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Opportunity for Oral PROTAC® Degrader Molecules to Selectively Clear Proteins that Cause Neurodegenerative Diseases

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Keystone- TPD

January 24, 2024

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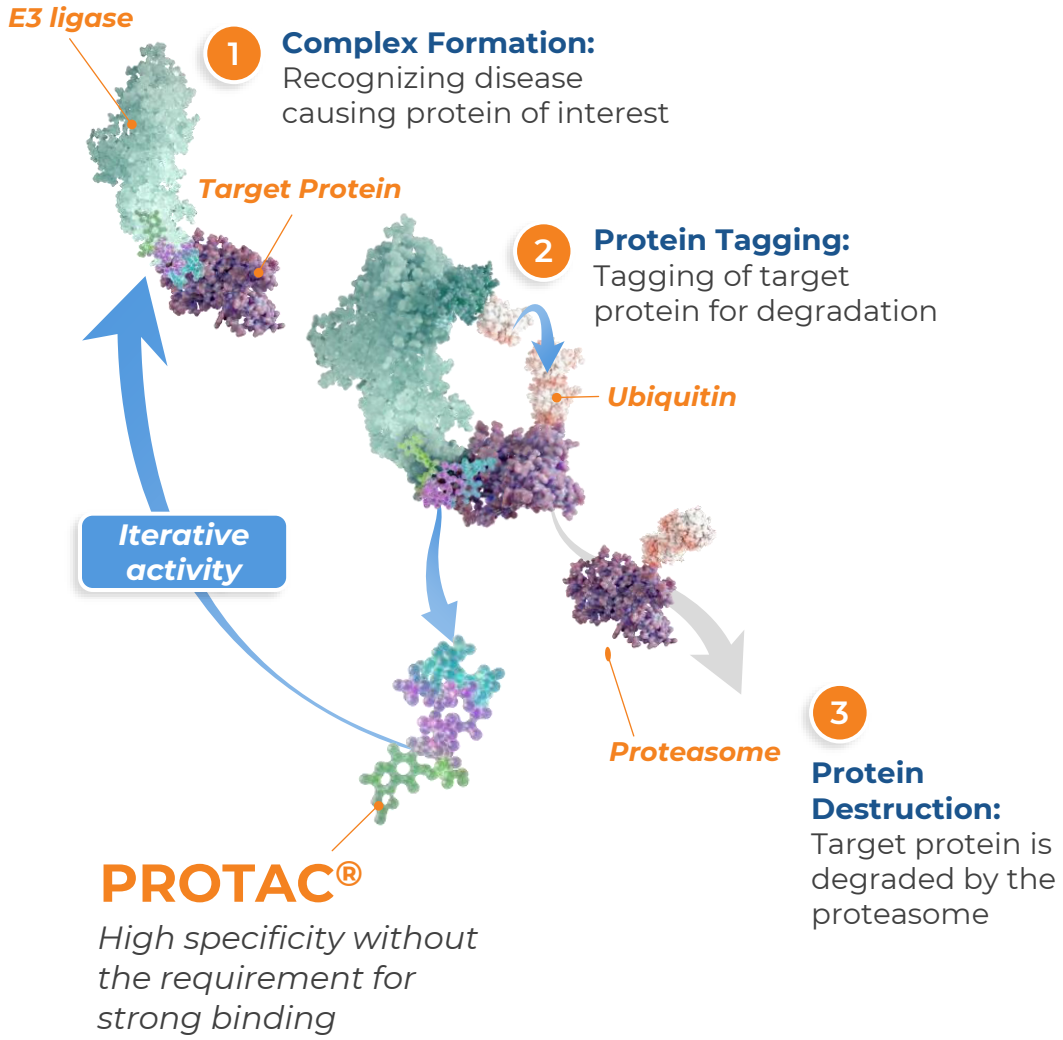
PROTAC® protein degraders combine the benefits of small molecules and gene-based knockdown technologies



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

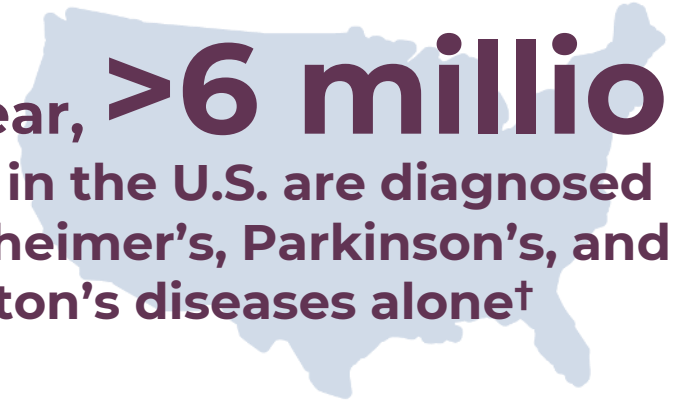
Program	Therapeutic Area / Indication	Preclinical	Phase 1/1b	Phase 2	Phase 3
Vepdegestrant (ARV-471) Global co-development/ co-commercialization partners with Pfizer	**Oncology:** ER+/HER2- Breast Cancer	★ **VERITAC-2:** vepdegestrant monotherapy 2L pivotal trial			
		★ ***Vepdegestrant plus palbociclib 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-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**			

[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.

Planned

★ *Pivotal Trial*

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†

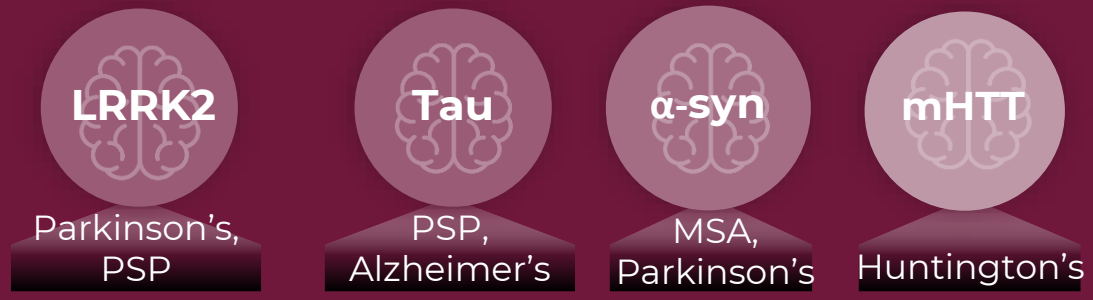
Opportunity for PROTAC® protein degraders:

- **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 could revolutionize the treatment of neuroscience 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

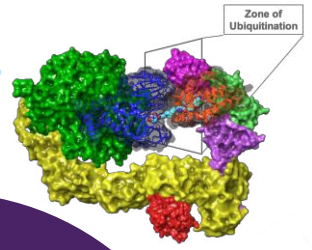
Integrated PROTAC® drug discovery for Neurology

Genetic Disease:
Protein is the cause of the disease

Translational Medicine:
Biomarkers support efficient path to assessing efficacy in humans

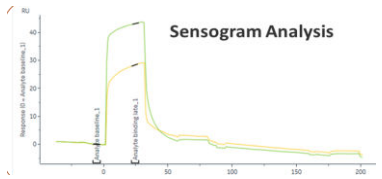
PK/PD Models:
Protein target engagement in vivo

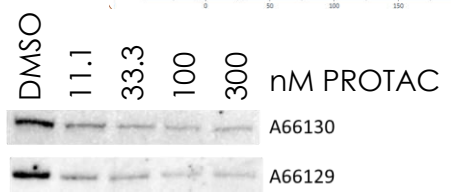
Neurodegeneration
Precision Medicine
Genetic/
Proteinopathy
Target root cause
PROTAC differentiator
Biomarker PoC



Discovery Engine:
Ligand ID-DEL, HTS, HT-chem/SAR
E3KnowlegeBASE, structure, AI

Discovery Engine:
Biophysics, Ternary, Mechanistic
Cellular Degradation, Proteomics

