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Oral PROTAC® Degrader Molecules to Selectively Clear Proteins in Neurodegenerative Diseases

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Keystone- Autophagy and Neurodegeneration

March 29, 2023

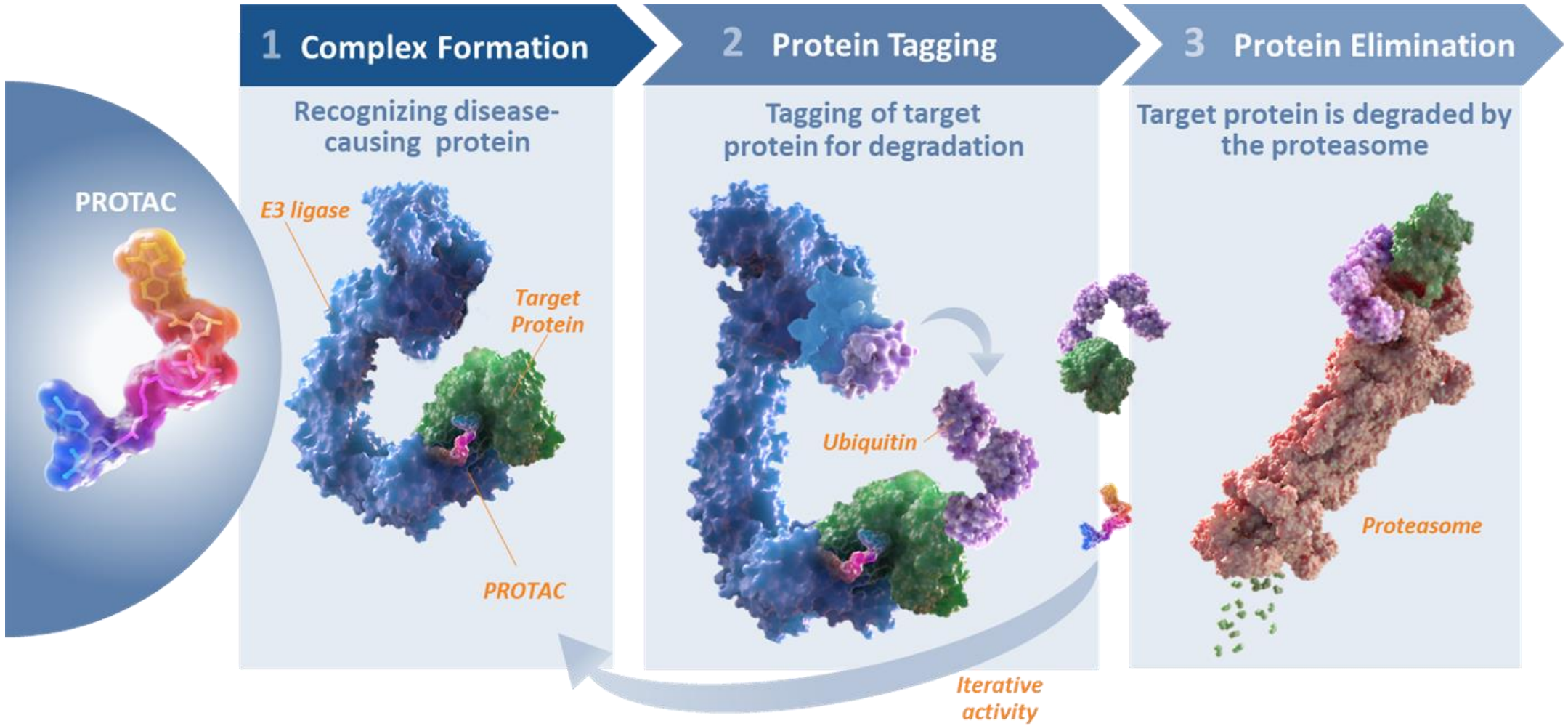
Safe harbor and forward-looking statements

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 receipt of upfront, milestone, and other payments under the Pfizer collaboration, the potential benefits of and the receipt of any related milestones in connection with our arrangements with our collaborative partnerships, statements regarding the potential advantages and therapeutic benefits of bavdegalutamide (ARV-110), ARV-471, ARV-766 and our other discovery programs, the development and regulatory status of our product candidates, such as statements with respect to the potential of our lead product candidates, bavdegalutamide (ARV-110), ARV-471, and ARV-766 and other candidates in our pipeline, and the timing of clinical trials, including the timing to complete enrollment, as well as the presentation and/or publication of data from those trials and plans for registration for our product candidates, and our discovery programs that may lead to our development of additional product candidates, the potential utility of our technology, our plans with respect to submission of investigational new drug/clinical trial authorization applications, the potential commercialization of any of our product candidates and companion diagnostic partnering, and the sufficiency of our cash resources All statements, other than statements of historical facts, contained in this presentation, including statements regarding our 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.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions, and expectations disclosed in the forward-looking statements we make as a result of various risks and uncertainties, including but not limited to: our and Pfizer, Inc.’s (“Pfizer”) performance of our respective obligations with respect to our collaboration with Pfizer; whether we and Pfizer will be able to successfully conduct and complete clinical development for ARV-471; whether we will be able to successfully conduct and complete development for bavdegalutamide (ARV-110) and our other product candidates, including whether we initiate and complete clinical trials for our product candidates and receive results from our clinical trials on our expected timelines, or at all; whether our cash and cash equivalent resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements; and other important factors, any of which could cause our 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, 2021 and subsequent other reports on file with the Securities and Exchange Commission. The forward-looking statements contained in this presentation reflect our current views as of the date of this presentation with respect to future events, and we 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 our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data and estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. This presentation is intended for the investor community only. It 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® molecules harness the ubiquitin-proteasome system to degrade proteins



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

Program	Therapeutic Area / Indication	Preclinical	Phase 1/1b	Phase 2	Phase 3
ARV-471 Global co-development/ co-commercialization partners with Pfizer	**Oncology:** **ER+/HER2- Breast Cancer**	★ **VERITAC-2:** ARV-471 monotherapy 2L pivotal trial			
		★ ***VERITAC-3: ARV-471 + palbociclib as 1L combination therapy***			
		★ ***ARV-471 monotherapy in the adjuvant setting***			
		VERITAC: ARV-471 monotherapy dose expansion (2L+)			
		TACTIVE-N: ARV-471 in neoadjuvant setting			
		TACTIVE-E: ARV-471 + everolimus			
		TACTIVE-U: ARV-471 in combination with ribociclib, abemaciclib, and other targeted therapies			
Bavdegalutamide (ARV-110)	**Oncology:** **Prostate Cancer**	★ ***Bavdegalutamide monotherapy (878/875+ 2L+)***			
		ARDENT: Bavdegalutamide monotherapy dose expansion (2L+)			
		Bavdegalutamide + abiraterone (2L+)			
ARV-766		**ARV-766 monotherapy dose expansion (2L+)**			
		ARV-766 monotherapy dose escalation (2L+)			
AR-V7†, BCL6, KRAS-G12D/V†, Myc†, HPK1 ***Undisclosed Targets***	**Oncology:** **Solid and Haematological Malignancies**	**BCL6 IND/CTA expected in 2023**	**2 additional programs in IND-enabling studies by end of 2023**		
LRRK2 **Tau†, α-Synuclein, mHTT** ***Undisclosed Targets***	**Neurodegenerative Disorders**	**LRRK2 IND/CTA expected in 2023**			

Anticipated

★ *Pivotal Trial*

These agents are currently under investigation. Their safety and effectiveness for these investigational uses have not yet been established.
IND, investigational new drug; CTA, clinical trial application
† Denotes historically undruggable proteins

