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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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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 receipt of upfront, milestone, and other payments under the Pfizer collaboration, the potential benefits of and the receipt of any related milestones in connection with our arrangements with our collaborative partnerships, statements regarding the potential advantages and therapeutic benefits of bavdegalutamide (ARV-110), ARV-471, ARV-766 and our other discovery programs, the development and regulatory status of our product candidates, such as statements with respect to the potential of our lead product candidates, bavdegalutamide (ARV-110), ARV-471, and ARV-766 and other candidates in our pipeline, 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 our discovery programs that may lead to our development of additional product candidates, the potential utility of our technology, our plans with respect to submission of investigational new drug/clinical trial authorization applications, the potential commercialization of any of our product candidates and companion diagnostic partnering, 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.

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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

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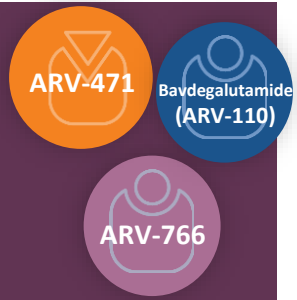
400+ team members

- 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

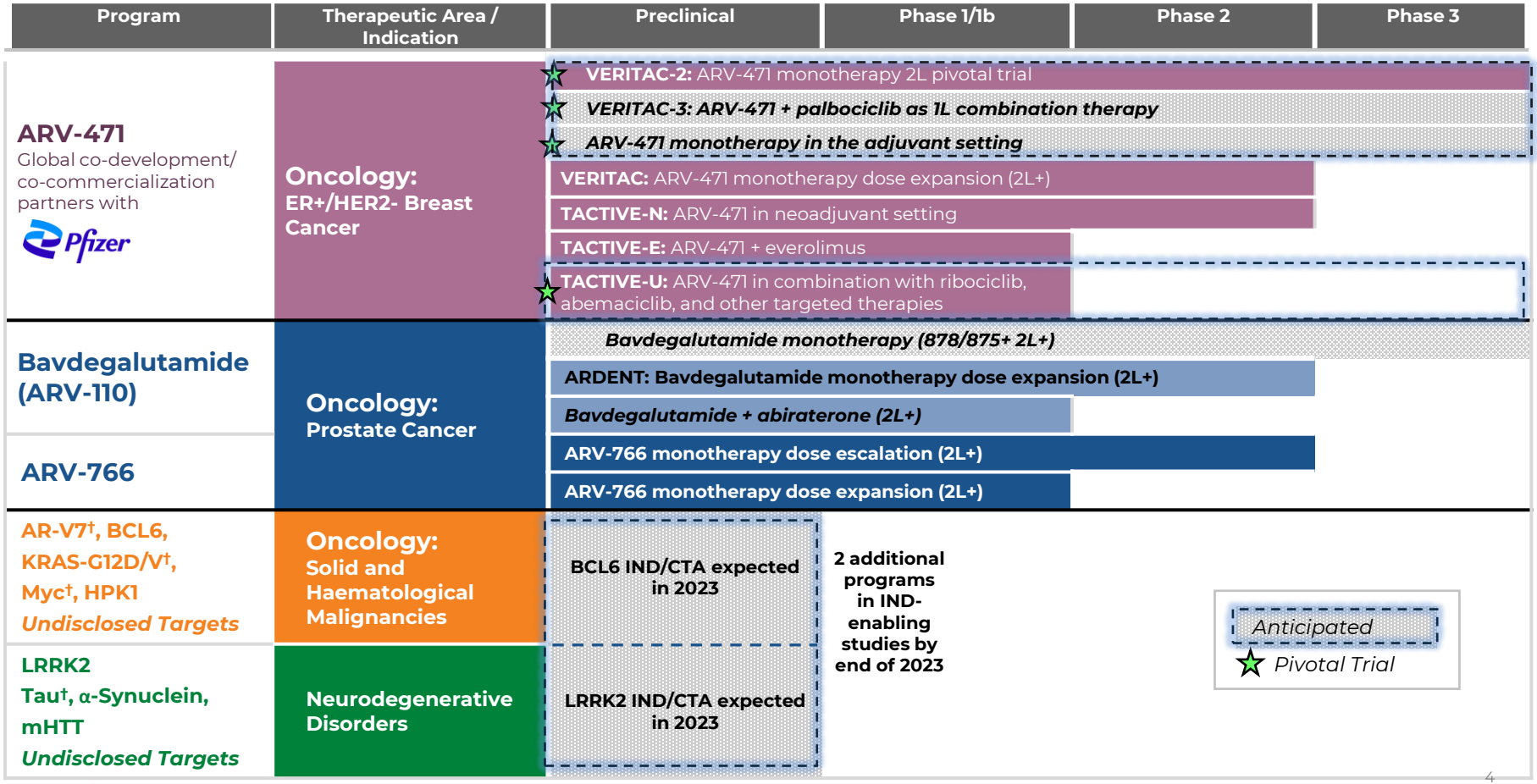
in oncology, I-O, and neuroscience

PARTNERED FOR SUCCESS

ARVINAS Pfizer

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



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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

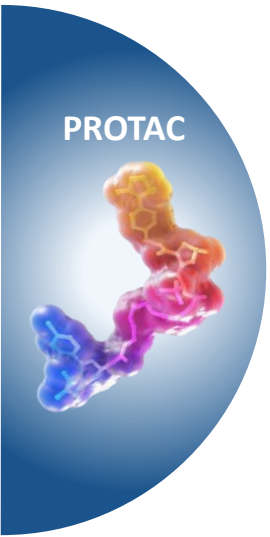
† Denotes historically undruggable proteins

Overview of Presentation

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

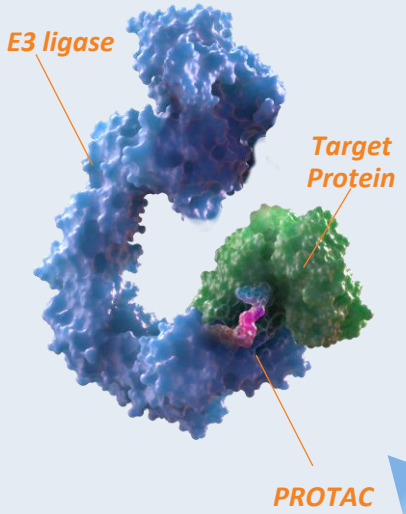
- Discovery Engine Highlights from biophysics toolbox
  - Library Screening SPR Assay – development of robust SPR assay for ligand ID using the Biacore8K+
  - Ternary SPR Experiments – supporting SAR for a novel ligase

