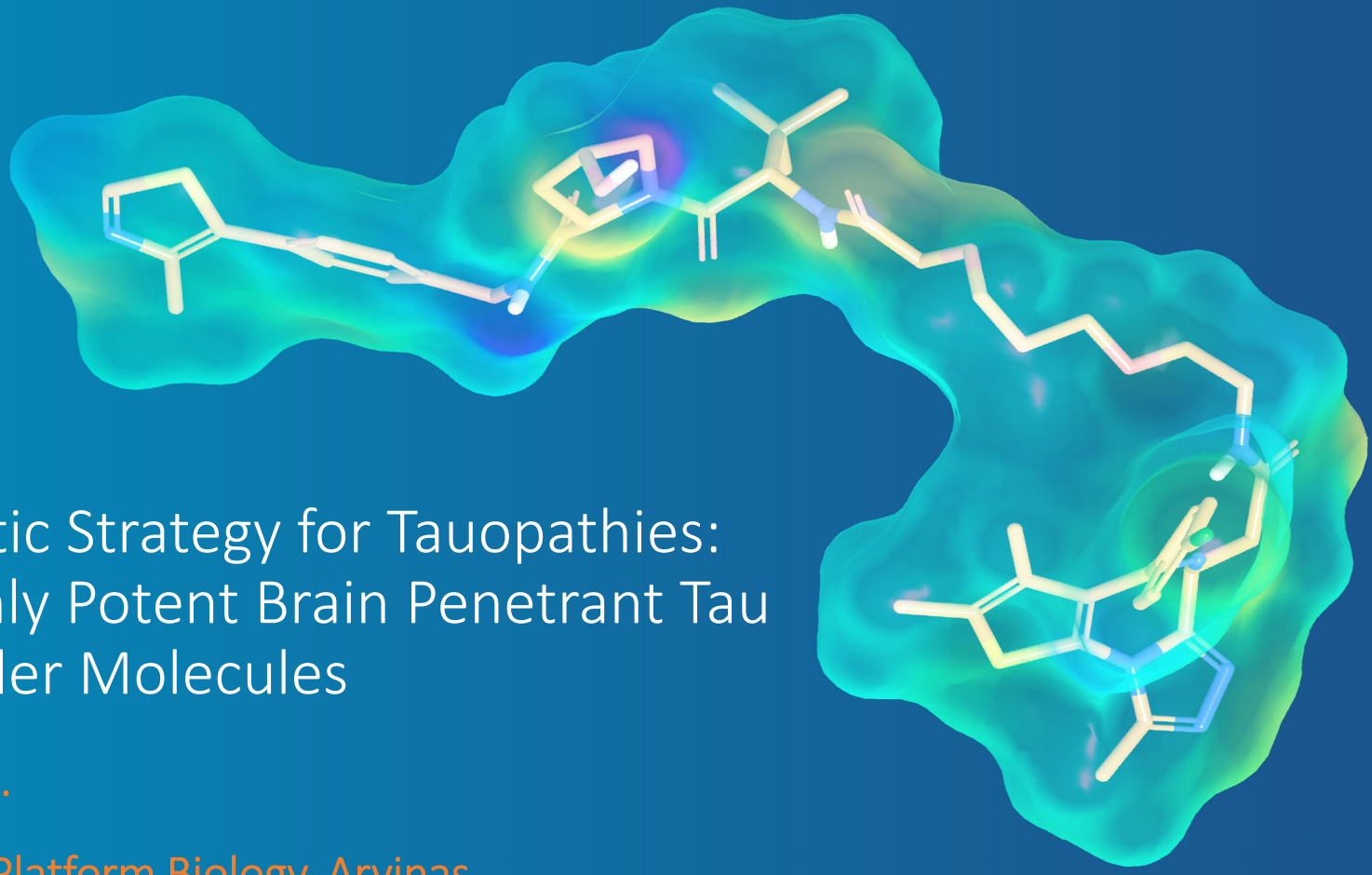

A New Therapeutic Strategy for Tauopathies: Discovery of Highly Potent Brain Penetrant Tau PROTAC ® Degrader Molecules

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VP Neuroscience & Platform Biology, Arvinas

July 18, 2019

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 and ARV-471, and the timing of IND submissions and clinical trials 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 product candidates, the potential commercialization of any of our product candidates, the potential benefits of our arrangements with Yale University and our collaborative partnerships, 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 a Phase 1 clinical trial for ARV-110, successfully initiate and conduct a Phase 1 clinical trial for ARV-471, 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, 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 with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law.

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Our Mission

To ***create a new class of drugs*** which *degrade pathogenic proteins* to ***treat diseases*** *with* ***serious unmet medical need*** and ***improve human health***

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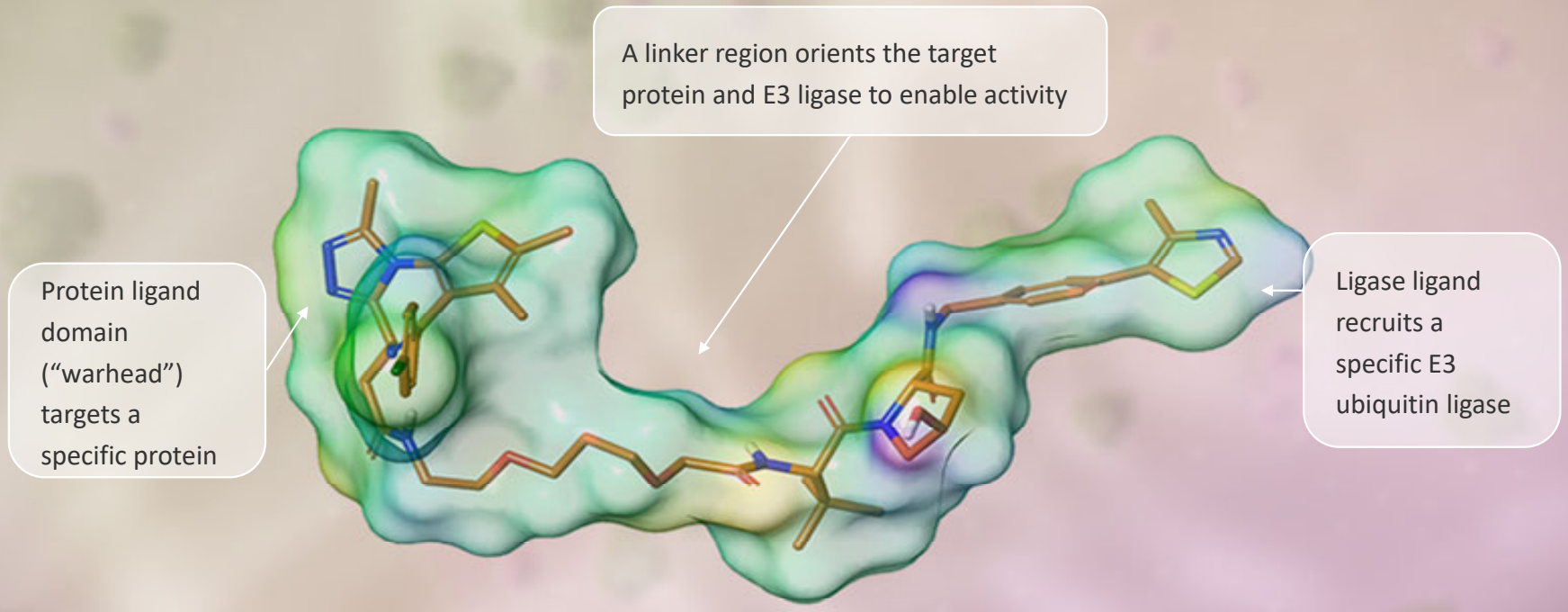
What is a PROTAC® Protein Degrader?

