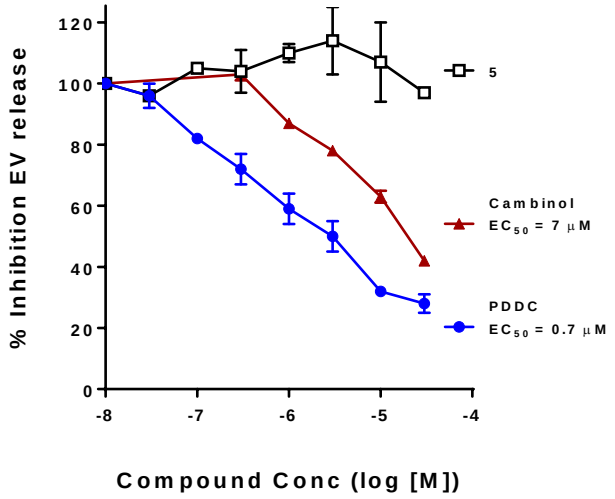


ORALLY BIOAVAILABLE IN MICE

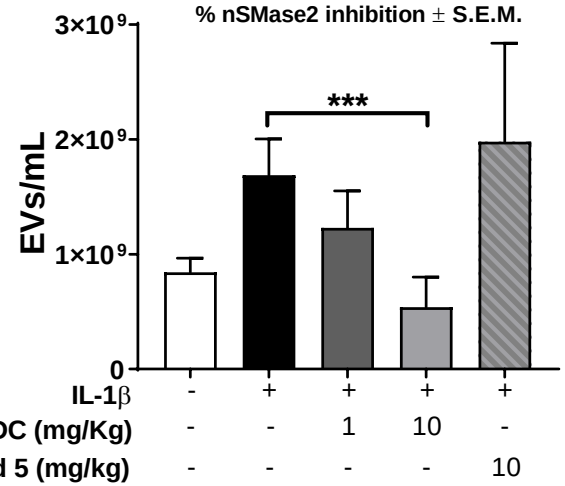
F=~90%

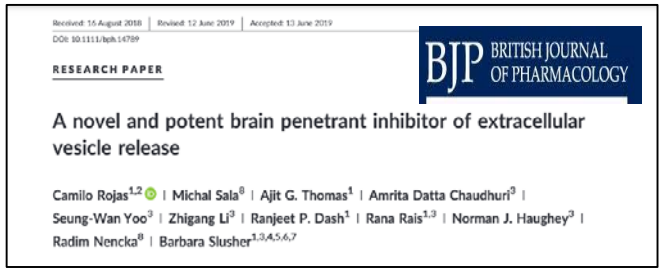


PDDC reduces *in vitro* EV release; Inactive analog had no effect



PDDC reduces *in vivo* EV release; Inactive analog had no effect





RESEARCH PAPER

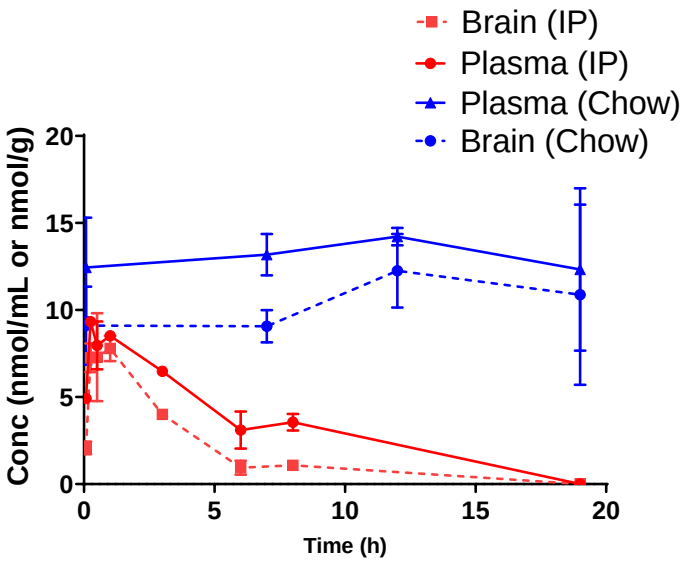
BJP BRITISH JOURNAL OF PHARMACOLOGY

A novel and potent brain penetrant inhibitor of extracellular vesicle release

Camilo Rojas[1,2] | Michal Sala[8] | Ajit G. Thomas[1] | Amrita Datta Chaudhuri[9] | Seung-Wan Yoo[3] | Zhigang Li[3] | Ranjeet P. Dash[1] | Rana Rais[1,3] | Norman J. Haughey[3] | Radim Nencka[8] | Barbara Slusher[1,3,4,5,6,7]

