Ligase Inhibition Workshop

3rd Annual Ligase Targeting Drug Development

Tuesday April 11th 2023

9:00 – 11:00

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Agenda

- Introduction to Ligases (Sumit) – 5 min
- Mechanisms of Inhibition (Sumit) – 5 min
- Ligand-ability of the ligase class (Xevi) – 5 min
- Review of the existing chemical matter (Xevi) – MDM2, VHL, IAP, SOCS2, KEAP1 – 10 min
- HDM2 Structure Based Drug Design (Xevi) – 25 min
- Break – 10 min
- DEL platform overview and advantage (Sumit) – 15 min
- Pellino1 case study (Sumit) – 25 min
- Q&A

Ubiquitin Ligase are Mediators of Cellular Signaling and Homeostasis

Nurix Drugs Engage Ligases for the Treatment of Cancer

Targeted Protein Modulation: TPM = TPD + TPE

A Powerful Cellular System

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

Harness ligases to decrease specific protein levels

Targeted Protein Degradation (TPD)

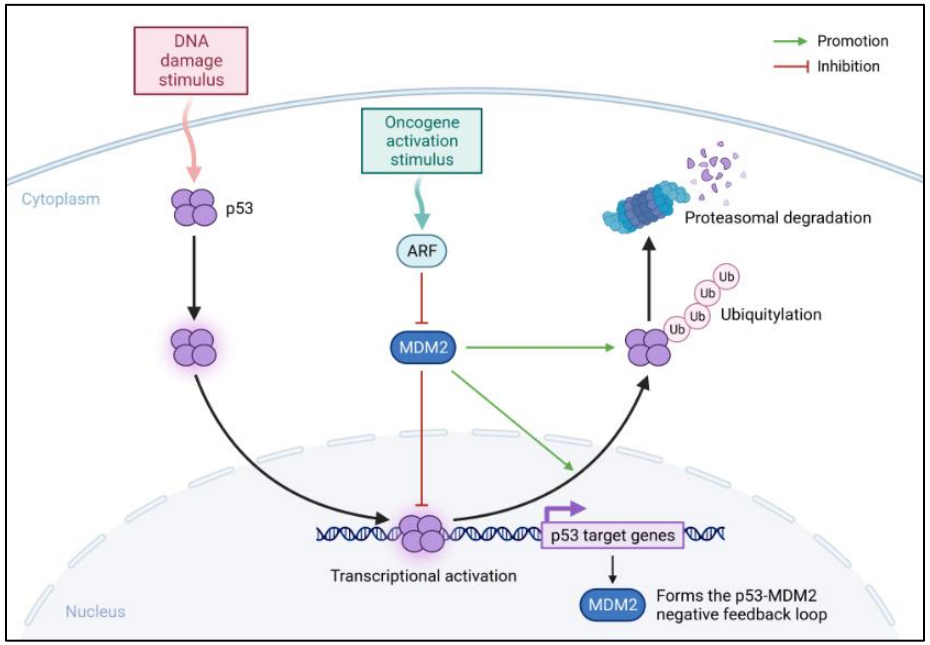
Targeted Protein Elevation (TPE)

Inhibit ligases to increase specific protein levels

Ligase Inhibition as a Therapeutic Strategy

- E3 ligases control cellular protein abundances in response to various stimuli
- They are key regulators of disease relevant cellular pathways

Oncogenic Signaling (e.g., MDM2)



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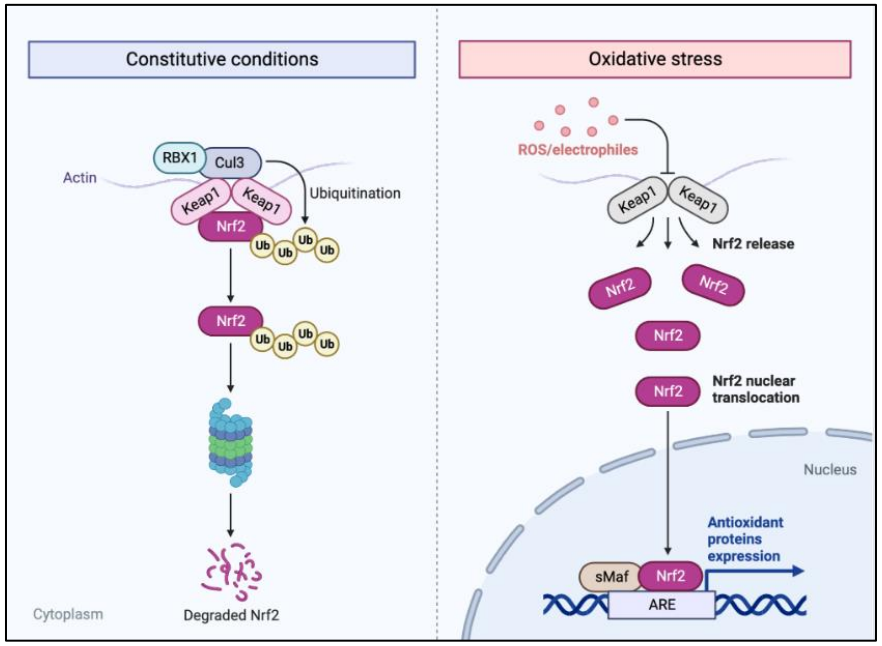
Redox Signaling (e.g., KEAP1)



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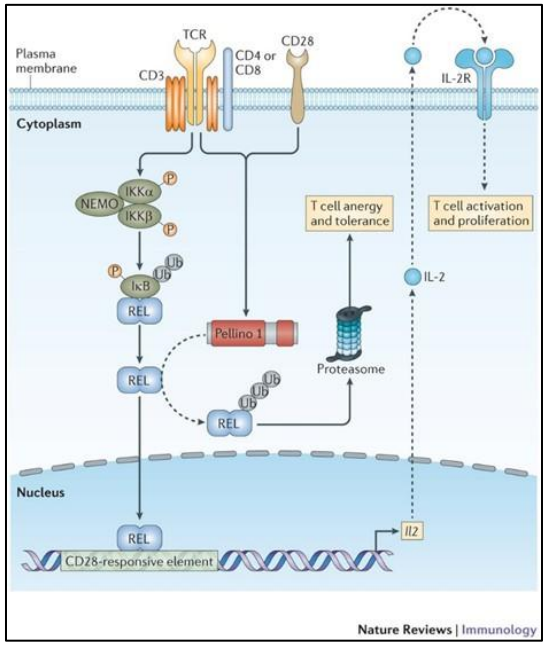
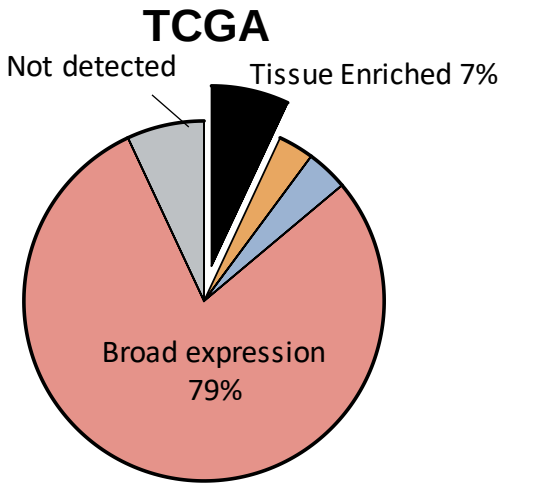
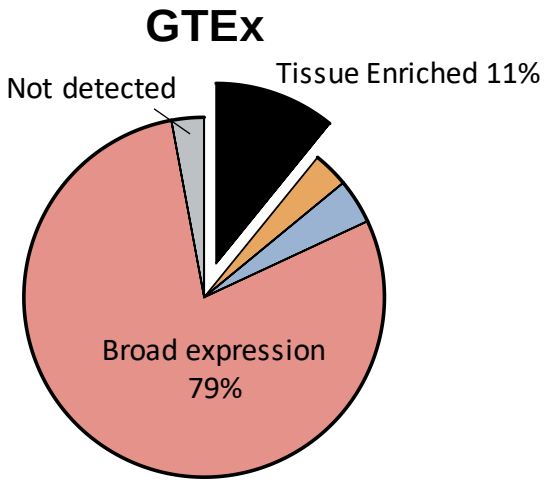
Receptor Signaling (e.g., Pellino1)



Moynagh PN, Nat Rev Immuno 2014

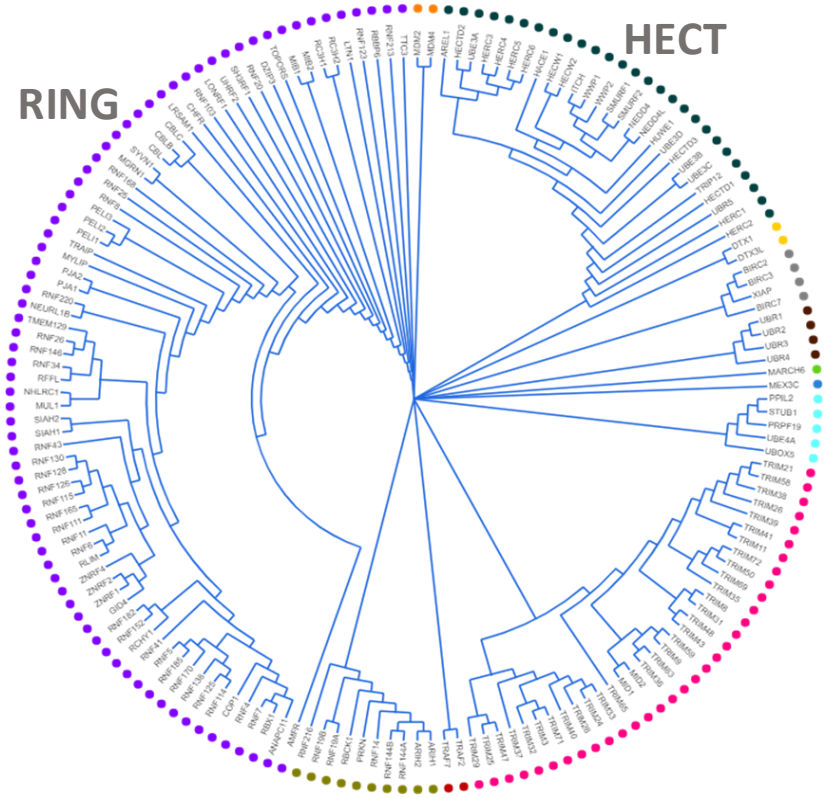
The Ubiquitin Ligase Family is Diverse with Over 600 Proteins