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



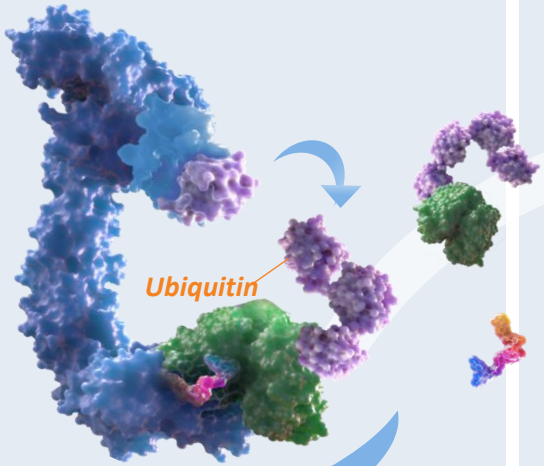
1 Complex Formation

Recognizing disease-causing protein



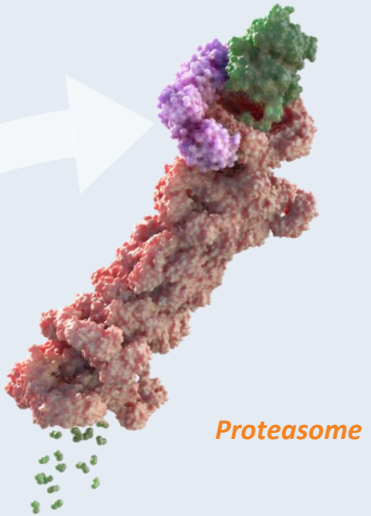
2 Protein Tagging

Tagging of target protein for degradation



3 Protein Elimination

Target protein is degraded by the proteasome



Iterative activity

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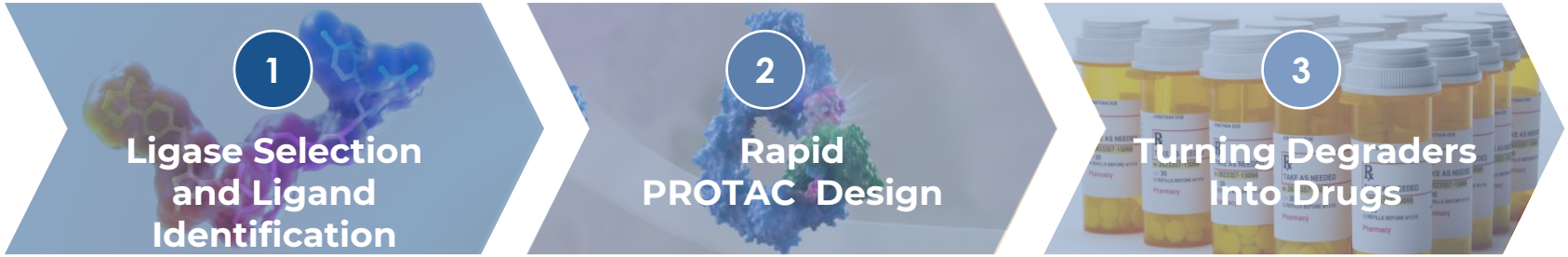
Arvinas' breakthroughs are driven by our integrated PROTAC® Discovery Engine

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

PROTAC Discovery Engine



- 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

- 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

- "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

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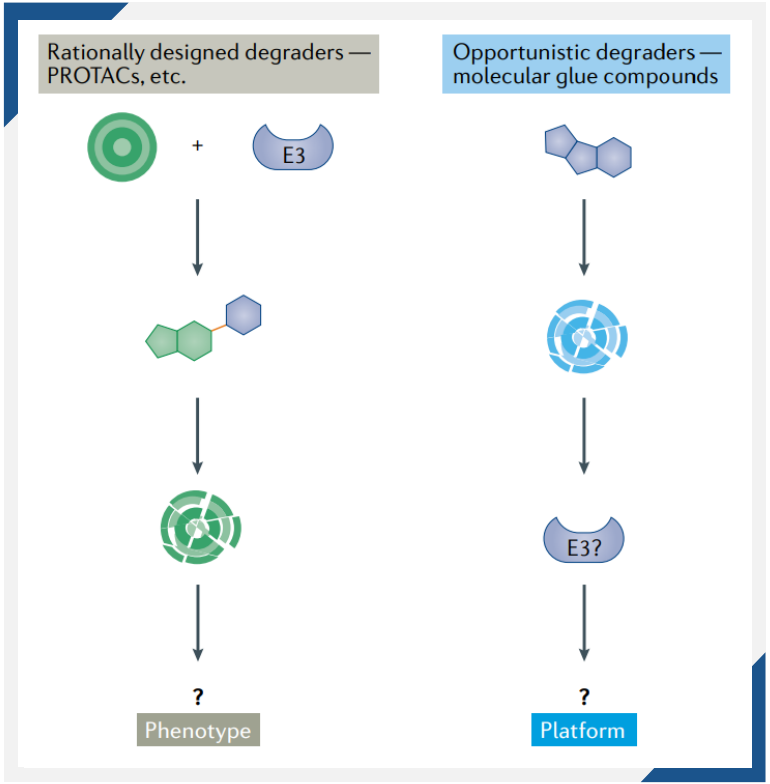
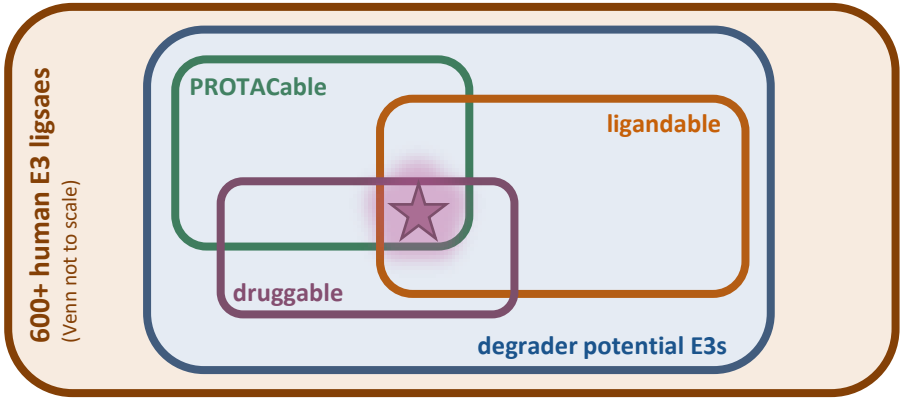
Arvinas PROTAC® Discovery Engine – Unlocking E3 ligases for degraders

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



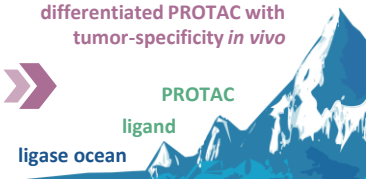


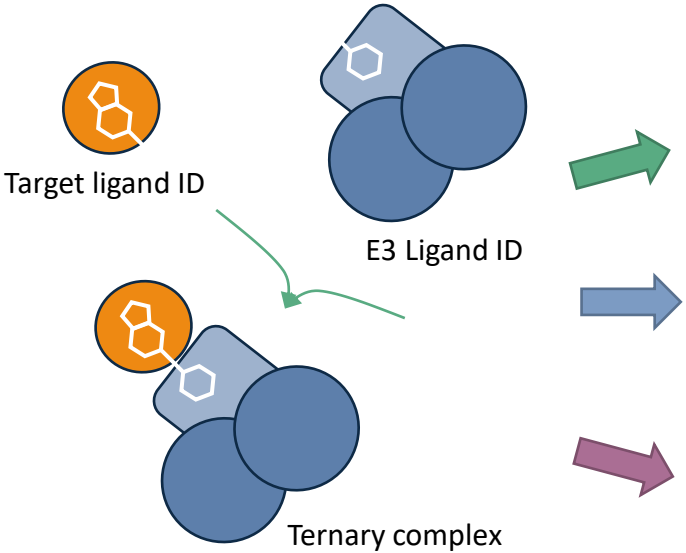
- **degrader potential E3** = E3 ligases with known function to target substrates for degradation
- **ligandable** = ability to discover a tool ligand (small molecule, peptide, hybrid, etc) that engages the E3 (aided by structure)
- **druggable** = ability to develop a drug-like molecule (ie orally bioavailable),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

ARVINAS Bekes, Langley, Crews (2022) NRDD

Arvinas PROTAC® Discovery Engine – Degrader Discovery in Platform Biology

Target + E3 selection → Deep understanding of target + E3 mechanisms → Target + E3 Ligand ID & optimization → Conversion to active PROTAC & MoA work → differentiated PROTAC with tumor-specificity *in vivo*





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

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Arvinas PROTAC® Discovery Engine – Degrader Discovery in Platform Biology

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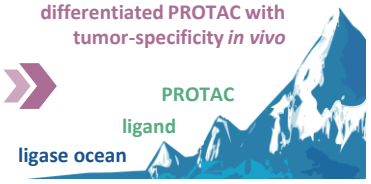
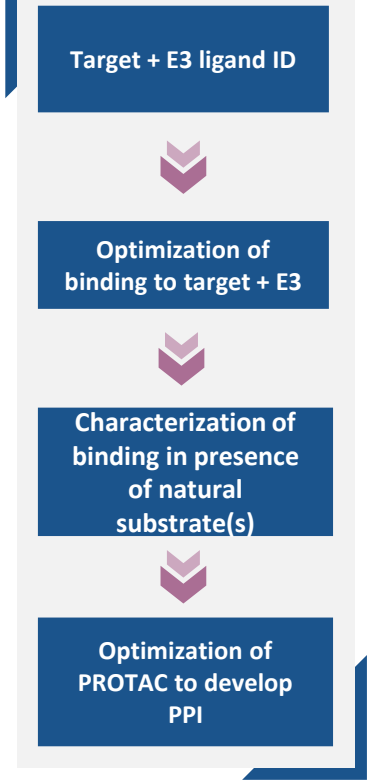


