Discovery & Optimization of PROTAC® Molecules That Selectively Reduce Mutant Huntingtin

Adam W Hendricson, PhD

Associate Director Neuroscience, Arvinas, Inc. | New Haven, CT | USA
April 24th, 2023 | CHDI Annual Meeting | Dubrovnik, Croatia
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 potential advantages and therapeutic benefits of ARV-471, bavdegalutamide (ARV-110), ARV-766 and our other candidates in our pipeline, the development and regulatory status of our product candidates, 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 the potential for protein degraders to treat patients with neurological diseases and the potential market opportunity, including with respect to mHTT. 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), ARV-766 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; our ability to protect our intellectual property portfolio; 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, 2022 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.

The Arvinas name and logo are our trademarks. We also own the service mark and the registered U.S. trademark for PROTAC®. The trademarks, trade names and service marks appearing in this presentation are the property of their respective owners. We have omitted the ® and ™ designations, as applicable, for the trademarks named in this presentation.

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 not intended to promote the products referenced herein or otherwise influence healthcare prescribing decisions. Any cross-trial comparisons are not based on head-to-head studies and no direct comparisons can be made.
PROTAC® protein degraders harness the ubiquitin-proteasome system to induce the degradation of disease-causing proteins.
Our broad pipeline includes the first pivotal trials for PROTAC® degraders

<table>
<thead>
<tr>
<th>Program</th>
<th>Therapeutic Area / Indication</th>
<th>Preclinical</th>
<th>Phase 1/1b</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bavdegalutamid (ARV-110)</td>
<td>Oncology: Prostate Cancer</td>
<td>Bavdegalutamid monotherapy (878/875+ 2L+)</td>
<td>ARDENT: Bavdegalutamid monotherapy dose expansion (2L+)</td>
<td>Bavdegalutamid + abiraterone (2L+)</td>
<td>ARV-766 monotherapy dose expansion (2L+)</td>
</tr>
<tr>
<td>ARV-766</td>
<td>Oncology: Solid and Haematological Malignancies</td>
<td>BCL6 IND/CTA expected in 2023</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR-V777, BCL6, KRAS-G12D/V1, Myc1, HPK1 Undisclosed Targets</td>
<td>Neurodegenerative Disorders</td>
<td>LRRK2 IND/CTA expected in 2023</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
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

<table>
<thead>
<tr>
<th>Baseline</th>
<th>After treatment 60 mg ARV-471</th>
<th>Baseline CT Scan</th>
<th>After 4 Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Baseline Image" /></td>
<td><img src="image2" alt="After treatment Image" /></td>
<td><img src="image3" alt="Baseline CT Scan Image" /></td>
<td><img src="image4" alt="After 4 Cycles Image" /></td>
</tr>
</tbody>
</table>

**Estrogen receptor**  **Nuclei**  **Cytokeratin**

**ER degradation tumor biopsies**

51% reduction in target lesions (RECIST partial response)

ARV-471 is currently under investigation. Safety and efficacy has not been established.

Data as presented 12/14/2020
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

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
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® Degraders:

• Very few disease-modifying therapies exist
• Blood-brain barrier penetration is a challenge for other modalities
• Traditional therapies have difficult routes of administration, e.g., intra-thecal

Arvinas Neuroscience Pipeline

**PROTAC degraders could revolutionize the treatment of neuroscience diseases**

• Cross the blood brain barrier and degrade disease-causing proteins inside cells
• Target pathogenic proteins in the brain without impacting healthy proteins
• Potential for oral therapies

† Global data, DecisionResources. mHTT, mutant Huntingtin protein; MSA, multiple systems atrophy; PSP, progressive supranuclear palsy
First reported mHTT PROTAC! CHDI ’709
2019 report showed POC for this modality for mHTT

Guided & inspired by the patients we all serve, our mHTT degrader program aims to:

- Develop a novel PROTAC which lowers soluble mHTT & spares WT HTT
- Identify the degree & duration of soluble mHTT lowering required to slow the progression of human disease
- Literature suggests threshold for phenotypic change in HD mice is ~40-50% mHTT lowering. Important to understand the current view of HD field about human translation
mHTT PROTAC discovery....
Targeting allele-selective, on-mechanism, soluble mHTT degraders

Today's Presentation

PK/PD Studies with Optimized Leads (work ongoing)

Today we will cover the discovery of mHTT PROTACs & discuss our approach to pharmacologic & mechanistic triage
To discretely target soluble mHTT, we designed a screening system devoid of insoluble mHTT.