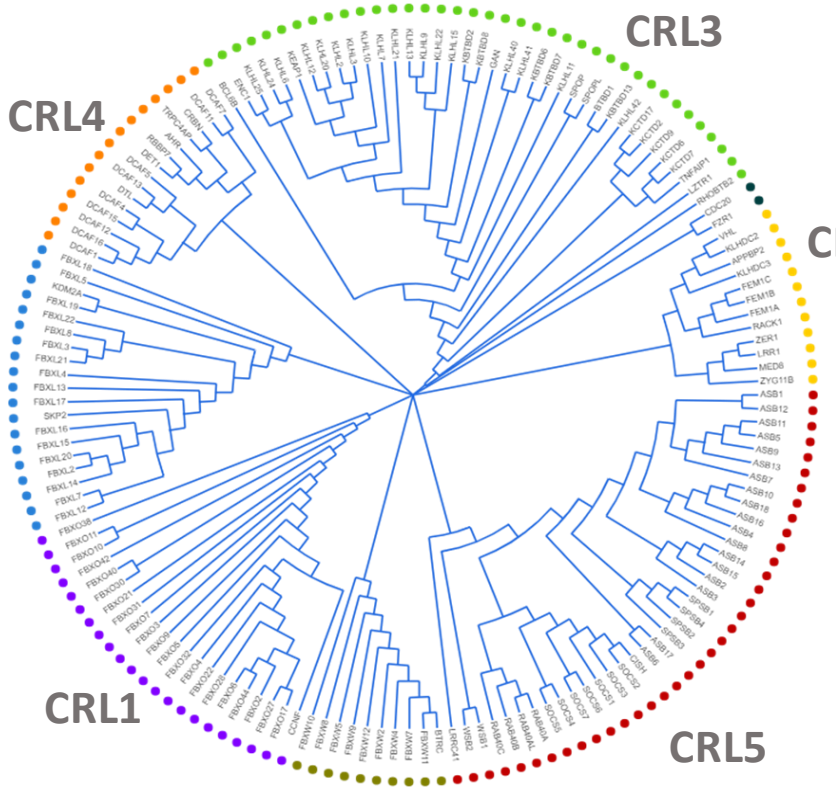
- Diverse family of proteins that are broadly expressed in most tissues
- Classified into single chain or multimeric ligases based on the functional assembled state
- Sub-classified based on their conserved motif or domains

Single Chain E3 ligases



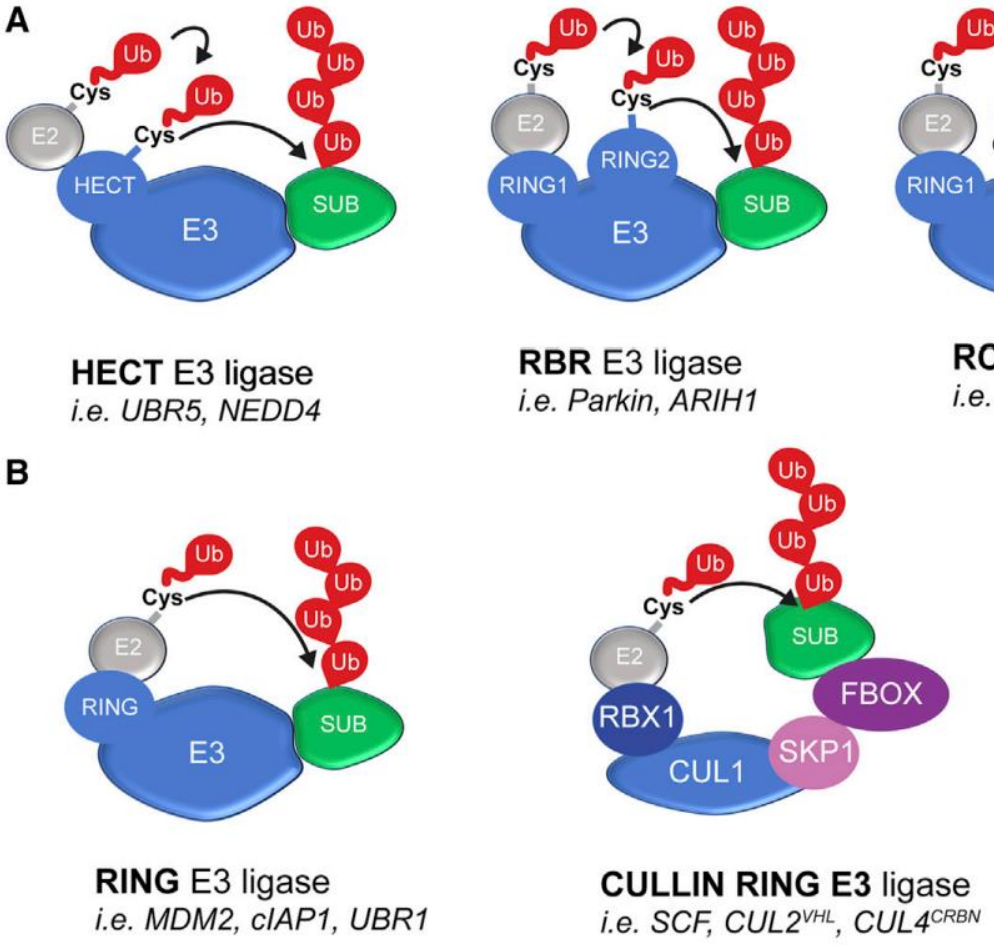
Multimeric E3 ligases

Substrate Binding Modules



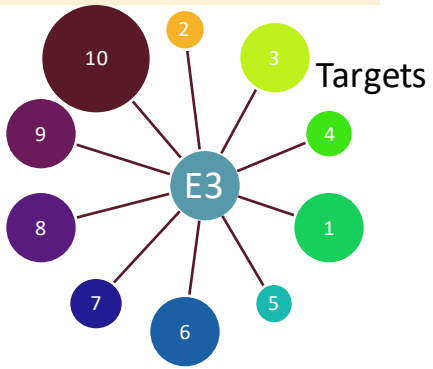
SGC UbiHUB

E3 Ligases assemble diverse ubiquitin chains on their substrates

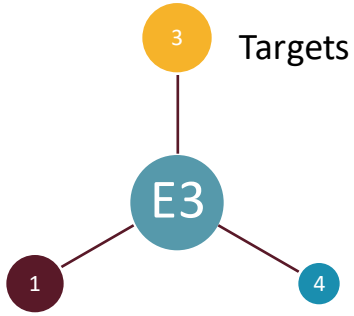


- Most E3 ligases lack a well-defined active site
- They work by inducing proximity between the target protein and activated E2~ubiquitin complex
- Ubiquitin forms a covalent bond with a lysine side chain on the target protein. Poly-ubiquitin chain is assembled when additional ubiquitin are attached to multiple the previous ubiquitin leading to a diversity of chain topologies
- Polyubiquitin chain binding receptors lead to distinct outcomes of the modified protein (e.g., Lys-48 linked linear or branched chains are effectively recognized by the proteasomal degradation complex)

Broad acting ligases



Narrow spectrum ligases



Predrag Jevtić, Diane L Haakonsen , Michael Rapé *Cell Chemical Biology* **2021** *28* (7), 1000-1013

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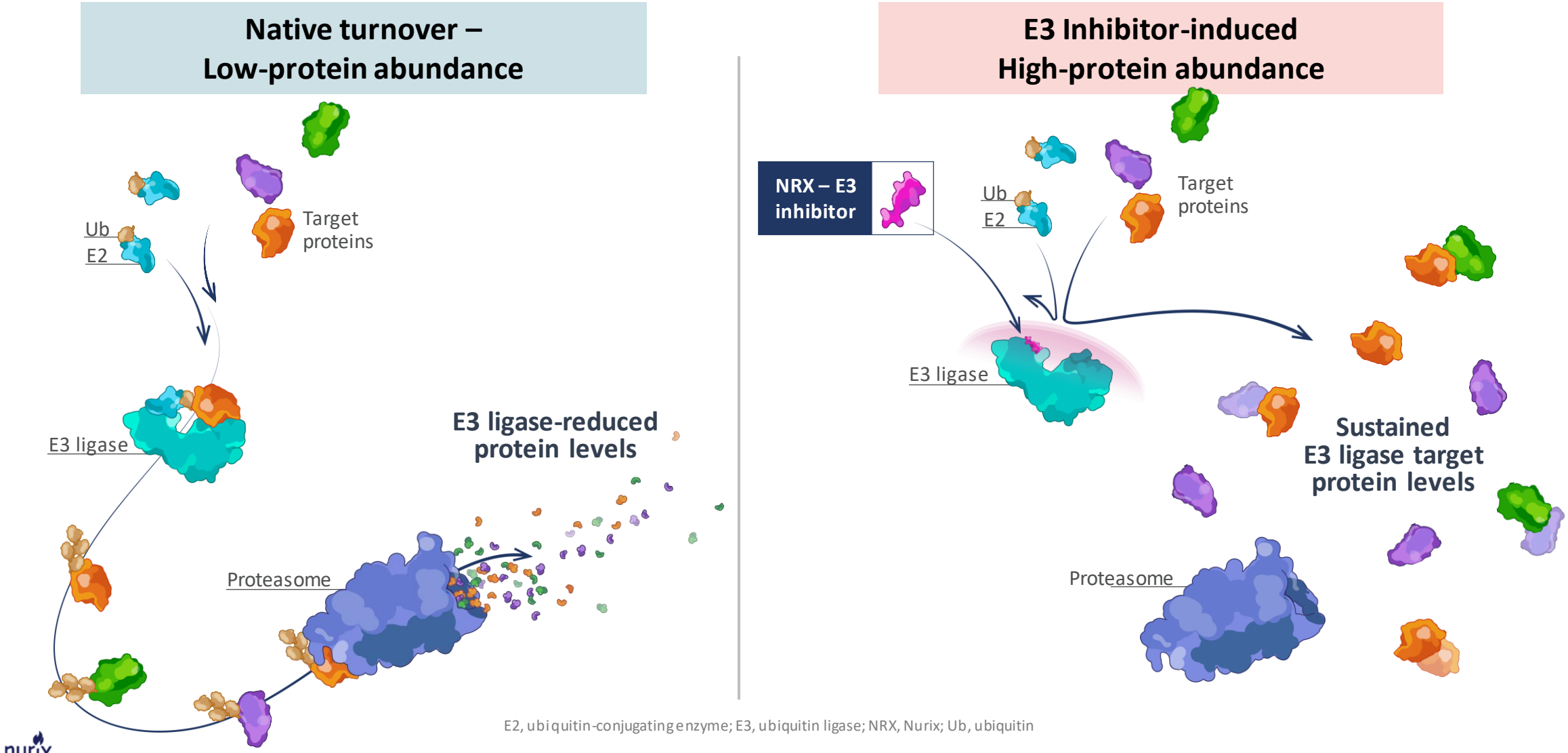
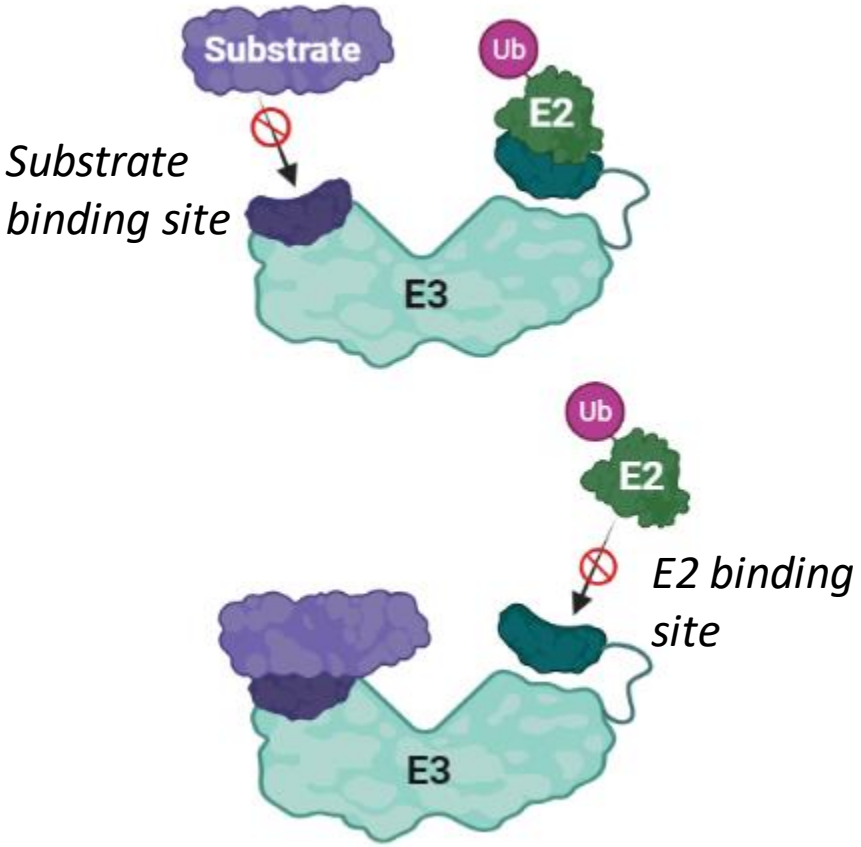
One E3 Ligase Controls Multiple Target Proteins and Pathways



