nurix

Leader in Targeted Protein Modulation

# Utilizing DEL as a Primary Discovery Engine for Targeted Protein Modulation

UCI Pharm Sci Spring Seminar Series

February 8, 2023

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# Nurix Is Focused on Ligase Drug Discovery with State-of-the Art Scientific Infrastructure

## Mission Bay, San Francisco

- >$300 million in collaboration revenue to date
- ~300 FTEs
- Experienced medicinal chemistry team with integrated structure-based design chemistry automation capabilities
- Biophysics, biochemistry, proteomics, cell biology and custom affinity screening capabilities
- Pharmacology PK/PD capabilities enabled by state-of-the-art in-house vivarium
- Clinical team prosecuting four wholly owned clinical programs in Phase 1 studies
- **We are hiring! Visit https://www.nurixtx.com/job-openings/**

# Nurix Drugs Engage Ligases for the Treatment of Cancer

## Targeted Protein Modulation: TPM = TPD + TPE

A Powerful Cellular System

Targeted Protein Elevation (TPE)

**Inhibit ligases** to increase specific protein levels

**Harness ligases** to decrease specific protein levels

Targeted Protein Degradation (TPD)

Ubiquitin is ligated to target proteins to tag them for degradation by the proteasome

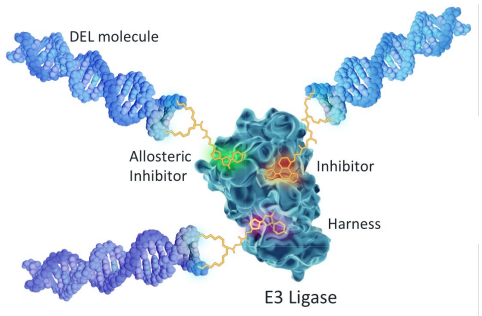
# Nurix Is Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

| MOA | Drug program | Target/delivery | Therapeutic area | Preclinical | Phase 1 | Phase 2 | Phase 3 |
|---|---|---|---|---|---|---|---|
| TPD | **NX-2127** Degrader | BTK-IKZF *Oral* | B-cell malignancies | | | ✓ Advanced to Ph 1b in CLL<br>✓ Efficacy established in CLL<br>✓ Single agent CR in DLBCL | |
| TPD | **NX-5948** Degrader | BTK *Oral* | B-cell malignancies | | | ✓ Dosed first patient in U.K.<br>✓ Demonstrated BTK degradation<br>✓ IND cleared for U.S. enrollment | |
| TPE | **NX-1607** Inhibitor | CBL-B *Oral* | Immuno-Oncology | | | ✓ Demonstration of CBL-B inhibition with novel biomarker<br>✓ IND cleared for U.S. enrollment | |
| TPE | **DeTIL-0255** Cell therapy | *Ex vivo CBL-B inhibition* | Gynecologic malignancies | | | ✓ Dosed first patient<br>✓ Completed safety run-in | |
| **TPM** | Wholly owned & partnered | 15 targets | Multiple | | | | |

Progress since January 2022

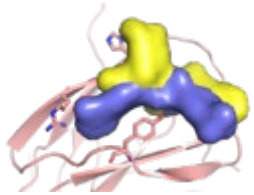
# Nurix's DELigase Protein Modulation Discovery Platform

## DEL Discovery



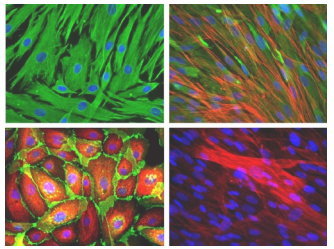

> 5 billion drug-like compounds that can be easily screened against hundreds of proteins to identify starting points for therapeutic discovery

## Rational and Empirical Chemistry



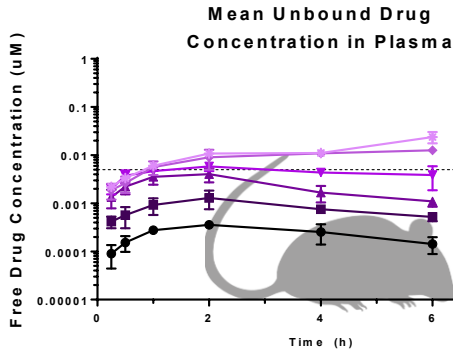
Structure Based Drug Design combined with chemistry automation enables broad exploration of lead-like chemical space for each program

## Direct-to-Cell Biology Capabilities



High throughput cellular assays monitor protein levels and biological phenotypes to assess impact on biology

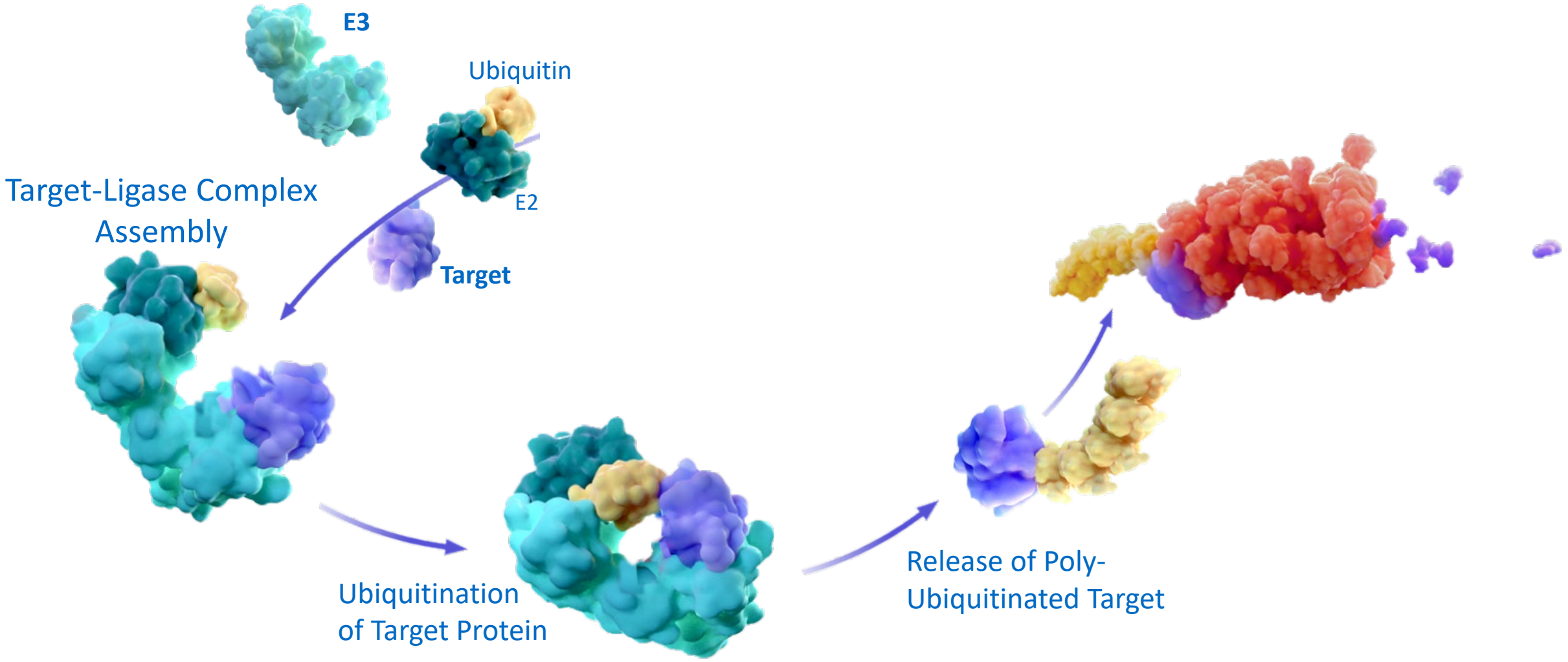
## Scaled Screening for in vivo exposure




Capacity to screen for ideal *in vivo* drug exposure profile and assess impact on disease biology

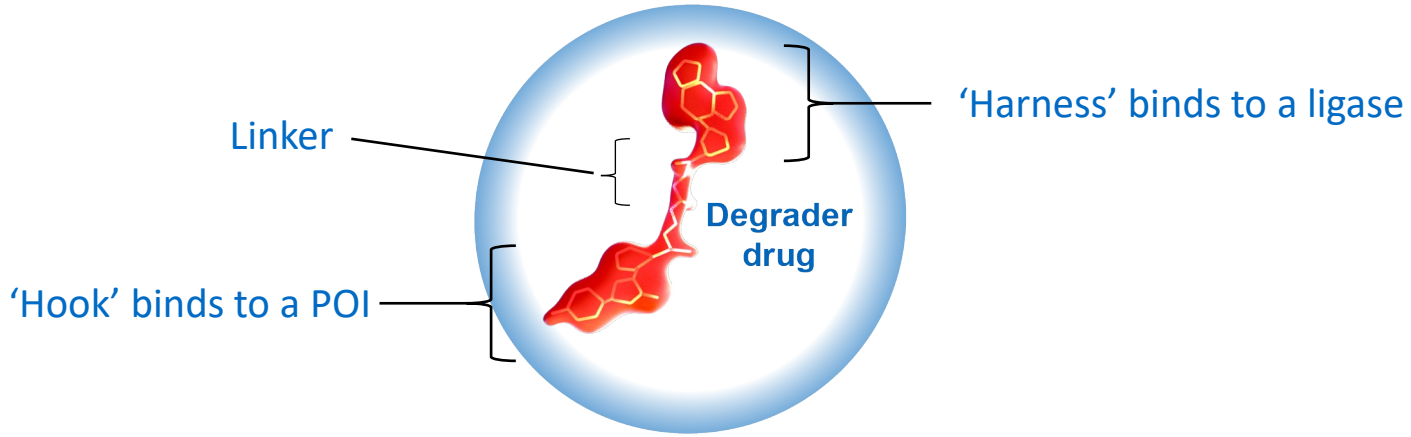
# What Is Targeted-Protein Degradation (TPD)?

*The ubiquitin proteosome system degrades proteins*



# What Is Targeted-Protein Degradation (TPD)?

*Harnessing the ubiquitin proteosome system to degrade a protein of interest (POI)*




A Degrader contains three moieties:

1. A ligase 'harness'
2. A linker
3. A 'Hook' to the POI

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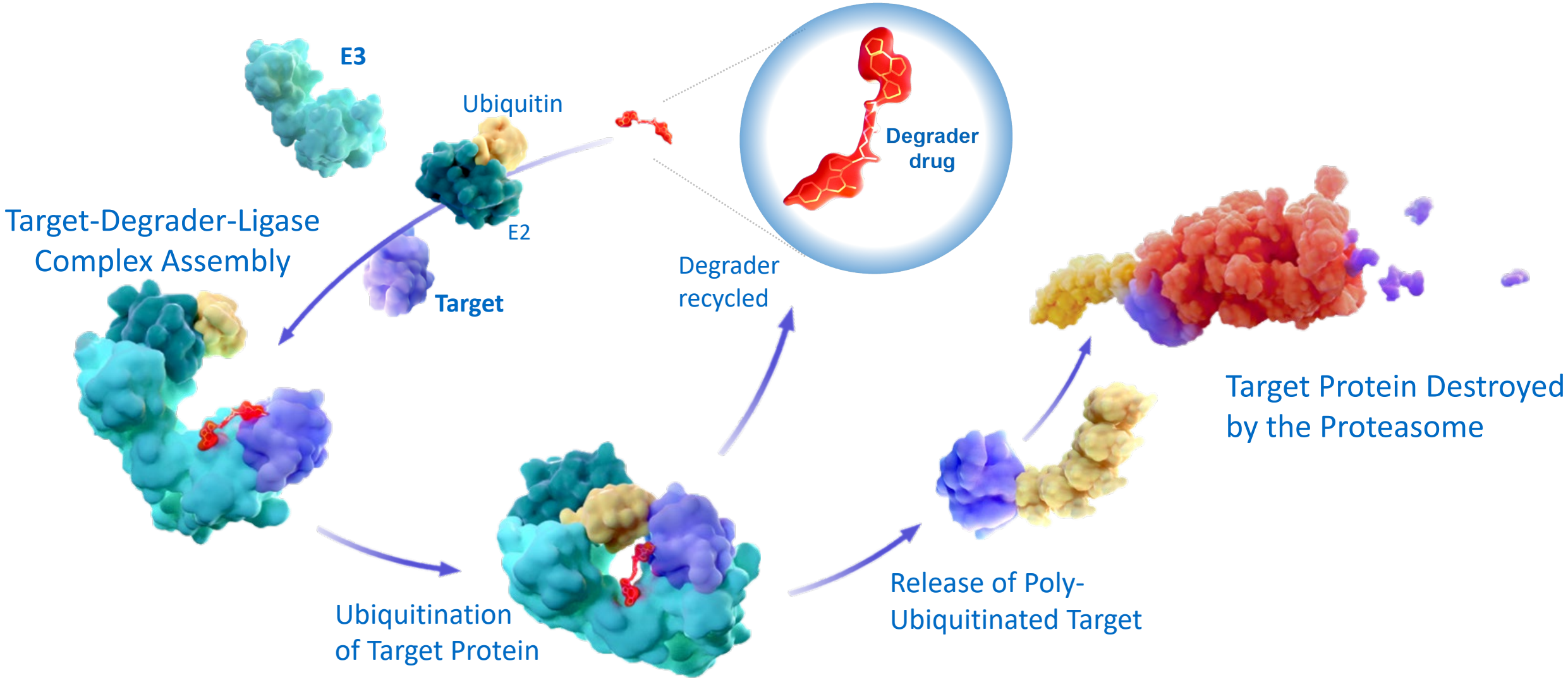
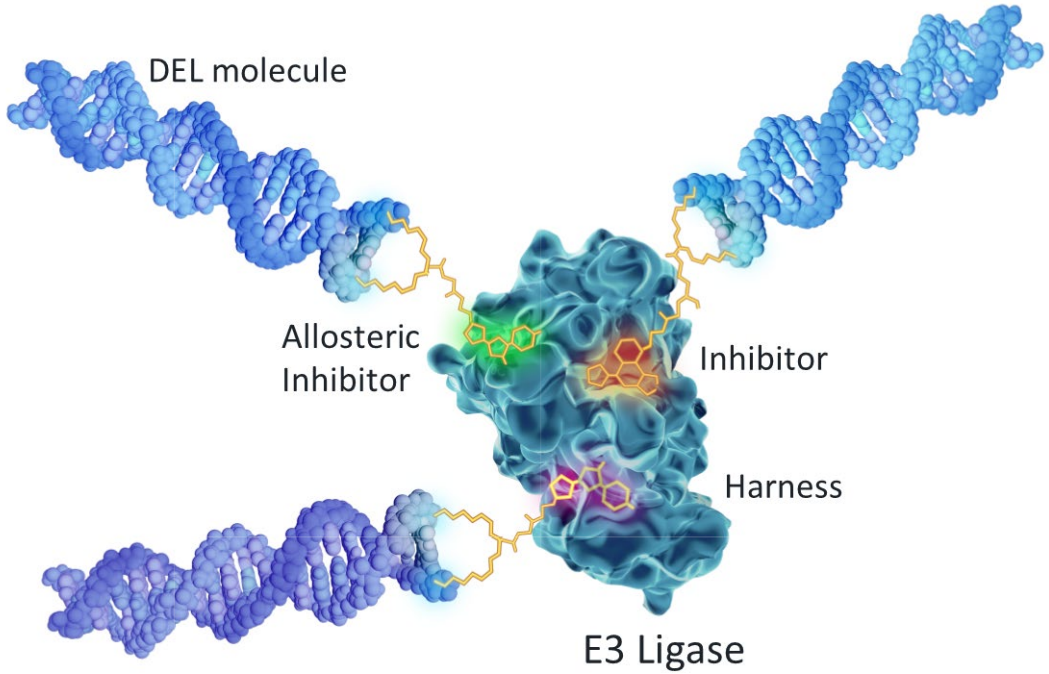