A proteolysis-targeting chimera (PROTAC®) degrader is a chimeric, modular small molecule engineered to induce the degradation of disease-causing proteins by the ubiquitin-proteasome system



All three regions of the PROTAC® degrader play a role in the specificity and potency of target degradation

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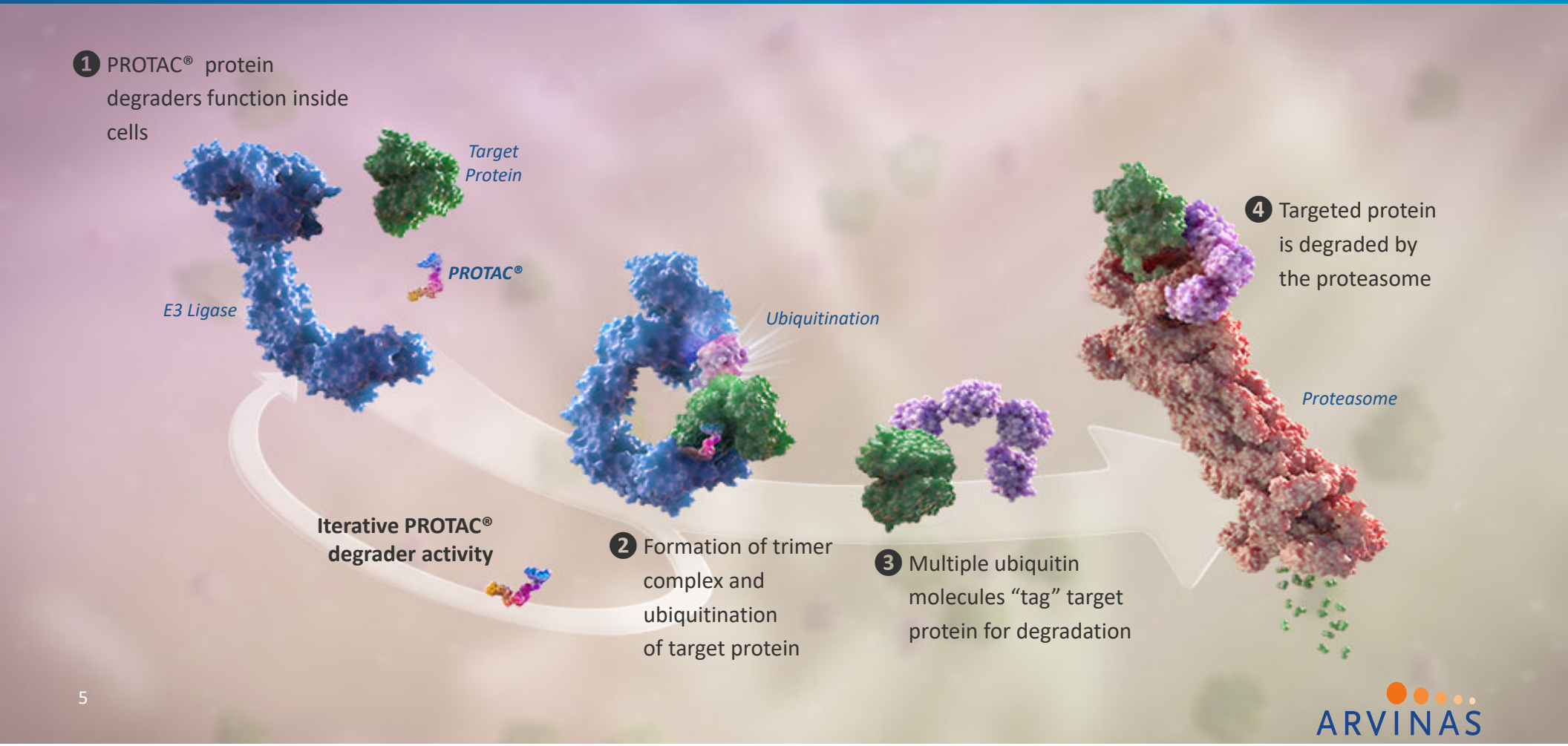
PROTAC® Protein Degraders Harness the Ubiquitin-Proteasome System to Induce the Degradation of Disease-Causing Proteins



