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Protein Degradation in CNS: A new era of disease modifying therapies

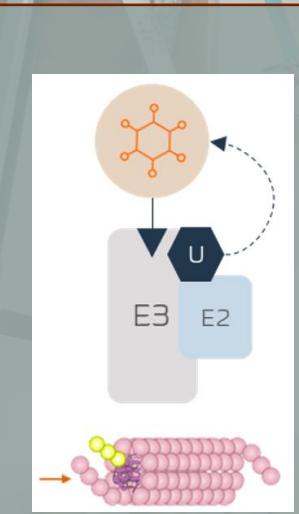
6th Annual TPD Boston 2023

Forward-Looking Statement

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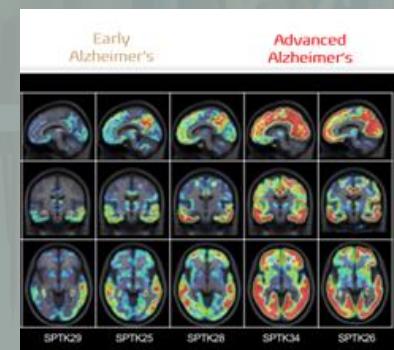
H I O N I R D H

New tools ...



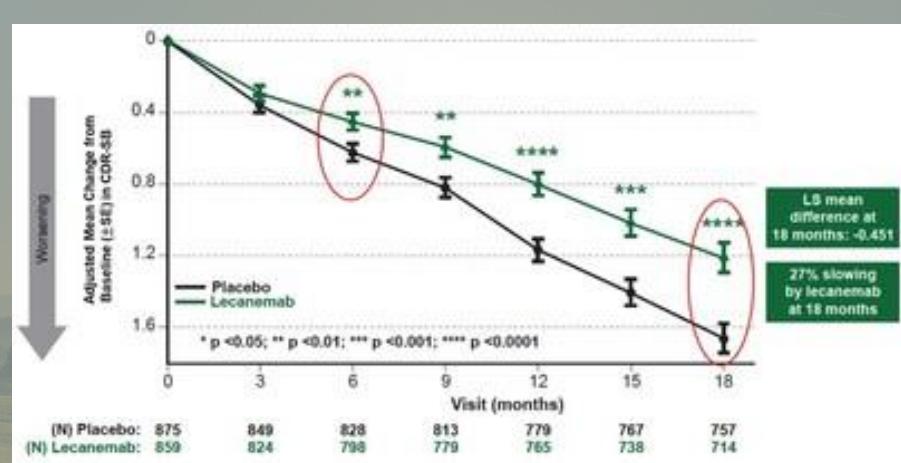
Protein
degradation

Biomarkers



New hope for AD ...

Lecanemab &
Donanemab



Paul Tempest PhD

Head of Medicinal Chemistry
Director, Board of Directors
Fired-up Chemist



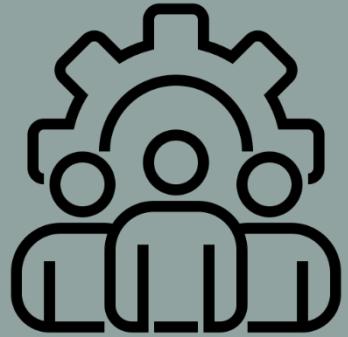


Tokyo, Japan

APRINOIA Therapeutics

Cambridge, MA

Taipei, Taiwan



*Founder, CSO
Ming-Kuei*



*Chief Executive Officer
Mark*



*Chief Medical Officer
Brad*



*Group General Counsel
Lana*



*Chief Financial Officer
Brian*



*Japan Site Head
Masa*

Phase 2/3 Tau PET Tracer

3,000+ Patients Imaged
Supporting Clinical Utility

Disease Modifying Tau and α -Synuclein Protein

Platform to develop modifying
therapies

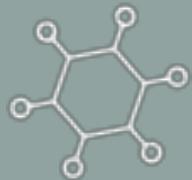
Phase 1 Tau Antibody

Disease-specific antibody





"Second most diverse patent portfolio among leading innovators for neurodegenerative disorders" *



Tau PET
aSyn PET
Tau degrader
aSyn degrader

Patent statistics:

