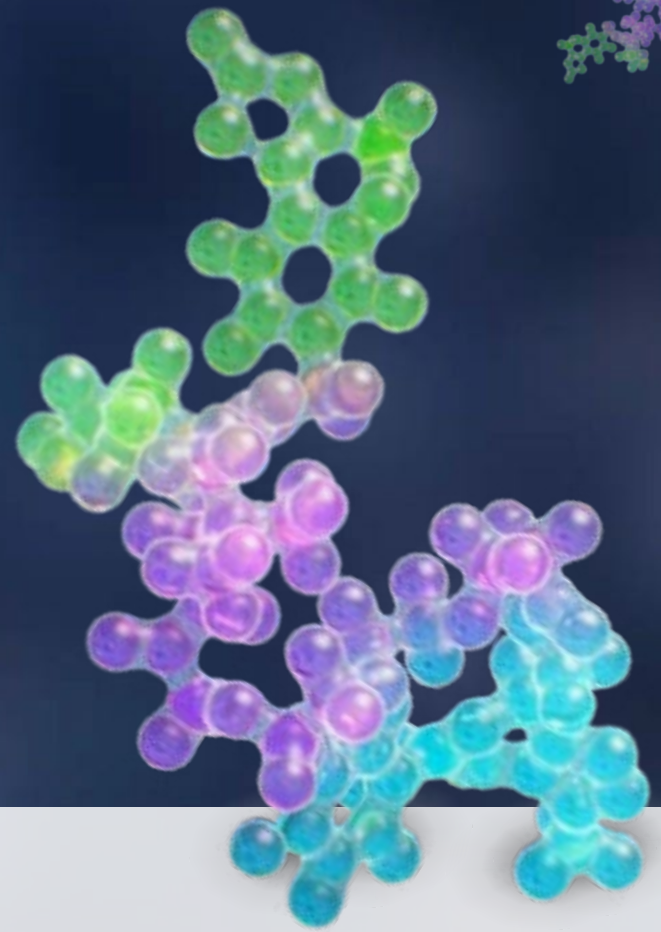
DEVELOPMENT OF POTENT, ORALLY BIOAVAILABLE PROTAC® LRRK2 DEGRADER MOLECULES AS POTENTIAL DISEASE MODIFYING THERAPEUTICS FOR NEURODEGENERATION

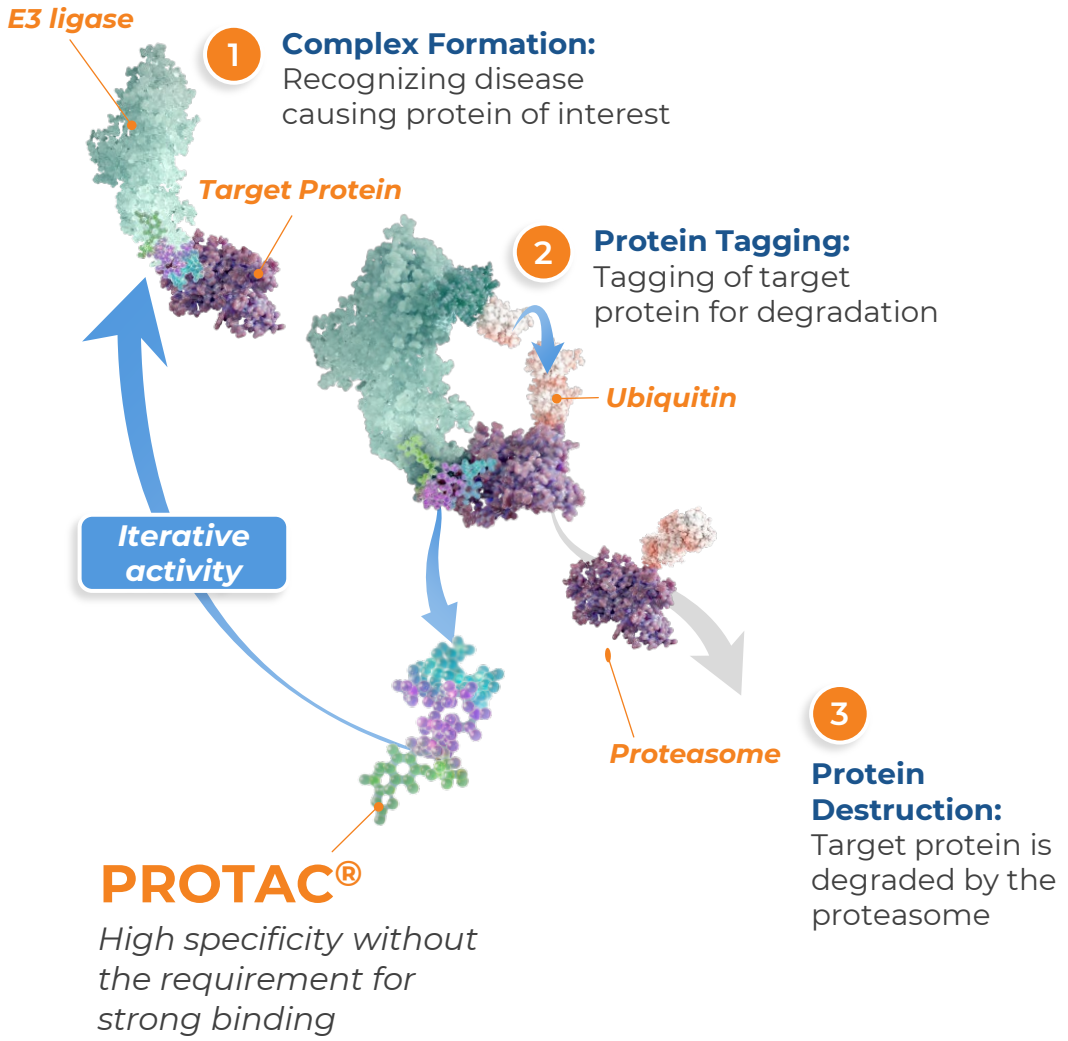


June 21, 2024

Kaela Kelly, PhD
Senior Research Scientist, Neuroscience, Arvinas, Inc.
Biennial International LRRK2 Meeting