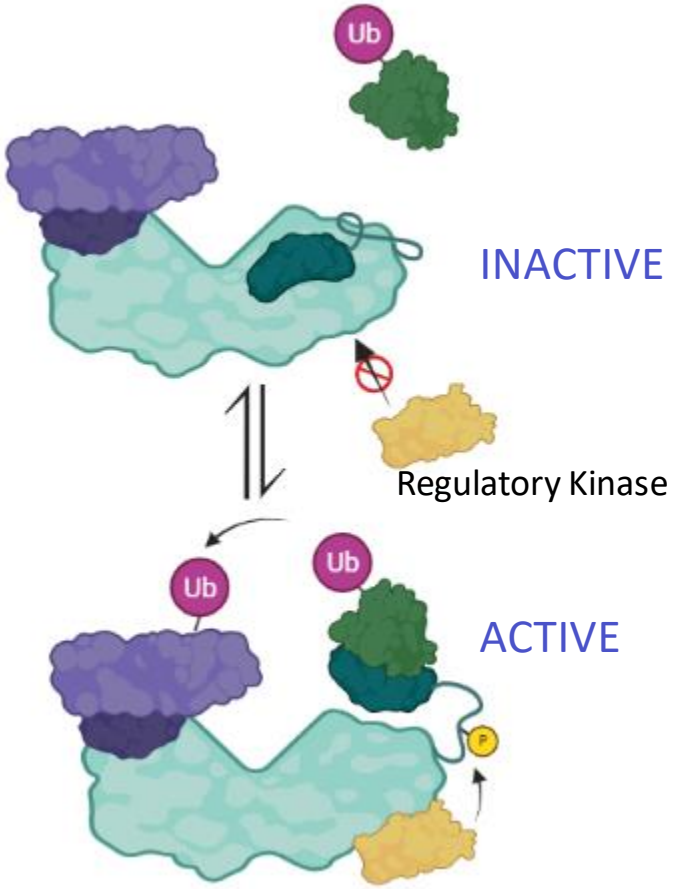
E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; NRX, Nurix; Ub, ubiquitin

Mechanisms Targeted by Small Molecule Inhibitors of E3 Ligase

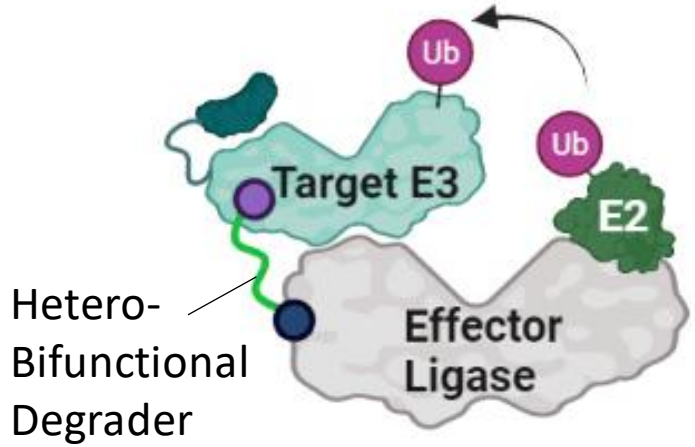
Protein-Protein Interaction



E3 Ligase Activation



E3 Ligase Degradation



Proteasomal Degradation

Enabling E3 Ligases Ligand Discovery with DNA-Encoded Library Screening

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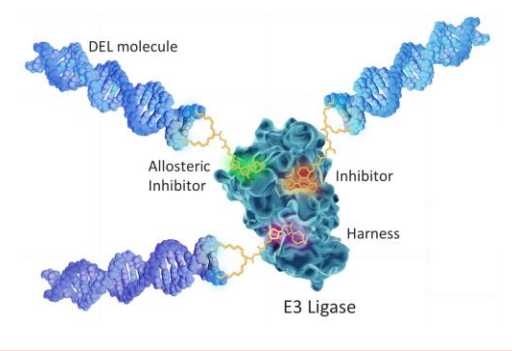
Nurix's Integrated Protein Modulation Discovery Platform

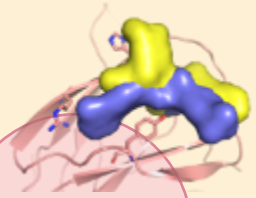
DEL Discovery



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

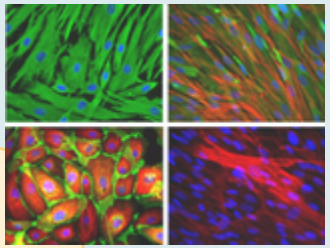
Supported by strength in Protein Sciences

Rational and Empirical Chemistry



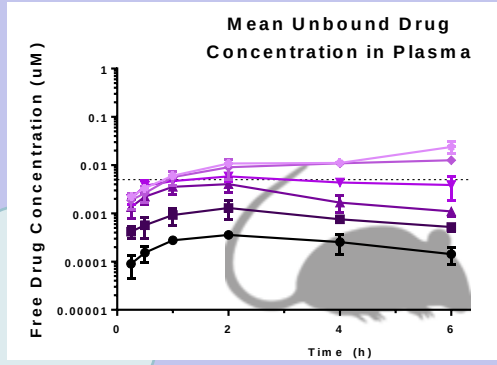
Structure Based Drug Design combined with chemistry automation enables broad exploration of lead-like chemical space for each program

Direct-to-Cell Biology Capabilities



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

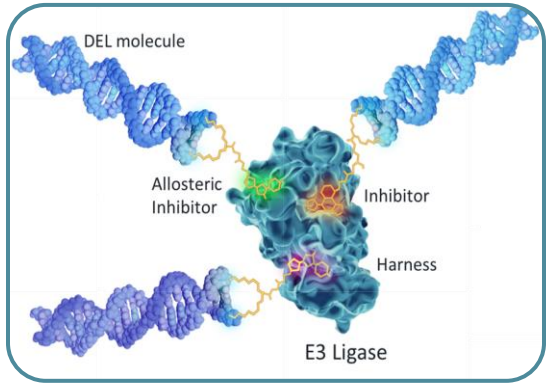
Scaled Screening for in vivo exposure



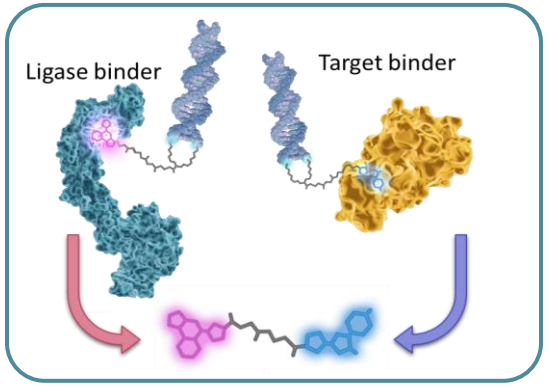
Capacity to screen for ideal *in vivo* drug exposure profile and assess impact on disease biology

Expertise in Oncology and immuno oncology

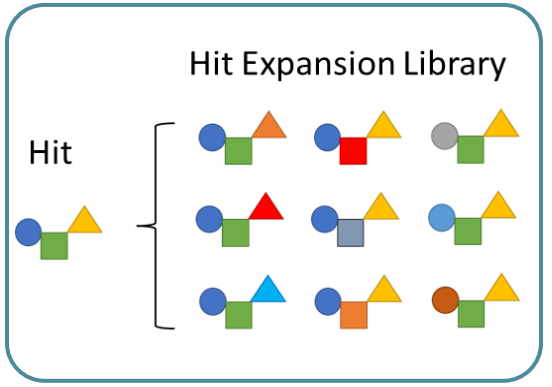
Why DNA Encoded Libraries?