37 issued

4 allowed

33 pending



Tau mAb

*09 Mar 2023

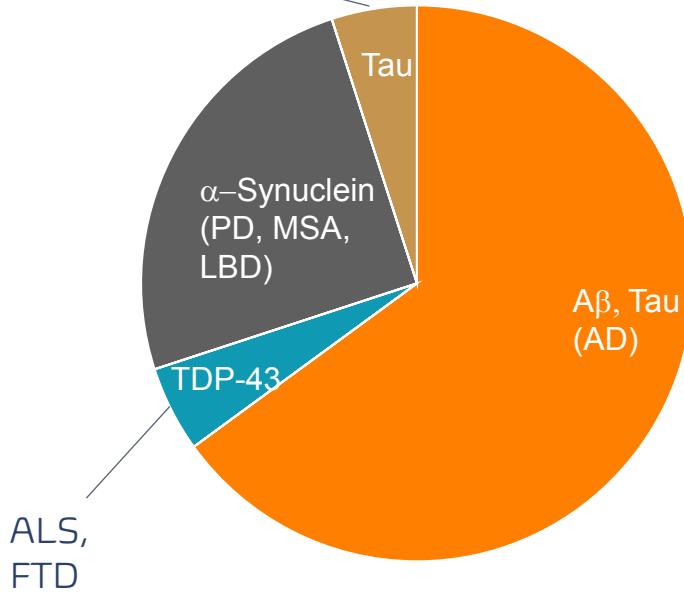
pharmaceutical-technology.com

Tau and α -Synuclein: AD and PD Neurodegeneration

Six tau isoforms lead to distinct pathologies

- 4R in PSP, CBD, etc.,
- 3R in Pick's disease
- 4R/3R mixed in AD

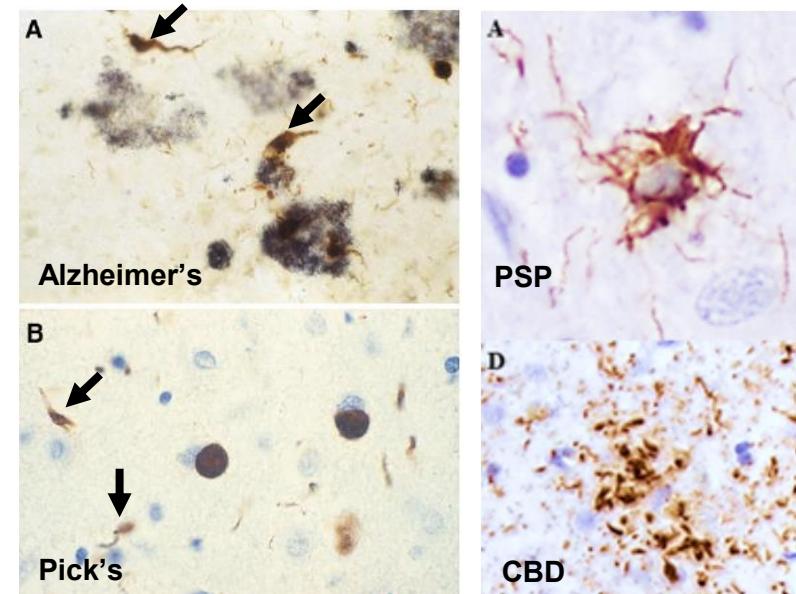
PSP, CBD, FTD,
PiD



Tau fibrils spread from cell to cell and build up inside neurons,

- correlates closely with cognitive decline in AD

Tauopathies



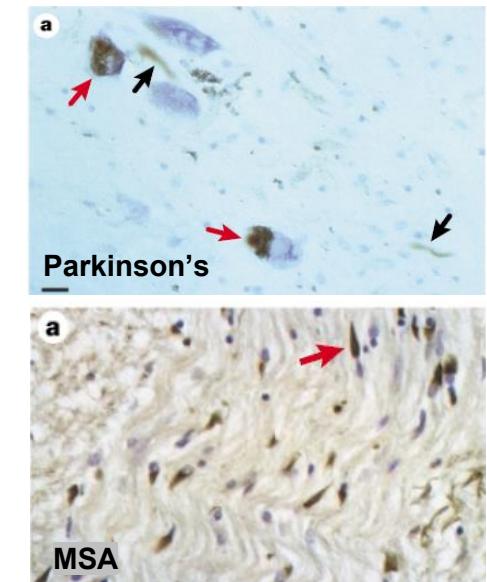
Goedert & Spillantini 2021

Parmera et al. 2022

Synucleinopathies characterized by

- misfolded, aggregated α -synuclein
- exacerbated by genetic mutations

Synucleinopathies



Goedert 2001

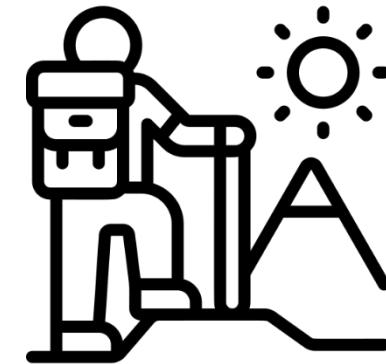
Targeting Tau and α -Synuclein with degradation

The Good:

- Oncology medicinal chemists have de-risked the modality
- Attacking intracellular targets proven undruggable by traditional means
- Potential lower bar for pharmacology (catalytic?, sporadic treatment?)
- New pathways to engage....(autophagy, chaperone, lysosome)

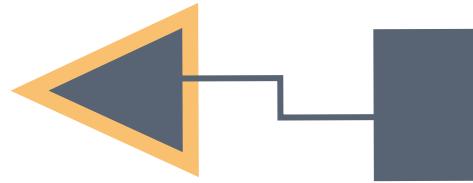
The Challenge:

- Aggregated protein binding site
- Brain penetration means we must persevere where Ro5 has failed

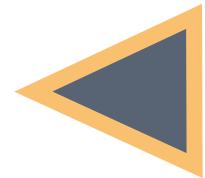


"Do not fear walking into the unknown,
for we are powerful" -Me

Degraders, one compounds in three parts



Targeting element



makes the degrader

Linker



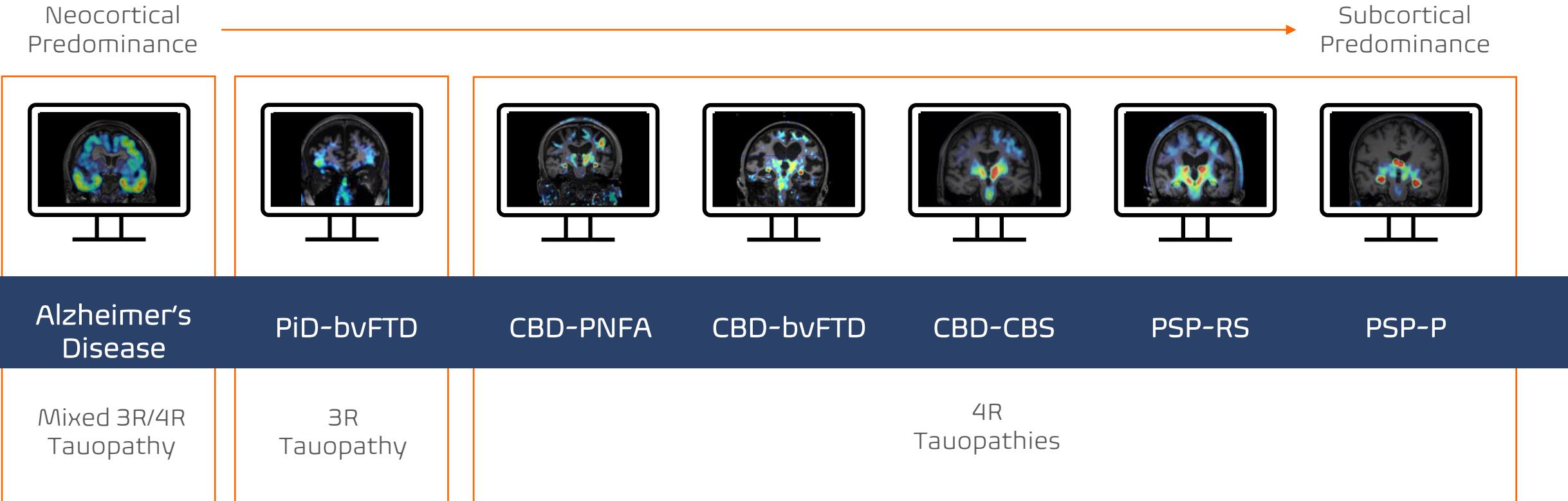
length / properties

E3 signaling



Cereblon / VHL /
novel

If we can **see** it ...



Florzolotau (APN-1607, PM-PBB3)

Over 3000 patients scanned

Binds only **pathological** tau

... we can **target** it

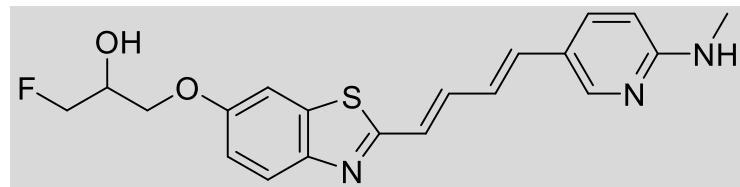


¹Tagai K, Ono M, Kubota M, et al. High-Contrast In Vivo Imaging of Tau Pathologies in Alzheimer's and Non-Alzheimer's Disease Tauopathies. *Neuron*. 2021;109(1):42-58

Biomarkers lead to ...