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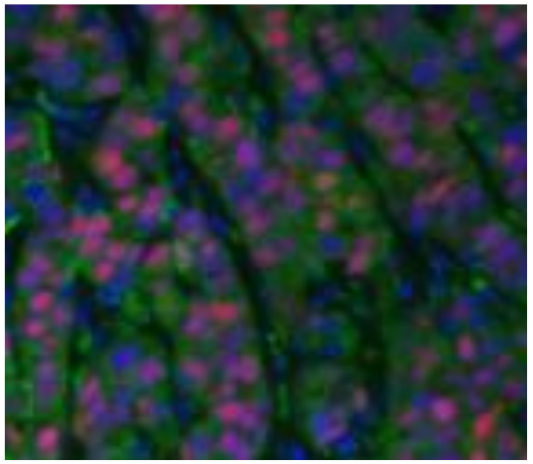
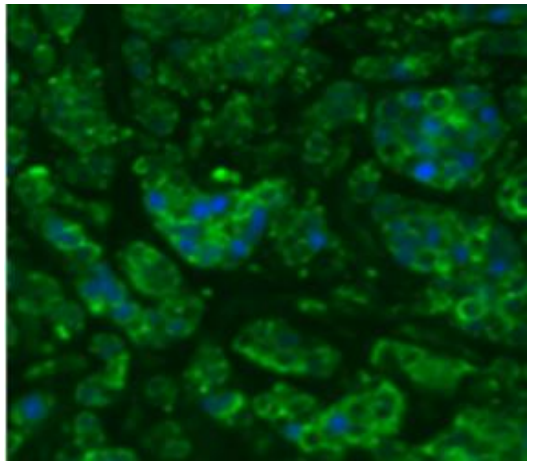
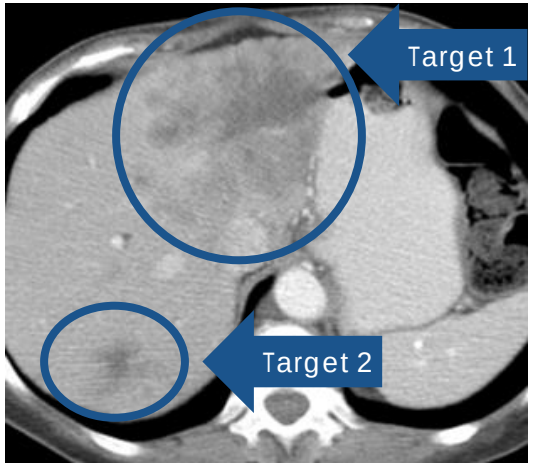
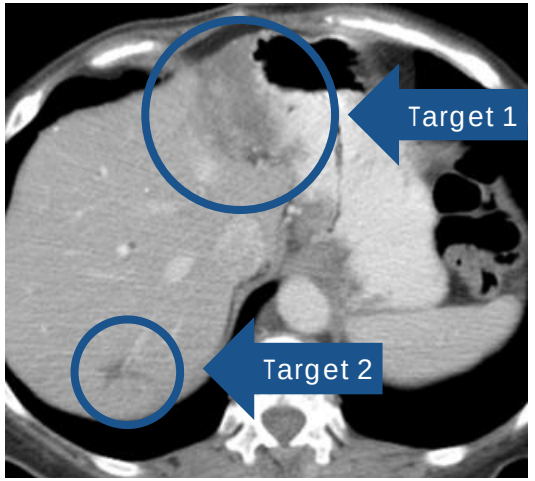
The Ultimate Platform Validation: PROTAC® shows therapeutic potential

ARV-471: ER Degradation & Confirmed RECIST Partial Response (cPR) in late-stage patients with extensive prior therapy

Baseline	After treatment 60 mg ARV-471	Baseline CT Scan	After 4 Cycles
			

Estrogen receptor Nuclei Cytokeratin

ER degradation tumor biopsies	51% reduction in target lesions (RECIST partial response)

**Different patients shown on left and right; Data as presented 12/14/2020; SABCS 2021*

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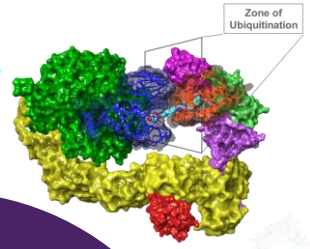
Integrated PROTAC® drug discovery for Neurology

Genetic Disease:
Protein is the cause of the disease

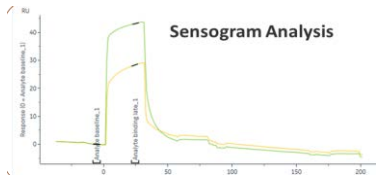
Translational Medicine:
Biomarkers support efficient path to assessing efficacy in humans

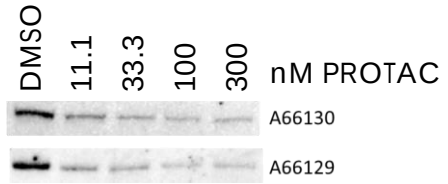
PK/PD Models:
Protein target engagement in vivo



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

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





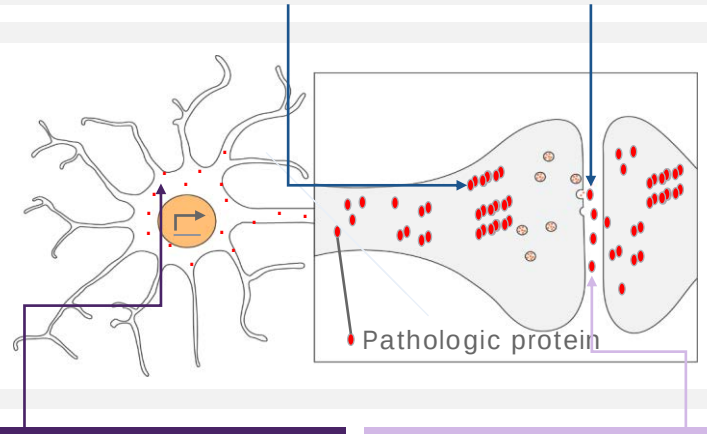
Neurodegeneration
Precision Medicine
Genetic/
Proteinopathy
Target root cause
PROTAC differentiator
Biomarker PoC

PROTAC® heterobifunctional degrader molecules create a strong opportunity in neuroscience compared to other modalities

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

PROTAC *Potential*

- Reduce intra- and extracellular pathologic protein
- Discriminate between wild type and pathologic protein
- Oral administration with BBB biodistribution



