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Leader in Targeted Protein Modulation

Utilizing DEL as a Primary Discovery Engine for Targeted Protein Degradation

5th Annual TPD Summit

Boston, MA

October 26th, 2022

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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

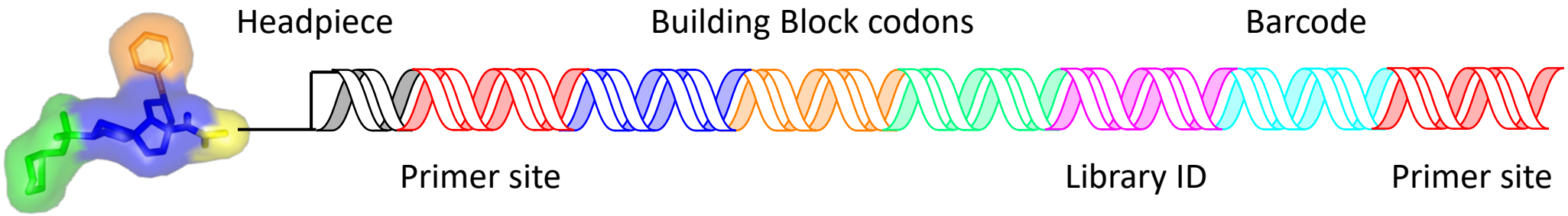
Targeted Protein Degradation (TPD)

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

Anatomy of a DEL Molecule

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

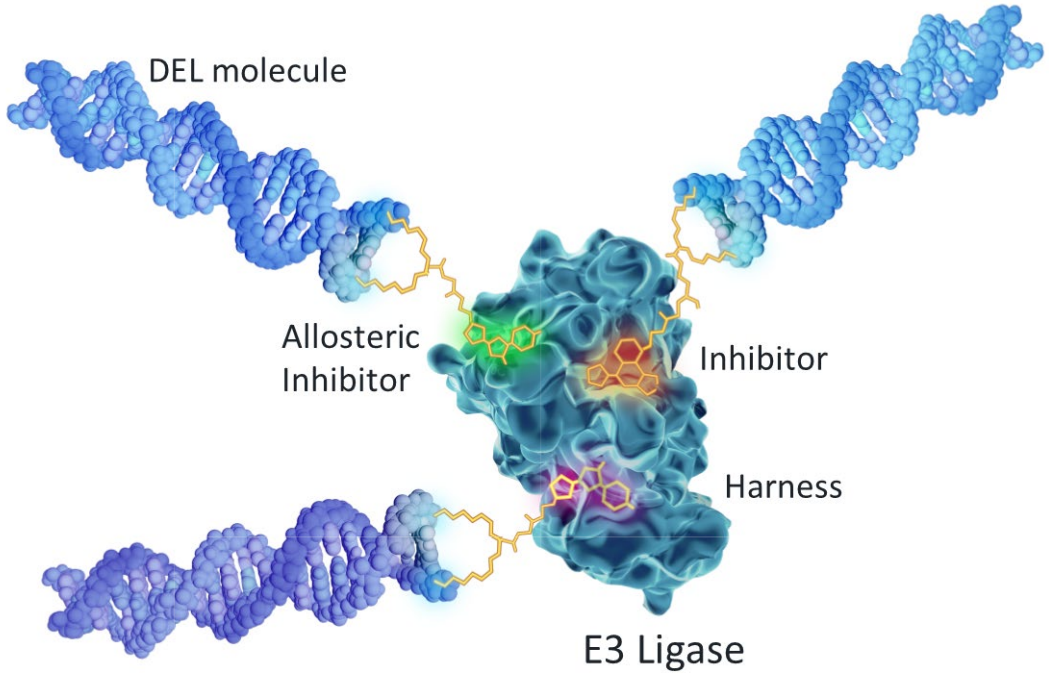
Small molecule “warhead”
*Not to scale



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

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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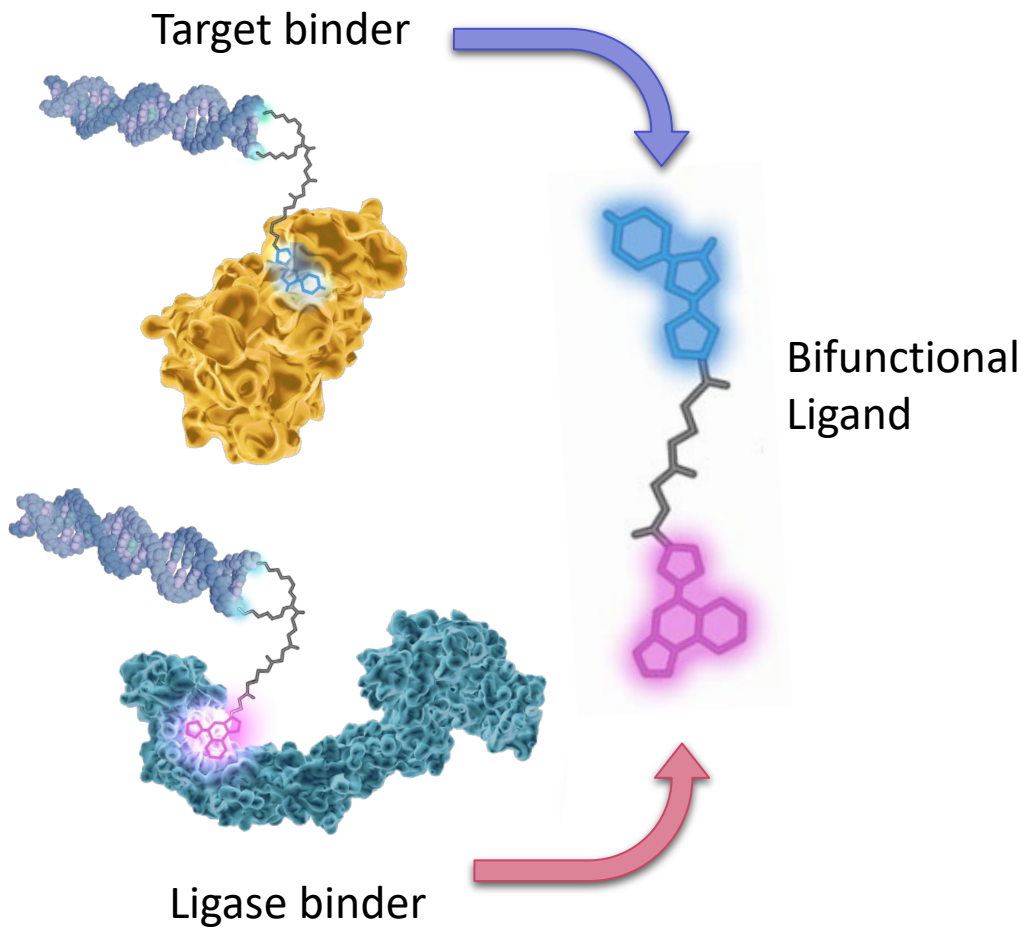

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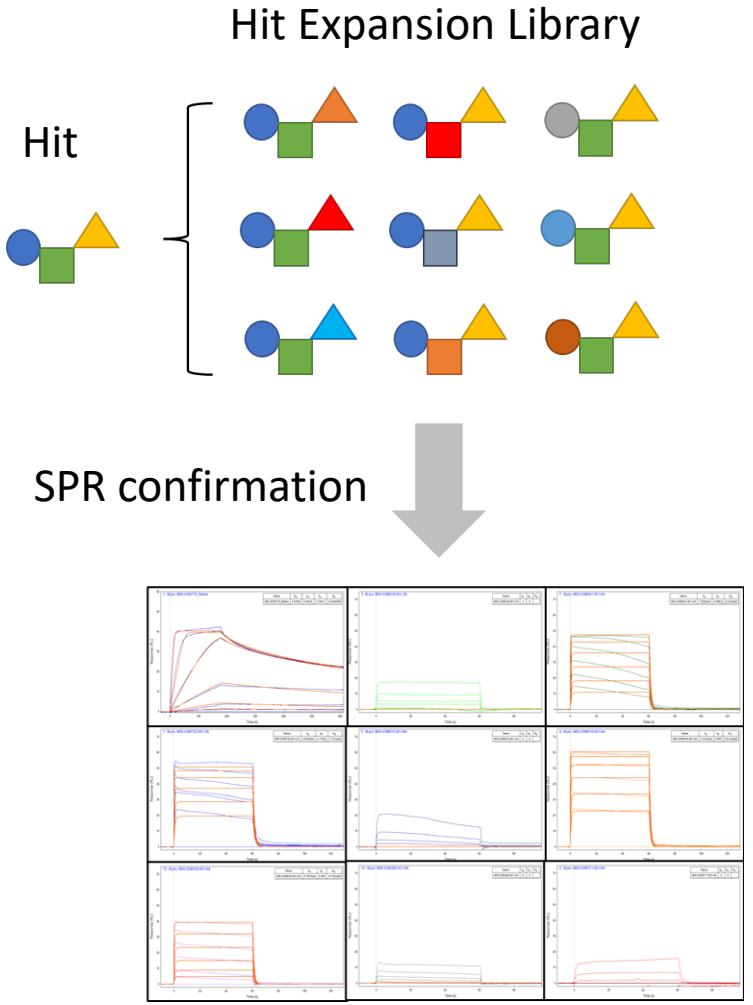