# Why DNA Encoded Libraries? – Advantages for TPM

- **Affinity-based ligand discovery is the ideal approach to enable TPD**
  - **Affinity-based screening is MoA agnostic – for E3 ligases we can identify ligands for TPD and inhibitors for TPE from the same screen**
- DNA attachment provides initial handle for bifunctional molecule synthesis
- Combinatorial design enables rapid hit follow up and optimization
- Low capital investment and per screen cost allows for a broad exploration of target and chemical space



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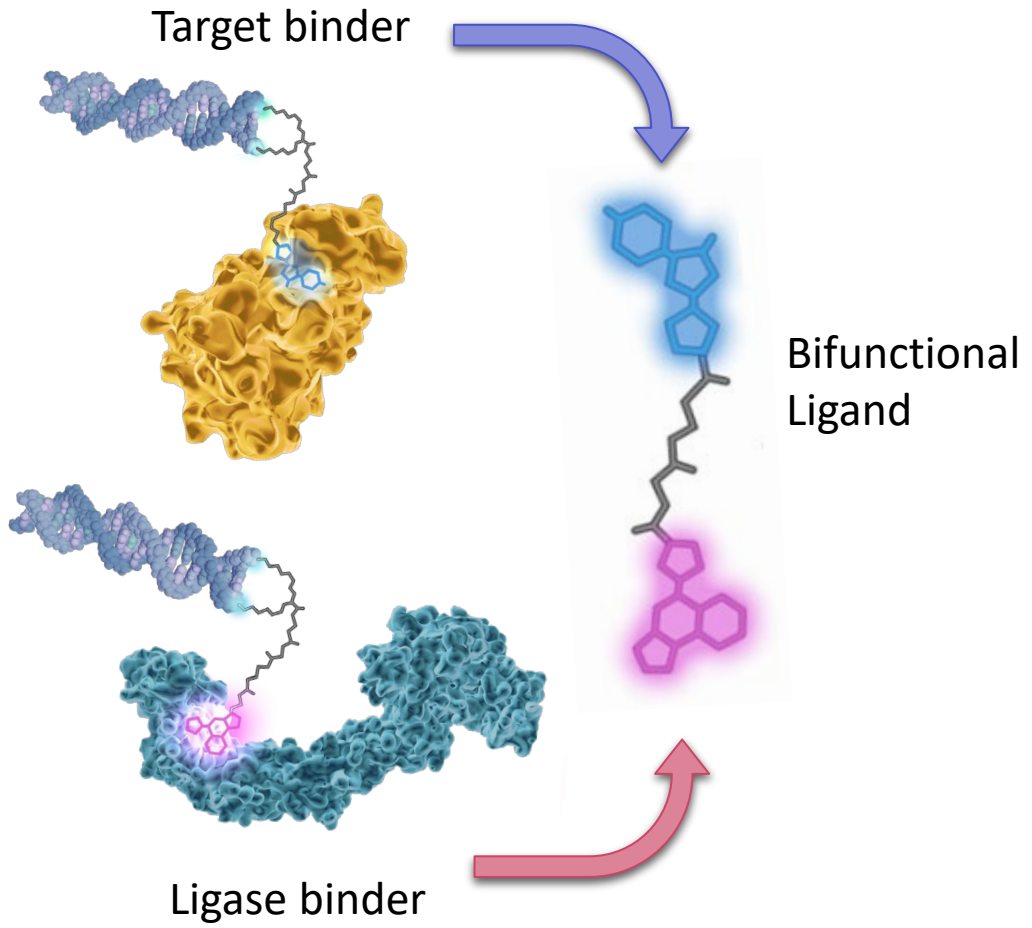

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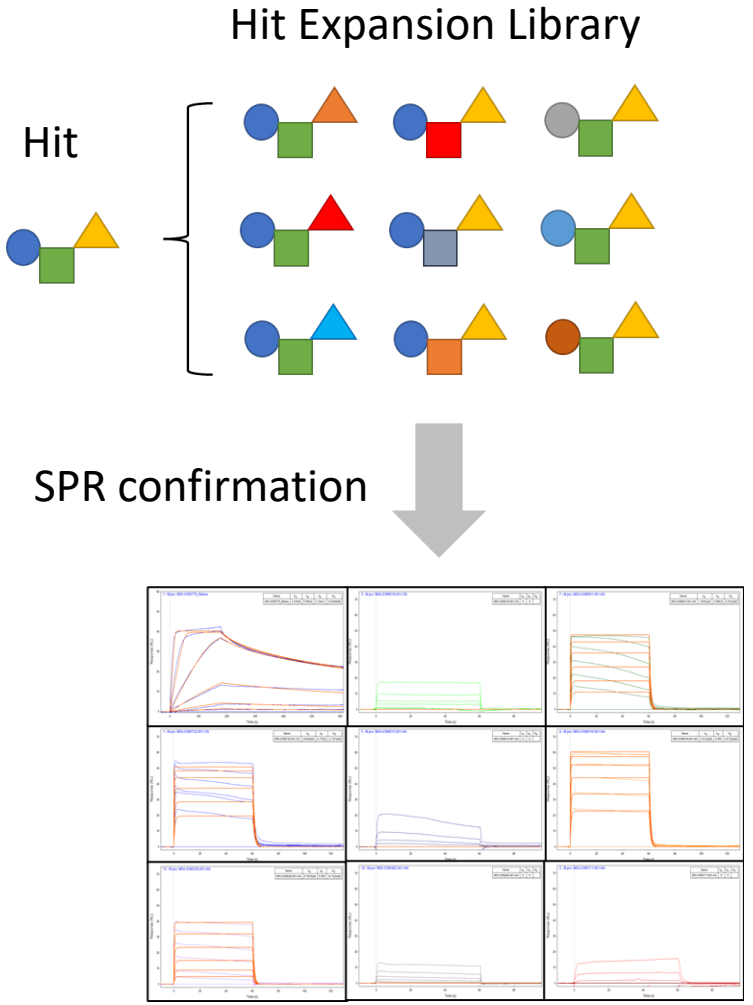

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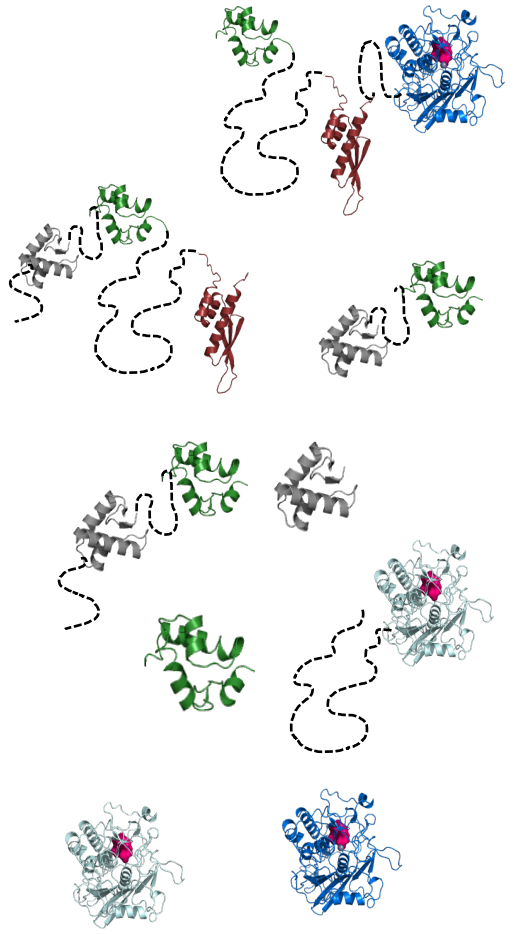
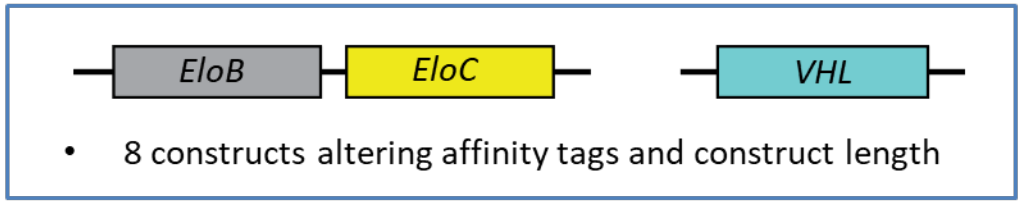
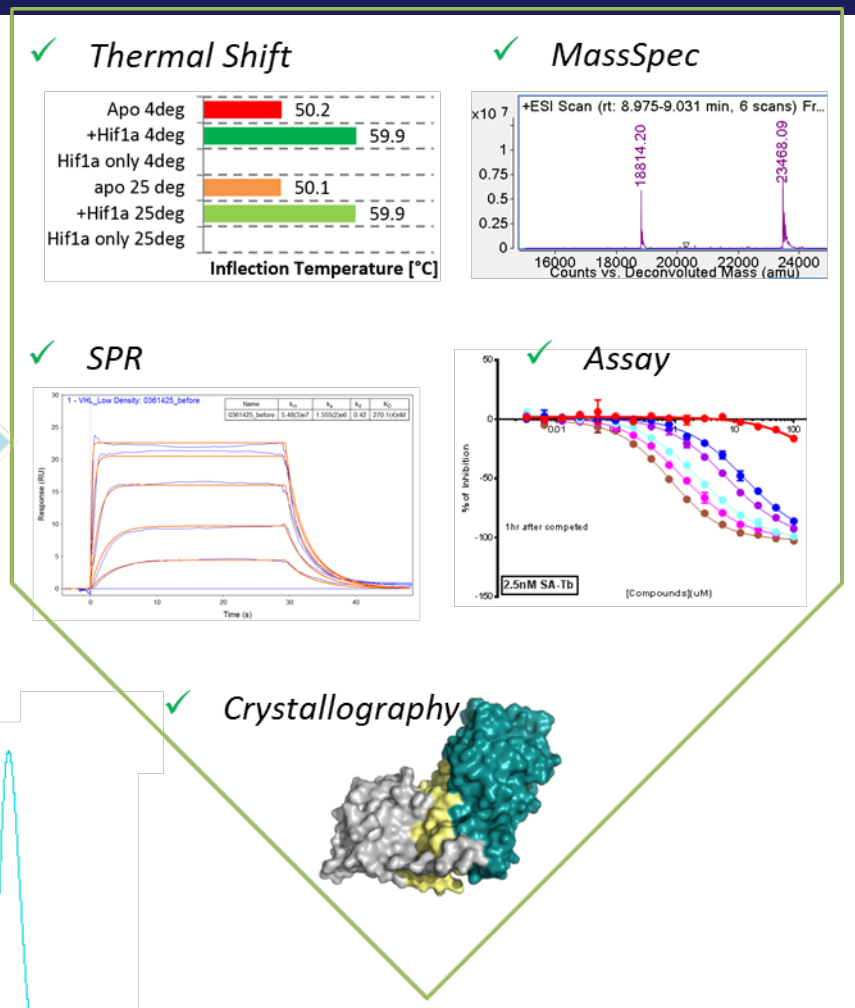
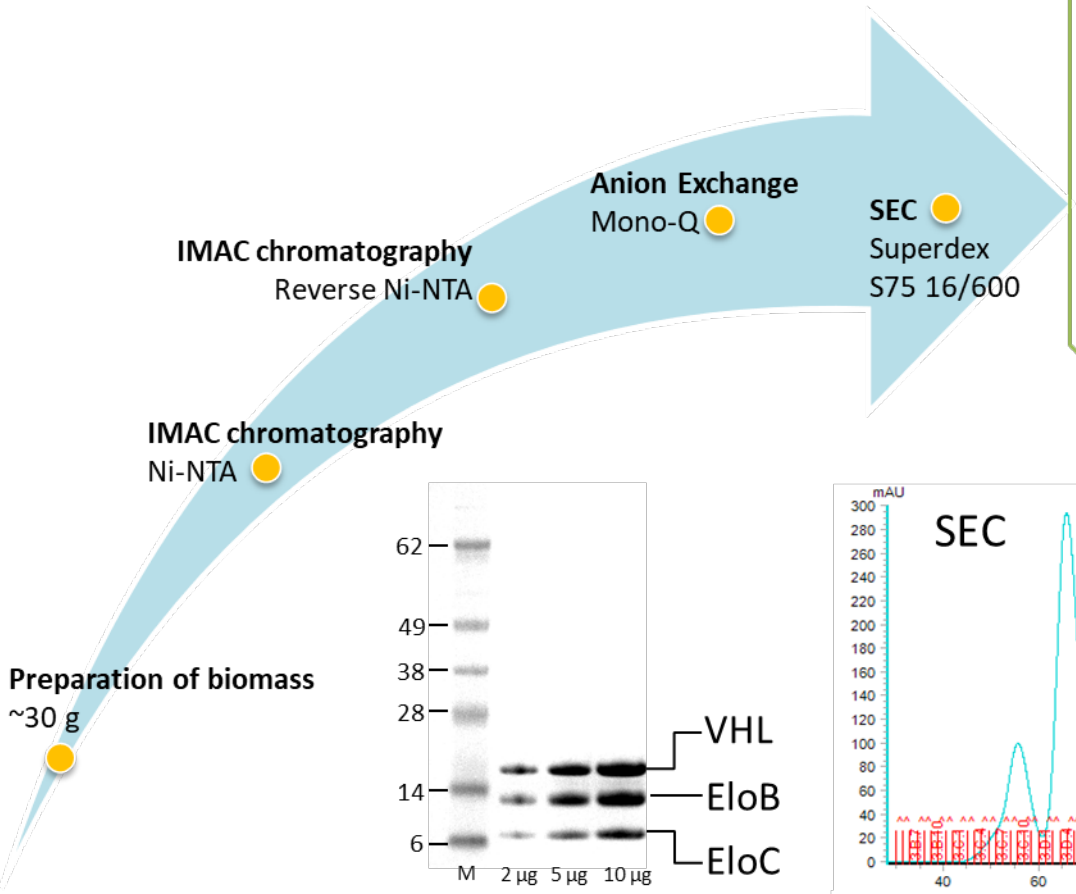


# Protein Quality Is Fundamental to DEL Screen Success



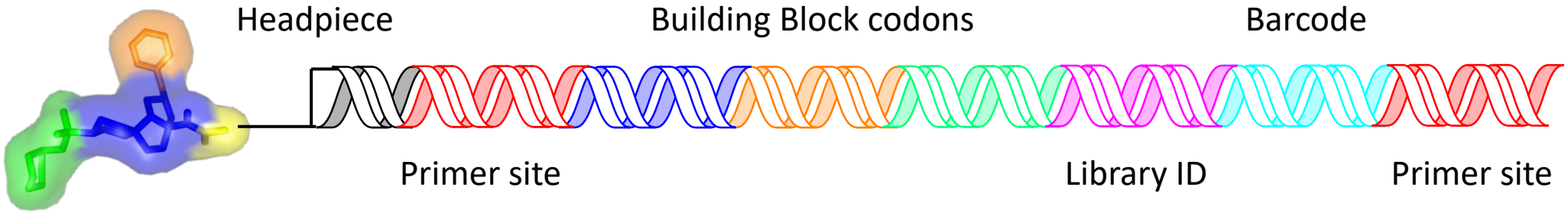




DEL Screen

# Anatomy of a DEL Molecule

DNA-based encoding schemes allow for screening and sequencing of pooled libraries across numerous binding conditions in parallel.

