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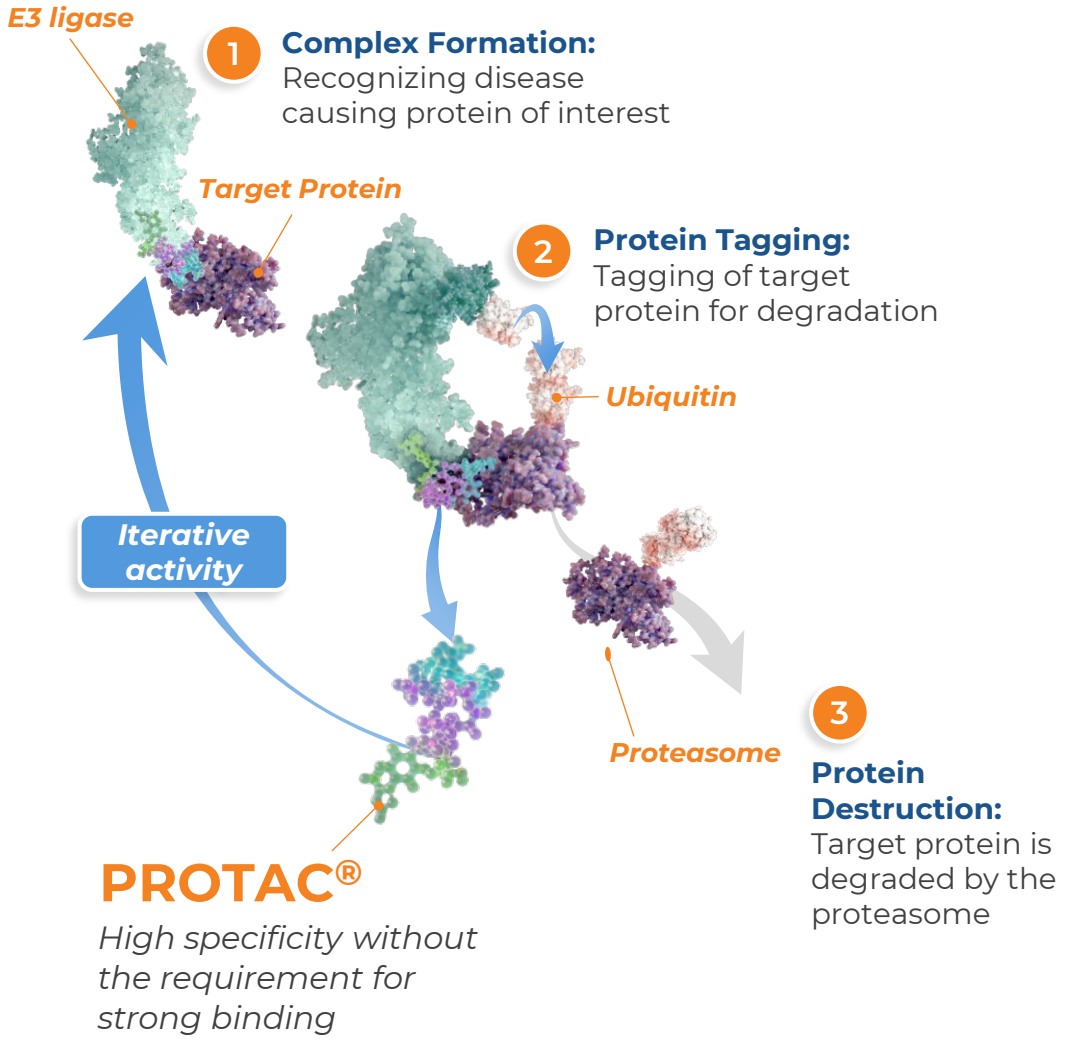
DEVELOPMENT OF POTENT, ORALLY BIOAVAILABLE PROTAC® LRRK2 DEGRADER MOLECULES AS POTENTIAL DISEASE MODIFYING THERAPEUTICS FOR PARKINSON'S DISEASE

Jere Meredith Jr., Kaela Kelly, Val Guss, Adrianna DeSantis, Lida Kimmel, Sierra Soletsky, Dianne Bryce, Rashaun Wilson, John Corradi, Stefanie Keenan, Greg Cadelina, Jennifer Pizzano, Juan Chavez, Steve Sparks, Angela M. Cacace

March 8, 2024

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



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

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

Arvinas development pipeline includes the first pivotal trials for PROTAC® protein degraders