Target + E3 de novo Ligand ID → Optimization of binding to target + E3 → Characterization of binding in presence of natural substrate(s) → Optimization of PROTAC to develop PPI

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 α-factor determination

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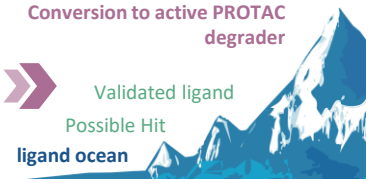
Arvinas PROTAC® Discovery Engine – Biophysical toolbox to enable ligand ID and optimization

Target + E3 de novo Ligand ID

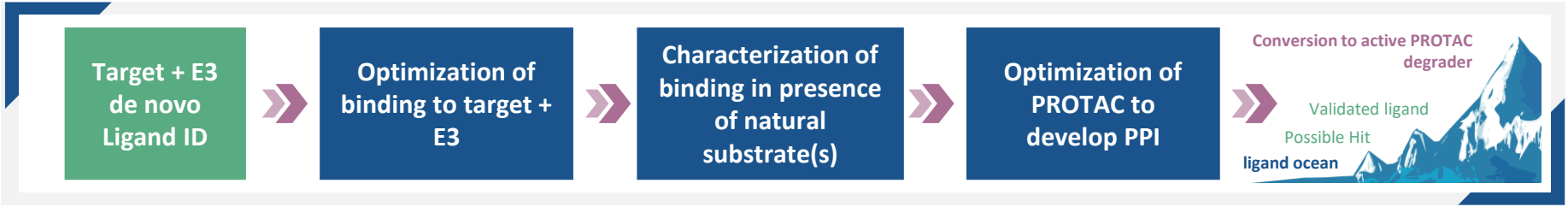
Optimization of binding to target + E3

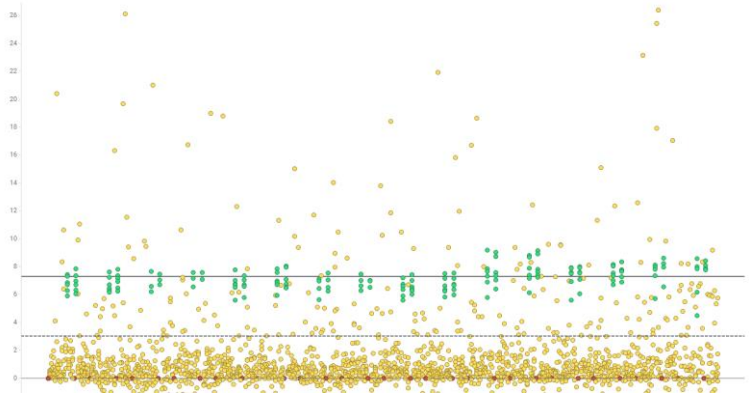
Characterization of binding in presence of natural substrate(s)

Optimization of PROTAC to develop PPI



Arvinas PROTAC® Discovery Engine – Biophysical characterization toolbox to enable ligand ID and optimization



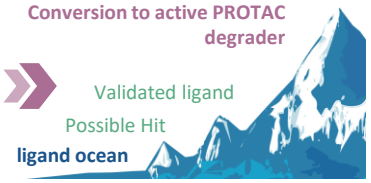


Library Screening – *structure based virtual screen, fragments, etc.*

- Screening fragments as single concentrations
- Screen can be normalized to known binder or run agnostic

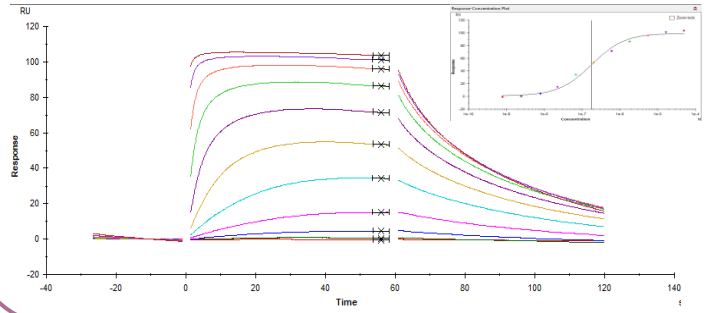
Arvinas PROTAC® Discovery Engine – Biophysical characterization toolbox to enable ligand ID and optimization

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



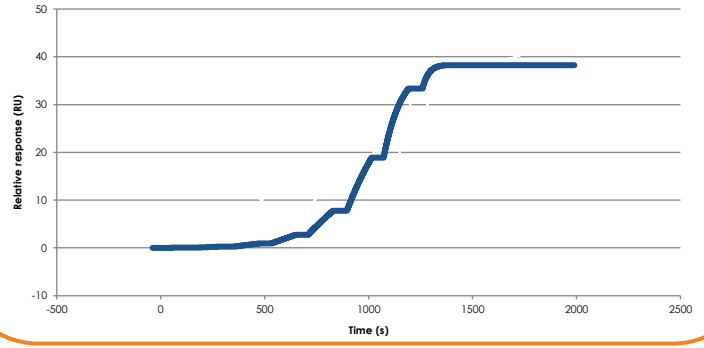
Binding Affinity Analysis - *Multicycle*

- 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



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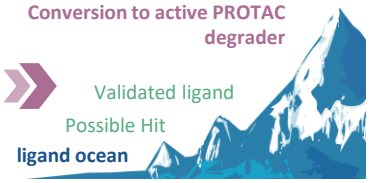
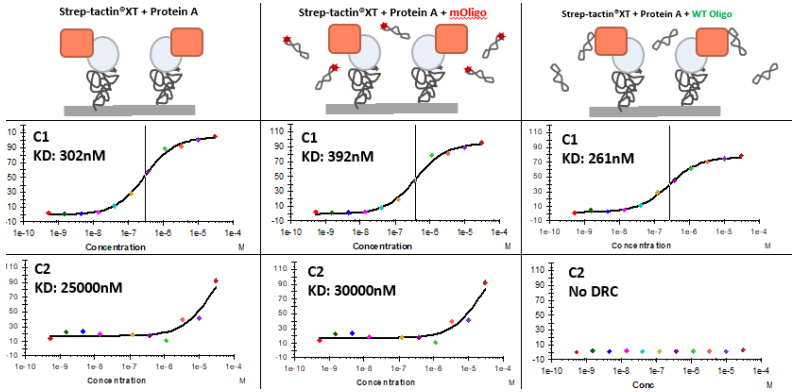
Arvinas PROTAC® Discovery Engine – Biophysical characterization toolbox to enable ligand ID and optimization