Florzolotau

3/4R tau binding PET tracer



4R tau PET back up program (structure not disclosed)

aSyn PET program (structure not disclosed)

- clinically validated binding sites
- binds only oligomers and aggregates
- use our established biomarkers

... **targeted** therapeutics



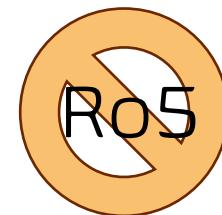
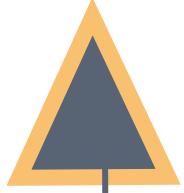
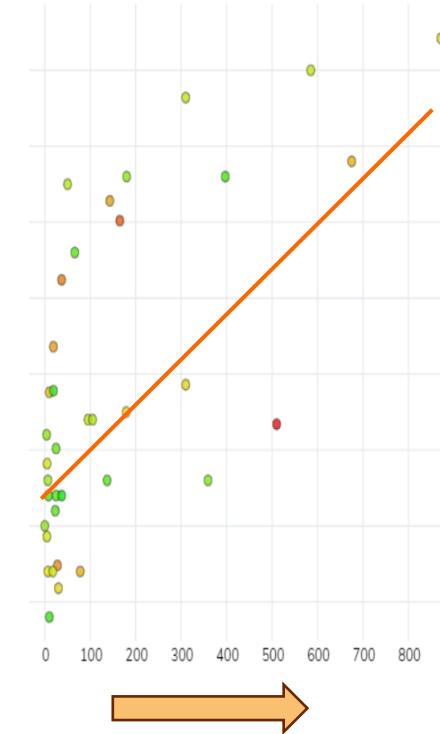
Our strategy for great degraders



Yih-Shyan



ADME property 1



Tau Degrader Screening Funnel

HEK + Neuronal
cellular
degradation assay

Validation of
degrader
mechanism

In vitro ADME

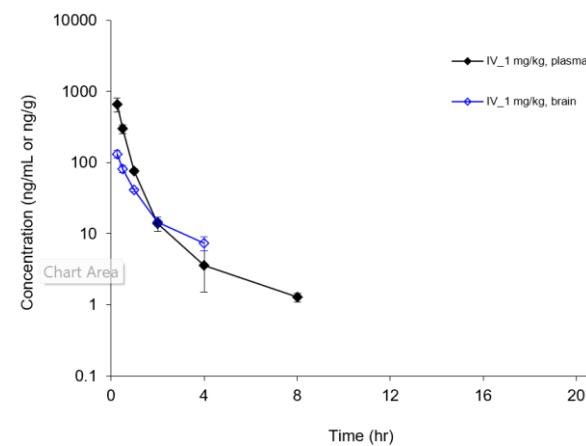
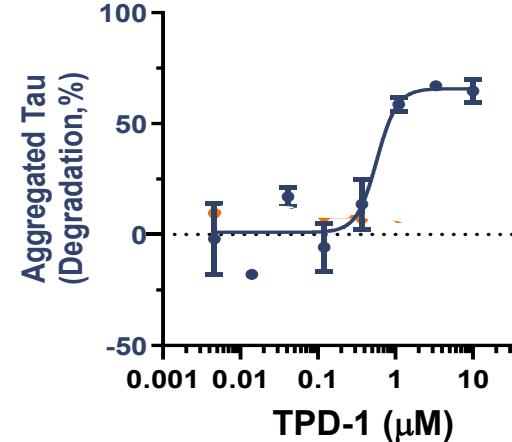
mPK

HEK DC₅₀ <1000 nM
Inhibition ≥ 50%
Confirmation in neuronal

confirmed

logP
Solubility
Etc...

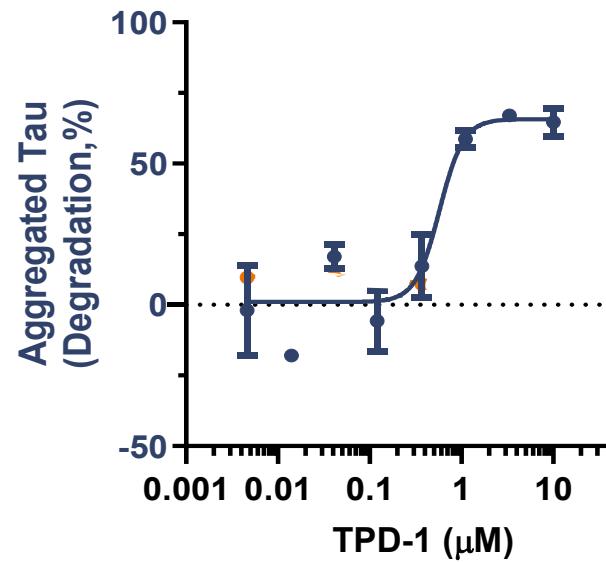
Br:PI
Kpuu%



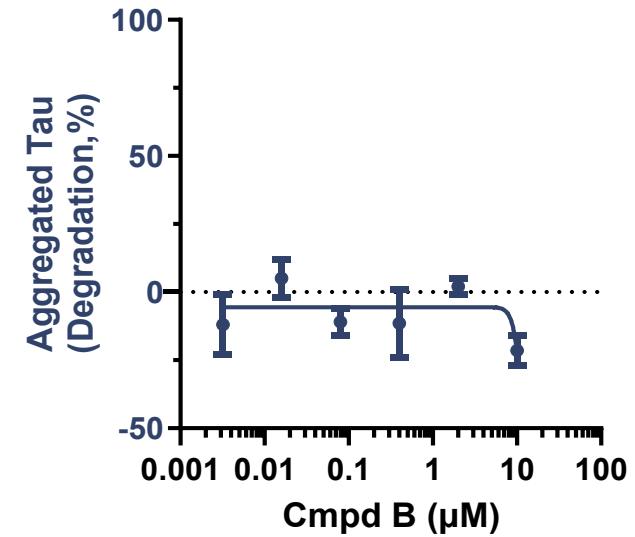
rTg4510
model

Tau degrader project...