Program	Therapeutic Area / Indication	Preclinical	Phase 1/1b	Phase 2	Phase 3
Vepdegestrant (ARV-471) Global co-development/ co-commercialization partners with Pfizer	**Oncology:** ER+/HER2- Breast Cancer	★ **VERITAC-2:** vepdegestrant monotherapy 2L+ pivotal trial			
		★ ***Vepdegestrant plus palbociclib and potentially other CDK4/6 inhibitors in 2L[a]***			
		★ **VERITAC-3:** vepdegestrant + palbociclib as 1L combination therapy *(study lead-in)*			
		★ ***Vepdegestrant plus CDK4 inhibitor (PF-07220060) in 1L[a]***			
		VERITAC: vepdegestrant monotherapy dose expansion (2L+)			
		TACTIVE-K: vepdegestrant in combination with CDK4i (PF-7220060)			
		TACTIVE-N: vepdegestrant in neoadjuvant setting (to inform potential adjuvant plan			
		TACTIVE-U: vepdegestrant in combination with ribociclib, abemaciclib and other targeted therapies			
		TACTIVE-E: vepdegestrant + everolimus			
ARV-766	**Oncology:** Prostate Cancer	★ ***ARV-766 monotherapy (mCRPC)***			
		ARV-766 monotherapy dose expansion (2L+)			
		ARV-766 Phase 1/2 combination with abiraterone (pre-NHA setting)			
ARV-393 (BCL6)	**Hematology**	**Phase 1 dose escalation**			
ARV-102 (LRRK2)	**Neuroscience**	**ARV-102 Phase 1 dose escalation**			
Preclinical programs	**Oncology and Neuroscience**	**20+ programs, including KRAS-G12D/V, AR-V7, Myc, HPK1, Tau, α-Synuclein, and mHTT**			

★ *Pivotal Trial* ***Planned***

[a] Pending Health authority feedback on potential pivotal trial
NHA, novel hormonal agent
These agents are currently under investigation; their safety and effectiveness for these investigational uses have not yet been established.

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

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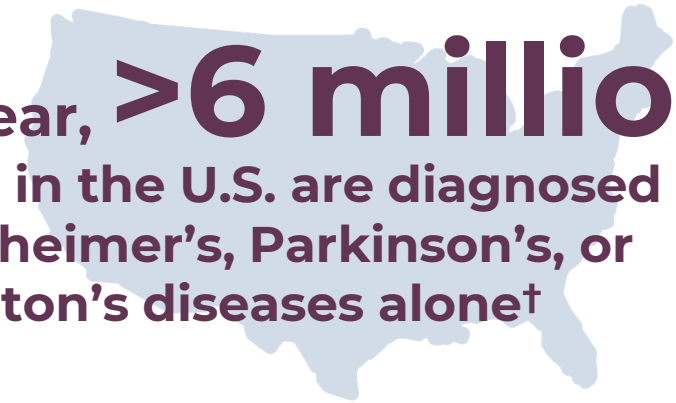


Each year, >6 million patients in the U.S. are diagnosed with Alzheimer's, Parkinson's, or Huntington's diseases alone†

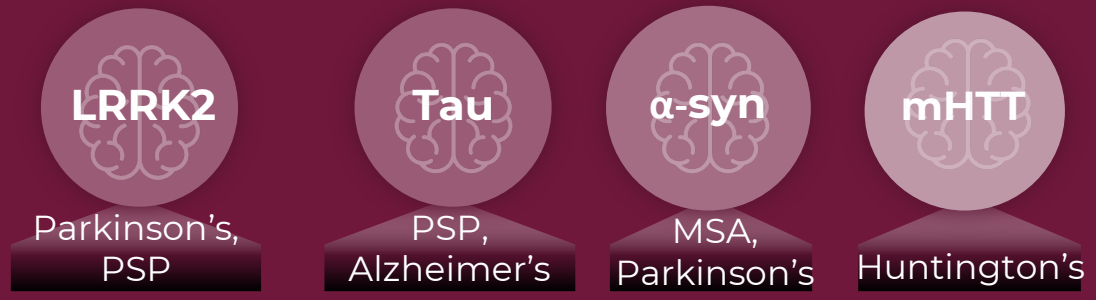
Opportunity for PROTAC® protein degraders:

- **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

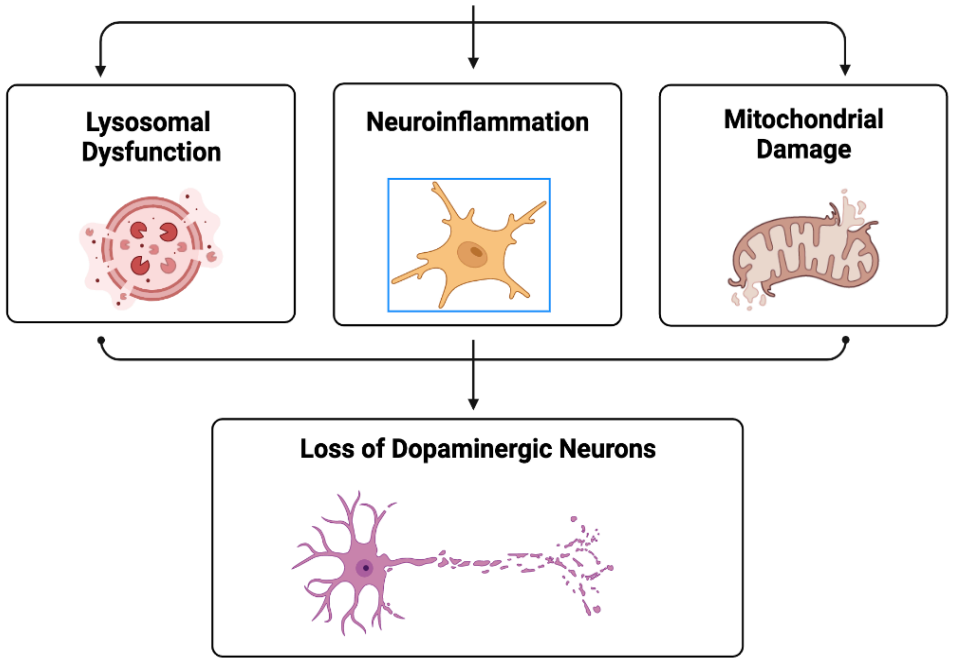
- **LRRK2 is a large multidomain scaffolding kinase**