Powered by PROTAC®

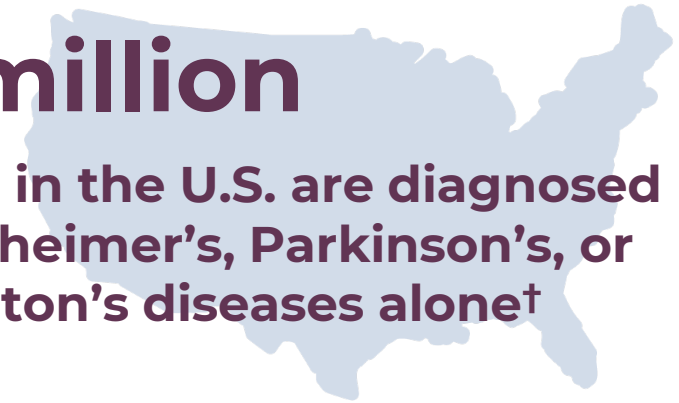
PROTAC® protein degraders combine the benefits of small molecules and gene-based knockdown technologies



Arvinas' PROteolysis-TArgeting Chimera (PROTAC ®) degraders can:

- Eliminate disease-causing proteins (rather than inhibit)
- Disrupt scaffolding functions of target proteins
- Bind and degrade classically "undruggable" proteins
- Act iteratively (catalytically)
- Potential for oral delivery and achieve broad tissue distribution, including across the blood-brain-barrier

Arvinas neuroscience pipeline addressing areas of tremendous unmet need in neurodegenerative diseases



> 6 million

patients in the U.S. are diagnosed with Alzheimer's, Parkinson's, or Huntington's diseases alone†

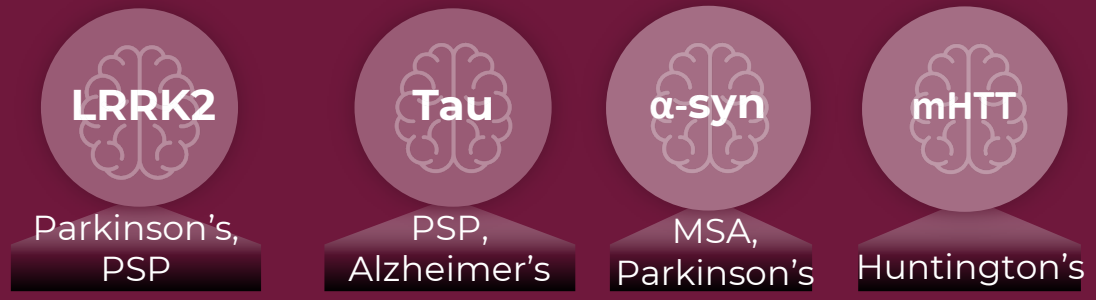
Opportunity for PROTAC® protein degraders:

- **Very few disease-modifying therapies exist**
- **Blood-brain barrier penetration is a challenge for other modalities**
- **Other potential therapies have difficult routes of administration, e.g., intra-thecal**

Arvinas Neuroscience Pipeline

PROTAC® protein degraders have the potential to change the treatment paradigm in neurodegenerative diseases

- Potential to cross the blood brain barrier and degrade disease-causing proteins inside cells
- Specifically target pathogenic proteins in the brain
- Potential for oral therapies



Phase 1 trial with PROTAC® LRRK2 degrader ARV-102 initiated Feb 2024

†Global data, DecisionResources.
mHTT, mutant Huntingtin protein; MSA, multiple systems atrophy; PSP, progressive supranuclear palsy; LRRK2, Leucine-rich repeat kinase 2

PROTAC®-induced LRRK2 degradation as a potential treatment for idiopathic Parkinson's disease and progressive Supranuclear palsy

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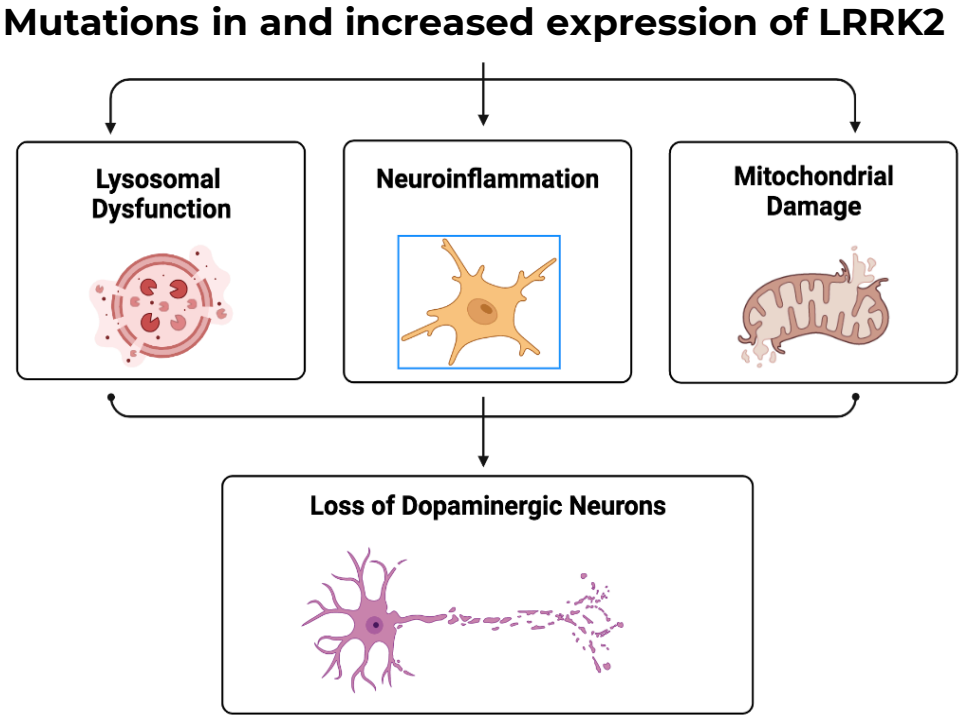
Human genetics and biology create a strong rationale for differential biology of PROTAC® LRRK2 degraders