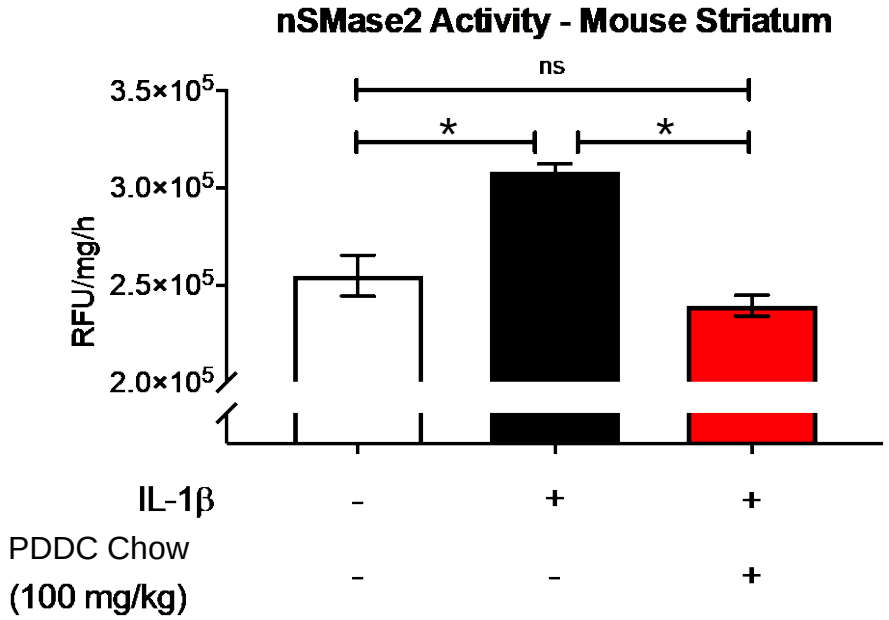
PDDC-containing chow leads to sustained brain levels, inhibits nSMase2 activity and blocks EV release

Sustained brain and plasma >IC50 value over 24h

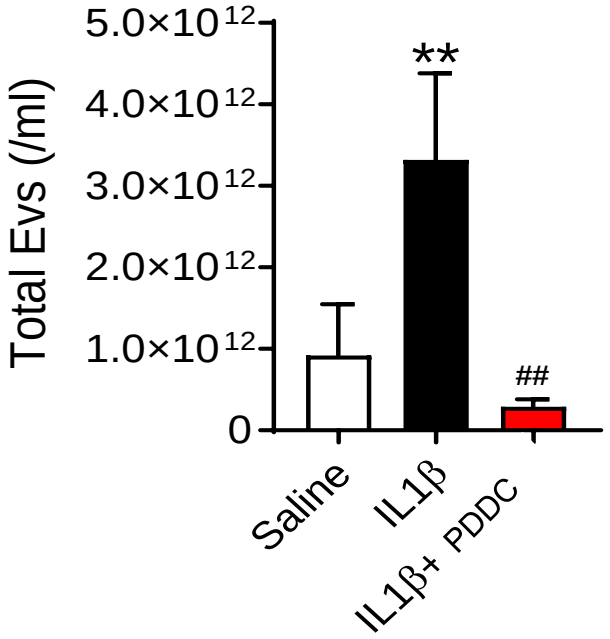


	Plasma	Brain	Plasma (Chow)	Brain (Chow)
Total Area	63.07	33.61	250.1	197.1
Std. Error	5.694	2.793	19.89	22.06