- **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

Mutations in and increased expression of LRRK2

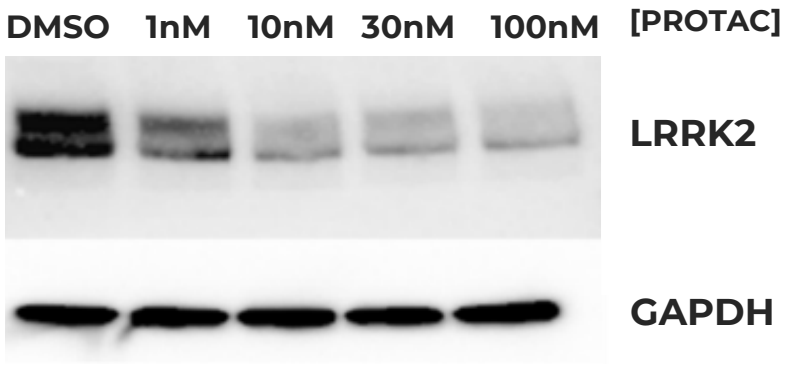


LRRK2, Leucine-rich repeat kinase 2; ASO, antisense oligonucleotide

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

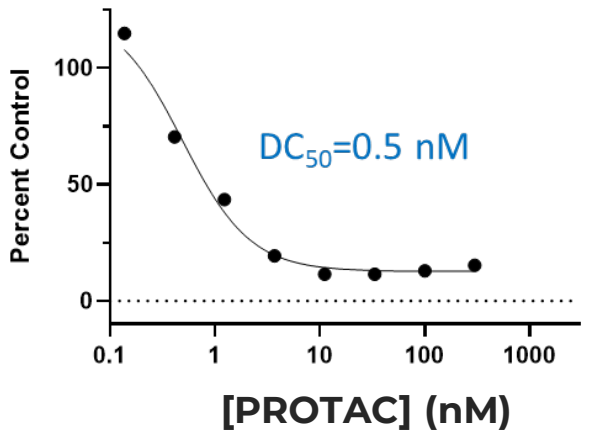
PROTAC® induces degradation of LRRK2 in human iPSC-derived microglia, in human PBMCs, and impacts lysosomal pathway

PROTAC -induced LRRK2 degradation in human iPSC-microglia is concentration dependent

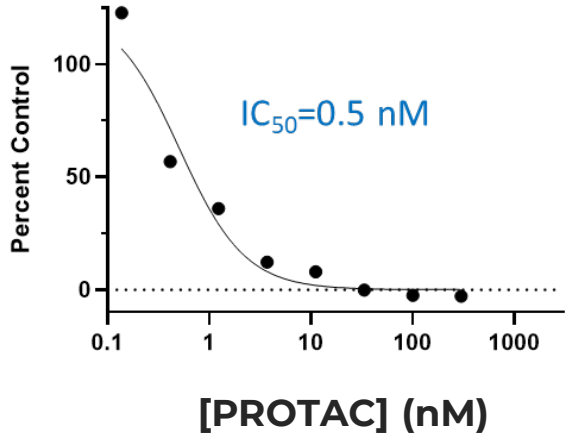


PROTAC-induced LRRK2 degradation aligns with effects on target & pathway engagement in human PBMCs

Target Engagement (Total LRRK2)



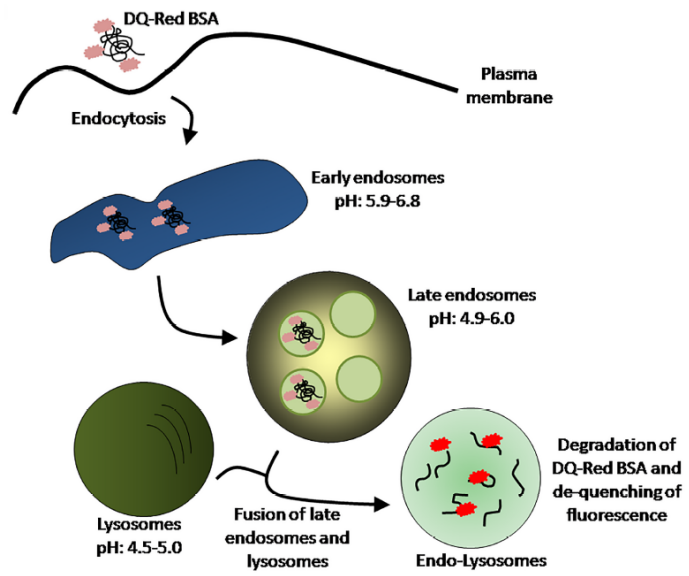
Lysosomal Pathway Engagement (Rab10 pT73)