- **LRRK2 is a large multidomain scaffolding kinase**

- **Parkinson's Disease (PD)** has a diagnosed prevalence of ~1M in the US, with more than 10M worldwide[1]
  - No approved disease-modifying therapies for PD
  - Familial mutations and sporadic variants implicate LRRK2 in PD ('breaks on lysosome clearance')

- **Progressive Supranuclear Palsy (PSP)** is a pure tauopathy with rapid progression to death within 5-7 years
  - No approved therapies for PSP
  - Genetic variants in the LRRK2 locus associated with accelerated progression time to death

- LRRK2 kinase inhibitors and an ASO in clinical trials

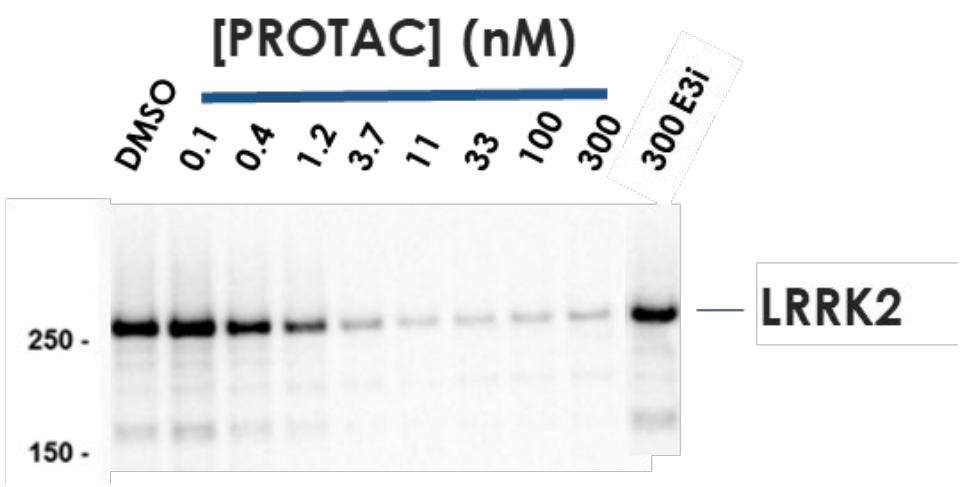


LRRK2, Leucine-rich repeat kinase 2; ASO, antisense oligonucleotide

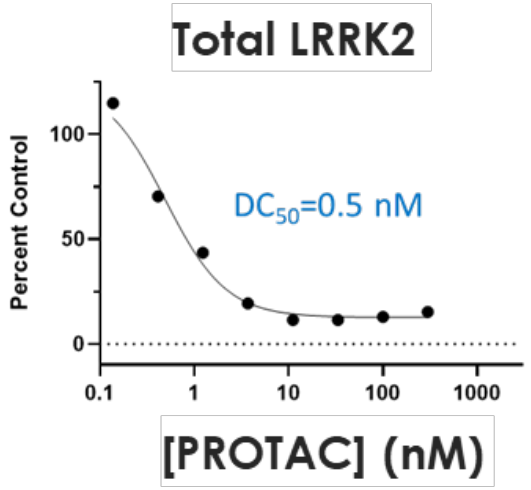
[1] Parkinson's Foundation. *Who has Parkinson's?* https://www.parkinson.org/understanding-parkinsons/statistics, accessed 01/06/24

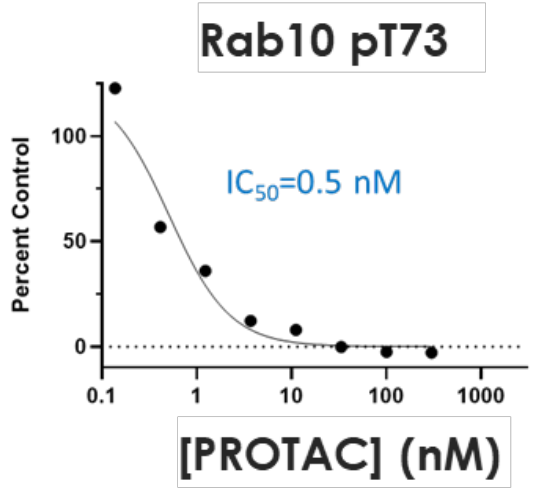
PROTAC® induces degradation of LRRK2 in in human PBMCs, impacts phospho-RAB pathway, and is on mechanism

PROTAC® LRRK2 degradation aligns with effects on target & pathway engagement *in vitro*



