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Discovery of oral PROTAC LRRK2 degraders as potential treatments for neurodegenerative disorders

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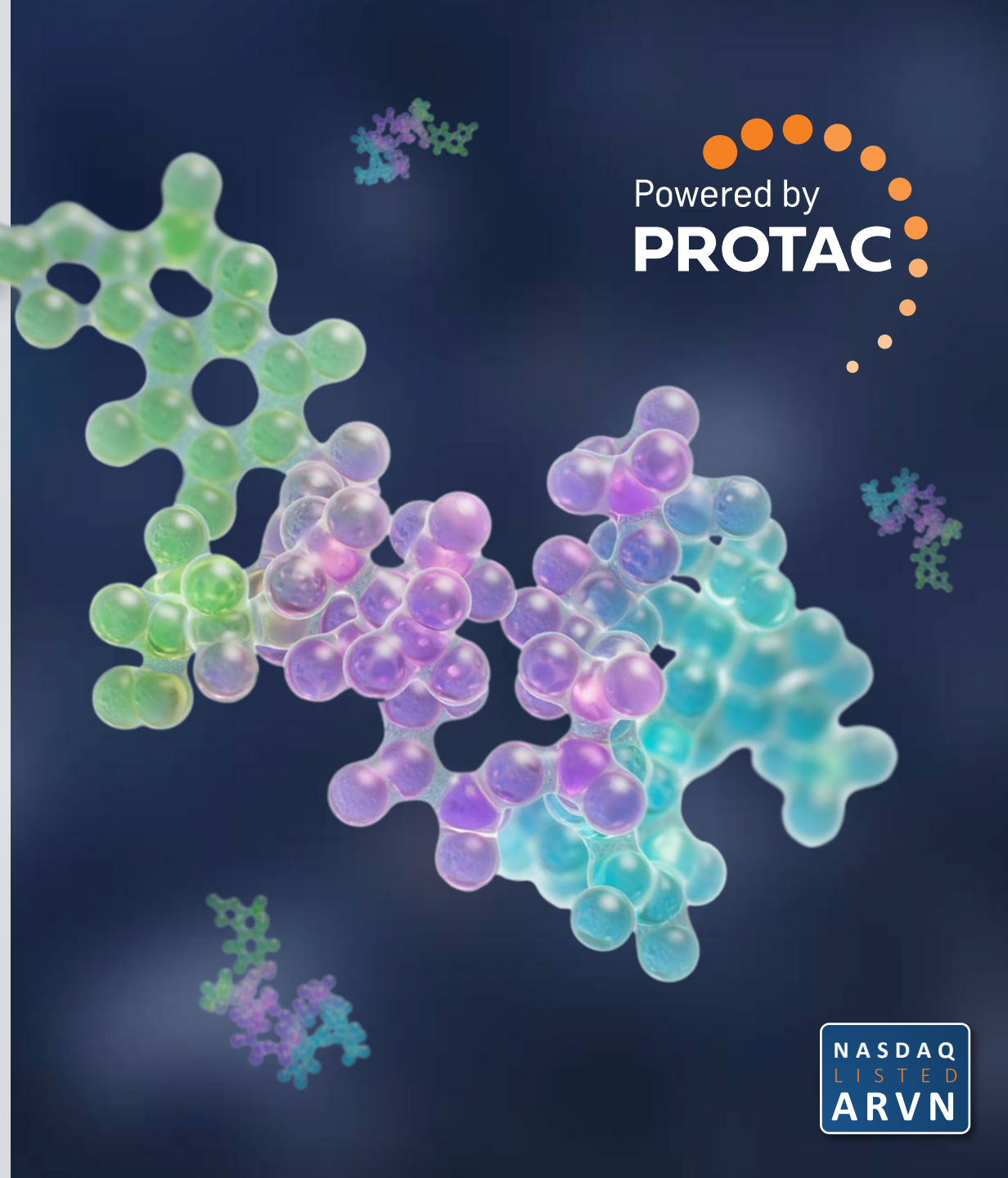
MJFF Conference, 2024



PROTAC Protein Degraders Combine the Benefits of Small Molecules and Gene-Based Knockdown Technologies to Eliminate Disease-Causing Proteins

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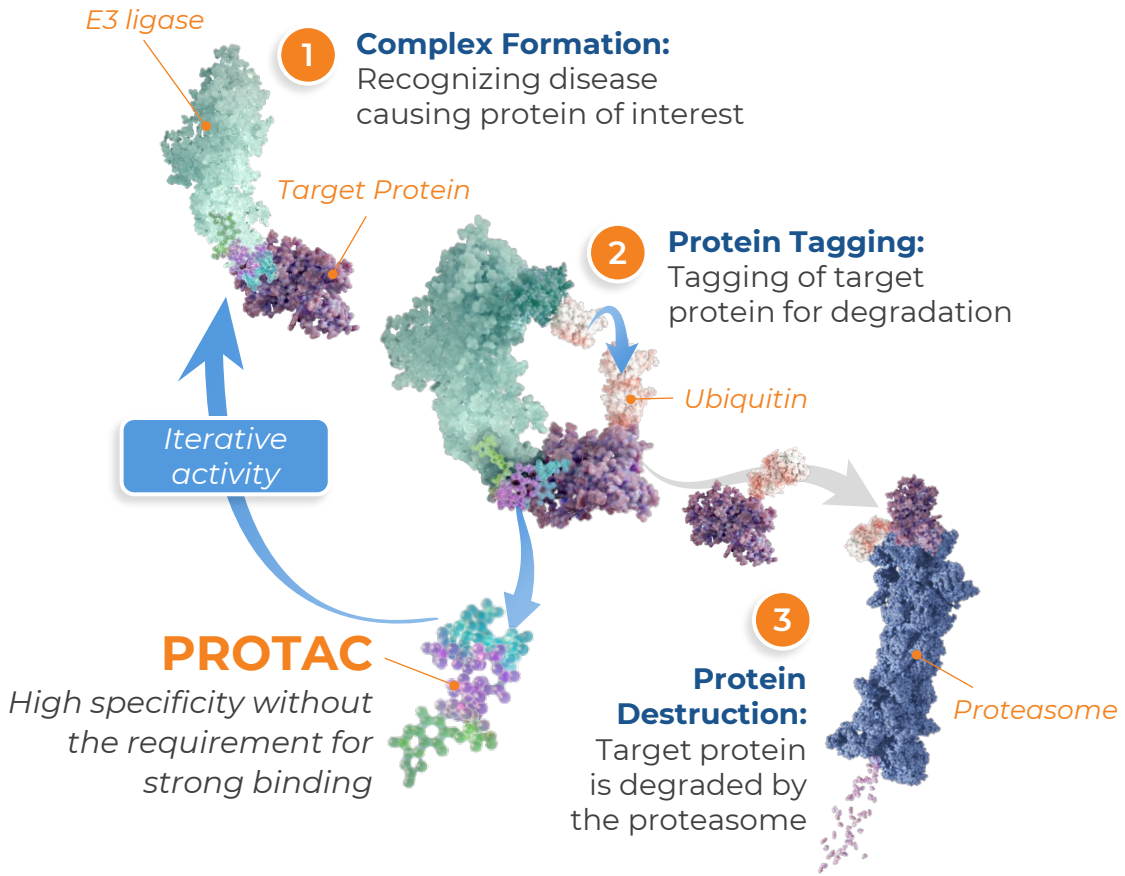

Arvinas' PROteolysis TArgeting Chimera (PROTAC) degraders can:

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

Arvinas neuroscience pipeline includes:

LRRK2	Tau	α-syn	mHTT
PSP, Parkinson's	PSP, Alzheimer's	MSA, Parkinson's	Huntington's

Our investigational PROTAC LRRK2 degrader, ARV-102, is currently being tested for safety and effects on LRRK2 levels and activity in healthy volunteers.

