ARVINAS

ARV-102: Arvinas' Oral LRRK2 PROTAC® Degrader

Enabling clearance of pathologic proteins that cause neurodegenerative disease

John Houston, Ph.D., Chairperson, Chief Executive Officer, and President
Angela Cacace, Ph.D., Senior Vice President, Neuroscience and Platform Biology

February 14, 2024

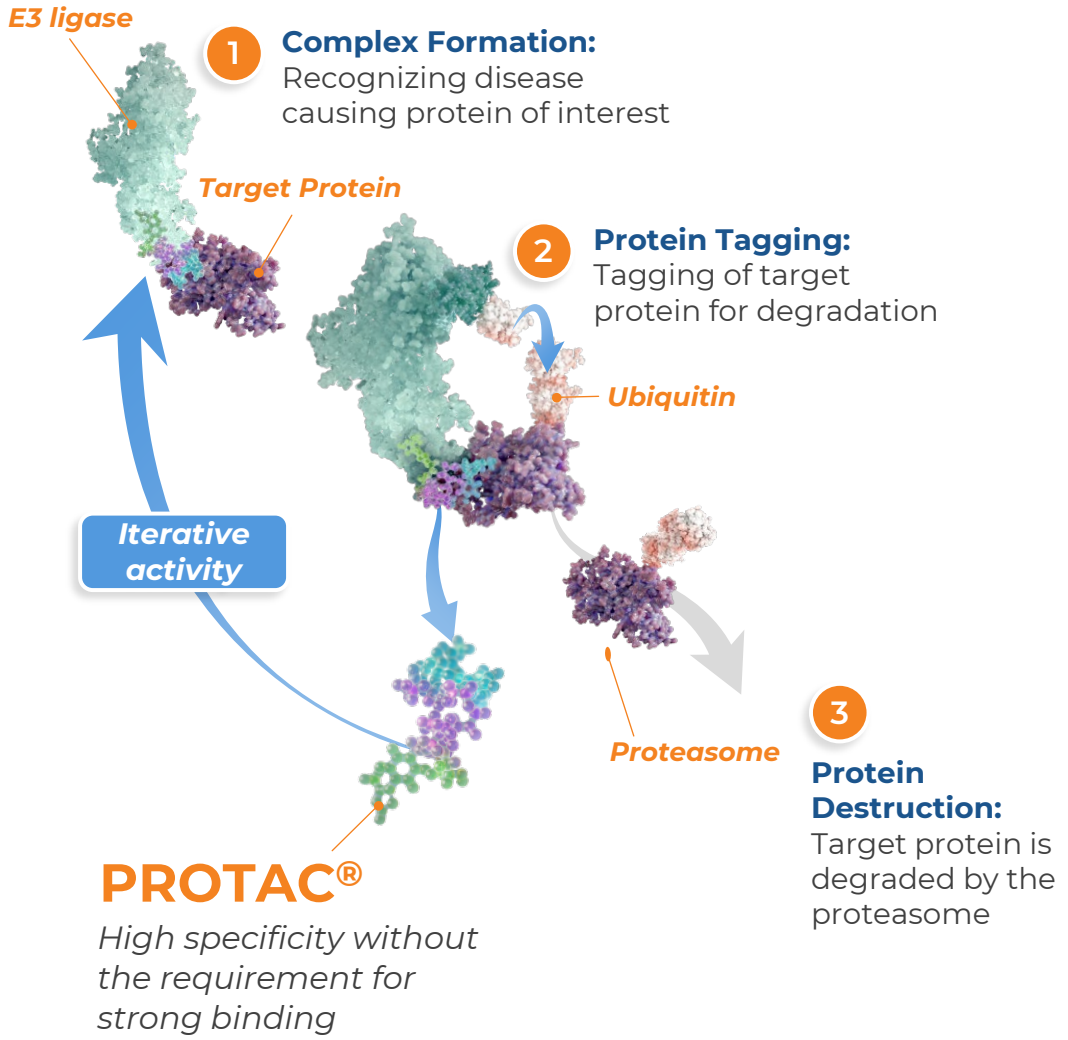
Safe harbor and forward-looking statements

