Clearance of Pathologic Proteins in Neurodegeneration by Heterobifunctional Degrader Molecules

NYAS- Neurodegeneration and Proteostasis

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ARVINAS
The PROTAC® Company

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 development and regulatory status of our product candidates, such as statements with respect to our lead product candidates, ARV-110, ARV-471 and ARV-766 and other candidates in our pipeline, and the timing of clinical trials and 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 and therapeutic potential of our product candidates, the potential commercialization of any of our product candidates, the potential benefits of our collaborative partnerships, and the Bayer joint venture, 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: whether we will be able to successfully conduct Phase 1/2 clinical trials for ARV-110 and ARV-471, initiate and complete other clinical trials for our product candidates, and receive results from our clinical trials on our expected timelines, or at all, whether our cash resources will be sufficient to fund our foreseeable and unforeseeable operating expenses and capital expenditure requirements, each party’s ability to perform its obligations under our collaborations and/or the Bayer joint venture, our expected timeline 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 quarterly and annual 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.

Arvinas: Advancing a new therapeutic modality to patients

PROTEIN DEGRADATION

- PROTAC® (proteolysis-targeting chimeras) protein degraders **eliminate** vs. inhibit disease-causing proteins
- Combines the power of genetic knockdown technology with the benefits of small-molecule therapeutics

PIPELINE

2 Programs in Phase 2
Clear efficacy signals in patients with difficult-to-treat breast and prostate cancers

1 Program in Phase 1

20+ Pipeline Programs
in oncology, I-O, and neuroscience

ARVINAS

290+ team members

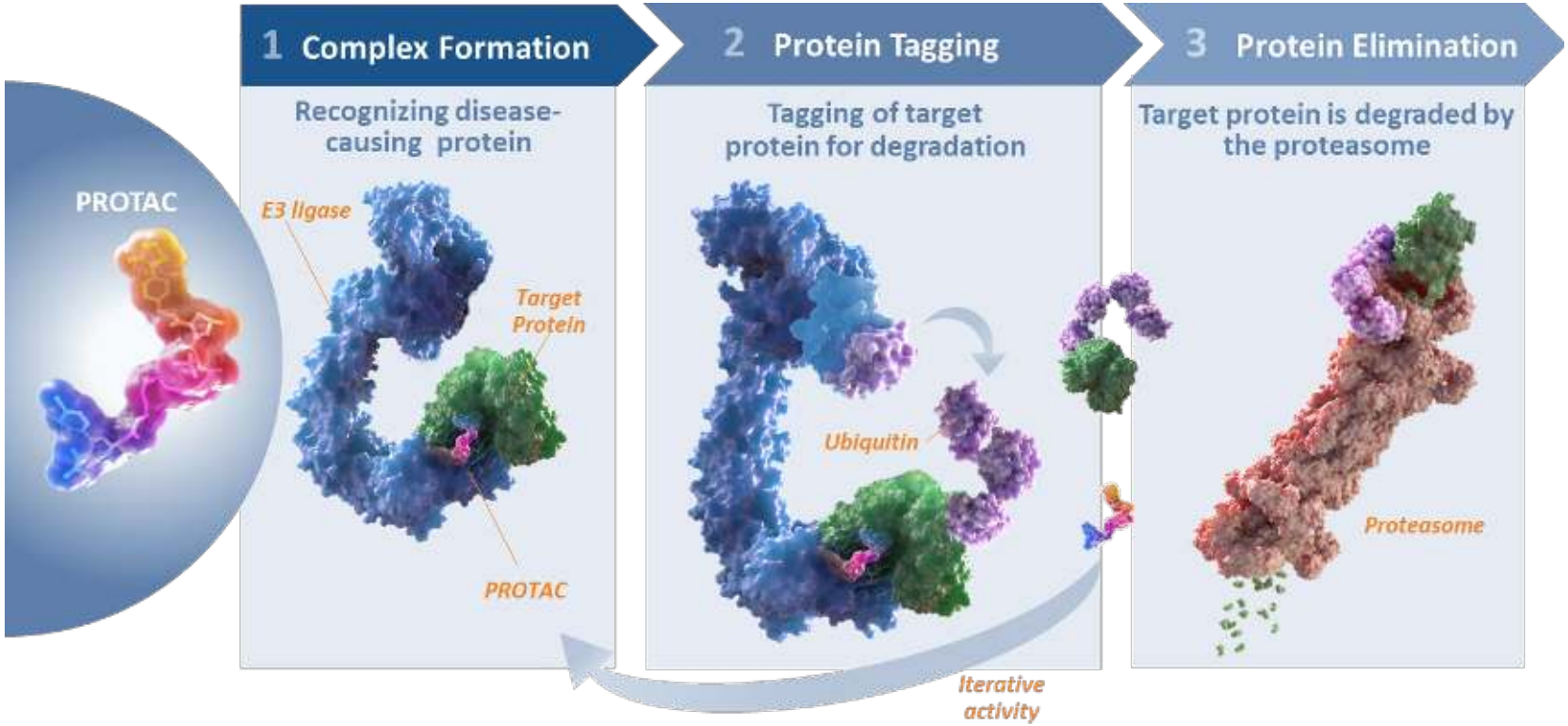
- Founded in 2013 by the original PROTAC pioneer
- Protein degradation platform with clinical proof of concept