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



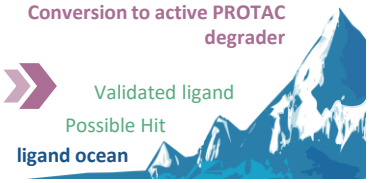


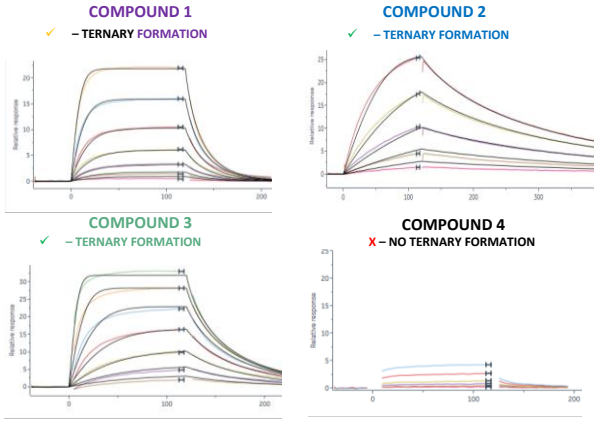
Competition Binding Analysis

- 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

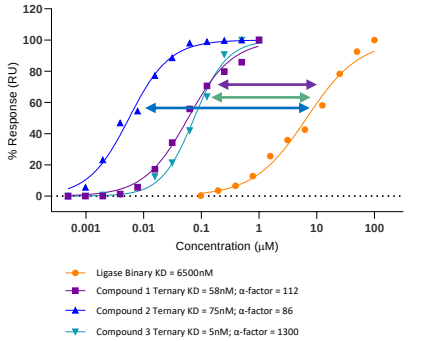




Calculate cooperativity factor to inform on quality of protein-protein interaction

$$\alpha\text{-factor} = \frac{\text{Ligase Binary KD}}{\text{Compound Ternary KD}}$$

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



Ternary PPI Binding Analysis

- Binary and ternary binding affinity determination (K_D, k_a, k_d, half-life)
- PPI cooperativity analysis using α-factor calculation

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

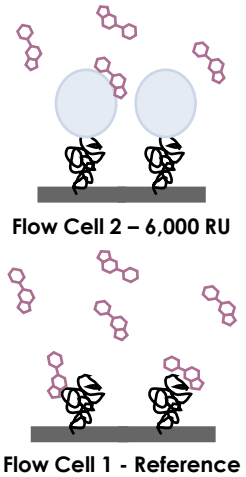
Millions
- Compound property/substructure-filtered
- Docked against crystal structure on AWS cluster

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

2.7K
- Clustered and singleton compounds selected based on docking score and interaction energies

Sensor Chip Immobilization Schematic

- His-tagged protein
- Ni-NTA directed coupled capture
- Prolonged baseline stability



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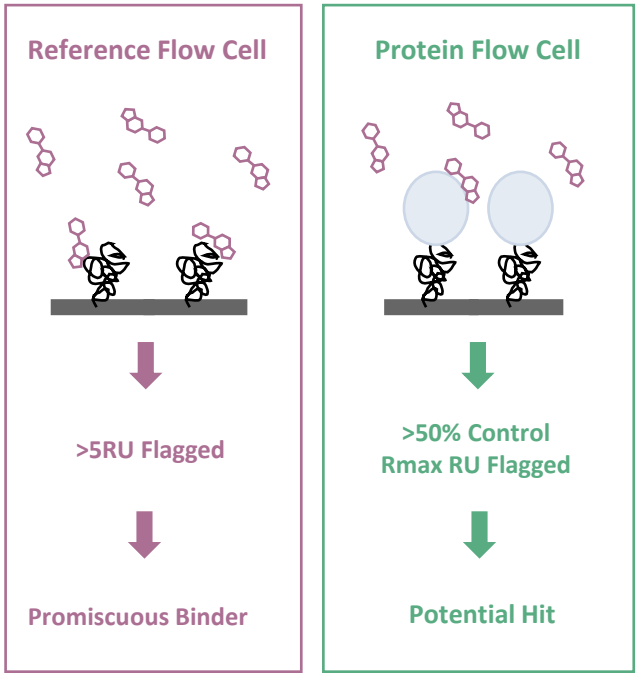
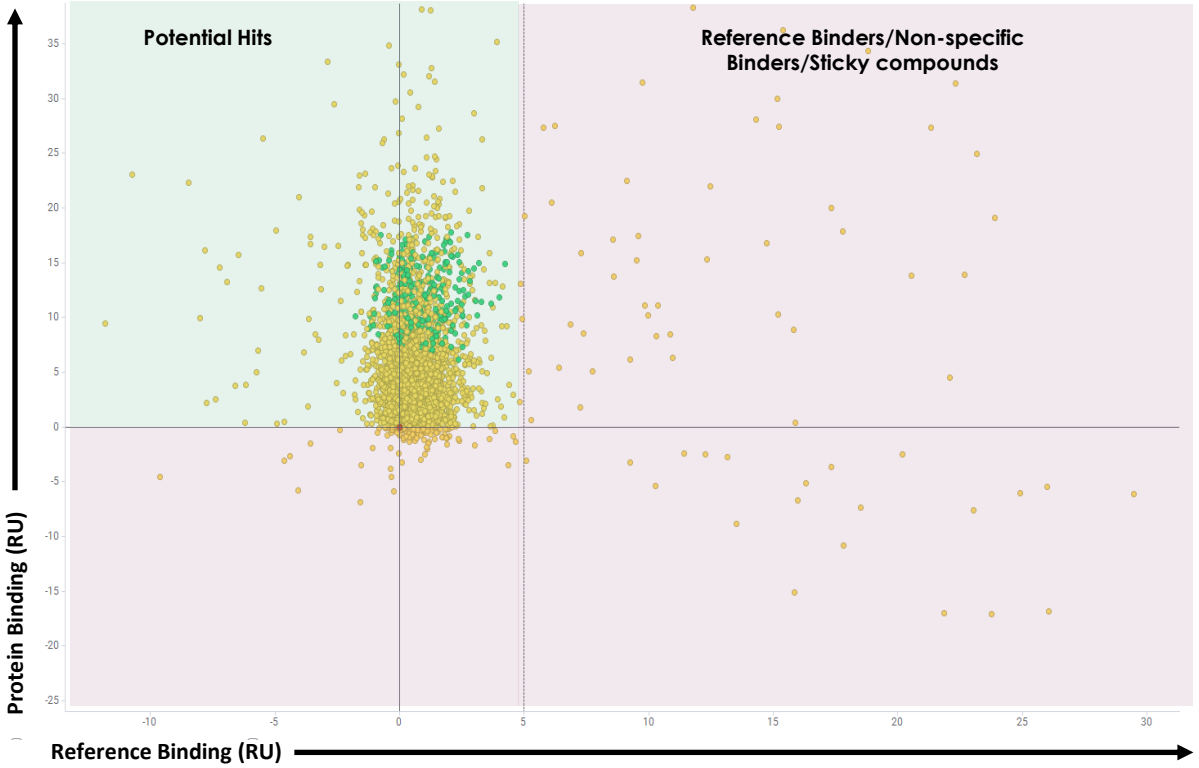
Qualification of primary screen data begins with identifying compounds that bind promiscuously to reference flow cell