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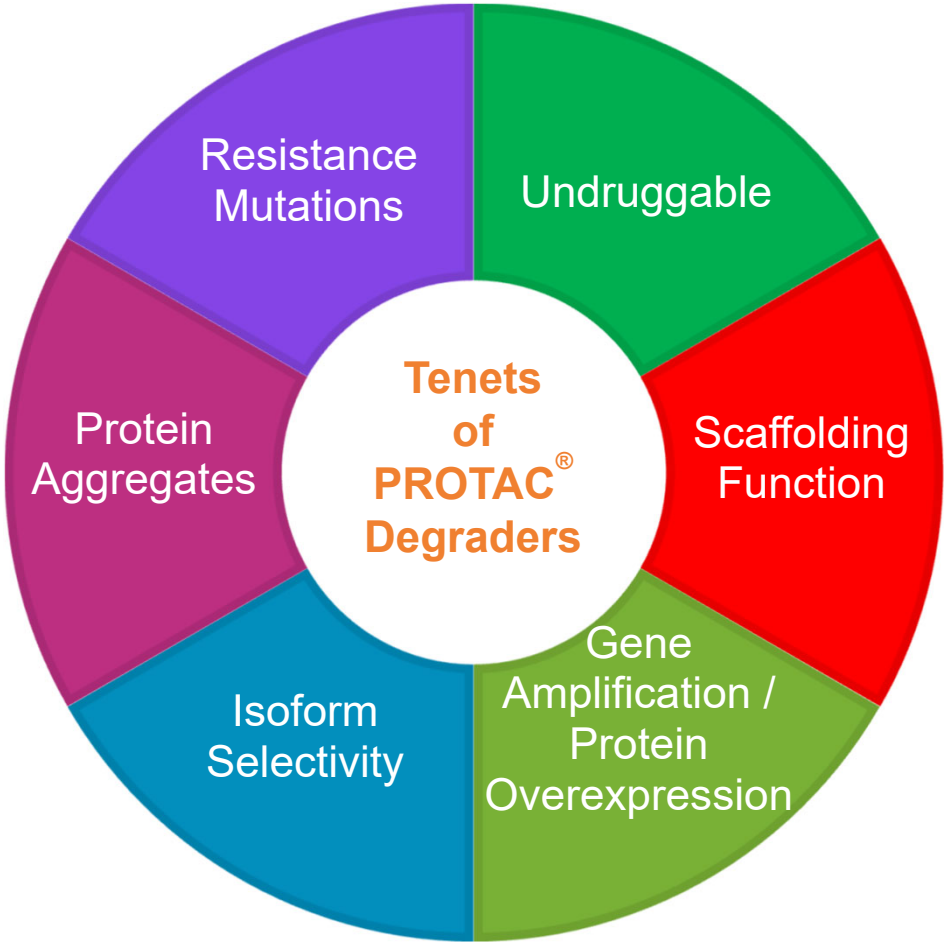
The "Tenets of PROTAC® Degraders"

Areas where the PROTAC mechanism of action is particularly well-suited



PROTAC® technology has proven to be robust:

- Degrade >95% of proteins tested & has potential to degrade any unwanted protein
- Broadly applicable across target classes & therapeutic areas
- Successfully degraded proteins using many different E3 ligases
- Highly potent (picomolar) and selective (isoform, mutant, conformation)
- Process is rapid (hours) and durable (days-weeks)
- Optimized oral bioavailability and engineered to cross blood brain barrier

Provide strong differential biology compared to inhibitors and superior biodistribution compared to genomic approaches (ASOs, siRNAs, etc.)

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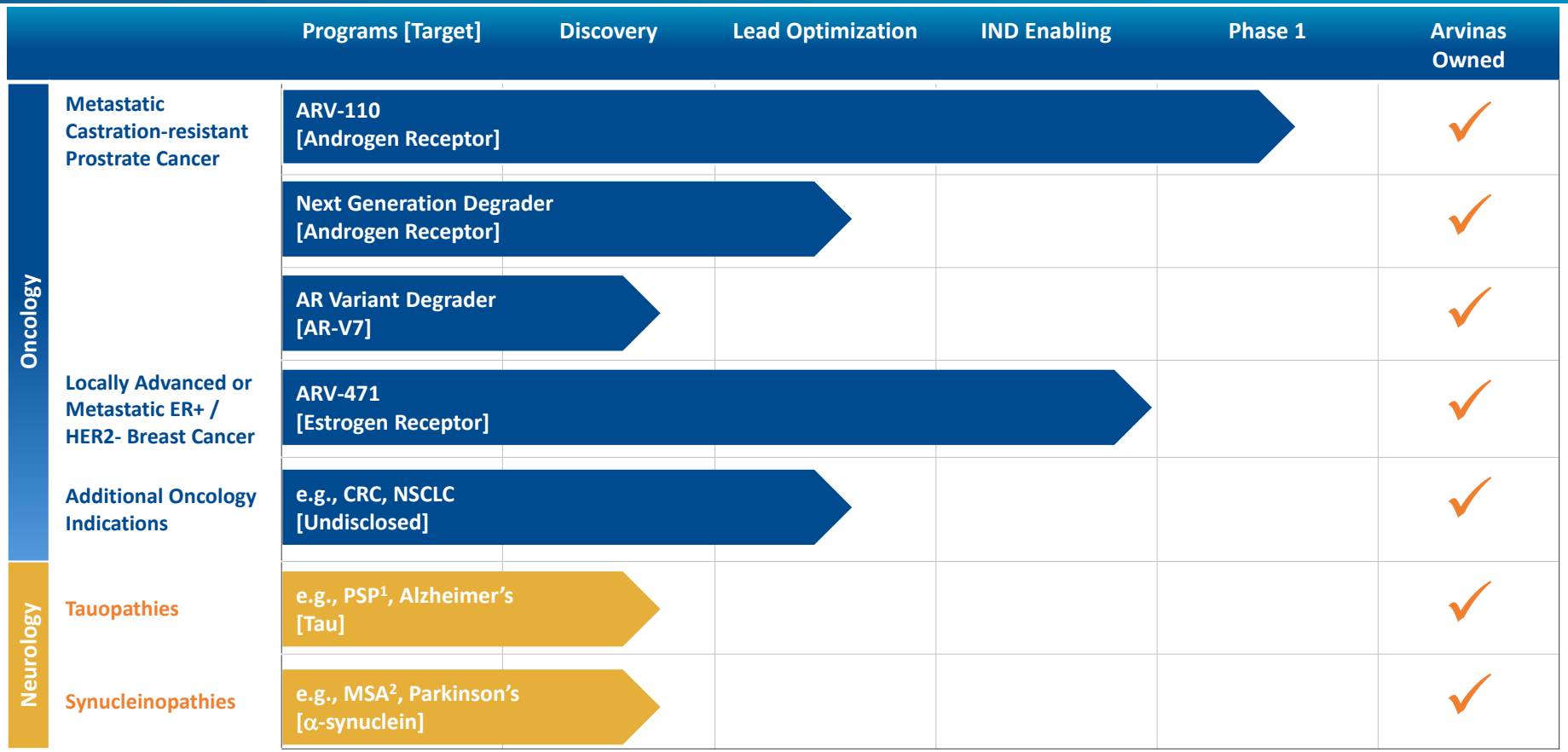
High potential PROTAC® pipeline, focused on cancer and neurology