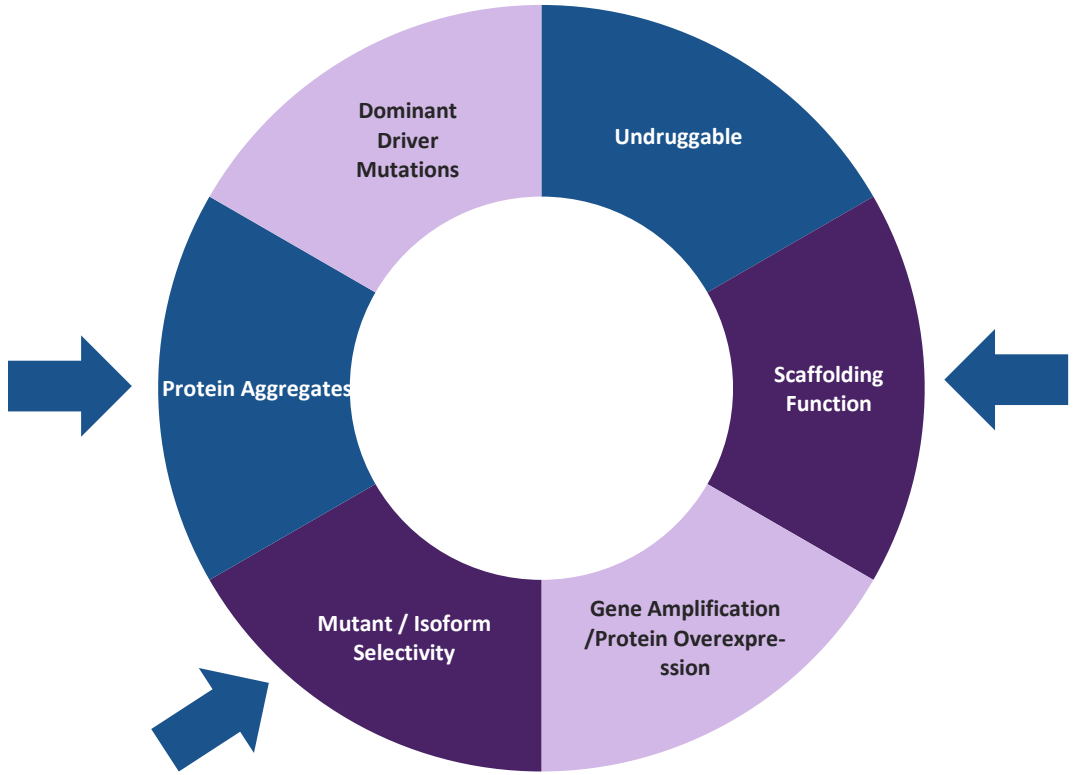
ASO

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

Ab

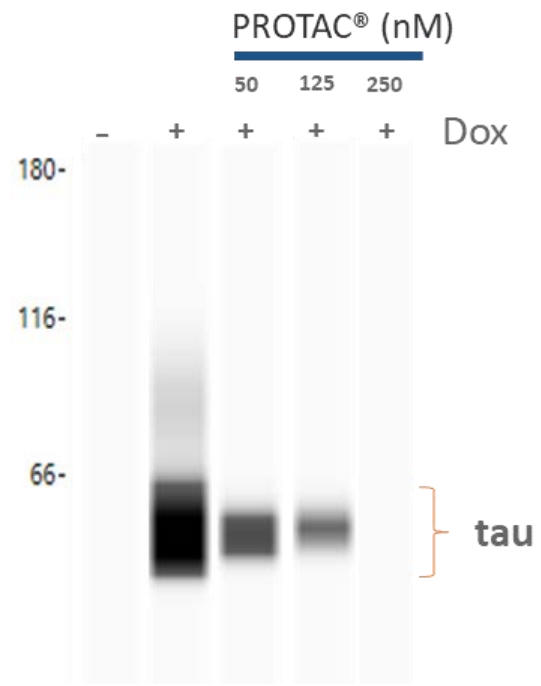
- Blocks only extracellular pathologic protein
- IV dosing results in only 0.5% in CSF

PROTAC *Tenets -- Differentiation from small molecule inhibitors*



PROTAC® small molecules can degrade tau P301L aggregates

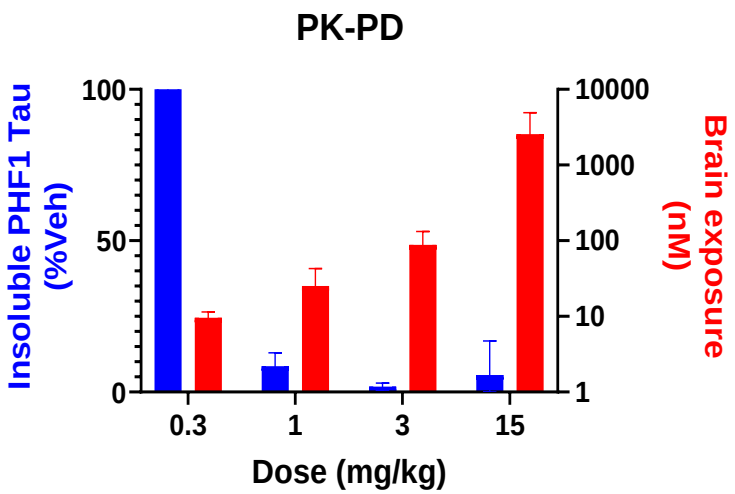
In vitro insoluble tau PROTAC degradation



*on mechanism

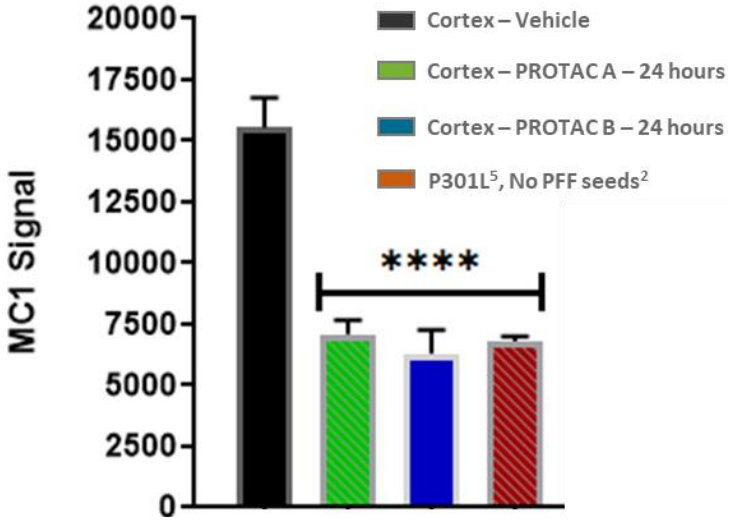
In vivo insoluble tau PROTAC degradation

Tg2508 24h post single PROTAC IV dose



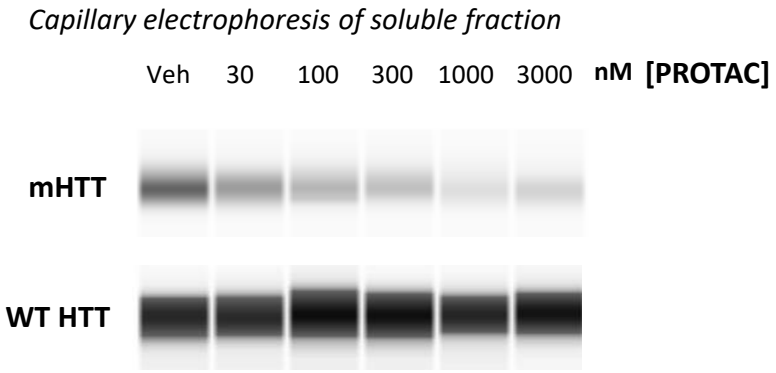
Reduced Seed Potential Ex vivo brain extracts

Tg2508 brain extracts 24h post single IV dose



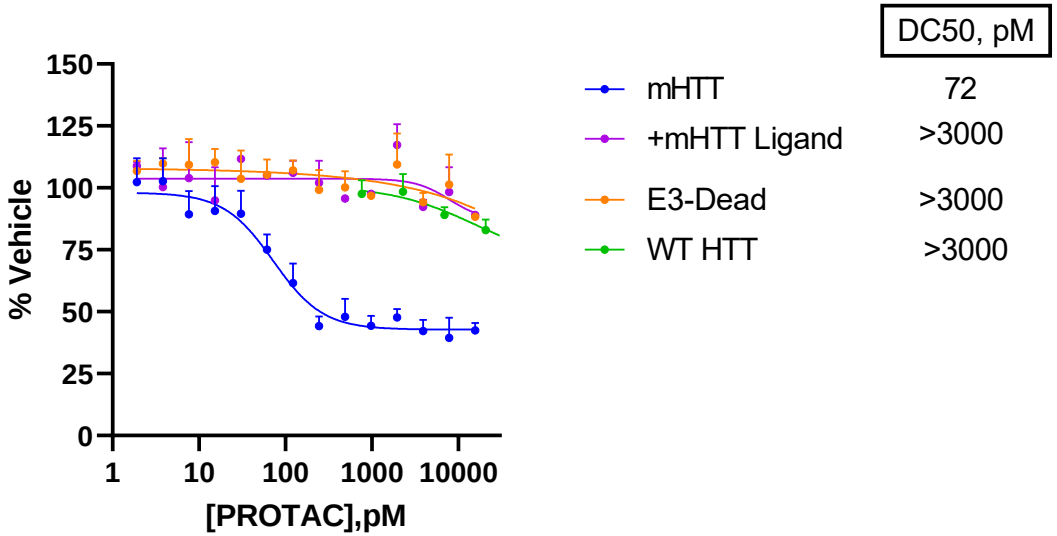
Huntington's Disease: Ligand chemistry enables mutant HTT (mHTT) protein selective PROTAC® degradation and spares wild-type HTT