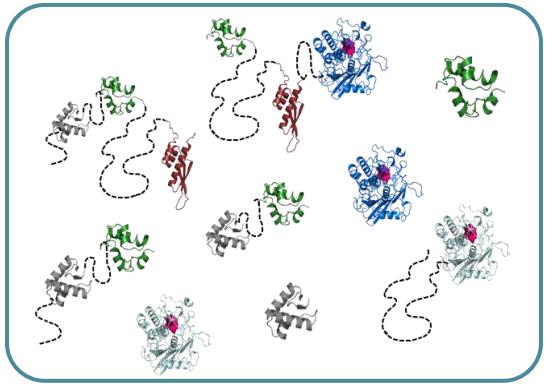
Affinity-based screening is MoA agnostic – for E3 ligases we can identify ligands for TPD and inhibitors for TPE from the same screen



DNA attachment provides initial handle for bifunctional molecule synthesis



Combinatorial design enables rapid hit follow up and optimization

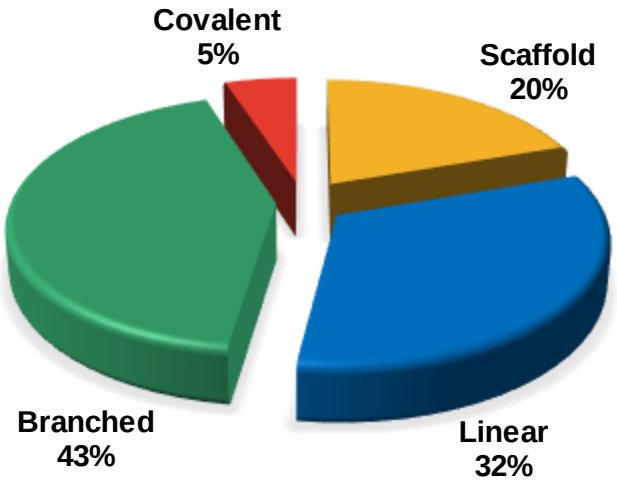


Low capital investment and per screen cost allows for a broad exploration of target and chemical space

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

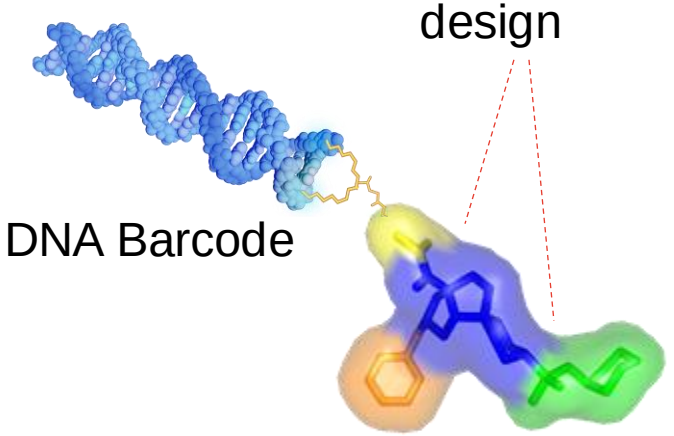
Nurix DEL Collection

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



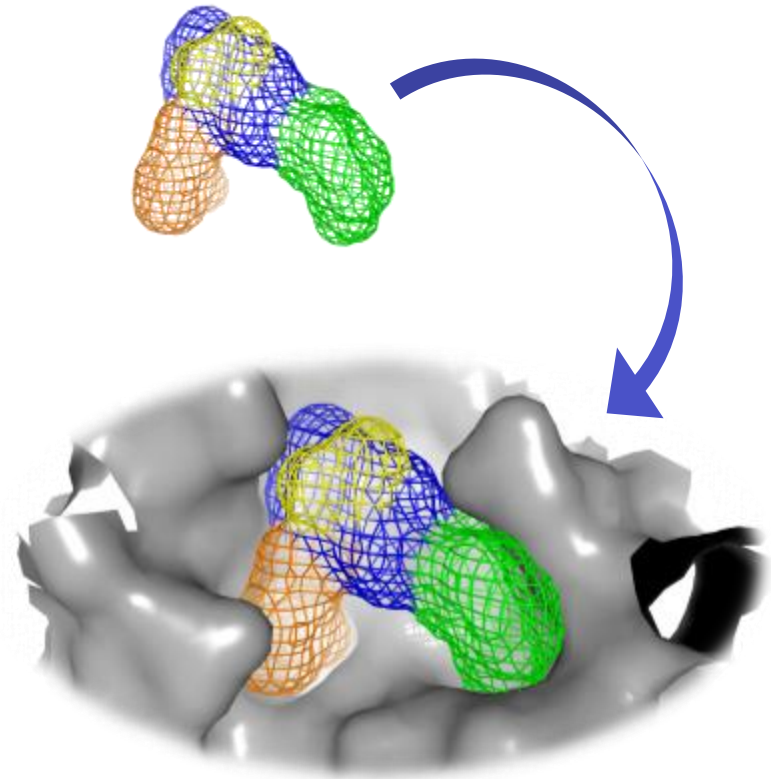
Scaffold Libraries Proving Essential for Delivering Ligands for "Undruggable" Targets (sole source of hits for 75% of these targets)

Three-dimensional design



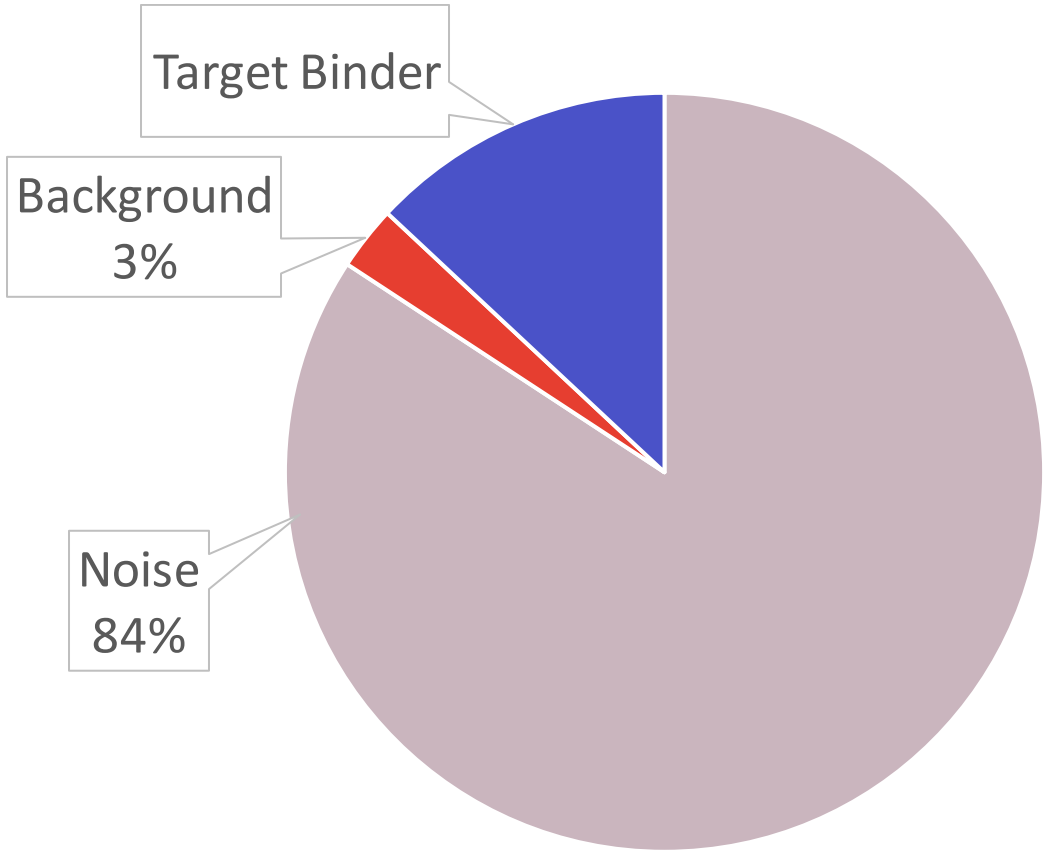
Our proprietary scaffold DELs provide unique geometry and high sp3 character, allowing molecules to achieve optimal pocket fit

Nurix scaffold designs show high pocket complementarity



Composition of DEL Screening Outputs

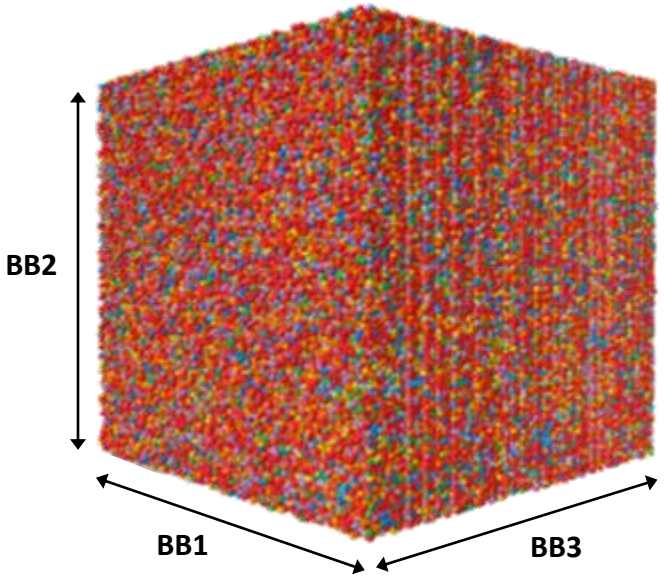
- Most of the DNA-linked compounds sequenced at the end of a selection are noise or background (matrix binders, non-specific protein binding, other enrichment not specific to the target)
    - Noise can be eliminated by experimental (replicates) OR analytical (thresholding) methods
    - Elimination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



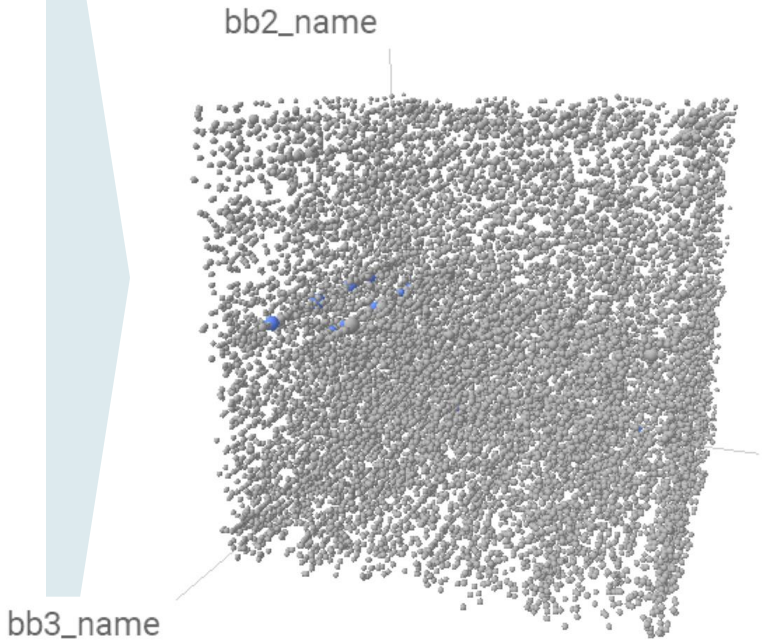
De-noising Example – VHL Replicates

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

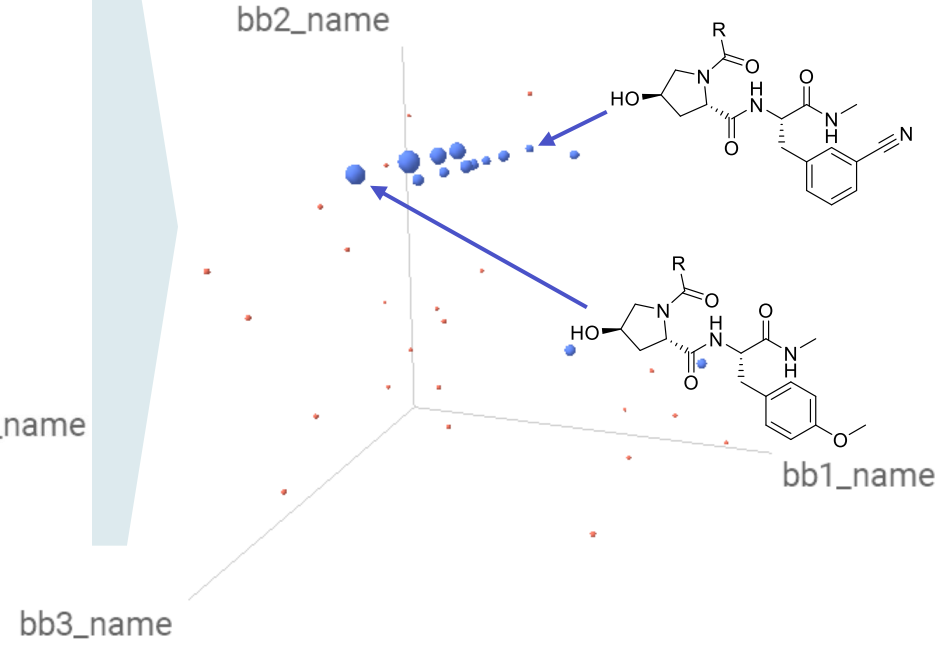
Nurix DEL Collection
>5 billion unique structures



