1222

PROTAC LRRK2 Degraders Reduce Pathological Tau and Modulate Endolysosomal–Neuroinflammatory Pathways in Translational Model Systems

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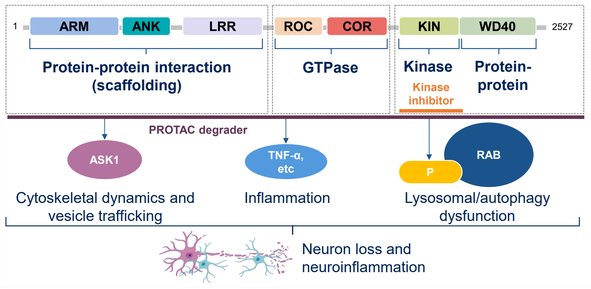
Background

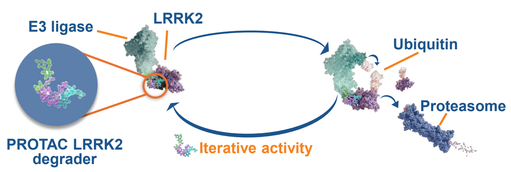
- Tau pathology is a key driver of neurodegeneration across Alzheimer's disease and related tauopathies, including PSP and Parkinson's disease[1,2]
- LRRK2 is a ubiquitous multidomain enzyme involved in endolysosomal, autophagic, and neuroinflammatory pathways[3,4]

LRRK2 structure and functional domains



- Variants of LRRK2 are associated with impaired endolysosomal function, reduced autophagic clearance, and pathological tau accumulation[5-12]
- A common genetic variant near the *LRRK2* locus was associated with PSP disease progression, and baseline *LRRK2* expression levels in monocytes predicted changes in disease severity over 1 year[7,13-15]
- PROTAC LRRK2 degraders induce the ubiquitination of LRRK2, leading to its degradation by the proteasome

PROTAC LRRK2 degrader mechanism of action[a]



[a]General PROTAC protein degrader is shown.

Objective

- To evaluate the effects of PROTAC-mediated LRRK2 degradation on pathological tau in preclinical models of tauopathy and downstream markers of lysosomal biology and neuroinflammation

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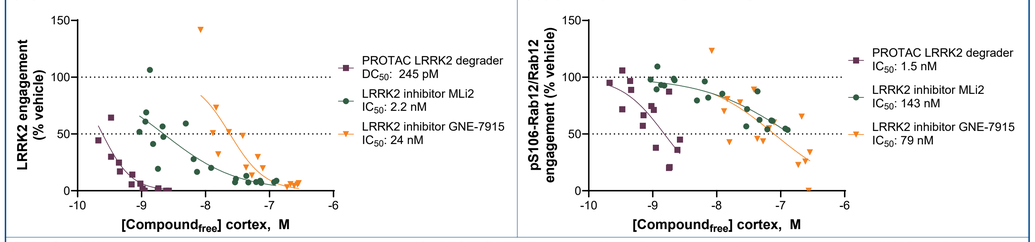
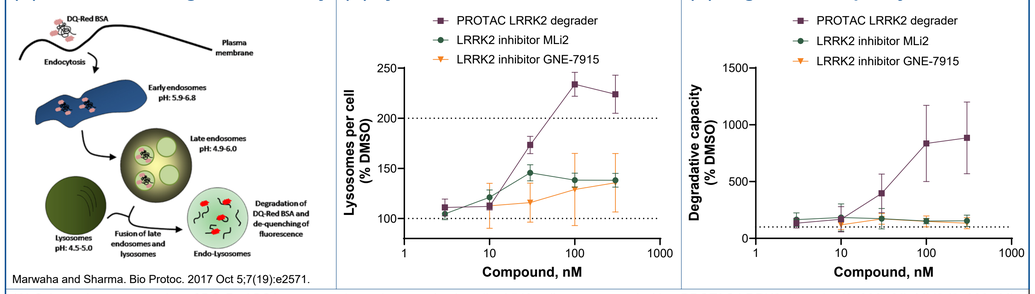
Figure 1: Target and lysosomal pathway engagement with LRRK2 degradation vs inhibition