E3 dead PROTAC (E3i) does not induce degradation of LRRK2

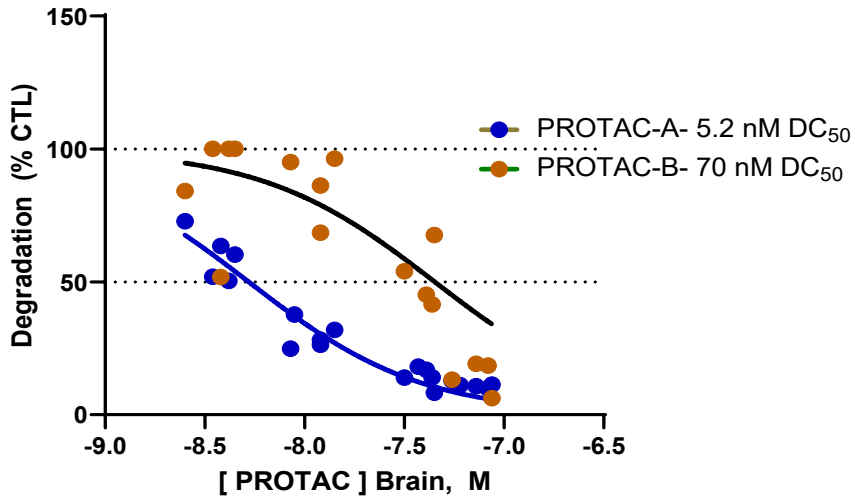




PBMC, peripheral blood mononuclear cell

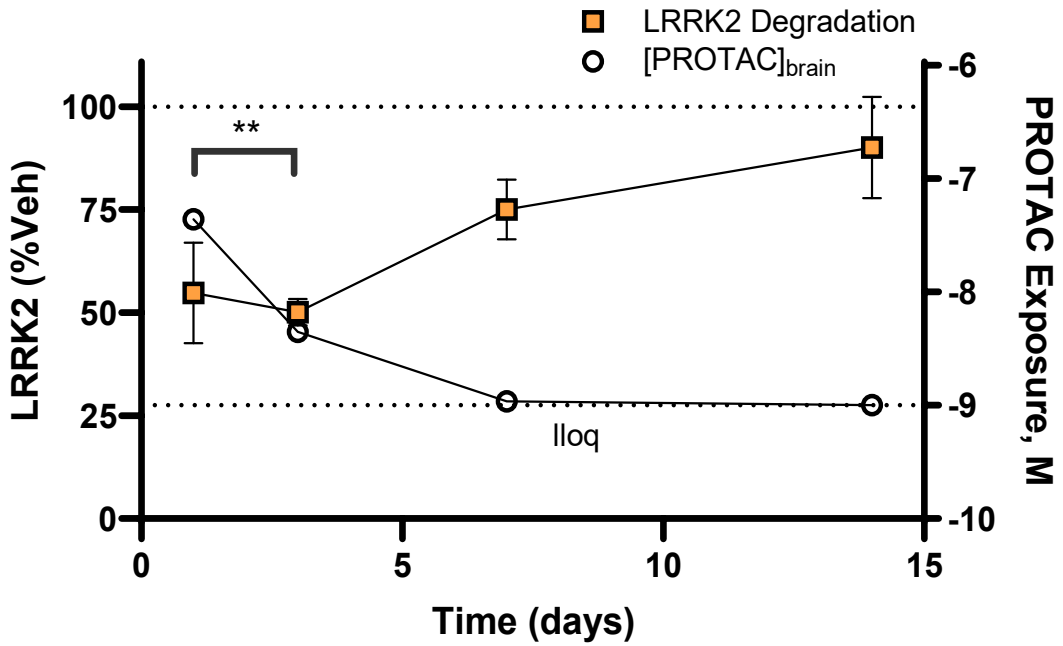
Single oral LRRK2 PROTAC® administration rapidly degrades target in mouse brain (concentration-dependent and durable)