All ligands present in a single screening condition

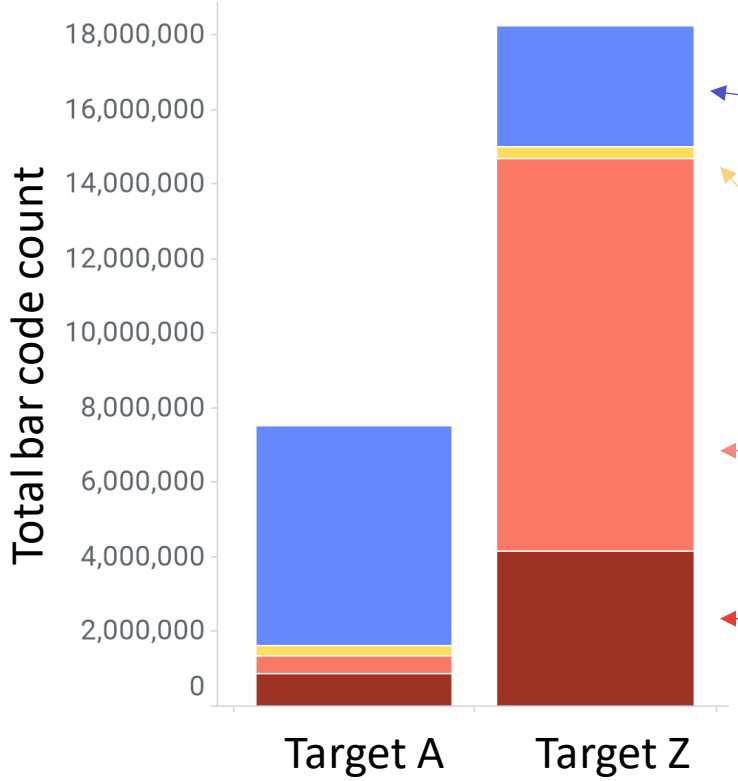


All ligands present in all three replicates



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

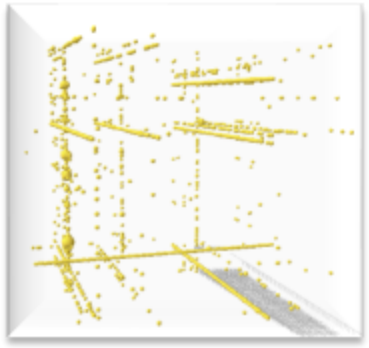
Pan-Kinase Binder – enriched against target kinase and only other kinase targets in the database

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

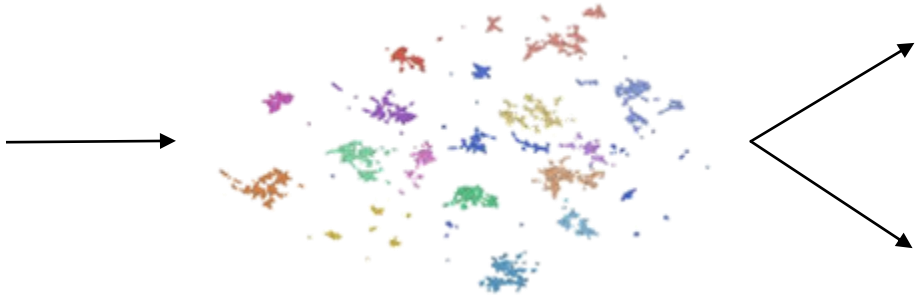
Experimental Background – background binders enriched in target and control selections

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

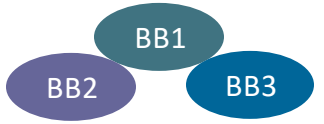
Large complex data sets require automated solutions to accelerate hit ID



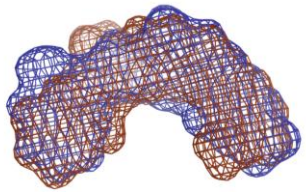
DEL Screen and filtering for target-specific binders



Automated Structure Analysis and Clustering



Hit Resynthesis (on- and off-DNA)



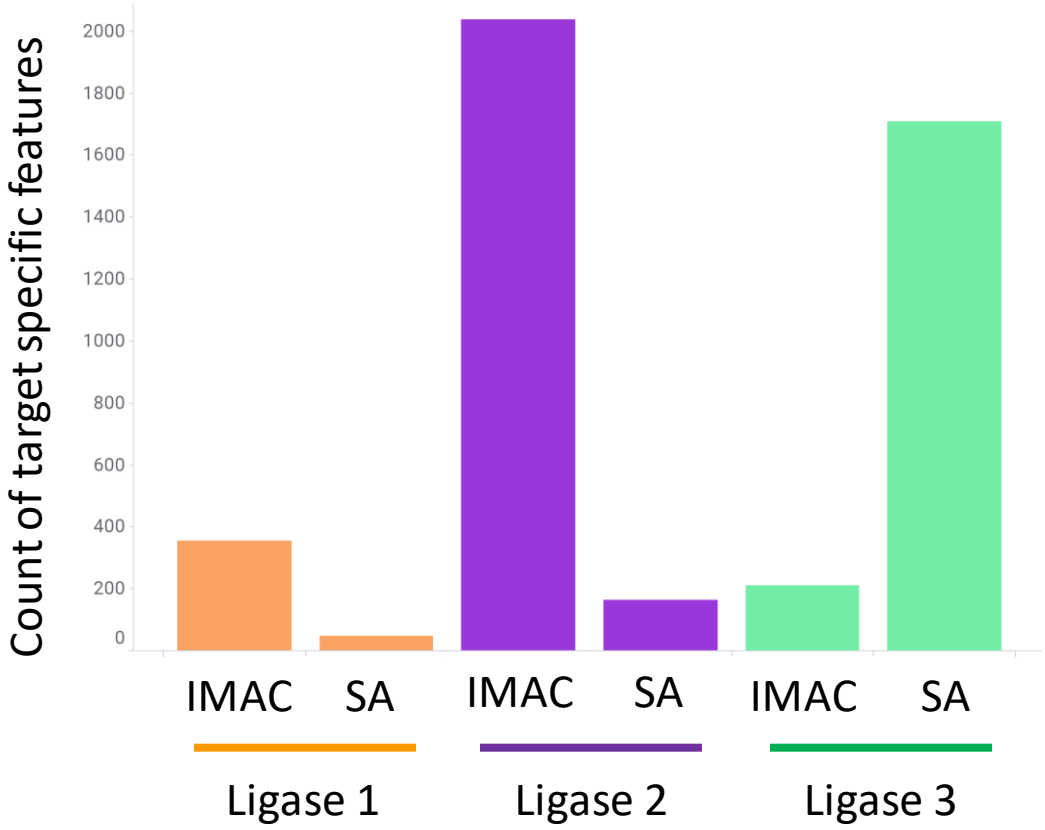
Machine Learning and Similarity Virtual Screening

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)

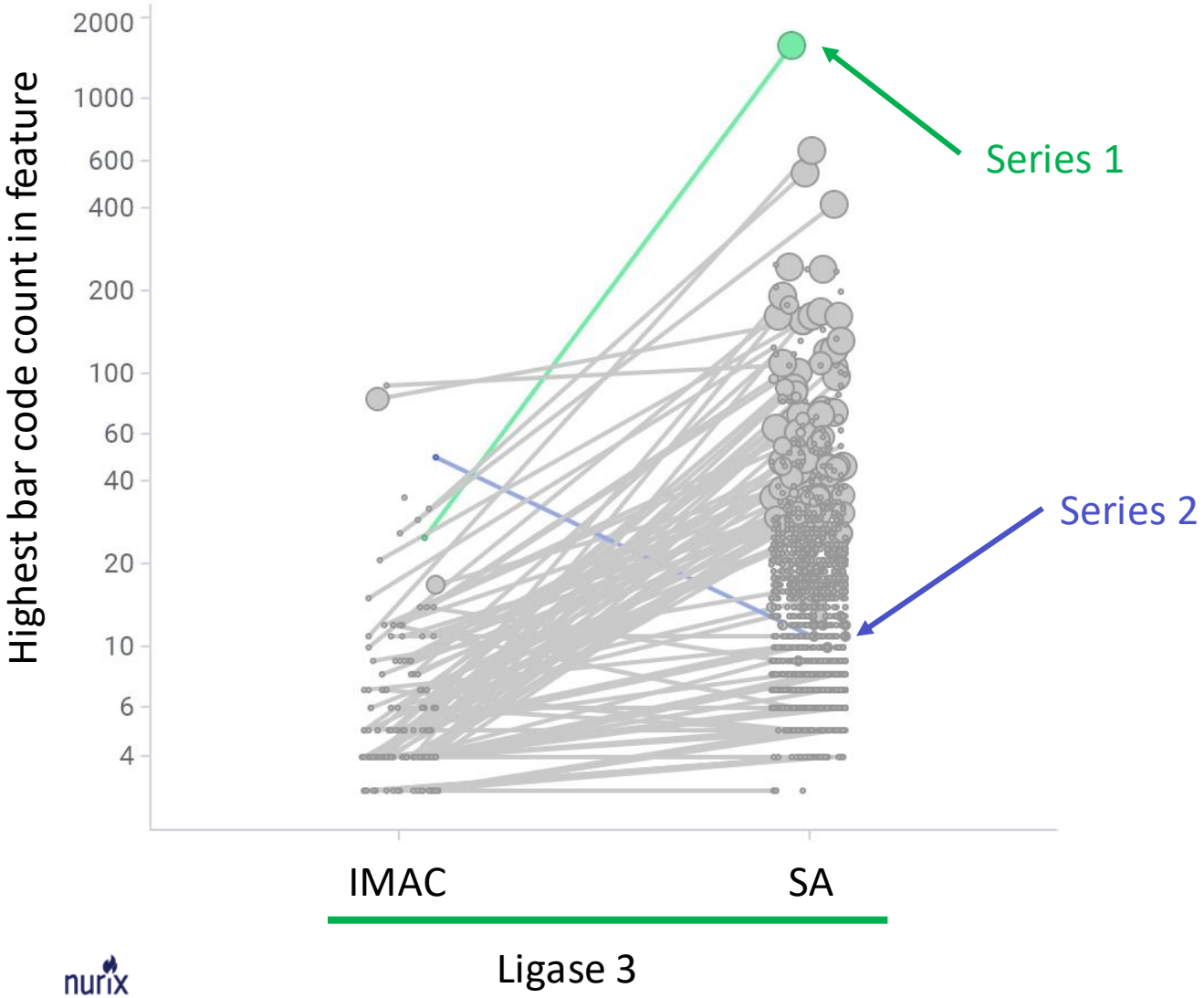
Screening and Follow Up Capacity – Finding the Most Productive Spaces for Novel Targets