LRRK2, Leucine-rich repeat kinase 2; iPSC, induced pluripotent stem cells; PBMC, peripheral blood mononuclear cells
Data presented at 2024 Keystone Summit: Targeted Protein Degradation

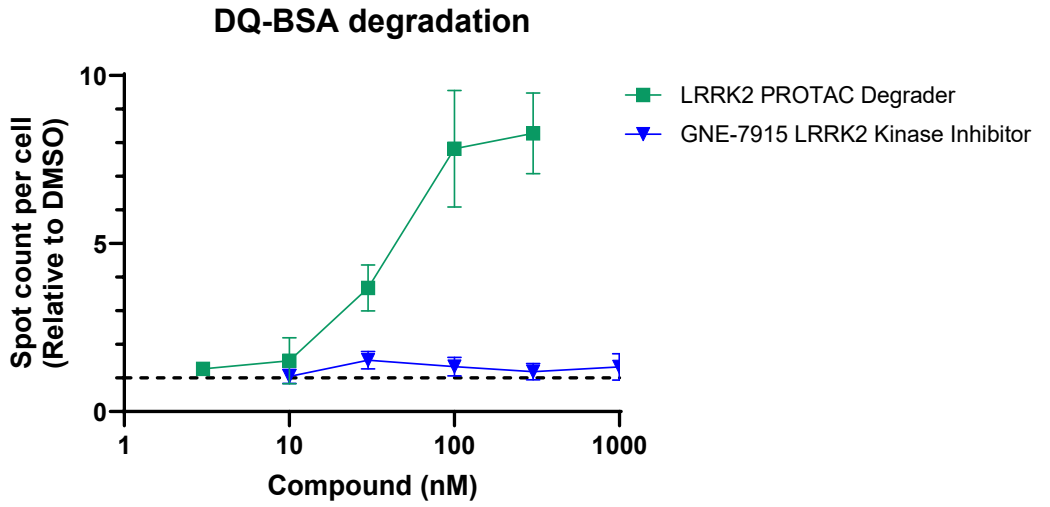
LRRK2 PROTAC® enhances lysosome-based degradation (to improve lysosomal protein clearance in neurodegeneration)

DQ-Red BSA can be used to monitor lysosome-mediated degradation



Marwaha and Sharma, Bio-protocol, 2017

LRRK2 PROTAC enhances lysosome degradation compared to a LRRK2 kinase inhibitor

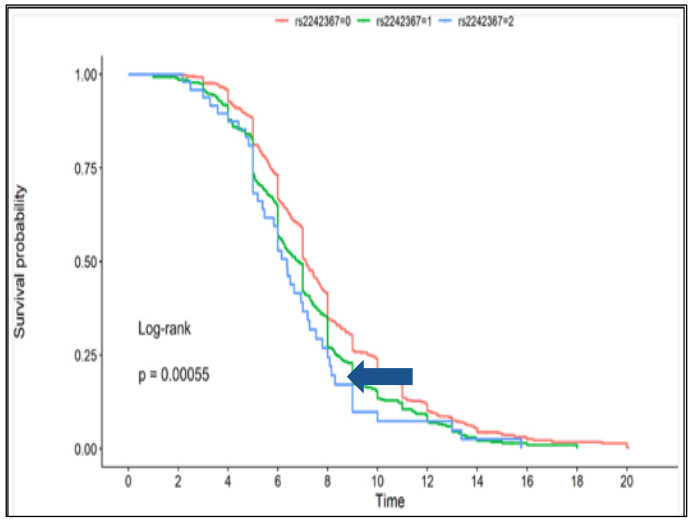


- Comparable pharmacology for target engagement observed for LRRK2 PROTAC and kinase inhibitors (data not shown)
- Ongoing studies in microglia, astrocytes, and neurons (in the context of fPD mutations and pathology)
- LRRK2 PROTAC differentiates from inhibitors by inducing enhanced lysosomal clearance and increasing lysome number (data not shown)