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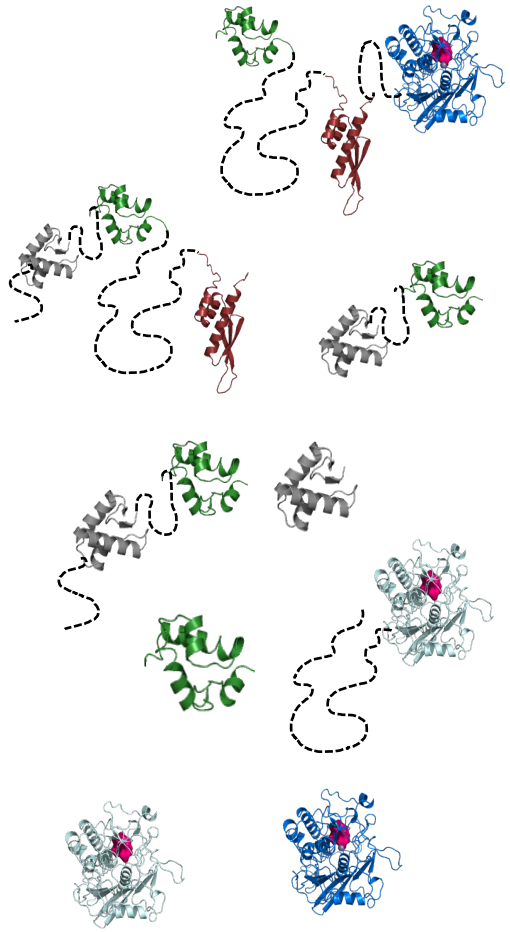
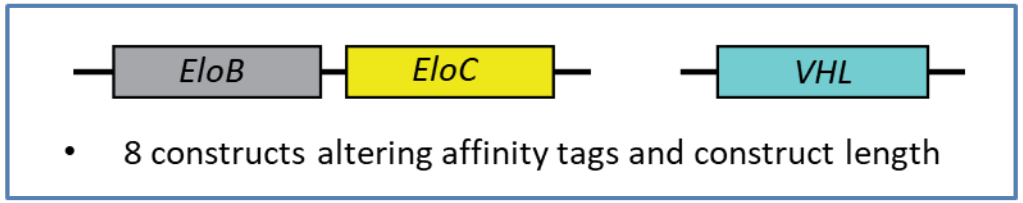
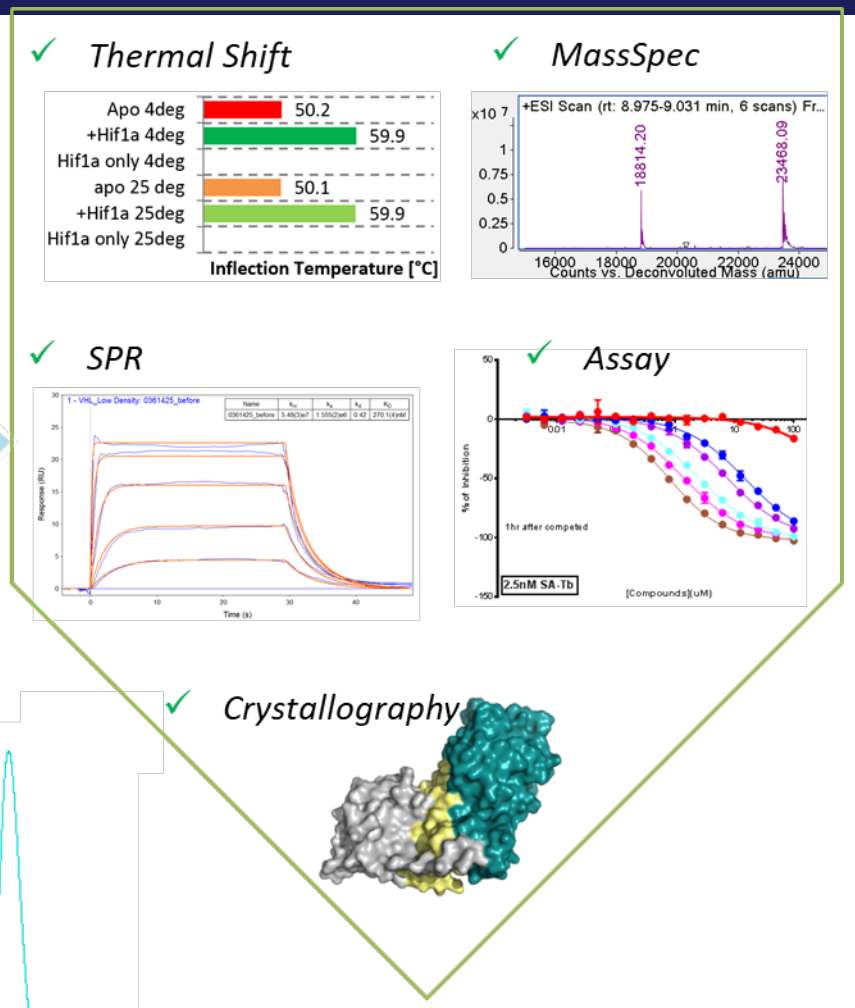
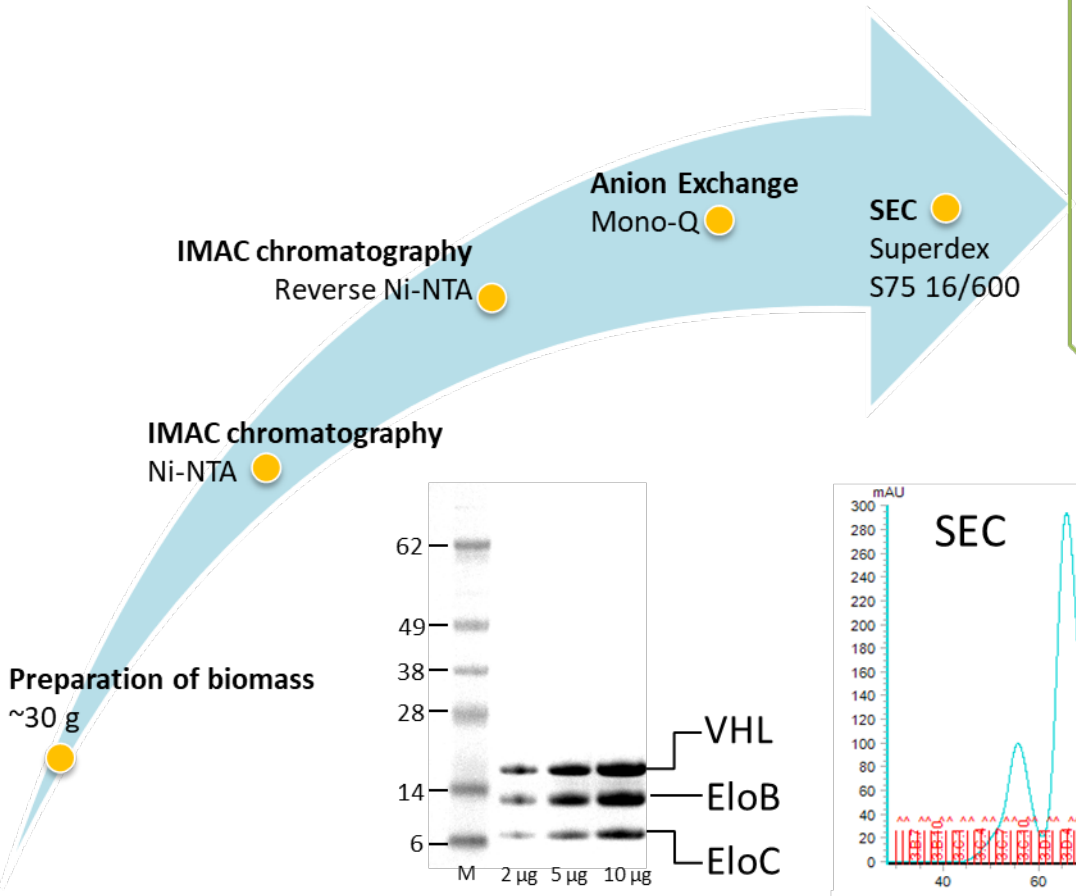


Protein Quality is Fundamental to DEL Screen Success



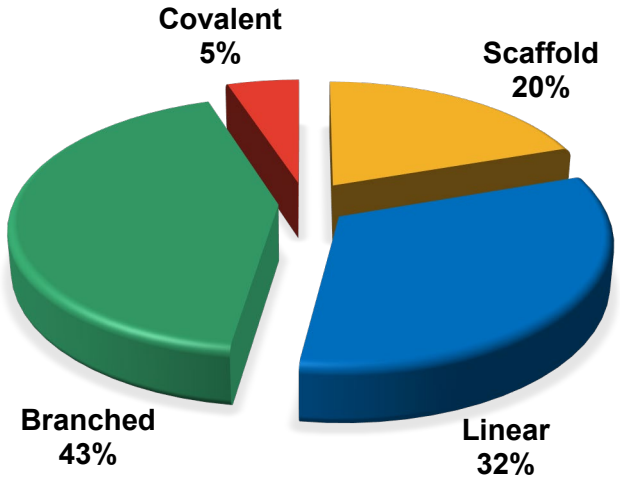




Custom Scaffold-Based DELs Enable Nurix To Identify Binders to Challenging Protein Surfaces

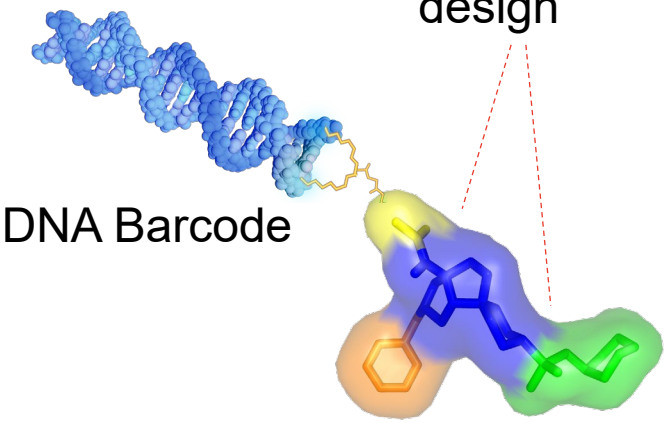
Nurix DEL Collection

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



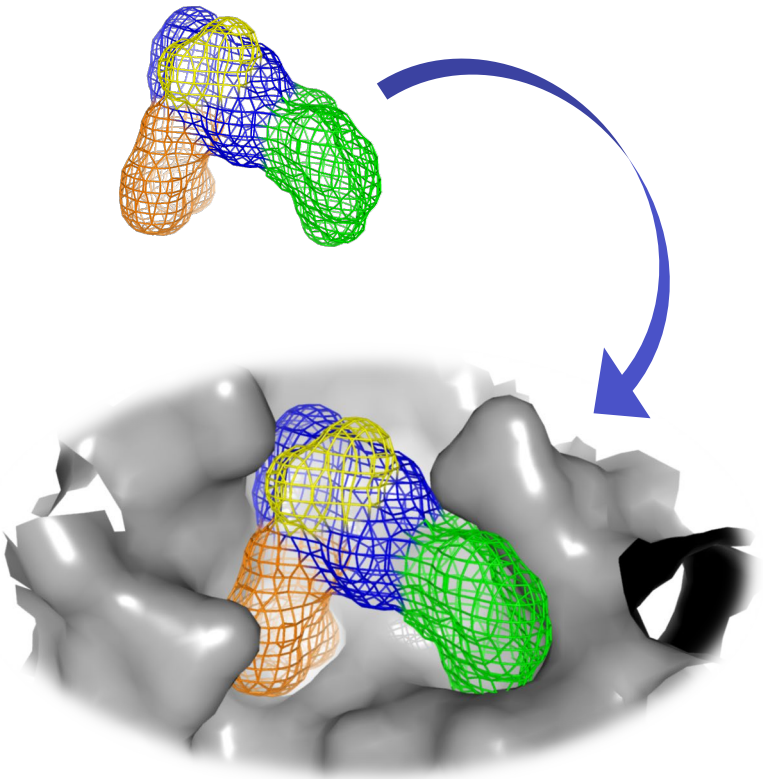
Scaffold Libraries Proving Essential for Delivering Ligands for "Undruggable" Targets (sole source of hits for 75% of these targets)

Three-dimensional design



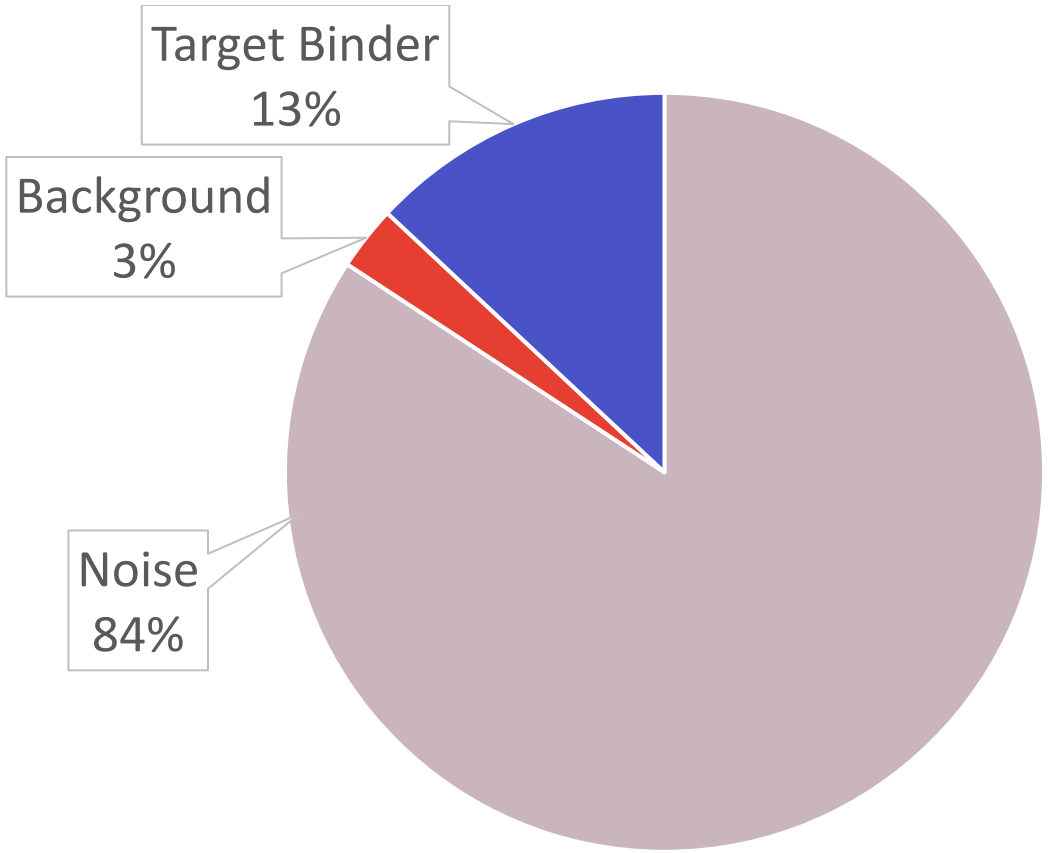
Our proprietary scaffold DELs provide unique geometry and high sp3 character, allowing molecules to achieve optimal pocket fit