G2019S-LRRK2 knock-in mice were administered a single oral dose of a PROTAC LRRK2 degrader (10 mg/kg; n=5) or the LRRK2 kinase inhibitors MLi2 (3 mg/kg; n=4–5) or GNE-7915 (30 mg/kg; n=5). Brain tissue was collected at 1 and 24 h post-dose. (**A**) pS935-LRRK2 and (**B**) pS106-Rab12 levels were plotted against free brain compound concentrations measured at T_{max} (24 h post-dose for the PROTAC LRRK2 degrader and 1 h post-dose for the LRRK2 kinase inhibitors). pS935-LRRK2 and pS106-Rab12 levels were normalized to HSC70 and expressed as a percentage of vehicle controls. Data represent 5–6 biological replicates for each compound from single experiments; DC_{50} and IC_{50} values were determined by nonlinear regression.

- Stronger target and lysosomal pathway engagement was observed with the PROTAC LRRK2 degrader vs LRRK2 kinase inhibitors, resulting in greater suppression of endolysosomal trafficking

Figure 2: Lysosome number and degradative capacity with LRRK2 degradation vs inhibition

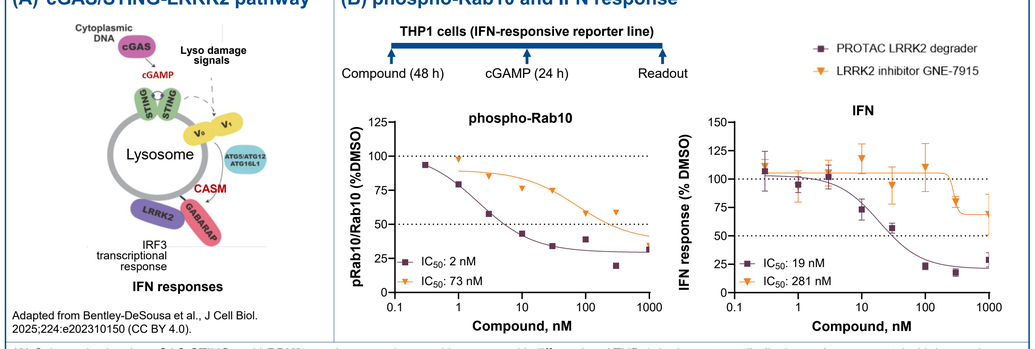


Marwaha and Sharma. Bio Protoc. 2017 Oct 5;7(19):e2571.

(**A**) Schematic representation of DQ-Red BSA cargo uptake and processing in cells. A549 cells were treated with a PROTAC LRRK2 degrader (3–300 nM), MLi2 (3–300 nM), or GNE-7915 (10–300 nM) for 24 h and then labeled with (**B**) Lysotracker or (**C**) DQ-BSA and imaged to assess lysosome number and protein turnover, respectively. Signal spot counts were normalized and expressed as a percentage of DMSO controls. Mean ± SD from 5 replicates per compound in a single experiment are shown. The dotted line indicates baseline in DMSO-treated cells.

- The PROTAC LRRK2 degrader differentially increased lysosome number and overall function compared with LRRK2 kinase inhibitors

Figure 3: cGAS/STING pathway stimulation with LRRK2 degradation vs inhibition

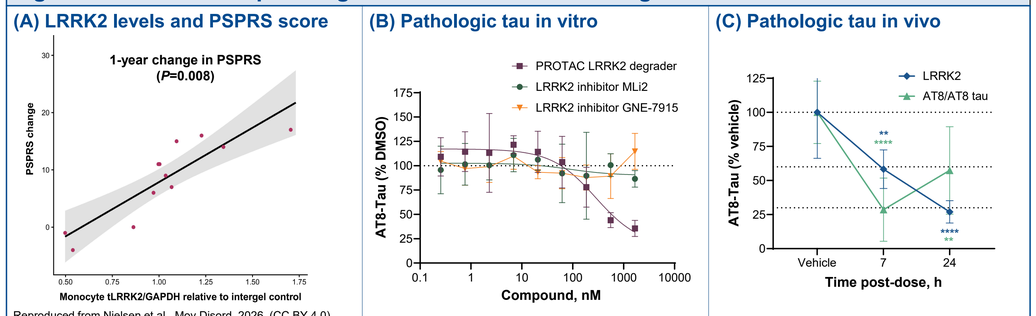


Adapted from Bentley-DeSousa et al., J Cell Biol. 2025;224:e202310150 (CC BY 4.0).