This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995 that involve substantial risks and uncertainties, including statements regarding the potential advantages and therapeutic benefits of ARV-102, including the potential for ARV-102 to change the treatment paradigm in neurodegenerative diseases, the plans and timing of the clinical trials of PROTAC® protein degraders, in Arvinas' pipeline, including clinical trials of vepdegestrant, ARV-766 and ARV-393, the potential benefits of Arvinas' PROTAC® protein degraders,, and the potential of PROTAC®-induced LRRK2 degradation as a treatment for idiopathic Parkinson's Disease and Progressive Supranuclear Palsy. All statements, other than statements of historical facts, contained in this presentation, including statements regarding its strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "might," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Arvinas may not actually achieve the plans, intentions or expectations disclosed in forward-looking statements, and you should not place undue reliance on its forward-looking statements. Actual results or events could differ materially from the plans, intentions, and expectations disclosed in the forward-looking statements Arvinas make as a result of various risks and uncertainties, including but not limited to: Arvinas' and Pfizer, Inc.'s ("Pfizer") performance of its respective obligations with respect to its collaboration with Pfizer; whether Arvinas and Pfizer will be able to successfully conduct and complete clinical development for vepdegestrant; whether Arvinas will be able to successfully conduct and complete development of its other product candidates and receive results from its clinical trials on its expected timelines, or at all; whether Arvinas' cash and cash equivalent resources will be sufficient to fund its foreseeable and unforeseeable operating expenses and capital expenditure requirements; Arvinas' ability to protect its intellectual property portfolio; and other important factors, any of which could cause its actual results to differ from those contained in the forward-looking statements, discussed in the "Risk Factors" section of the Company's Annual Report on Form 10-K for the year ended December 31, 2022 and subsequent other reports on file with the U.S. Securities and Exchange Commission. The forward-looking statements contained in this presentation reflect its current views as of the date of this presentation with respect to future events, and Arvinas assume no obligation to update any forward-looking statements except as required by applicable law.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and other data about its industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue insight to such data and estimates. In addition, projections, assumptions and estimates of its future performance and the future performance of the markets in which Arvinas operate are necessarily subject to a high degree of uncertainty and risk. This presentation is not intended to promote the products referenced herein or otherwise influence healthcare prescribing decisions. Cross-trial comparisons are not based on head-to-head studies and no direct comparisons can be made.

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

Our broad pipeline includes the first pivotal trials for PROTAC® degraders

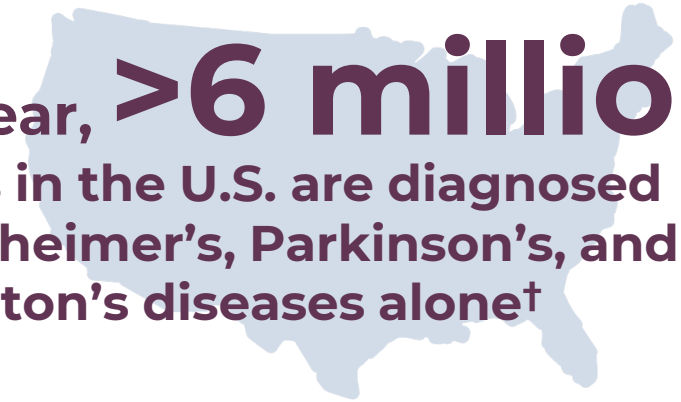
ARVINAS

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**	**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.

Neuroscience: High potential in an area of tremendous unmet need



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

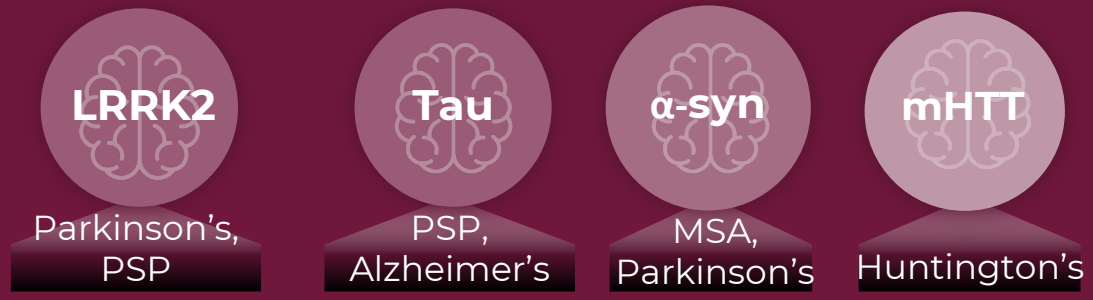
Opportunity for PROTAC® protein degraders:

- **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 LRRK2-targeting PROTAC (ARV-102) anticipated in 1H 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