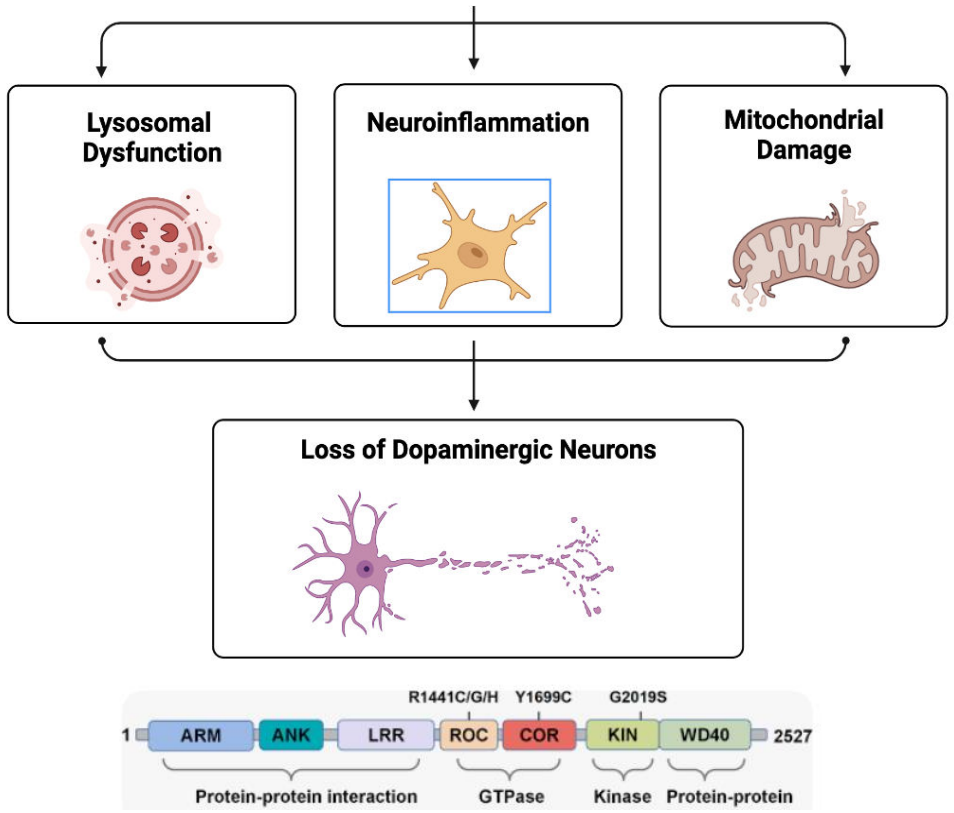




PROTAC®-induced LRRK2 degradation as a potential treatment for idiopathic Parkinson's Disease and Progressive Supranuclear Palsy

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

- Parkinson's Disease (PD) is the second most common neurodegenerative disease. Diagnosed prevalence of 2.5M between US, EU5, and Japan
  - No approved disease-modifying therapies for PD
  - Familial mutations & sporadic variants implicate LRRK2 in PD
  - 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
- Progressive Supranuclear Palsy (PSP) is a pure tauopathy with rapid progression to death within 5-7 years
  - LRRK2 genetic variants associated with progression time to death
  - LRRK2 kinase inhibitors and an ASO in clinical trials



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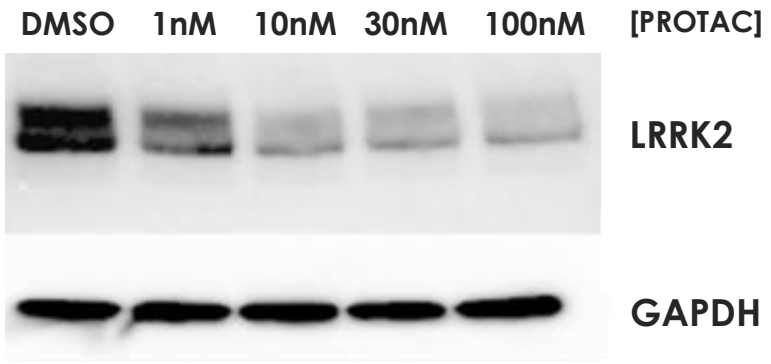
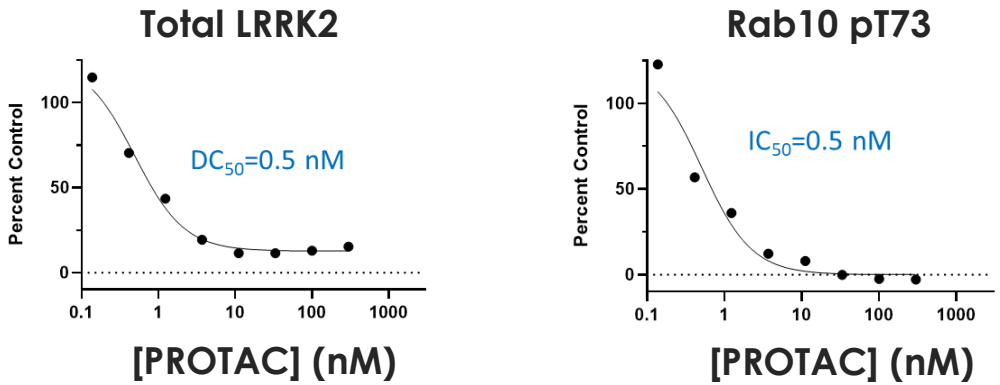
Wang, 2021, Zhao, 2017, Henderson, 2019, Zheng, 2022

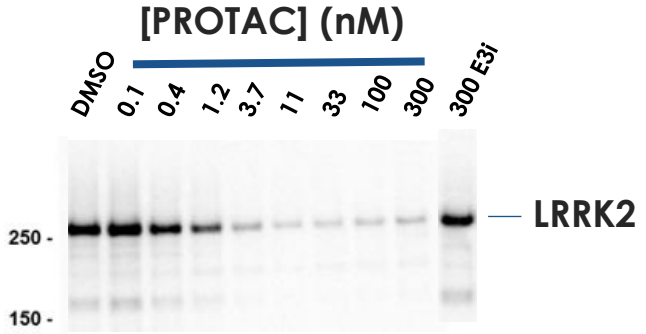
PROTAC induces degradation of LRRK2 in iPSC-derived microglia, in human PBMCs, impacts pRAB pathway, and is on mechanism

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



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



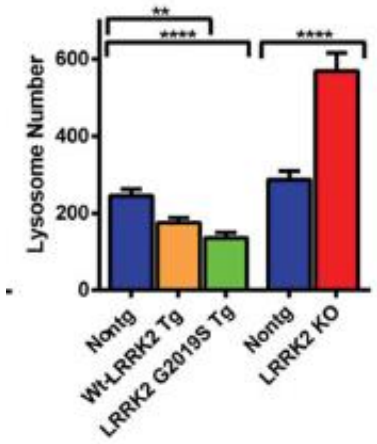


E3 dead PROTAC (E3i) does not induce degradation of LRRK2

Lysosome # is reduced in familial PD (G2019S): LRRK2 KO and PROTAC degrader increases lysotracker spot count per cell

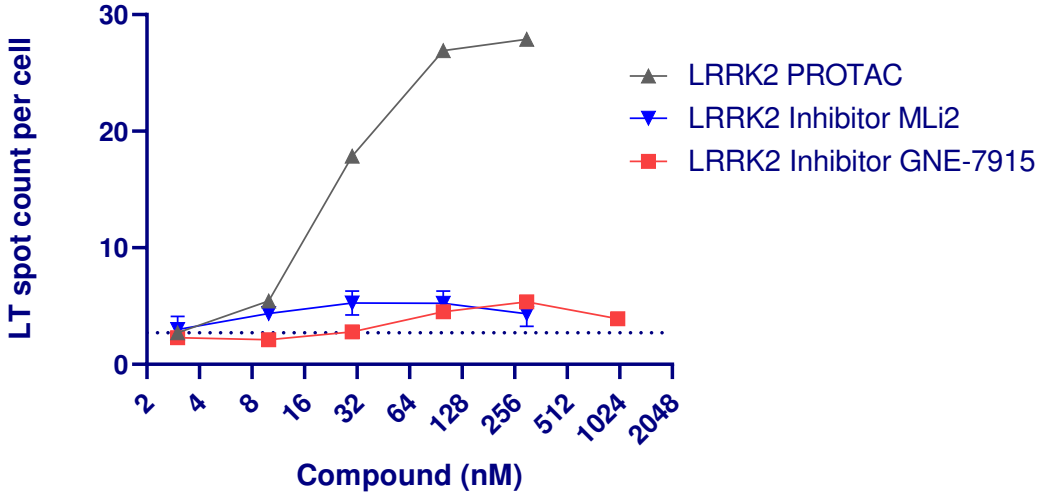
LRRK2 PROTACs induce robust increase in lysotracker (LT) spot count per cell