Arvinas' Neuroscience Exemplifies Our Commitment to Address Tremendous Unmet Need in Parkinson's and Related Diseases

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PATIENTS IN THE U.S.†

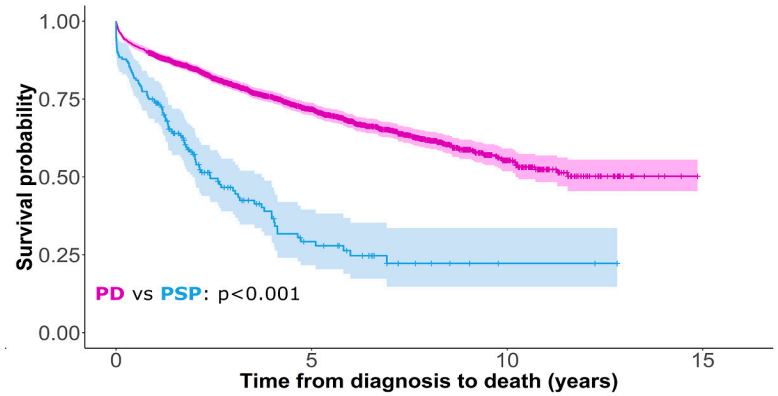
30,000
Progressive Supranuclear Palsy (PSP)

Similarities between PSP and PD

>1 million
Parkinson's Disease (PD)

- Neuropathology- Concomitant Tau pathology
- Genetics (e.g. LRRK2/ increased expression and activity)
- Environmental exposures
- Aging
- Molecular / cellular events (e.g. 'breaks' on lysosomal clearance, mitochondrial dysfunction, neuroinflammation, etc.)

Survival of individuals with PSP is significantly worse than individuals affected with idiopathic PD



Differences between PSP and PD:

- PSP worsens quickly, severe disability within 3-5 years post initial symptoms
- PSP-forward leaning posture, fixed gaze, and reduced sense of smell
- Lack of response to levodopa in PSP
- PD is also a synucleinopathy

Street D., et al. Prediagnostic Progressive Supranuclear Palsy – Insights from the UK Biobank
Parkinsonism & Related Disorders Volume 95, February 2022, Pages 59-64; † Parkinson's disease foundation and CurePSP; Herbst et al., 2022; Jabbari et al., 2021

PROTAC-Induced LRRK2 Degradation is being Researched 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

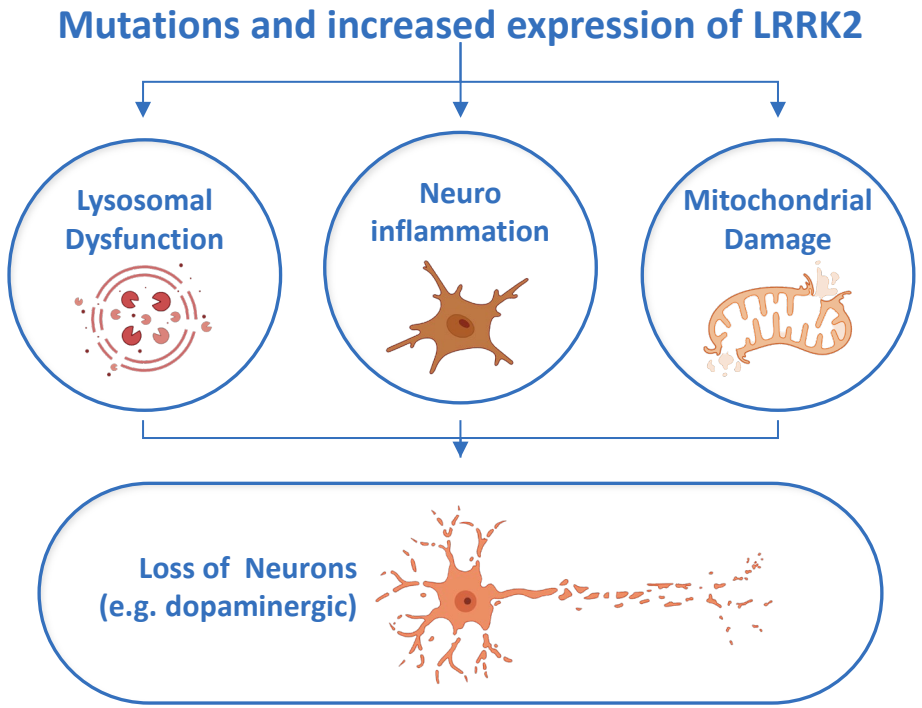
Progressive supranuclear palsy (PSP) is a pure tauopathy with rapid progression to death within 5-7 years

- Data linking increased LRRK2 activity and Tau secretion and/or tau mediated neurotoxicity
- LRRK2 genetic variants associated with accelerated progression time to death

Parkinson's disease (PD) is the second-largest tauopathy

- No approved disease-modifying therapies for PD
- Familial mutations & sporadic variants implicate LRRK2 in PD and are associated with tau pathology—G2019S LRRK2 enhances the neuronal transmission of tau
- LRRK2 is a large multidomain scaffolding kinase contributing to pathology in the disease (*breaks on lysosomal clearance*)
- Protective PD variant and preclinical animal model data suggest that reduction of 50% of LRRK2 protein may impact pathology and dysfunction in PD

LRRK2 kinase inhibitors and an ASO in clinical trials

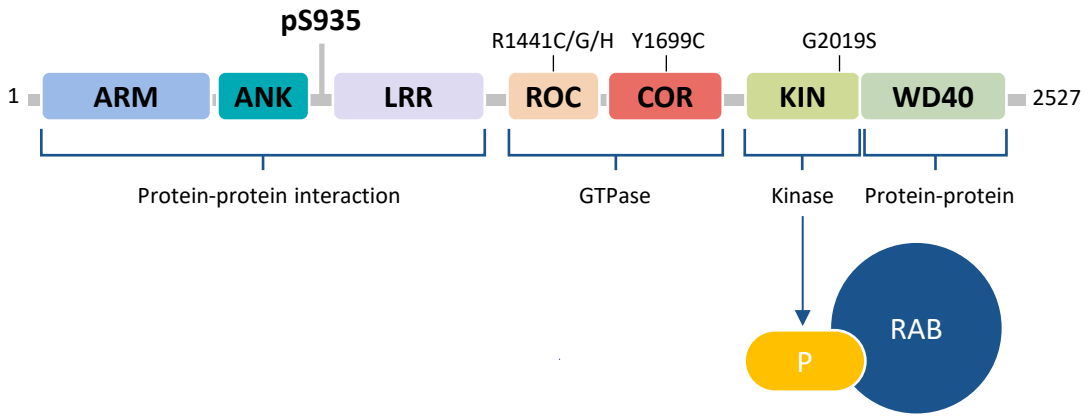


LRRK2 mutations increasingly associated with diverse pathologies in PD and PSP

Wang,et al., 2021, Zhao,et al., 2017, Henderson, et al., 2019, Zheng, et al., 2022; Herbst, et al., 2022; Castro-Sanchez, et al., 2020)

PROTAC-Induced LRRK2 Degradation has the Potential to Differentiate From Kinase Inhibition

LRRK2 is a large multidomain scaffolding kinase



LRRK2 PROTAC key differentiators

		Inhibitor	PROTAC
LRRK2	Kinase activity	✓	✓
	GTPase activity	✗	✓
	Signaling scaffold	✗	✓
	Increased protein level	✗	✓

Target and pathway engagement measures

- Kinase inhibitor engagement is measured by phosphorylation of amino acid 935 (pS935)
- PROTAC engagement is measured by total LRRK2 protein levels
- Pathway engagement is measured by phosphorylation of Rab GTPases (pRAB) that put the brakes on the lysosome