Nurix scaffold designs show high pocket complementarity



Composition of DEL Screening Outputs

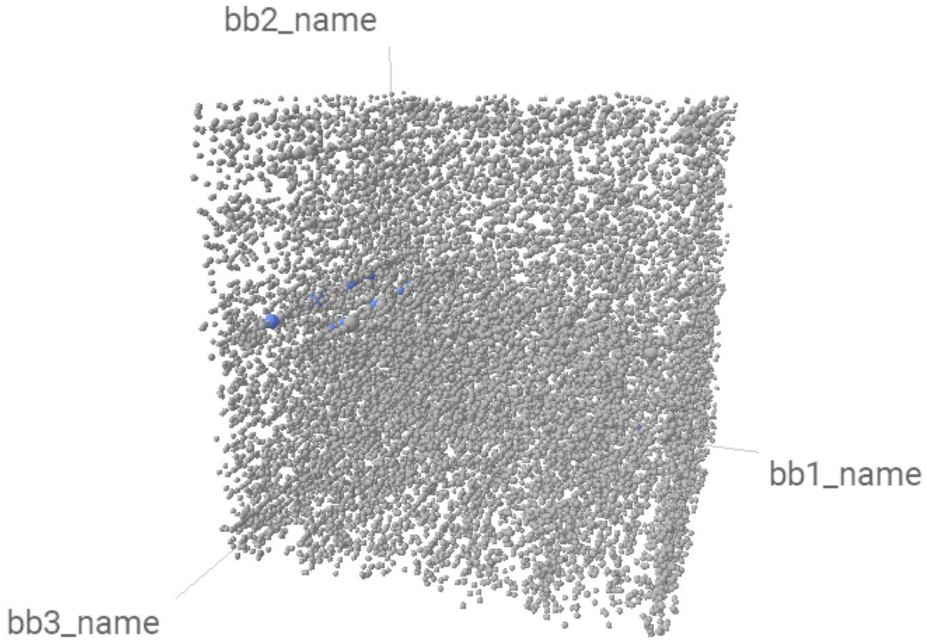
- Most of the DNA-linked compounds sequenced at the end of a selection are noise or background (matrix binders, non-specific protein binding, other enrichment not specific to the target)
    - Noise can be eliminated by experimental (replicates) OR analytical (thresholding) methods
    - Elimination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



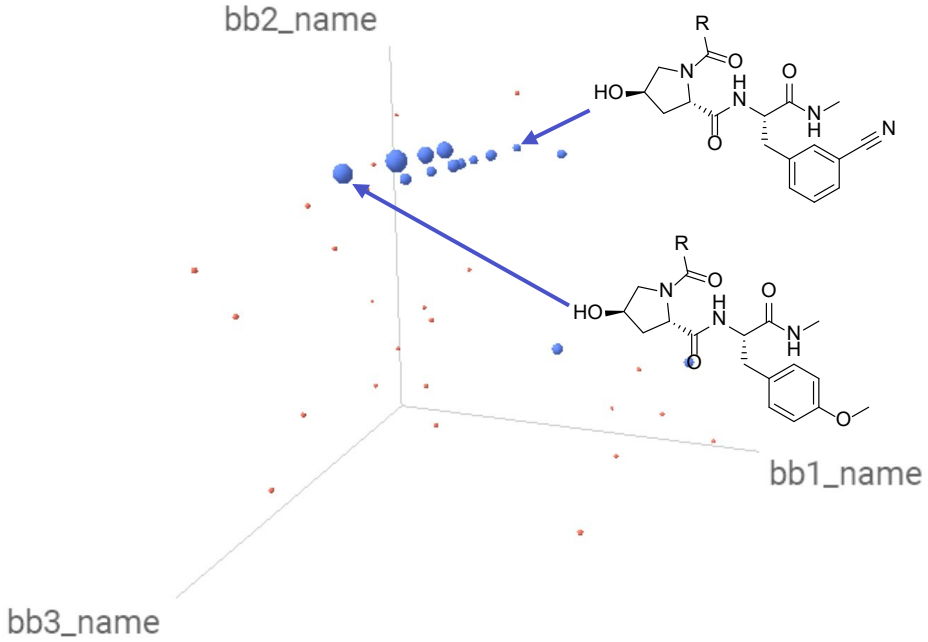
De-noising Example – VHL Replicates

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

All ligands present in a single screening condition

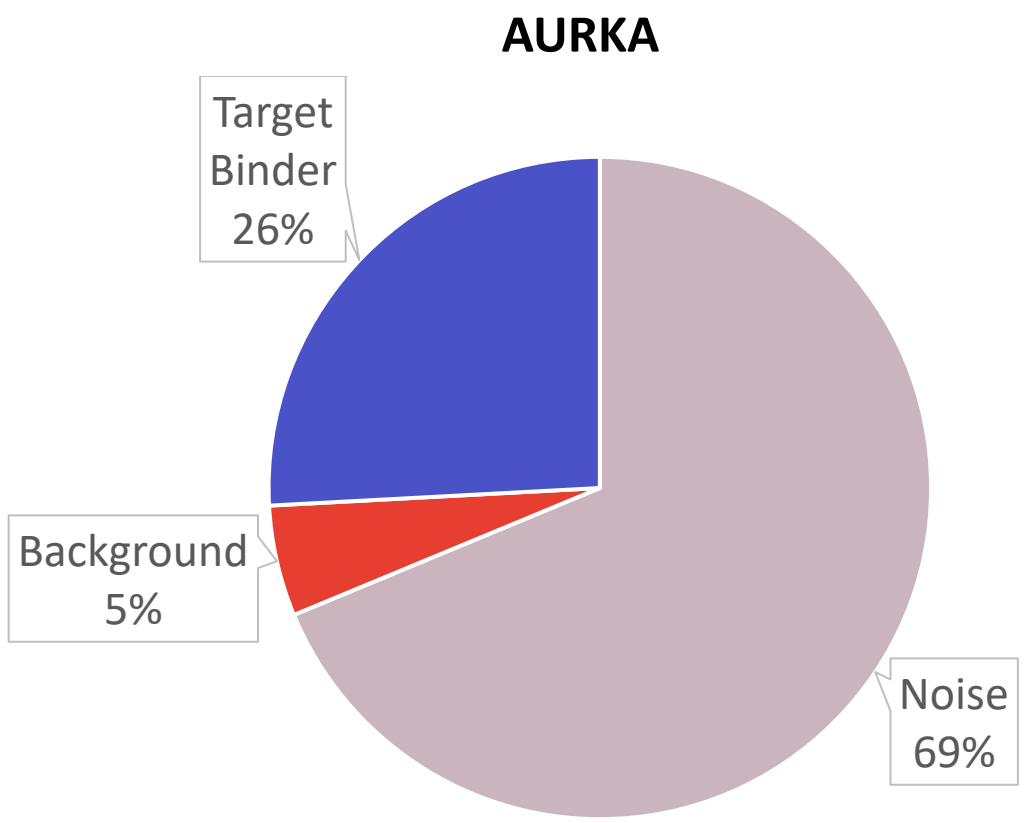


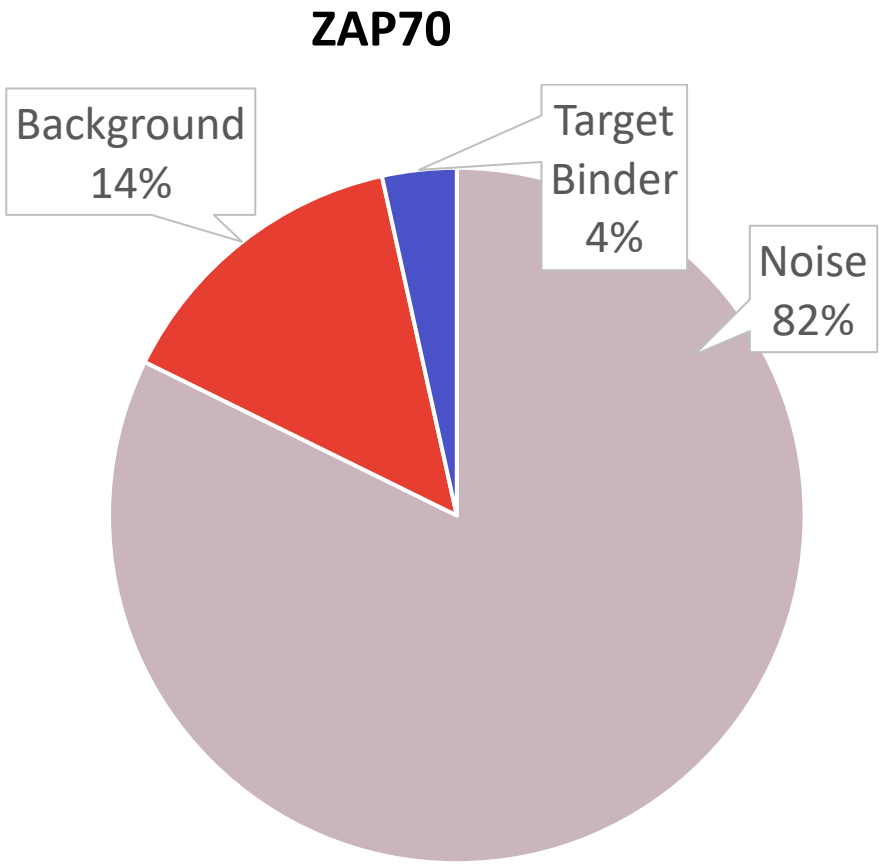
All ligands present in all three replicates



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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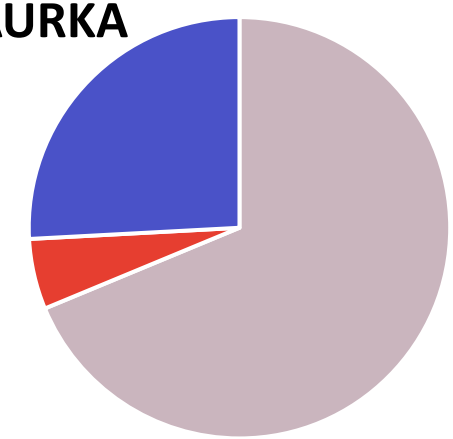

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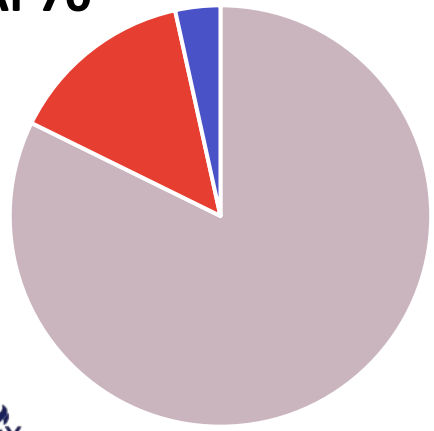
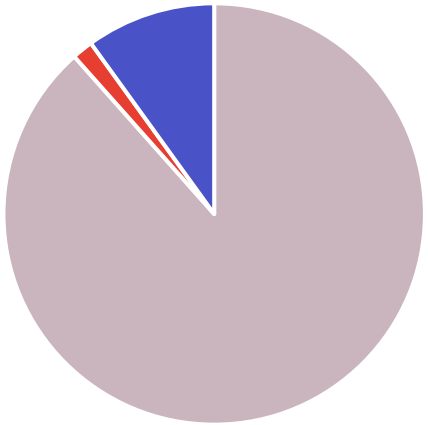
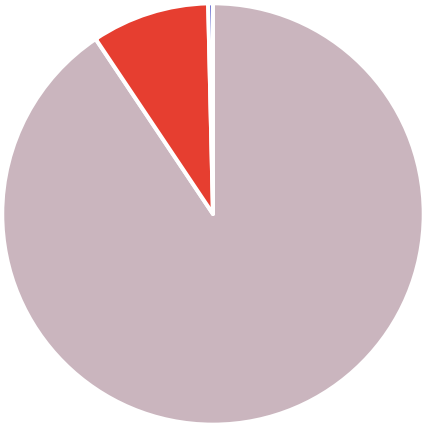
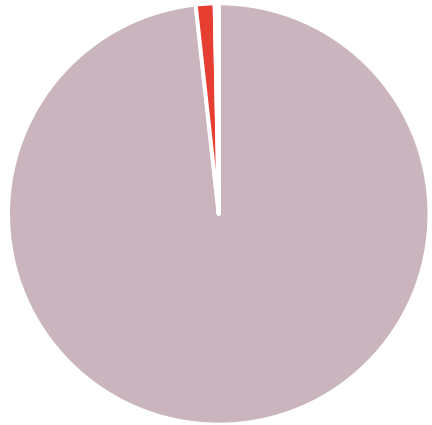
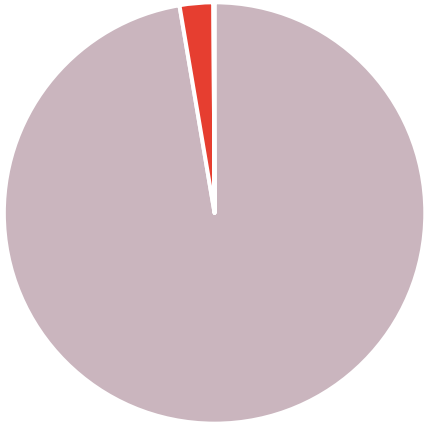