Small molecule “warhead”
*Not to scale

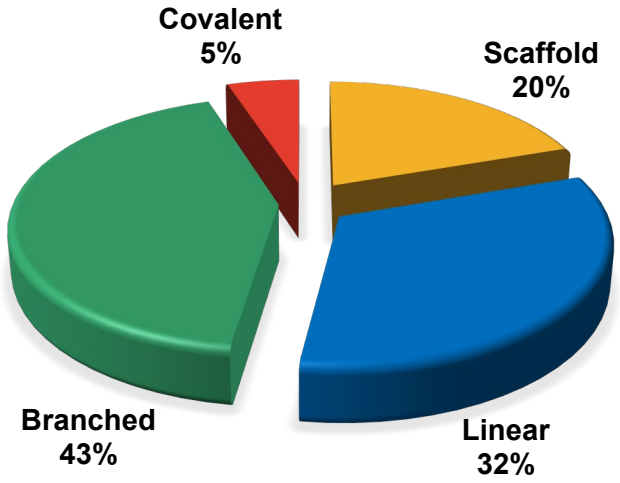



Headpiece – short, covalently-linked, DNA duplex – the handle for chemistry and molecular biology
Primer sites – for quantitation, amplification, and sequencing
Codons – building block identities
Library ID – chemistry carried out on the building blocks
Barcode – unique molecular identifier for every molecule in the screen

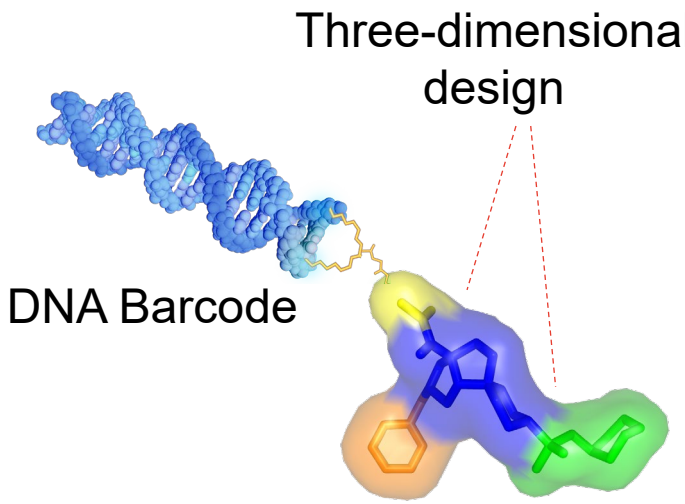
# Custom Scaffold-Based DELs Enable Nurix To Identify Binders to Challenging Protein Surfaces

Nurix DEL Collection

- >5 billion unique structures
- Includes proprietary, 3D complex, custom scaffolds

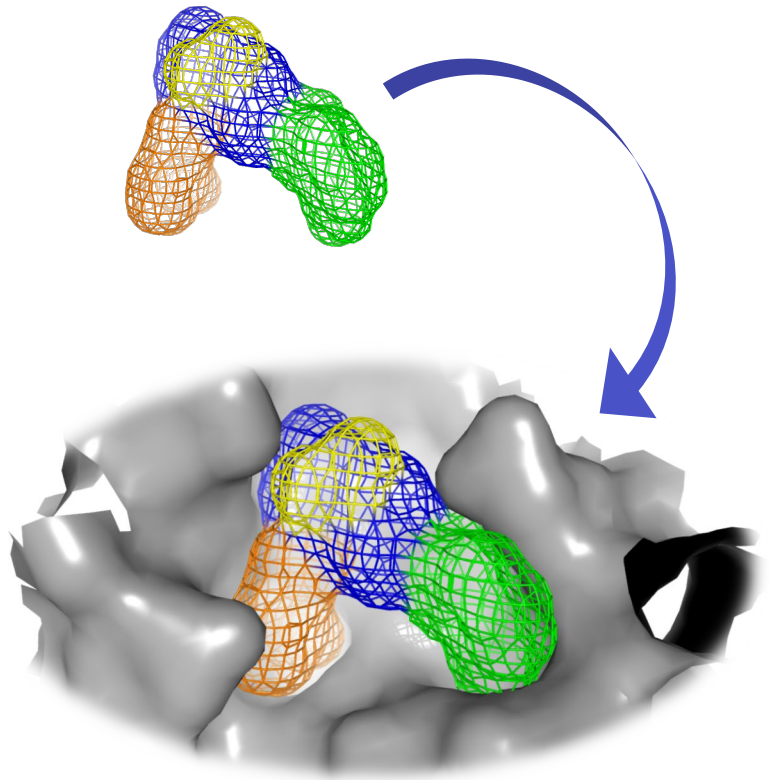



Scaffold Libraries Proving Essential for Delivering Ligands for "Undruggable" Targets (sole source of hits for 75% of these targets)



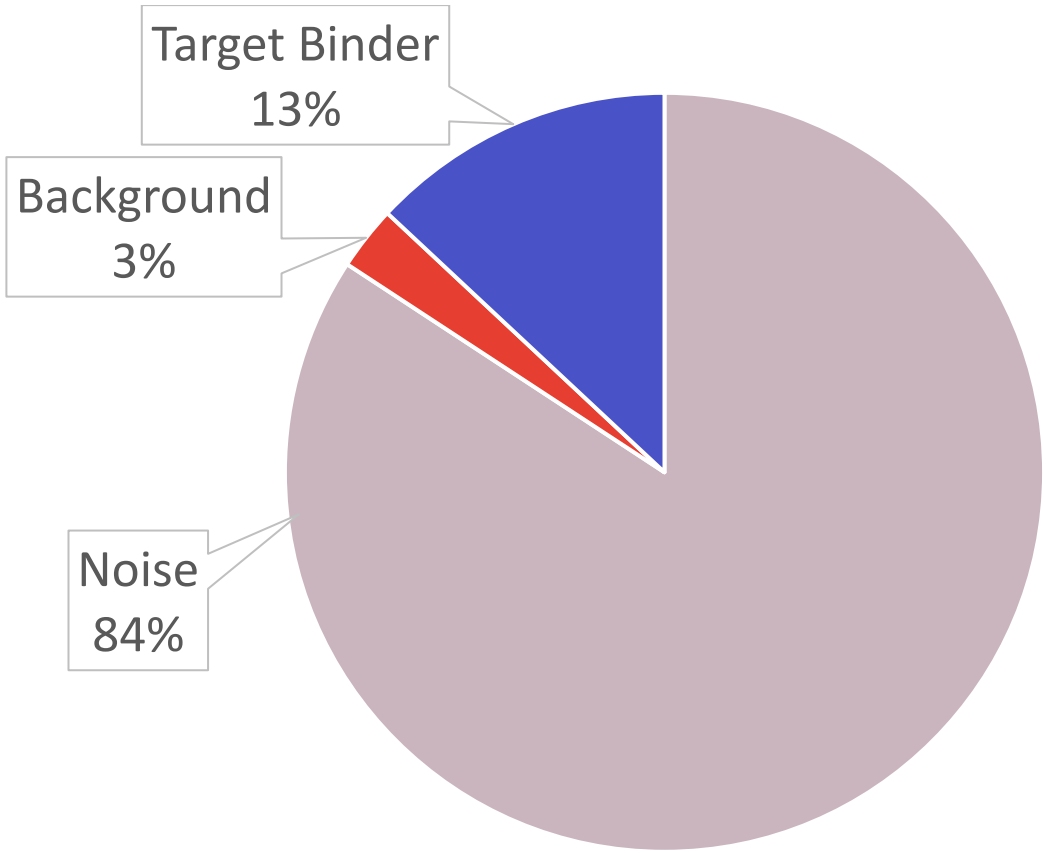

Our proprietary scaffold DELs provide unique geometry and high sp3 character, allowing molecules to achieve optimal pocket fit

Nurix scaffold designs show high pocket complementarity



# Composition of DEL Screening Outputs

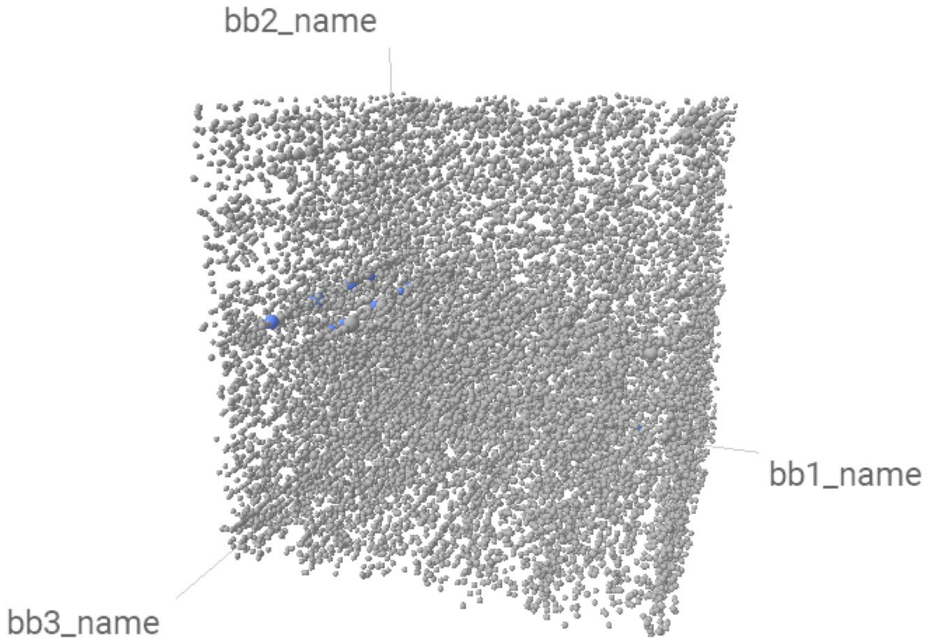
- Most of the DNA-linked compounds sequenced at the end of a selection are noise or background (matrix binders, non-specific protein binding, other enrichment not specific to the target)
    - Noise can be eliminated by experimental (replicates) OR analytical (thresholding) methods
    - Elimination of background signal requires the combination of experimental AND analytical methods.



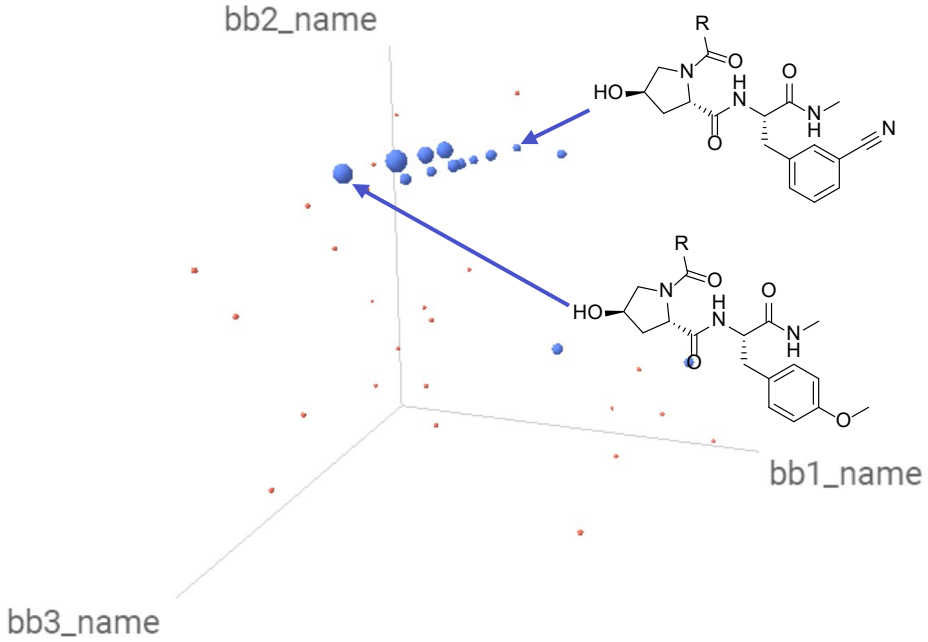
# De-noising Example – VHL Replicates

- Noise by its nature is not reproducible, but real binding events are.