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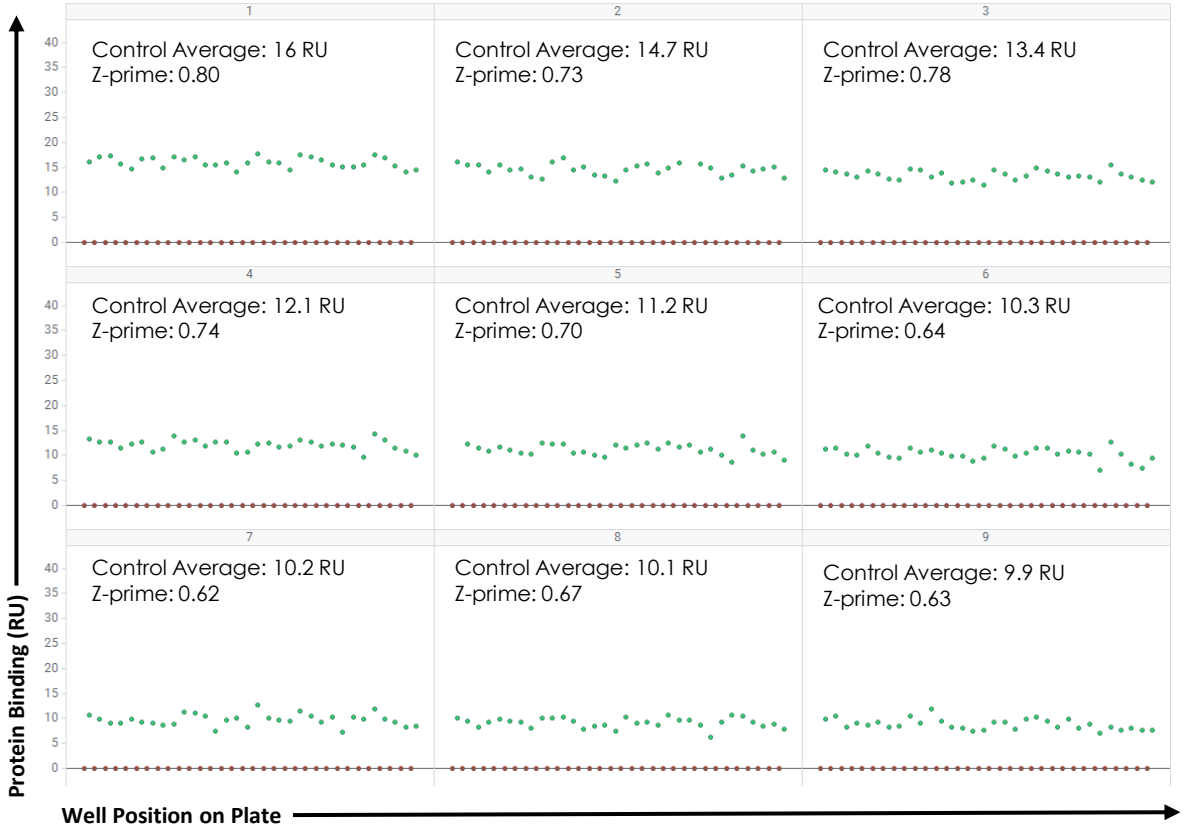
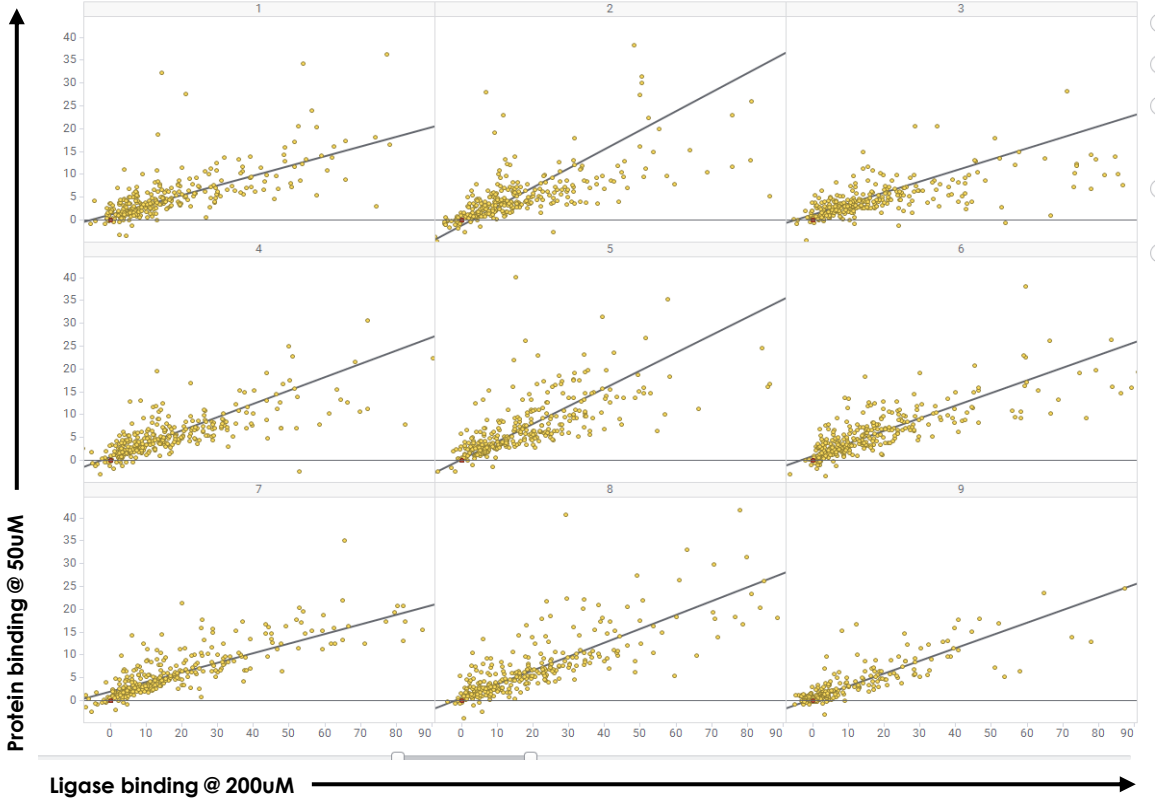
Statistical analysis of screening controls by plate reveals robust, durable assay

- 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

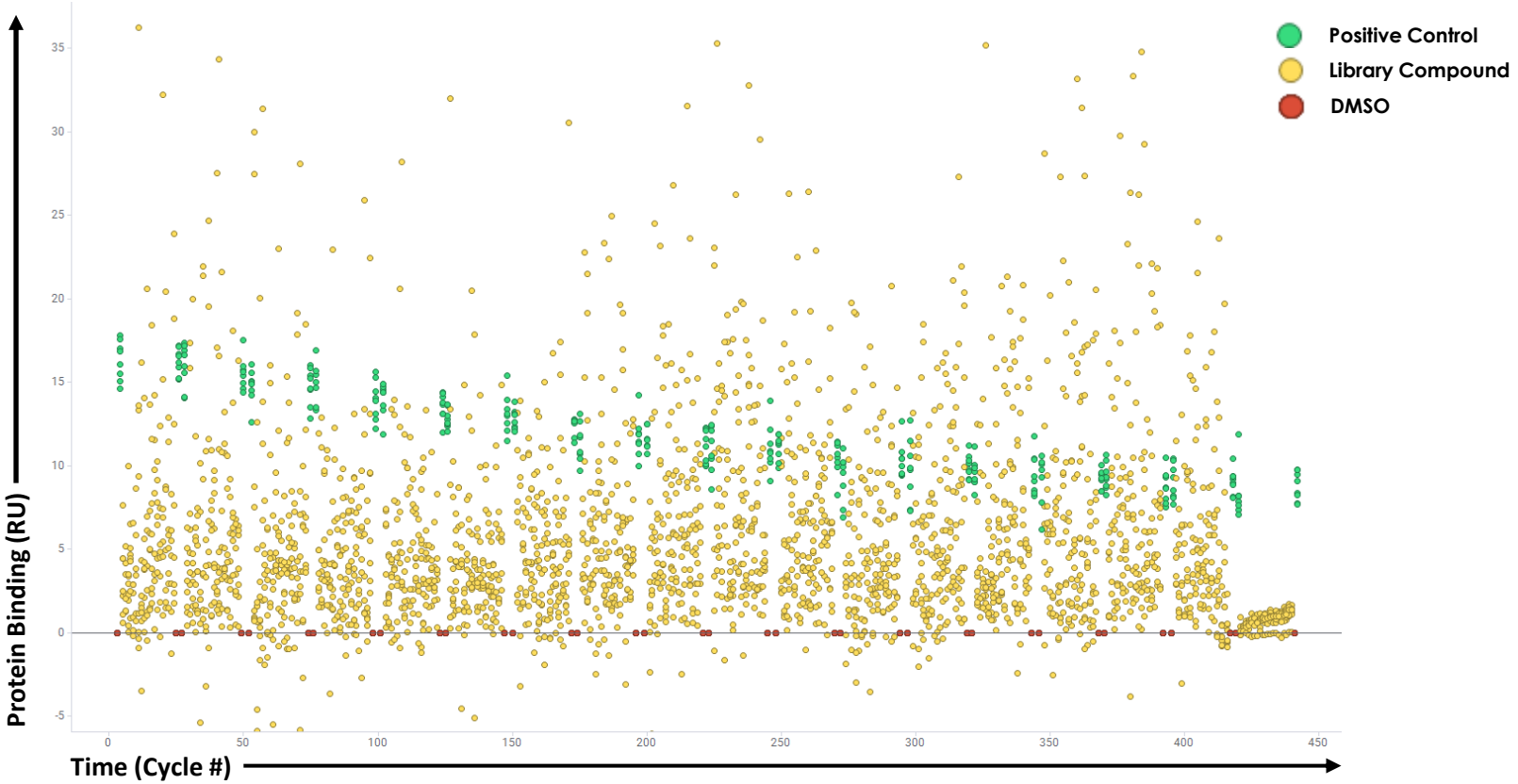


Correlation of screening controls at two concentrations builds confidence in hit rate – 50µM and 200µM single concentration