Inhibits elevated brain nSMase 2 activity following IL-1β injection



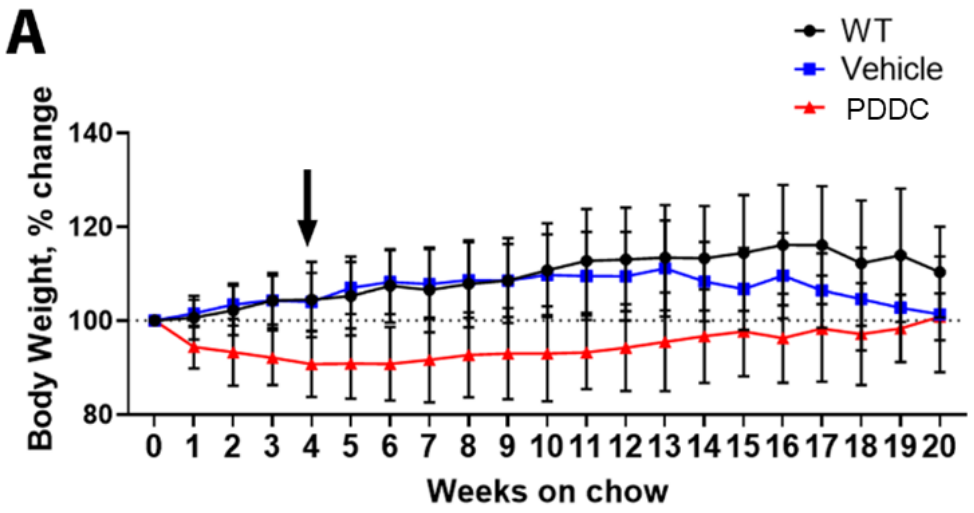
Inhibits brain EV release following IL-1β injection



n=4-5

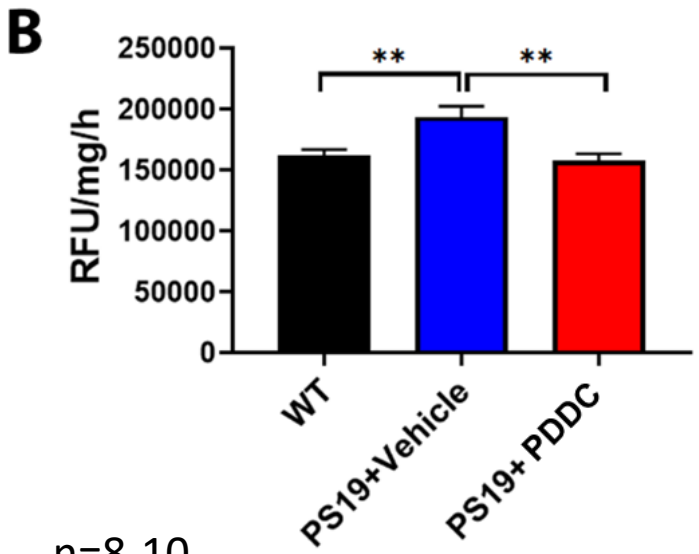
Chronic PDDC treatment inhibits brain nSMase2 without toxicity in PS19 AD mice