ARVINAS

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

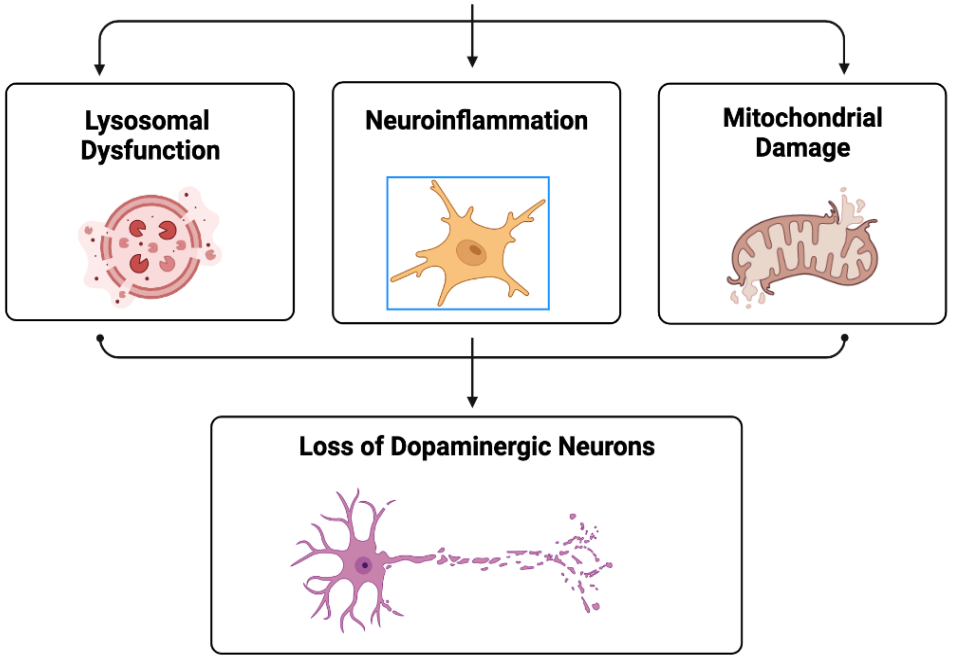
- **LRRK2 is a large multidomain scaffolding kinase**

- **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
  - LRRK2 genetic variants associated with accelerated progression time to death

- LRRK2 kinase inhibitors and an ASO in clinical trials

Mutations in and increased expression of LRRK2

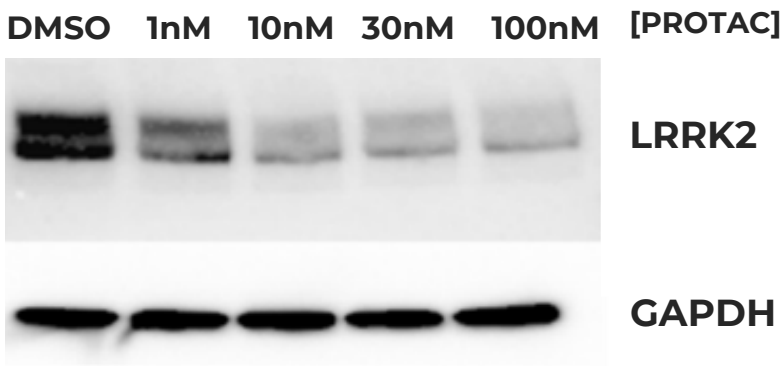


LRRK2, Leucine-rich repeat kinase 2; ASO, antisense oligonucleotide

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

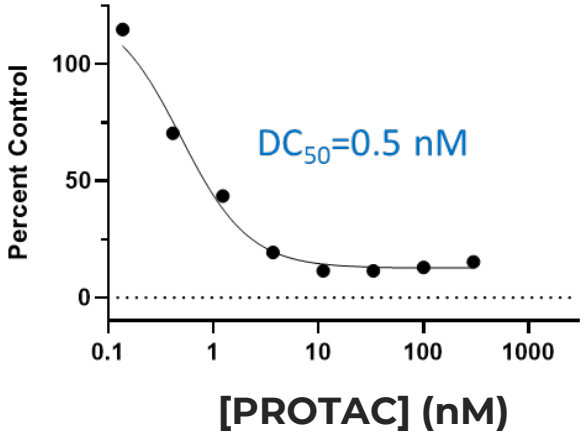
PROTAC® induces degradation of LRRK2 in human iPSC-derived microglia, in human PBMCs, and impacts lysosomal pathway

PROTAC-concentration induced degradation of LRRK2 in human iPSC-microglia

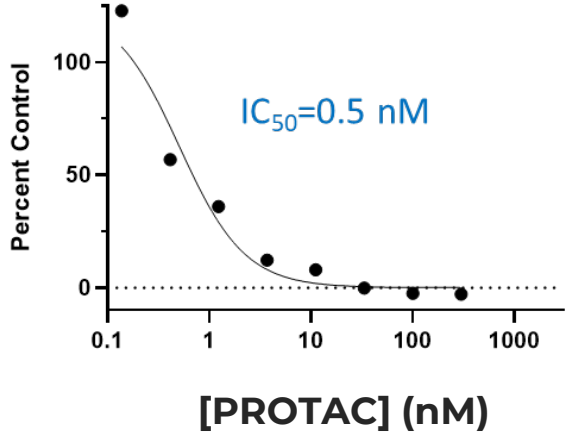


In human PBMCs, PROTAC LRRK2 degradation aligns with effects on target & pathway engagement

Target Engagement (Total LRRK2)



Lysosomal Pathway Engagement (Rab10 pT73)