Lysosome number is reduced in familial PD (G2019S), and is increased in LRRK2 KO astrocytes



Henry et al., 2015

LRRK2 PROTAC(s) increase lysotracker 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)

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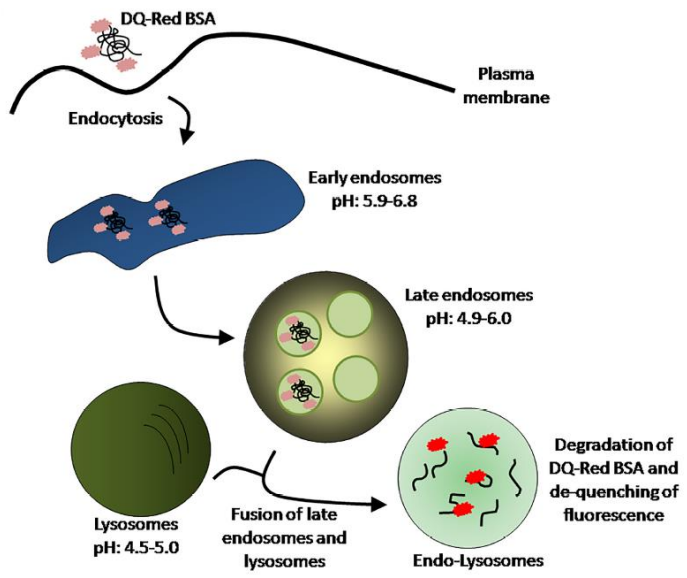
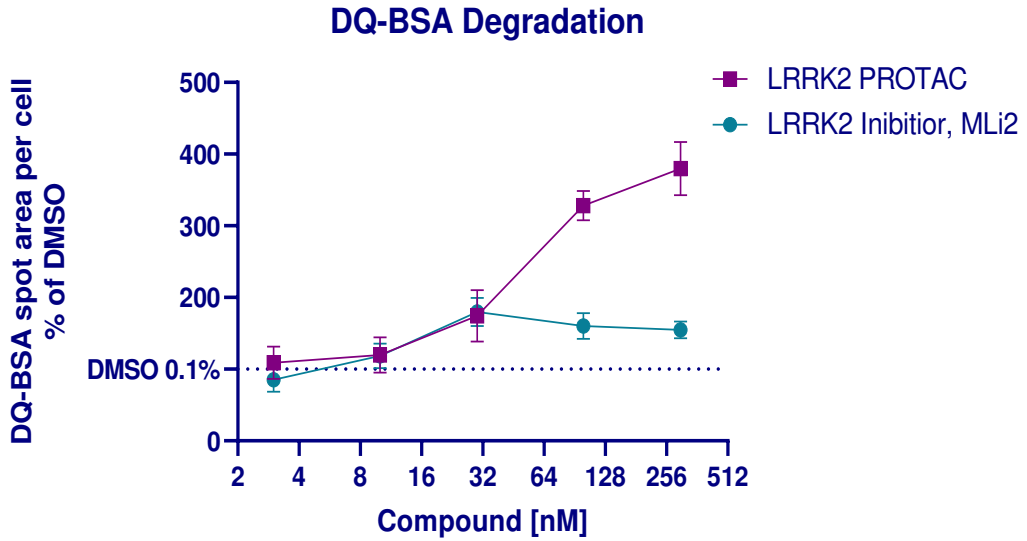
LRRK2 PROTAC degraders enhance lysosome-based degradation

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



LRRK2 PROTAC enhances lysosome degradation



GNE-7915 had no impact
No impact on Transferrin uptake

- Comparable pharmacology for target engagement observed for LRRK2 PROTAC and MLi2 kinase inhibitor (data not shown)
- Ongoing studies in microglia, astrocytes, and neurons (in the context of fPD mutations and pathology)
- Data support LRRK2 PROTAC induces enhanced lysosomal clearance

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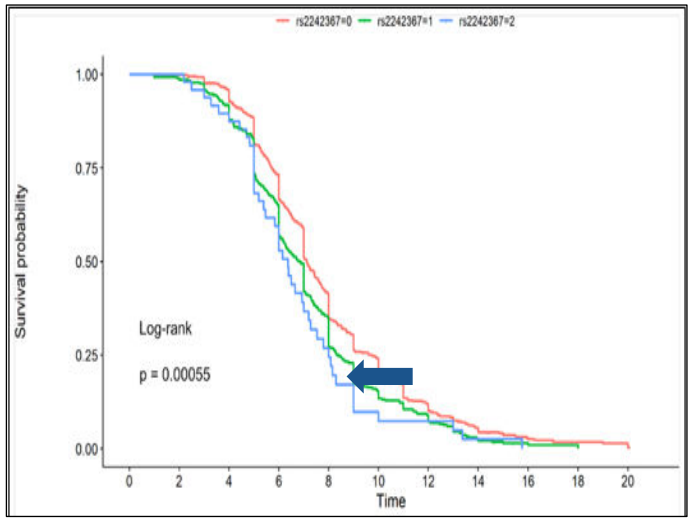
PSP genetics implicate LRRK2 in progression of disease
LRRK2 PROTAC degraders induce reduction of pathologic tau

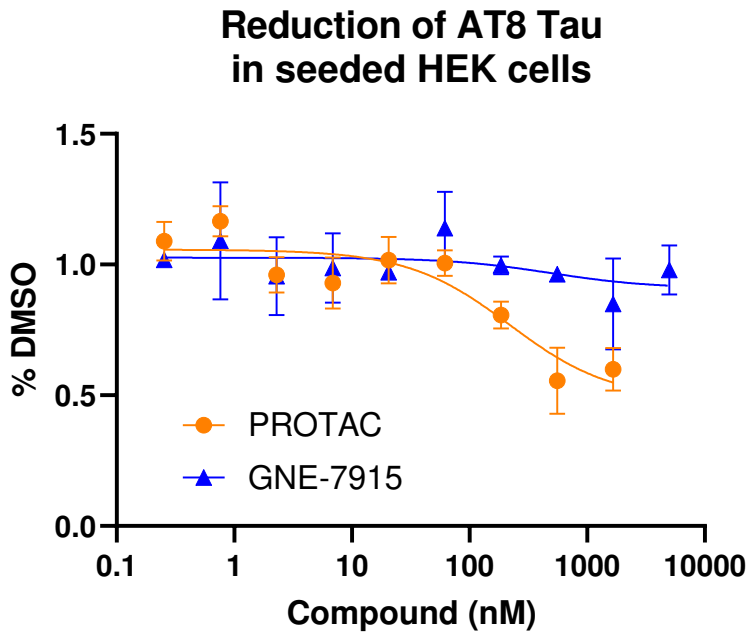
LRRK2 snp implicated in progression accelerated time to death by 1 year in PSP



- 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

Jabbari et al., 2021

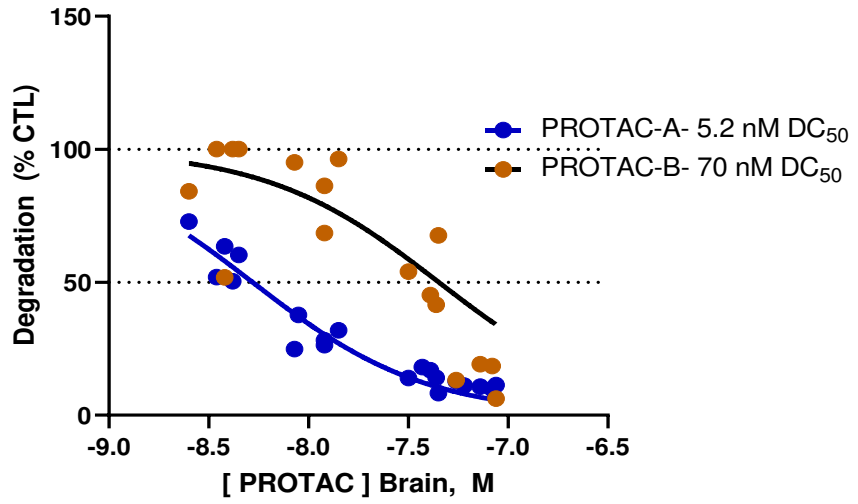
LRRK2 PROTAC induces clearance of AD induced pathologic AT8-tau