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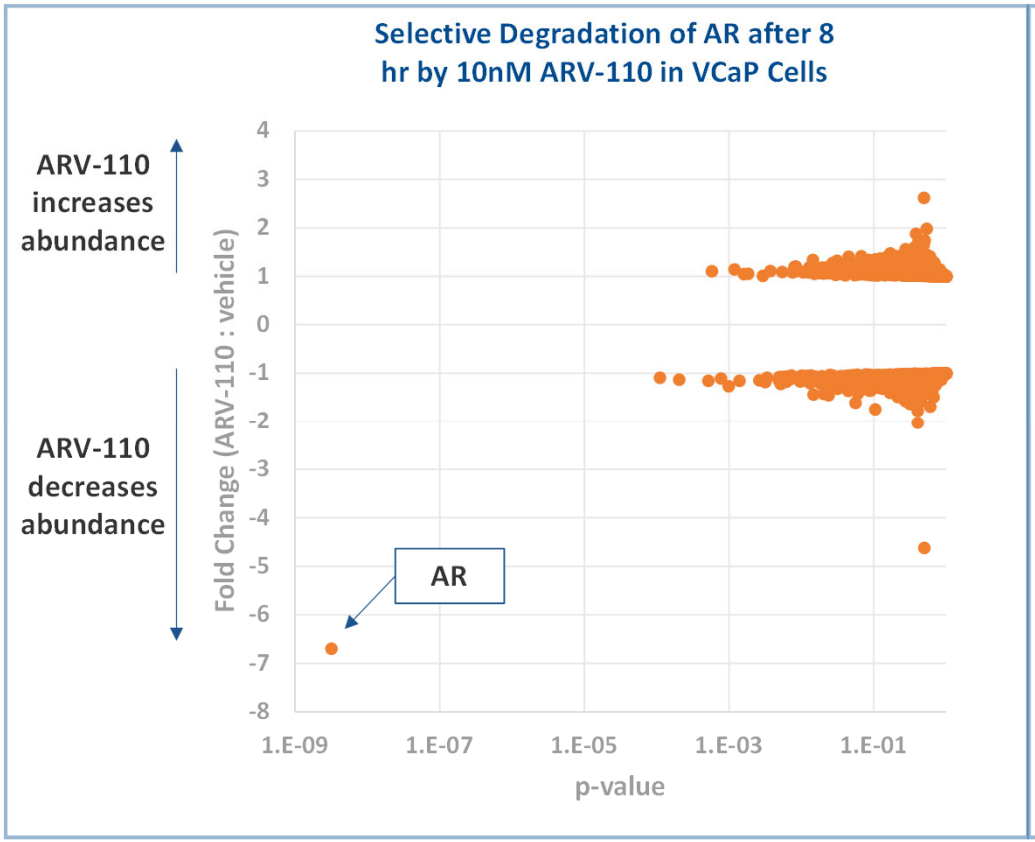
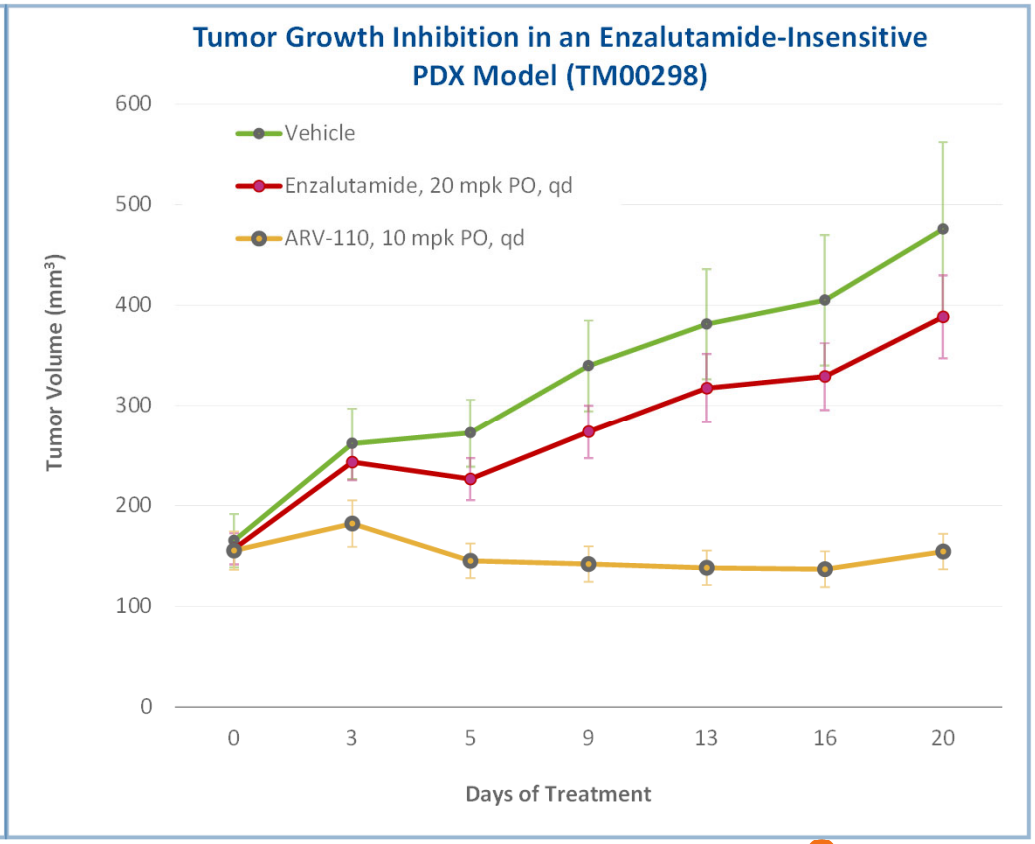
Oral Androgen Receptor-Targeting PROTAC® Degrader - ARV-110: Demonstrates Selective Degradation and Potent Tumor Inhibition