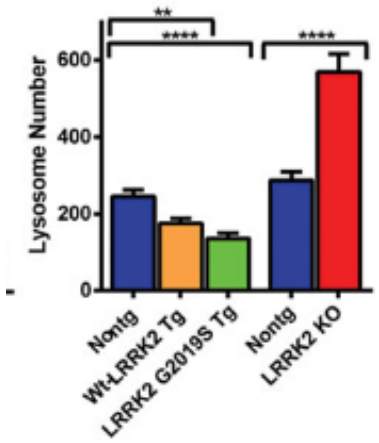


LRRK2, Leucine-rich repeat kinase 2; iPSC, induced pluripotent stem cells; PBMC, peripheral blood mononuclear cells
Data presented at 2024 Keystone Summit: Targeted Protein Degradation

Lysosome number is reduced in PD models and increased by LRRK2 genomic knock out and by PROTAC® degraders

Lysosome number is reduced in PD patients* and models

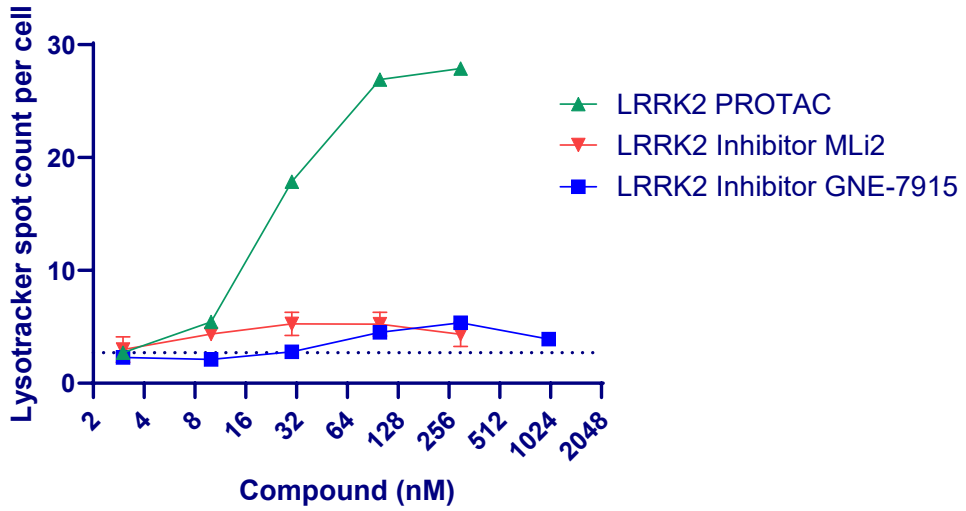
Lysosome number is reduced in PD models, and is increased in LRRK2 KO astrocytes



Henry et al., 2015

LRRK2 PROTAC degrader induces increase in lysosome number per cell compared to LRRK2 Inhibitor(s)

LRRK2 PROTAC degrader increase lysotracker (LT) spot count compared to kinase inhibitors in A549 cells

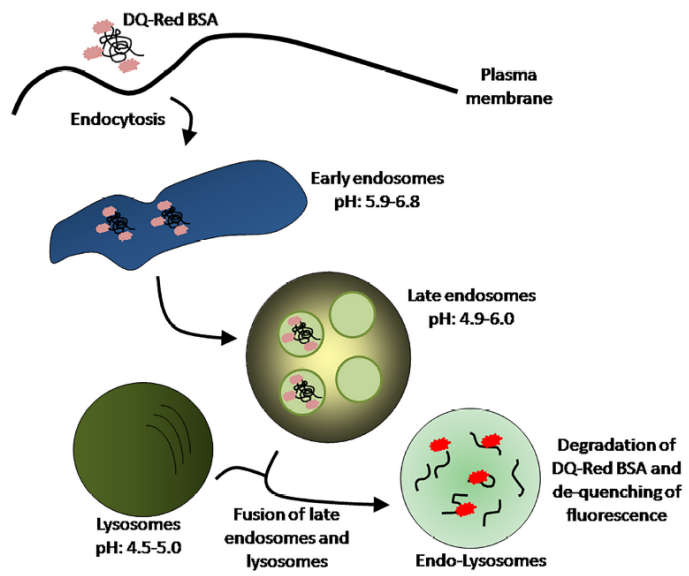


- Mutant familial PD and increased LRRK2 expression puts the brakes on the lysosomal clearance system.
- Autophagy (clearance dependent on lysosome) is reduced with increased LRRK2 expression, LRRK2 familial mutation (G2019S), and LRRK2 activity/levels in rat neurons (R. Wallings et al., 2019)
- LRRK2 PROTAC activity is consistent with literature showing an increase in lysotracker spot count observed in LRRK2 KO astrocytes (Henry et al., 2015)

LRRK2, Leucine-rich repeat kinase 2; PD, Parkinson's disease
*Dehey et al., 2013. Lysosomal impairment in Parkinson's disease
Data presented at 2023 Keystone Summit: Autophagy and Neurodegeneration