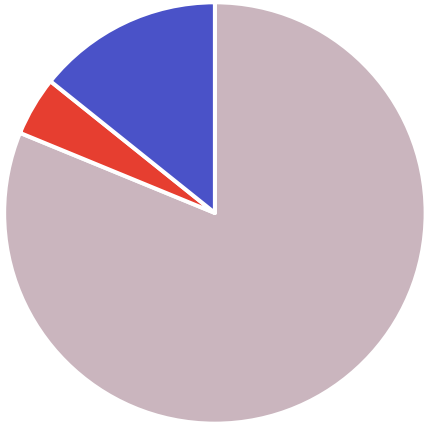
Other DEL targets with confirmed sub-uM hits











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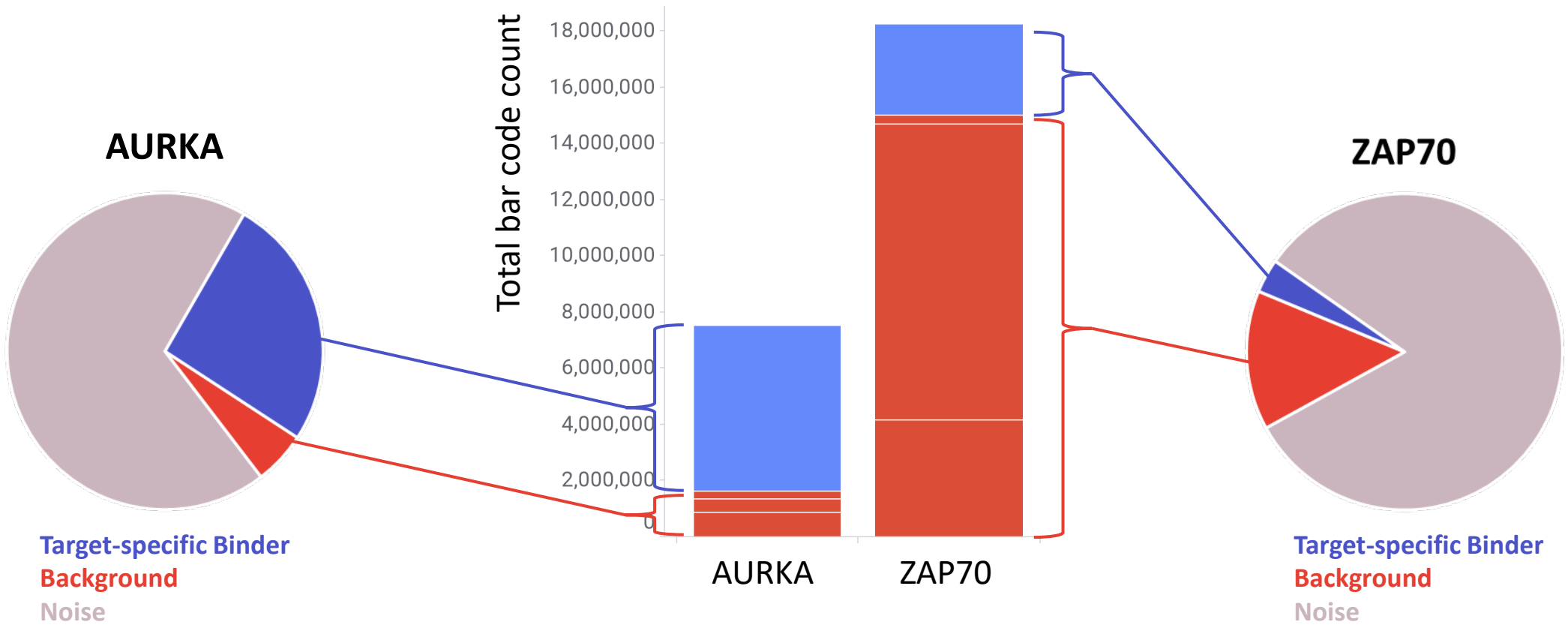
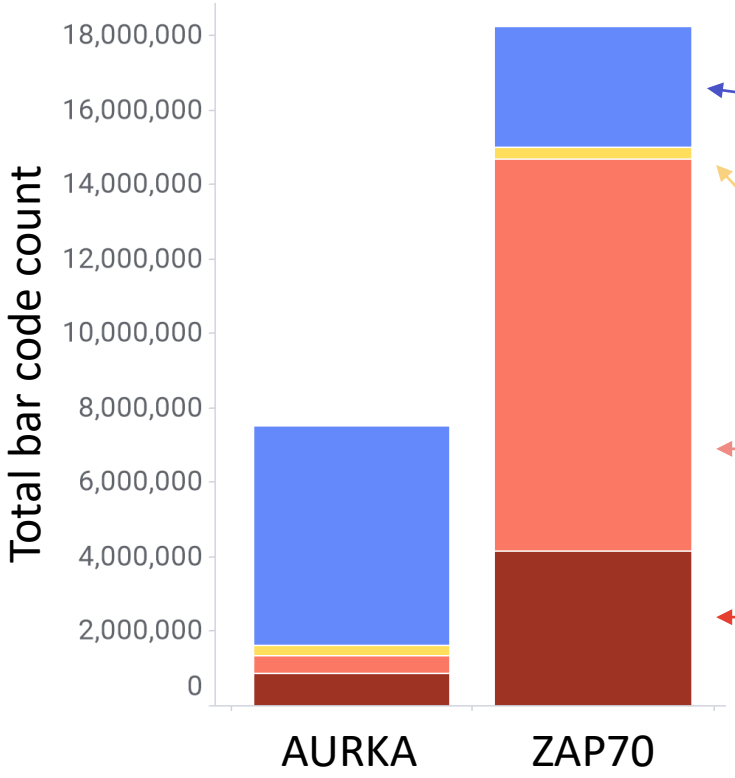
Zooming in on the Enriched Fraction



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

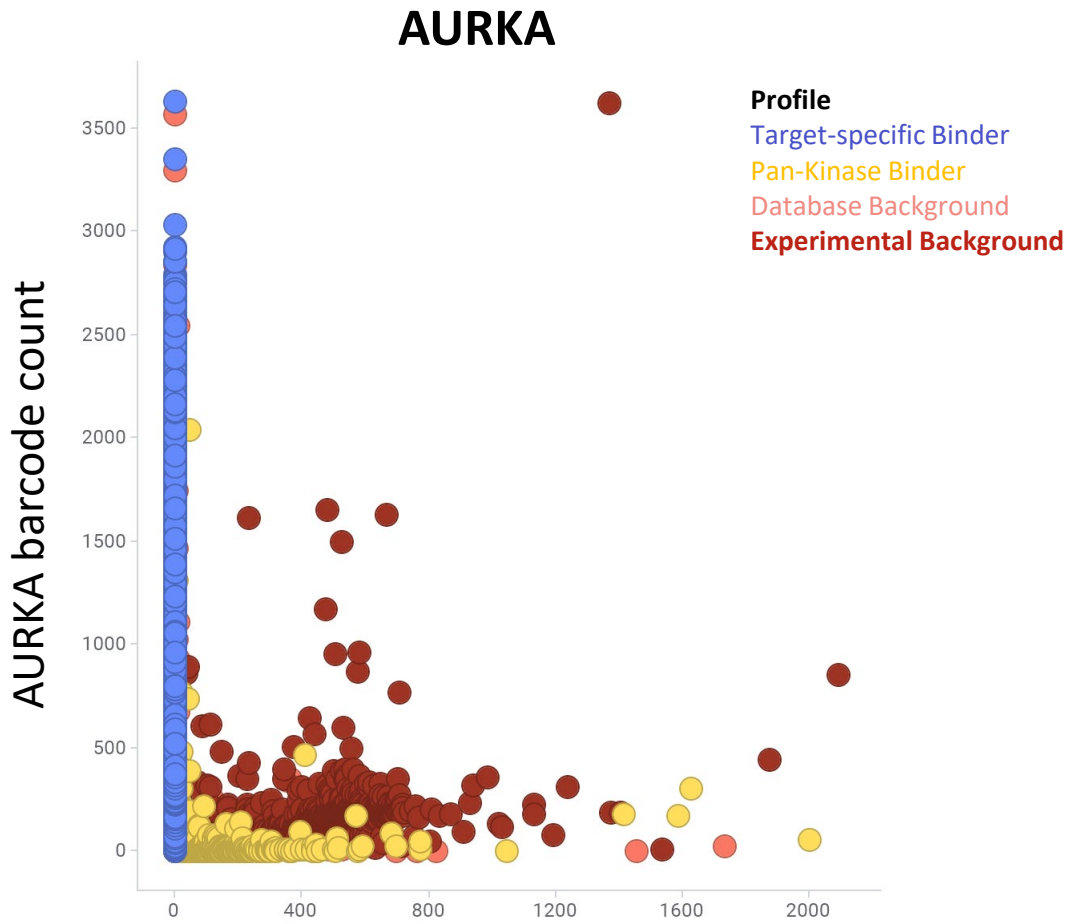
Target-specific Binder – ligands enriched only against the target of interest

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

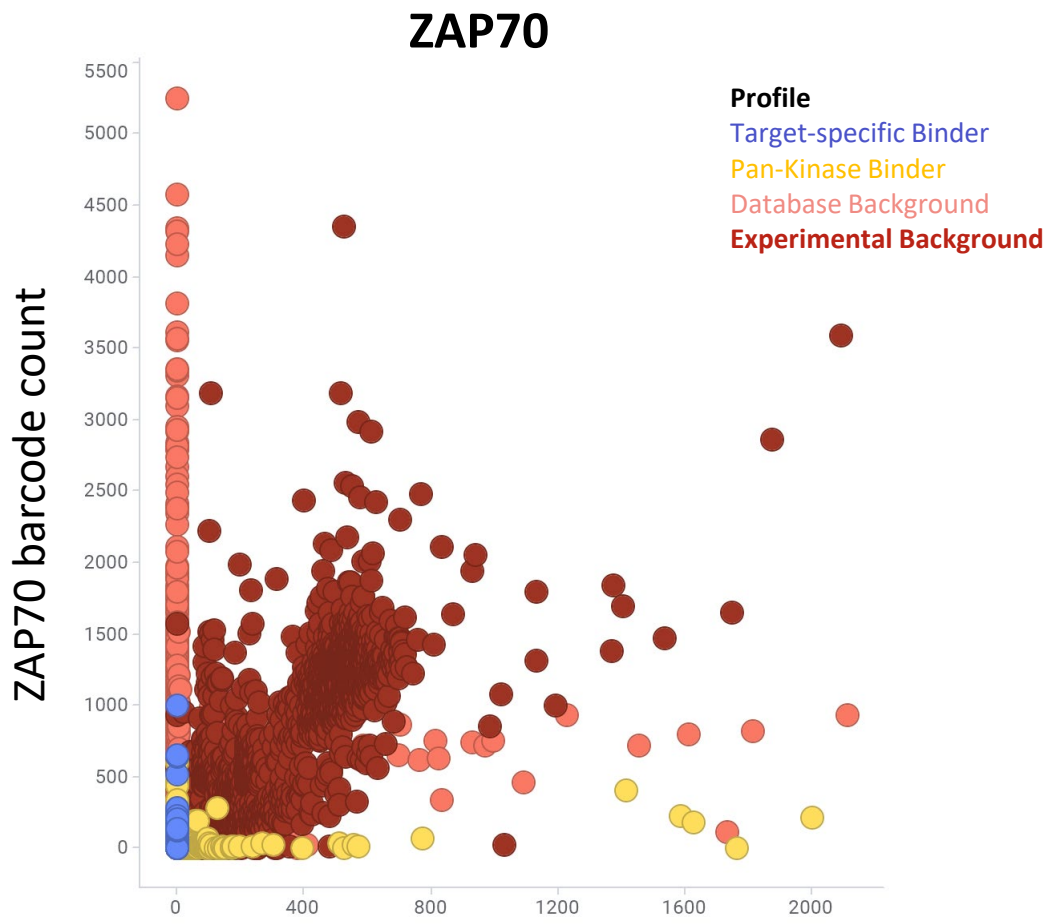
Database Background – background binders enriched in the target selection and selections from other screening campaigns