All ligands present in a single screening condition

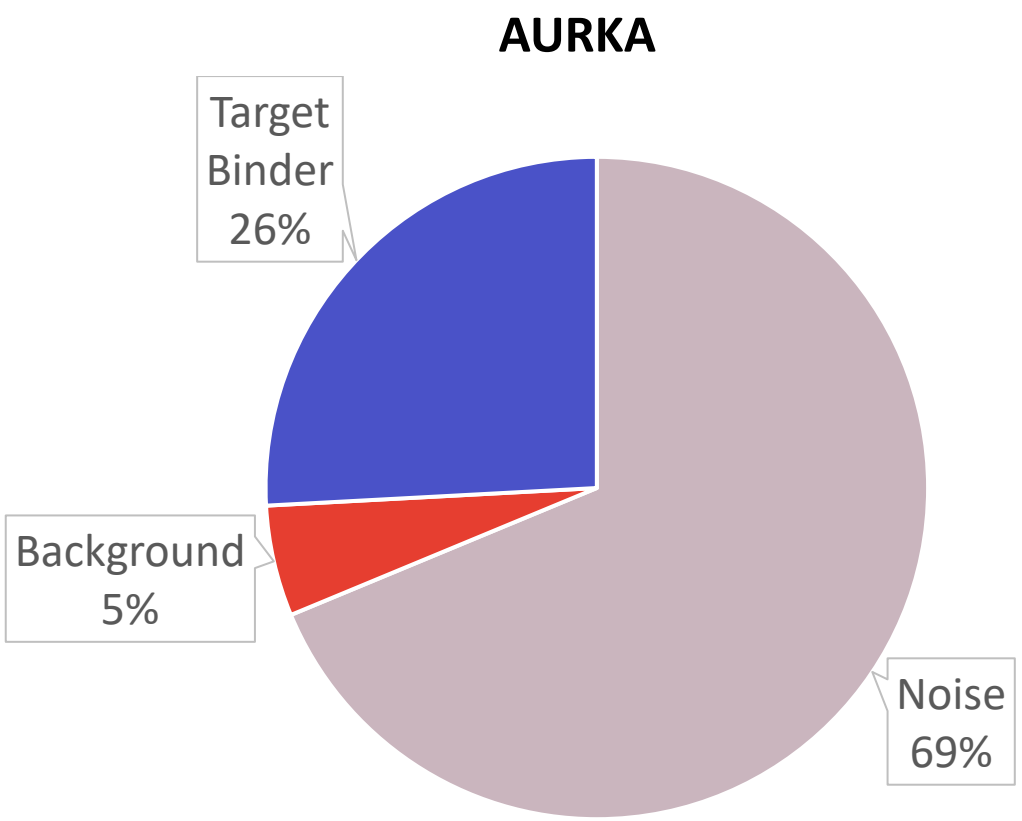


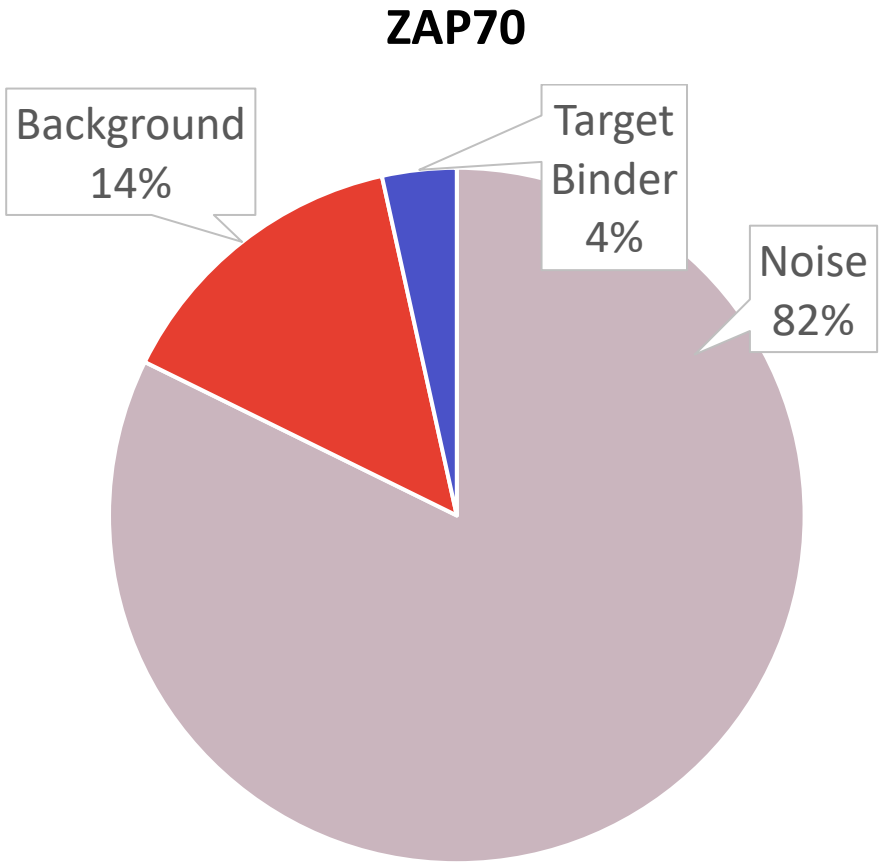

All ligands present in all three replicates



# Target Binder Yields Vary Across Screens

- Not all screens are equally productive at the sequencing level, but with the right analysis they can be equally productive sources of hits.



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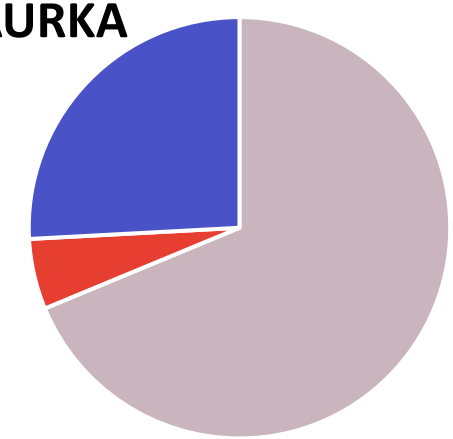
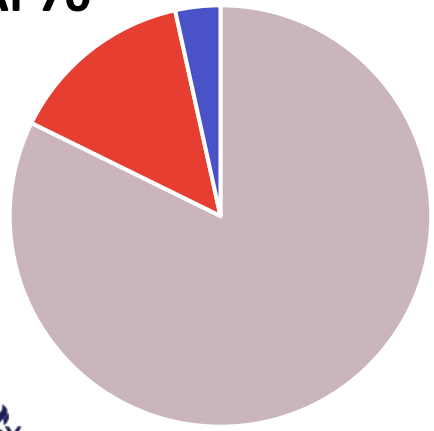
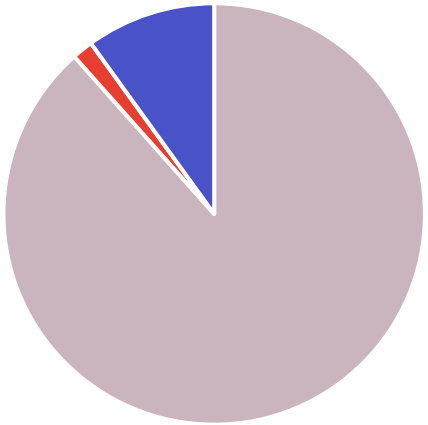
**AURKA**

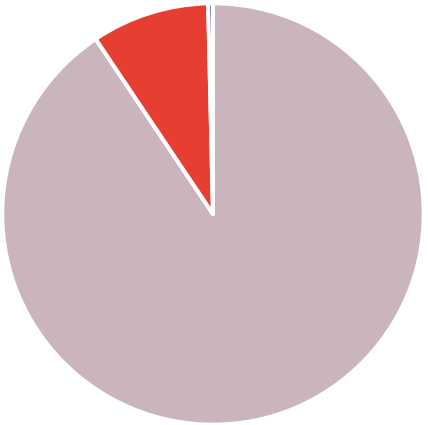


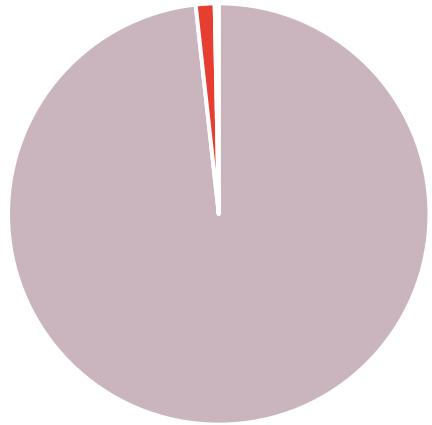
**ZAP70**

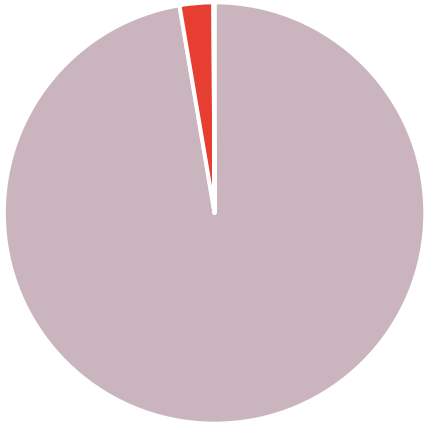


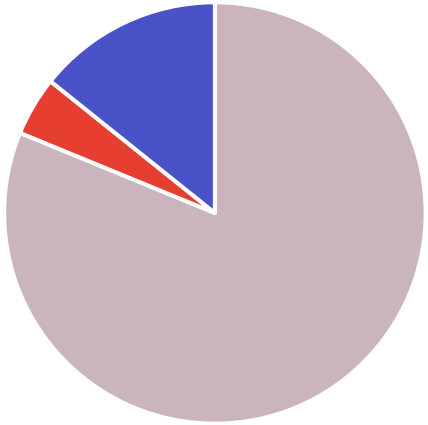
**Other DEL targets with confirmed sub-uM hits**





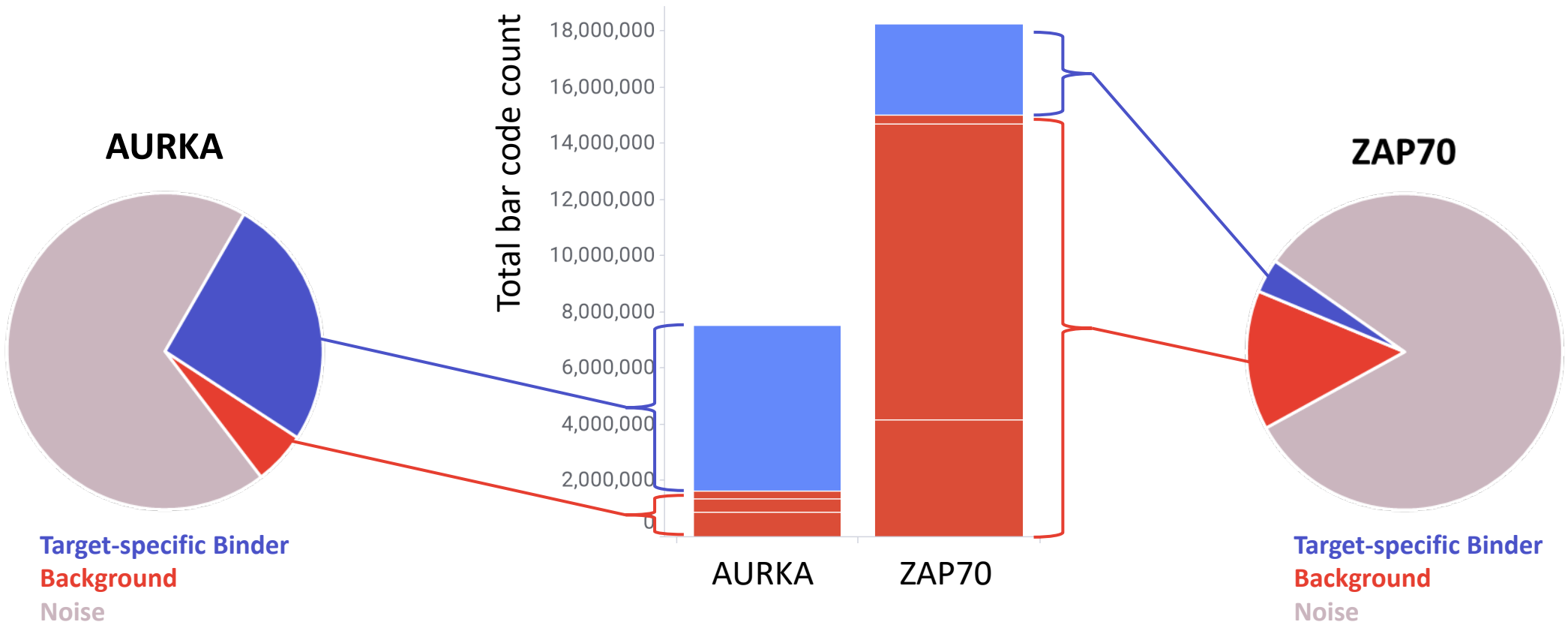






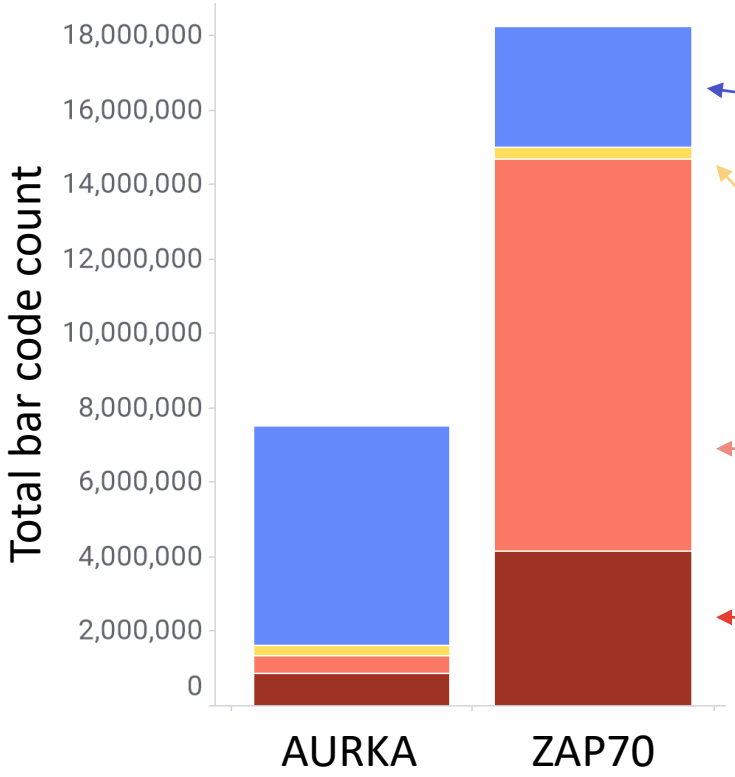
Target-specific Binder
Background
Noise

# Zooming in on the Enriched Fraction



# A Robust Database Is Necessary for Effectively Identifying Background

- A combination of experimental AND analytical methods are required to effectively eliminate background.
- Not all background binders are identified in control screens.
- The capacity of the platform enables screening across many targets, which powers a database that can effectively remove background binders and identify selective (and non-selective) target binders.




