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

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

- Protein ligand domain ("warhead") targets a specific protein
- A linker region orients the target protein and E3 ligase to enable activity
- Ligase ligand recruits a specific E3 ubiquitin ligase
PROTAC® Protein Degraders Harness the Ubiquitin-Proteasome System to Induce the Degradation of Disease-Causing Proteins

1. PROTAC® protein degraders function inside cells

2. Formation of trimer complex and ubiquitination of target protein

3. Multiple ubiquitin molecules “tag” target protein for degradation

4. Targeted protein is degraded by the proteasome

Iterative PROTAC® degrader activity
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.)
High potential PROTAC® pipeline, focused on cancer and neurology

<table>
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<tr>
<th>Programs [Target]</th>
<th>Discovery</th>
<th>Lead Optimization</th>
<th>IND Enabling</th>
<th>Phase 1</th>
<th>Arvinas Owned</th>
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<tr>
<td>Locally Advanced or Metastatic ER+ / HER2- Breast Cancer</td>
<td>ARV-471 [Estrogen Receptor]</td>
<td>e.g., CRC, NSCLC [Undisclosed]</td>
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<td>Additional Oncology Indications</td>
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<td>e.g., PSP, Alzheimer’s [Tau]</td>
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<td>e.g., MSA, Parkinson’s [α-synuclein]</td>
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Oral Androgen Receptor-Targeting PROTAC® Degrader - ARV-110: Demonstrates Selective Degradation and Potent Tumor Inhibition

Selective Degradation of AR after 8 hr by 10nM ARV-110 in VCaP Cells

Tumor Growth Inhibition in an Enzalutamide-Insensitive PDX Model (TM00298)

1 VCaP, Vertebral Cancer of the Prostate
2 D_max, maximal degradation
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**
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).

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

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

PROTAC® Potential
- Reduce intra- and extracellular pathologic tau
- Discriminate between wild type and pathologic tau
- Oral administration with BBB biodistribution
PROTAC® Targeted Molecules Degrade P301L tau *in vitro* are Potent and On-Mechanism

*In vitro* Potent tau PROTAC®

Degrade tau
DC50 <50nM

<table>
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<tr>
<th>tau PROTAC® (nM)</th>
<th>+</th>
<th>250</th>
<th>125</th>
<th>50</th>
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<tr>
<td>kDa: 180</td>
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<td></td>
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<td></td>
<td>-</td>
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<td>116</td>
<td>+</td>
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<tr>
<td>66</td>
<td>+</td>
<td></td>
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(+): Dox induction of P301L Tau expression
(-): Absence of induction

tau PROTAC®-on Mechanism
(competed by E3 Ligand and warhead)
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
- 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

<table>
<thead>
<tr>
<th>PROTAC®</th>
<th>Species</th>
<th>Dose (mg/kg)</th>
<th>[Plasma 1h] (ng/mL)</th>
<th>[Brain 1h] (ng/g)</th>
<th>B/P ratio</th>
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<td>1425</td>
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</table>
Multiple Tau PROTAC Lead Molecules Degrade >95% of Pathologic Tau in Tg2508 Brain Following Parenteral Administration in vivo

Pathologic tau (Wes) Tg2508 Cortex

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

K18 Tau Preformed Fibrils Induce Tau Seeding

- P301L + 100 nM K18
- No P301L No seeds

Tau PROTAC Treatment Inhibit Tau Seeding ex-vivo

- CTX-Vehicle
- CTX-PROTAC A 24 hrs
- CTX-PROTAC B 24 hrs
- No P301L No seeds

Modified from Holmes et al., 2014
Aged animal studies are being executed to assess the ability of the proteasome to degrade pathologic tau (may be compromised in neurodegeneration/age)
Tau Species Targeted by PROTAC® – Targets for Cell-Autonomous and Non-Cell-Autonomous Pathology

- **Normal**
  - Axonal Microtubule Stabilizer

- **Pathology**
  - Somatodendritic NMDA dysfunction
  - Synaptic Spread/pathologic seeding

- **Tau Monomer**
- **Tau Post-translational modifications**
  - Phosphorylation/Other
  - Truncation

- **Conformational change**
- **Aggregation**

- **Total Tau:**
  - HT7/Tau5 (human)

- **Pathologic Phospho Tau**
  - pT181, pT231, PHF1, AT8

- **Conformational Pathologic Tau:**
  - Tau: MC1

- **Sarkosyl Insoluble Tau:**
  - Western Blot Tau5

- **Tau PROTAC®**

**Targeted Tau Species**
- Tau Monomer
- Tau Post-translational modifications
- Conformational change
- Aggregation
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
Thank You & Patients We Hope to Serve

Thank You Arvinas Team!
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Ian Taylor
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