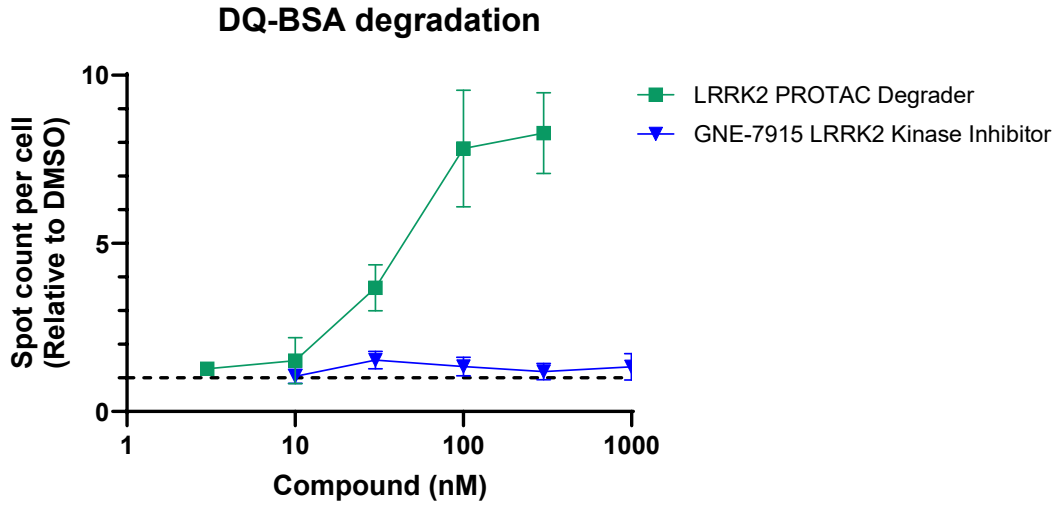
LRRK2 PROTAC® enhances lysosome-based degradation (to improve lysosomal protein clearance in neurodegeneration)

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



Marwaha and Sharma, Bio-protocol, 2017

LRRK2 PROTAC enhances lysosome degradation compared to the inhibitor

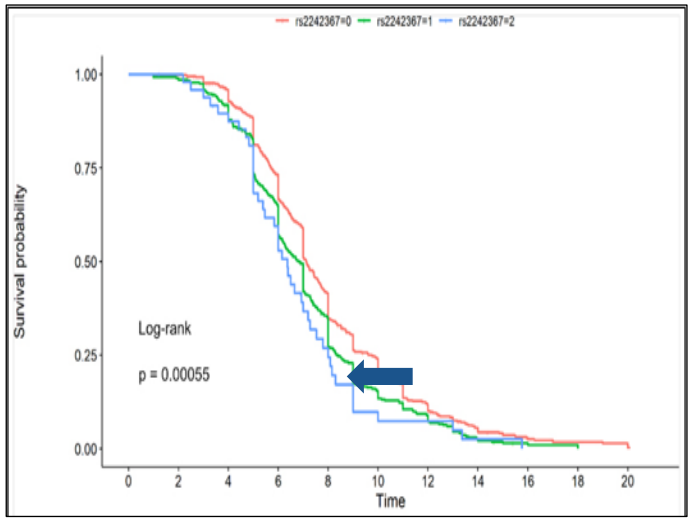


- Comparable pharmacology for target engagement observed for LRRK2 PROTAC and kinase inhibitors (data not shown)
- Ongoing studies in microglia, astrocytes, and neurons (in the context of fPD mutations and pathology)
- LRRK2 PROTAC induces enhanced lysosomal clearance

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

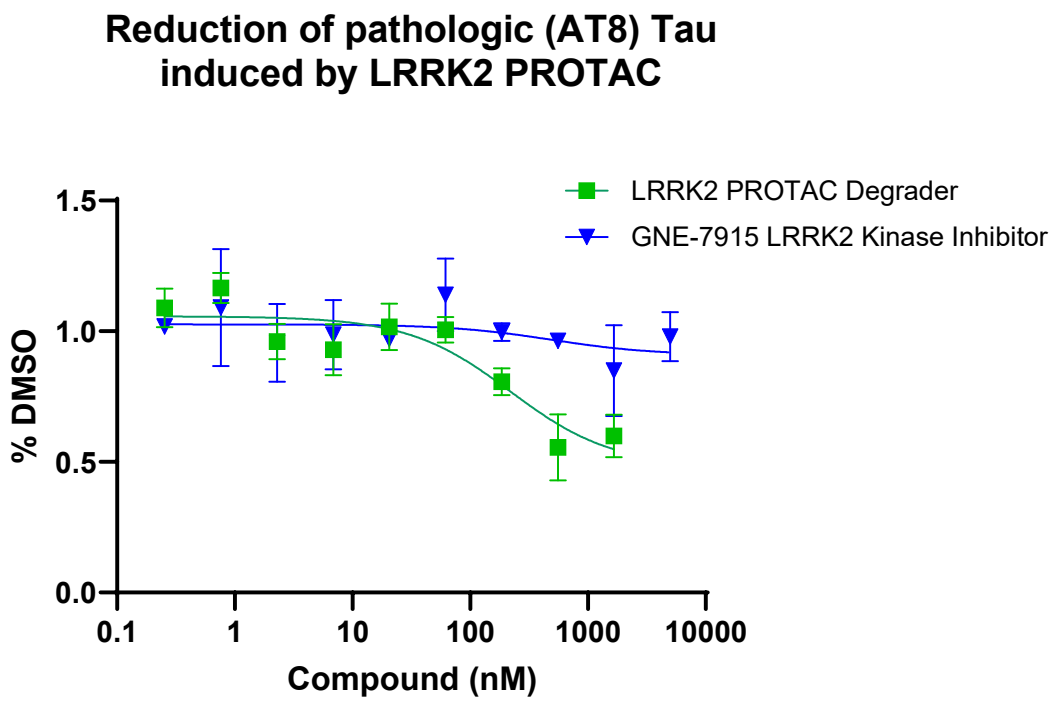
PSP genetics implicate LRRK2 in progression of disease
LRRK2 PROTAC® degraders induce reduction of pathologic tau