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

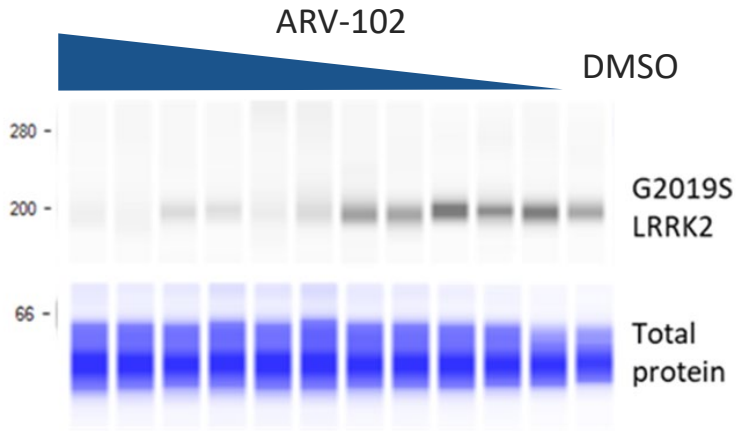
1. Parkinson's Foundation. Who has Parkinson's? https://www.parkinson.org/understanding-parkinsons/statistics, accessed 01/06/24; Gregory et al., 2024

Investigational PROTAC protein degrader ARV-102 Induces LRRK2 Degradation and Lysosomal Pathway Engagement

PROTAC-induced potent LRRK2 degradation in human PD G2019S iPSC-microglia

G2019S human microglia

PROTAC Target Engagement
(LRRK2 Degradation)

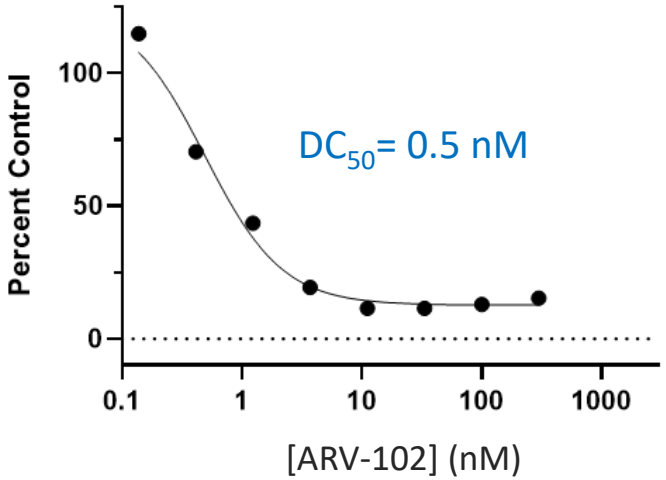


DC_{50}= 0.6 nM
D_{max}= 94% degradation

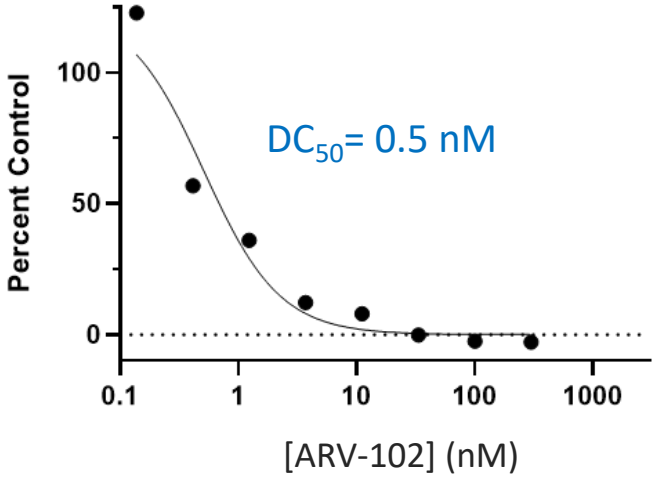
PROTAC-induced LRRK2 degradation aligns with effects on target & pathway engagement in human PBMCs

Human Peripheral Blood Monocytes (PBMCs)

PROTAC Target Engagement
(LRRK2 Degradation)



Lysosome Pathway Engagement
(phospho-Rab10 pT73)



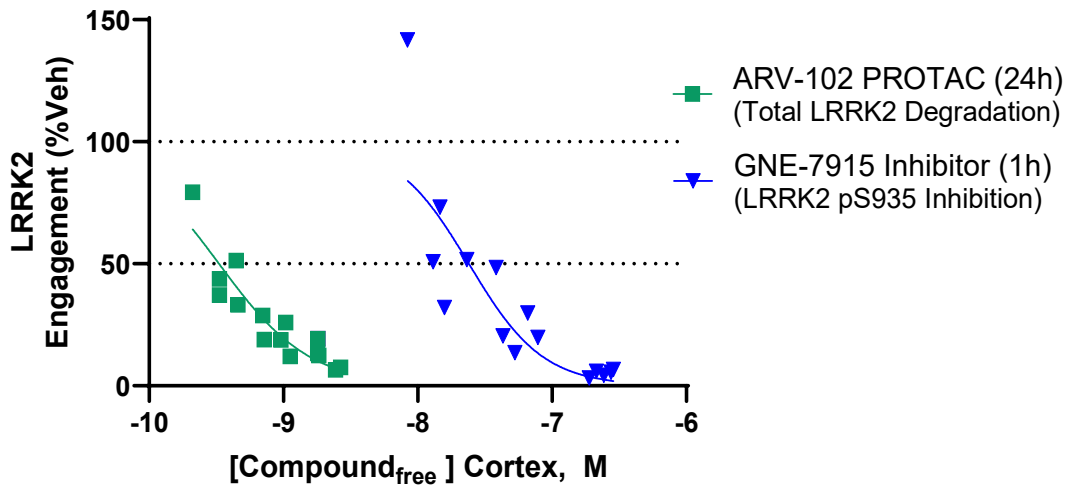
LRRK2 degradation is E3-dependent and on mechanism (data not shown)

LRRK2, Leucine-rich repeat kinase 2; iPSC, induced pluripotent stem cells; Data presented at 2024 Keystone Summit: Targeted Protein Degradation; E3i- PROTAC with Chemically inactivated E3 binder; DC50 =half-maximal degradation concentration that makes a protein for 50% degradation; Dmax= maximal % reduction of a protein

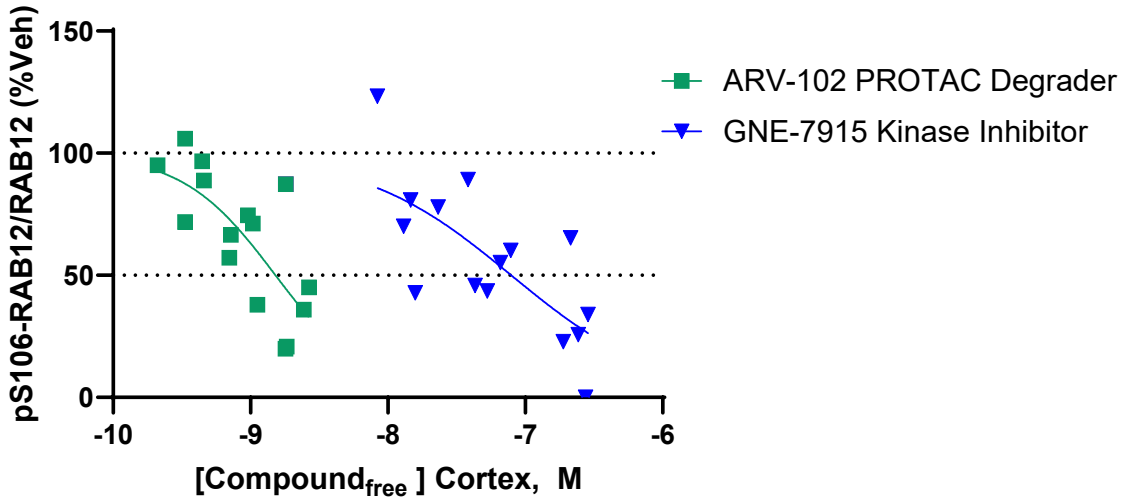
Oral ARV-102 LRRK2 Degrader Shows Better Target Engagement, Enhanced Potency and Pathway Engagement Versus a LRRK2 Kinase Inhibitor