LRRK2, Leucine-rich repeat kinase 2; fPD, familial Parkinson's Disease

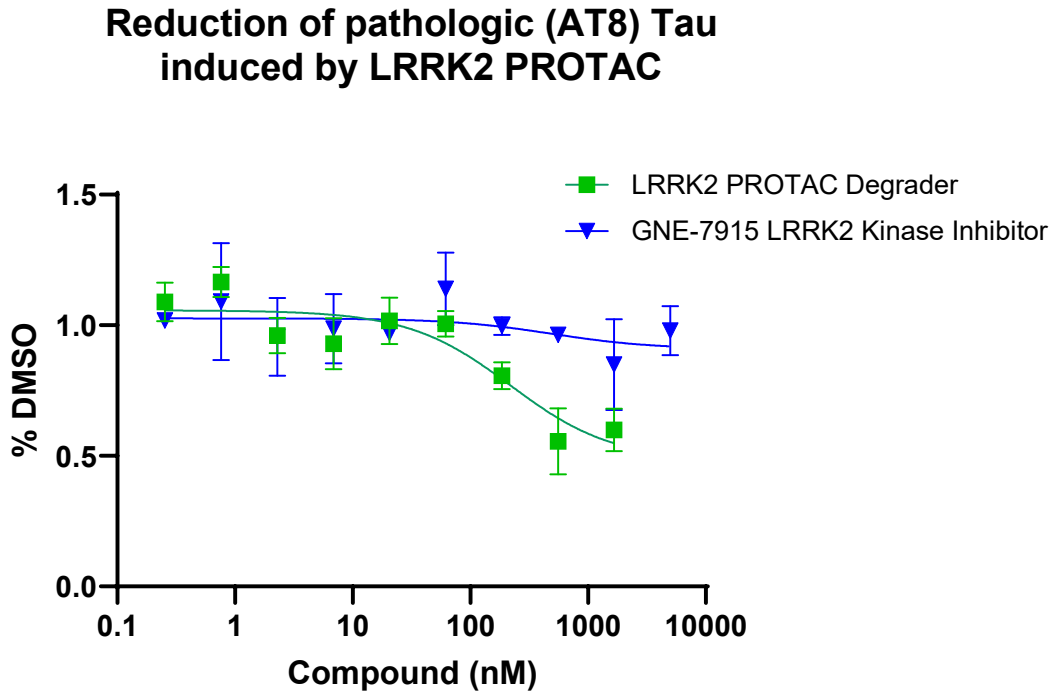
PSP genetics implicate LRRK2 in progression of disease
LRRK2 PROTAC® degraders induce reduction of pathologic tau

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



- Stage 1: 1001 PSP cases, 841 pathology confirmed, ~5 million SNPs for analysis
- Stage 2 confirmation analysis: 415 pathology confirmed PSP; Pooled analysis: 1239 PSP cases

LRRK2 PROTAC induces reduction of AD induced pathologic tau compared to LRRK2 kinase inhibitor



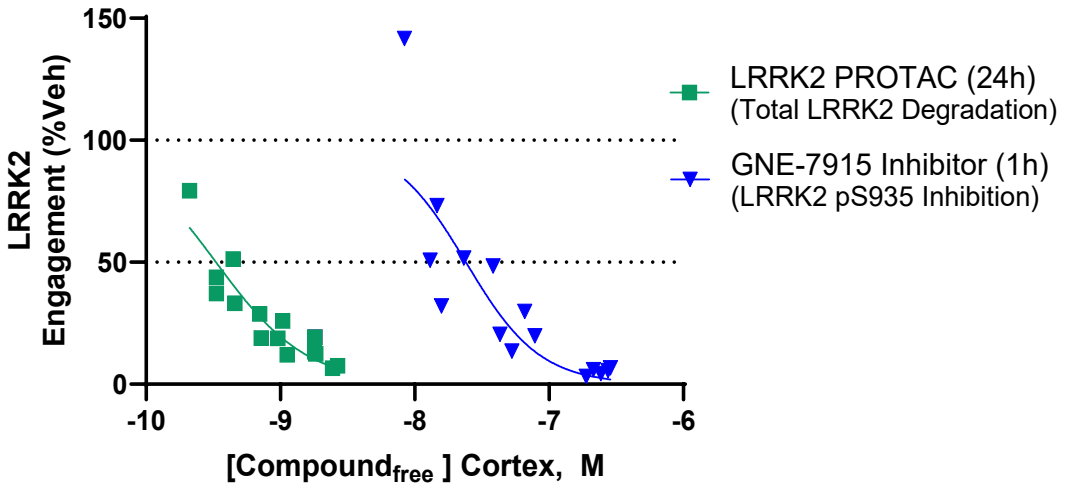
Preliminary data indicate LRRK2 PROTAC induces pathologic tau protein reduction in two tauopathy mouse models (Tg4510 and PS19)

SNP, Single Nucleotide Polymorphism
†Jabbari et al., 2021
Data presented at 2024 Keystone Summit: Targeted Protein Degradation