LRRK2 PROTAC® Optimization Dose-Response PK/PD in Cortex 24h post dose



*PK/PD- Pharmacokinetic and Pharmacodynamic effect relationship

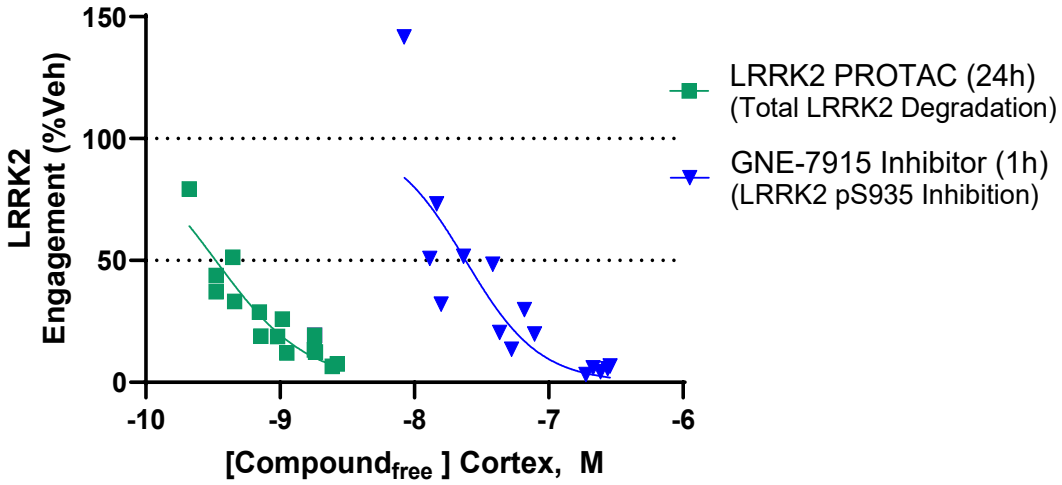
LRRK2 PROTAC® Time-Course - Cortex



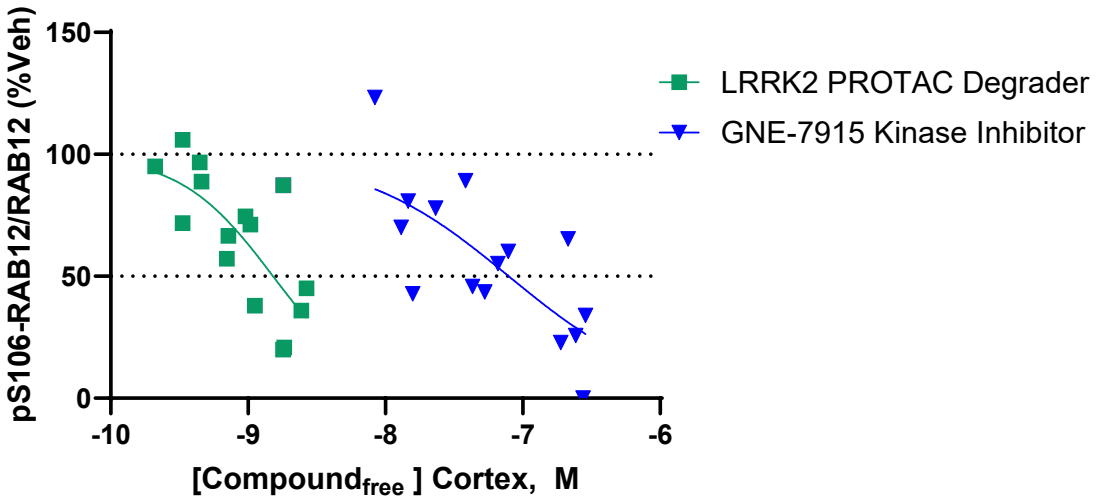
PROTAC® LRRK2 degrader shows better target engagement, enhanced potency and pathway engagement versus a LRRK2 inhibitor in G2019S KI mice

Iterative and catalytic PROTAC® advantage results in stronger LRRK2 and RAB pathway engagement versus a LRRK2 kinase inhibitor[a]

LRRK2 Target Engagement
LRRK2 PROTAC vs. Kinase inhibitor at Tmax



RAB Pathway Engagement
(LRRK2 PROTAC vs. Inhibitor)



[a] G2019S familial Parkinson's Disease mouse model
LRRK2, Leucine-rich repeat kinase 2
Data presented at 2023 Keystone Summit: Autophagy and Neurodegeneration

PROTAC® LRRK2 degrader induced less severe Type II pneumocyte enlargement in mice despite full target engagement

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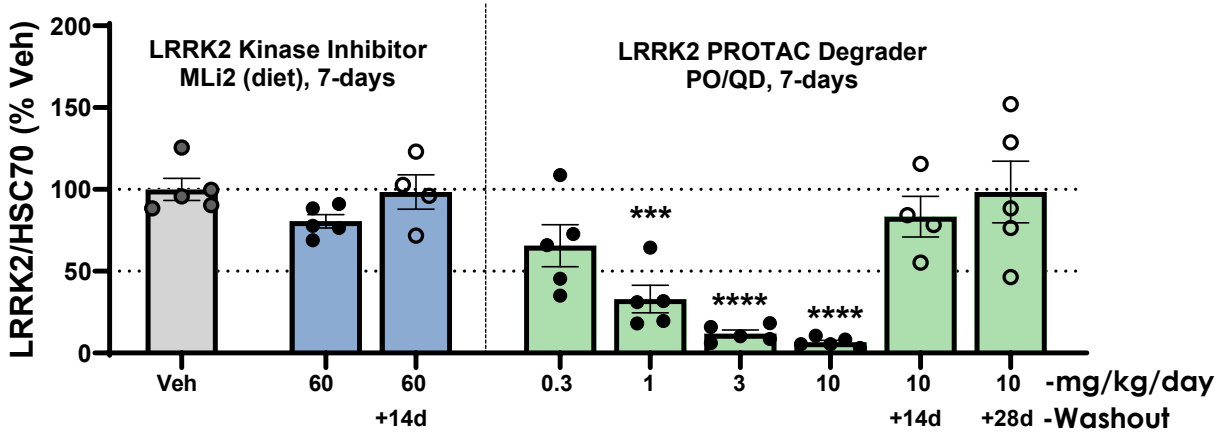
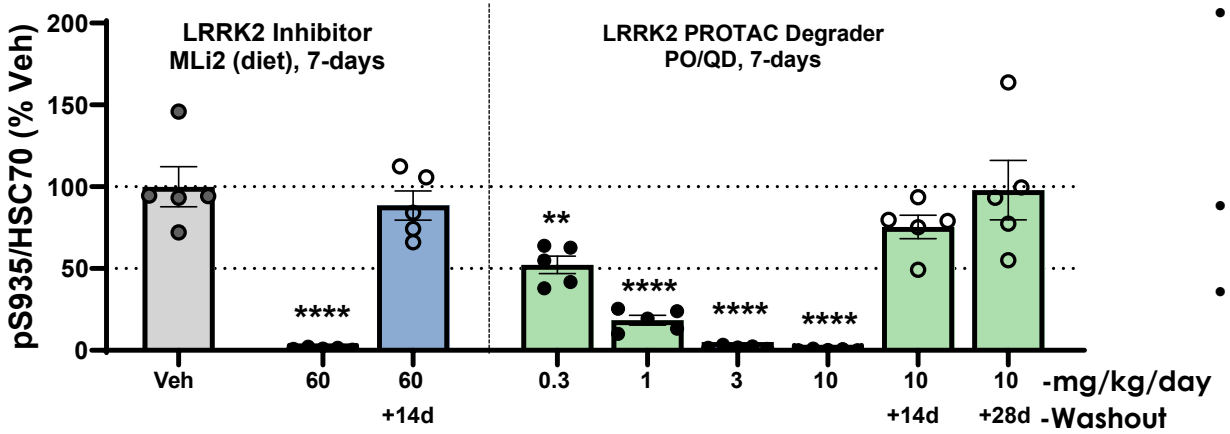
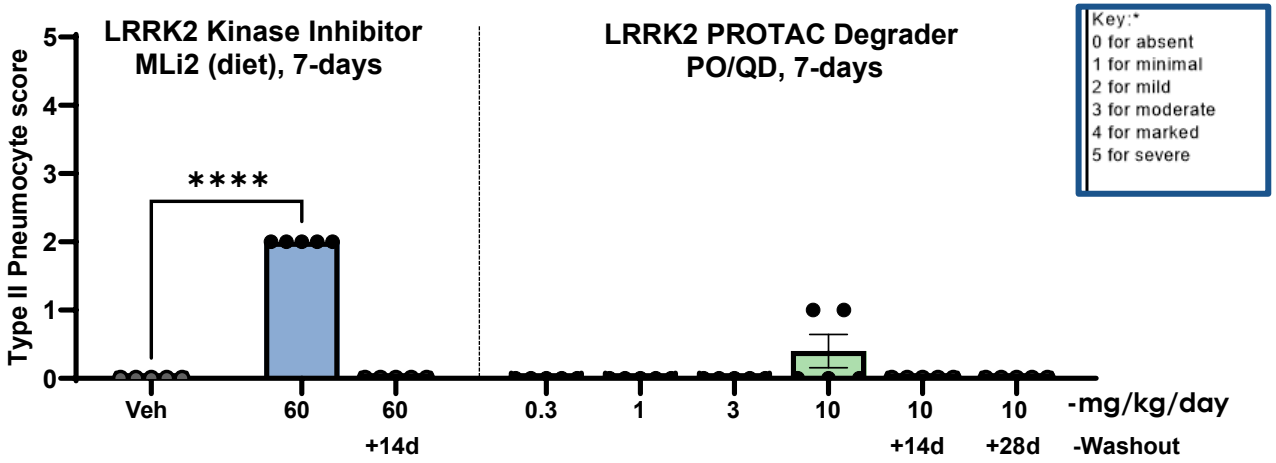
LRRK2 Degradation/ Target Engagement