Iterative PROTAC degradation results in stronger LRRK2 and downstream pRAB pathway engagement versus LRRK2 kinase inhibitor in the brain[a]

LRRK2 Target Engagement
LRRK2 PROTAC vs. Kinase inhibitor at Tmax



Downstream pRAB Pathway Engagement
(LRRK2 PROTAC vs. Inhibitor)

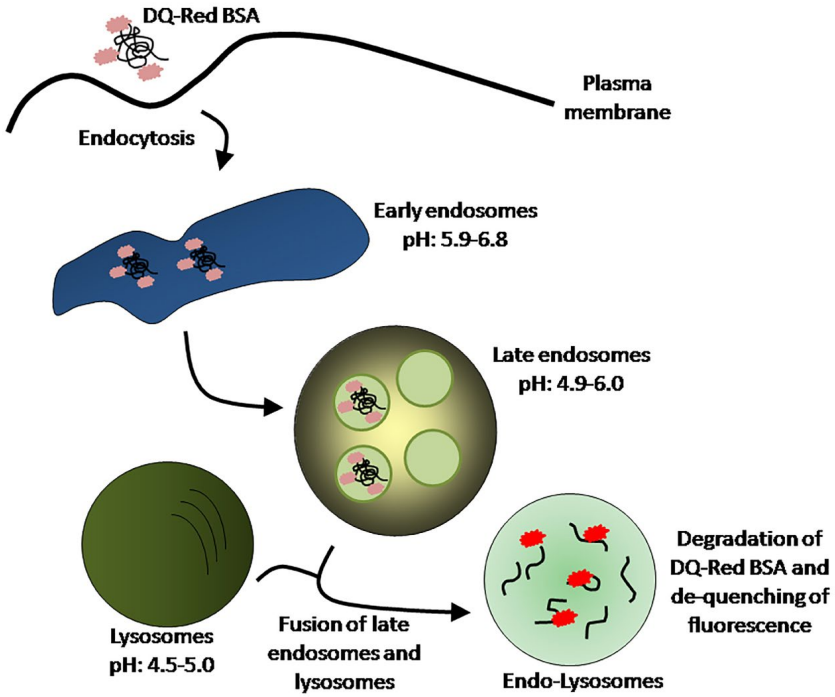


a. G2019S familial Parkinson's Disease mouse model

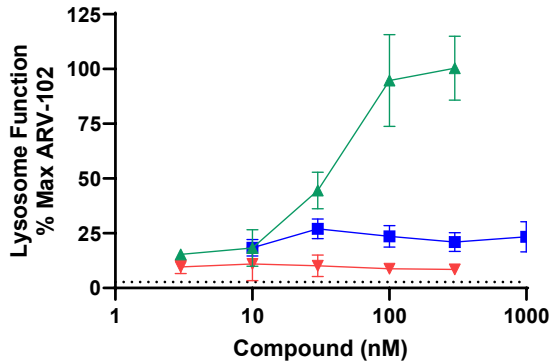
LRRK2, Leucine-rich repeat kinase 2; Tmax = time to achieve maximal pharmacologic effect

ARV-102 Increases Lysosome Functional Degradative Capacity and Number in cells

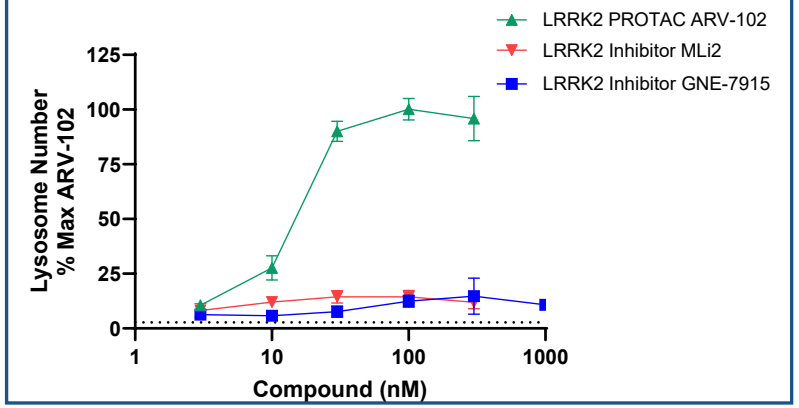
Lysosome function and number are reduced in PD patients[a] and models.
ARV-102 dose-dependently increased degradation efficiency and number compared to kinase inhibitors



ARV-102 increases lysosome **degradation** in A549 cells



ARV-102 increases lysosome **number** in A549 cells

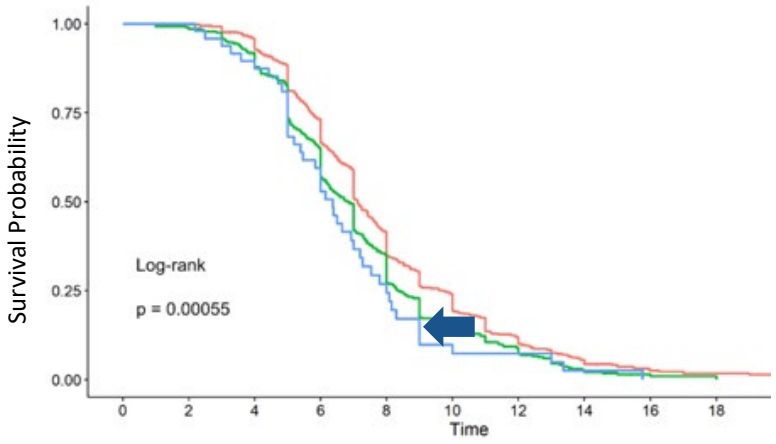


- Mutant familial PD and increased LRRK2 expression 'puts the brakes' on lysosomal clearance system.
- Autophagy (clearance dependent on lysosome) is reduced with increased LRRK2 expression, LRRK2 familial mutation (G2019S), and LRRK2 activity/levels in rodent neurons[b]
- LRRK2 PROTAC activity is consistent with literature showing an increase in lysotracker spot count observed in LRRK2 KO astrocytes[c]

LRRK2, Leucine-rich repeat kinase 2; PD, Parkinson's disease
KO, genetic knock out; DQ-BSA, Dye Quenched-Bovine Serum Albumin
a. Dehey et al., 2013. Lysosomal impairment in Parkinson's disease; b. R. Wallings et al., 2019; c. Henry et al., 2015
Data presented at 2023 Keystone Summit: Autophagy and Neurodegeneration; Figure: Marwaha and Sharma, Bio-protocol, 2017

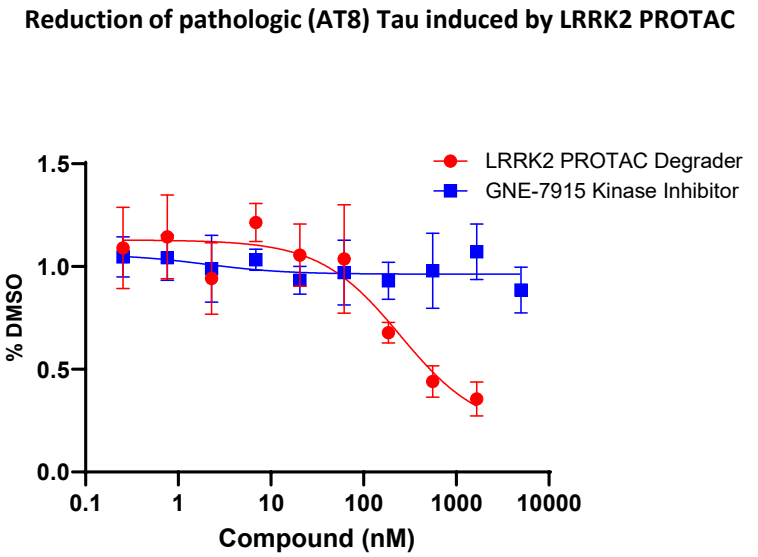
In Vitro and *In Vivo* Data Indicate that LRRK2 PROTAC Degraders Induce Reduction of Pathologic Tau