- Cell-based screening system calibrated vs. time & target induction level to produce soluble mHTT only.
Soluble mHTT screening system to dial out toxicity while driving allele-selective PROTAC molecules

- **Hits-to-leads process** delivered potent, non-toxic, allele-selective SAR starting points
Mechanistic triage: Optimizing for ternary complex formation

Ternary Complex
1. Target (mHTT)
2. E3-ligase (ubiquitinating enzyme)
3. PROTAC that links target & E3

- Full PROTAC shown to induce concentration-dependent increase in ternary formation
- Ligand alone (lacks E3 to complete the ternary) is inactive; negative control
Initial mechanism triage: Confirming on-target, proteasome-dependent pharmacology

- **E3-ligand**: will pharmacological excess of E3 compete with PROTAC E3 recruitment?
- **E3-dead**: will chemically disabling the PROTAC E3 reduce or eliminate degradation?
- **mHTT Ligand**: will an excess of ligand compete with PROTAC binding to target?

![Graph showing PROTAC Mechanism Study](image)

- >50% mHTT clearance with 0 change in WT HTT
- DC$_{50}$, pM:
  - mHTT: 67
  - +E3 Ligand: 2414
  - +mHTT Ligand: >3000
  - +E3-Dead: >3000
  - WT HTT: >3000
Confirmation of pharmacology by capillary electrophoresis: Early leads show highly selective degradation of soluble mHTT with pM potency

With early SAR starting points identified, focus shifts to **key questions** surrounding translation into preclinical models.
Key questions as we pivot to translation

- HD patients can be **mosaic for ‘Q’ expansions** across brain regions, & progression can be attended by somatic expansion of PolyQ
  - How do we design our clinical candidate to address these realities?
- HD patient postmortem brain has frequent **insoluble mHTT inclusions**, development of a mHTT PET tracer to enable reliable detection is key
  - How do we leverage new diagnostic tools in our biomarker strategy?
    - Will this be useful for PROTAC target engagement?
    - Can we demonstrate that depletion of soluble mHTT can move insoluble mHTT, the building block of inclusion bodies and relieve proteostasis?
- How do we use **primary rodent and animal cell models** to evaluate minimum efficacious exposure profiles in HD mice and patient iPSC lines?
PROTAC competition with mHTT tracer CHDI-180 in a soluble mHTT assay system

Data suggest overlapping binding with the mHTT-inclusion labelling CHDI-180 in an mHTT cellular assay system where insoluble mHTT is BLQ.

Further competition studies in HD brain are ongoing to help inform biomarker strategy.
PROTACs do not directly reduce insoluble mHTT

- **Result:** PROTACs directly reduce soluble mHTT, but not insoluble mHTT
- **This result led us to ask:** Will chronically starving the cell of soluble mHTT indirectly reduce formation of insoluble mHTT?
Chronic PROTAC lowers soluble and insoluble mHTT:

- Implication = We can design chronic exposure mouse PK/PD studies to measure changes in both soluble and insoluble endpoints and translate these perspectives to our HD biomarker strategy.
PROTAC degradation of mHTT in AAV-transduced rat neurons

- **AAV-driven mHTT in neurons allows:**
  - Direct comparison of mHTT PROTACs in primary cells
  - Flexibility in mHTT ‘Q’ expansion size & expression levels (via MOI)
  - Modelling treatment paradigms without the exposure / free-fraction variables inherent to mouse work

- Chronic PROTAC potently reduces soluble (2B7/4C9 ELISA) & aggregated (MW8/8 ELISA) mHTT with no effect on secreted LDH (i.e. no cyto-tox)
- Important POC for translation of mHTT lowering to mouse brain

**7d chronic study in rat neurons**

- Soluble mHTT
- Aggregated mHTT
- LDH

![Graph showing PROTAC degradation of mHTT in AAV-transduced rat neurons](image-url)
mHTT PROTACs cross the BBB at pharmacologically relevant levels

Free drug in brain covers in vitro DC$_{50}$ for >8h at single dose

CNS exposures consistent with substantial in vitro clearance of mHTT are attained
We have discovered oral PROTAC® induced degradation with biodistribution to deep anatomic brain regions in primates targeting LRRK2.

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

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

- Mouse
- Rat
- Cyno


- Robust POC for multi-species target degradation in CNS & delivery of PROTACs to deep brain regions in primates.
Summary

• ARVN PROTACs **potently & selectively degrade soluble mHTT** in multiple cellular readouts including rodent neurons

• Exploring all avenues for biomarker approaches including PET-based, & initiating studies in HD brain

• Our *in vitro* & *ex vivo* data suggests that **chronic lowering of soluble mHTT** leads to reduced insoluble mHTT

• **Selective degradation of mHTT via PROTAC** may have promise for disease modification without the dose-limiting effects of WT-HTT lowering
PROTAC® degraders could revolutionize the treatment of patients with neurological diseases

We are creating PROTAC® degraders that can:

- Cross the blood-brain barrier
- Reach targets in “deep brain” regions
- Degrade disease-causing proteins inside cells
- Differentiate between mutant and wild-type proteins, e.g., mutant huntingtin
- Be delivered orally

PROTAC degraders provide significant potential advantages over existing modalities
Acknowledgements