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 inhibitor

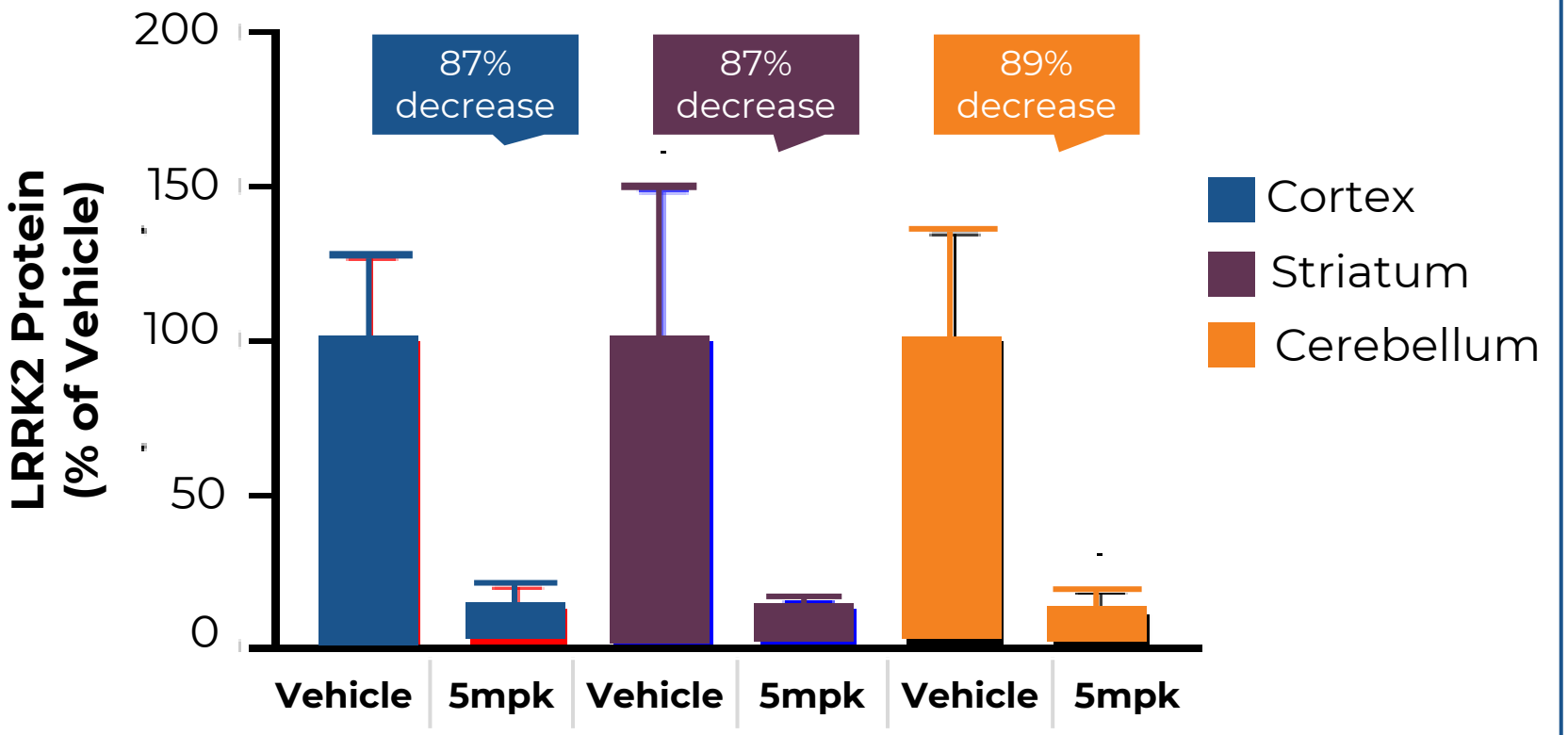


Preliminary data indicate LRRK2 PROTAC induces pathologic tau protein reduction in two tauopathy mouse models (Tg4510 and PS19)