PROTAC degradation of soluble mHTT



PROTAC spares wild-type HTT

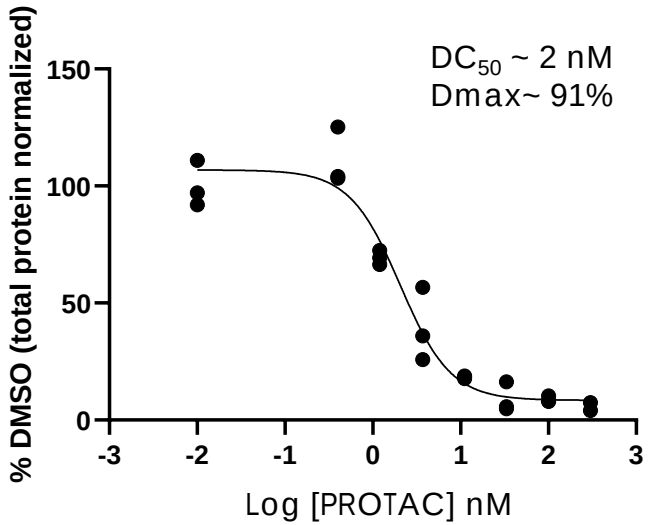
PROTAC-induced degradation of mHTT, spares WT HTT, and is on mechanism



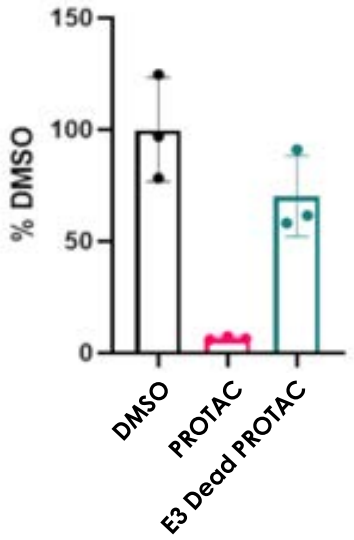
Neuromuscular Target: PROTAC® degraders remove toxic aggregating protein within myotubes

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

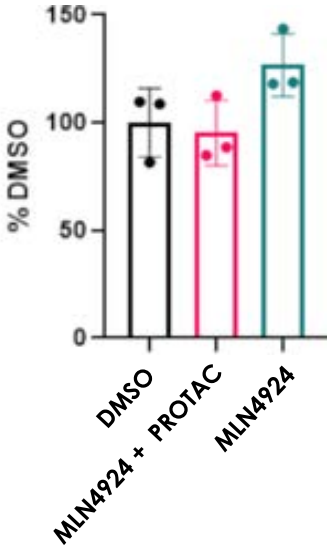
PROTAC is a degrader of toxic protein in iPSC- myotubes from patients



PROTAC requires E3 binding to induce degradation



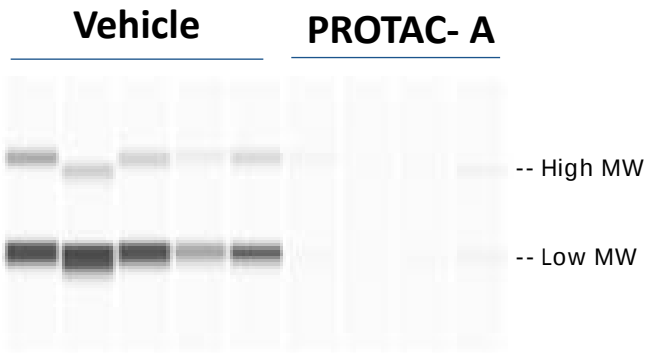
PROTAC is dependent on the Ubiquitin-Proteasome System for degradation



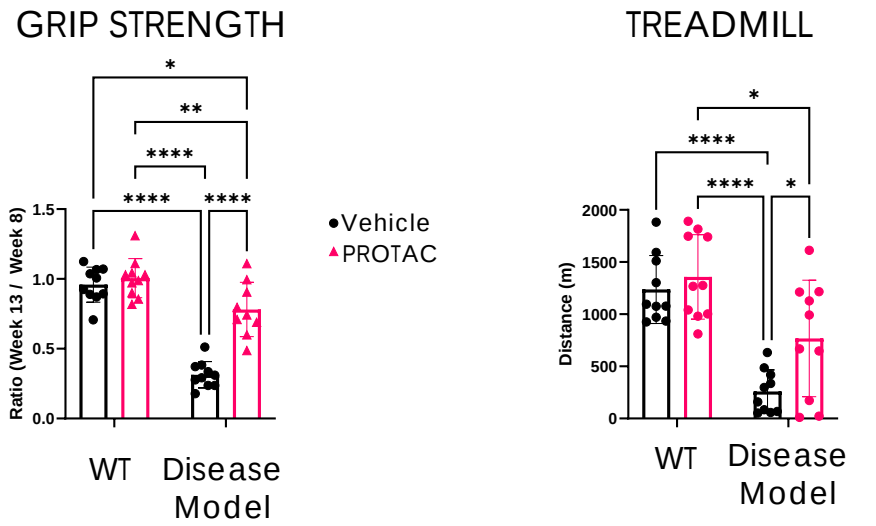
Oral PROTAC® administration removes toxic protein within muscle and improves muscle function

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)



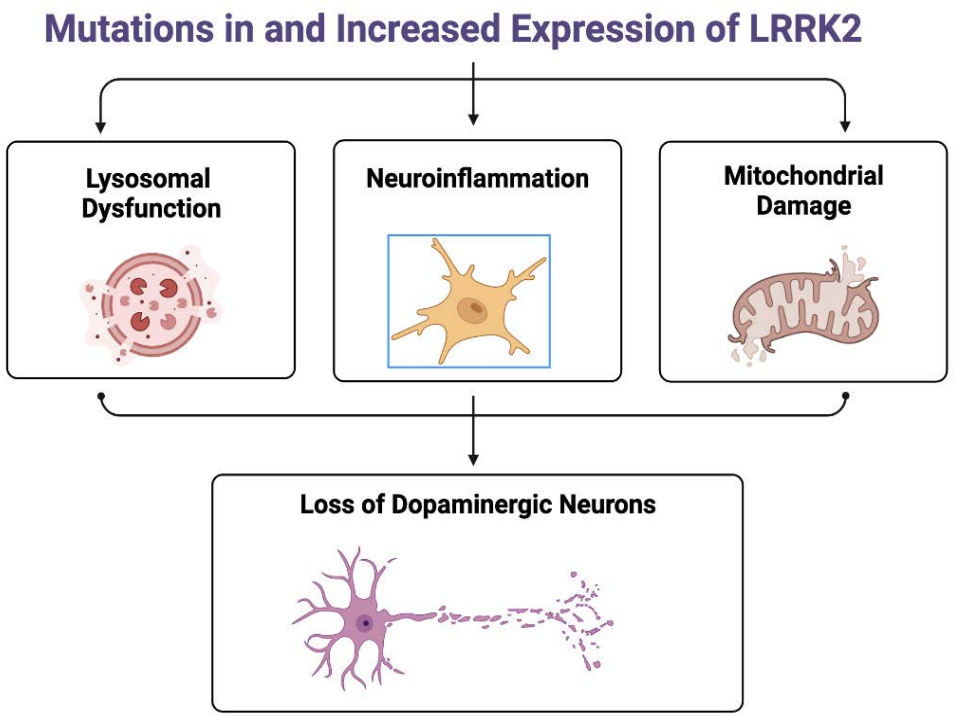
Neuromuscular degeneration Mouse Model (PROTAC chronic oral administration) improves function and endurance