LRRK2 Kinase Inhibition/ Target Engagement



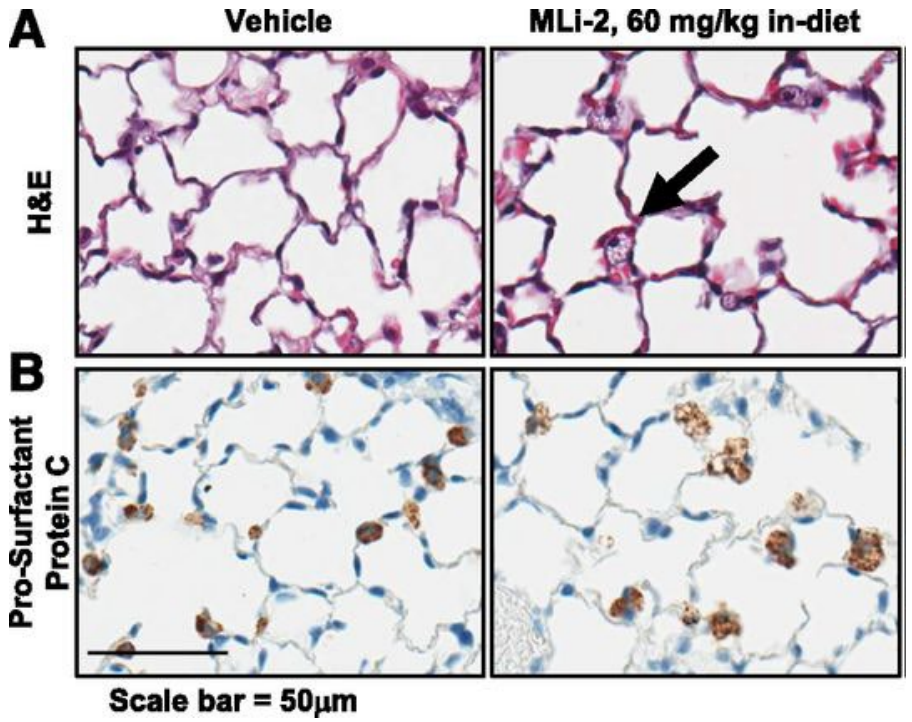
Lung Type II Pneumocyte Enlargement/ Hypertrophy (Histopathologic Score)



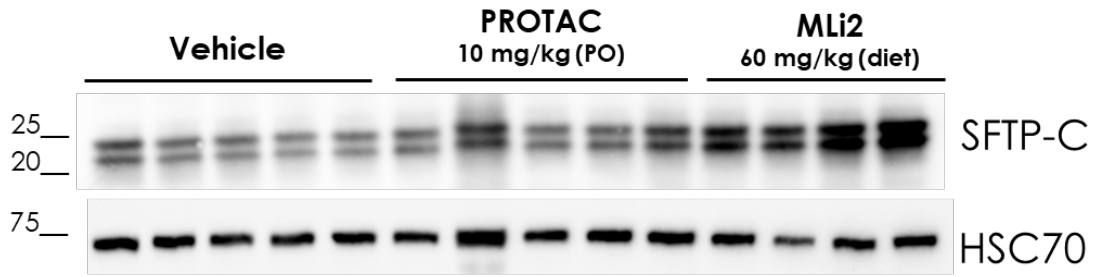
- Expected lung phenotype observed with LRRK2 PROTAC and kinase inhibitor MLi2 (positive control for type II pneumocyte enlargement)
- Effect is reversible after 14-day wash-out
- No evidence of collagen deposition in lung with LRRK2 PROTAC® degraders in primate (tox studies to date)