Body weight maintained with drug holiday initiation



n=18-19

PDDC inhibited brain nSMase 2 activity in PS19 mice



n=8-10

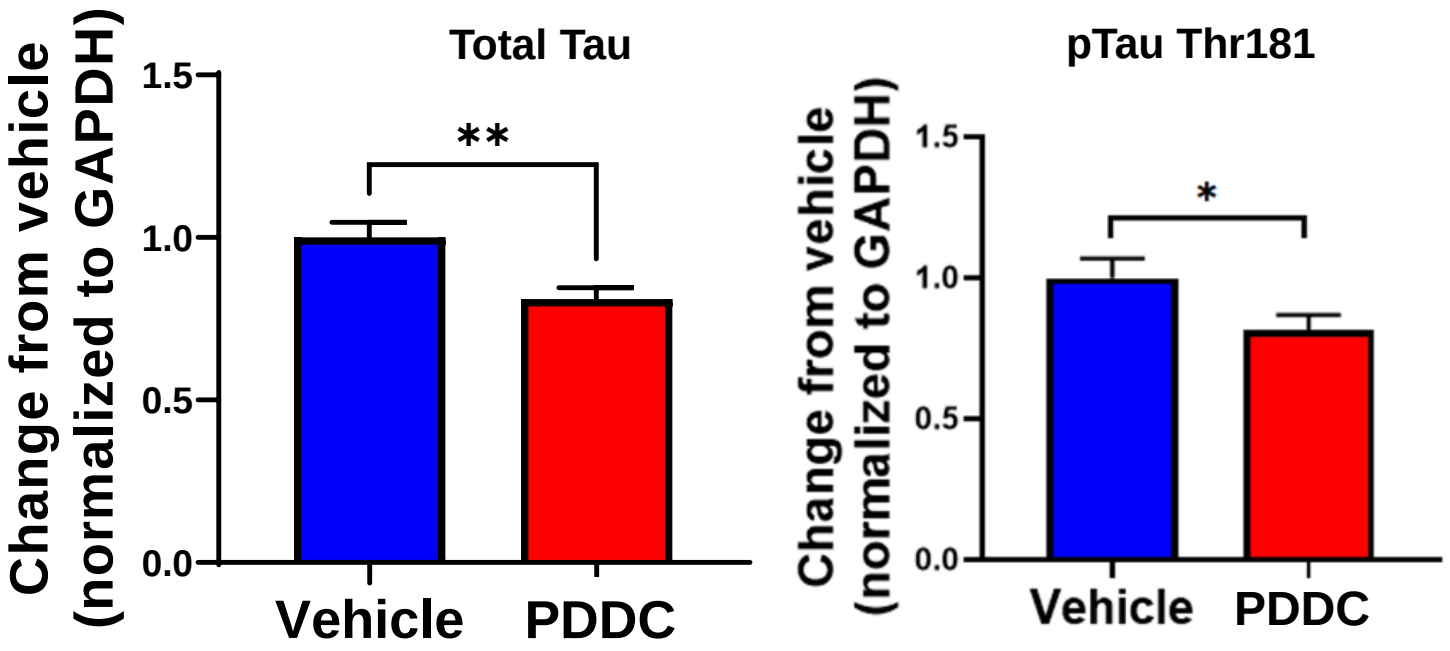
Clinical chem parameters within normal range

Parameter	Vehicle	PDDC	normal range	P Value
ALB	3.125	2.975	2.5-3.0	0.854
ALB/GLOB	1.243	1.35		0.892
ALP	101	181.5	54-240	0.2071
ALT	55.5	52.25	18-82	0.9997
AST	177.8	137	54 - 298	0.957
BUN	24.25	24.25	18-36	0.9999
BUN/CREAT	79.17	30.05		0.9294
CA	10.45	9.725	9.5-11.2	0.6797
CA (ALB)	10.8	10.25		0.8013
CA (TP)	11.45	10.95		0.8293
CA/PHOS	1.125	1.175		0.9919
CK	309.5	76.75	63-445	*0.0113
CREAT	0.45	0.8333	0.2-0.9	0.234
GLOBULIN	2.575	2.225		0.4908
GLUC	191.8	206.3	67-177	0.9722
LDH	404.3	260	259-873	0.7898
PHOS	9.4	8.6	4.9-11	0.8957
TBILI	0.1	0.475	0.1-0.9	0.2268
TP	5.725	5.2	3.5-7.2	0.2925

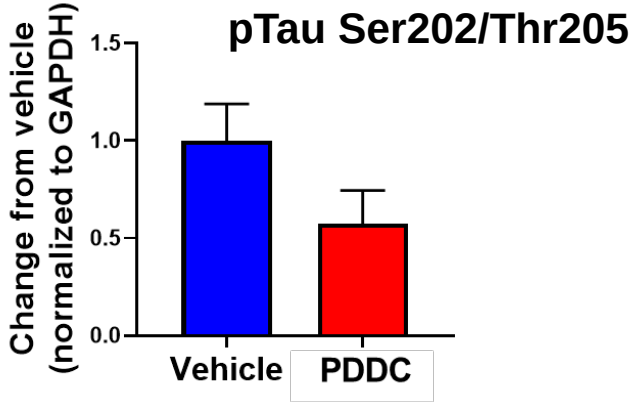
n=5

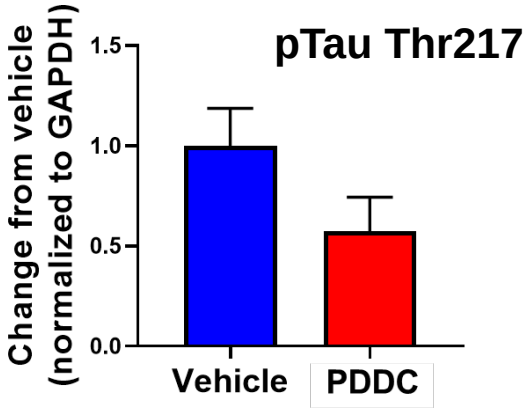
PDDC treatment lowers hippocampal tau levels in PS19 mice