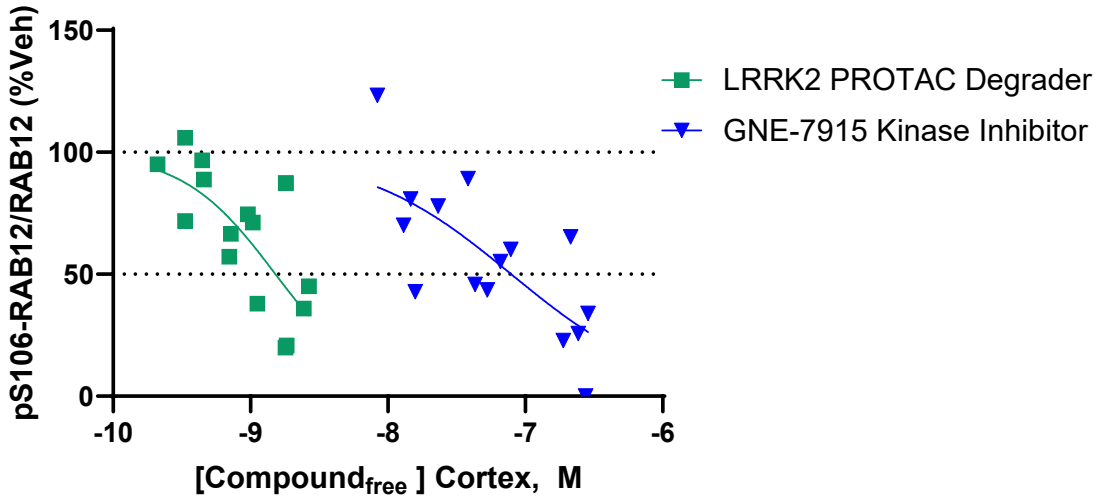
PROTAC® LRRK2 degrader shows better target engagement, enhanced potency and pathway engagement versus a LRRK2 inhibitor

Iterative and catalytic PROTAC advantage results in stronger LRRK2 and lysosomal pathway engagement vs. a LRRK2 kinase inhibitor[a]

LRRK2 PROTAC vs. Kinase inhibitor (Tmax)



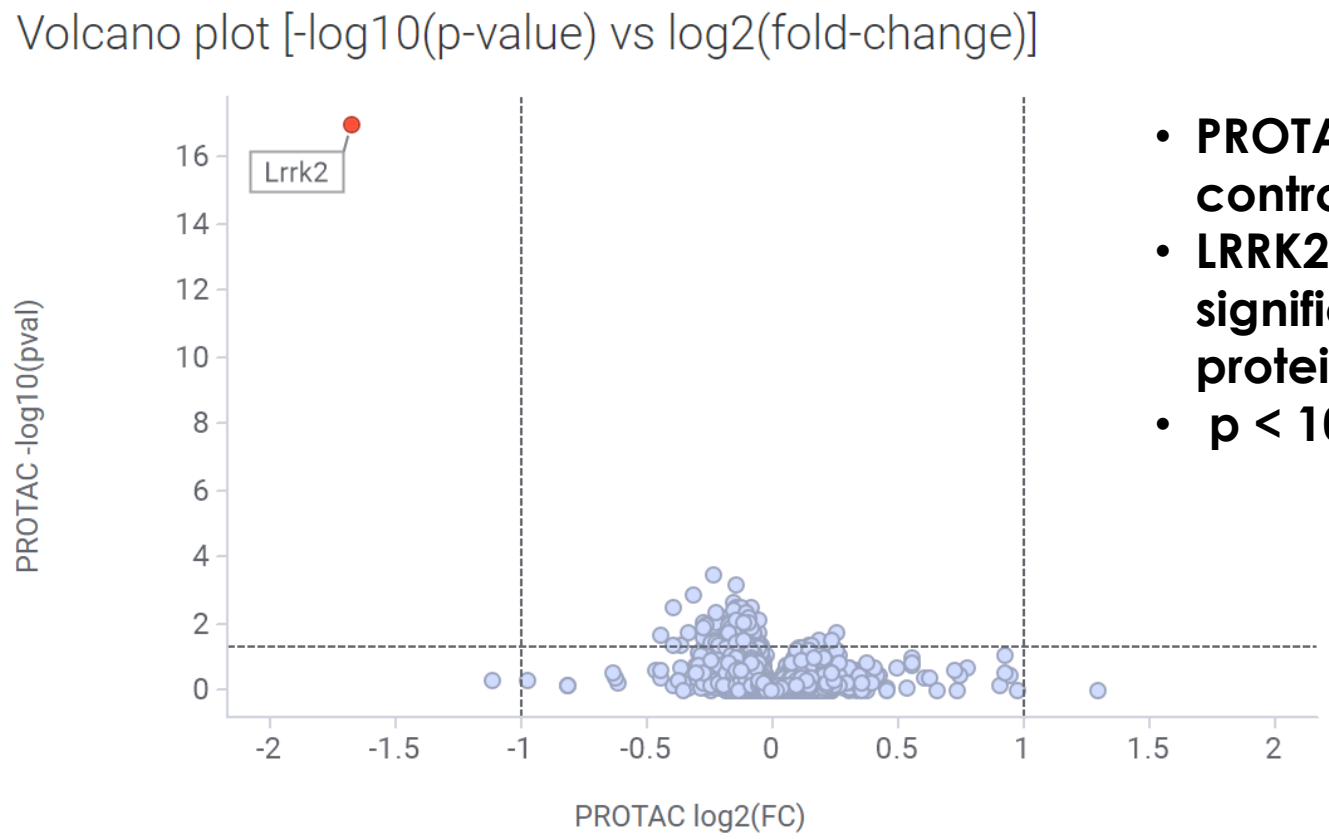
Lysosomal Pathway Engagement (LRRK2 PROTAC vs. Inhibitor)