- 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

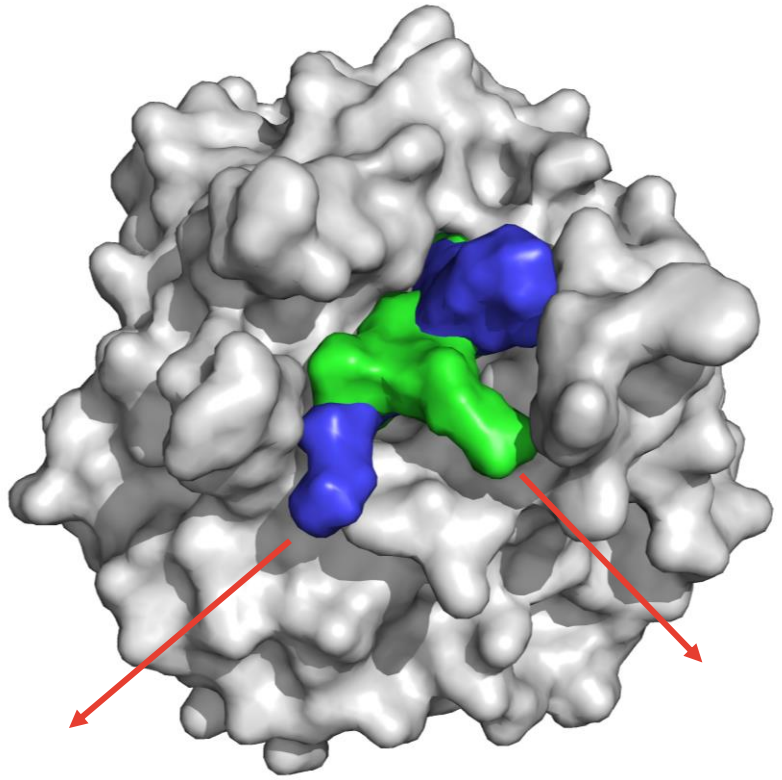
Example – three ligases screened in parallel using Immobilized metal affinity (IMAC) and streptavidin (SA) beads



Broad Follow Up Maximizes the Opportunities from DEL Screens



Overlay of Series 1 & 2
bound to ligase 3



Unprecedented ligase with two confirmed vectors for bifunctional attachment

Conclusions

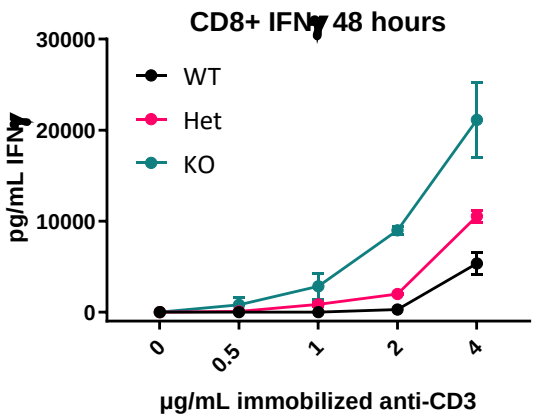
- DEL provides significant advantages as a ligand discovery platform for targeted protein modulation
- These advantages can only be realized when coupled to high-quality, well-validated target proteins and a diverse collection of libraries
- Leveraging the low cost per screening condition and the ability 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

Pellino1 Case Study

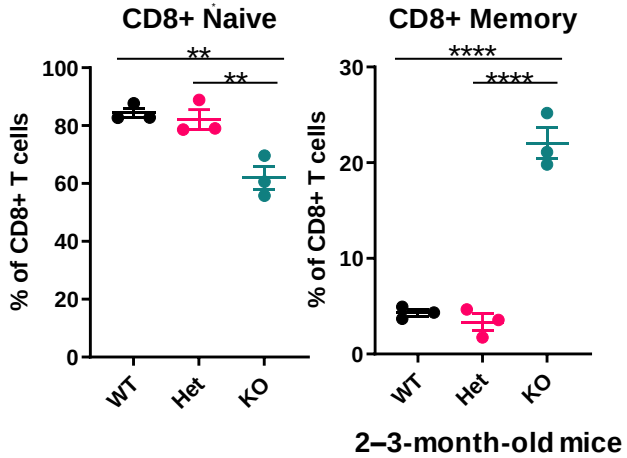
Pellino1 is an Immuno-oncology Target

- Pellino1 is an E3 ligase which is a negative regulator of T cell activation
- Therapeutic hypothesis: Degradation of Pellino1 will result in an anti-tumor response by increasing T cell activation
- Peli1 knockout mice display phenotypes consistent with therapeutic hypothesis:
  - T cells display hyperactivation when profiled ex vivo
  - T cells display increased memory markers in vivo
  - Knockout mice display a tumor growth inhibition phenotype