Total tau and pTau Thr181 significantly reduced



pTau Ser202/Th205 and Thr217 showed reduction trends



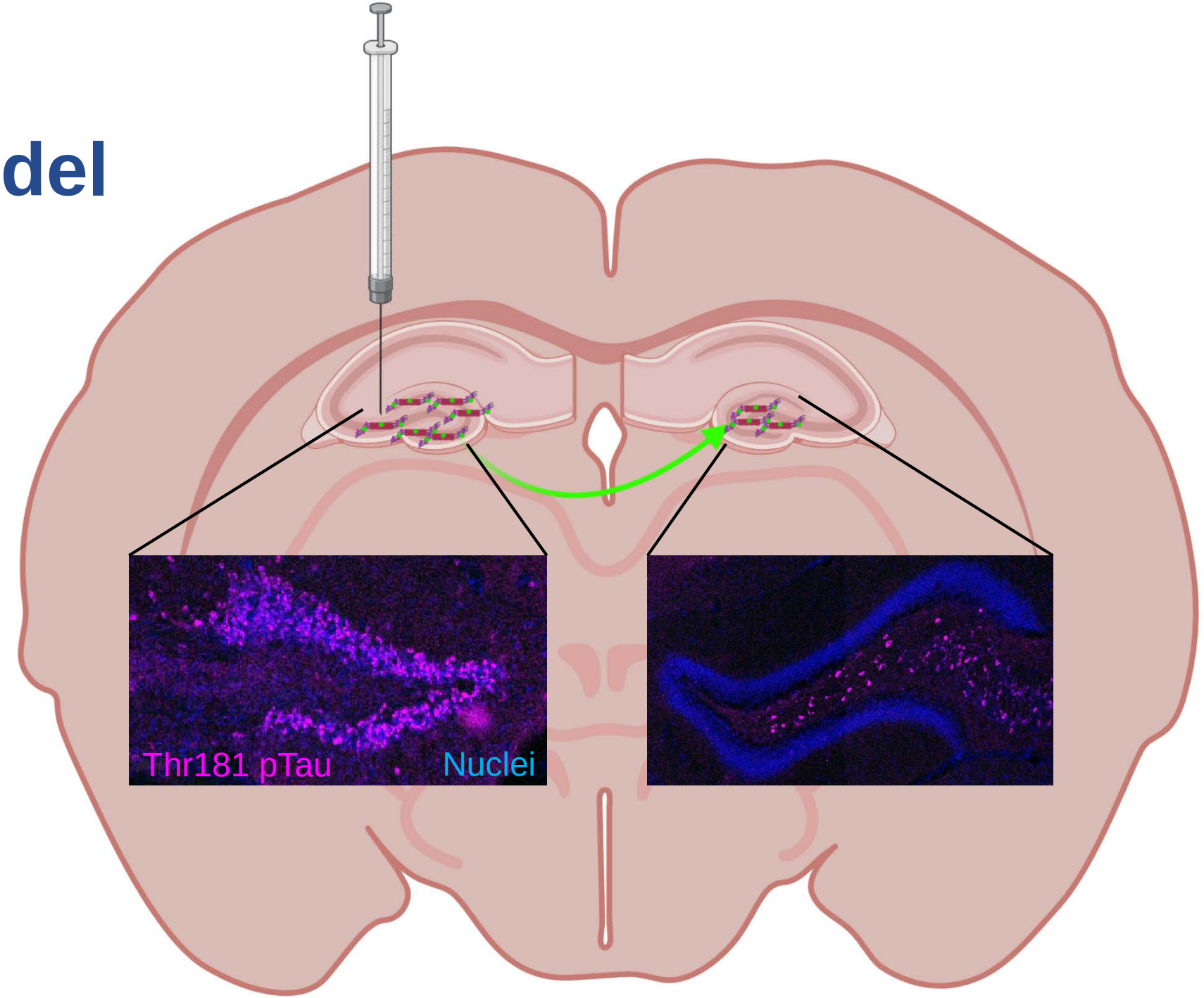