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

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



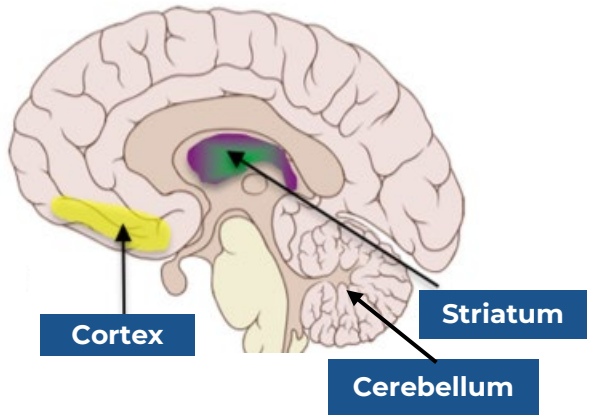


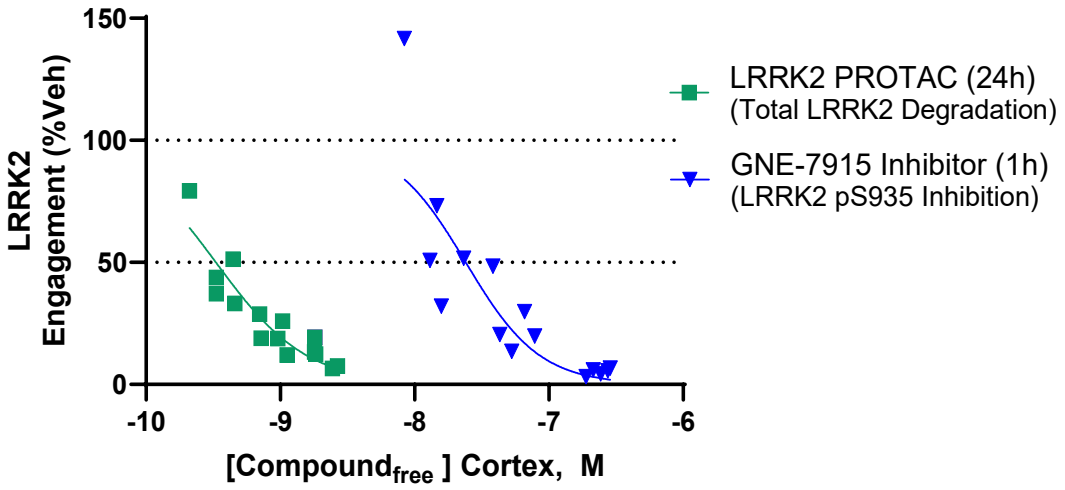
Figure modified from Beuriat et al. 2022

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

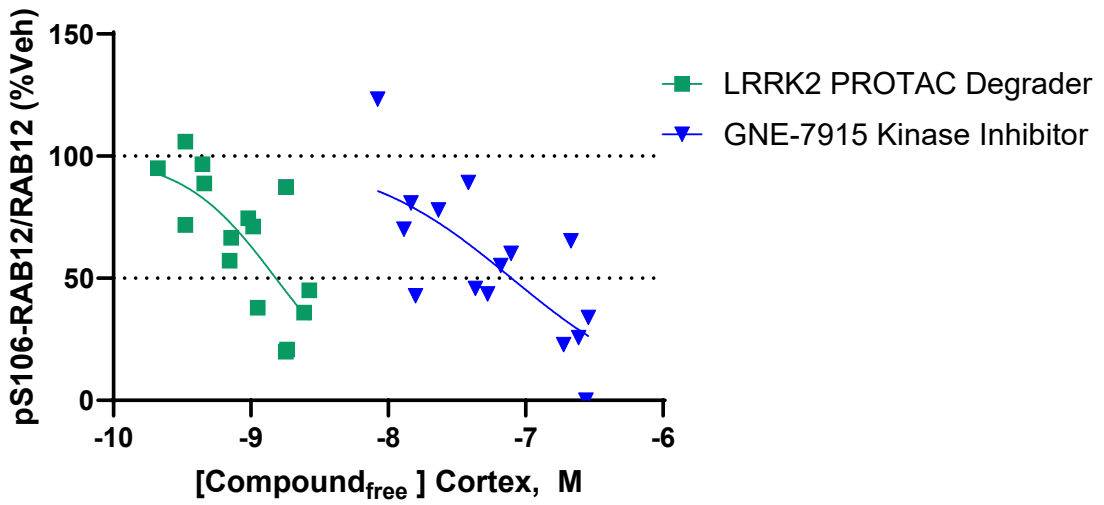
PROTAC® LRRK2 degrader shows better target engagement, enhanced potency and pathway engagement versus a LRRK2 inhibitor