- Preliminary data indicate pathologic protein clearance in in two tauopathy mouse models

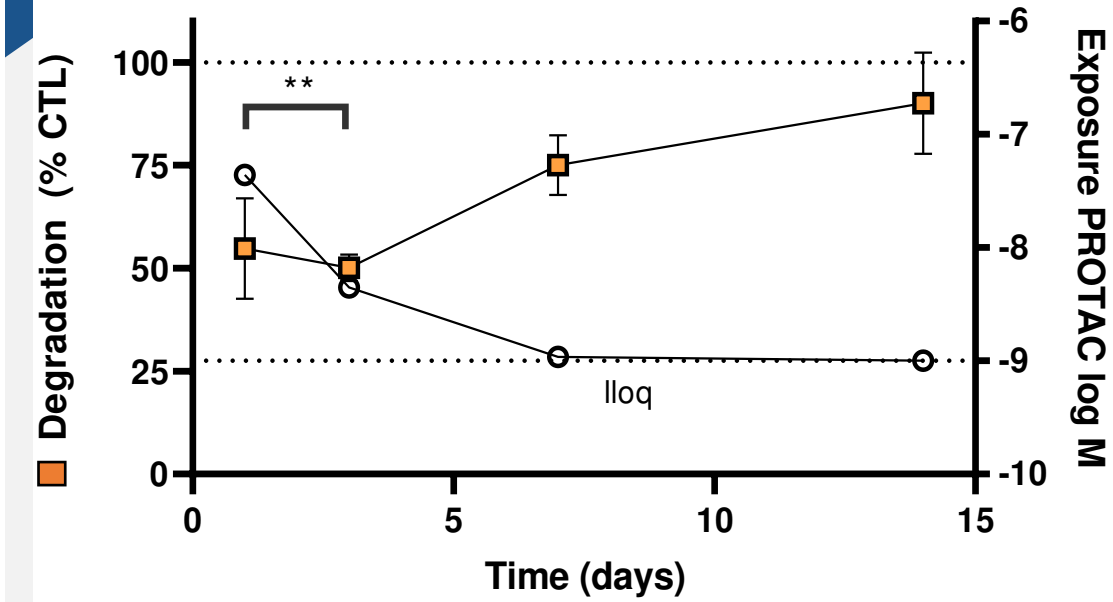
Single oral LRRK2 PROTAC® administration rapidly degrades target in brain (concentration-dependent and durable)

LRRK2 PROTAC-optimization -Dose-Response PK/PD In Cortex 24h post single oral dose



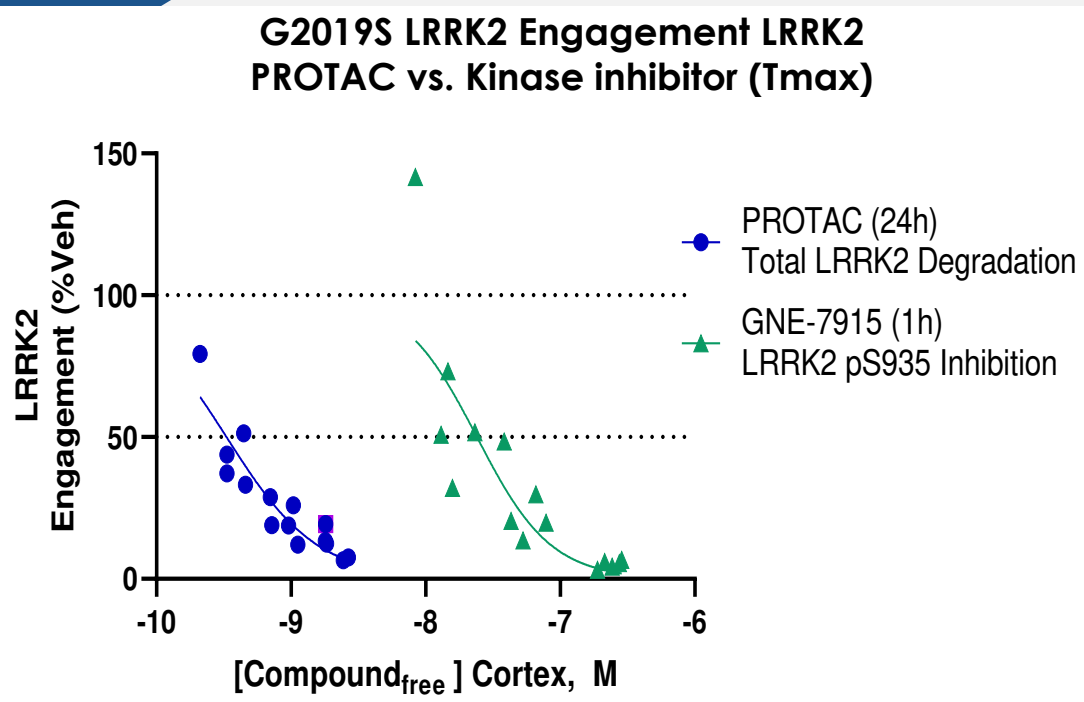
*PK/PD- Pharmacokinetic and Pharmacodynamic effect relationship

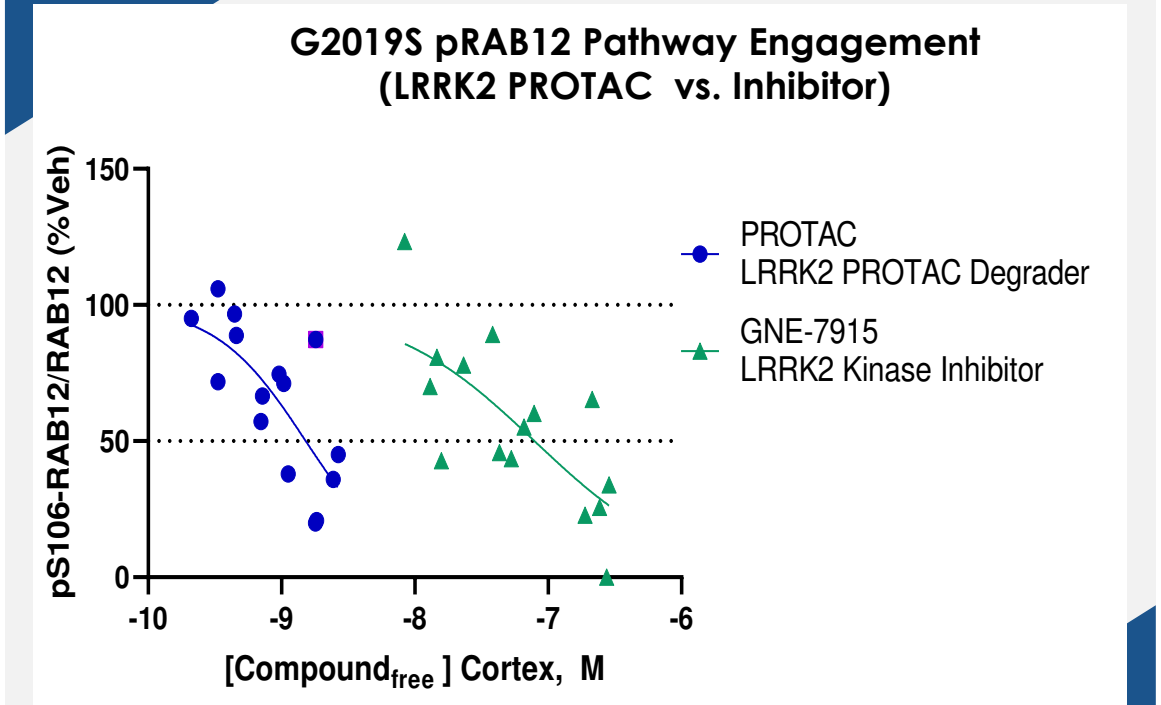
LRRK2 PROTAC PK/PD Time-Course - Cortex



Oral, potent LRRK2 PROTAC® Differential Pharmacology vs. LRRK2 Kinase Inhibitor in fPD G2019S mouse model