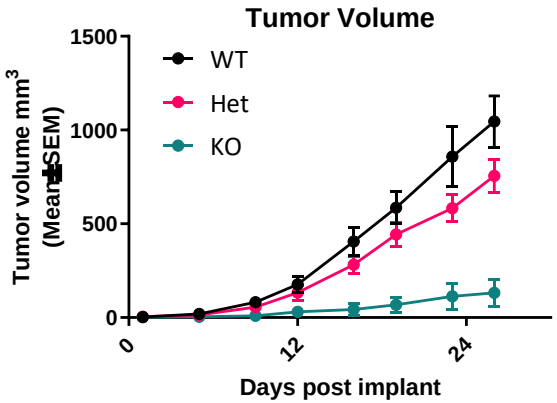
Enhanced Cytokine Secretion



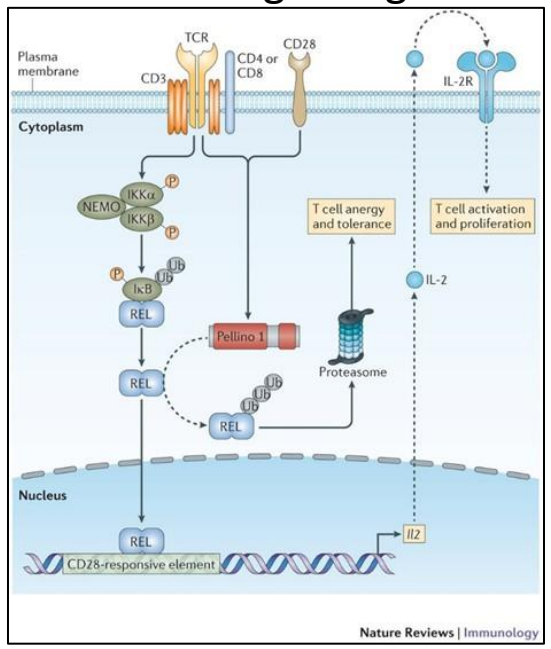
Increased Memory T Cells



Tumor Growth Inhibition

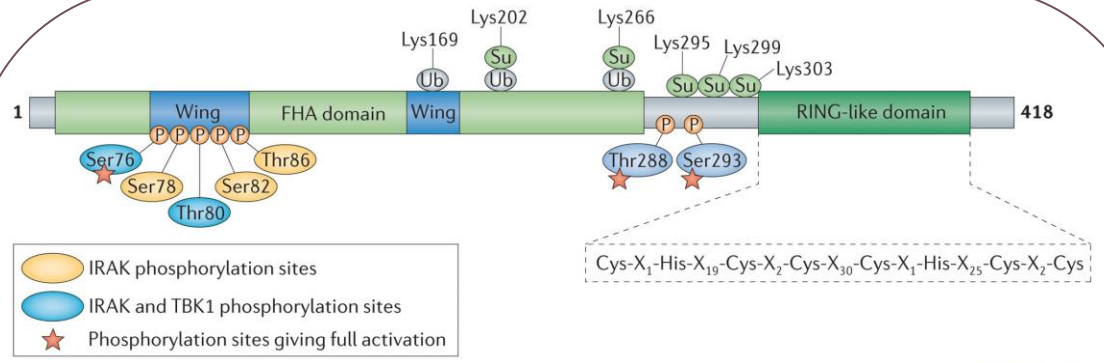


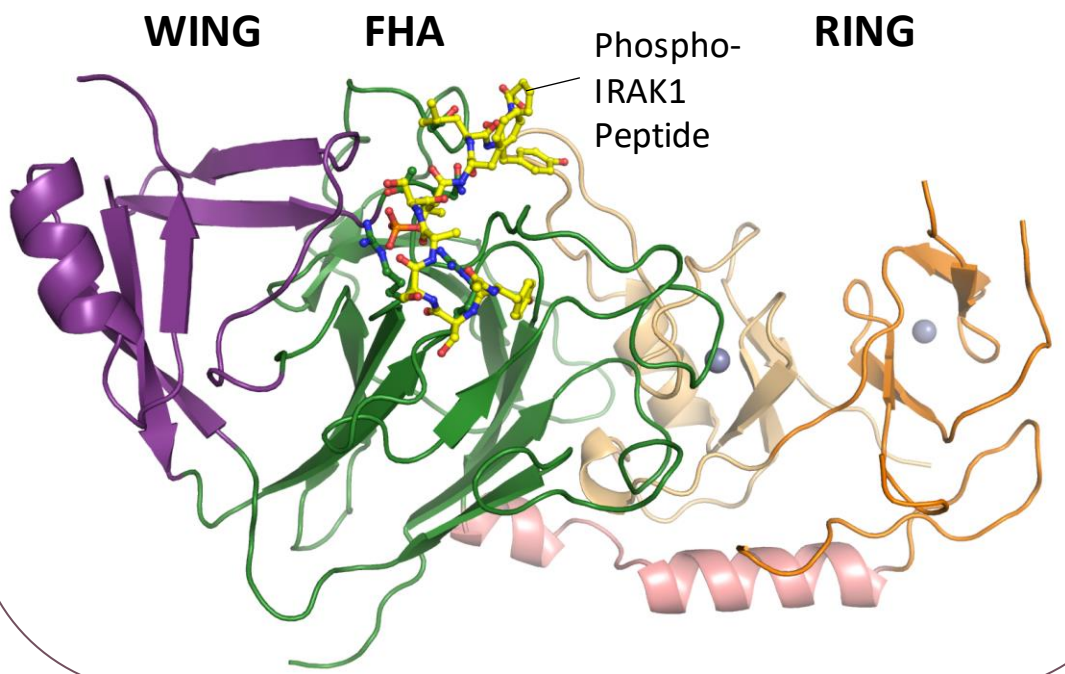
TCR Signaling



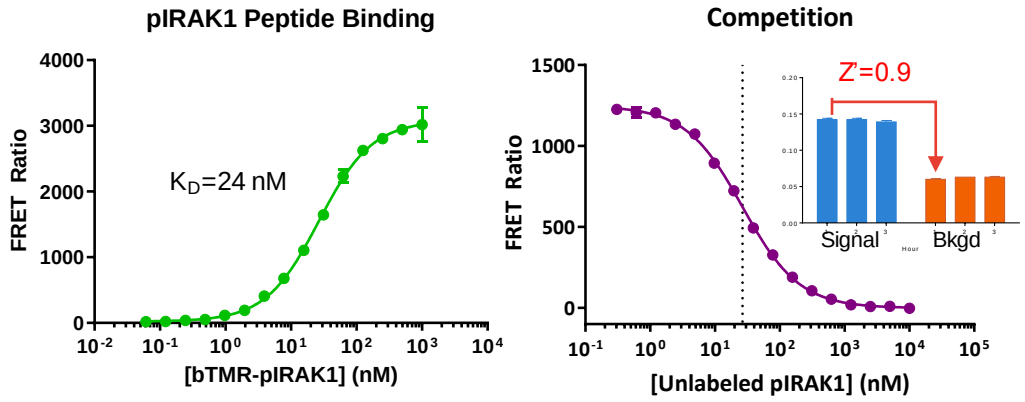
Moynagh PN, Nat Rev Immuno 2014

Pellino1 is a RING E3 ligase activated by phosphorylation

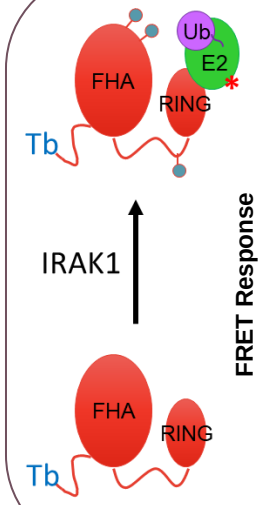


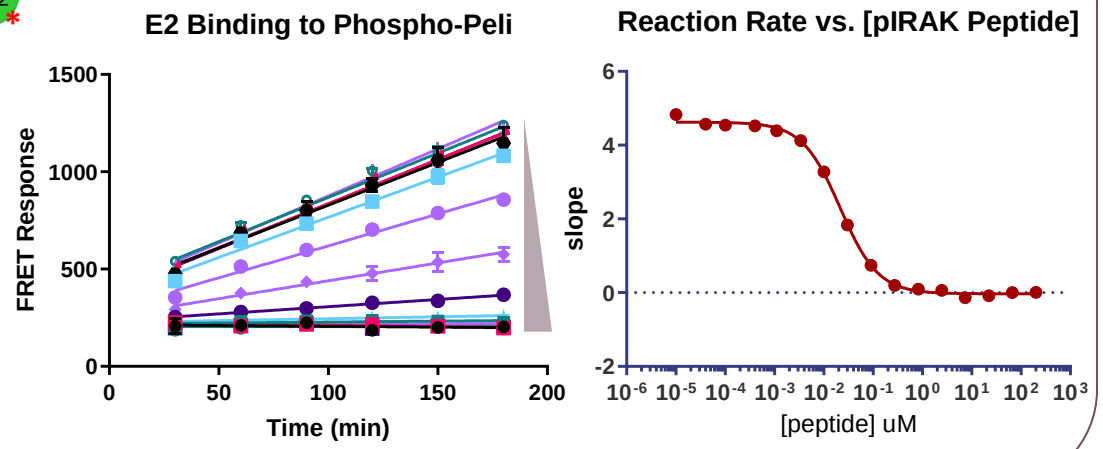


IRAK1 Phospho-Peptide Displacement TR-FRET

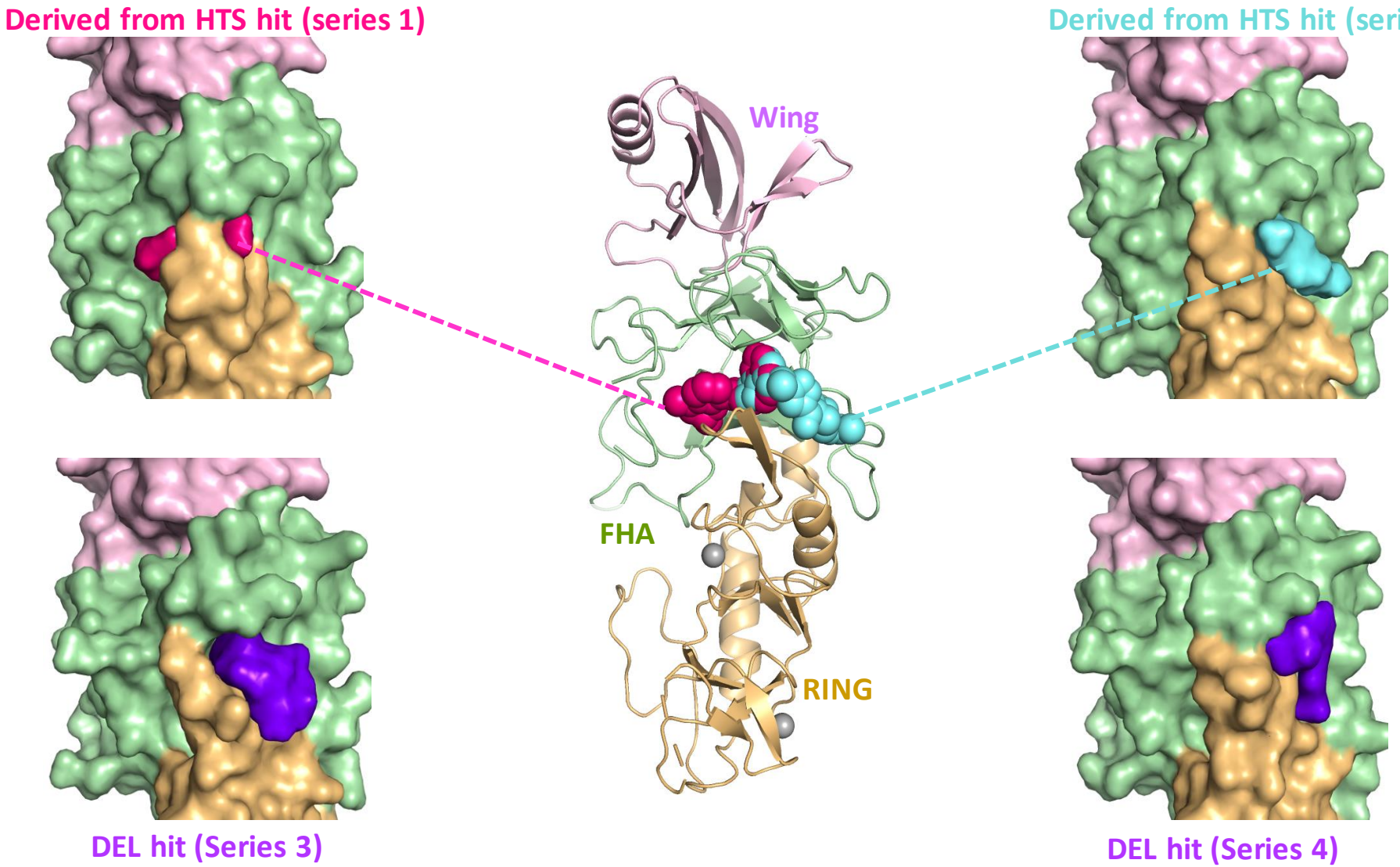


Pellino1 Activation E2 Binding TR-FRET





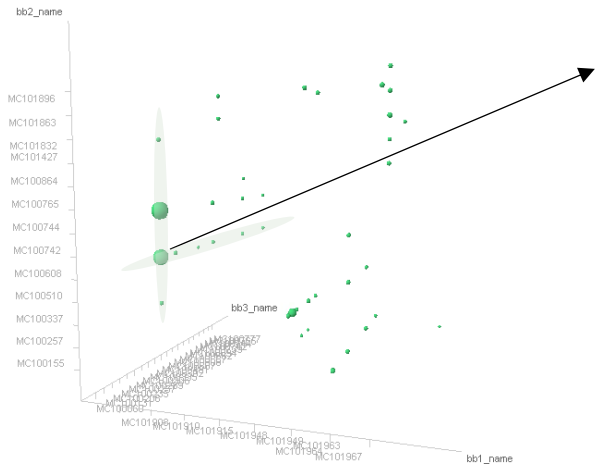
Multiple Hit Finding Approaches Yield Pellino1 Binders



Robbins, Ligase Targeting Drug Discovery April 2022

Two Series Confirmed as Pellino1 Binders from DEL Screen

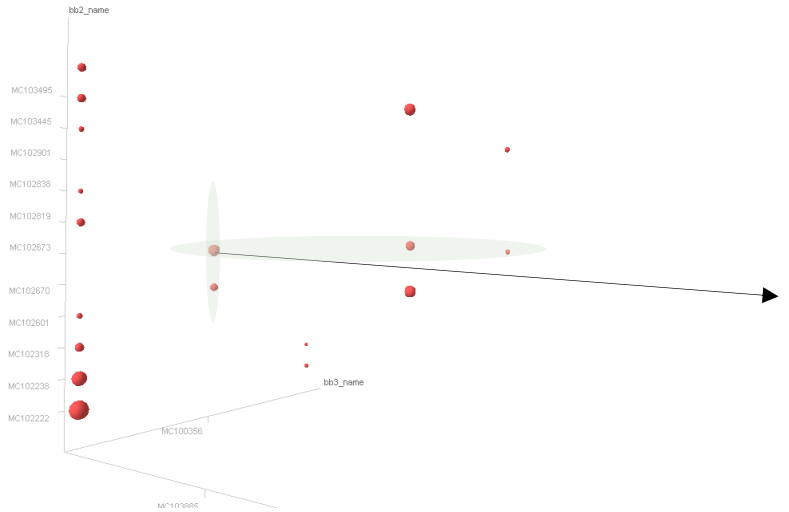
DEL Output



NRX-1

MW = 542.6
cLogP = 2.1
LE = 0.24
LipE = 4.8

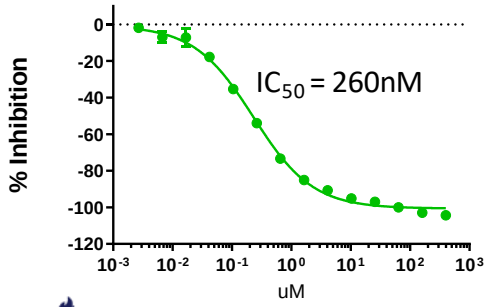
DEL Output



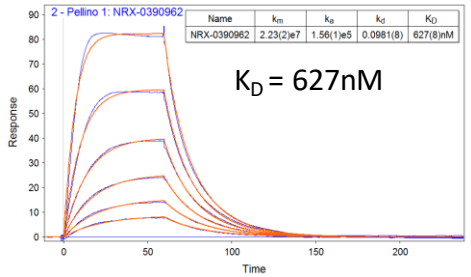
NRX-2

MW = 472.6
cLogP = 3.6
LE = 0.25
LipE = 2.7

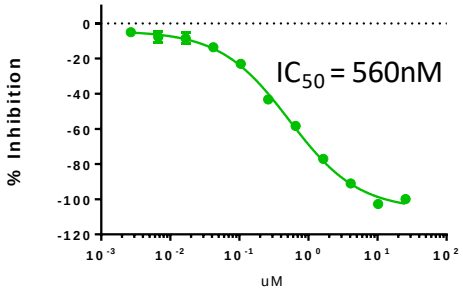
Peptide Binding Inhibition (FRET EC_{30})