(**A**) Schematic showing cGAS-STING and LRRK2 recruitment to damaged lysosomes. Undifferentiated THP-1 dual reporter cells (Invivogen) were treated with increasing concentrations of a PROTAC LRRK2 degrader or the kinase inhibitor GNE-7915 for 24 h and then stimulated with 5 μg/mL 2′3′cGAMP for 24 h in the presence of PROTAC or inhibitor to induce IFN secretion. (**B**) Concentration response curve of pT73-Rab10 levels normalized to total Rab10 and expressed as a percentage of DMSO control. Points represent single measures from 1 experiment. (**C**) IFN induction was measured using QuantiLUC to quantitate secreted luciferase activity as a measure of IFN response pathway activation. Technical replicates (n=4) from a single experiment are shown. IC_{50} values were determined by nonlinear regression.

- The PROTAC LRRK2 degrader more effectively suppressed phospho-Rab10 and downstream IFN responses following cGAS/STING stimulation than LRRK2 kinase inhibition

Figure 4: PSP-induced pathologic tau levels with LRRK2 degradation vs inhibition



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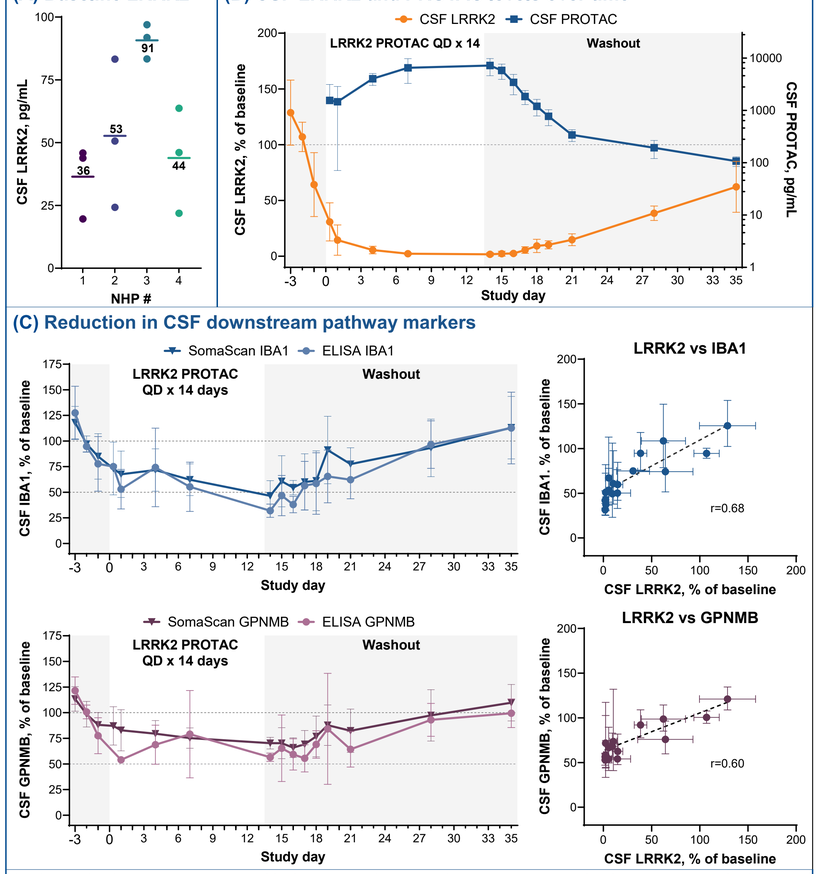
(**A**) Baseline monocyte total LRRK2 levels vs 1-year change in PSPRS score.[13] (**B**) HEK293 cells expressing human wild-type (0N4R) tau were treated for 72 h with PSP patient-templated tau fibrils and increasing concentrations (0.25–2000 nM) of a PROTAC LRRK2 degrader or the kinase inhibitors MLi2 or GNE-7915. AT8+ phospho-tau inclusions were quantified by high-content imaging. Data are expressed as a percentage of DMSO control. Mean ± SD of 4 replicates from a single experiment are shown. (**C**) PS19 mice (~12 weeks old) were administered a single oral dose of a PROTAC LRRK2 degrader (30 mg/kg), and brain tissue was collected at 7 or 24 h post-dose. Cortical LRRK2 and soluble midbrain AT8-tau (pS202/205) levels were normalized to total protein and expressed as a percentage of vehicle control (n=7–10/group). Statistical significance was determined by one-way ANOVA with Tukey's multiple-comparisons test.