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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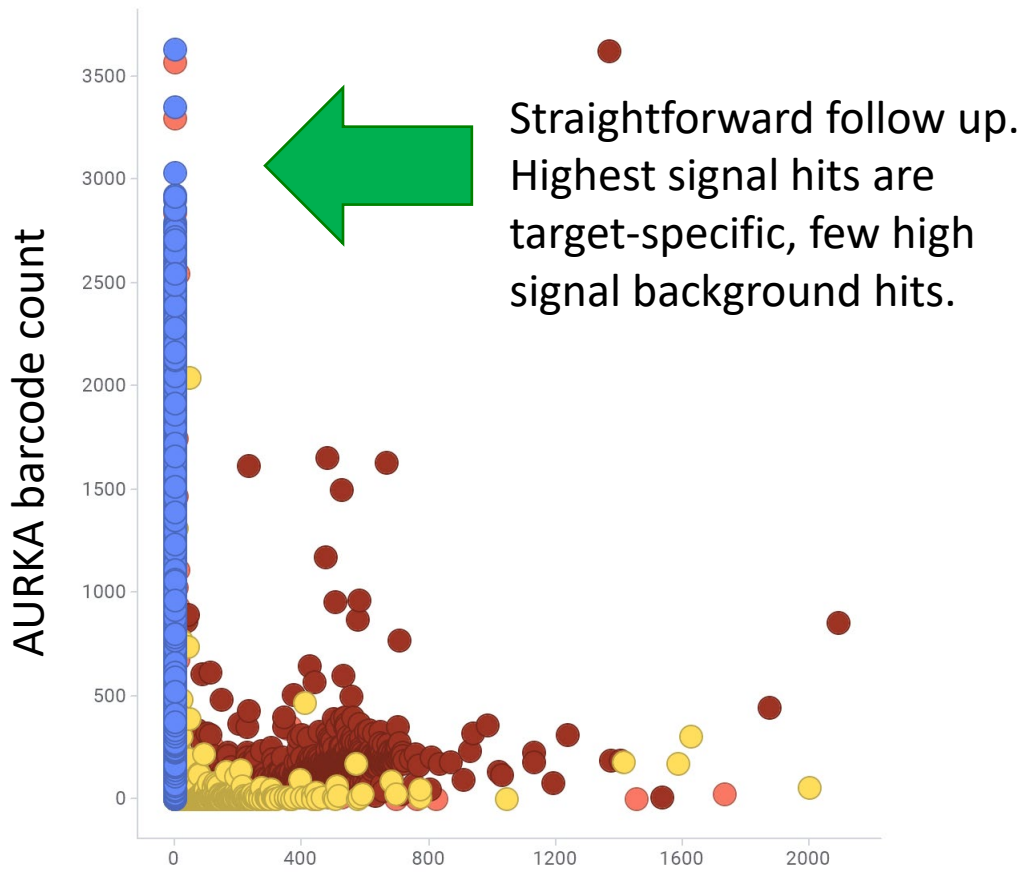
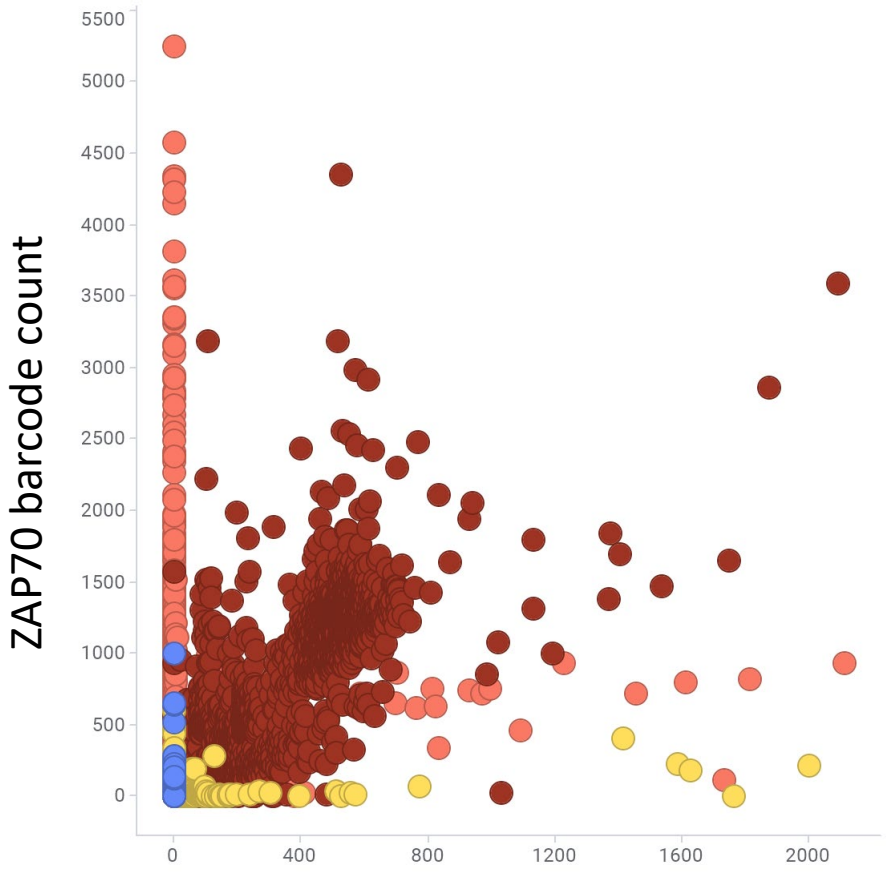


Straightforward follow up. Highest signal hits are target-specific, few high signal background hits.

Highest barcode count in control selections

ZAP70



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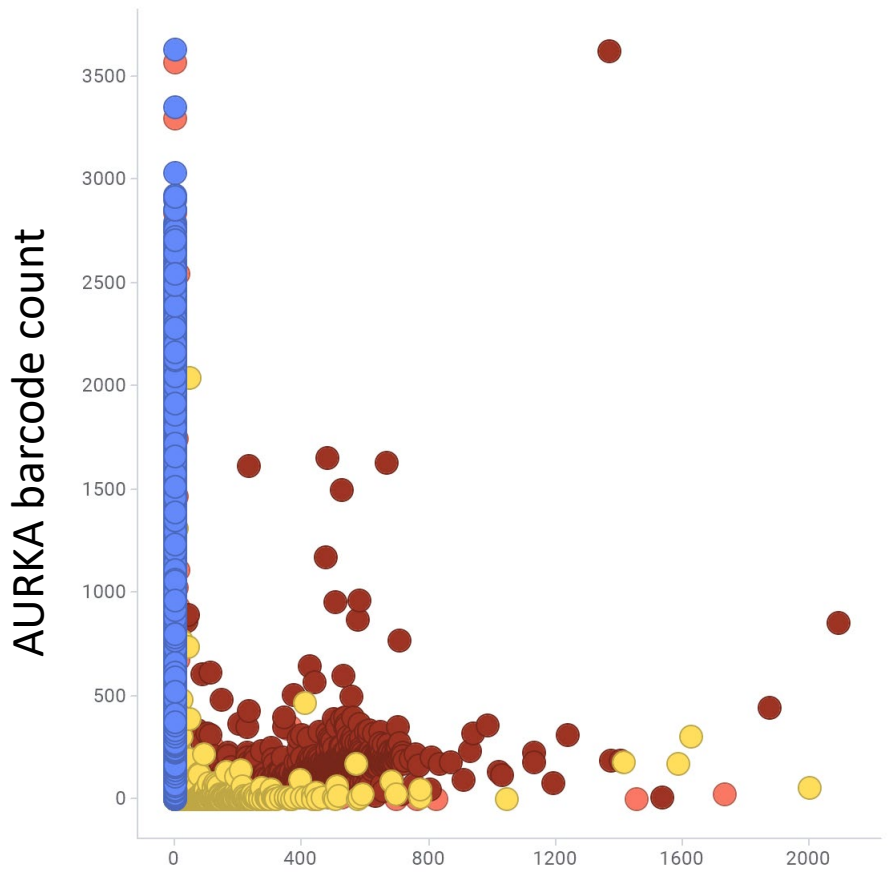

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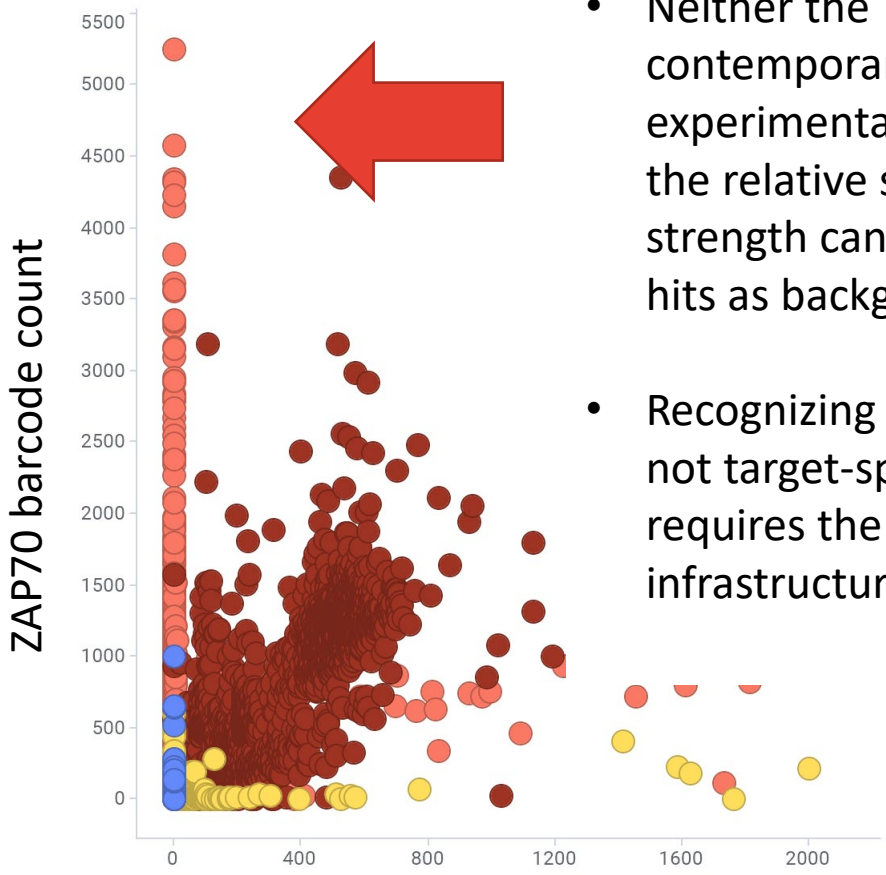

Highest barcode count in control selections

- 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

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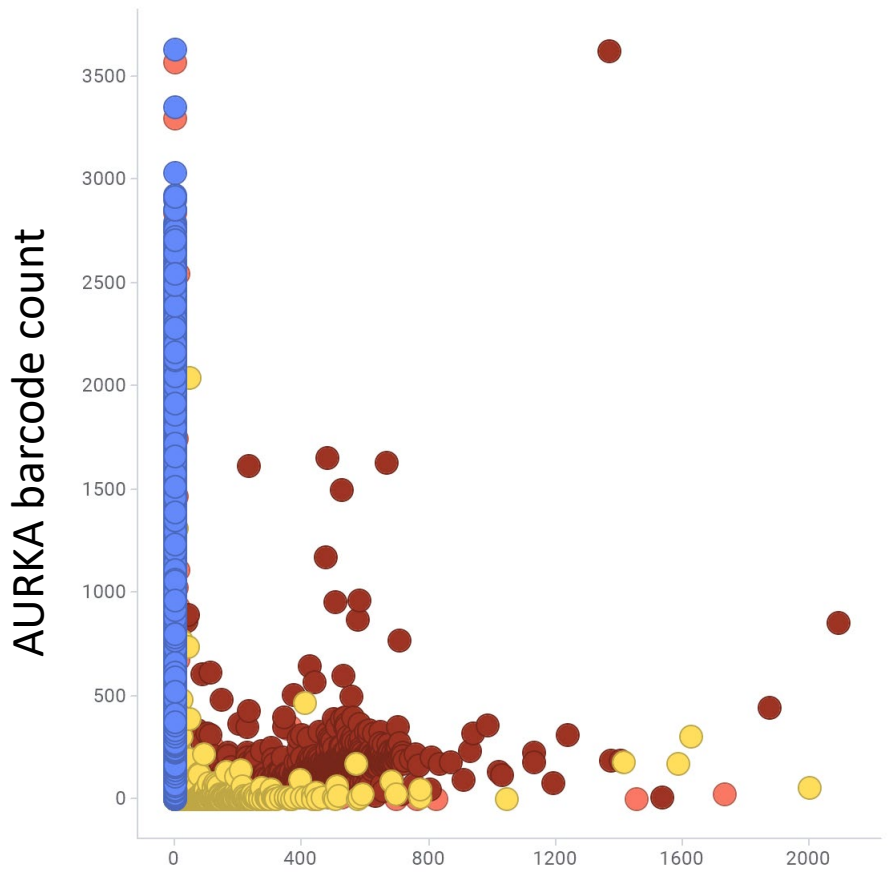