- 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



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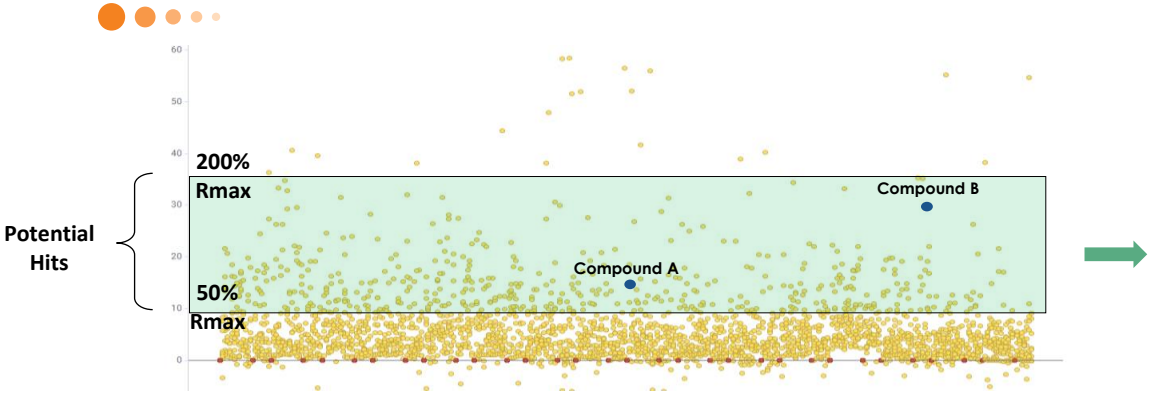
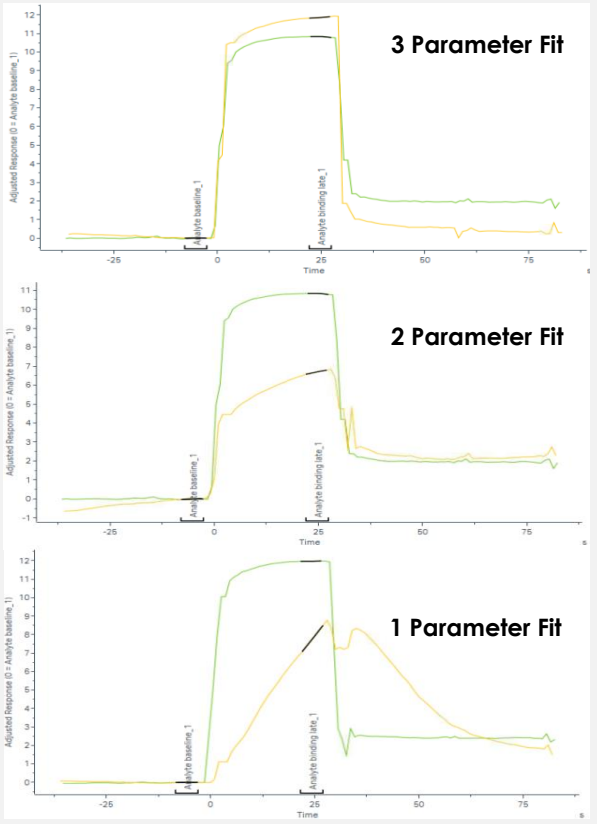
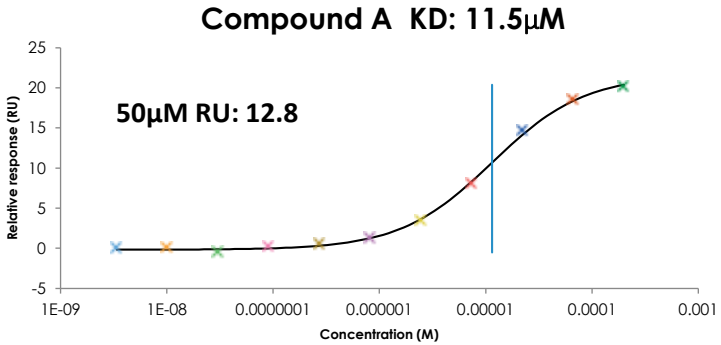
Further qualification of potential hits through sensogram analysis of binding parameters

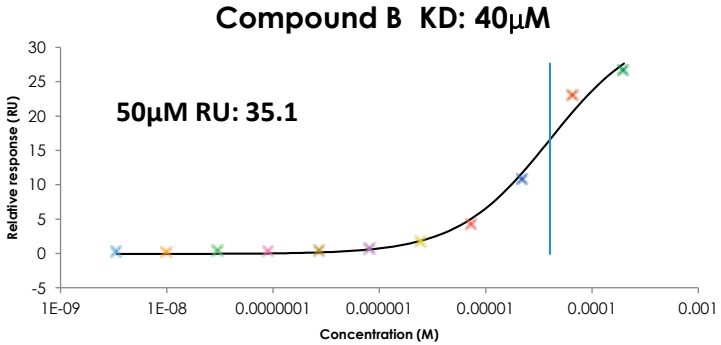




- Each compound sensogram is evaluated against three parameters: Rmax, slope and dissociation
  - Compared with positive control sensogram to further prioritize potential hits
  - Provides context to observed RU value; not just a number
- Offers advantage over traditional HTS methods as compound binding 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

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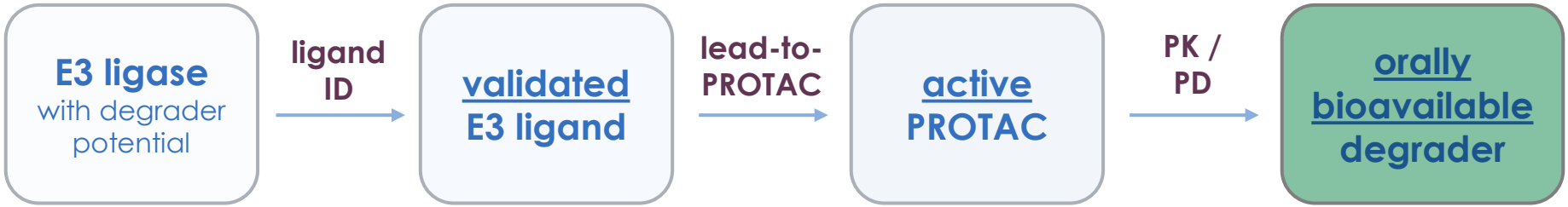
Arvinas Discovery Engine Highlights:
Ternary Complex SPR

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?