HEK293 TauP301L cells, seed induced



Degradation

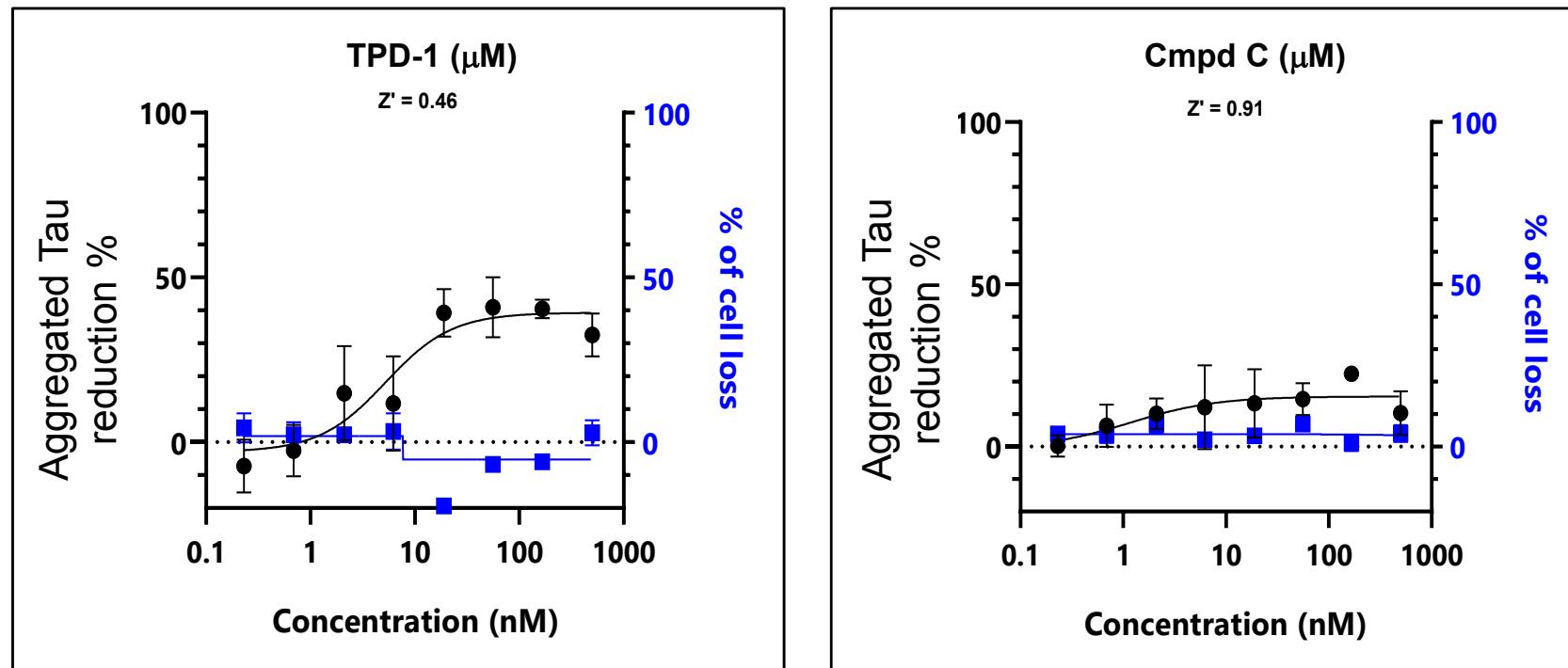


No degradation

... shows in vitro degradation...

... in multiple cellular assays

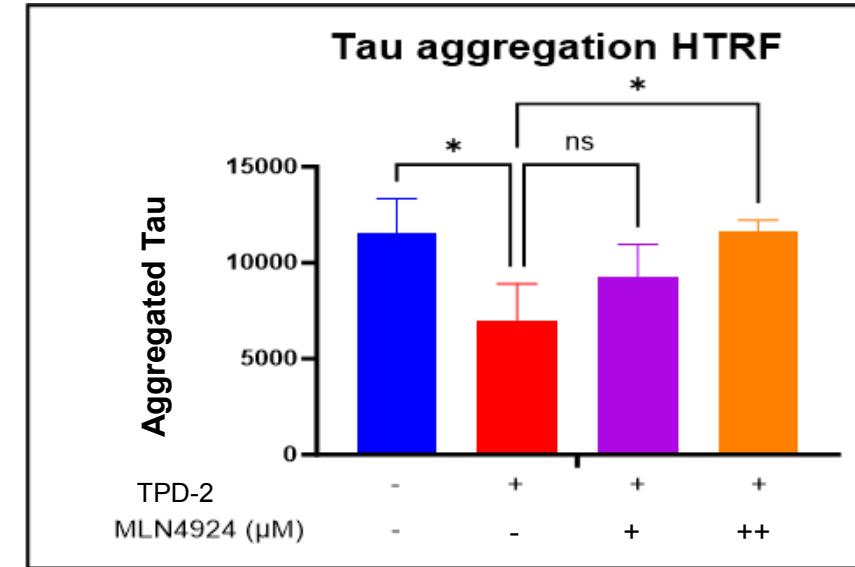
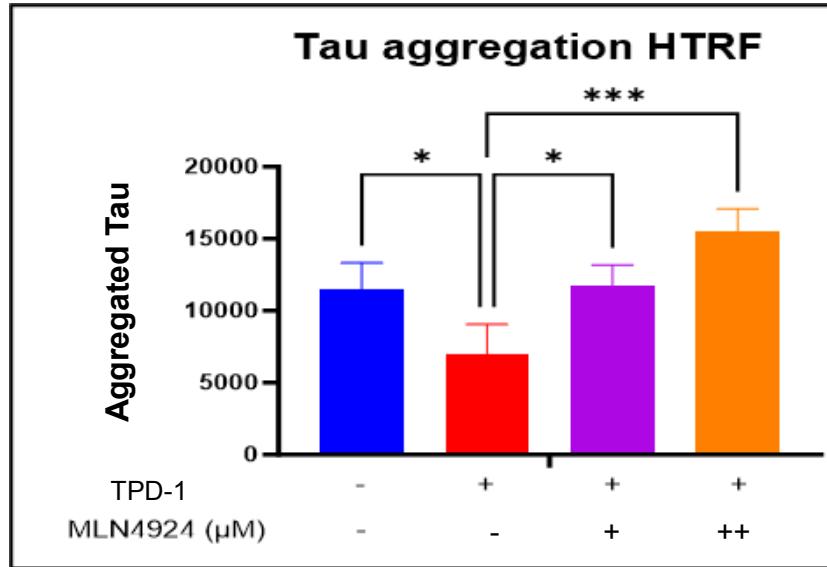
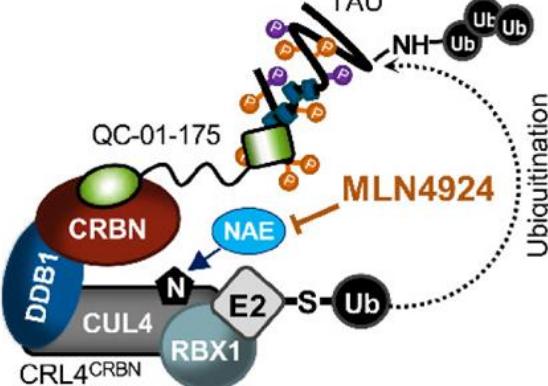
Primary mouse cortical neurons, seed induced