**Profile**

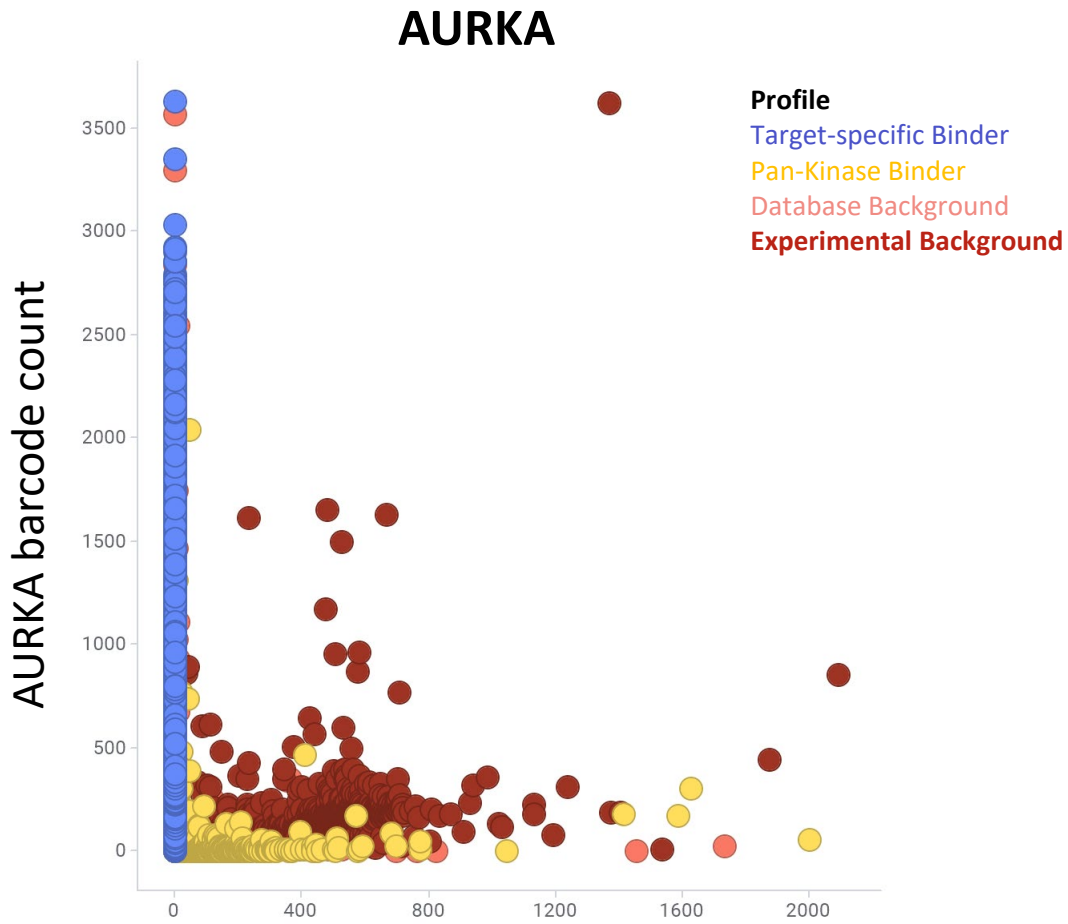
Target-specific Binder – ligands enriched only against the target of interest

Pan-Kinase Binder – enriched against target kinase and only other kinase targets in the database

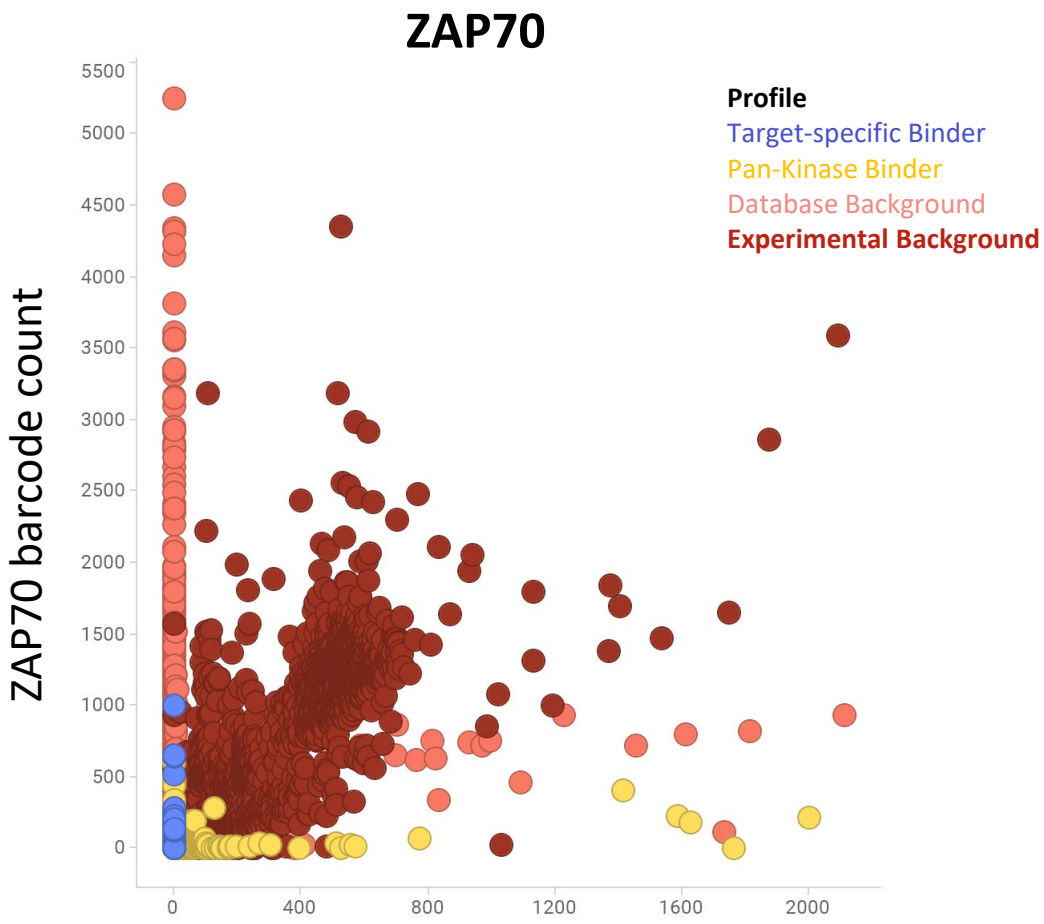
Database Background – background binders enriched in the target selection and selections from other screening campaigns

**Experimental Background** – background binders enriched in target and control selections

# Data Drives the Right Decisions in Follow-up Chemistry




Highest barcode count in control selections

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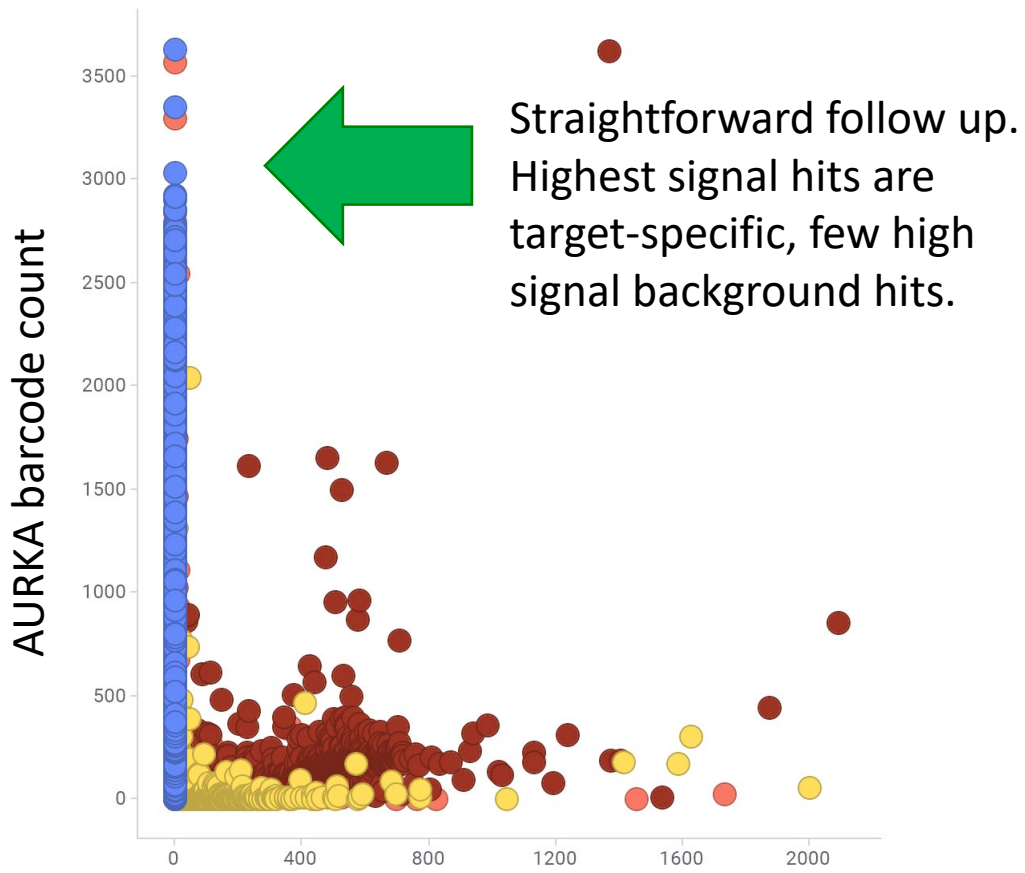
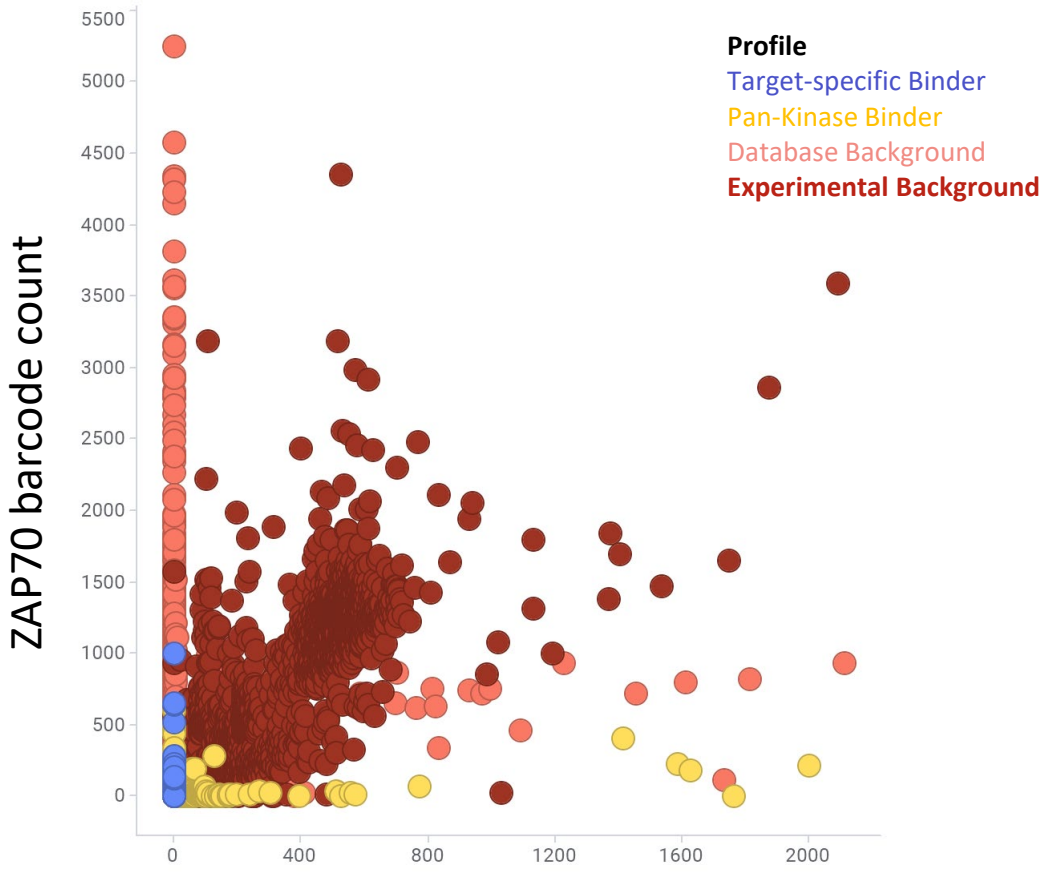



Straightforward follow up. Highest signal hits are target-specific, few high signal background hits.

Highest barcode count in control selections

## ZAP70

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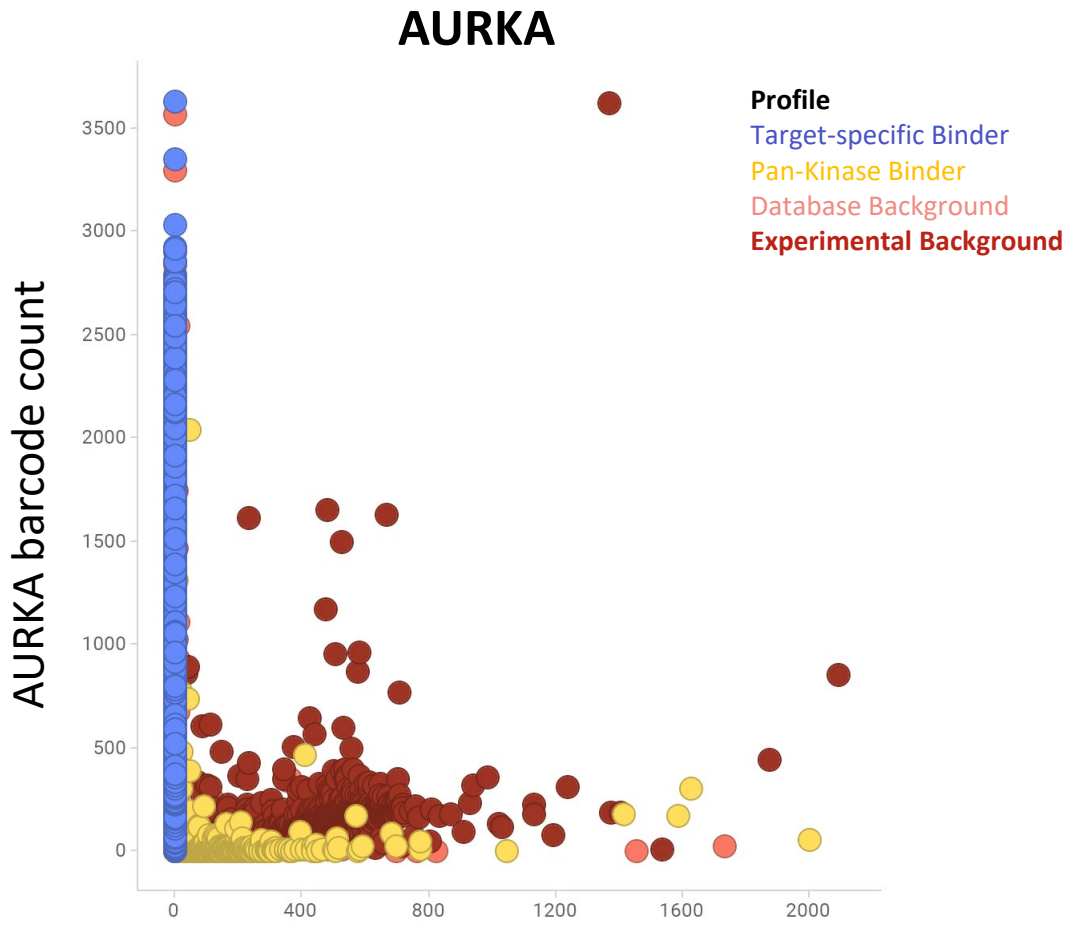