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

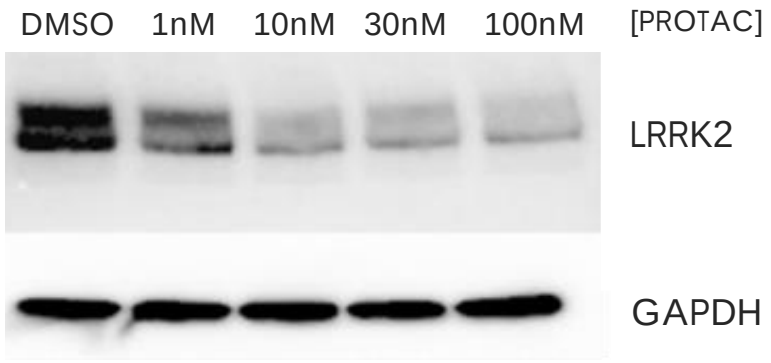
Human Genetics and biology create a strong rationale for differential biology of LRRK2 PROTAC degraders

- 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 (N551K/R1398H) and preclinical animal model data suggest that reduction of 50% of LRRK2 protein may impact pathology and dysfunction in PD (Wang, 2021, Zhao, 2017, Henderson, 2019)
- 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

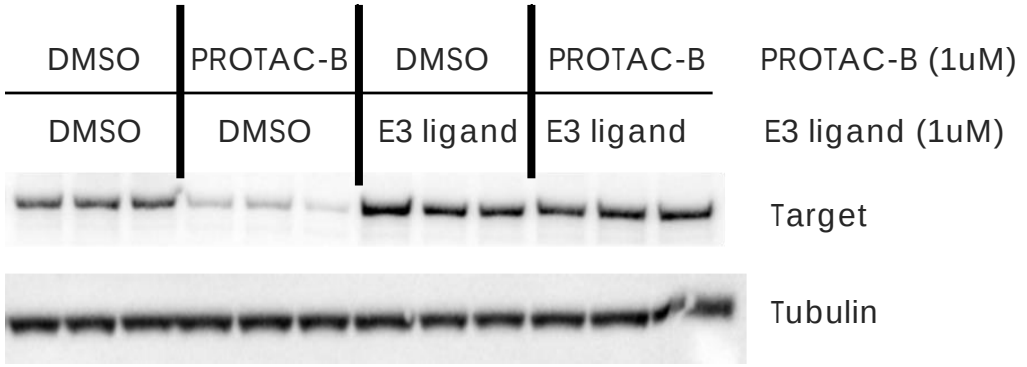


LRRK2 PROTAC® degrades LRRK2 in iPSC-derived microglia and is on mechanism

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



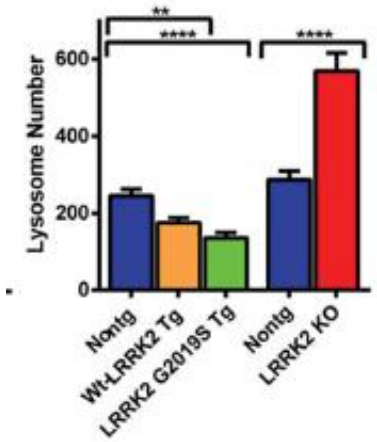
PROTAC-induced LRRK2 degradation is E3 ligase dependent



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

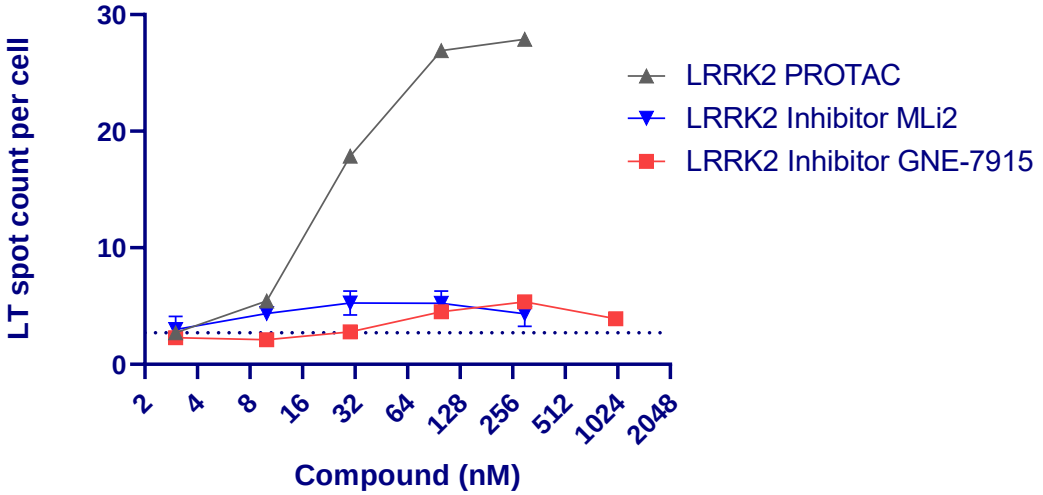
LRRK2 PROTACs induce robust increase in lysotracker (LT) spot count per cell

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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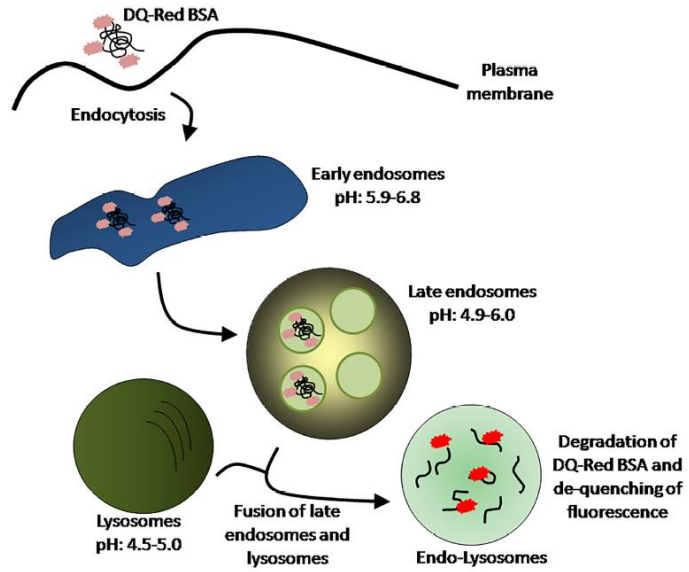
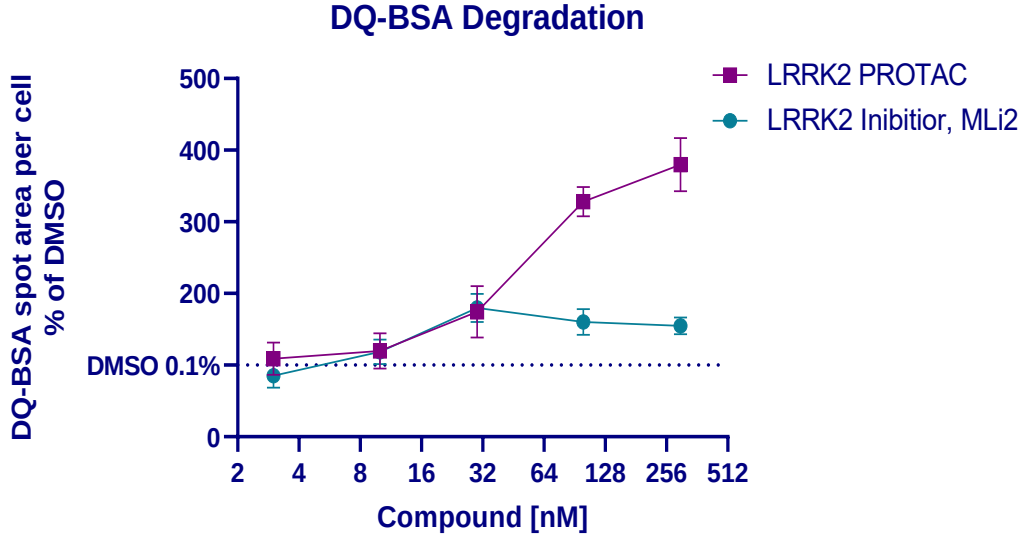
LRRK2 PROTAC enhances lysosome-based degradation