Degradation

No degradation

Tau degrader MOA - HEK cells

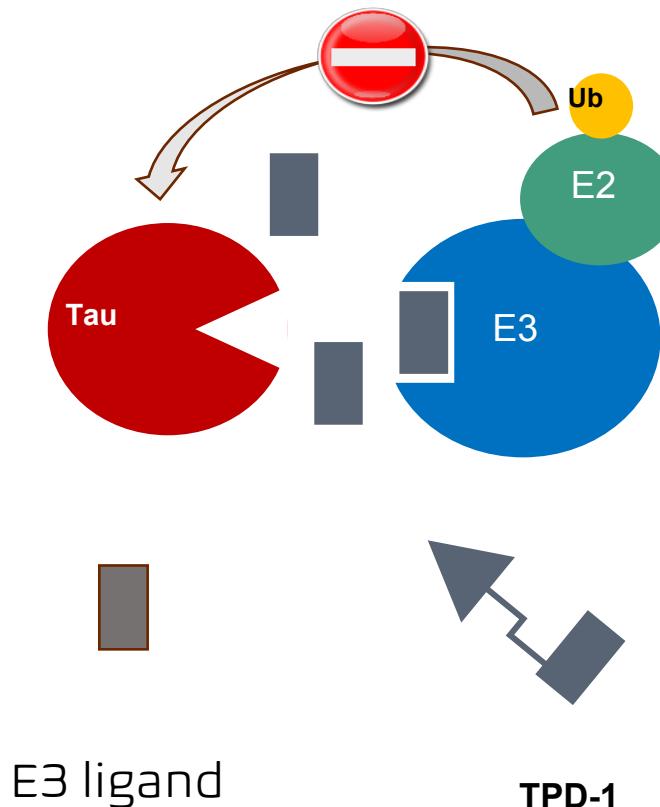


MLN4924 significantly reverses the degradation activity in HEK cells

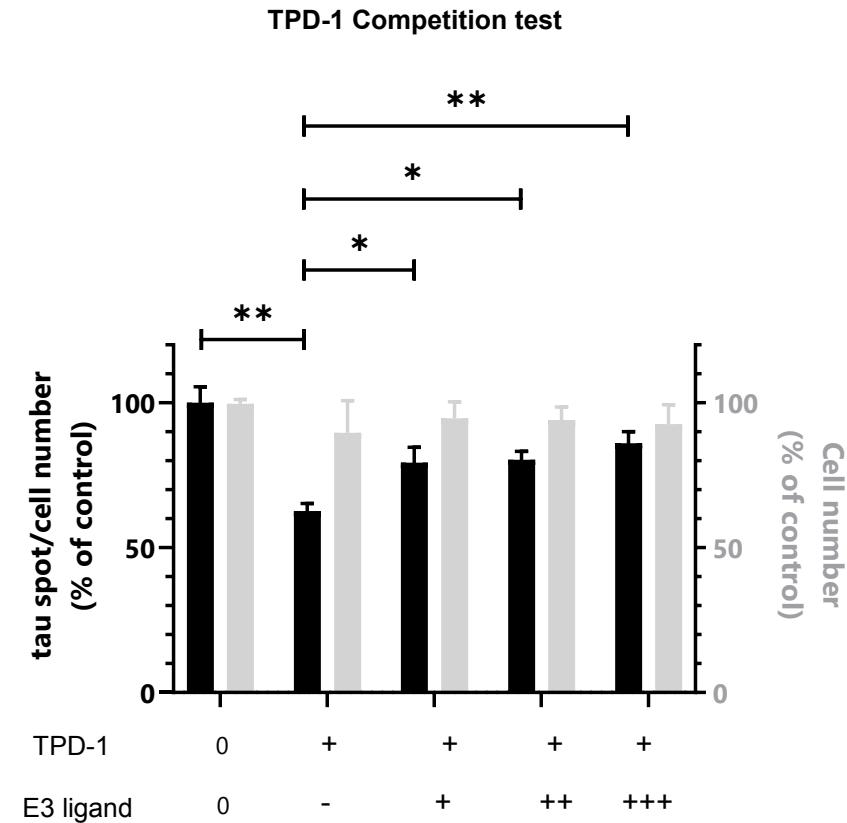
... consistent with degradation MOA

Tau degrader MOA - Neuronal cells

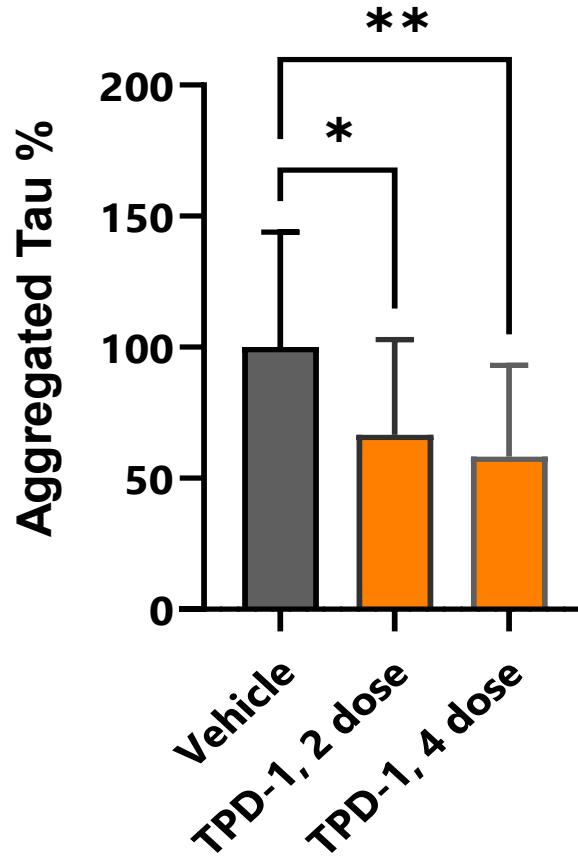
E3 ligand competes to inhibit proteasome degradation



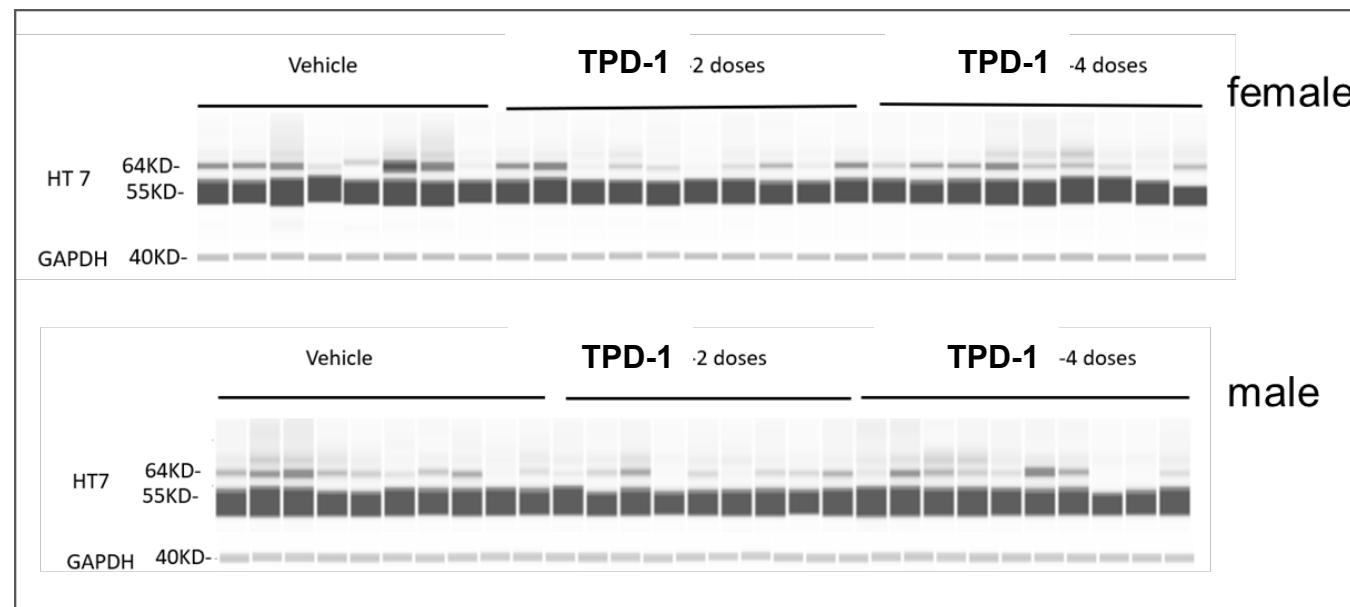
E3 ligand competition reverses degrader activity, In neuronal cells



