The Arvinas PROTAC® Discovery Engine:

PROTAC biophysical characterization fuels the discovery of target and E3 ligase ligands for optimized PROTAC degrader molecules

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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

400+ team members

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
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>
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<tr>
<td>Bavdegalutamide</td>
<td>Oncology: Prostate Cancer</td>
<td>Bavdegalutamide monotherapy (878/875+ 2L+)</td>
<td>ARDENT: Bavdegalutamide monotherapy dose expansion (2L+)</td>
<td>Bavdegalutamide + abiraterone (2L+)</td>
<td>ARV-766 monotherapy dose escalation (2L+)</td>
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<td>ARV-766</td>
<td>AR-V7†, BCL6, KRAS-G12D/V†, Myc†, HPK1</td>
<td>BCL6 IND/CTA expected in 2023</td>
<td>2 additional programs in IND-enabling studies by end of 2023</td>
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<td>Undisclosed Targets</td>
<td>Oncology: Solid and Haematological Malignancies</td>
<td>LRRK2 IND/CTA expected in 2023</td>
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<td>LRRK2 IND/CTA expected in 2023</td>
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</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
Overview of Presentation

- High level overview of Arvinas biophysics toolbox
  - Focus on SPR techniques

- Discovery Engine Highlights from biophysics toolbox
  - Library Screening SPR Assay – development of robust SPR assay for ligand ID using the Biacore8K+
  - Ternary SPR Experiments – supporting SAR for a novel ligase
PROTAC® protein degraders harness the ubiquitin-proteasome system to induce the degradation of disease-causing proteins.
Arvinas’ breakthroughs are driven by our integrated PROTAC® Discovery Engine

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

**PROTAC Discovery Engine**

1. **Ligase Selection and Ligand Identification**
   - 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 ligands for previously undruggable targets

2. **Rapid PROTAC Design**
   - 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

3. **Turning Degraders Into Drugs**
   - “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

AI, artificial intelligence
The next frontier is developing new E3 ligases for TPD – how do we think about them?

- **degrader potential E3** = E3 ligases with known function to target substrates for degradation
- **ligandable** = ability to discover a tool ligand (small molecule, peptide, hybrid, etc) that engages the E3 (aided by structure)
- **druggable** = ability to develop a drug-like molecule (ie orally bioavailable), that exerts function on, or functionalizes, the E3
- **PROTACable** = ability to design heterobifunctional* molecules that impart degradation of multiple targets via an E3
Arvinas PROTAC® Discovery Engine - Degrader Discovery in Platform Biology

**Mechanistic Cell Biology**
- E3 distribution in cell lines & tissues
- E3 : degron (substrate) validation
- Cell-based mechanism studies & HTS degradation assays for degrader discovery

**Mechanistic Biochemistry**
- Biochemical displacement assays
- Biophysical binding assays
- Cell-based target-engagement assays
- Ligand ID campaigns (HTS, CADD, DEL, AI)

**Structural Biology**
- Structural biology of targets & E3s with ligands, including ternary complexes
- CryoEM of holo-E3 complexes to understand & exploit E3 assembly for PROTACs

**Deep understanding of target + E3 mechanisms**

**Conversion to active PROTAC & MoA work**
- E3 distribution in cell lines & tissues
- E3 : degron (substrate) validation
- Cell-based mechanism studies & HTS degradation assays for degrader discovery

**Target + E3 selection**

**Target + E3 Ligand ID & optimization**

**Structural biology of targets & E3s with ligands, including ternary complexes**

**CryoEM of holo-E3 complexes to understand & exploit E3 assembly for PROTACs**

**Ternary complex**

**Target ligand ID**

**E3 Ligand ID**
Arvinas PROTAC® Discovery Engine - Degrader Discovery in Platform Biology

1. Target + E3 selection
2. Deep understanding of target + E3 mechanisms
3. Target + E3 Ligand ID & optimization
4. Conversion to active PROTAC & MoA work