1 VCaP, Vertebral Cancer of the Prostate
2 D_{max}, maximal degradation

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Development Status

Preliminary clinical data for ARV-110 expected in 2H19

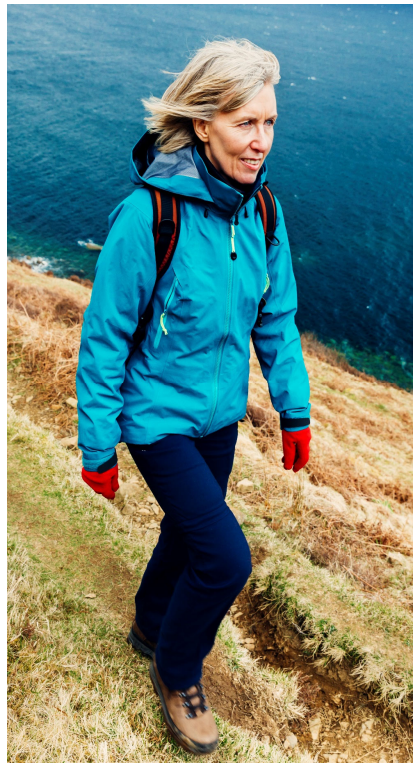
- Potential to be the first-in-class AR degrader
- Phase 1 clinical trial initiated in 1Q19
- Received FDA “Fast Track” designation in May 2019

Estrogen Receptor Degrader, ARV-471, IND cleared in 2Q-

Phase 1 to start 3Q

- Potential to be the first-in-class ER degrader
- For treatment resistant Estrogen Receptor dependent breast cancer
- FDA safe to proceed granted June, 2019

Programs wholly owned by Arvinas



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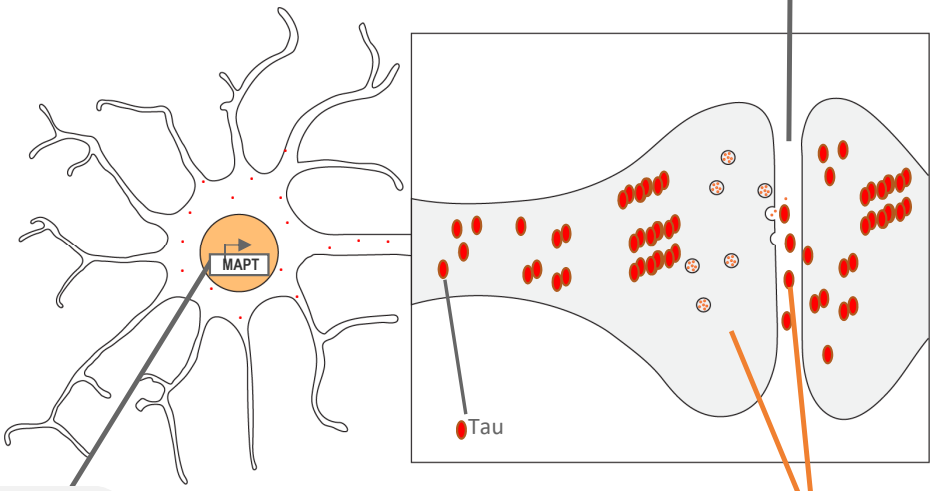
Why Are We Excited about the Opportunity for PROTAC® Degraders in Neurological Diseases?

- PROTAC® degraders may overcome the limitations of other platforms, including antisense oligonucleotides (ASO) and monoclonal antibodies (Ab)

Ab
- Blocks only extracellular pathologic tau
- IV dosing results in only 0.1% in CSF



ASO
- Degrades mRNA, impacting intra- and extracellular tau
- Does not discriminate between wild type and pathologic tau
- Requires intrathecal dosing

PROTAC® *Potential*
- Reduce intra- and extracellular pathologic tau
- Discriminate between wild type and pathologic tau
- Oral administration with BBB biodistribution

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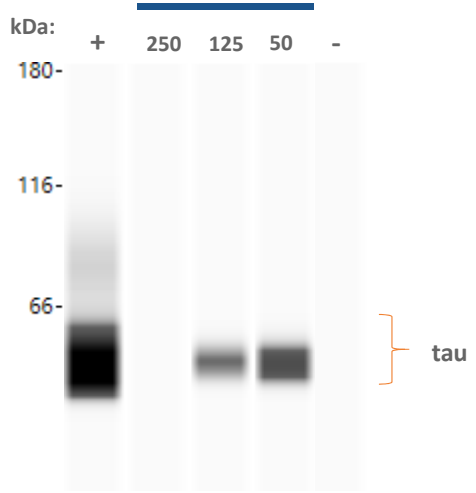
PROTAC® Targeted Molecules Degrade P301L tau *in vitro* are Potent and On-Mechanism

In vitro Potent tau PROTAC®

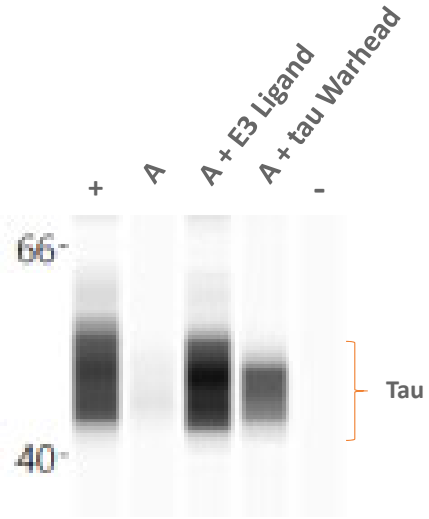
Degrade tau

DC50 <50nM



tau PROTAC® -on Mechanism

(competed by E3 Ligand and warhead)