n=10-11

Rapid AAV-htau propagation model

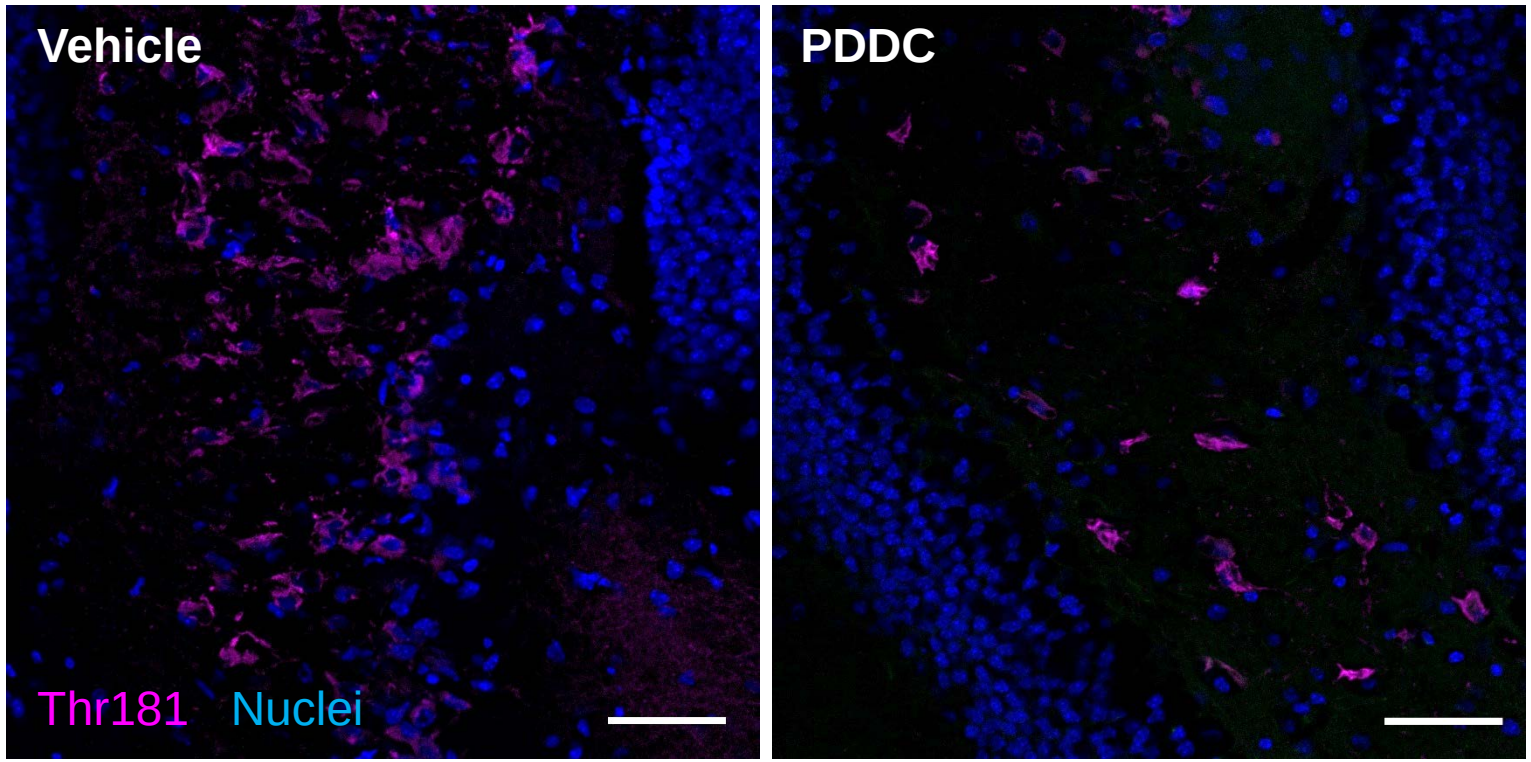
- AAV-hTau (P301L) injected into left CA3/DG region of hippocampus