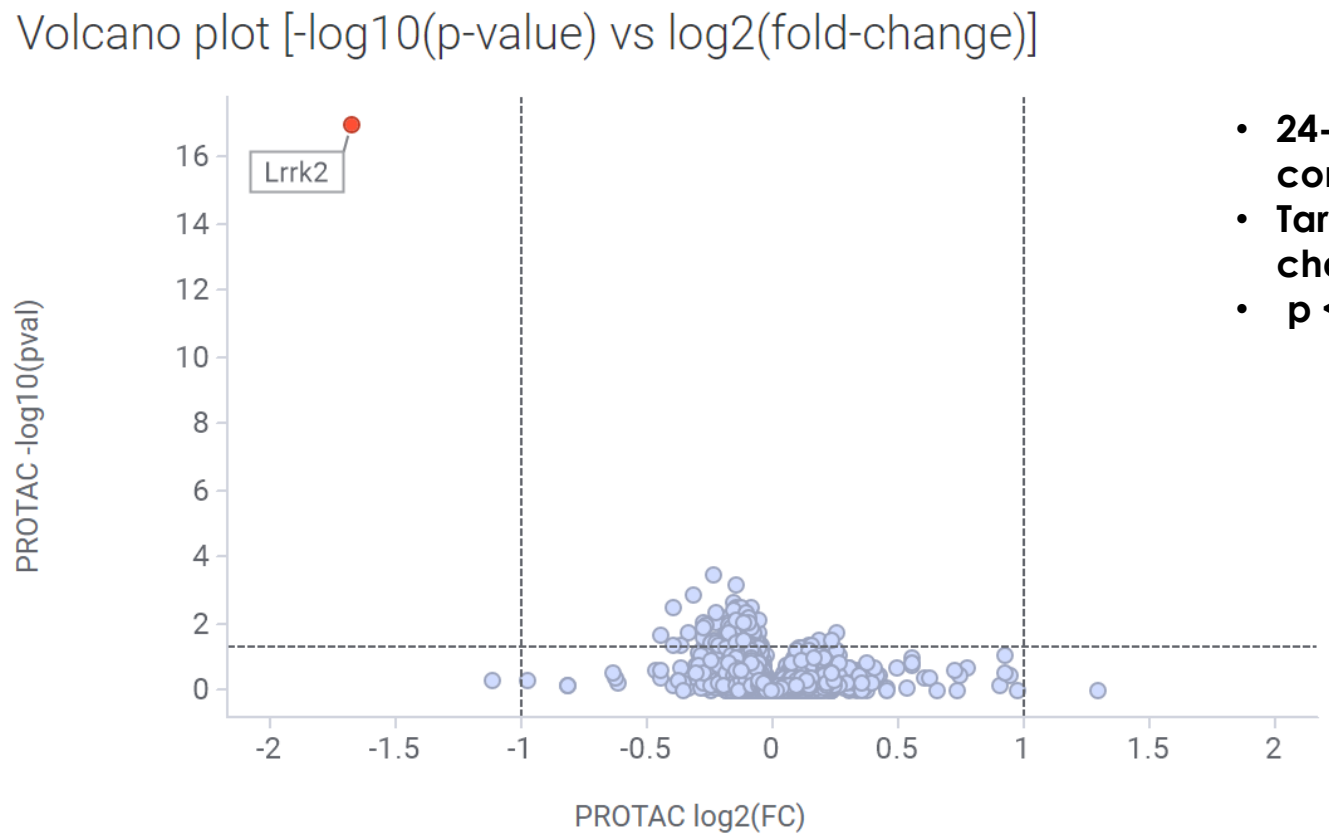
PROTAC advantage (event-driven pharmacology) results in iterative activity compared to kinase inhibition





LRRK2 oral PROTAC® degraders are highly selective in brain

LRRK2 PROTAC degrader is a highly selective degrader molecule

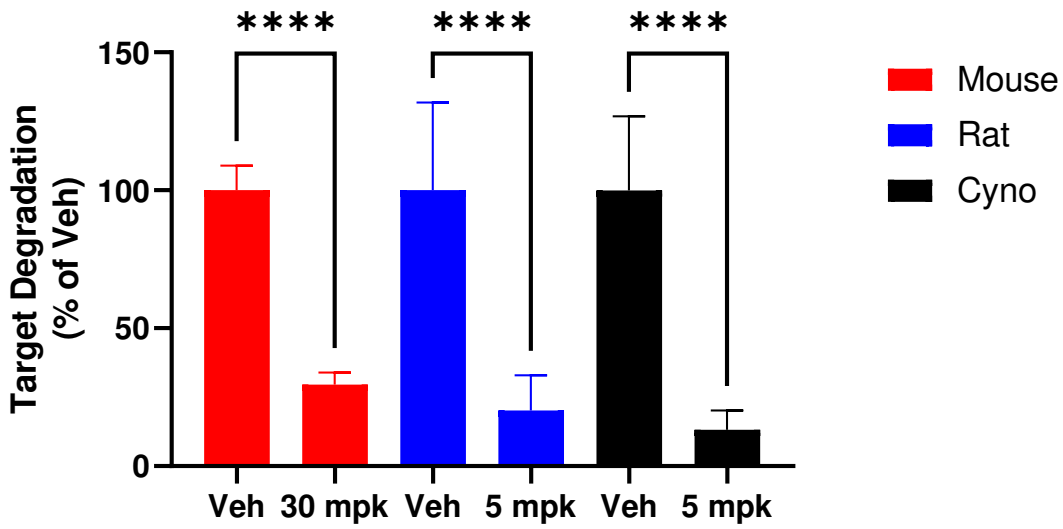


- **24-hits PROTAC vs vehicle control**
- **Target is most significantly changed protein in cortex**
- **$p < 10^{-16}$**

TMT Proteomic analysis in brain 24 h following oral administration

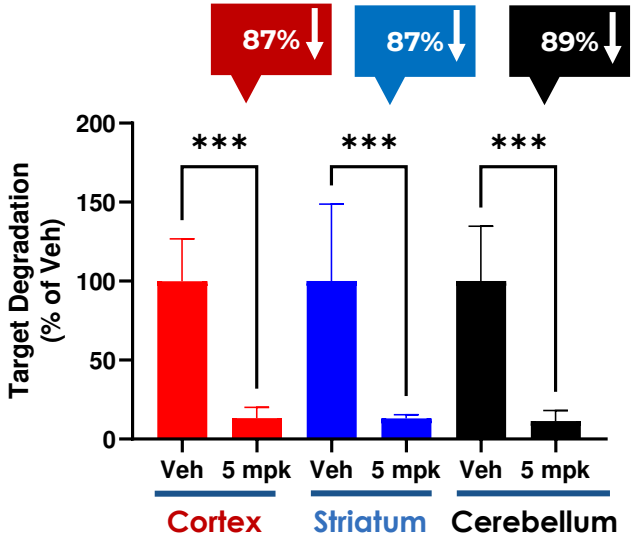
Oral LRRK2 PROTAC® induced degradation with biodistribution to deep anatomic brain regions in Primates

Target degradation in brain across species (mouse, rat, cyno) after oral PROTAC dosing



Robust biodistribution in cynomolgus monkey brain after oral dosing (cortex, cerebellum, & striatum)

>85% LRRK2 degradation in deep brain regions after oral dosing in primate

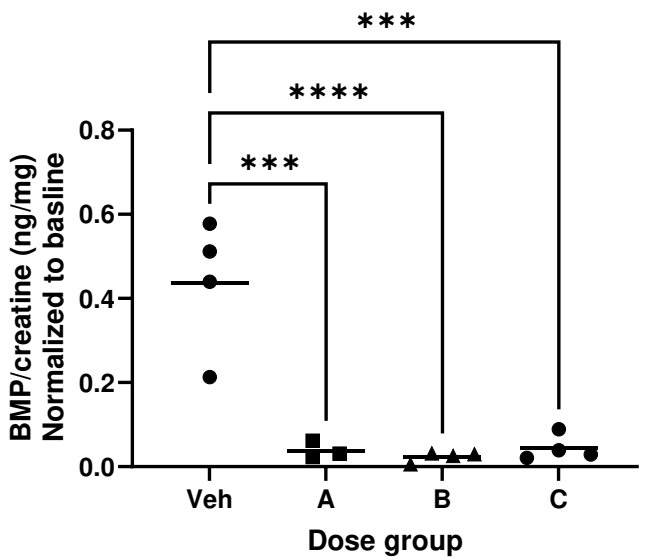


*** p <0.0001

Oral LRRK2 PROTAC® demonstrates biomarker changes that reinforce confidence in MoA in brain and periphery