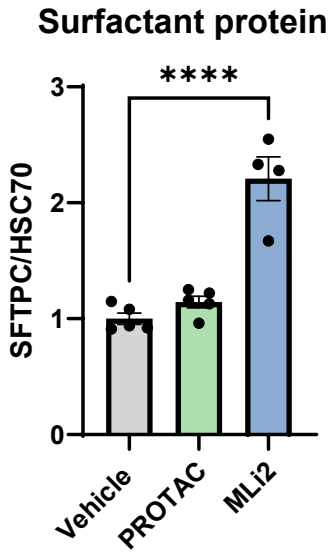
Surfactant protein accumulation in mouse lung observed with LRRK2 kinase inhibitor MLi2, but not PROTAC® degrader

SFTP-C is localized exclusively to type II pneumocytes and appears elevated after 7 days in-diet dosing with LRRK2 kinase inhibitor



Adapted from Bryce, et al. JPET, 2021





SFTPC, surfactant protein C

Arvinas' oral PROTAC® LRRK2 degrades LRRK2 in multiple deep anatomic brain regions in non-human primates

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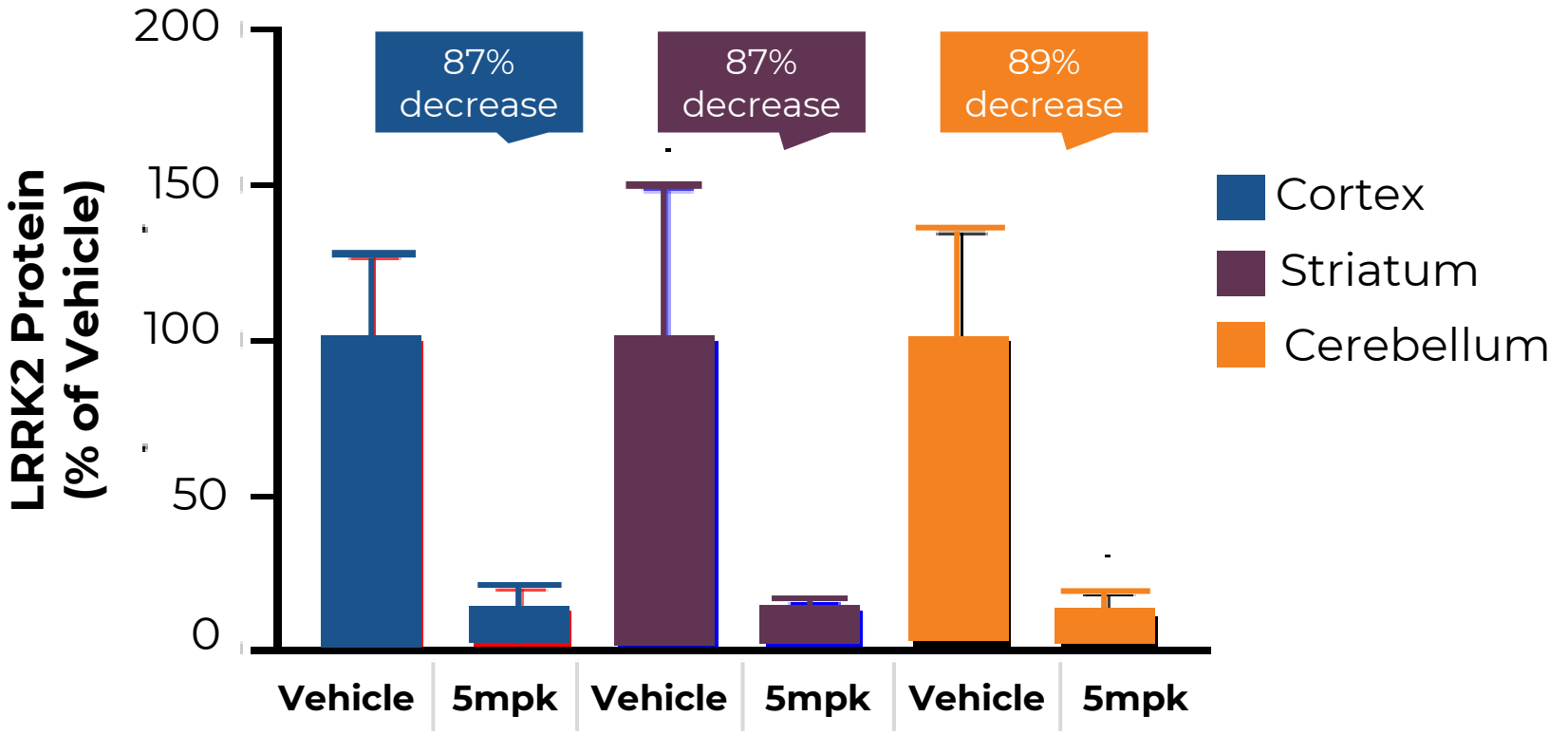
>85% LRRK2 degradation in deep brain regions of cynomolgus monkeys after oral dosing