PARTNERED FOR SUCCESS

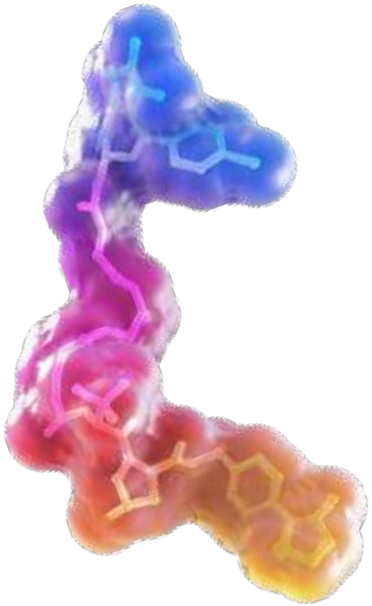
ARVINAS Pfizer

Global collaboration with Pfizer to co-develop and co-commercialize ARV-471 in ER+ breast cancer announced in July 2021

PROTAC® protein degraders harness the ubiquitin-proteasome system to induce the degradation of disease-causing proteins



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



PROTAC protein degraders have distinct advantages over both small molecule inhibitors and gene-based medicines	PROTAC Protein Degraders	Small Molecule Inhibitors	Gene-Based Medicines
Eliminate disease-causing proteins	✓		✓
Disrupt scaffolding function	✓		✓
Potential to treat “undruggable” proteins	✓		✓
Iterative mechanism of action	✓		
Broad tissue penetration	✓	✓	
Oral dosing	✓	✓	
Ease of manufacturing	✓	✓	

Developing therapeutics for validated and “undruggable” targets

	Program	Indication	Preclinical	Phase 1/1b	Phase 2	Phase 3	Next milestone
Oncology / Immuno-Oncology	ARV-471 Global co-development and co-commercialization partners with Pfizer	ER+/HER2- Breast Cancer	ARV-471 monotherapy dose escalation (2L+)				*Completed*
			ARV-471 + IBRANCE® (palbociclib) (1L)				Phase 1b data (2022)
			ARV-471 VERITAC monotherapy dose expansion (2L+)				Final Phase 2 data (2022)
	Bavdegalutamide (ARV-110)	mCRPC	Bavdegalutamide monotherapy dose escalation (2L+)				*Completed*
			Bavdegalutamide ARDENT monotherapy dose expansion (2L+)				Final Phase 2 data
			Bavdegalutamide + abiraterone (2L+)				Phase 1b data
	ARV-766	mCRPC	ARV-766 monotherapy dose escalation (2L+)				Phase 1 data (2022)
	AR-V7†, BCL6, KRAS-G12D/V†, Myc†, HPK1	Solid and haematological malignancies					4 INDs through 2023
Neuro	Tau†, α-Synuclein, mHTT	Neurodegenerative Disorders					

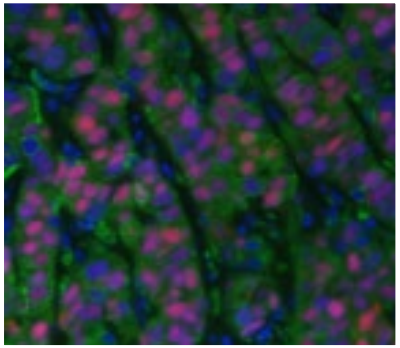
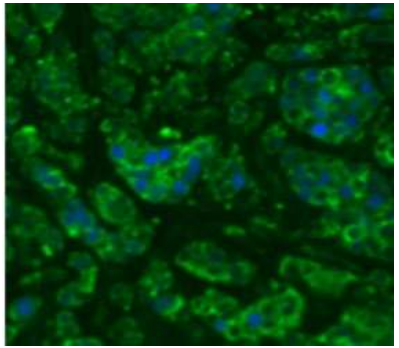
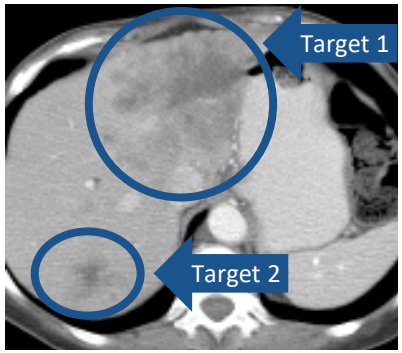
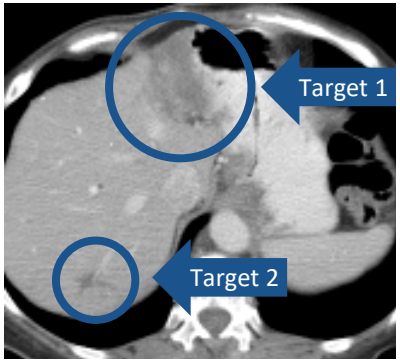
Note: Pipeline is non-exhaustive