LRRK2 SNP accelerated time to death by 1 year in PSP†

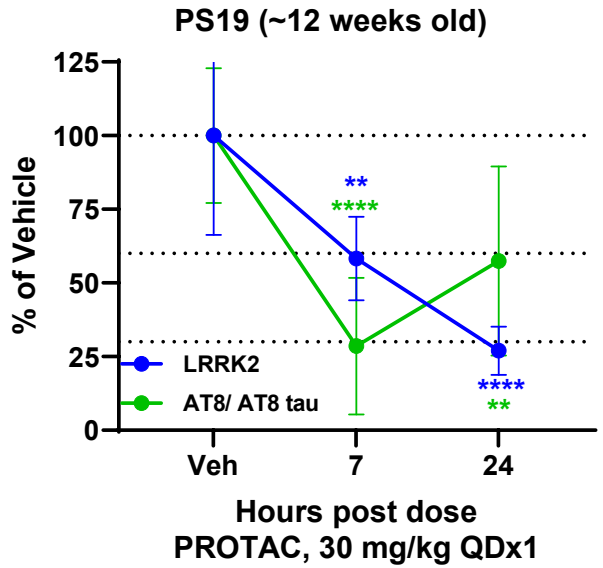


- Pooled analysis from 1239 PSP cases
- Arrow indicates accelerated time death for LRRK2 SNP

LRRK2 PROTAC induces reduction of PSP induced pathologic AT8-tau, *in vitro*



LRRK2 PROTAC degraders induce pathologic tau protein reduction *in vivo*

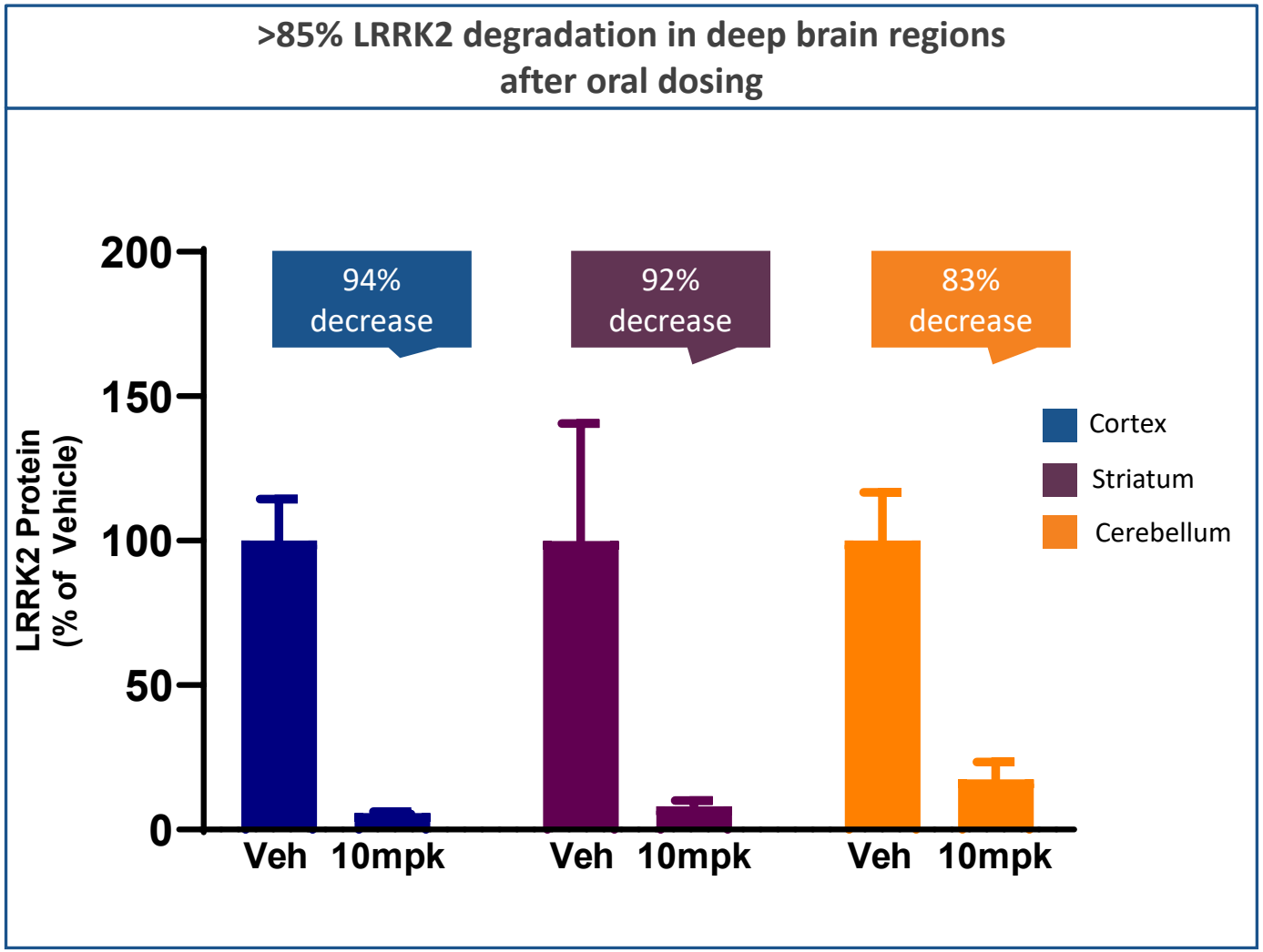


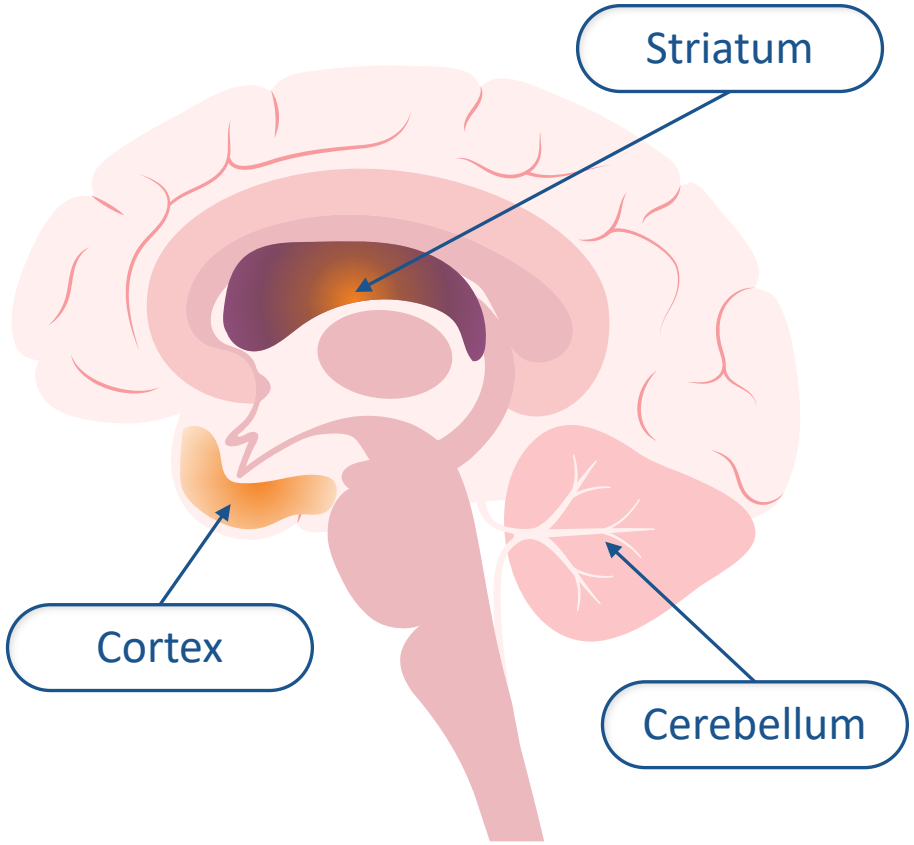
Reductions of soluble AT8+ tau aggregates occur as early as 7 hours post dose in both Tg4510 (data not shown) and PS19 mouse brain tissue