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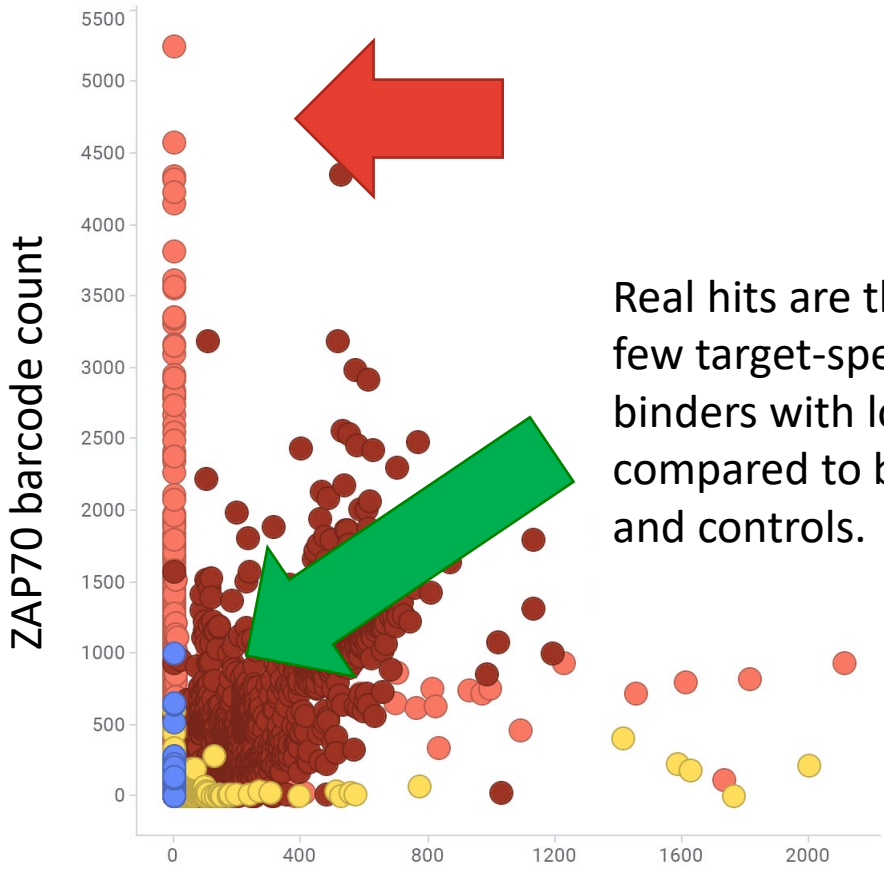
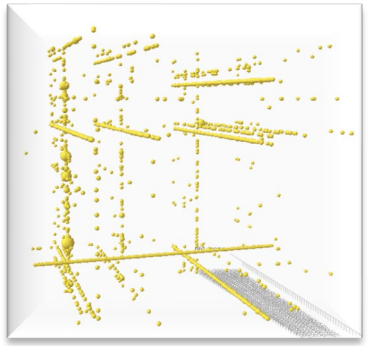


Real hits are the relatively few target-specific binders with low signal compared to background and controls.

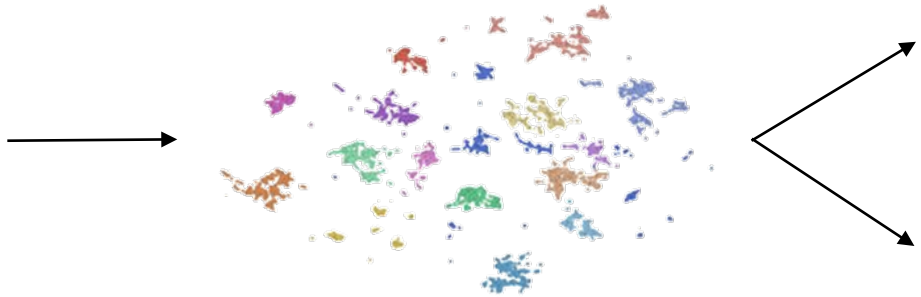
Highest barcode count in control selections

Wading Through the Data - Nurix's Analysis and Follow Up Pipeline is Designed to Access Broad Chemical Space

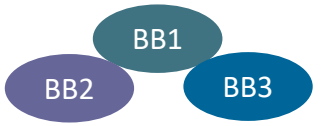
Large complex data sets require automated solutions to accelerate hit ID



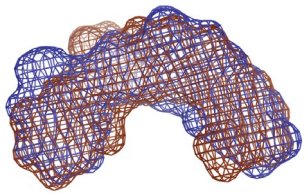
DEL Screen and filtering for target-specific binders



Automated Structure Analysis and Clustering



Hit Resynthesis (on- and off-DNA)

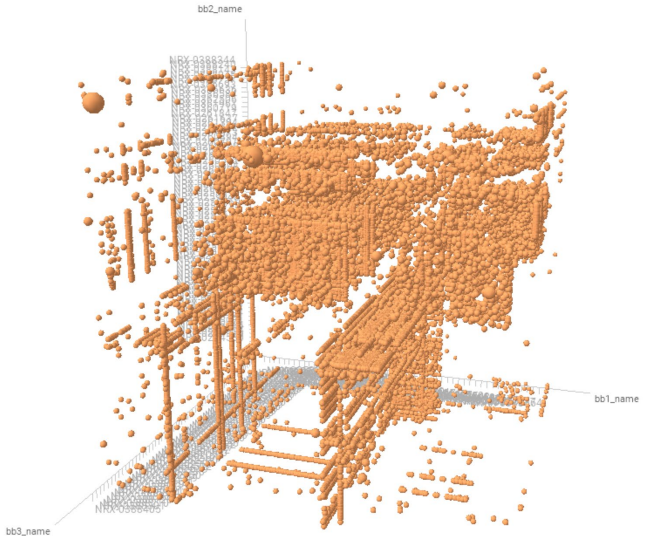


Machine Learning and Similarity Virtual Screening

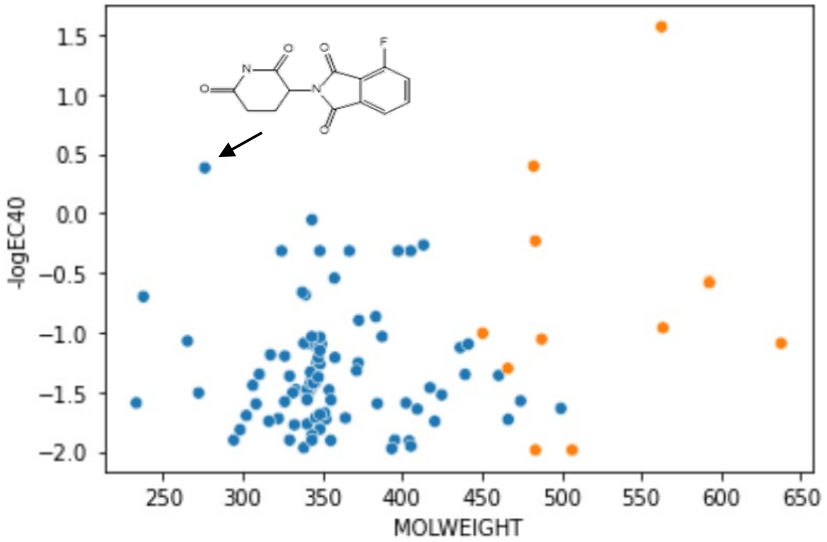
Follow up	Source	Volume	Hit Confirmation Assay
Off-DNA	Single compound synthesis	10s	SPR (Quantitative)
On-DNA	Parallel Synthesis of single recipes	100s	ASMS (Qualitative)
ML/Similarity	Catalog order	100s	ASMS then SPR (Quantitative)

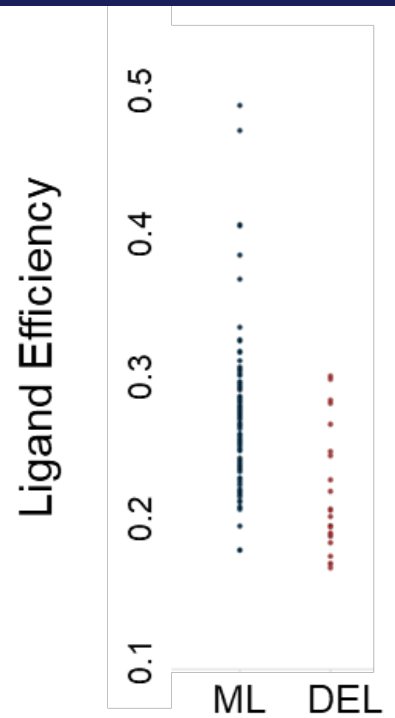
Leveraging Computational Methods to Search Beyond DEL Space to Discover Potent and Diverse CRBN Binders

CRBN DEL Screen
(Filtered to Target Binders)



Off-DNA and
ML follow up

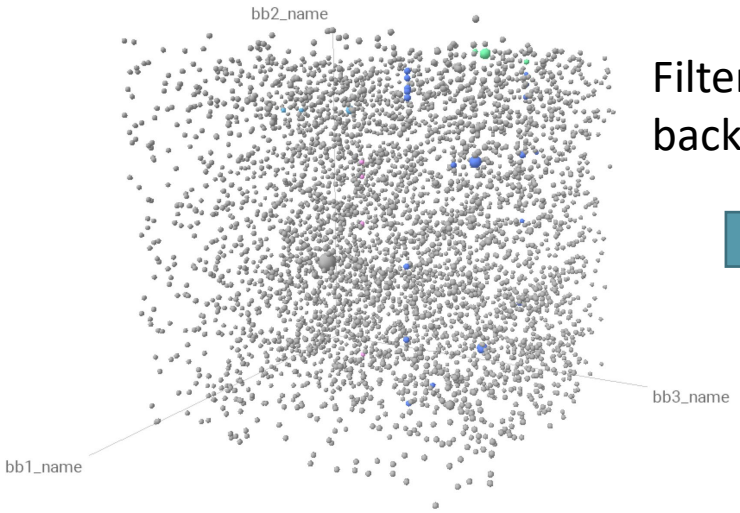




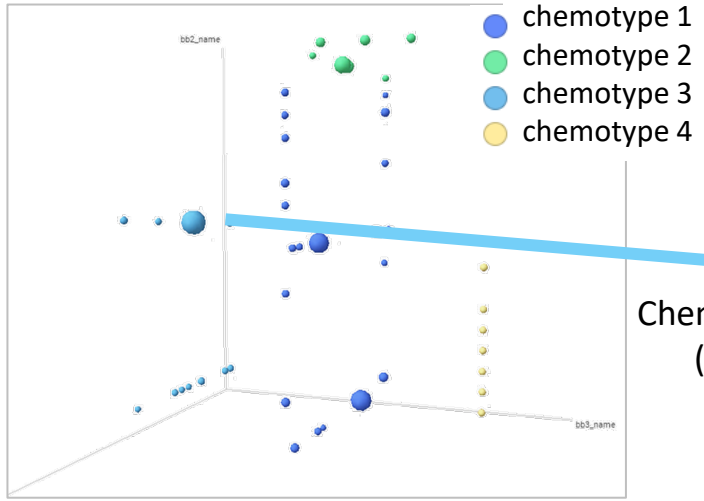
Combining traditional and computationally-driven DEL follow up allows us to discover more binders in desirable chemical space and maximize the diversity of confirmed hits.