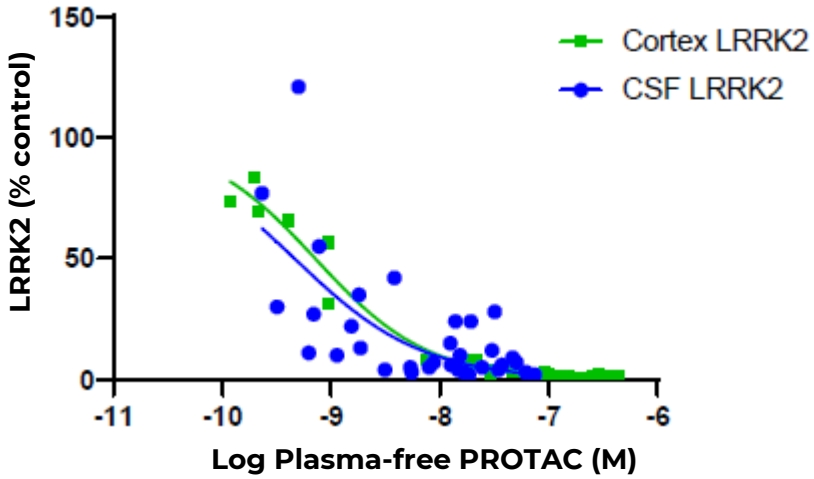
PROTAC-induced reductions observed in key lysosomal marker in cynomolgus monkey urine

BMP* reductions in cynomolgus monkeys



PK-PD of LRRK2 Reduction in cortex and CSF following oral dosing in cyno

CSF* LRRK2 reductions in cynomolgus monkeys; surrogate compartment for brain



BMP- bis(monoacylglycerol)phosphate; CSF-cerebrospinal fluid

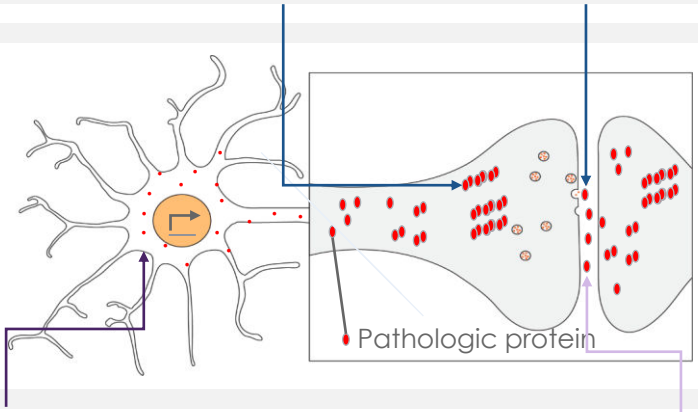
Data presented at the 2023 International Congress of Parkinson's Disease and Movement Disorders in Copenhagen, Denmark, August 27-31, 2023

PROTAC® heterobifunctional degrader molecules create a strong opportunity for removal of pathologic proteins compared to other modalities

PROTAC® degrader small molecules may overcome the limitations of other platforms

PROTAC *Potential*

- Reduce intracellular pathologic protein/source of extracellular protein
- Discriminate between Arvinas wild type and pathologic protein
- Oral administration with BBB biodistribution



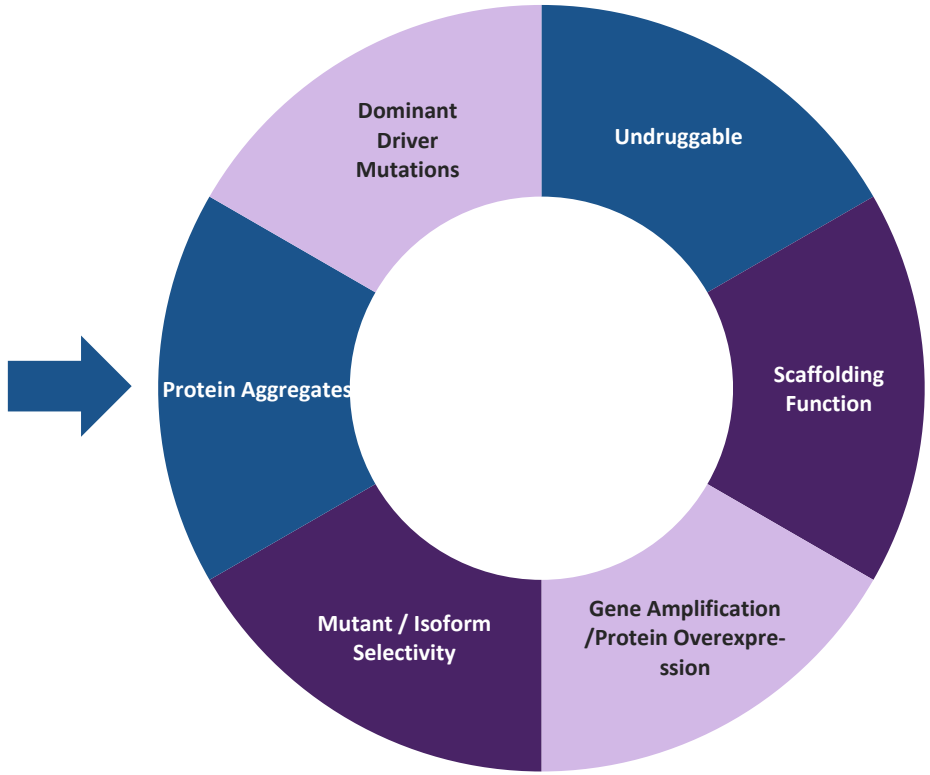
ASO

- Requires intrathecal dosing
- Does not discriminate wt from pathologic protein

Ab

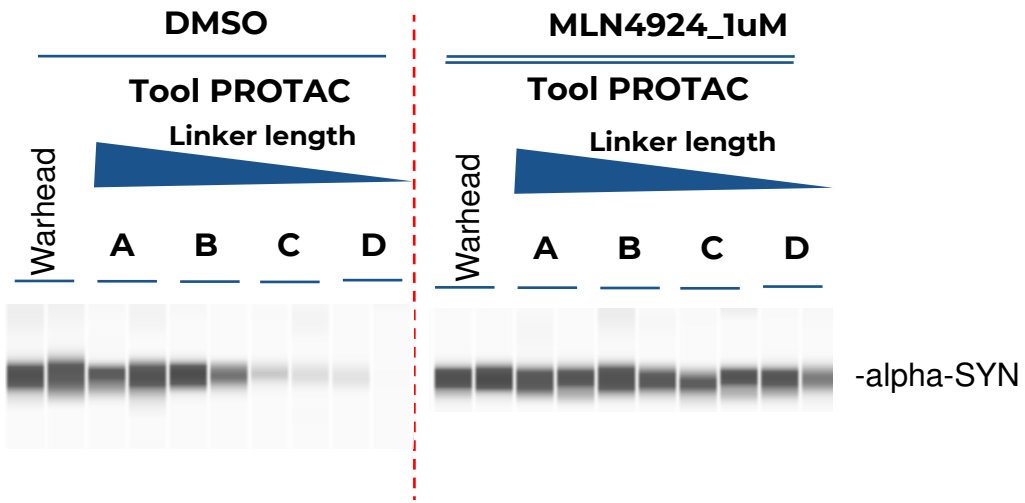
- Blocks only extracellular pathologic protein
- IV dosing results in only 0.5% in CSF