SNP, single nucleotide polymorphism

†Jabbari et al., 2021

Oral ARV-102 LRRK2 Degrader Reaches Multiple "Deep Brain" Regions in Non Human Primates (NHPs) and Degrades LRRK2

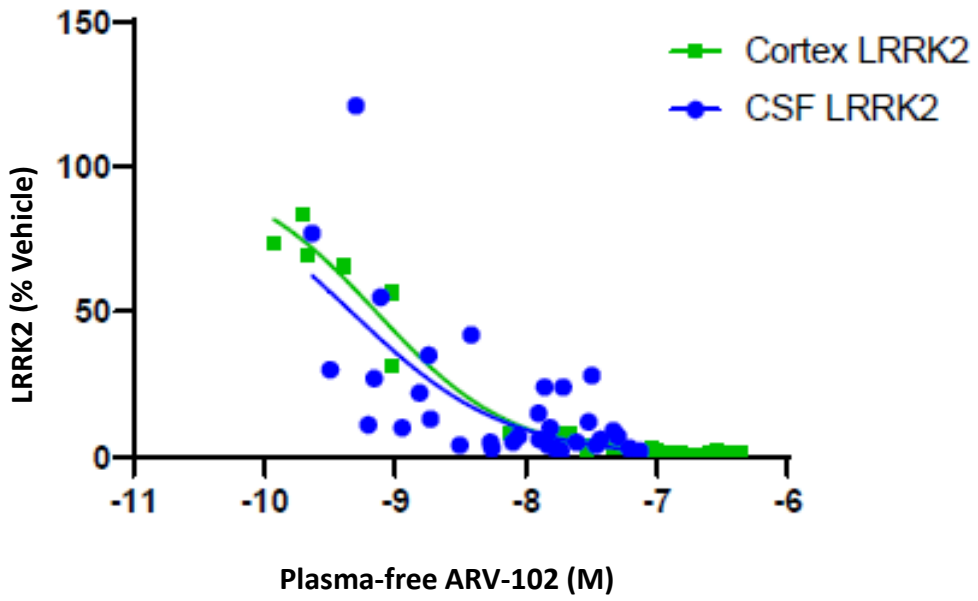




LRRK2, leucine-rich repeat kinase 2; mpk, milligrams per kilogram;
Figure adapted from Beuriat et al. 2022

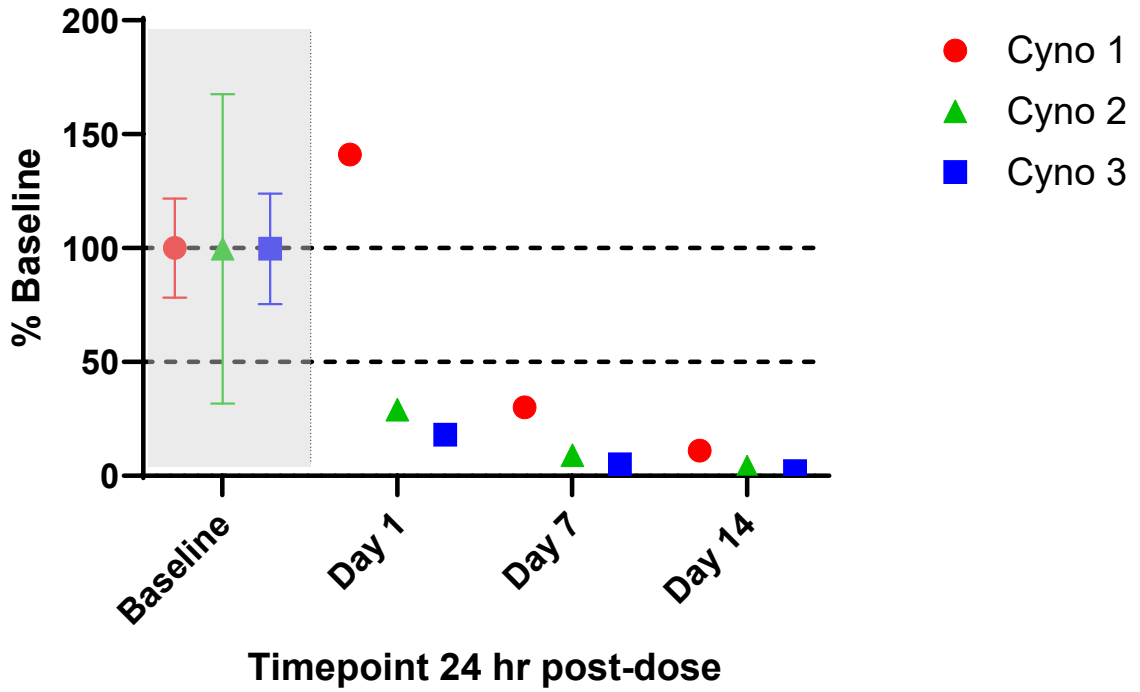
Oral ARV-102 Crosses the Blood-Brain Barrier and Reduces CSF LRRK2 levels in NHPs

PK/PD of LRRK2 are reduced in cortex and CSF following oral dosing in NHP



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

CSF LRRK2 levels are reduced in ported NHP study following ARV-102, 10 mg/kg oral single daily dose



ARV-102 CSF drug levels are retained across time-course (Data not shown)

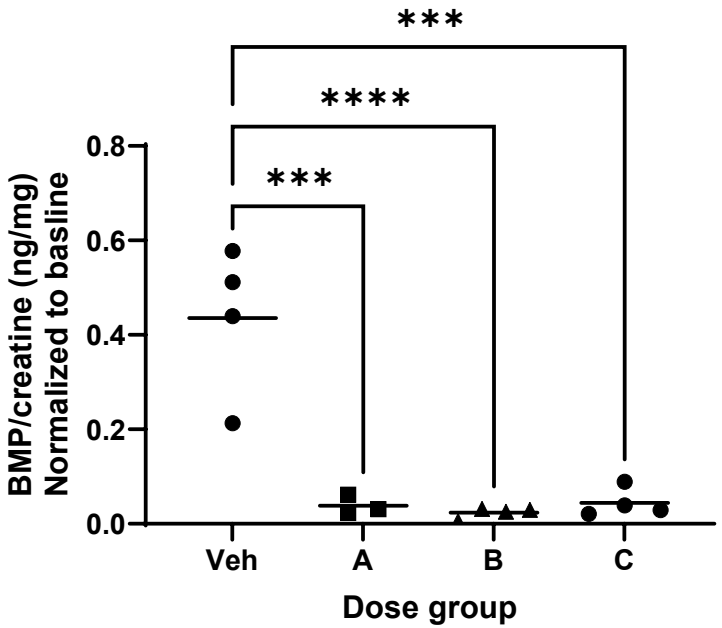
CSF, Cerebrospinal fluid

*Human CSF LRRK2 levels in healthy volunteers range from 5 – 104 pg/mL, averaging 32 pg/mL. The average in LRRK2+PD+ is 68 pg/mL ~2 fold elevated LRRK2 levels.