† Denotes historically undruggable proteins; †† Trial may potentially be part of a planned umbrella study with Pfizer to explore multiple combination agents

mCRPC, metastatic castration-resistant prostate cancer; ER+/HER2-, estrogen receptor+/human epidermal growth factor receptor 2-; IND, investigational new drug

The Ultimate Platform Validation: PROTAC®s have the potential to be Drugs

***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

Data as presented 12/14/2020

ER degradation tumor biopsies

51% reduction in target lesions (RECIST partial response)

Integrated PROTAC® drug discovery for Neurology

Genetic Disease:
Protein is the cause of the disease

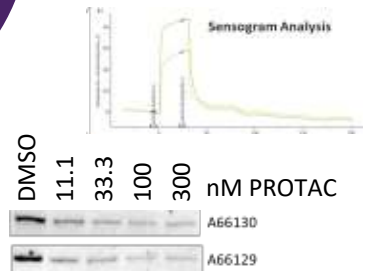
Translational Medicine:
Biomarkers support efficient path to assessing efficacy in humans

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

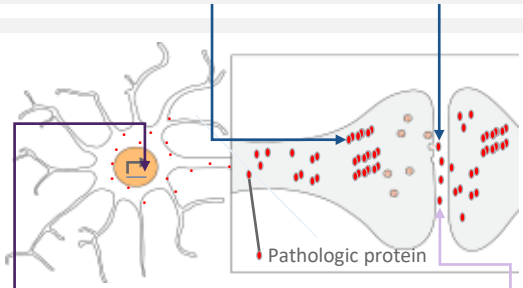


PROTAC® heterobifunctional degrader molecules create a strong opportunity in neuroscience compared to other modalities

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



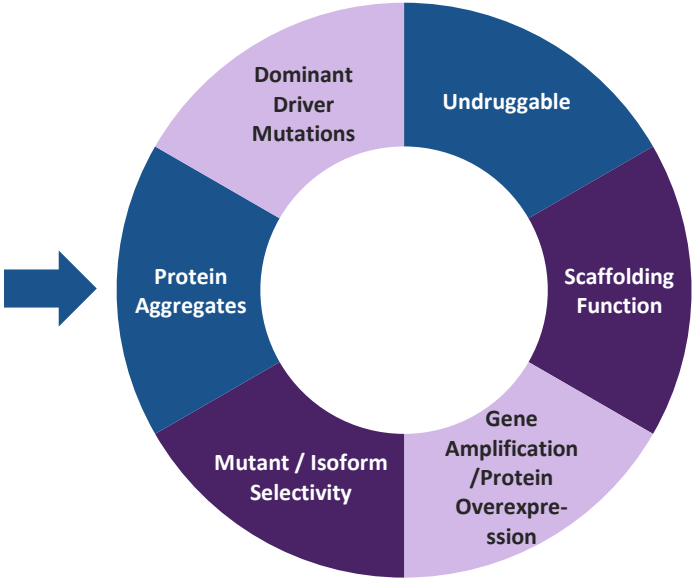
ASO

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

Ab

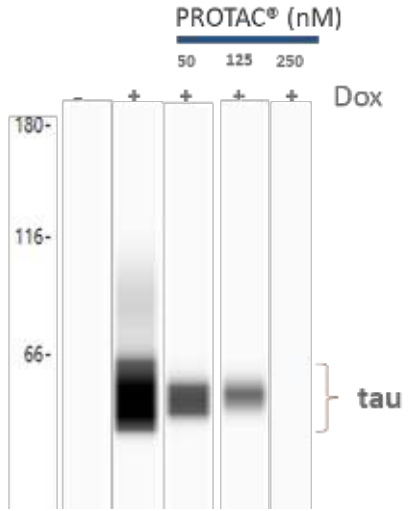
- Blocks only extracellular pathologic protein
- IV dosing results in only 0.5% in CSF