PROTAC *Tenets -- Differentiation from small molecule inhibitors*



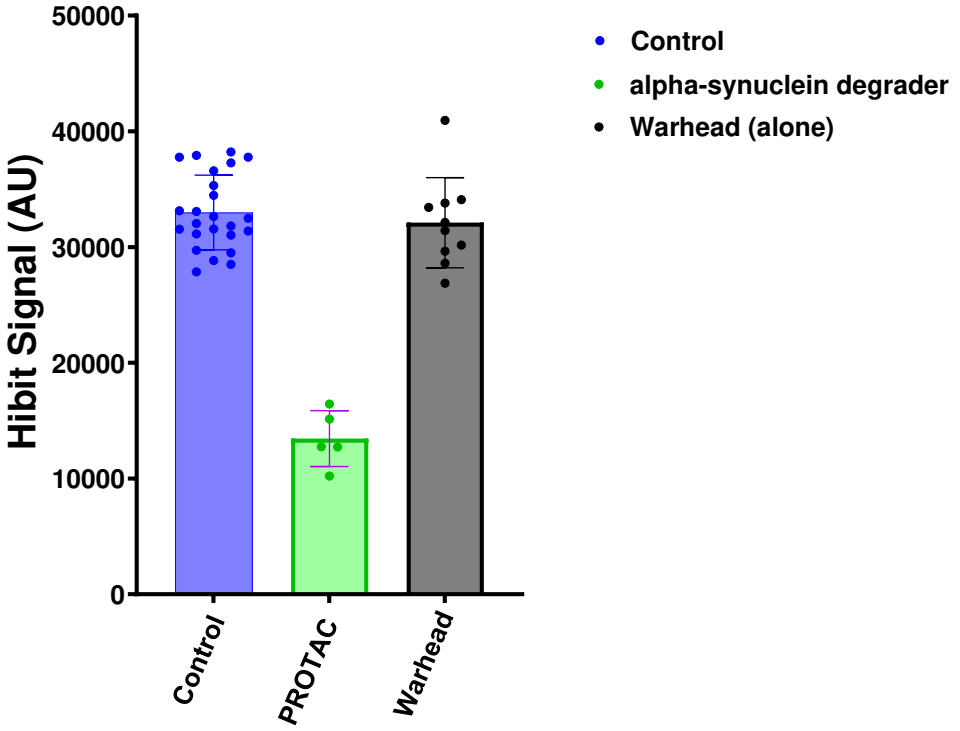
Novel alpha-synuclein monomer degrader tool molecules are active in human iNeurons

Induced degradation of alpha-synuclein is UPS-dependent in recombinant HEK cells



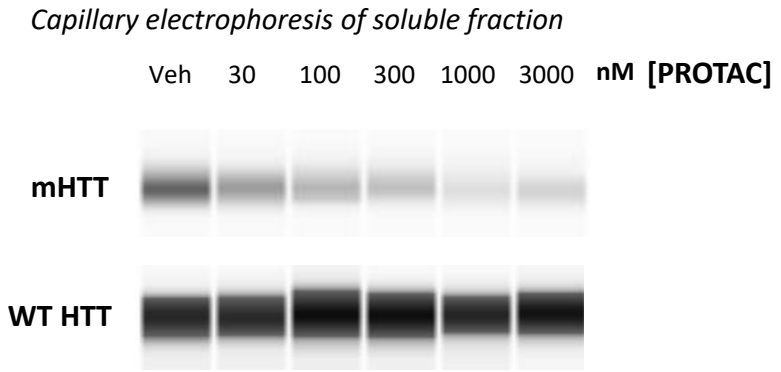
Capillary electrophoresis (MJFR1)

Degradation of alpha-synuclein in human iPSC Neurons



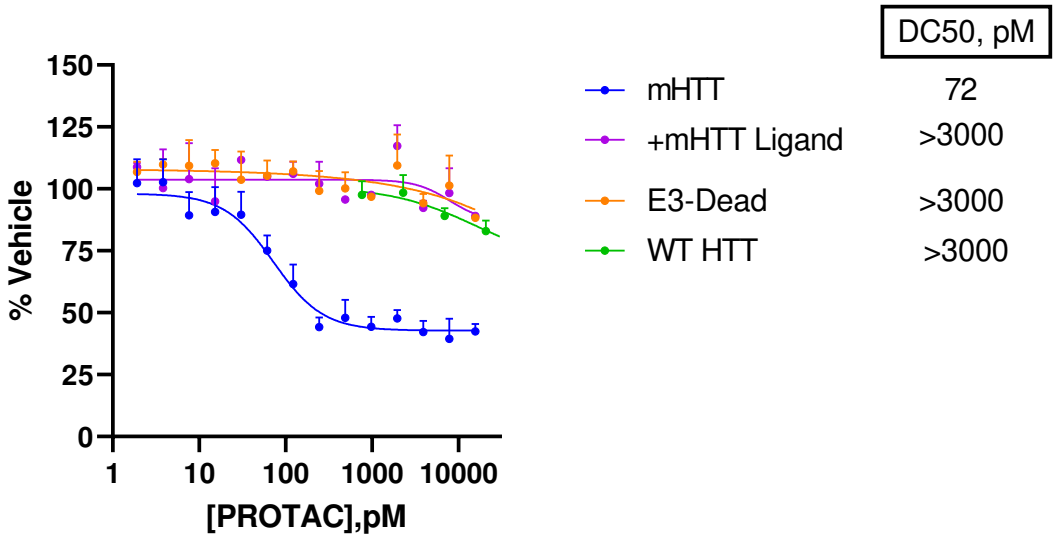
Huntington's Disease: Ligand chemistry enables mutant HTT (mHTT) protein selective PROTAC® degradation and spares wild-type HTT

PROTAC degradation of soluble mHTT



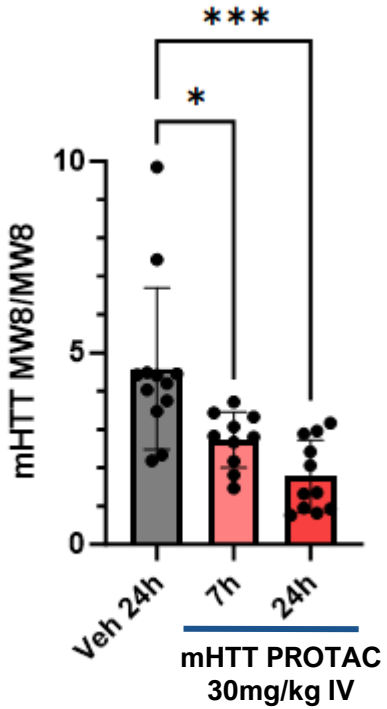
PROTAC spares wild-type HTT

PROTAC-induced degradation of mHTT, spares WT HTT, and is on mechanism

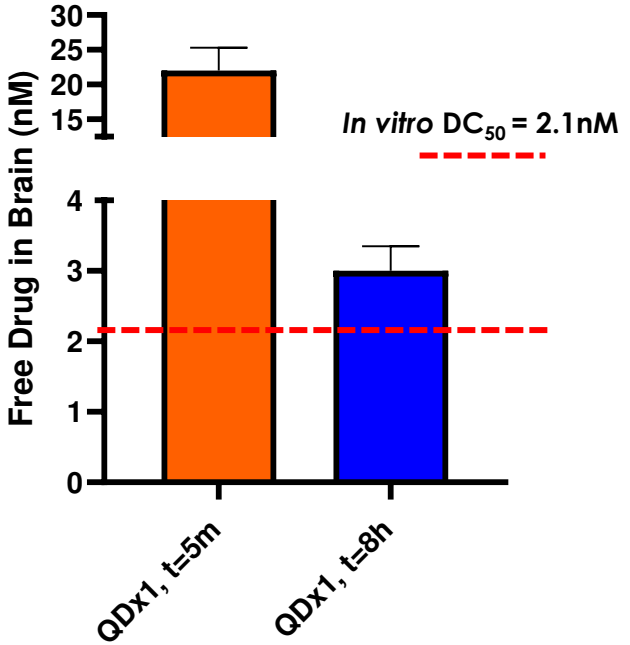


PROTAC® mHTT degraders cross the BBB at pharmacologically relevant levels and degrade Q80 mHTT in mouse brain

mHTT selective PROTAC induces 50% reduction of Q80 mHTT in mouse cortex



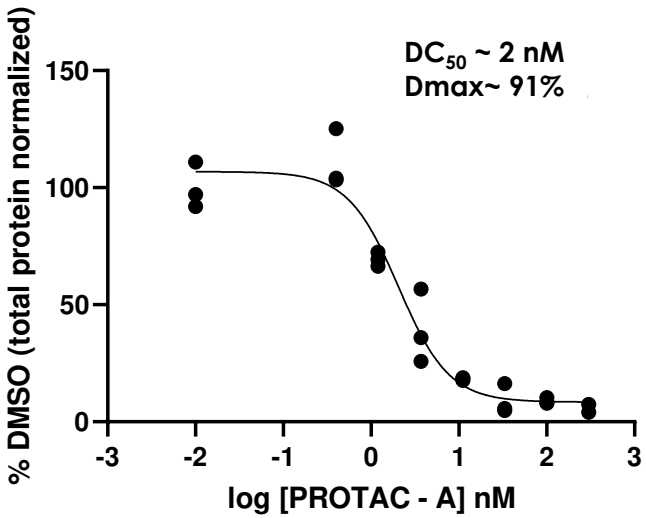
Oral PROTACs with free drug in brain covers *in vitro* DC_{50} after single dose