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



LRRK2 PROTAC enhances lysosome degradation

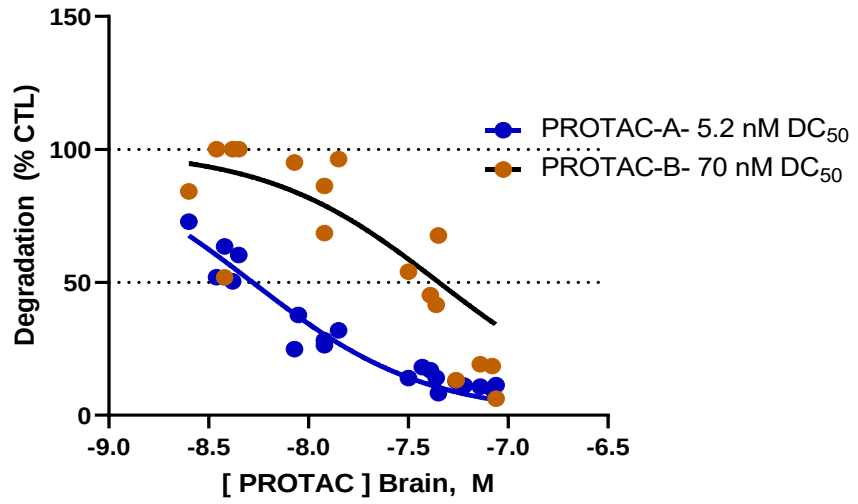


No impact on Transferrin uptake

- 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
- Currently examining pathologic protein clearance in synucleinopathy and tauopathy mouse models

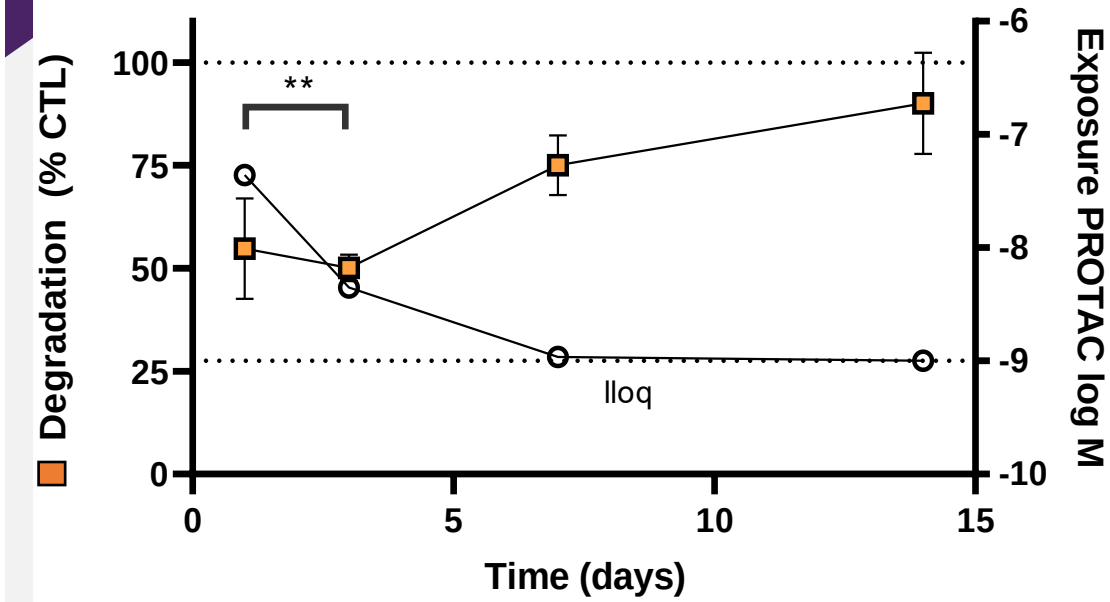
Single oral LRRK2 PROTAC® administration rapidly degrades target in brain (concentration-dependent and durable)

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



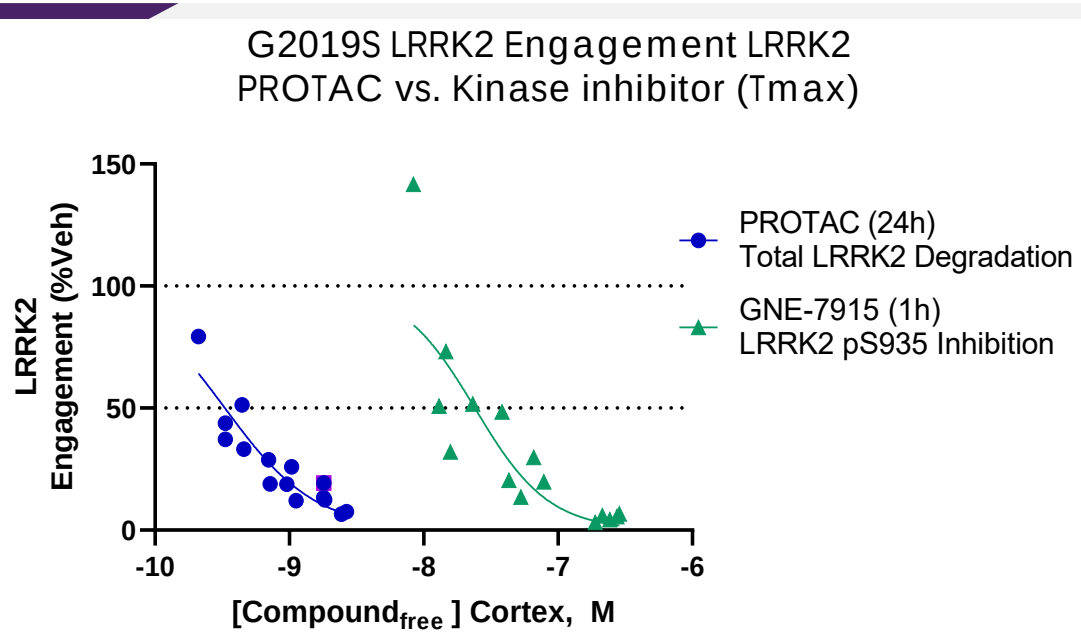
*PK/PD- Pharmacokinetic and Pharmacodynamic effect relationship