- Elevated monocyte LRRK2 levels are associated with faster PSP progression[13]
- The PROTAC LRRK2 degrader differentially reduced PSP-seeded phospho-tau compared with LRRK2 kinase inhibitors
- PROTAC LRRK2 degradation significantly reduced phospho-tau levels in PS19 mice

Figure 5: CSF LRRK2 degradation and downstream pathway marker reductions with a PROTAC LRRK2 degrader in NHPs[16]



(**A-B**) NHPs (n=4) with elevated LRRK2 in CSF (mean >35 pg/mL; panel A) were dosed with a PROTAC LRRK2 degrader QD for 14 days. CSF samples were obtained by spinal port before treatment (baseline) and periodically during the 14-day dosing and washout periods. LRRK2 levels in CSF were measured by single-molecule array. In panel A, dots represent individual longitudinal pre-dose measurements and horizontal lines are means. In panel B, values plotted are mean ± SD. (**C**) Direct immunoassays were run on CSF samples to orthogonally confirm proteomic results. Values plotted are mean (± SD) change in analyte expressed as percent of baseline.

- PROTAC LRRK2 degradation in NHPs drove parallel reductions in downstream lysosomal and inflammatory markers, including IBA1 (-68.0%) and GPNMB (-43.5%), as measured by ELISA
- These changes were similar to LRRK2-dependent biomarker changes observed in healthy volunteers and participants with Parkinson's disease in phase 1 clinical trials of ARV-102[17,18]

Conclusions

- LRRK2 degradation reduced phospho-tau in preclinical models, supporting a link between LRRK2 and tau pathology
- LRRK2 degradation had differential effects on downstream lysosomal and inflammation pathways vs LRRK2 kinase inhibitors in vitro and reduced pathway biomarkers in NHPs, healthy volunteers, and patients with Parkinson's disease
- These data support LRRK2 degradation as a potentially differentiated disease-modifying approach for tauopathies and other neurodegenerative disease

Abbreviations

ANK=ankyrin
ANOVA=analysis of variance
ARM=armadillo
ASK1=apoptosis signal-regulating kinase 1
ATG=autophagy-related protein
BSA=bovine serum albumin
CASM=conjugation of ATG8 to single membranes
cGAS=cyclic GMP-AMP synthase
COR=C-terminal of ROC
CSF=cerebrospinal fluid
DC_{50}=half-maximal degradation concentration
DMSO=dimethyl sulfoxide
DQ-BSA=dye-quenched bovine serum albumin
ELISA=enzyme-linked immunosorbent assay
GABARAP=gamma-aminobutyric acid receptor-associated protein
GPNMB=glycoprotein nonmetastatic melanoma protein B
IBA1=ionized calcium-binding adapter molecule
IFN=interferon
IC_{50}=half-maximal inhibitory concentration
IRF=interferon regulatory factor
KIN=kinase
LRR=leucine-rich repeat
LRRK2=leucine-rich repeat kinase 2
NHP=nonhuman primate
PROTAC=PROteolysis TArgeting Chimera
PSP=progressive supranuclear palsy
PSPRS=progressive supranuclear palsy rating scale
QD=once daily
Rab=Rab GTPase
ROC=Ras of complex
STING=stimulator of interferon genes
T_{max}=time to maximum observed plasma concentration
TNF-α=tumor necrosis factor α

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