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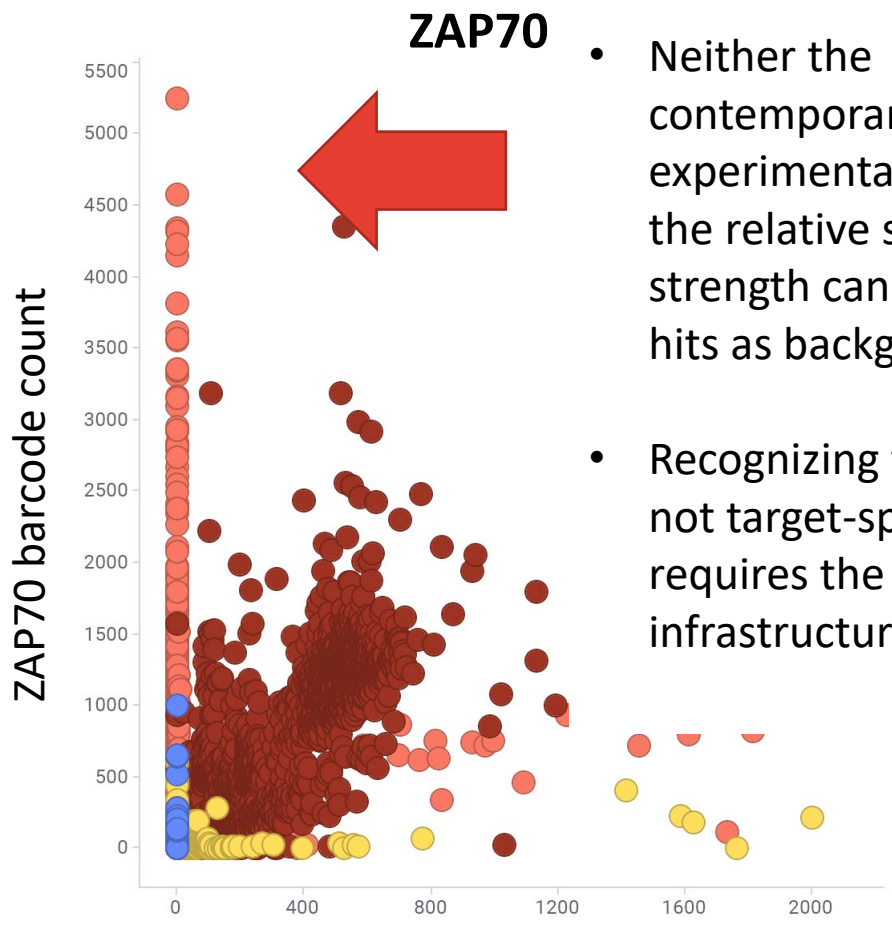
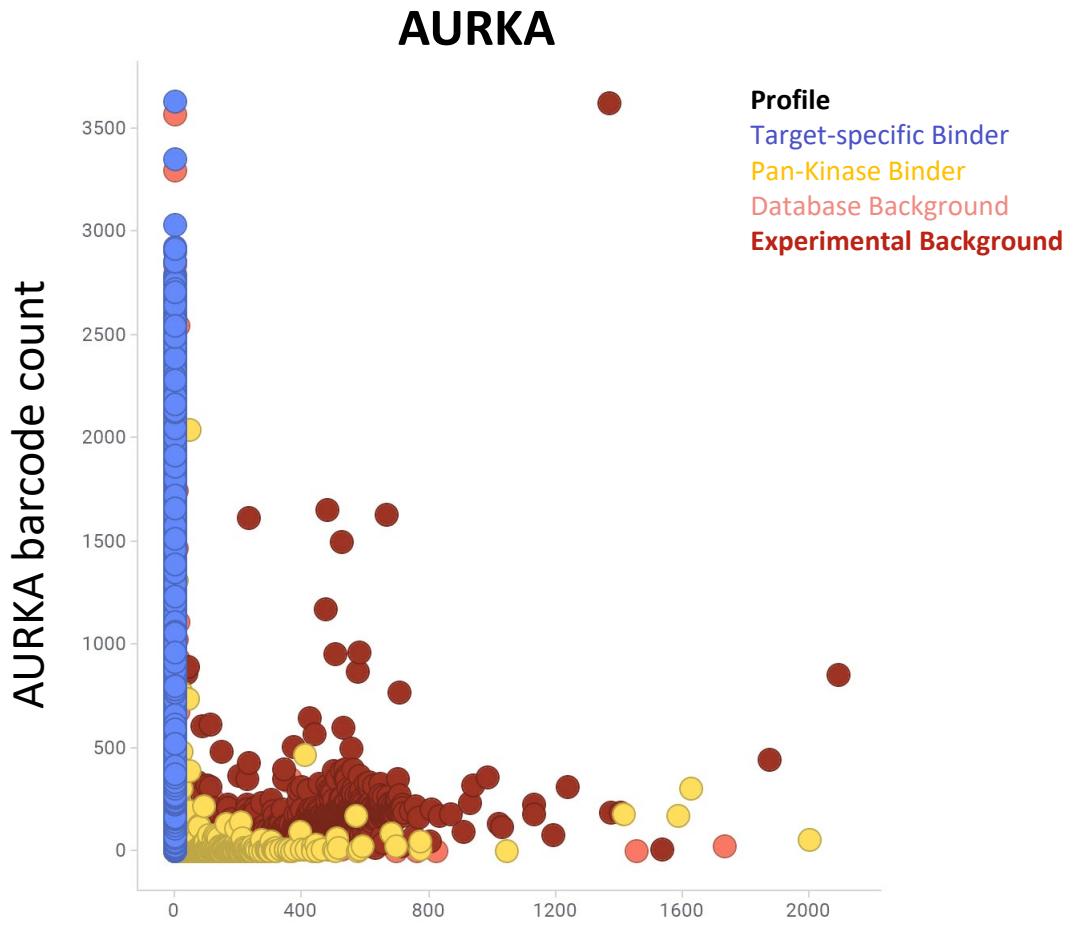


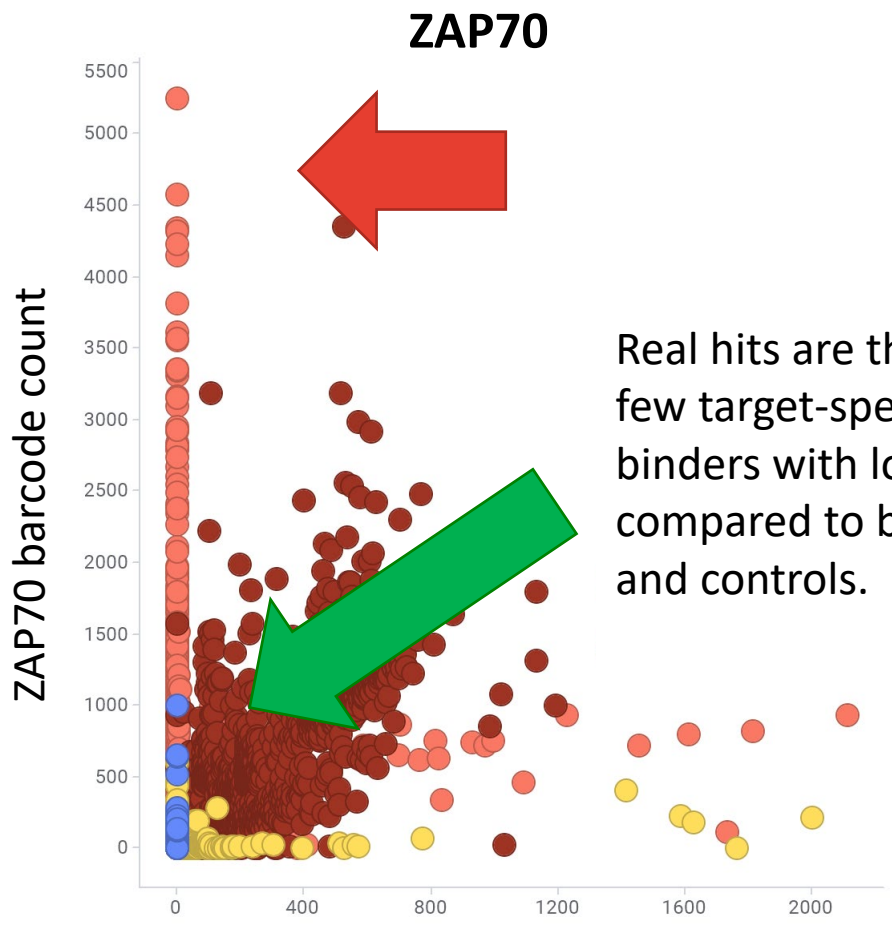

Highest barcode count in control selections

- Neither the contemporary experimental controls or the relative signal strength can flag these hits as background.
- Recognizing this signal is not target-specific requires the right data infrastructure.

# Data Drives the Right Decisions in Follow-up Chemistry




Highest barcode count in control selections

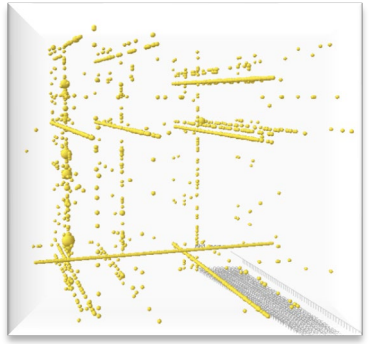



Real hits are the relatively few target-specific binders with low signal compared to background and controls.

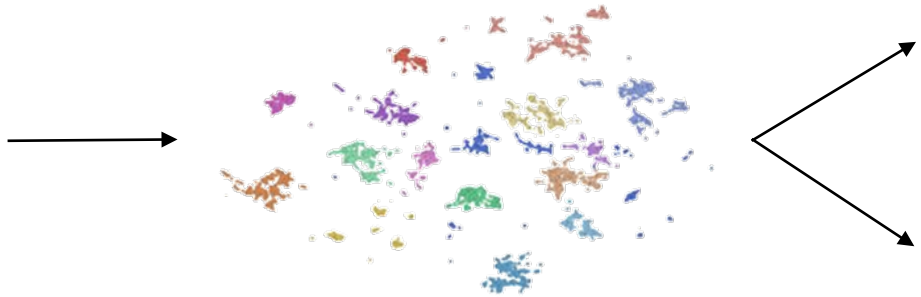
Highest barcode count in control selections

# Wading Through the Data - Nurix's Analysis and Follow Up Pipeline Is Designed To Access Broad Chemical Space

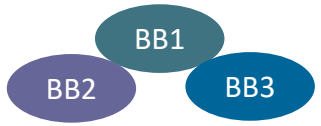
Large complex data sets require automated solutions to accelerate hit ID



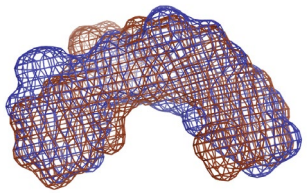
DEL Screen and filtering for target-specific binders



Automated Structure Analysis and Clustering




Hit Resynthesis (on- and off-DNA)

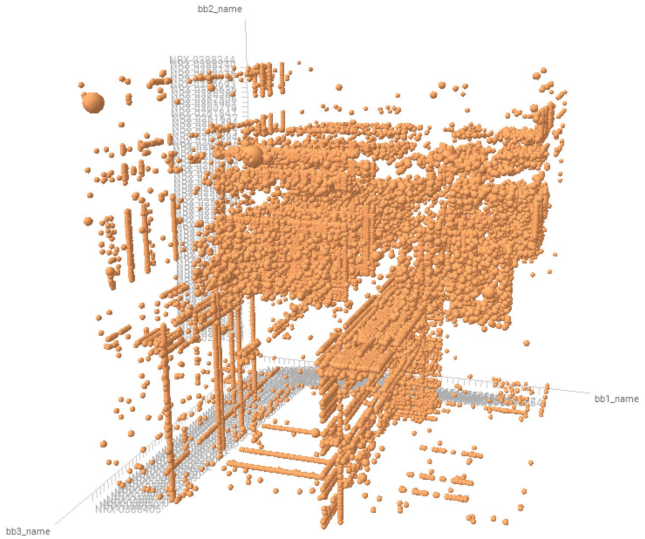


Machine Learning and Similarity Virtual Screening

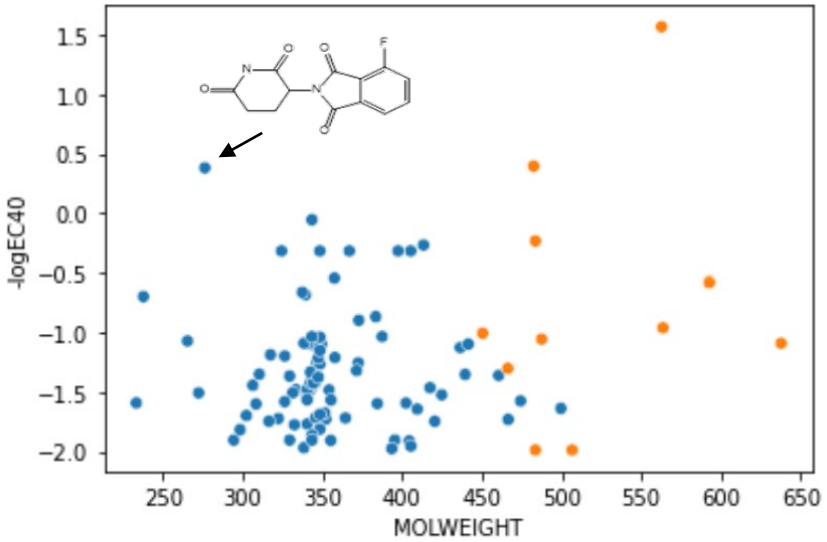
| Follow up | Source | Volume | Hit Confirmation Assay |
|---|---|---|---|
| Off-DNA | Single compound synthesis | 10s | SPR (Quantitative) |
| On-DNA | Parallel Synthesis of single recipes | 100s | ASMS (Qualitative) |
| ML/Similarity | Catalog order | 100s | ASMS then SPR (Quantitative) |

# Leveraging Computational Methods To Search Beyond DEL Space To Discover Potent and Diverse CRBN Binders

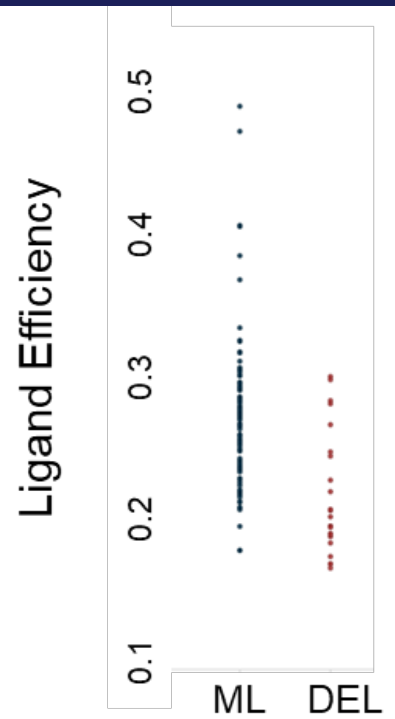
CRBN DEL Screen
(Filtered to Target Binders)