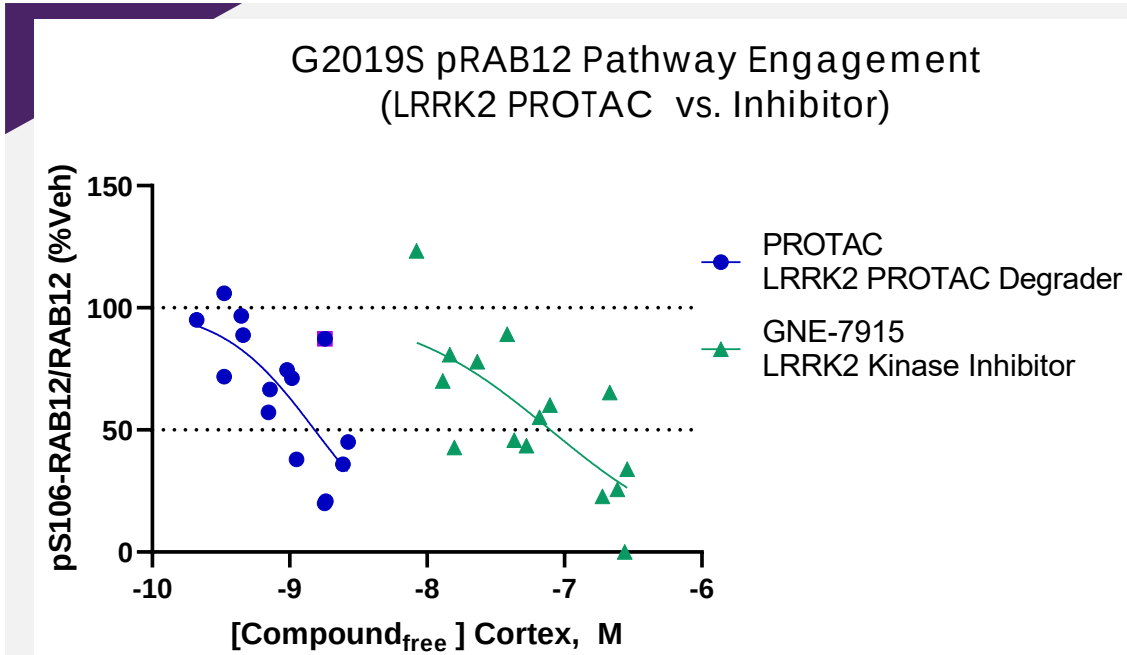
LRRK2 PROTAC PK/PD Time-Course - Cortex



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

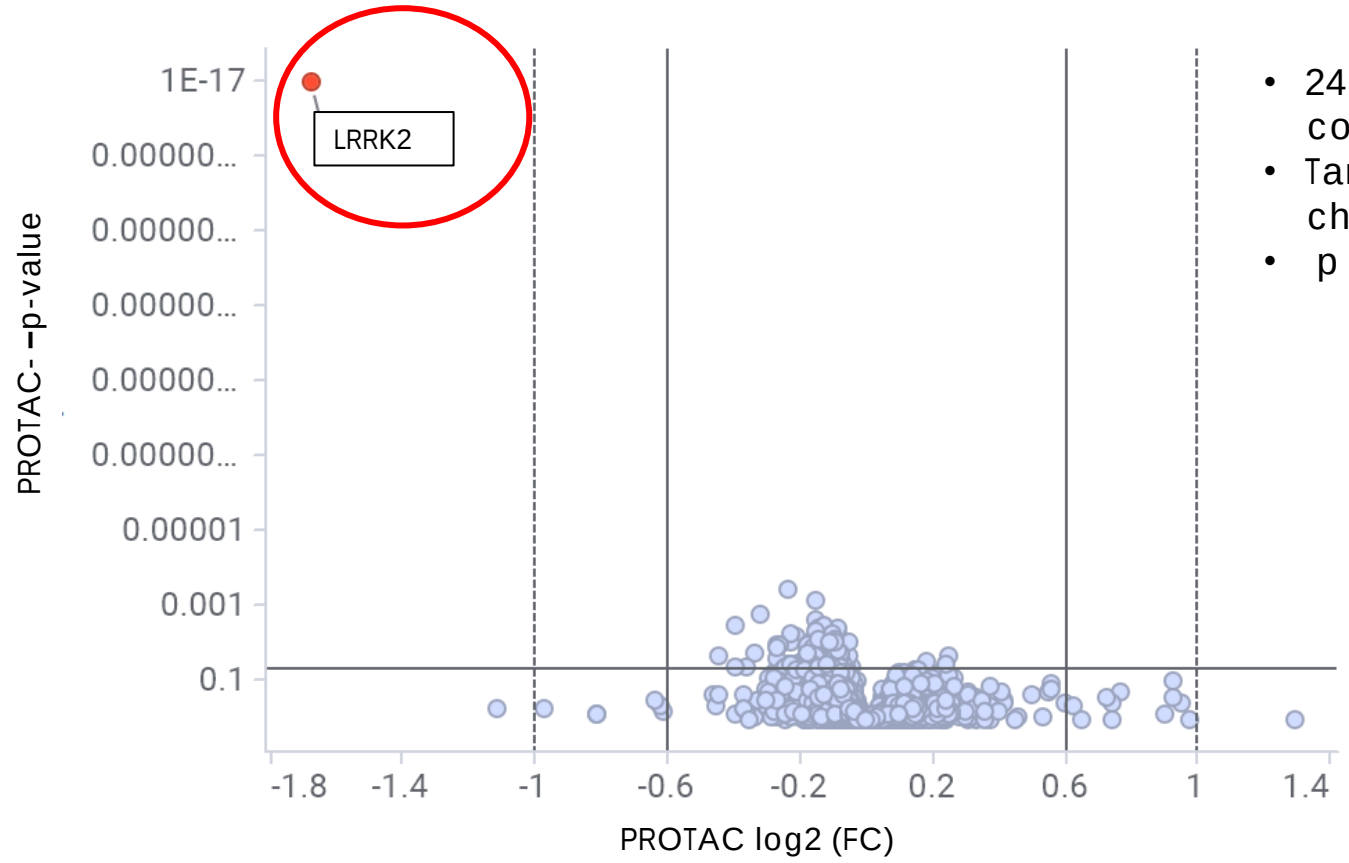
PROTAC advantage (event-driven pharmacology) results in iterative activity compared to kinase inhibition





Oral PROTAC® degrader molecule is highly selective in brain

PROTAC is a highly selective degrader molecule

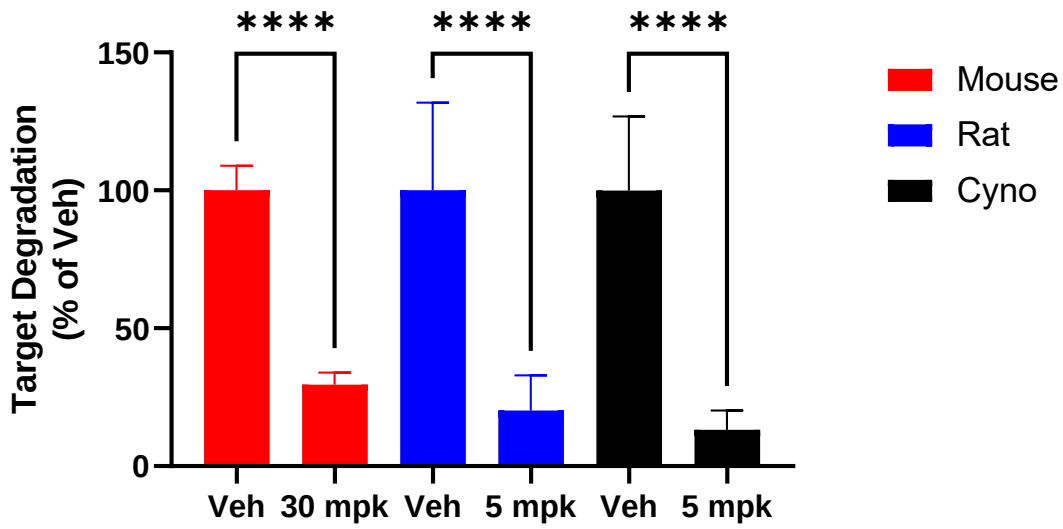


- 24-hour PROTAC vs vehicle control
- Target is most significantly changed protein in cortex
- $p > 10^{-17}$

TMT Proteomic analysis in brain 24 h following oral administration

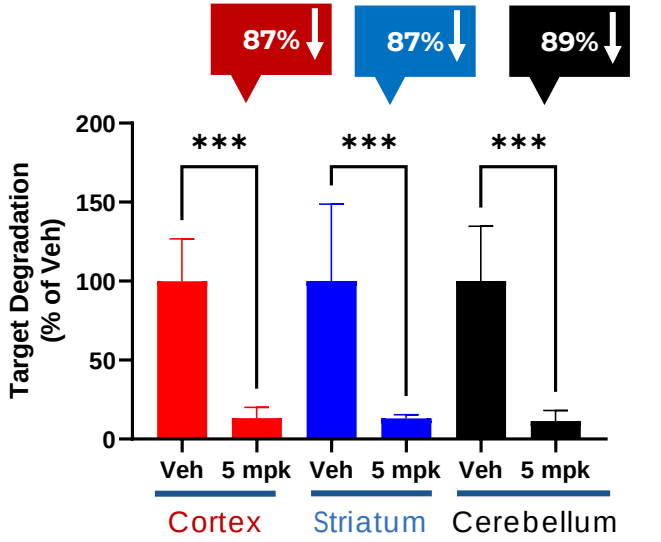
Oral LRRK2 PROTAC® induced degradation with biodistribution to deep anatomic brain regions in Primates