PROTAC *Tenets -- Differentiation from small molecule inhibitors*



PROTAC® small molecules can degrade tau P301L insoluble aggregates

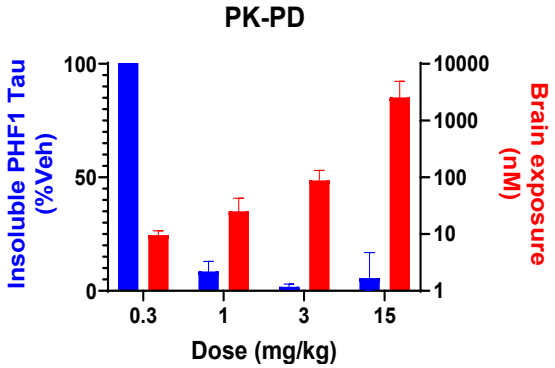
In vitro insoluble tau PROTAC degradation



*on mechanism

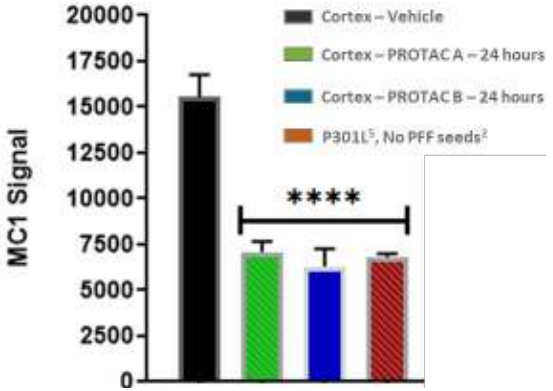
In vivo insoluble tau PROTAC degradation

Tg2508 24h post single PROTAC parenteral dose



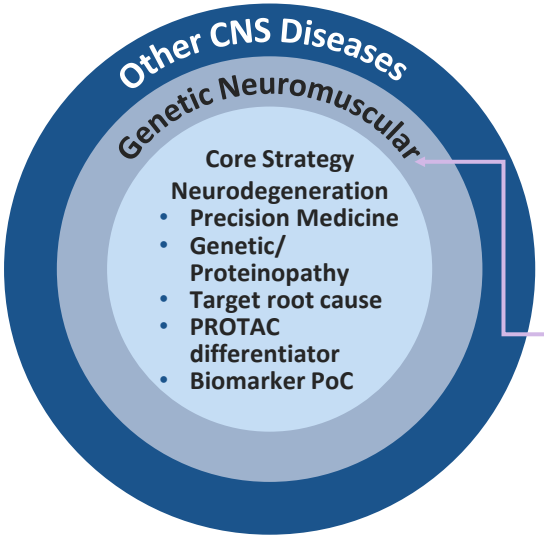
Reduced Seed Potential Ex vivo brain extracts

Tg2508 brain extracts 24h post single parenteral dose

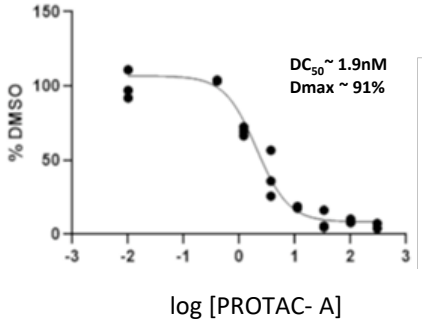


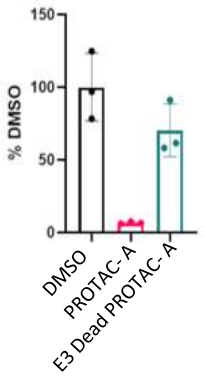
Neuromuscular Diseases: PROTAC® degraders remove toxic aggregating protein within muscle cells

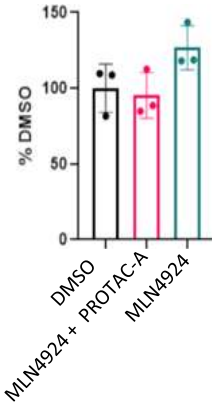
Fit with Neuroscience Strategy



PROTAC degrades toxic aggregating protein in iPSC- myotubes from patients and is on mechanism.