Oral Dosing of ARV-102 Induced Reductions in Bis-Monoacylglycero Phosphate (BMP) Lysosomal Biomarker in NHP in Both Urine and in CSF

Oral ARV-102-induced reductions observed in lysosomal biomarker BMP in urine

Urine BMP reductions in NHP

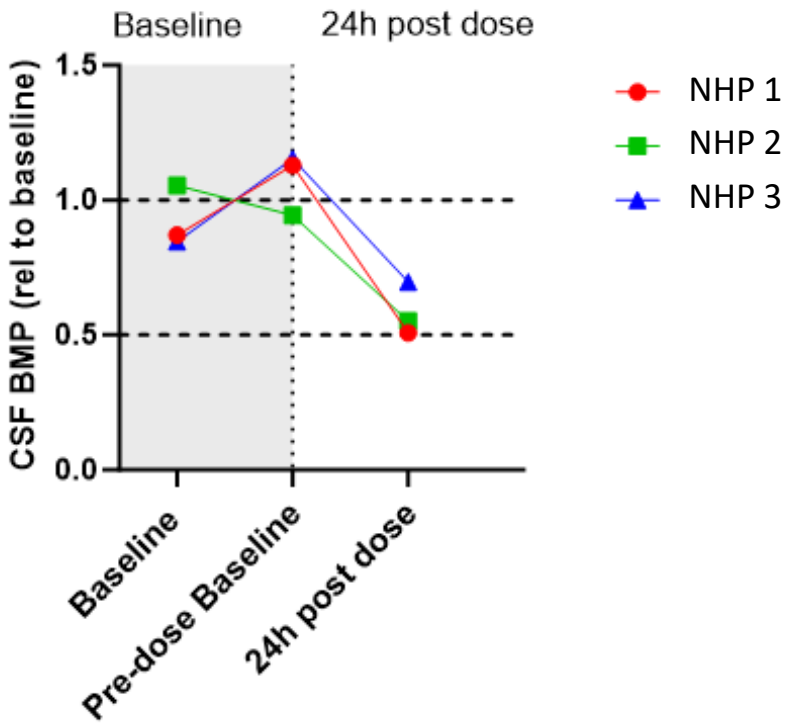


*** p < 0.001
**** p < 0.0001

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

Oral ARV-102-induced reductions in CSF BMP lysosomal marker in ported NHP

Baseline normalized BMP in CSF



BMP,- bis monoacylglycero phosphate; lysosomal phospholipid

Putative LRRK2-Dependent Protein Pathway Biomarker Discovery Utilizing PPMI and LRRK2 PROTAC Degrader Treated NHP Cerebral Spinal Fluid

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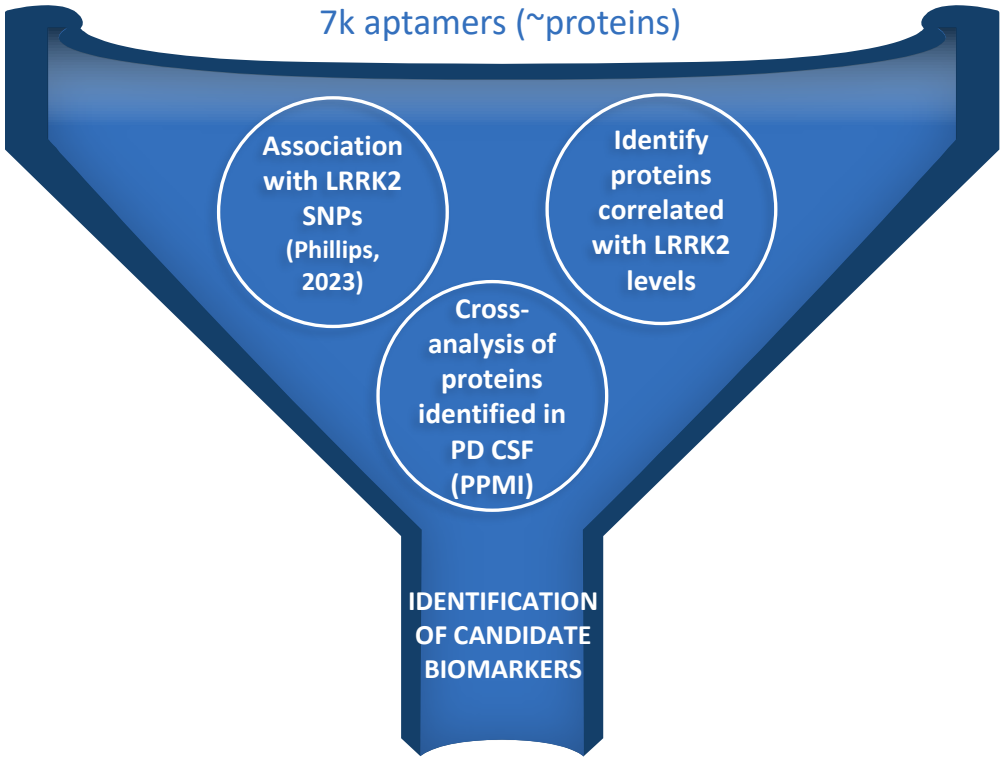
Global analysis of SomaScan data from ported NHP CSF study



Identified proteins enriched in pathways related to **neuroinflammatory response and lysosomal function**

Group comparisons to PPMI baseline human CSF SomaScan data

Parkinson's Progression Markers Initiative

Cohort	N
Healthy Controls	**183**
Idiopathic PD	393
PD+ / LRRK2+	**149**
PD- / LRRK2+	**178**

SomaScan-Identified LRRK2 Protein Pathway Biomarkers that Concord with LRRK2 Protein Levels in NHP CSF

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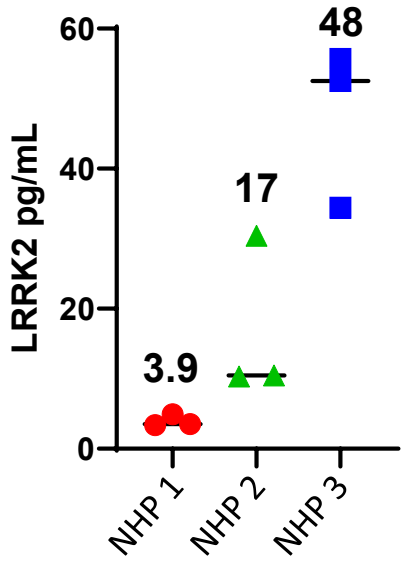
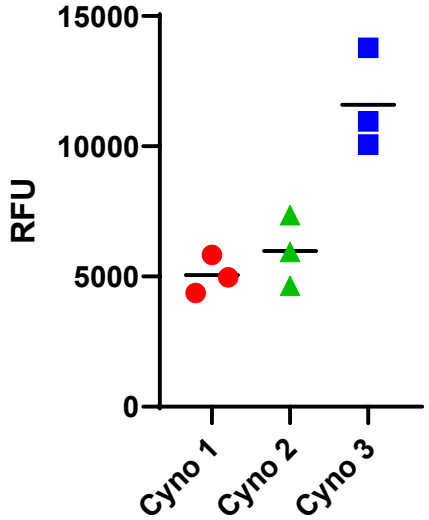
Baseline NHP CSF LRRK2 levels



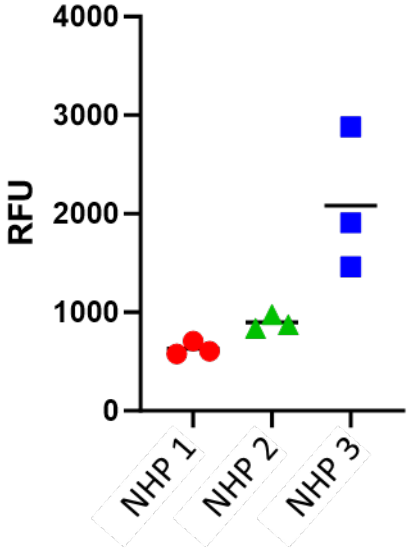
CSF protein analysis of PD-PPMI SomaScan Markers that are increased and associated with LRRK2 pathway/ genetics