Tau degrader in vivo - rTg4510 mouse



ON4RTau with P301L mutation
Aggressive tau aggregation
High variability necessitates large N for studies



	n/group	total n	Power (vehicle vs 2 and 4 doses)
one way ANOVA	20	60	0.84

aSyn Degrader Screening Funnel

Neuronal cellular degradation assay



Validation of degrader mechanism



In vitro ADME



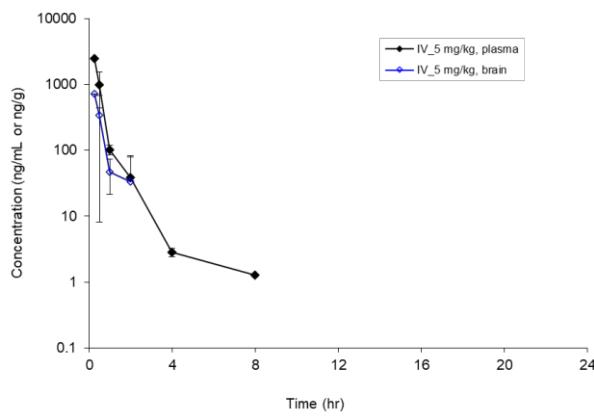
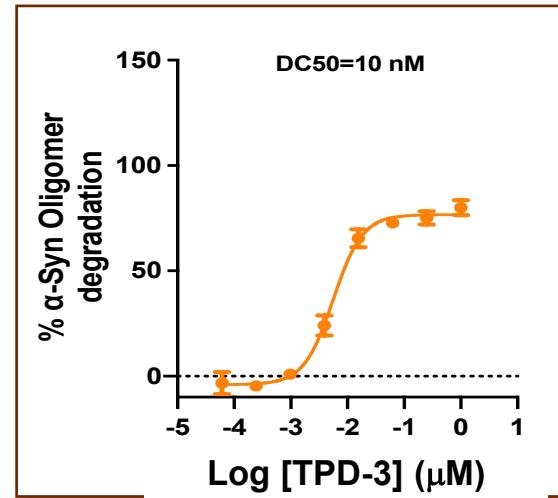
mPK

DC₅₀ <100 nM
Inhibition ≥ 50%

confirmed

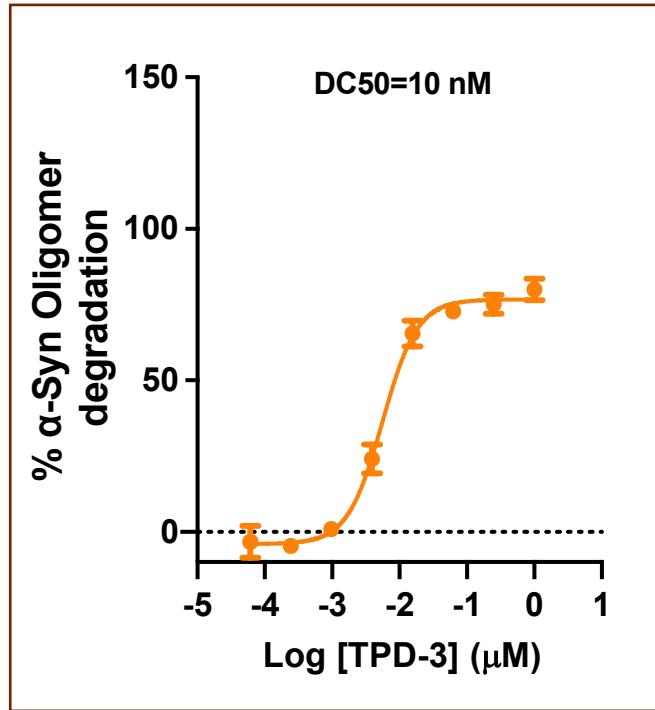
logP
Solubility
Etc...