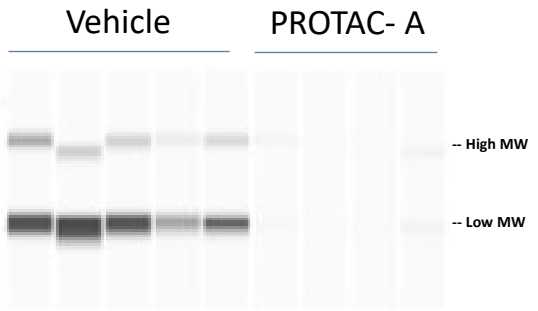




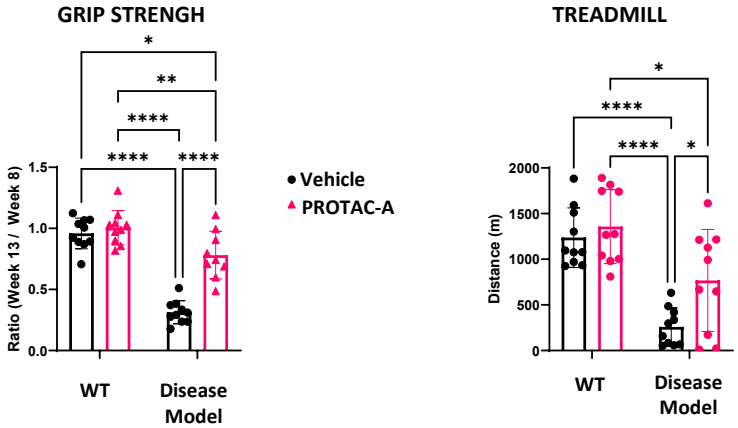
Neuromuscular Diseases: PROTAC® degraders remove toxic aggregating protein within muscle resulting in improved functional effect

PROTAC degrades toxic aggregating protein in muscle following oral administration in a disease mouse model, increased lifespan (data not shown), improves function (grip strength) and endurance (treadmill).

Neuromuscular degeneration Mouse Model (3xQD PO)

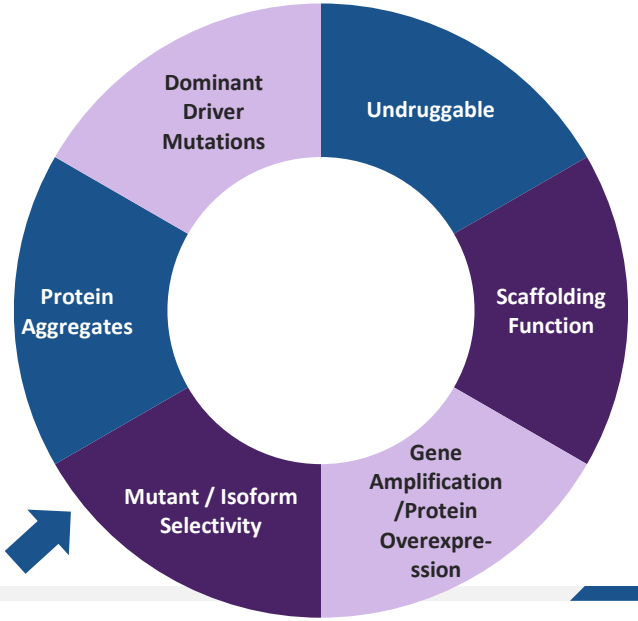


Neuromuscular degeneration Mouse Model (PROTAC A chronic oral administration) improves function and endurance

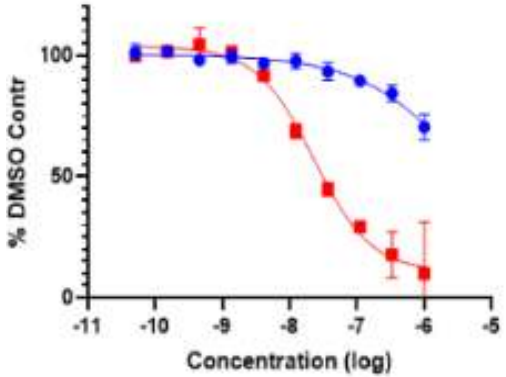


PROTAC® targets mutant and spares WT to tackle genetically defined disease target in CNS