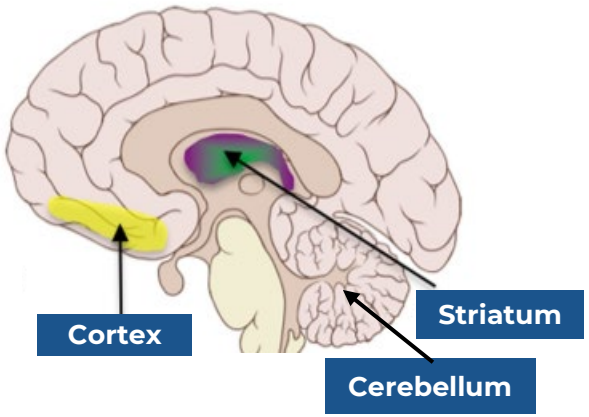


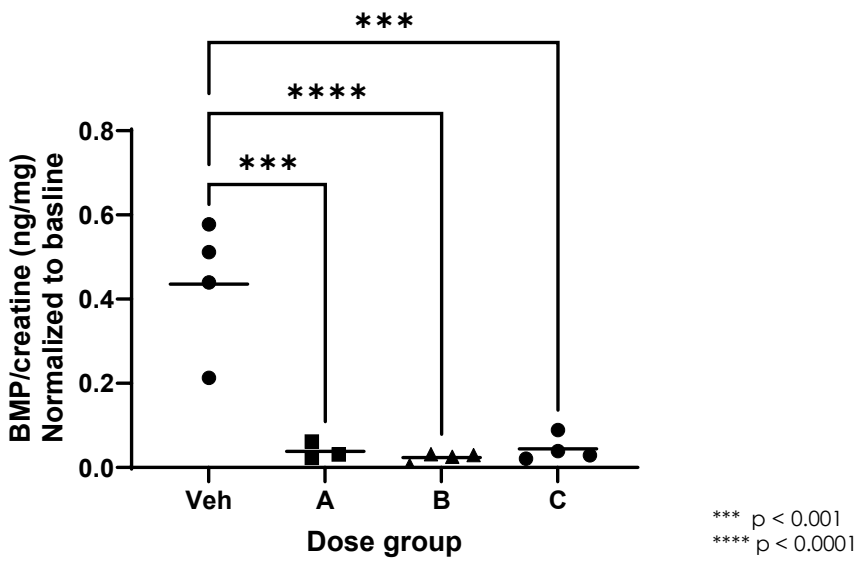
Figure modified from Beuriat et al. 2022

LRRK2, leucine-rich repeat kinase 2; mpk, milligrams per kilogram;

Our LRRK2 degrader induces biomarker changes that reinforce confidence in the PROTAC® mechanism of action in the brain and periphery

PROTAC® -induced reductions observed in key lysosomal marker in cynomolgus monkey

BMP reductions in cynomolgus monkeys

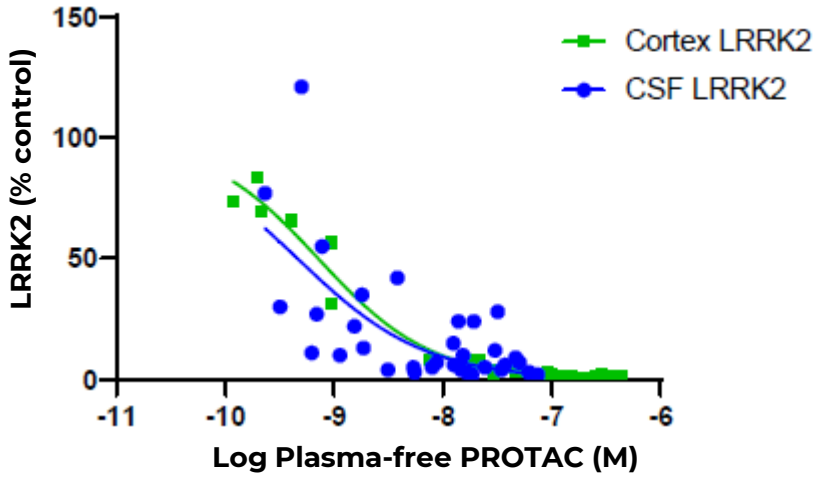


*** p < 0.001
**** p < 0.0001

BMP levels were measured by UPLC-MS/MS and normalized to creatinine and then expressed relative to baseline.

PK/PD of LRRK2 reduction in cortex and CSF following oral dosing in cynos

CSF LRRK2 reductions in cynomolgus monkeys; surrogate compartment for brain



Equivalent PK/PD supports the utility of measuring CSF LRRK2 as a surrogate for monitoring LRRK2 reductions in the brain.

LRRK2, Leucine-rich repeat kinase 2; PK/PD, pharmacokinetic-pharmacodynamic; CSF, cerebrospinal fluid; BMP, Bis(monoacylglycerol)phosphate: a lysosomal lipid
Data presented at 2024 Keystone Summit: Targeted Protein Degradation

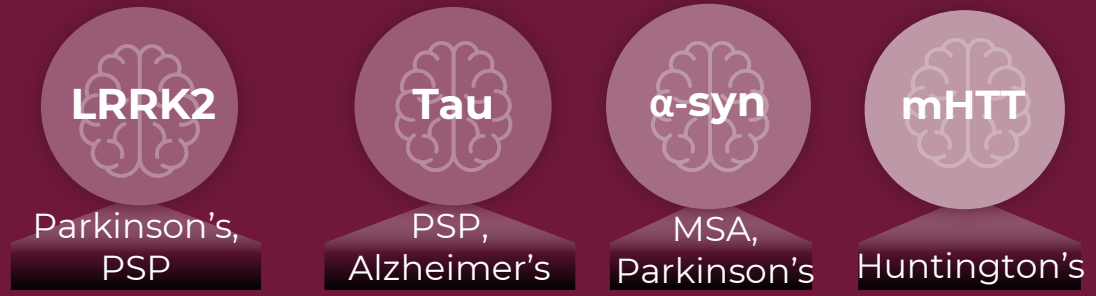
PROTAC® protein degraders have the potential to change the treatment paradigm in neurodegenerative diseases

Preclinically, PROTAC® LRRK2 degraders:

- Achieve potent, selective, and durable target engagement in brain following oral dosing
- Show better target engagement, enhanced potency and pathway engagement compared to inhibitors
- Induce less severe type 2 pneumocyte enlargement and there's no accumulation of surfactant protein C, compared to MLi2
- Impact clinically relevant biomarkers in primates

Arvinas Neuroscience Pipeline

- Potential to cross the blood brain barrier and degrade disease-causing proteins inside cells
- Specifically target pathogenic proteins in the brain
- Potential for oral therapies



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Thank you - Team Arvinas!