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



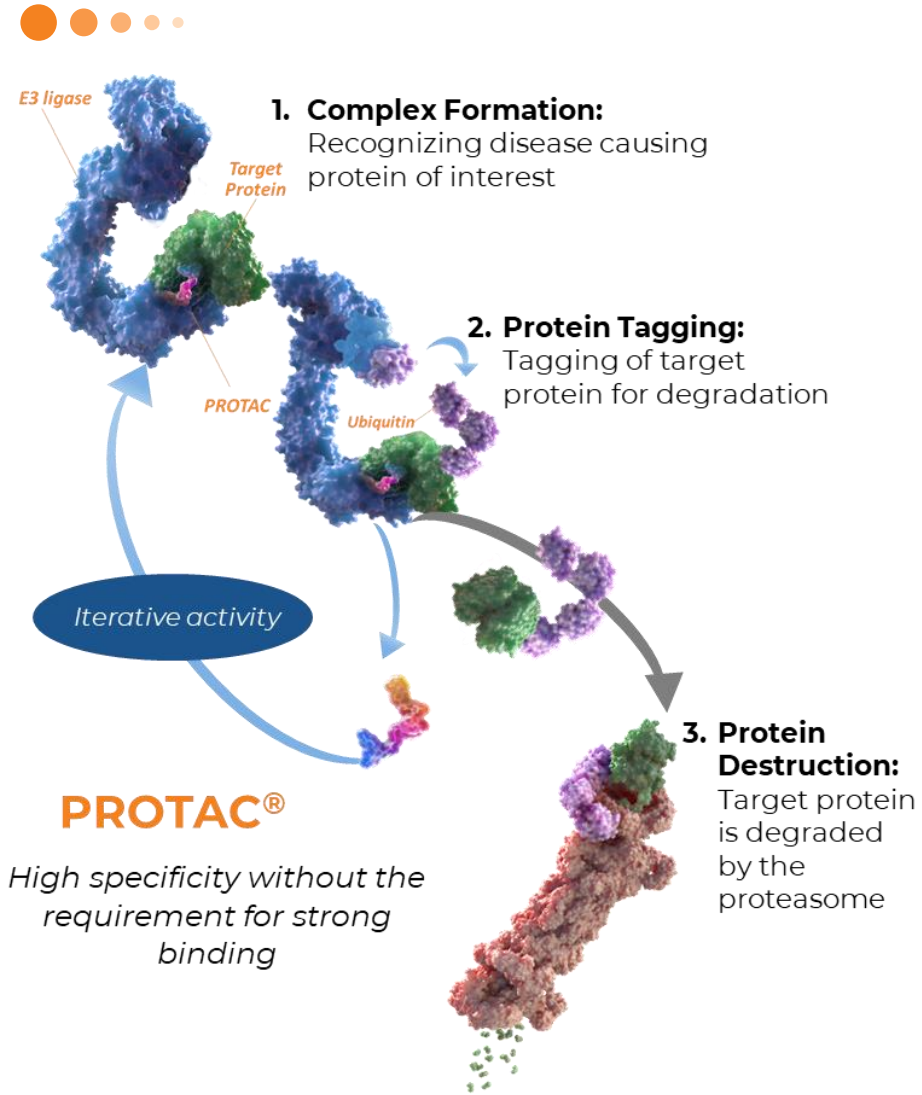
Robust biodistribution in cynomolgus monkey brain after oral dosing (cortex, cerebellum, & striatum)

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



*** p <0.0001

PROTAC® degraders could revolutionize the treatment of patients with neurological diseases (combining the benefits of small molecules and gene-based knockdown technologies)

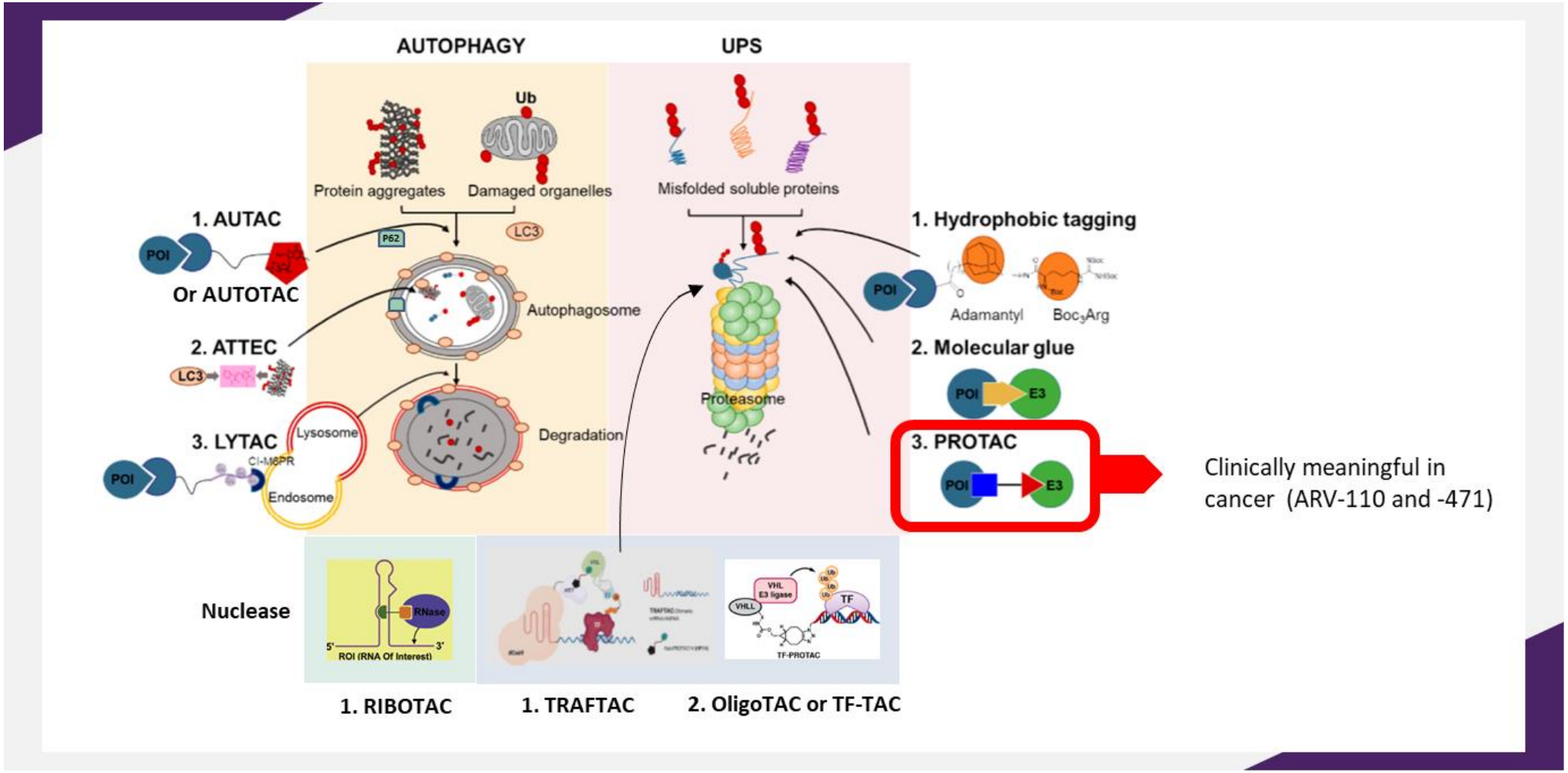


Arvinas' proteolysis-targeting chimera (PROTAC®) degraders can:

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

PROTAC degraders provide significant potential advantages over existing modalities

Emerging cellular protein degradation pathways and other chemical-biology targeted protein degradation approaches



Modified from: Hyun, S.et al., Life (2021), 11, 607; Samarasinghe KTG et al(2021) Cell Chem Biol., Zhang P et al(2021) J. Am.Chem. Soc., Li J et al(2021) J. Am.Chem. Soc ., Ji et al., (2022) Nat. Comm.

Thank you- Team Arvinas!