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

LRRK2 oral PROTAC® degraders are highly selective in brain

Example proteomics data from a lead LRRK2 PROTAC degrader

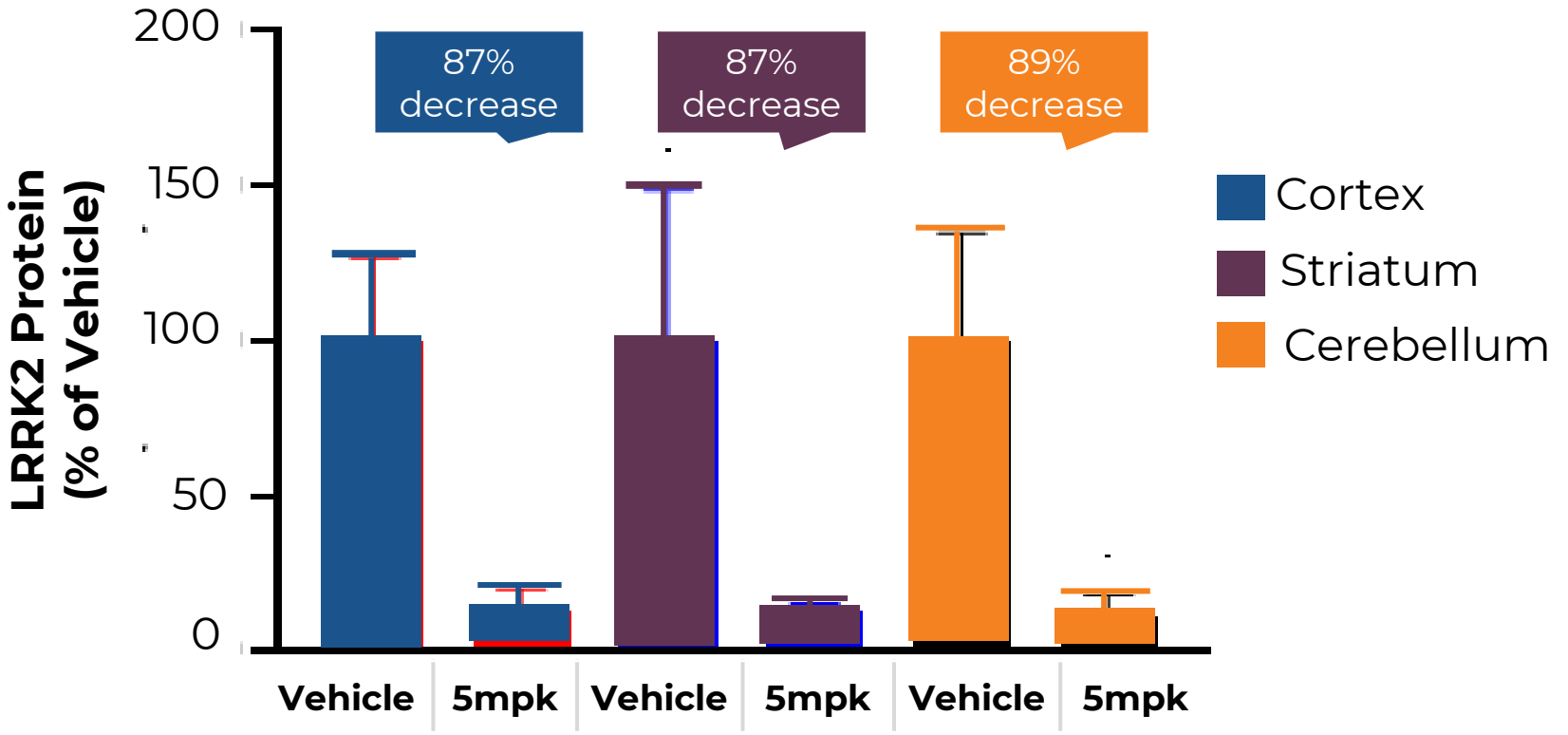


- **PROTAC vs vehicle control**
- **LRRK2 target is most significantly changed protein in cortex**
- **$p < 10^{-16}$**

TMT Proteomic analysis in brain 24 h following oral administration

Arvinas' oral PROTAC® LRRK2 degrader reaches multiple "deep brain" regions in non-human primates and degrades LRRK2