Off-DNA and
ML follow up





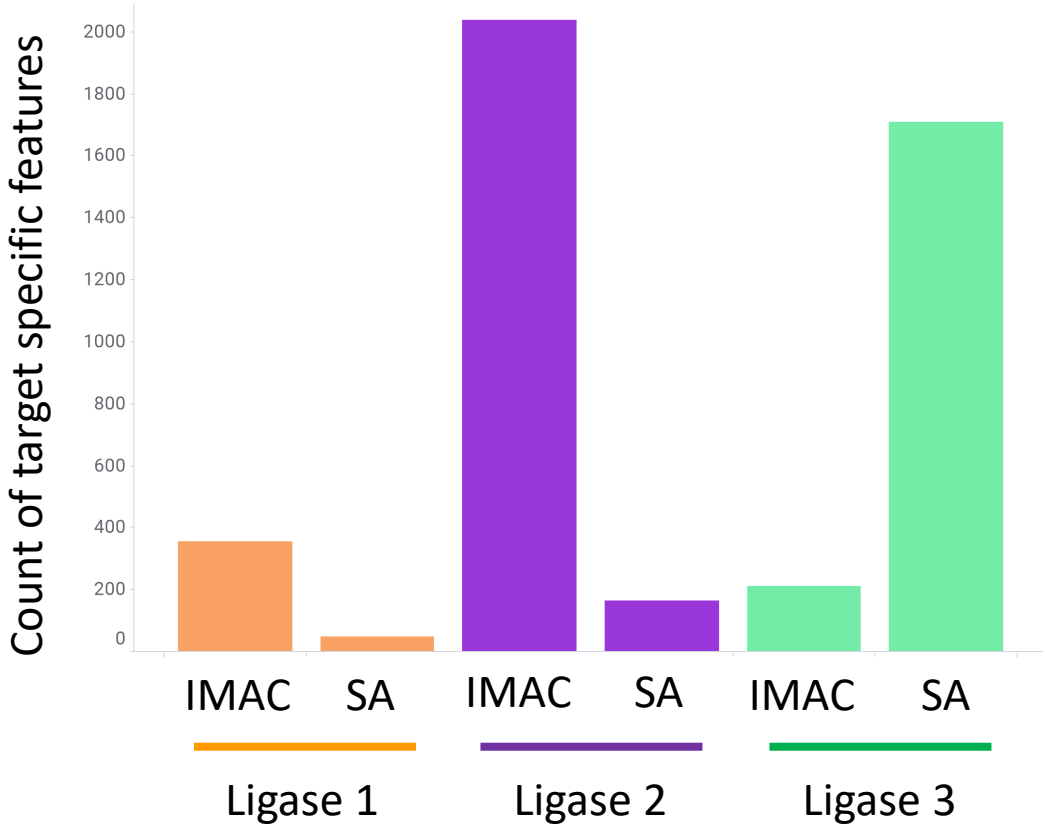



Combining traditional and computationally-driven DEL follow up allows us to discover more binders in desirable chemical space and maximize the diversity of confirmed hits.

# Screening and Follow Up Capacity – Finding the Most Productive Spaces for Novel Targets

- Screening multiple ligases in parallel, with multiple constructs and tags for each ligase
- Nurix routinely screens multiple target constructs immobilized through different matrices
  - The most productive construct/matrix combinations needs to be determined empirically

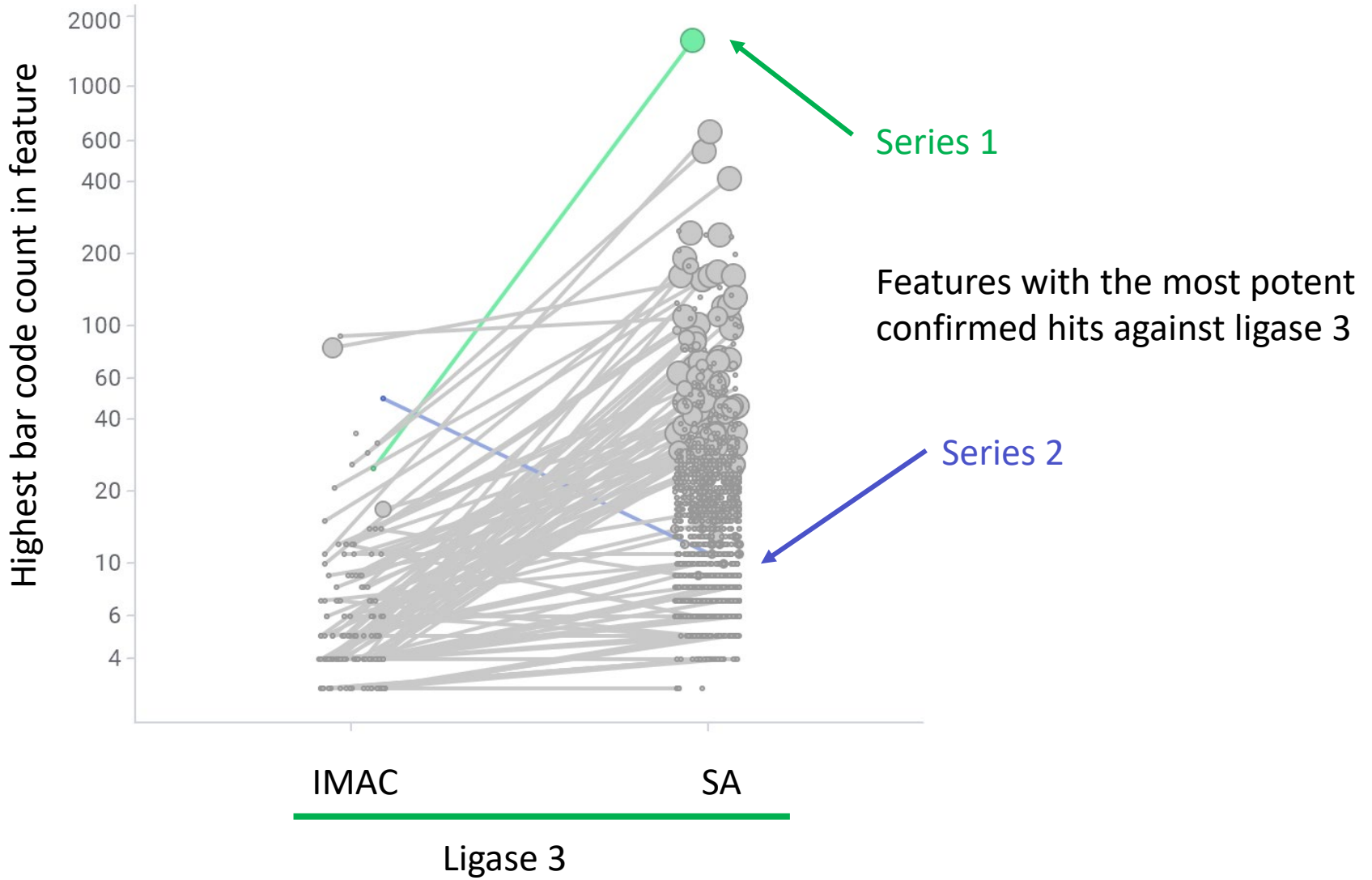
Example – three ligases screened in parallel using Immobilized metal affinity (IMAC) and streptavidin (SA) beads



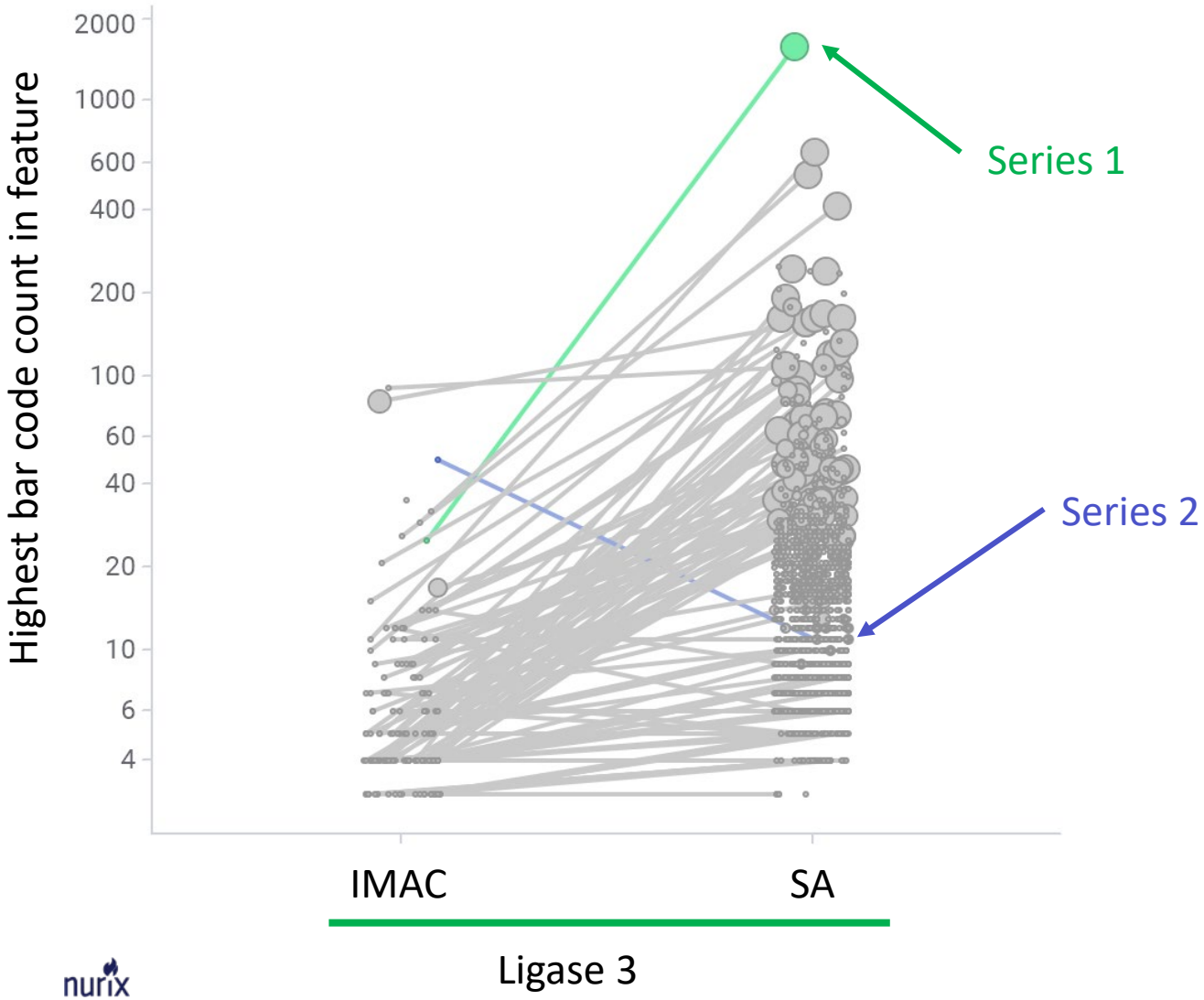
# Broad Follow Up Maximizes the Opportunities from DEL Screens

Lines link identical features between selections

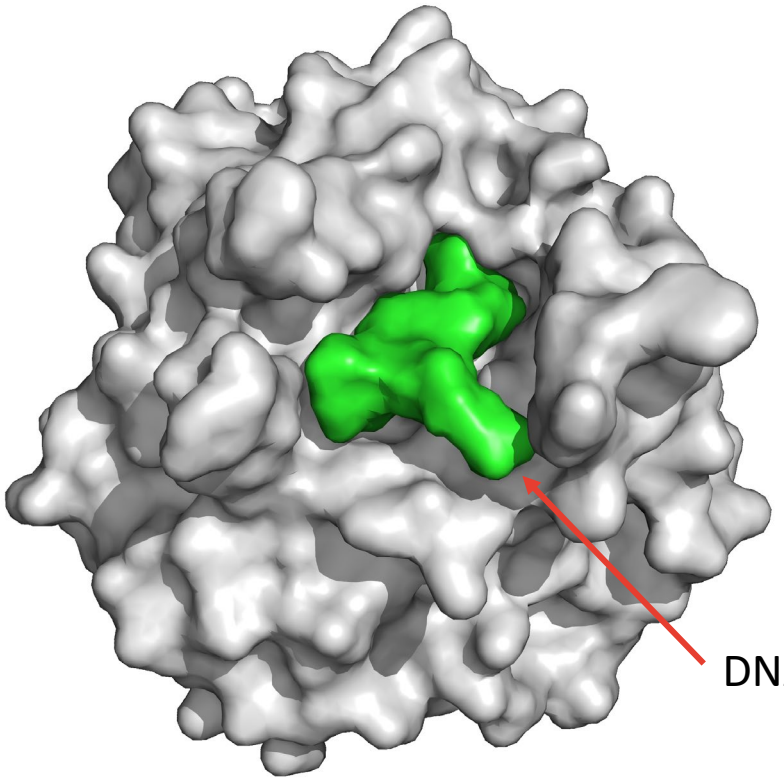
Size denotes number of ligands within the feature