(+) Dox induction of P301L Tau expression

(-) Absence of induction

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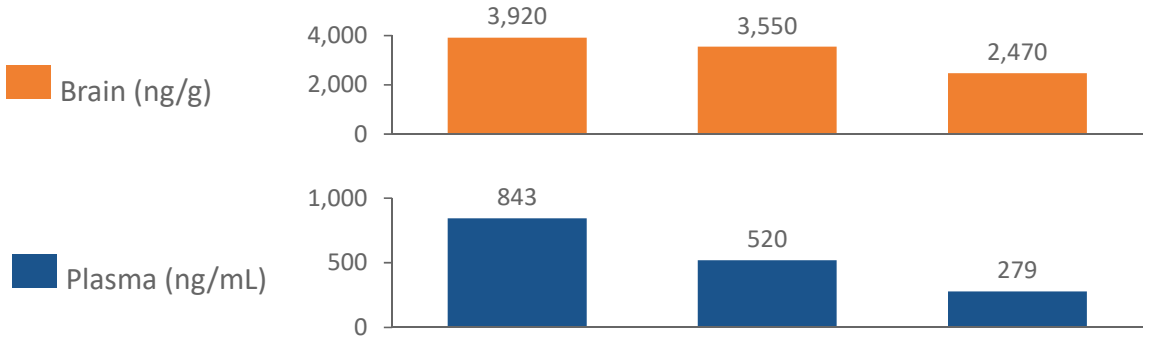
Successful Engineering of PROTAC® Degraders Have Enabled Crossing of the Blood-Brain Barrier (BBB) at micromolar levels

- Brain-to-plasma ratio >0.5 achievable with PROTAC® degraders

PROTAC®	Species	Dose (mg/kg)	[Plasma 1h] (ng/ml)	[Brain 1h] (ng/g)	B/P ratio
1	mouse	10	309	227	0.8
2	mouse	10	843	3920	4.7
3	mouse	10	285	1425	5.0

- Over a 4-hour time course, PROTAC® degraders are more durable in brain than plasma
- BBB-penetrant, active PROTAC® enable tau degradation studies in tauopathy rodent brain



Time (hours)	1	2	4
B/P Ratio	4.7	6.8	8.9

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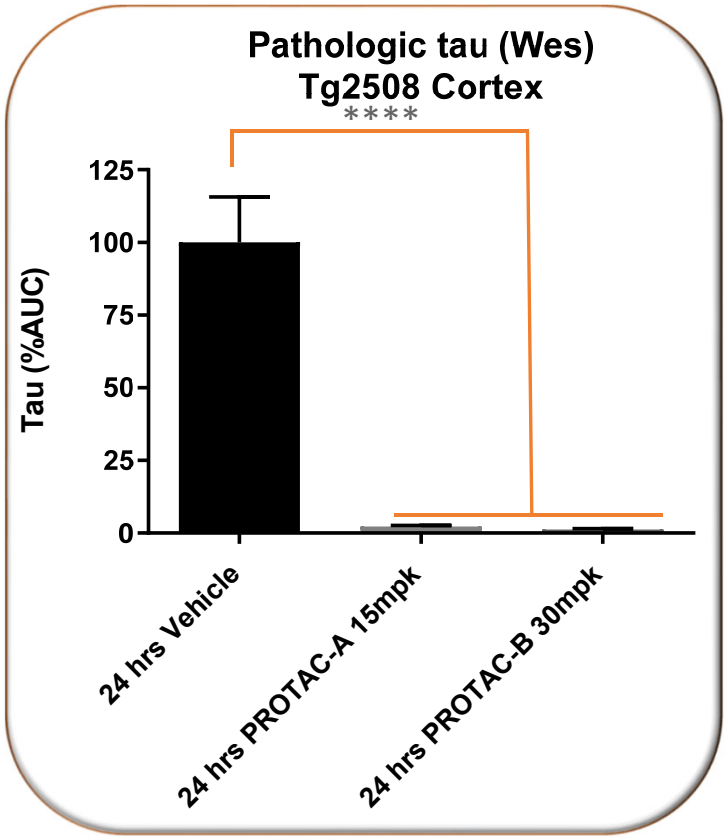
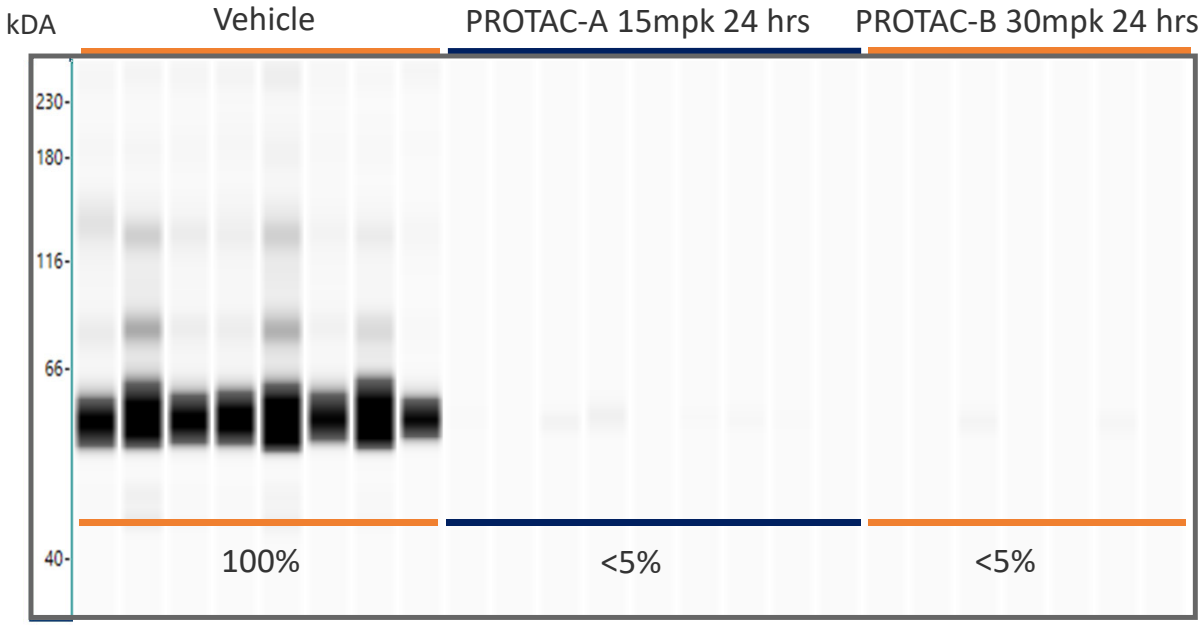
Multiple Tau PROTAC Lead Molecules Degrade >95% of Pathologic Tau in Tg2508 Brain Following Parenteral Administration *in vivo*



**** Tukey's multiple comparisons test P < 0.0001

Wes –Tau Detection



24 hr post dose:

- >95% of pathologic tau is degraded
- No significant change in total soluble tau 24 h post dose (data not shown)