- Target + E3 de novo
- Ligand ID
- Optimization of binding to target + E3
- Characterization of binding in presence of natural substrate(s)
- Optimization of PROTAC to develop PPI

Differentiated PROTAC with tumor-specificity in vivo
Arvinas PROTAC® Discovery Engine – Biophysical characterization toolbox

Compound Library Screening
- Utilization of Biacore8K+ with single concentration analysis

Binding Affinity Analysis
- Multi-cycle and single-cycle approaches

Competition Binding Analysis
- Mapping of ligand binding sites based on competition with known binder

Ternary Protein-Protein Interaction Analysis
- Assessment of PPI through $\alpha$-factor determination
Arvinas PROTAC® Discovery Engine – Biophysical toolbox to enable ligand ID and optimization

1. Target + E3 de novo Ligand ID
2. Optimization of binding to target + E3
3. Characterization of binding in presence of natural substrate(s)
4. Optimization of PROTAC to develop PPI

Conversion to active PROTAC degrader
Validated ligand
Possible Hit
ligand ocean
Arvinas PROTAC® Discovery Engine – Biophysical characterization toolbox to enable ligand ID and optimization

**Library Screening** – *structure based virtual screen, fragments, etc.*
- Screening fragments as single concentrations
- Screen can be normalized to known binder or run agnostic
Arvinas PROTAC® Discovery Engine – Biophysical characterization toolbox to enable ligand ID and optimization

- **Target + E3 de novo Ligand ID**
- **Optimization of binding to target + E3**
- **Characterization of binding in presence of natural substrate(s)**
- **Optimization of PROTAC to develop PPI**

**Conversion to active PROTAC degrader**

**Validated ligand Possible Hit**

**Ligand ocean**

**Binding Affinity Analysis - Multicycle**
- Steady State or kinetic analysis of compound binding
- Binding Affinity ($K_D$, $k_a$, $k_d$, half-life)

**Binding Affinity Analysis – Single cycle**
- Single cycle kinetic experiments that specifically designed to provide stability to disordered proteins
Arvinas PROTAC® Discovery Engine – Biophysical characterization toolbox to enable ligand ID and optimization

- Target + E3 de novo
- Optimization of binding to target + E3
- Characterization of binding in presence of natural substrate(s)
- Optimization of PROTAC to develop PPI

**Conversion to active PROTAC degrader**

**Validated ligand**

**Possible Hit**

**ligand ocean**

**Competition Binding Analysis**
- Compound binding with and without known site competitor
- Helps determine compound binding site
- Help characterize binding in presence of natural substrate
Arvinas PROTAC® Discovery Engine – Biophysical characterization toolbox to enable ligand ID and optimization

**Target + E3 de novo Ligand ID**

**Optimization of binding to target + E3**

**Characterization of binding in presence of natural substrate(s)**

**Optimization of PROTAC to develop PPI**

**Conversion to active PROTAC degrader**

**Validated ligand Possible Hit ligand ocean**

**Ternary PPI Binding Analysis**
- Binary and ternary binding affinity determination ($K_D$, $k_a$, $k_d$, half-life)
- PPI cooperativity analysis using $\alpha$-factor calculation

**Calculate cooperativity factor to inform on quality of protein-protein interaction**

\[
\alpha = \frac{\text{Ligase Binary KD}}{\text{Compound Ternary KD}}
\]

- $>1$ indicates positive cooperativity
- $=1$ indicates no cooperativity
- $<1$ indicates negative cooperativity

**Example Calculations**

- Ligase Binary KD = 6500nM
- Compound 1 Ternary KD = 58nM; $\alpha$-factor = 112
- Compound 2 Ternary KD = 75nM; $\alpha$-factor = 86
- Compound 3 Ternary KD = 5nM; $\alpha$-factor = 1300

**Graphs**

- Compound 1: Ternary formation
- Compound 2: Ternary formation
- Compound 3: Ternary formation
- Compound 4: No ternary formation

**Concentration (µM)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ternary Formation</th>
<th>Ternary KD (nM)</th>
<th>$\alpha$-factor</th>
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<tr>
<td>Ligase Binary</td>
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<td>Compound 1</td>
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<td>58</td>
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<tr>
<td>Compound 4</td>
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</table>