Baseline IBA1



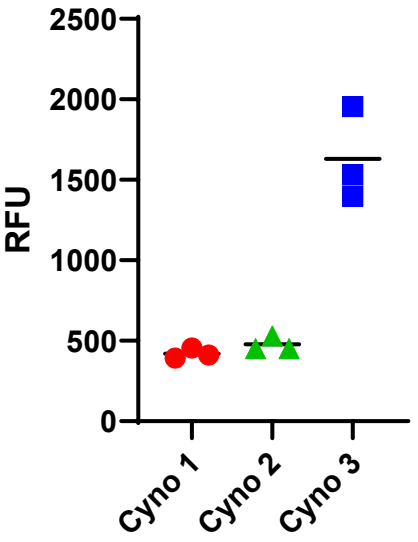
Marker of pathologic neuroinflammation; Reduction of IBA1 associated with neuronal rescue

Baseline Cathepsin B



Lysosomal hydrolase, implicated in PD and involved in the clearance of synuclein

Baseline GPNMB



Lysosomal marker increased in glia in neuroinflammation; CSF proteins significantly associated with the PD risk SNP '798[a]

* Human CSF LRRK2 levels in HVs range from 5 – 104 pg/mL, with an average of 32 pg/mL. Average in LRRK2+PD+ is 68 pg/mL .

IBA1 is a microglia marker, also known as "Allograft Inflammatory Factor 1" (AIF-1); GPNMB or transmembrane glycoprotein NMB (GPNMB) was identified as a "Damage-Associated Microglia" (DAM) neurodegeneration protein

a. B Phillips, 2023; *Mabrouk, 2020

CSF LRRK2 Pathway Biomarkers Exhibited Unprecedented Reductions in NHPs Following a Single Oral Dose of ARV-102 LRRK2 PROTAC Degrader

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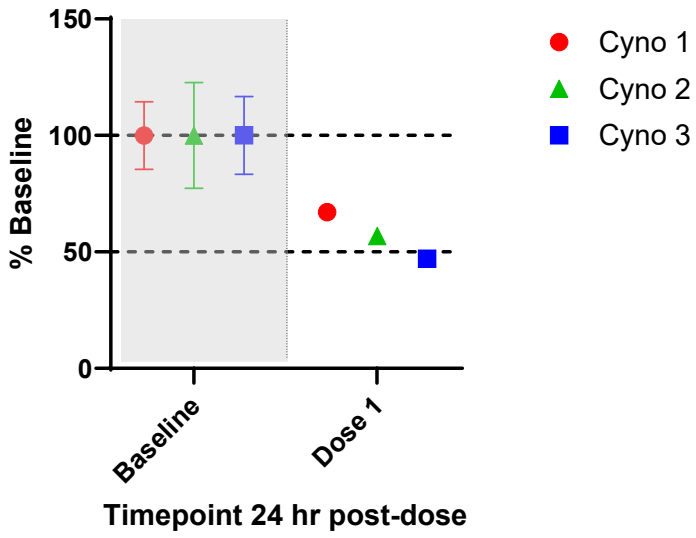
PD-PPMI SomaScan markers that are associated with LRRK2 pathway/genetics are reduced in NHP CSF following a single oral dose of ARV-102

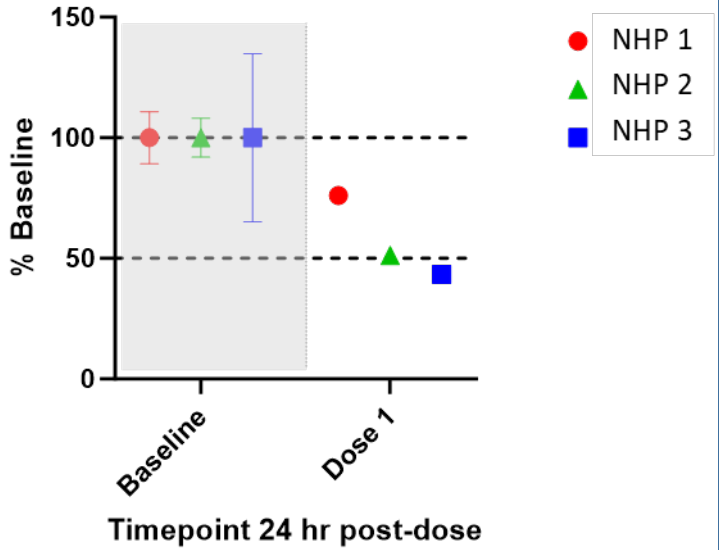
Marker of pathologic neuroinflammation

IBA1 is reduced in response to ARV-102



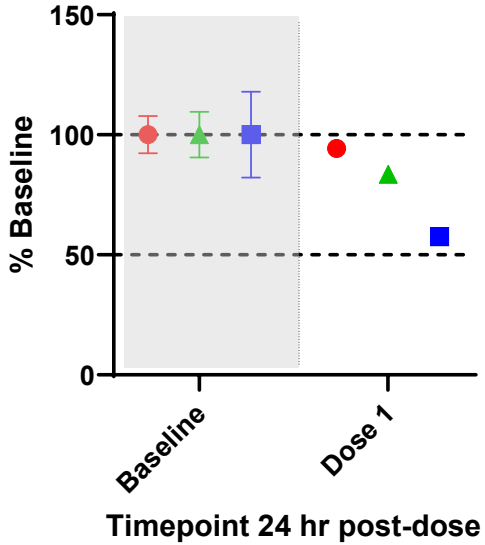
Lysosomal hydrolase implicated in PD

Cathepsin B reduction in CSF by ARV-102



Lysosomal marker increased in glia in neuroinflammation

GPNMB is reduced by ARV-102



Opportunity to further explore LRRK2-dependent biomarkers in PD

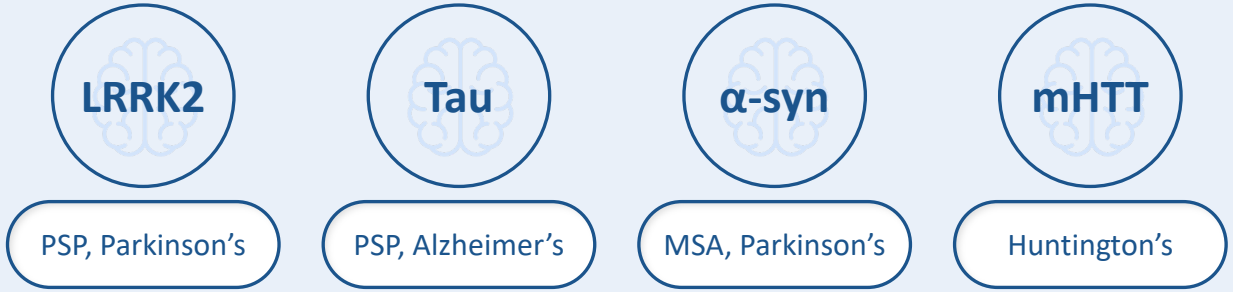
PROTAC Protein Degraders have the Potential for a New Transformational Therapeutic Approach to Neurodegenerative Diseases

Preclinically, oral ARV-102 PROTAC LRRK2 degrader:

- Achieves potent, selective, and durable target engagement in the brain following oral dosing
- Shows better target engagement, enhanced potency, and pathway engagement compared to kinase inhibitors
- Induces less severe type 2 pneumocyte enlargement without accumulation of surfactant protein C, compared to MLi2. No collagen deposition to date. (data not shown)
- Oral ARV-102, crosses the BBB and impacts clinically relevant LRRK2-dependent biomarkers in the CNS of NHPs.

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



Investigational PROTAC protein degrader ARV-102 is the first PROTAC LRRK2 degrader to demonstrate potential in addressing neurodegenerative diseases. Our pre-clinical research findings support future evaluation of ARV-102 in patients with Parkinson's disease or PSP.

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

Singularly focused on developing a new class of medicines that transform patient lives and challenging the perceived limits of drug discovery.

ARVINAS