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



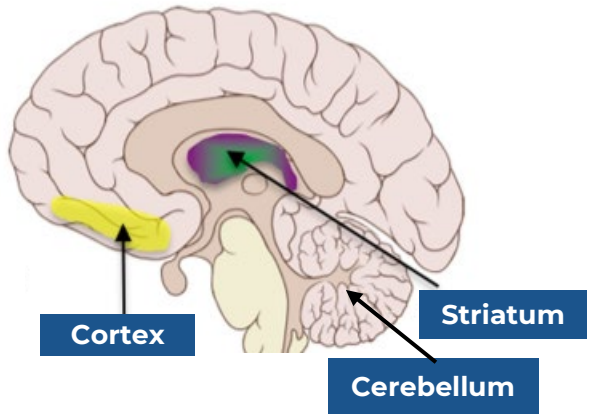


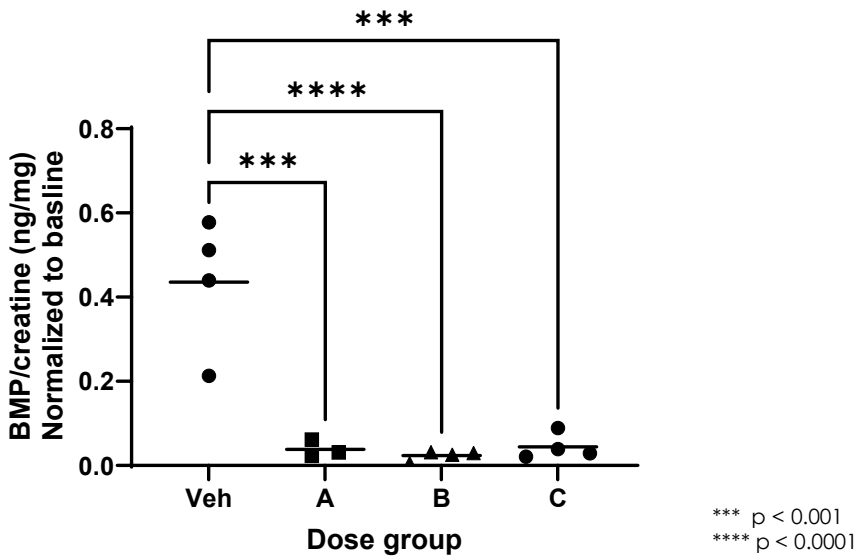
Figure modified from Beuriat et al. 2022

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

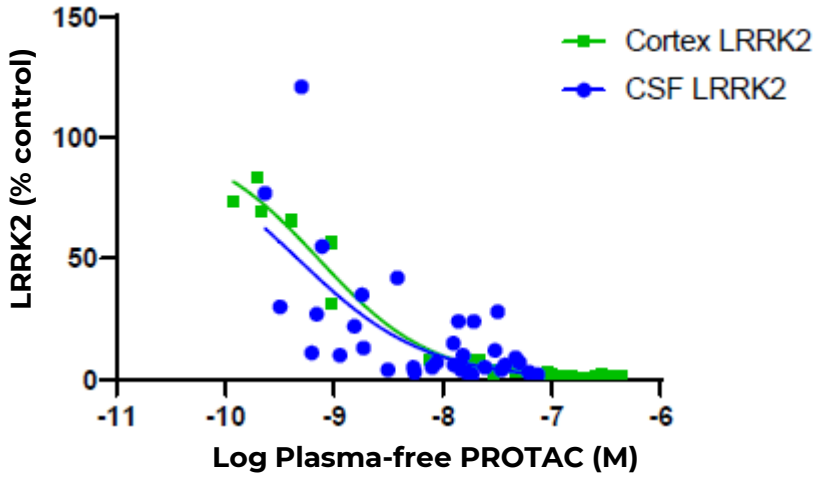


*** p < 0.001
**** p < 0.0001

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

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Preclinically, PROTAC LRRK2 degraders:

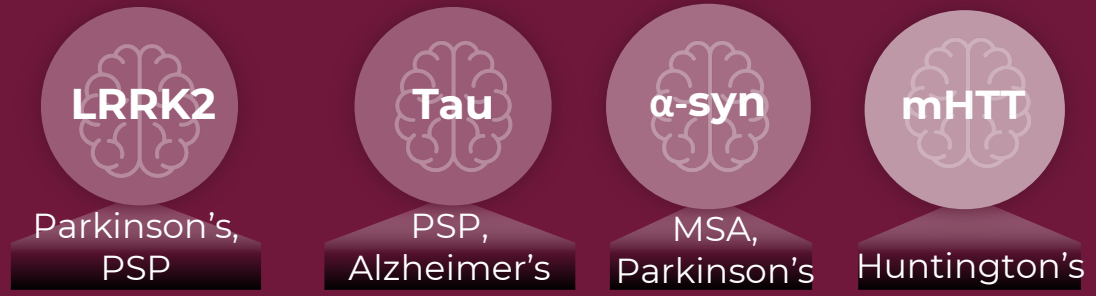
- Increase lysosome number and degradative capacity
- Reduce pathologic tau
- Degrade in deep brain regions following oral dosing
- Impact clinically relevant biomarkers in primates

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

- 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!