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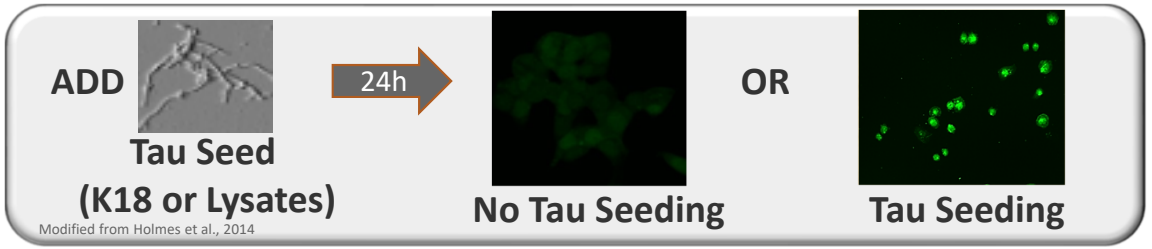
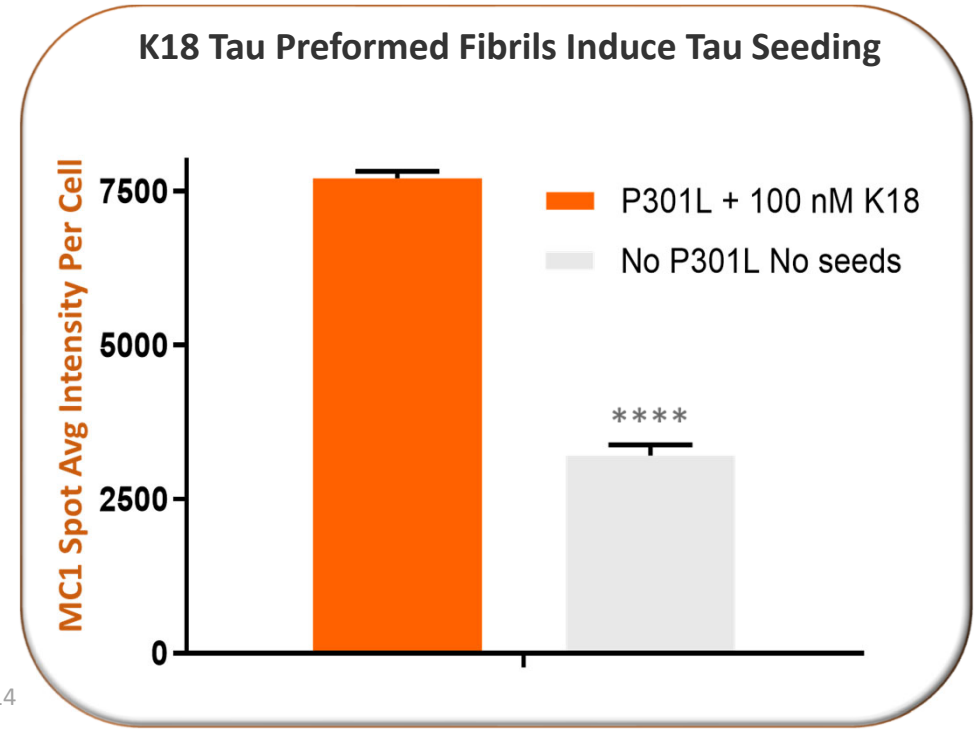
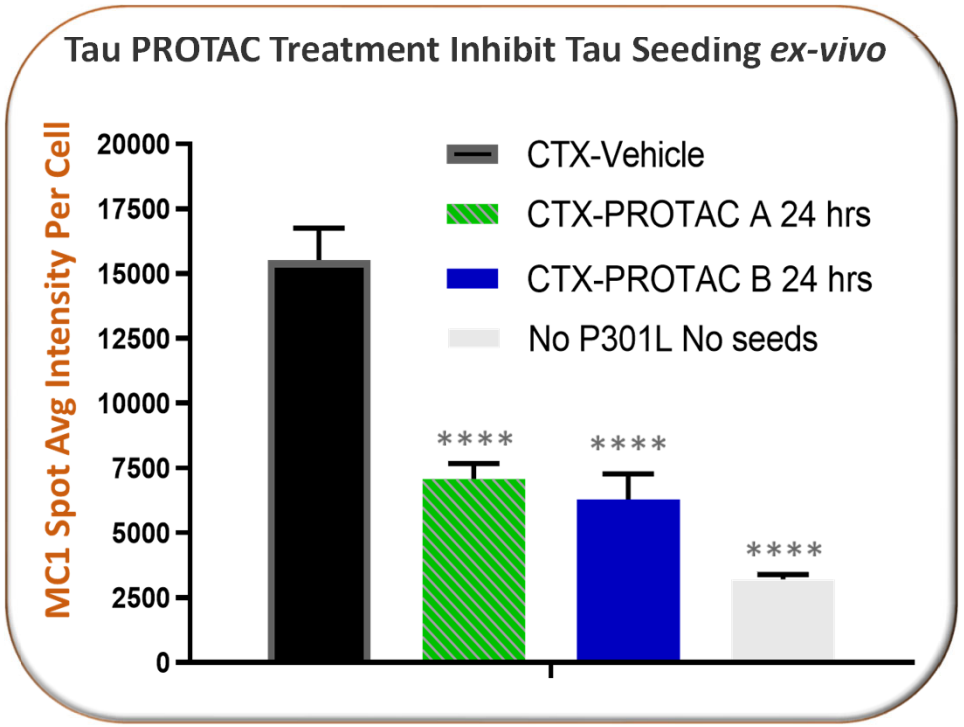
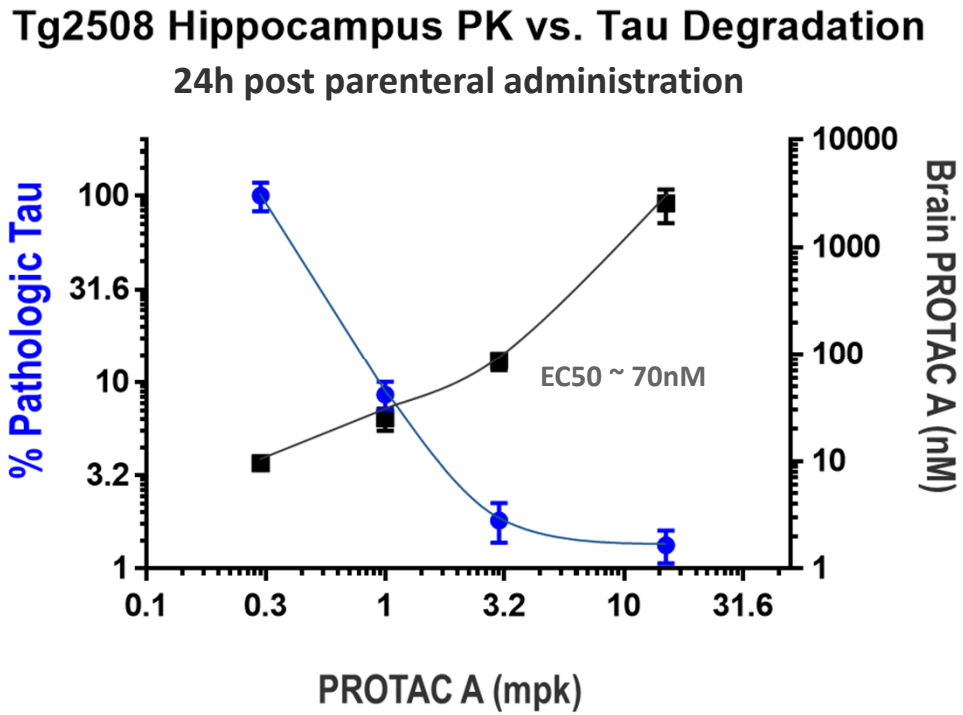
PROTAC tau Degraders Inhibit Tg2508 *ex-vivo* Seeding of P301L CHO MC1 High Content Assay