Fit with Tenets of PROTACs



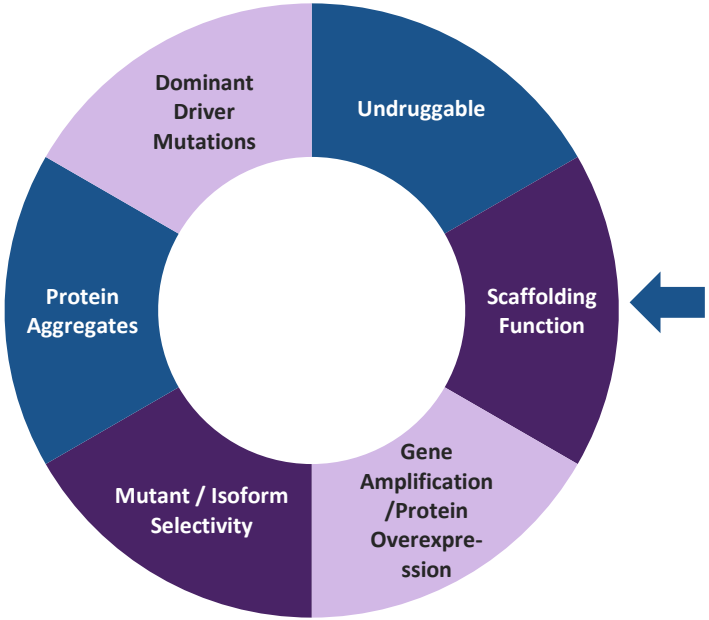
PROTAC selectively degrades mutant and spares WT protein



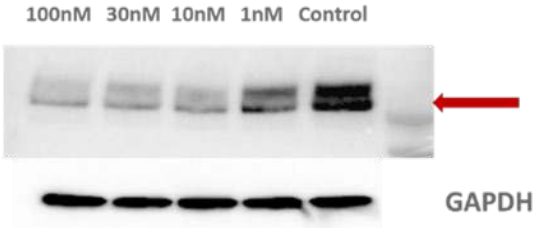
WT DC_{50} >5µM
Mutant protein DC_{50} = 23nM

PROTAC®-B is on mechanism and degrades endogenous target in iPSC-derived microglia