Br:PI
Kpuu%

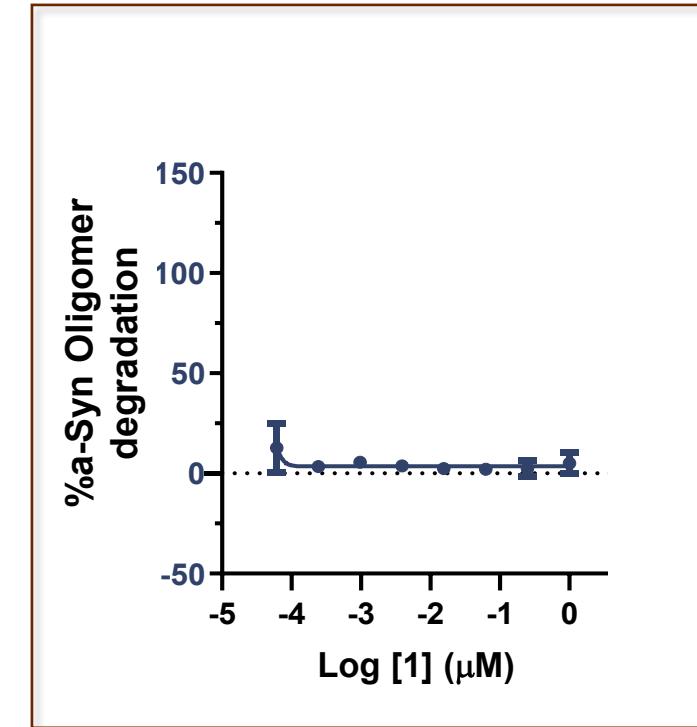


LINE61 aSyn mouse

α Syn cellular degradation – LUHMES cell

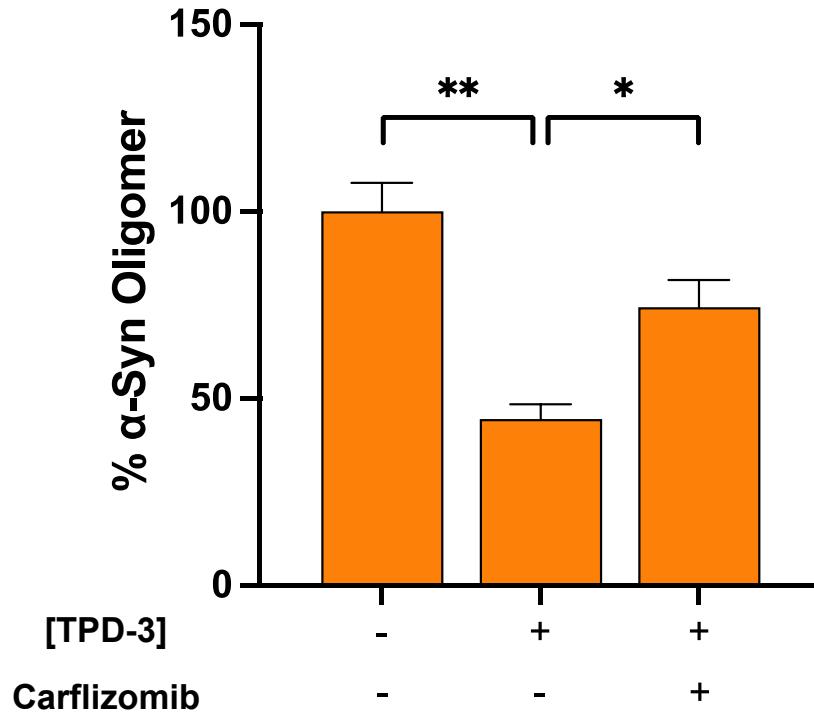


Degradation



No degradation

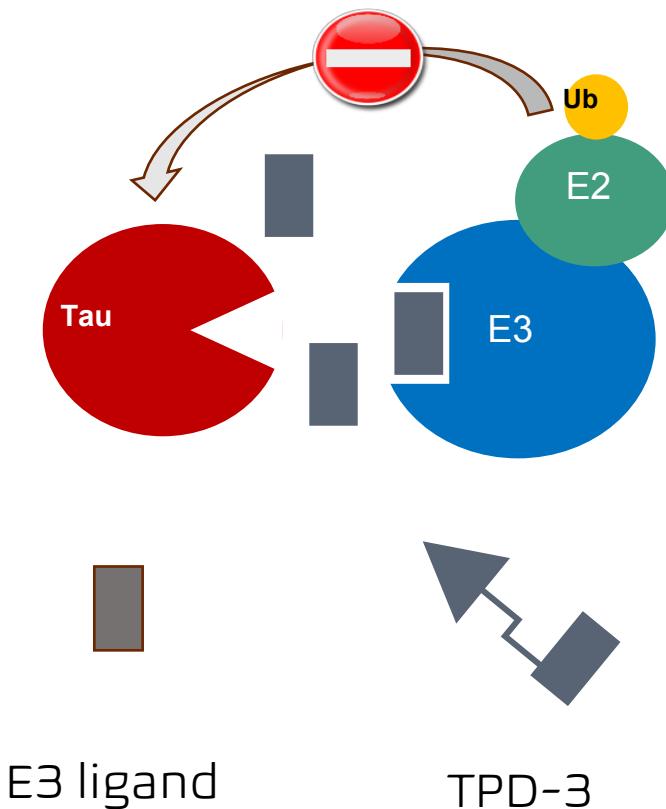
aSyn degradation MOA - 1



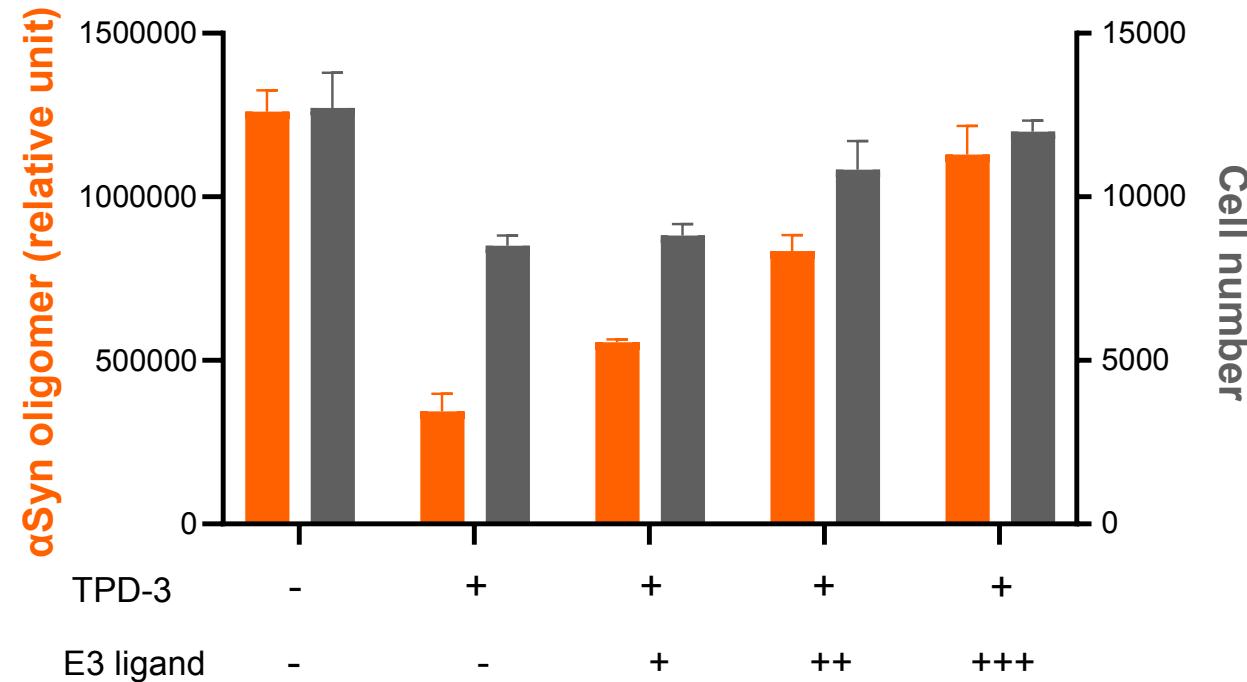
- Carfilzomib proteasome inhibitor
- TPD-3 degradation activity reversed by proteasome inhibitor