- Angela Cacace
- Jere Meredith
- Larry Snyder
- Michael Berlin
- Robert (Bob) Kyne
- Jen Pisano
- Juan Chavez
- Ian Taylor
- Garrett Naumann
- Kathleen Farmer
- Stefanie Keenan
- Brian Tanaka
- Yeontae Jeong
- Yosif Ganat

- Debra Nickischer
- Jamie Gregory
- Michele Matchett
- Leofal Soto
- Dustin Revell
- James Landro
- Amanda Downtin
- Miklos Bekes
- Alicia Morgan
- Jacques Mercier
- Katie Digianantonio
- Gabi Miklossy
- Rashaun Wilson
- Jordan Clark
The Arvinas Team (now nearing 500!)
Soluble mHTT screening system to dial out toxicity while driving allele-selective PROTAC molecules

1) Optimizing molecules for degradation of mHTT (without cellular toxicity)

2) Optimizing molecules for selective degradation of mHTT (without impacting wtHTT)

- **Hits-to-leads process** delivered potent, non-toxic, allele-selective SAR starting points
<table>
<thead>
<tr>
<th>Authors</th>
<th>Model</th>
<th>% change mHTT</th>
<th>Phenotype</th>
<th>notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez-Lebron et al Mol Ther 2005</td>
<td>R6/1 mice</td>
<td>intrastratal AAV5 anti-Htt shRNA lowered mHTT mRNA in the striatum by <strong>78% and protein levels by 28%</strong>.</td>
<td>delayed motor dysfunction</td>
<td></td>
</tr>
<tr>
<td>Boudreaux et al Mol Ther 2009</td>
<td>HDN171-82Q</td>
<td>75% reduction of human mHTT and endogenous wild-type mouse Htt mRNA</td>
<td>prevented motor and neuropathological deficits</td>
<td></td>
</tr>
<tr>
<td>Drouet et al Ann Neurol 2009</td>
<td>Rat HD model</td>
<td><strong>35% mRNA reduction</strong></td>
<td>Delayed progression of behavioral phenotypes</td>
<td></td>
</tr>
<tr>
<td>Kordasiewicz et al, Neuron 2012</td>
<td>R6/2</td>
<td>ASO-mediated reduction human mutant exon1 mRNA in R6/2 mouse brain by <strong>43%</strong></td>
<td>prevented brain weight loss and extended life</td>
<td></td>
</tr>
<tr>
<td>Kordasiewicz et al, Neuron 2012</td>
<td>YAC 128</td>
<td>ASO reduced mHTT mRNA and protein levels in YAC128 mice by <strong>58% and 56%</strong></td>
<td>restored motor deficits to the performance level of nontransgenic controls</td>
<td></td>
</tr>
</tbody>
</table>
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

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

**PIPELINE**
- 3 Programs in Phase 2
  Clear efficacy signals in patients with difficult-to-treat breast and prostate cancers
- 20+ Pipeline Programs in oncology, I-O, and neuroscience

**PARTNERED FOR SUCCESS**
Global collaboration with Pfizer to co-develop and co-commercialize ARV-471 in ER+ breast cancer announced in July 2021
Arvinas’ breakthroughs are driven by our integrated PROTAC® Discovery Engine

- E3 KnowledgeBase – matching the correct E3 ligase to correct target
- Leveraging AI and structural understanding of ligases to identify and design ligands
- Arvinas’ DNA-encoded libraries for advanced screening
- Identification of new “warheads” for previously undruggable targets

1. Ligase Selection and Ligand Identification

- Zone of Ubiquitination – we design PROTAC degraders to predict the precise location where a protein can be tagged
- Predictive computational modeling
- State-of-the-art proteomics capabilities

2. Rapid PROTAC Design

- “Arvinas Rules” for drug-like properties, including blood-brain barrier penetration and oral bioavailability in humans
- Deep knowledge of molecular features allow us to create PROTAC degraders with drug-like properties and activities

3. Turning Degraders Into Drugs

Arvinas’ platform is built from nearly 20 years of experience, know-how, and IP

AI, artificial intelligence
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**

<table>
<thead>
<tr>
<th>Feature</th>
<th>PROTAC Protein Degraders</th>
<th>Small Molecule Inhibitors</th>
<th>Gene-Based Medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eliminate disease-causing proteins</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Disrupt scaffolding function</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Potential to treat “undruggable” proteins</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Iterative mechanism of action</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad tissue penetration</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Oral dosing</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Ease of manufacturing</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>
PROTAC® protein degraders harness the ubiquitin-proteasome system to induce the degradation of disease-causing proteins.

1. **Complex Formation**
   - Proteasome
   - PROTAC

2. **Target Ubiquitination**
   - PROTAC
   - E3 ligase
   - Ubiquitinating enzyme (E3)
   - mHTT

3. **Target Elimination**
   - Ubiquitin
   - Iterative activity
   - mHTT is degraded by the proteasome

See animations in viewer mode.