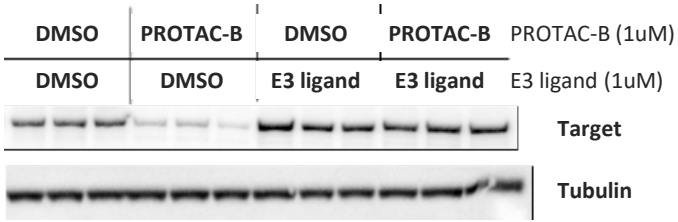
Fit with Tenets of PROTACs



PROTAC-B degrades endogenous target in iPSC-derived microglia

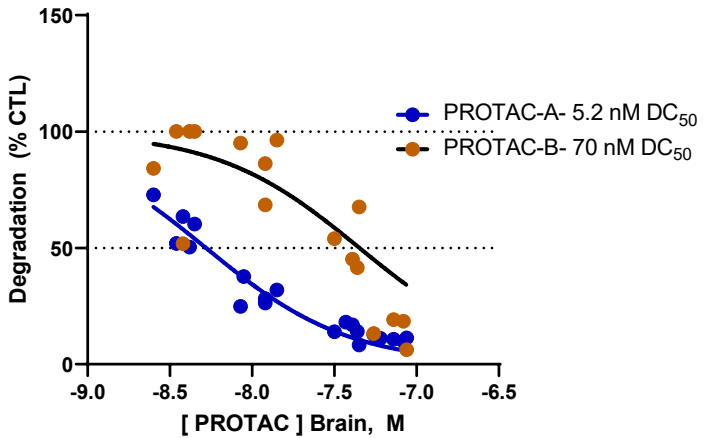


PROTAC-B degrades endogenous target and is on Mechanism

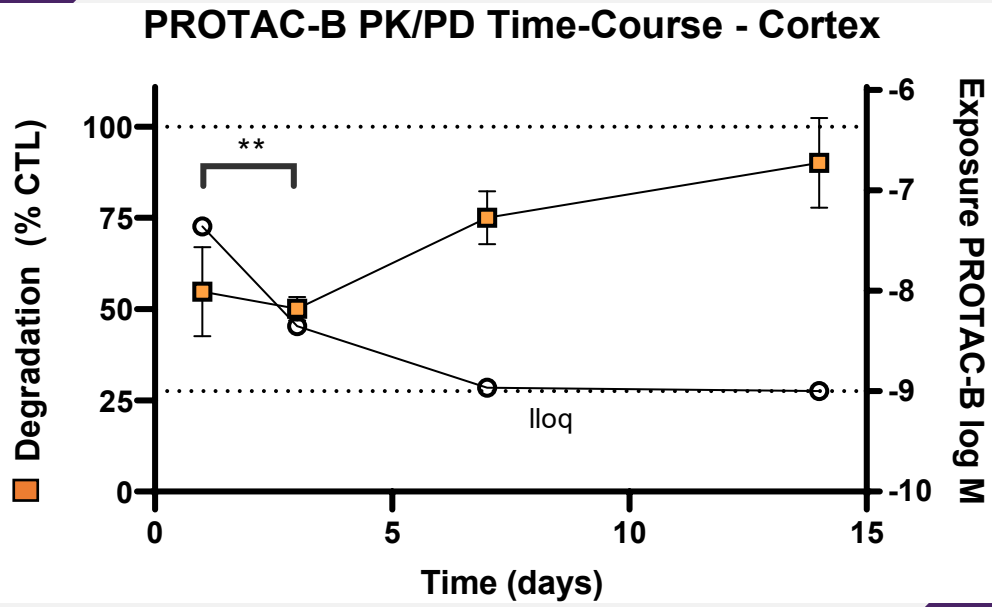


PROTAC®-B dose-dependently and durably degrades target in brain 24h following single oral administration

PROTAC-A and B Dose-Response PK/PD In Cortex 24h post dose

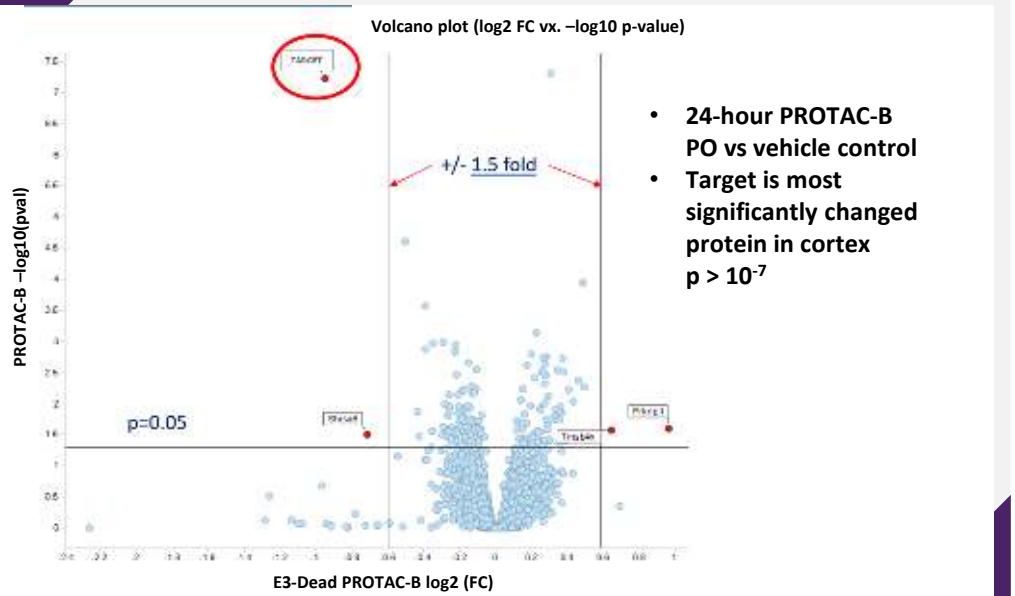


PROTAC-B PK/PD In Cortex following time-course



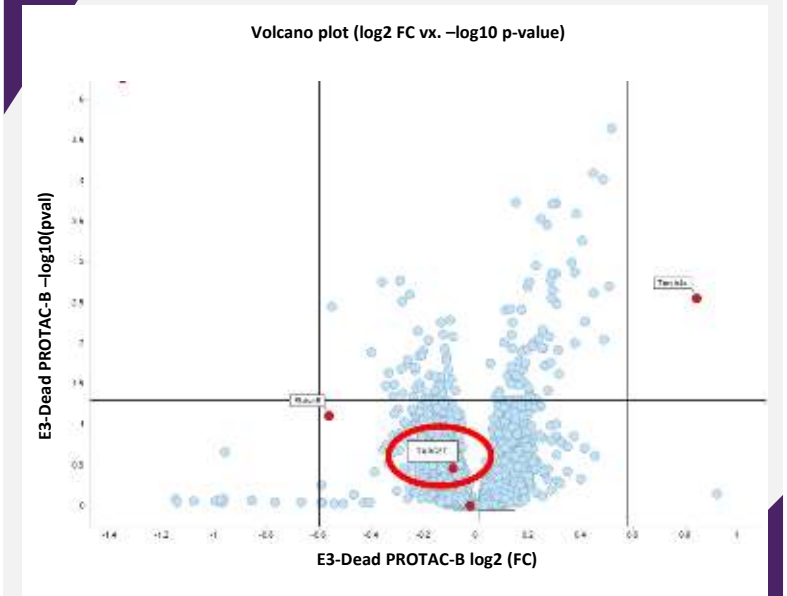
PROTAC®-B is on-mechanism and highly selective by proteomic analysis in brain following oral administration