**% Response (RU)**

- $R_h$ = 100% 
- $R_l$ = 0% 
- $R_{50}$ = 50%
Arvinas Discovery Engine Highlights: Library Screening
Utilization of Biacore8K+ capacity to screen compound library decks in support of novel ligand identification

Structure Based Virtual Screen Metrics

- Compound property/substructure-filtered
- Docked against crystal structure on AWS cluster

Millions

- Top-scoring compounds evaluated for protein-ligand interaction energies

Ten-thousands

- Clustered and singleton compounds selected based on docking score and interaction energies

2.7K

Sensor Chip Immobilization Schematic

- His-tagged protein
- Ni-NTA directed coupled capture
- Prolonged baseline stability
Qualification of primary screen data begins with identifying compounds that bind promiscuously to reference flow cell.

- >5RU Flagged
- >50% Control
- Rmax RU Flagged
- Potential Hit
- Reference Flow Cell
- Protein Flow Cell

Potential Hits
Reference Binders/Non-specific Binders/Sticky compounds

Protein Binding (RU)
Reference Binding (RU)
Statistical analysis of screening controls by plate reveals robust, durable assay

- **z-factor Analysis of control compound per plate indicates robust assay**
  - All plates > 0.5 = excellent
  - Total of 9 plates screened
  - 32 positive controls per plate
  - 32 negative controls per plate

- Some control RU loss overtime
  - ~32-hour runtime on SPR
  - Data was analyzed per plate to call hits

- Impressive, sustained protein viability overtime allows for high confidence in screening hits

<table>
<thead>
<tr>
<th>Well Position on Plate</th>
<th>Protein Binding (RU)</th>
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<td></td>
<td>Control Average</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
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<td></td>
<td>16 RU Z-prime: 0.80</td>
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<td></td>
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<td>8</td>
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<td>11</td>
<td>9.9 RU Z-prime: 0.63</td>
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</tbody>
</table>
Correlation of screening controls at two concentrations builds confidence in hit rate - 50μM and 200μM single concentration

- Controls cluster nicely between replicates
  - Run on same day, different Biacore8K+ instruments

- Good linear agreement between compounds at both concentrations
  - Analyzed per plate
Overall result of primary screen data collected on Biacore8K+ - 50µM single concentration

![Graph showing protein binding (RU) vs. time (cycle #)]
Further qualification of potential hits through sensogram analysis of binding parameters

- Each compound sensogram is evaluated against three parameters: Rmax, slope, and dissociation
  - Compared with positive control sensogram to further prioritize potential hits
  - Provides context to observed RU value; not just a number
- Offers advantage over traditional HTS methods as compound binding can be characterized more thoroughly and false positives identified quickly
Validation of single concentration screening hits through concentration dose response and orthogonal assay confirmation

Compound A identified as validated SPR hit
• Single concentration (50μM) RU: 12.8
• Multi-cycle KD: 11.5μM

Compound B identified as validated SPR hit
• Single concentration (50μM) RU: 35.1
• Multi-cycle KD: 40μM
• Confirmed binding by ASMS

SPR is a powerful tool for identification of novel ligands across protein targets
• Quickly identify possible hits using Biacore8K+ screening capability
• Qualify potential hits using sensogram shape to prioritize follow-up
• Validate screening hits with concentration response curves
Arvinas Discovery Engine Highlights: Ternary Complex SPR
PROTAC discovery – one case study from the Arvinas E3 repertoire

The next frontier is developing new E3 ligases for TPD – how do we develop them?