aSyn degrader MOA - 2

E3 ligand competes to inhibit proteosome degradation

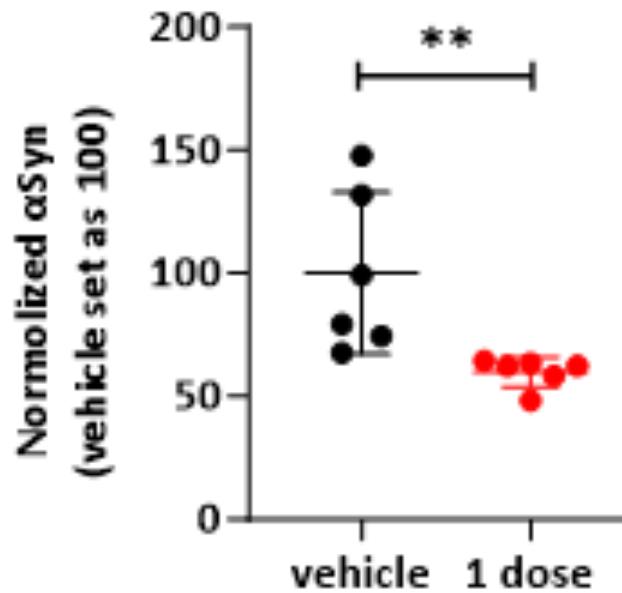


E3 ligand competition reverses degrader activity, In neuronal cells

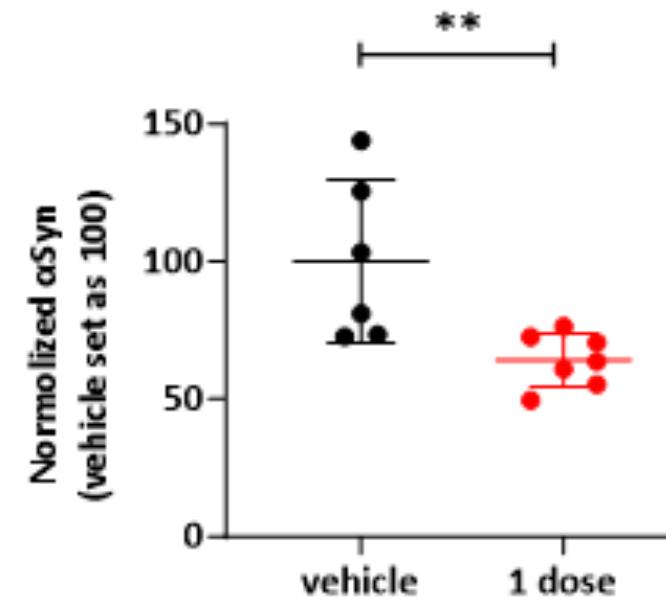


aSyn degrader in vivo - LINE61 mouse

Insoluble fraction brain lysates



TPD-3

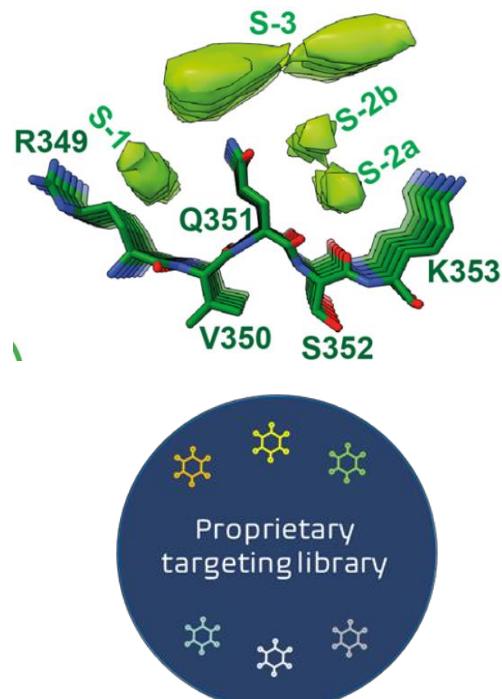


TPD-4

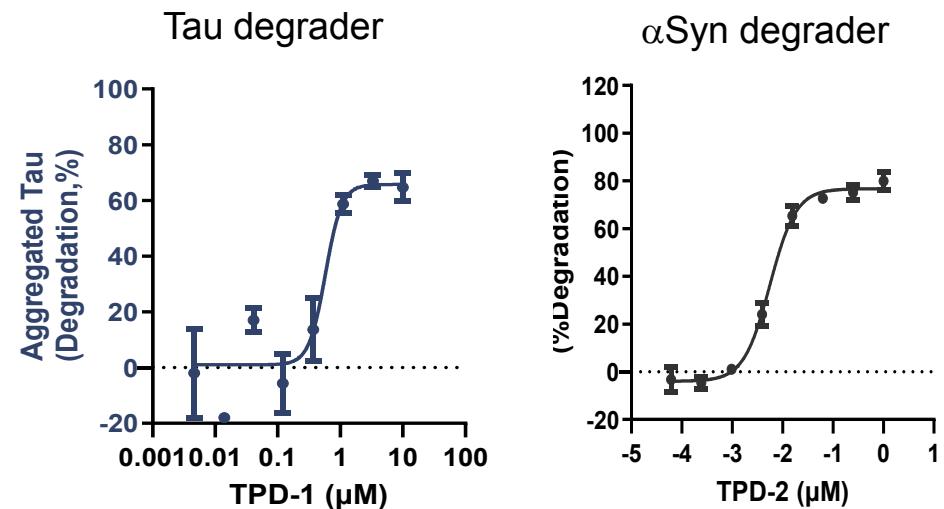
ADME and PK studies
predicted ranked
highest ...

APRINOIA Degraders Summary 2023

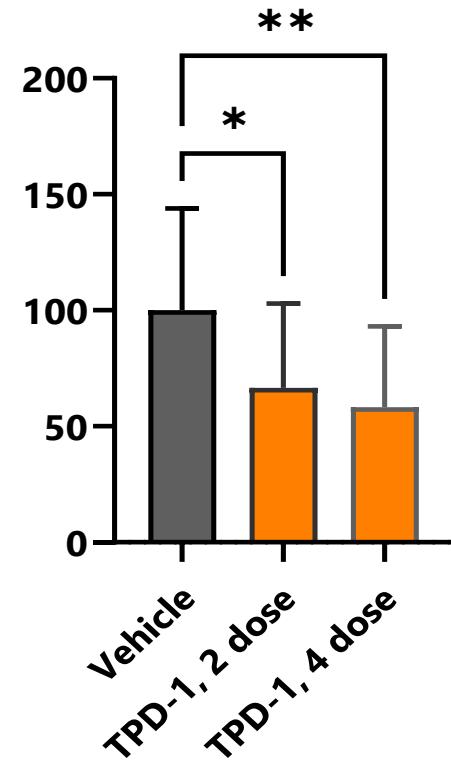
Proprietary small molecule collection
derived from
Florzolotau programs



Two cellular degradation assays
established – HEK and neuronal cells
MoA studies confirm mechanism



Potent degrader identified in in vivo models



[flaticon.com](https://www.flaticon.com)



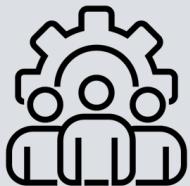
[Darius Dan](#)



[Freepik](#)



[Freepik](#)



[srip](#)



[Freepik](#)

unsplash.com



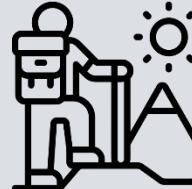
[Federico Respini](#)



[Barn Images on Unsplash](#)



[Daniel Leone](#)



[Smashicons](#)



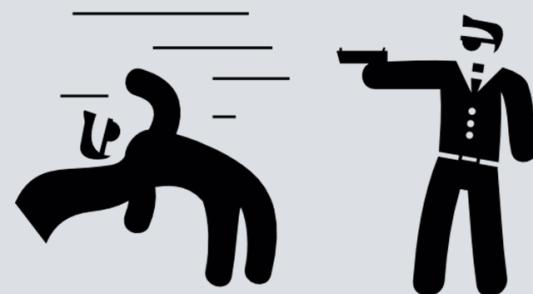
[sketchandbuild](#)



Chemistry

Yih-Shyan Lin
Steve Paget
Silas Wang

*VMIC
*Pharmaron



Our
compounds

Blood brain
barrier

Biology

Ming-Kuei Jang
Lili Zhang
Haou-Tzong Ma
Chen-Hua Zhang
Andy Lai

*QPS

PK ADME

George Lai

*Pharmaron
*ChemPartner



Clinical

Brad Navia
Drew Campbell
Siddharth Parulkar
Dorothy T-C Yen

*Makoto Higuchi - QST