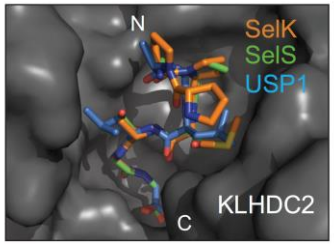


E3 ligand-to-PROTAC discovery → novel $CRL2^{KLHDC2}$ PROTAC degraders

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

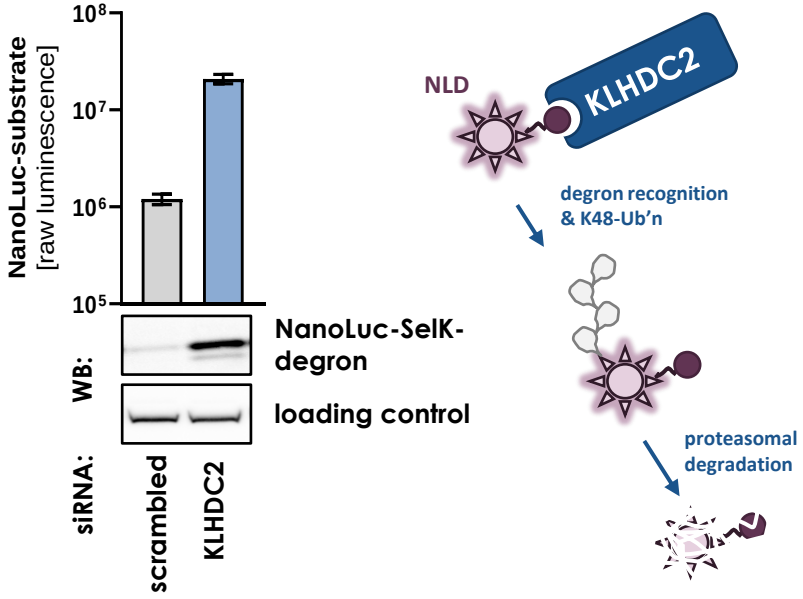
KLHDC2 is an active E3 ligase that can be exploited for PROTAC discovery



- 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

Rusnac et al (2018) Mol Cell / Lin et al (2018) Mol Cell / Koren et al (2018) Cell

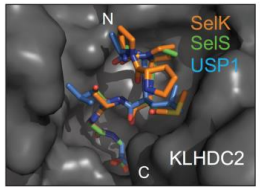
In-house validation of KLHDC2 as a C-terminal degron targeting CRL2 E3 ligase using NanoLuc-degron (NLD) fusions



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



CADD

de novo ligand design

compound 1

SelK aLISA IC_{50} [nM]: **14000**
SPR K_d [nM]: **20000**
SelK TR-FRET IC_{50} [nM]: ND

compound X

SelK aLISA IC_{50} [nM]: **68**
SPR K_d [nM]: **95**
SelK TR-FRET IC_{50} [nM]: **100**

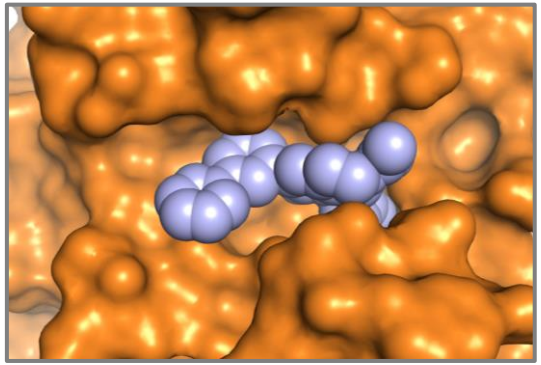
compound Z

SelK aLISA IC_{50} [nM]: **9**
SPR K_d [nM]: **120**
SelK TR-FRET IC_{50} [nM]: **8**

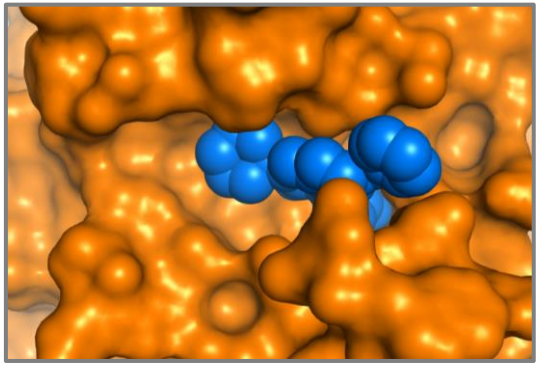
E3-dead

SelK aLISA IC_{50} [nM]: **1000**
SelK TR-FRET IC_{50} [nM]: **810**
SPR K_d [nM]: ND

- 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



$KLHDC2_{KD}$: compound Y @ 1.8 Å



$KLHDC2_{KD}$: compound W @ 1.6 Å

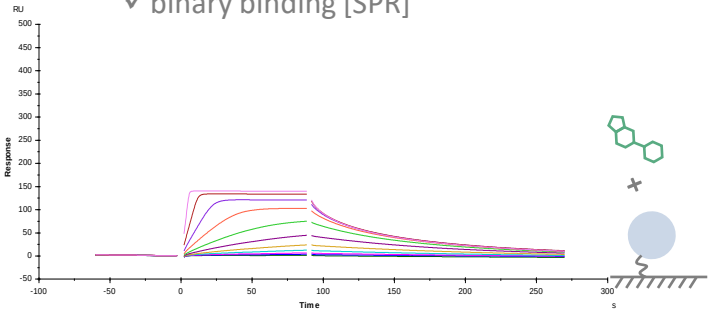
KLHDC2-BRD4 linker SAR points to efficient ternary complex inducing PROTACs as potent degraders

KLHDC2-BRD4 PROTAC	KLHDC2 ligand / linker combo	HiBiT-BRD4 DC_{50} [nM]	HiBiT-BRD4 D_{max} [%]	BRD4-BD2 K_d [nM]	KLHDC2 K_d [nM]	Ternary complex by SPR
PROTAC a1	active / linker-A	67	13	40	318	-
PROTAC a2		8.7	16	531	19	-

PROTAC a1

BRD4-BD2 + PROTAC

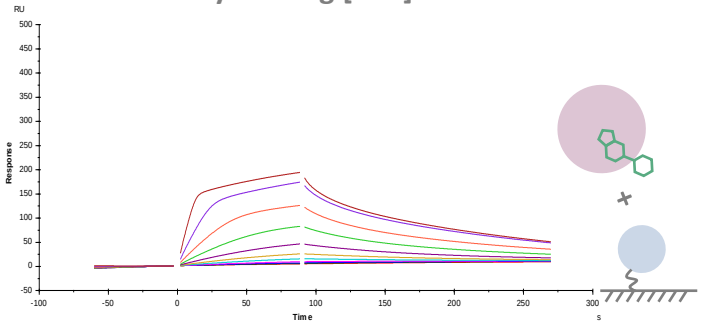
✓binary binding [SPR]



PROTAC a1

BRD4-BD2 + PROTAC + $KLHDC2_{KD}$

- ternary binding [SPR]



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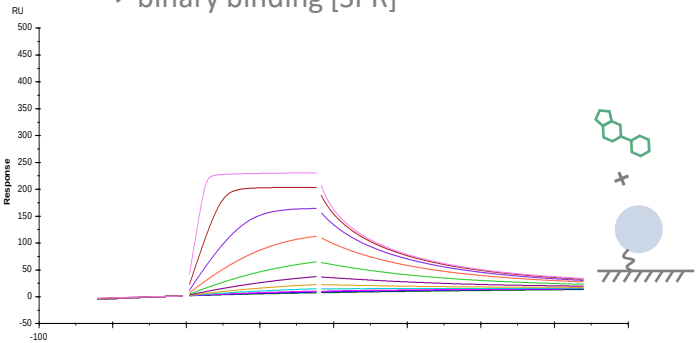
KLHDC2-BRD4 linker SAR points to efficient ternary complex inducing PROTACs as potent degraders

KLHDC2-BRD4 PROTAC	KLHDC2 ligand / linker combo	HiBiT-BRD4 DC_{50} [nM]	HiBiT-BRD4 D_{max} [%]	BRD4-BD2 K_d [nM]	KLHDC2 K_d [nM]	Ternary complex by SPR
PROTAC a1	active / linker-A	67	13	40	318	-
PROTAC a2		8.7	16	531	19	-
PROTAC b1	active / linker-B	37000	20	61	10	-/+
PROTAC b2		1300	60	140	652	-/+