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



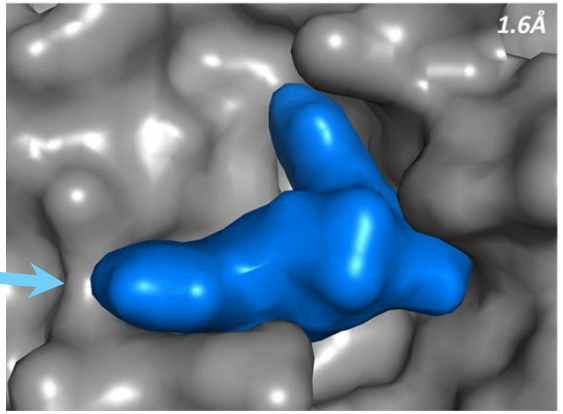
Filter to remove background



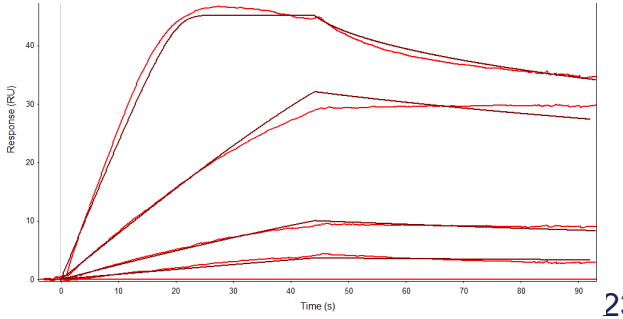
Only a few potential hits remain

Chemotype 3 (blue)

Single digit nanomolar, non-covalent MPro inhibitor



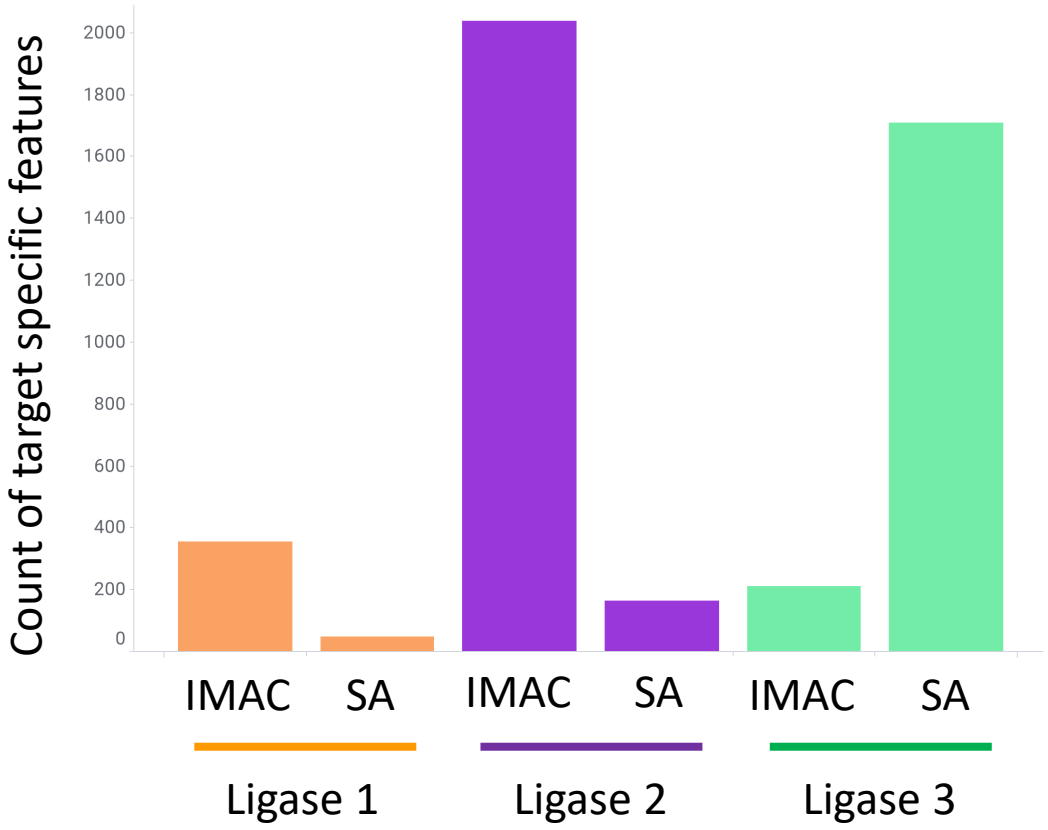
Structure and SPR trace of chemotype 3 with MPro



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

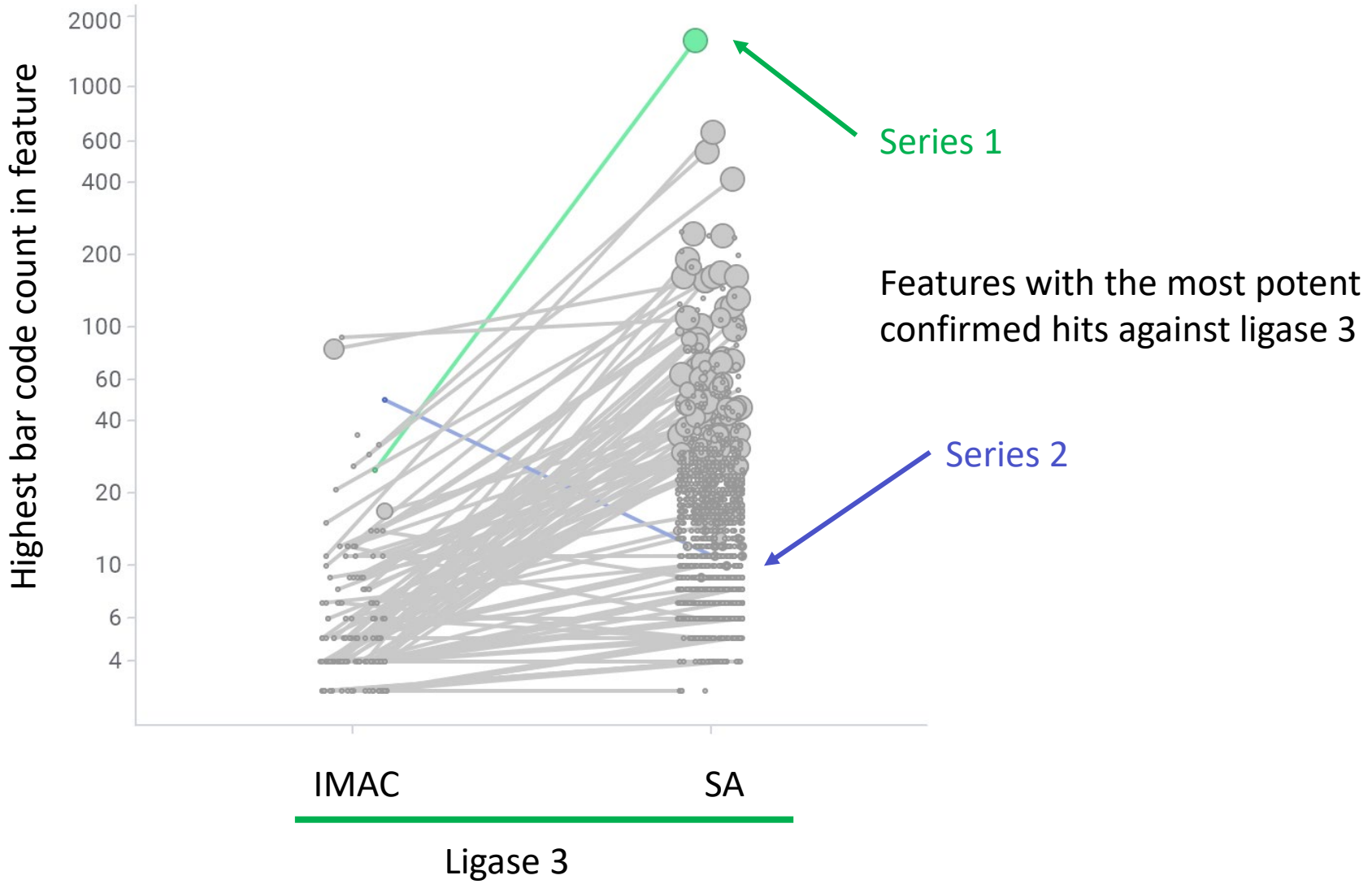
Example – three ligases screened in parallel using Immobilized metal affinity (IMAC) and streptavidin (SA) beads



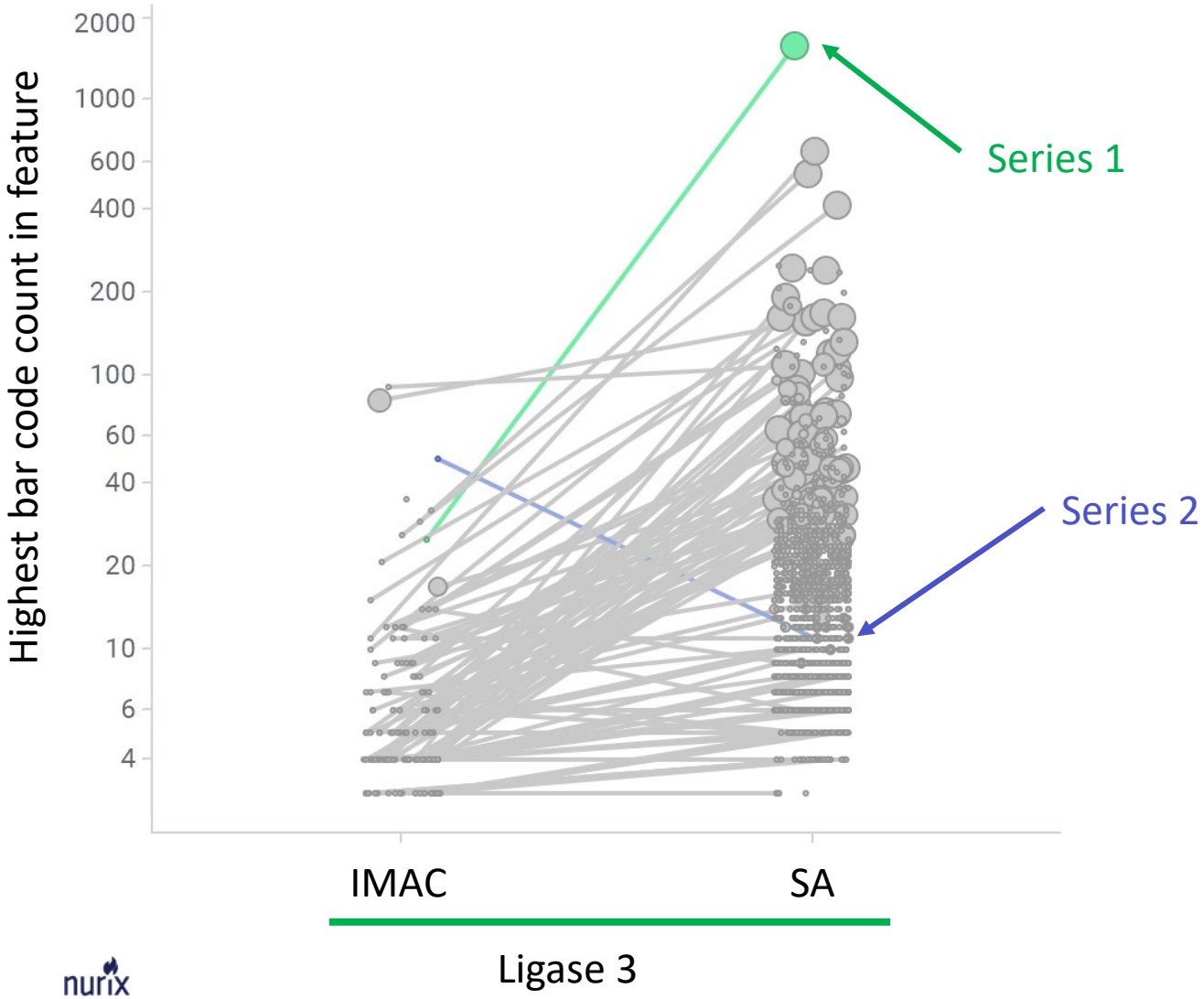
Broad Follow Up Maximizes the Opportunities from DEL Screens

Lines link identical features between selections

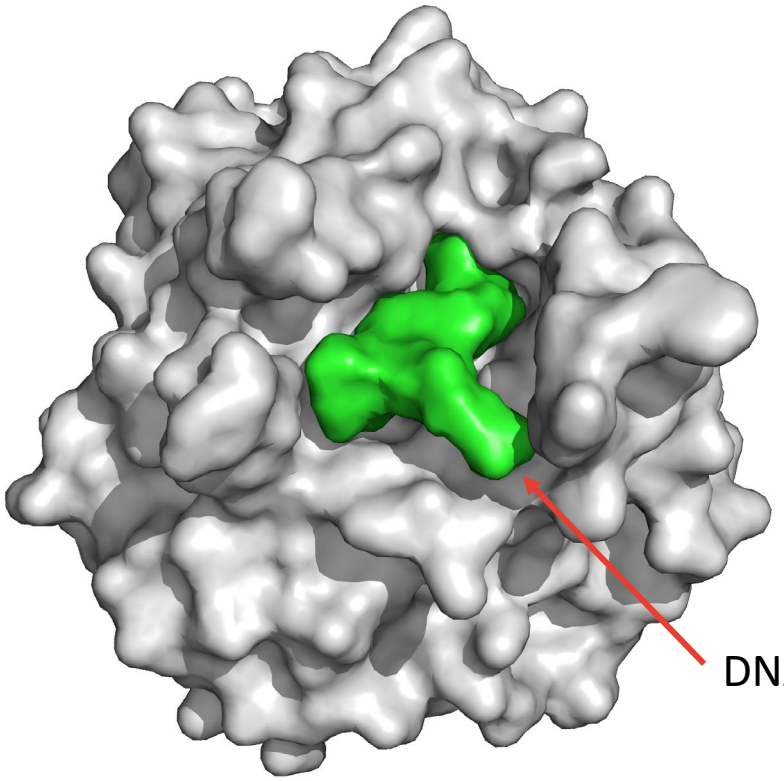
Size denotes number of ligands within the feature