- Propagation occurs to the polymorphic layer of contralateral DG /CA3 region at 6 weeks following injection

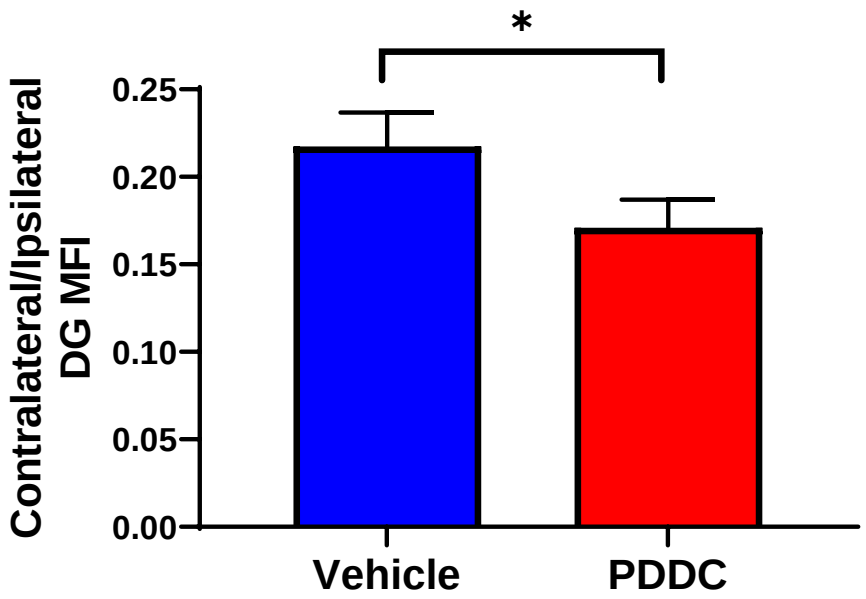


PDDC reduces pTau Thr181 in rapid AAV tau propagation model

Reduces pTau Thr181 in the polymorphic layer of the contralateral DG



Reduces pTau Thr181 intensity



N=40-50 images between 4-6 mice

Conclusions

- PDDC provides sustained brain drug levels which inhibit nSMase2 activity and EV release
- PDDC reduces total tau and Thr181 phosphorylated tau in PS19 AD model
- PDDC reduces contralateral Thr181 phosphorylated tau in a rapid AAV-tau propagation model

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Mohammed Moniruzzaman

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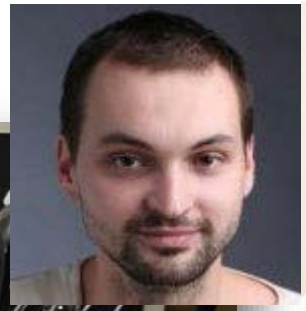
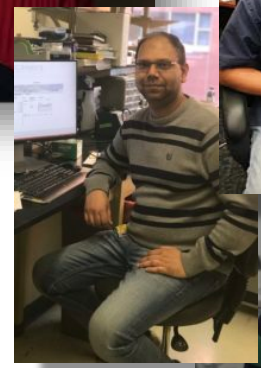
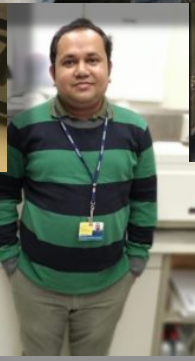
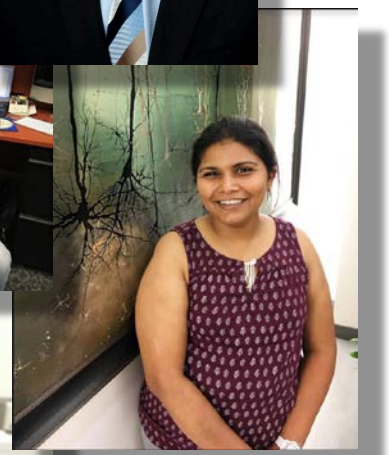
Radim Nencka
Michal Sala
Evzen Boura









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