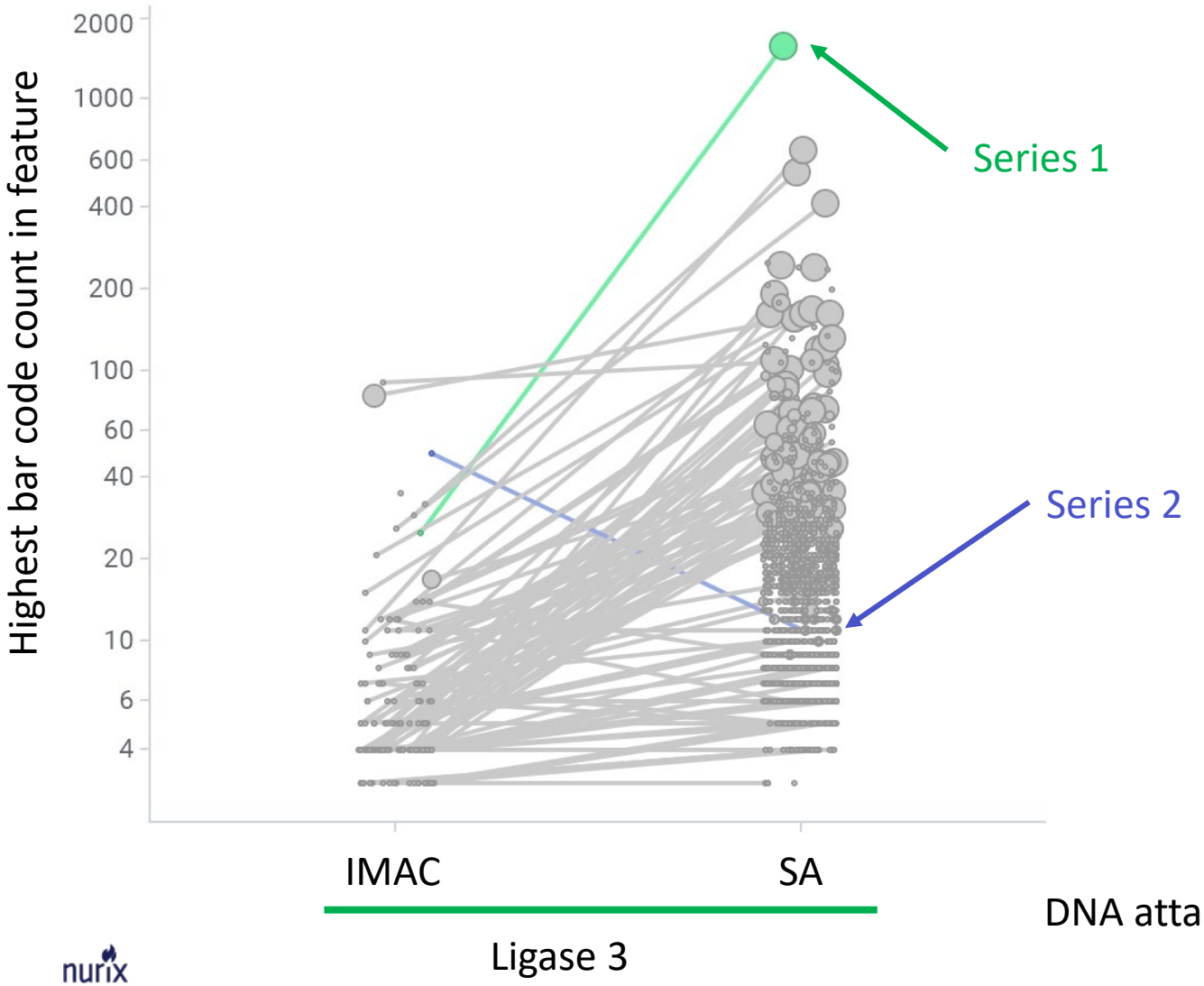
# Broad Follow Up Maximizes the Opportunities from DEL Screens



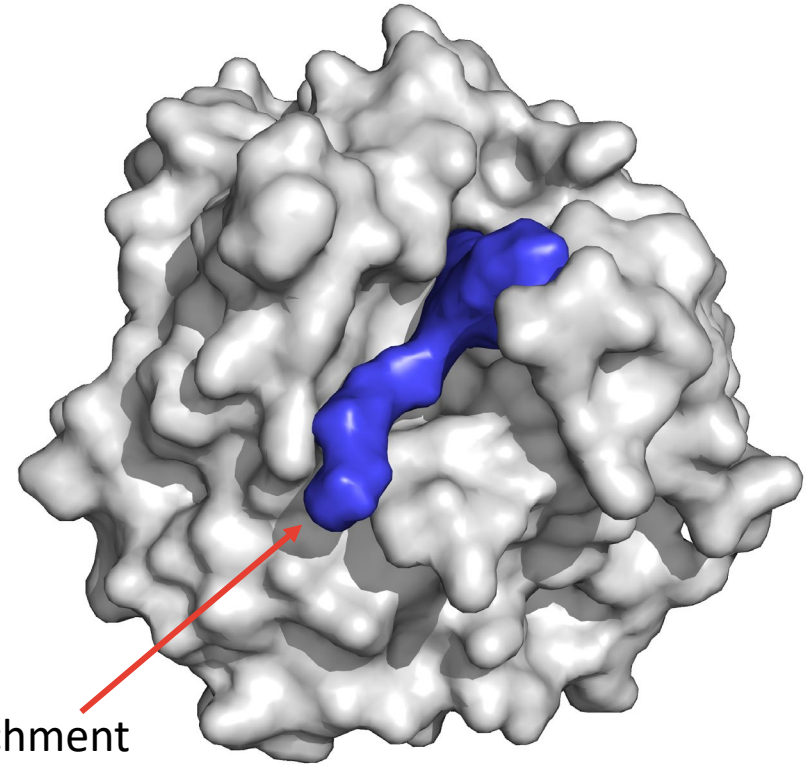

X-ray crystal structure of
Series 1 bound to ligase 3



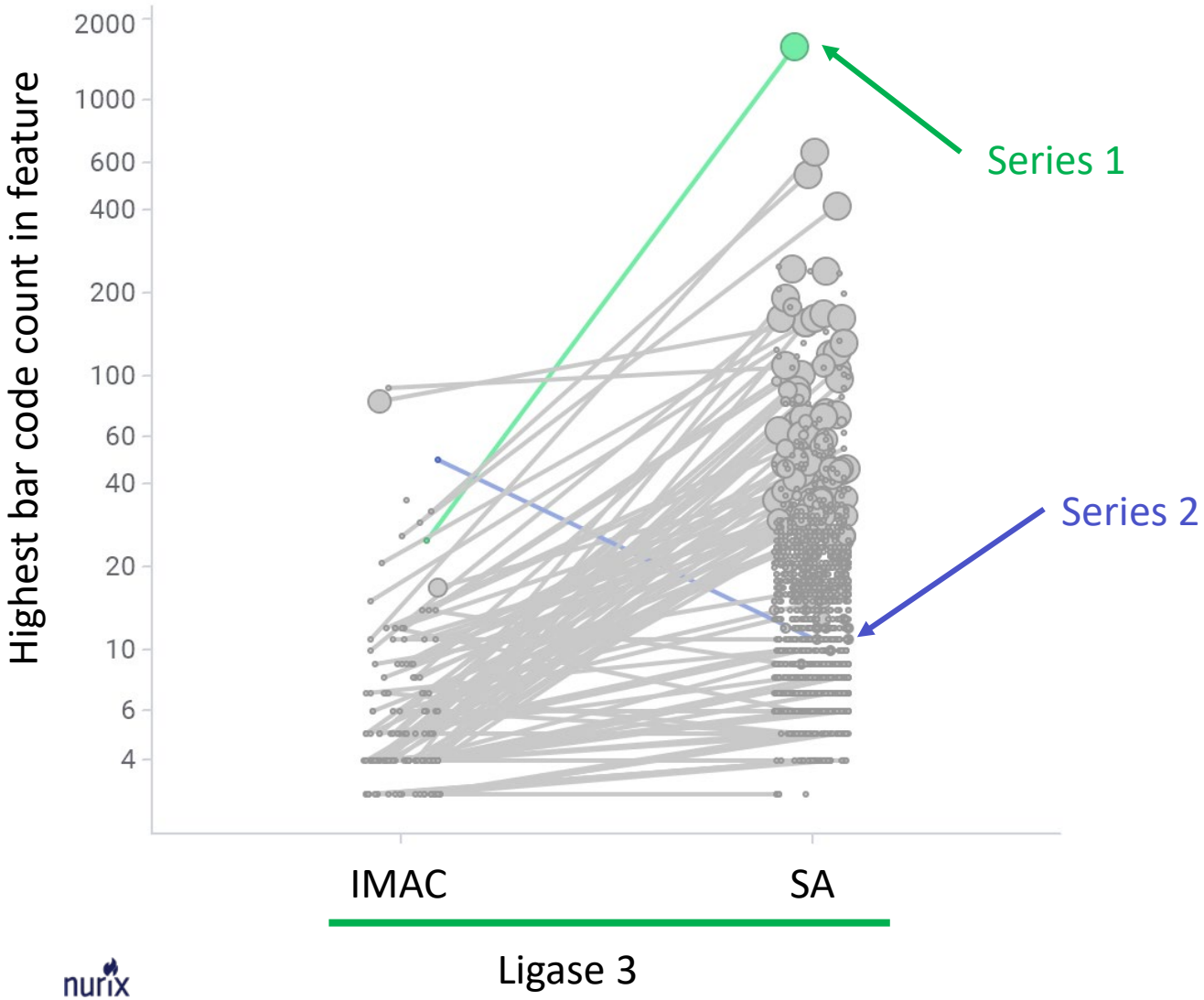
# Broad Follow Up Maximizes the Opportunities from DEL Screens



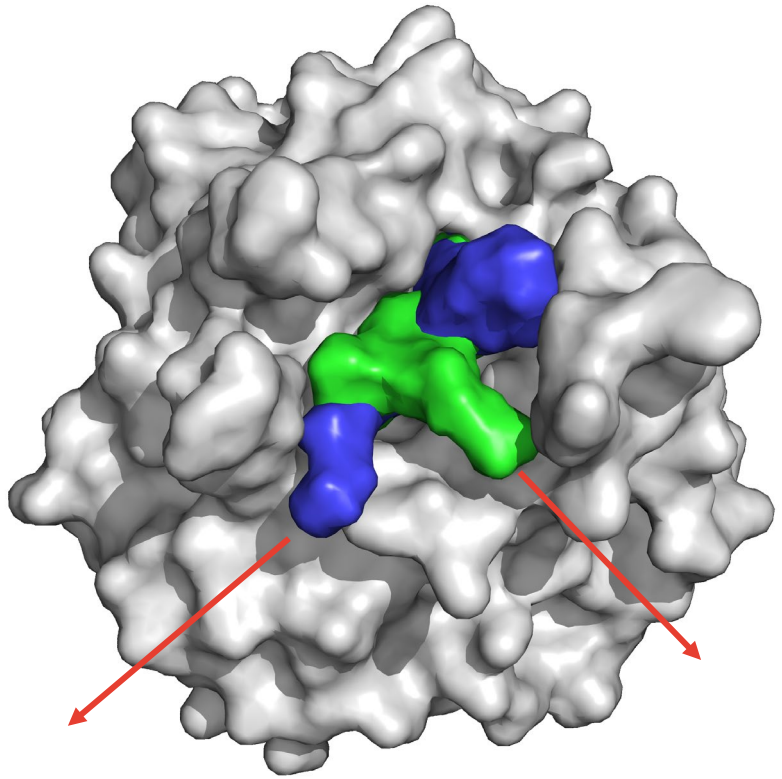

X-ray crystal structure of
Series 2 bound to ligase 3



# Broad Follow Up Maximizes the Opportunities from DEL Screens



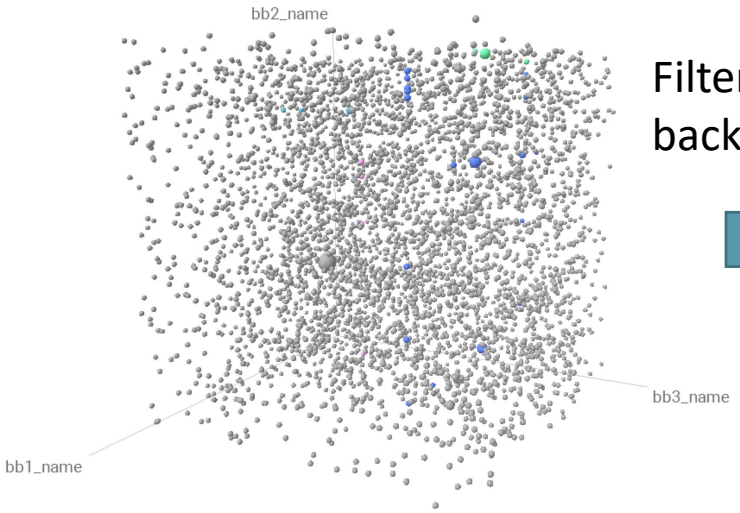

Overlay of Series 1 & 2
bound to ligase 3



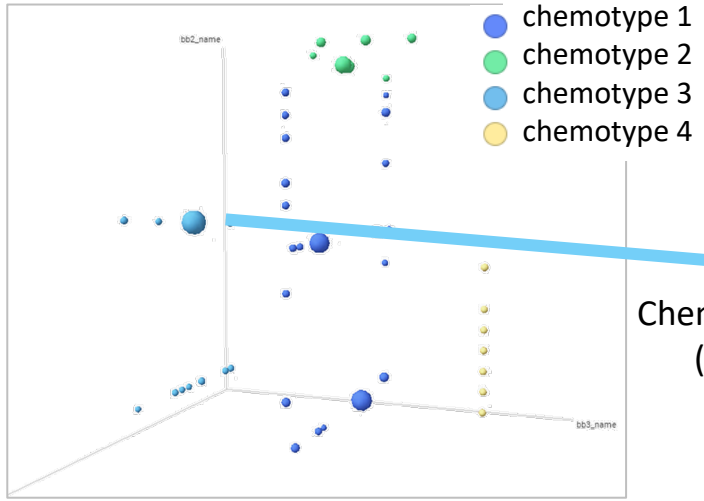
Unprecedented ligase with two confirmed vectors for bifunctional attachment

# Quality of Hits Is Not Proportional to Quantity of Screen Output

- Filtering away the noise and background reveals a small set of target specific binders with SAR



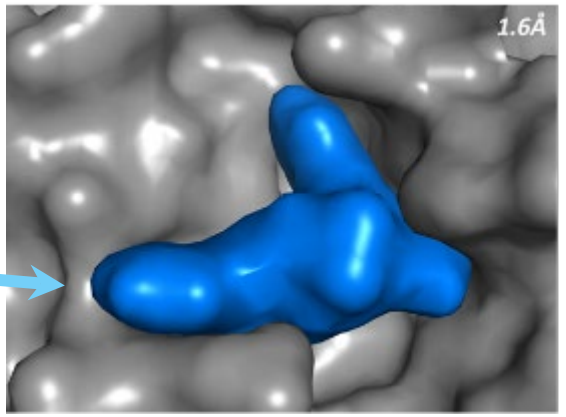

Filter to remove background



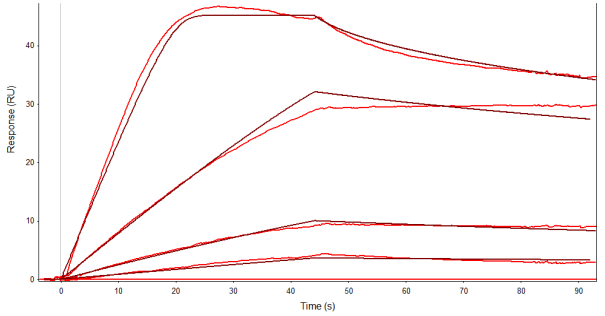

Only a few potential hits remain

Chemotype 3 (blue)

Single digit nanomolar, non-covalent MPro inhibitor




Structure and SPR trace of chemotype 3 with MPro



# Conclusions

- DEL provides significant advantages as a ligand discovery platform for targeted protein modulation
- These advantages can only be realized when coupled to high-quality, well-validated target proteins and a diverse collection of libraries.
- Leveraging the low cost per screening condition and the ability to broadly scan the chemical space of hits are key to maximizing the productivity of the platform.
- Assembling a comprehensive database of screening results from a broad exploration of target space is key to navigating through the data to find the highest quality hits.

# Thank You!