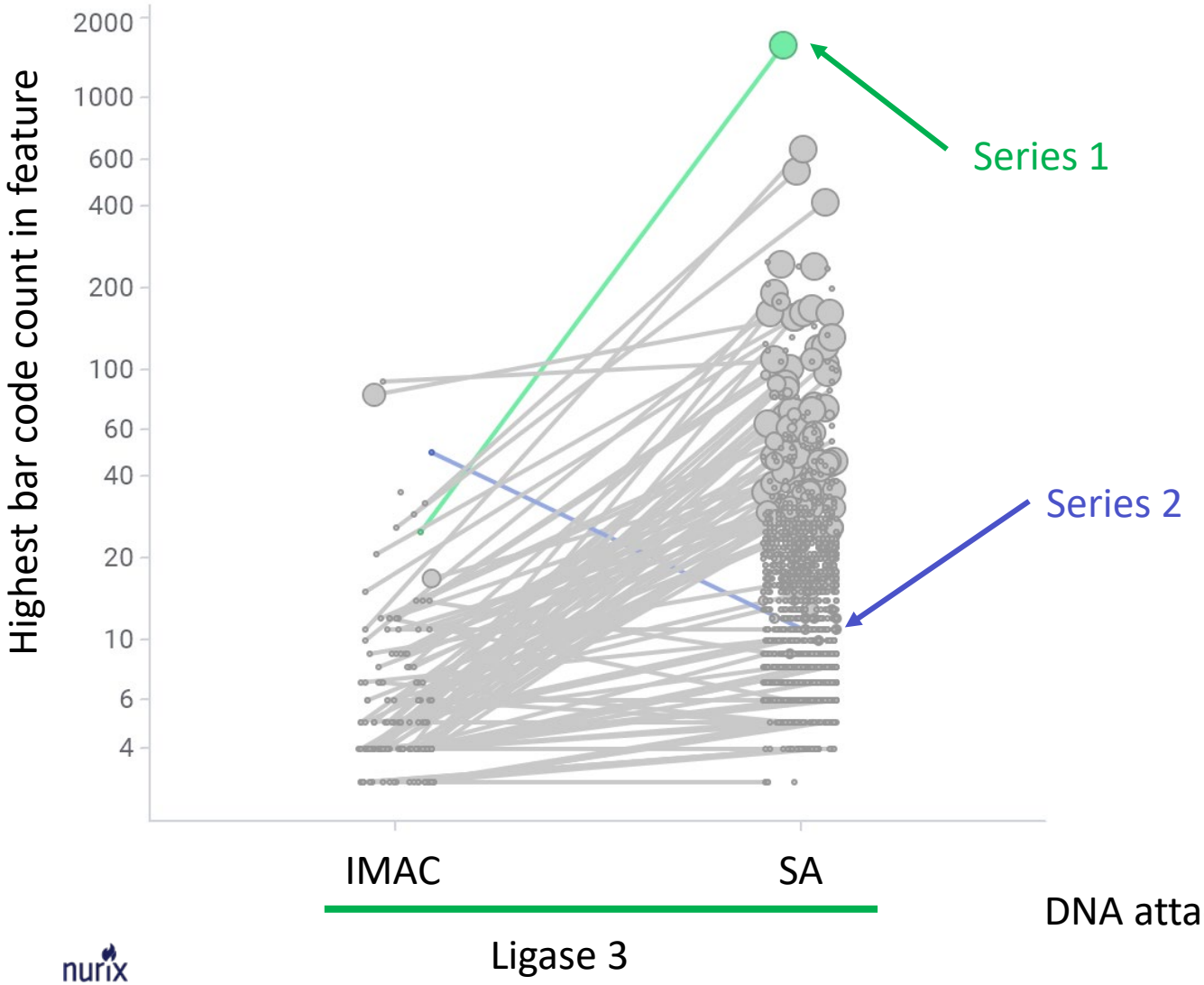
Broad Follow Up Maximizes the Opportunities from DEL Screens



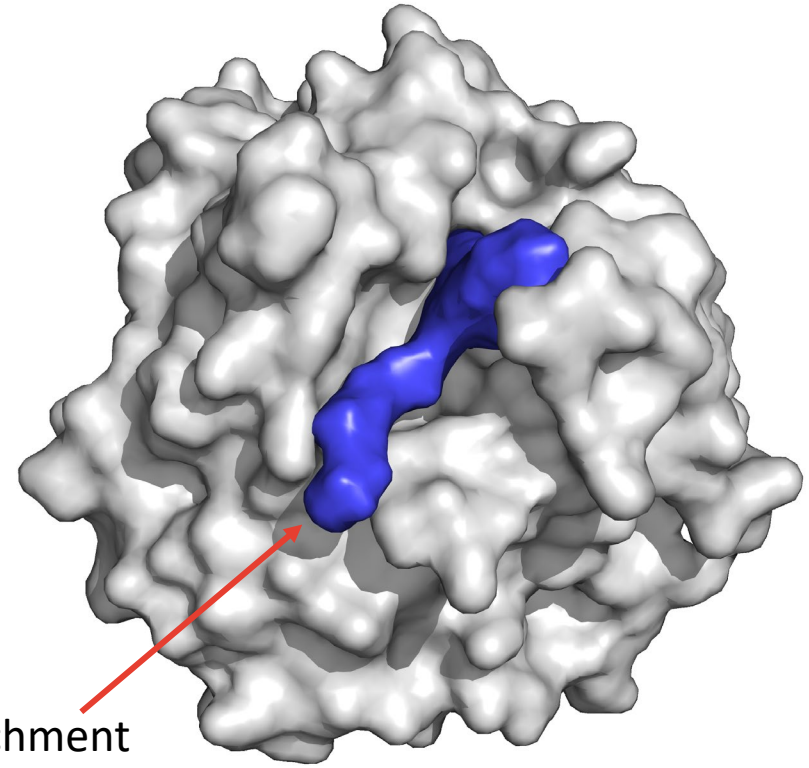
X-ray crystal structure of
Series 1 bound to ligase 3



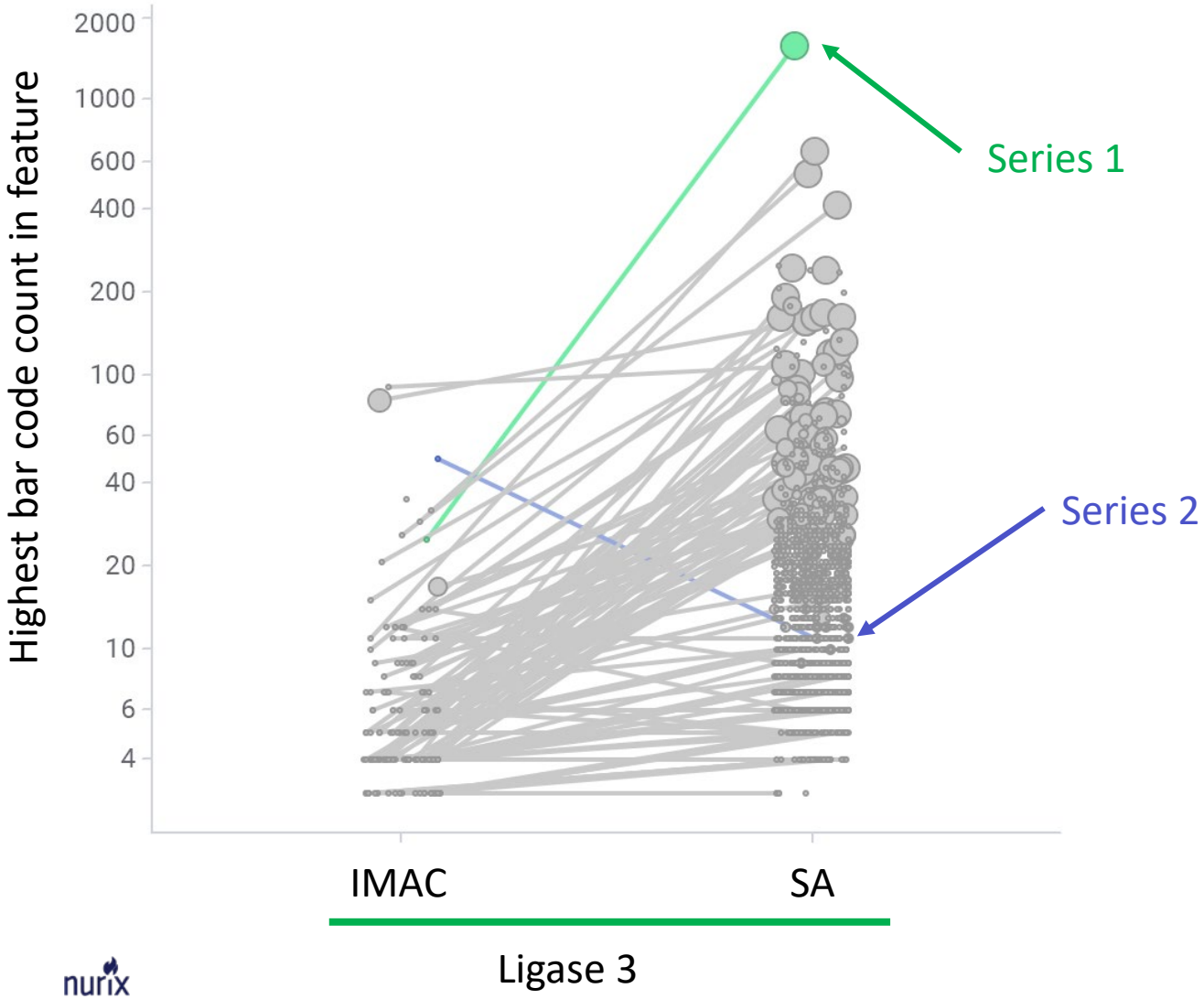
Broad Follow Up Maximizes the Opportunities from DEL Screens



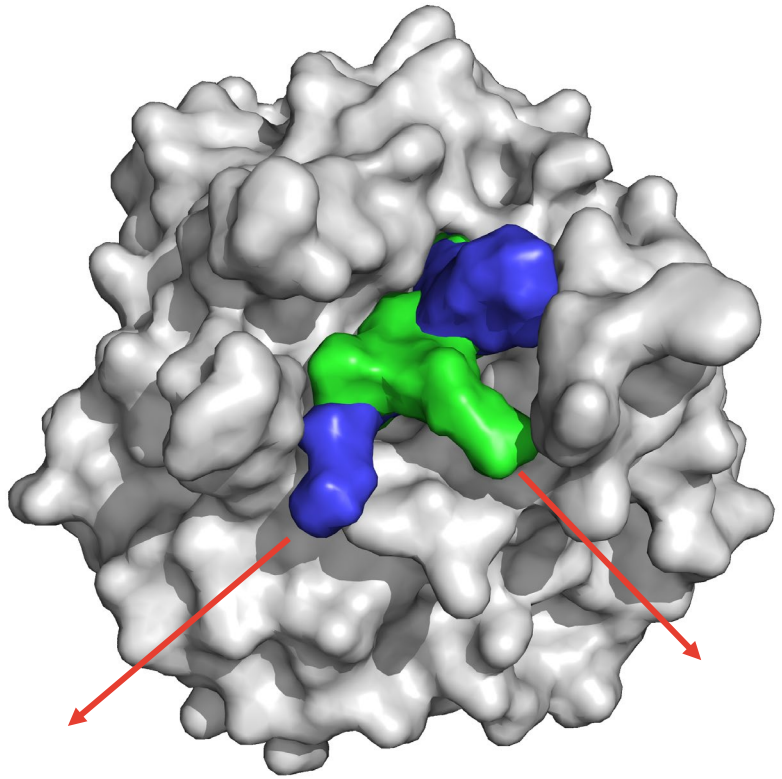
X-ray crystal structure of
Series 2 bound to ligase 3



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

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!