Tau PROTAC® Dose Dependently Reduce Tau (PK/PD) in the Brain of Tauopathy Mice



Aged animal studies are being executed to assess the ability of the proteasome to degrade pathologic tau (may be compromised in neurodegeneration/ age)

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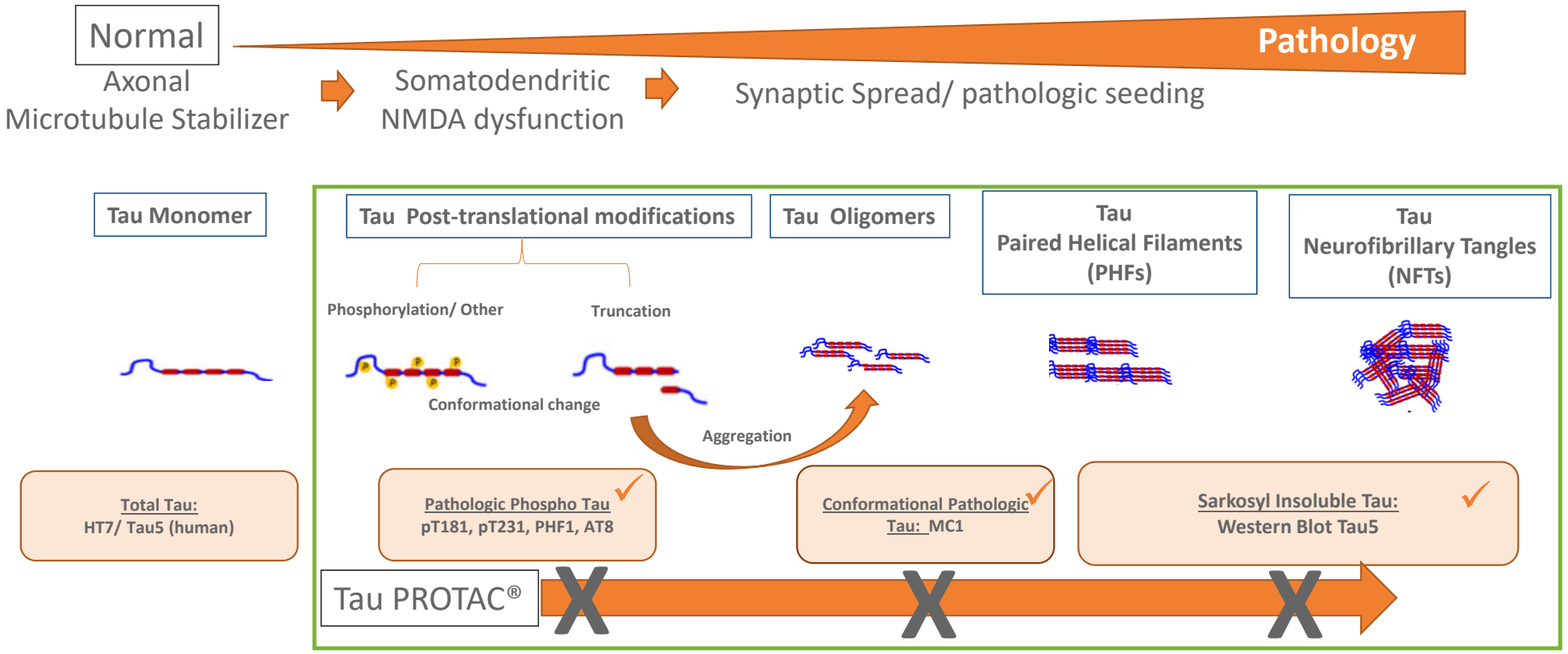
Tau Species Targeted by PROTAC® –Targets for Cell-Autonomous and Non-Cell-Autonomous Pathology



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Arvinas' Approach in Neurodegeneration

Approach: Prove the concept with PROTAC® degraders in defined populations while pursuing larger, multifactorial indications using accessible biomarkers

Conceptual

Tau	FTDP-17 (~3K)	Progressive supranuclear palsy (~20K)	ApoE4 AD risk allele carriers (~600-900K)	Alzheimer's (~6M)
α-synuclein	Synuclein mutations, e.g., duplication/ triplication (~4K)	Multiple systems atrophy (~50K)	GBA PD risk allele carriers (~500K)	Parkinson's (~1M)

Expanding our neurology portfolio to focus on 'monogenic' toxic-gain of function / neurodegenerative diseases

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Thank You &
Patients We Hope to Serve

Thank You Arvinas Team!
Julian Chandler
Michael Berlin
Lida Kimmel
Stefanie Keenan
John Flanagan
Yongqing Huang
Andy Crew
Ian Taylor
John Houston

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