E3 ligase with degrader potential → ligand ID → validated E3 ligand → lead-to-PROTAC → active PROTAC → orally bioavailable degrader

E3 ligand-to-PROTAC discovery → novel CRL2\textsuperscript{KLHDC2} PROTAC degraders

Discovery & characterization of KLHDC2 ligands for PROTAC applications:

1) Rapid de novo ligand design by CADD & ligand evolution
2) Ligand-to-PROTAC conversion & on-mechanism activity validation
3) Mechanistic & structural understanding of E3 assembly
KLHDC2 is an active E3 ligase that can be exploited for PROTAC discovery

- KLHDC2 is a CRL2-associated substrate receptor
- KLHDC2 has been shown to recognize C-terminal glycine residues as a high affinity degron
- C-term Gly recognition has been structurally elucidated

In-house validation of KLHDC2 as a C-terminal degron targeting CRL2 E3 ligase using NanoLuc-degron (NLD) fusions

NanoLuc-substrate [raw luminescence]

NLD

NanoLuc-substrate

WB:

siRNA:

scrambled

KLHDC2

loading control

So, we wondered early on for KLHDC2...

- ... can small molecule KLHDC2 ligands be discovered?
  - ... would they work as E3 handles for induced proximity?
  - ... would they work as heterobifunctional PROTACs?
Structure-based, *de novo* ligand design by CADD & rapid ligand evolution yielded potent and novel KLHDC2 ligands

- Multiple co-crystal structures solved with our CADD-based KLHDC2 ligands
- KLHDC2 ligands extensively occupy and fill the substrate-binding pocket
- Crystal structures allow rational design of an E3-dead analogue; and illuminate multiple exit vectors for PROTAC development
KLHDC2–BRD4 linker SAR points to efficient ternary complex inducing PROTACs as potent degraders

<table>
<thead>
<tr>
<th>KLHDC2-BRD4 PROTAC</th>
<th>KLHDC2 ligand / linker combo</th>
<th>HBiT-BRD4 DC_{50} [nM]</th>
<th>HBiT-BRD4 D_{max} [%]</th>
<th>BRD4-BD2 K_{d} [nM]</th>
<th>KLHDC2 K_{d} [nM]</th>
<th>Ternary complex by SPR</th>
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<tr>
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**PROTAC a1**
- BRD4-BD2 + PROTAC
- binary binding [SPR]

**PROTAC a1**
- BRD4-BD2 + PROTAC + KLHDC2_{KD}
- ternary binding [SPR]
KLHDC2-BRD4 linker SAR points to efficient ternary complex inducing PROTACs as potent degraders

<table>
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**KLHDC2-BRD4 linker SAR points to efficient ternary complex inducing PROTACs as potent degraders**

<table>
<thead>
<tr>
<th>KLHDC2-BRD4 PROTAC</th>
<th>KLHDC2 ligand / linker combo</th>
<th>HiBiT-BRD4 DC$_{50}$ [nM]</th>
<th>HiBiT-BRD4 D$_{max}$ [%]</th>
<th>BRD4-BD2 K$_d$ [nM]</th>
<th>KLHDC2 K$_d$ [nM]</th>
<th>Ternary complex by SPR</th>
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- Advanced BRD4 PROTACs show ternary complex formation [as measured by SPR] and robust degradation

**PROTAC A1**
BRD4-BD2 + PROTAC
✓ binary binding [SPR]

**PROTAC A1**
BRD4-BD2 + PROTAC + KLHDC2$_{KD}$
+++ ternary binding [SPR]
KLHDC2-based PROTAC optimization using JQ1 yields potent pan-BET degraders

![HiBiT degradation assay for BRD4](image)

**Ternary complex SPR is a powerful tool to support PROTAC linkerology that provides a unique SAR perspective toward degradation**

- Characterize negatively cooperative PPI
- Qualitative analysis of sensogram shape provides PPI information that is not reflected in quantitative analysis
Diversity of biophysical toolbox highly impacts PROTAC design at Arvinas

Through our industry-leading PROTAC Discovery Engine, Arvinas has:

- Developed a biophysical toolbox to meet the demands of our diverse project portfolio
- Optimized opportunities for novel ligand discovery campaigns through biophysics and structure-based drug discovery collaboration
- Utilized toolbox to provide critical data to bridge the gap, driving PROTAC degradation
Acknowledgements – the entire Arvinas Team (now 400+!)

Thank you!