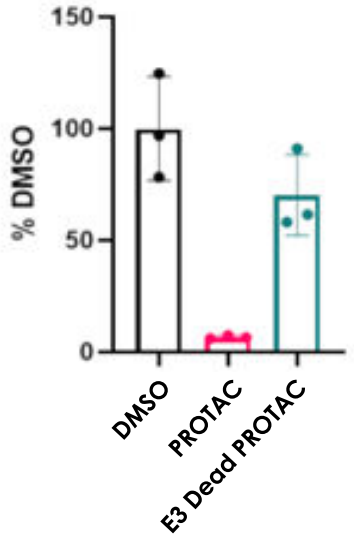
Undisclosed Neuromuscular Target: PROTAC® degraders remove toxic aggregating protein within myotubes

PROTAC degrades toxic aggregating protein in iPSC- myotubes from patients via E3/proteosome-dependent mechanism

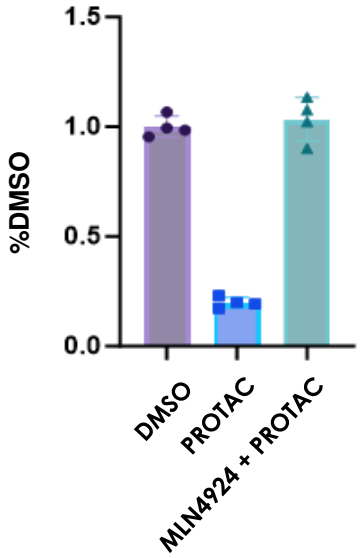
PROTAC is a degrader of toxic protein in iPSC- myotubes from patients



PROTAC requires E3 binding to induce degradation



PROTAC is dependent on the Ubiquitin-Proteasome System for degradation



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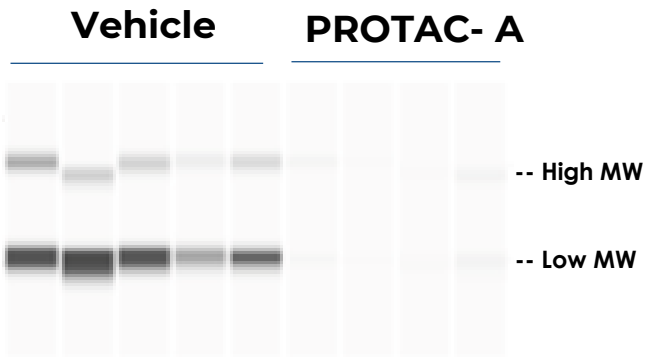
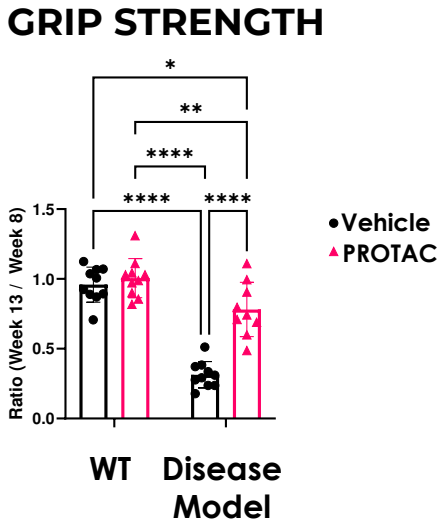
Oral PROTAC® administration removes toxic protein within muscle and improves muscle function

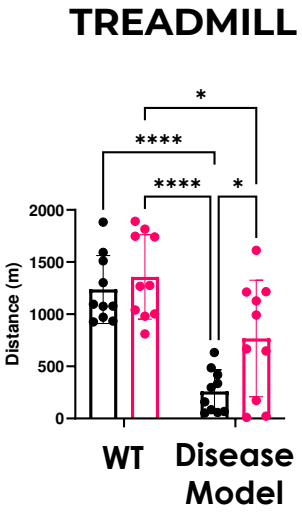
PROTAC degrades toxic protein aggregates in a highly aggressive murine disease model with improved function (grip strength), endurance (treadmill), and lifespan (not shown).

Neuromuscular degeneration Mouse Model (3xQD PO)



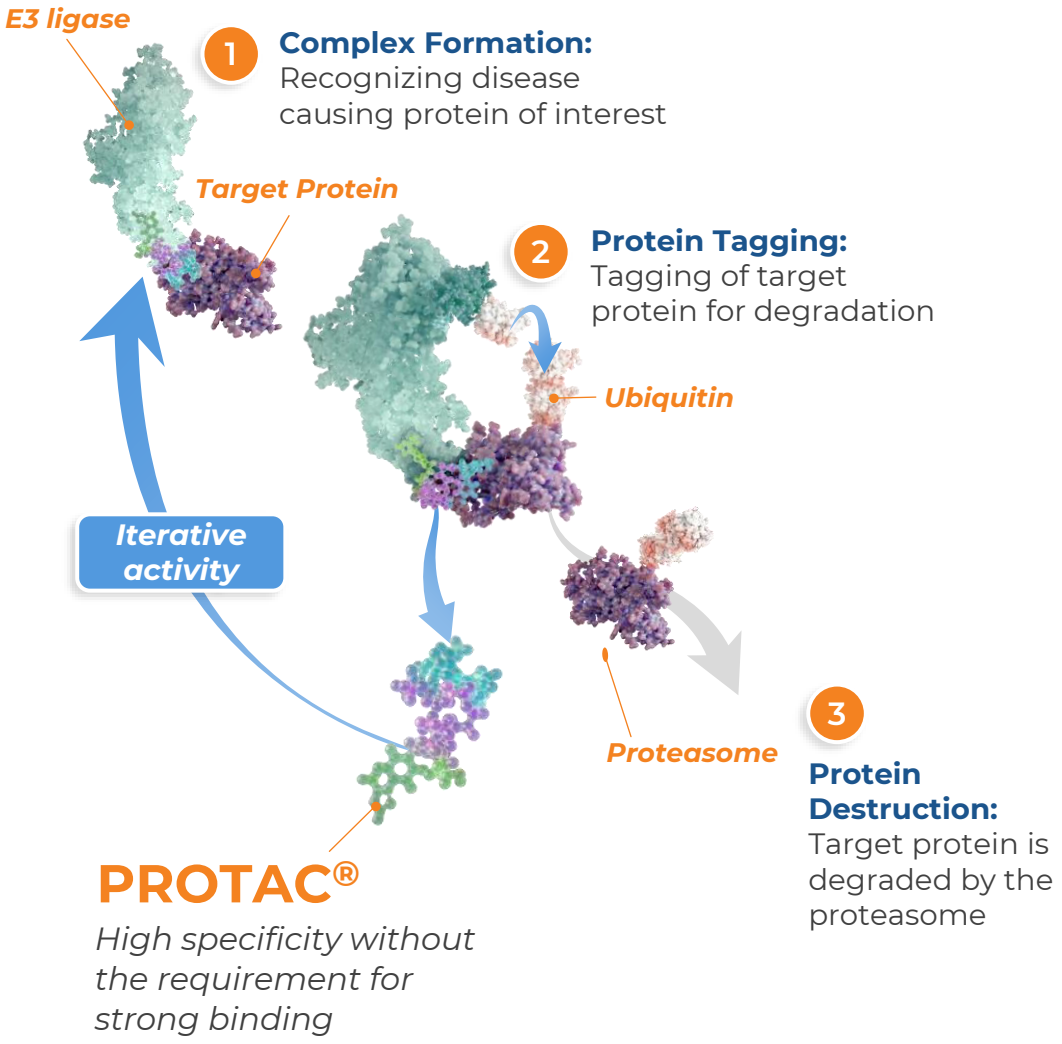
Neuromuscular degeneration Mouse Model (PROTAC chronic oral administration) improves function and endurance





PROTAC® degraders could revolutionize the treatment of patients with neurological diseases

PROTAC degraders provide significant potential advantages over existing modalities



Arvinas' proteolysis-targeting chimera (PROTAC®) degraders can:

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

Phase 1 trial with LRRK2-targeting PROTAC® degrader anticipated in 1H 2024

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Thank you- Team Arvinas!