PROTAC b1

BRD4-BD2 + PROTAC

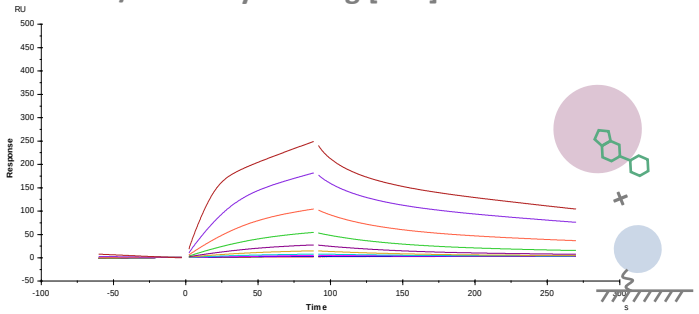
✓binary binding [SPR]



PROTAC b1

BRD4-BD2 + PROTAC + $KLHDC2_{KD}$

-/+ ternary binding [SPR]



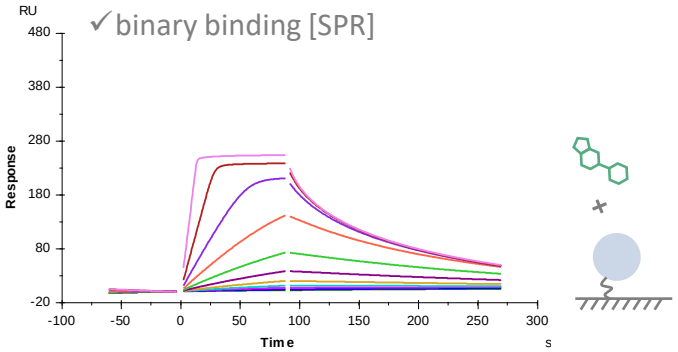
KLHDC2-BRD4 linker SAR points to efficient ternary complex inducing PROTACs as potent degraders

KLHDC2-BRD4 PROTAC	KLHDC2 ligand / linker combo	HiBiT-BRD4 DC_{50} [nM]	HiBiT-BRD4 D_{max} [%]	BRD4-BD2 K_d [nM]	KLHDC2 K_d [nM]	Ternary complex by SPR
PROTAC a1	active / linker-A	67	13	40	318	-
PROTAC a2		8.7	16	531	19	-
PROTAC b1	active / linker-B	37000	20	61	10	-/+
PROTAC b2		1300	60	140	652	-/+
PROTAC A1	active / linker-C	480	88	8	8	+++
PROTAC A2		97	89	60	189	+++
PROTAC A3	E3-dead / linker-C	1300	15	28	28000	-

PROTAC A1

BRD4-BD2 + PROTAC

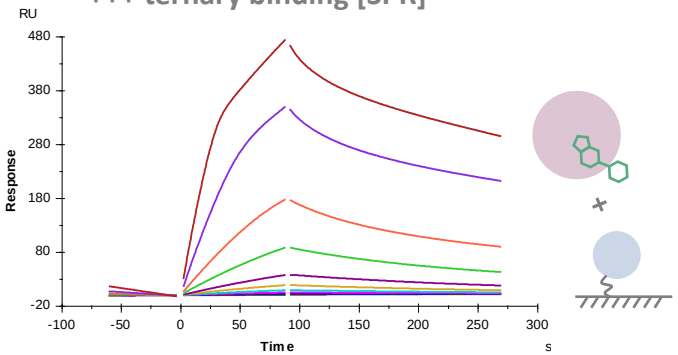
✓binary binding [SPR]



PROTAC A1

BRD4-BD2 + PROTAC + $KLHDC2_{KD}$

+++ ternary binding [SPR]



- **Advanced BRD4 PROTACs show ternary complex formation [as measured by SPR] and robust degradation**

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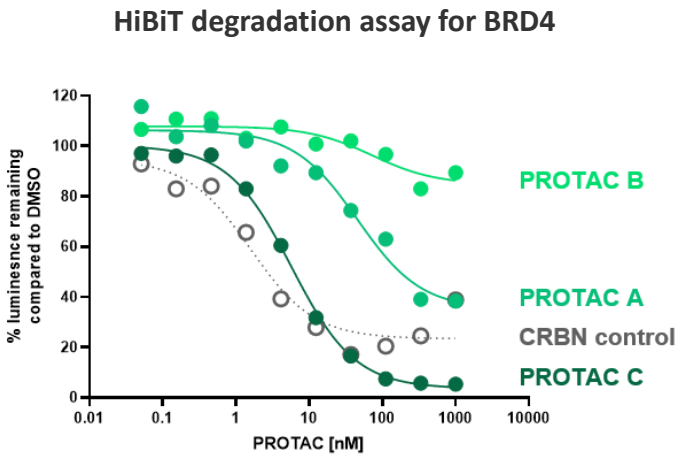
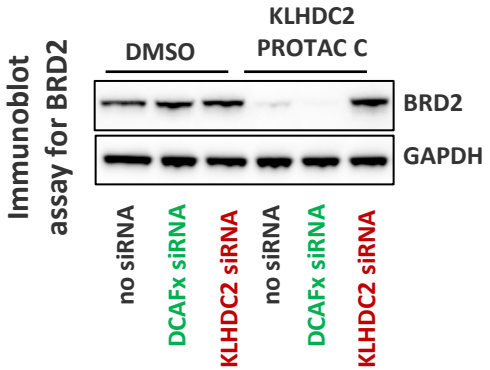
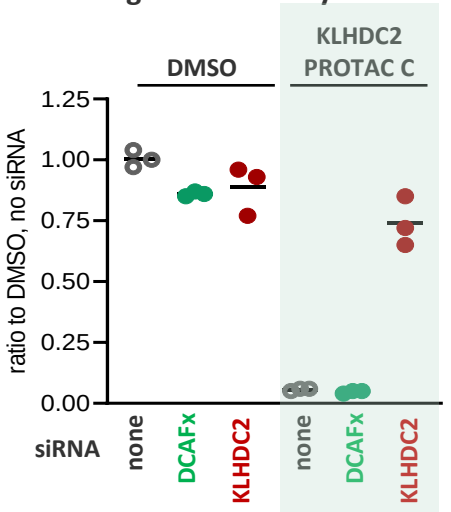
KLHDC2-based PROTAC optimization using JQ1 yields potent pan-BET degraders







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

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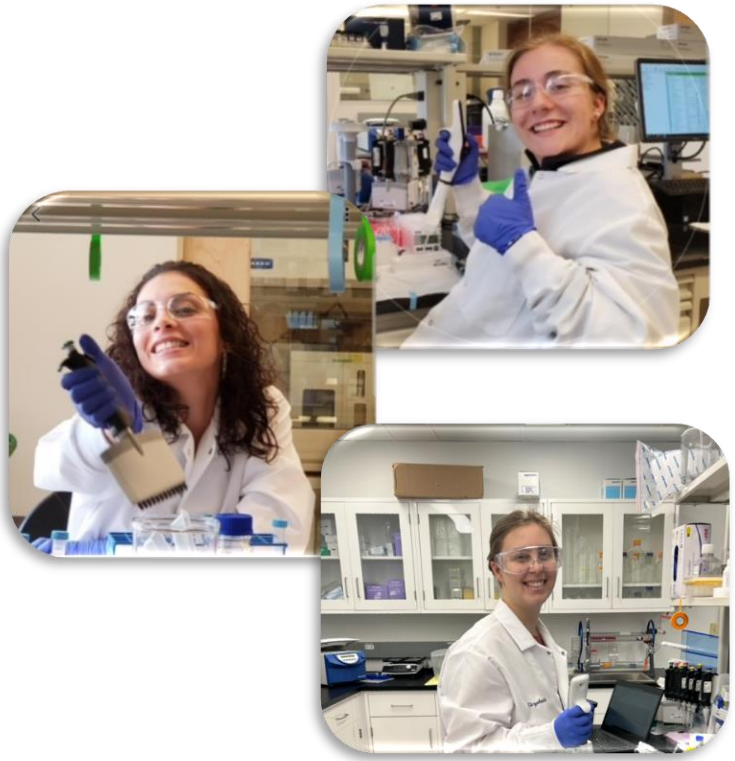
Diversity of biophysical toolbox highly impacts PROTAC design at Arvinas



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!