Proteomic analysis of Cortex following 24h post single oral dose demonstrates PROTAC- B is a highly selective degrader molecule

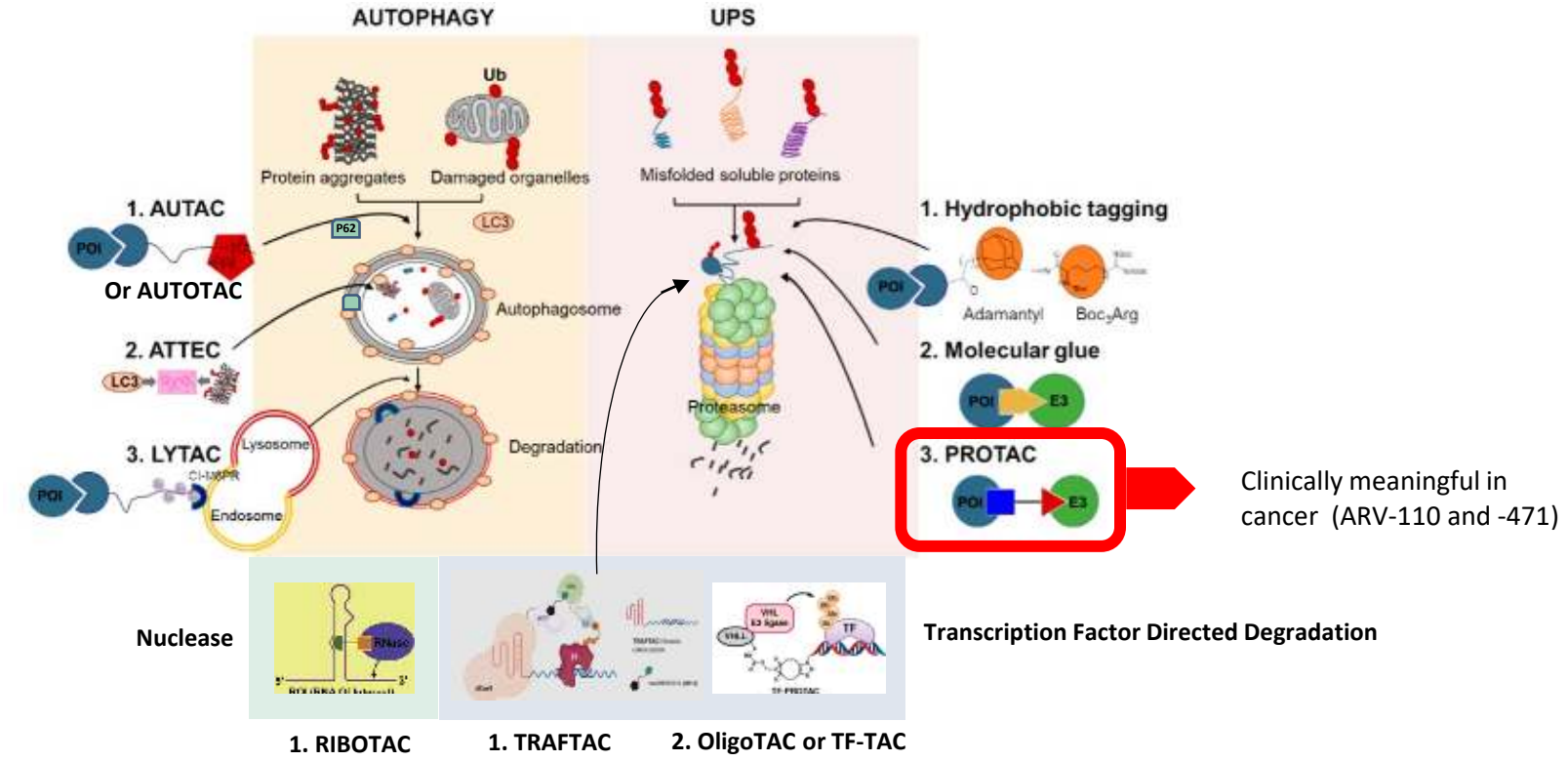


- 24-hour PROTAC-B PO vs vehicle control
- Target is most significantly changed protein in cortex $p > 10^{-7}$

E3-Dead PROTAC-B does not degrade target in Cortex 24h post oral dose



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



Clinically meaningful in cancer (ARV-110 and -471)

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 to the fantastic team at Arvinas!!! Join us!

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Arvinas, Inc.

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