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

LRRK2 PROTAC vs. Kinase inhibitor (Tmax)



Lysosomal Pathway Engagement (LRRK2 PROTAC vs. Inhibitor)

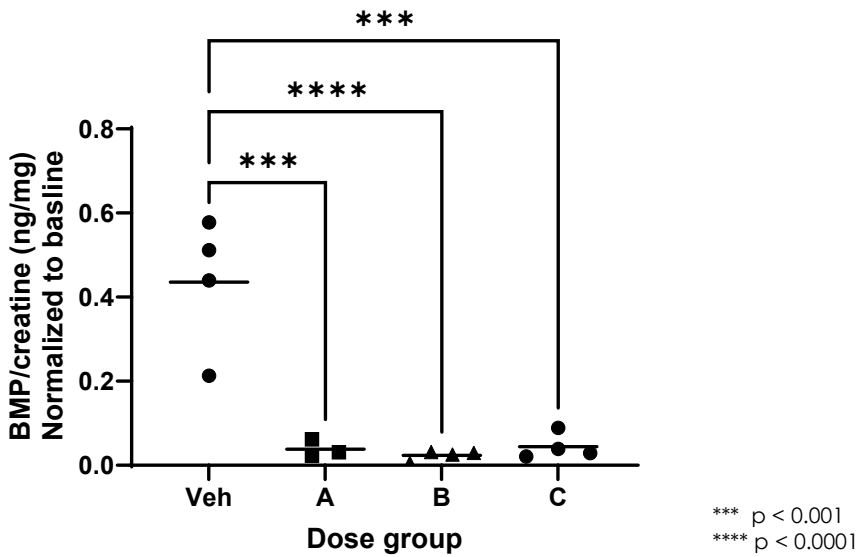


[a] G2019S familial Parkinson's Disease mouse model
LRRK2, Leucine-rich repeat kinase 2
Data presented at 2023 Keystone Summit: Autophagy and Neurodegeneration

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

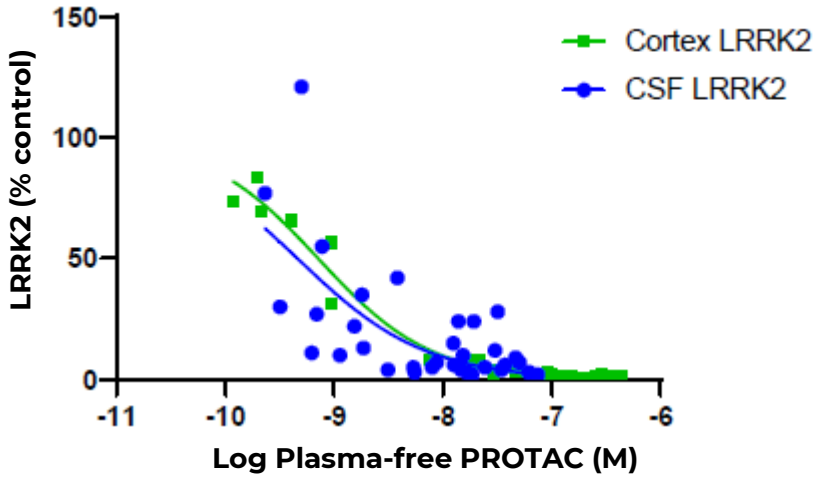


*** p < 0.001
**** p < 0.0001

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

ARVINAS

Preclinically, LRRK2 PROTAC protein degraders:

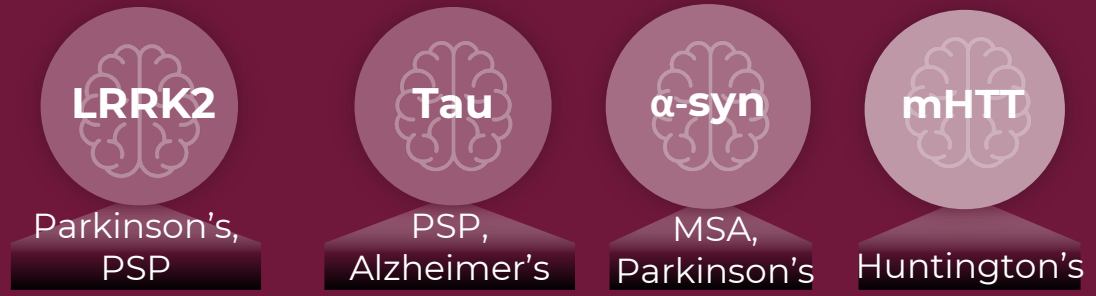
- Increase lysosome number and degradative capacity
- Reduce pathologic tau
- Degrade in deep brain regions following oral dosing
- Impact clinically relevant biomarkers in primates

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



Phase 1 trial with LRRK2-targeting PROTAC (ARV-102) anticipated in 1H 2024

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

Thank you - Team Arvinas!