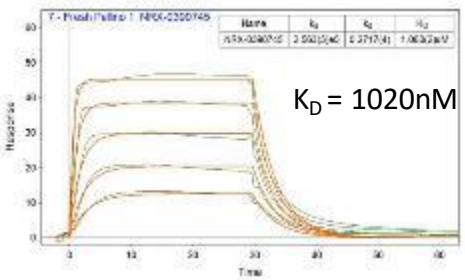
Surface Plasmon Resonance



Peptide Binding Inhibition(FRET EC_{30})



Surface Plasmon Resonance



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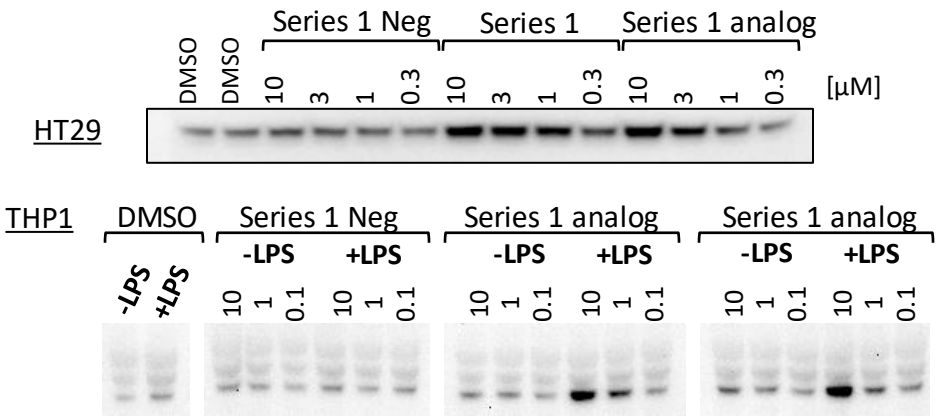
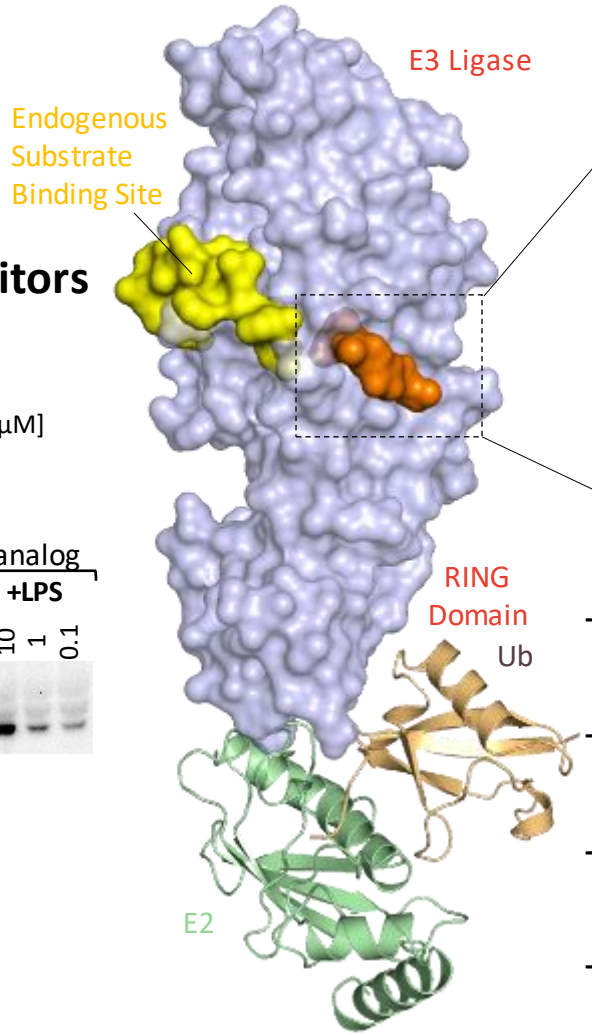
Multiple Linker Vectors Identified from Pellino1 Binders

Pellino1 Cellular Levels Increased by Inhibitors

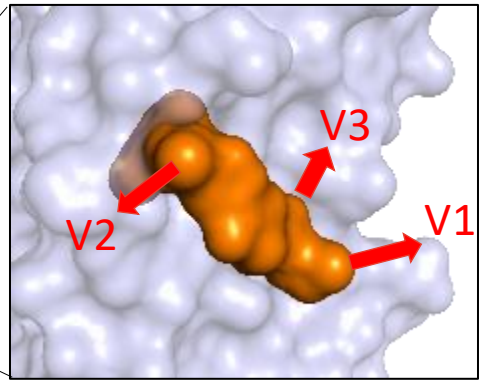


Cells treated with compounds for 24 hours



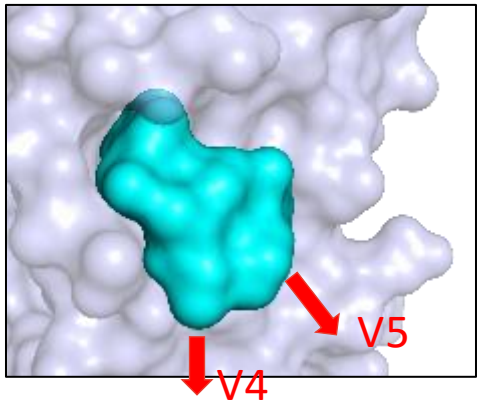
Modeled E2~Ub binding

Series 1: Optimized Series Derived from HTS



IC_{50} = 2nM

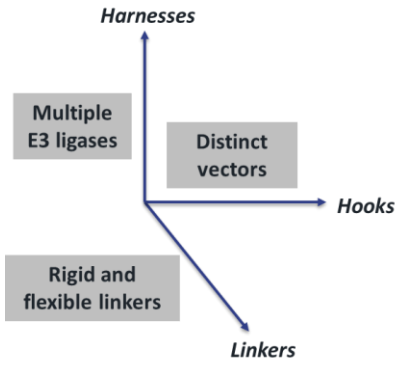
Series 3: Unoptimized DEL Series



IC_{50} = 260 nM

- HTS Series was optimized to very potent Pellino1 binder with IC50 = 2 nM
- Unoptimized DEL series identified with IC50 = 260 nM
- Multiple X-ray structure solved of binders in complex with Pellino1
- HTS-derived and DEL-derived series progressed to degrader synthesis to access multiple linker vectors

Matrix Approach to Degrader Hit Identification and Optimization

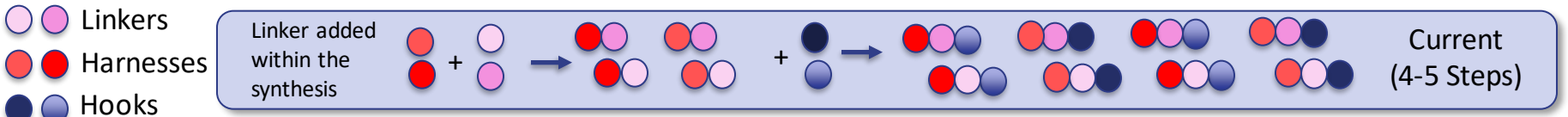


Binders from DEL and HTS
Affinity < 1 µM

Degrader Matrix
Linkers = 6
Multiple linker vectors
Harnesses = 5
Total = >100 bifunctional degraders

HiBit and/or Western Blot to Examine Pellino1 Degradation

- One compound/well combinatorial libraries
- Up to 5 steps before purification
- Typically, 200-400 degrader compounds made over 4-6 weeks



Diverse combinatorial libraries synthesized

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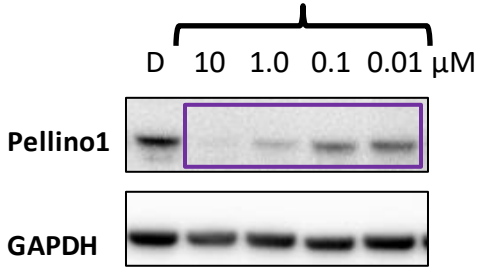
Multiple E3 Ligases Enable Pellino1 Degradation

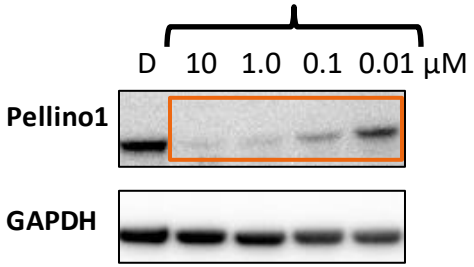
VHL

VHL-based degrader



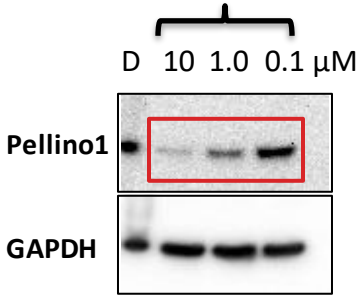
CRBN

CRBN-based degrader



IAP

IAP-based degrader

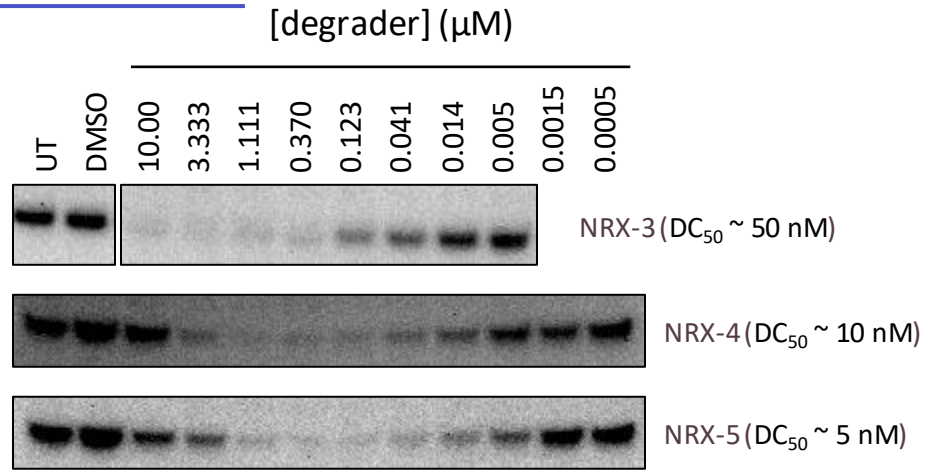


- Multiple ligases identified as being active for Pellino1 degradation
- CRBN-based degraders selected for further exploration

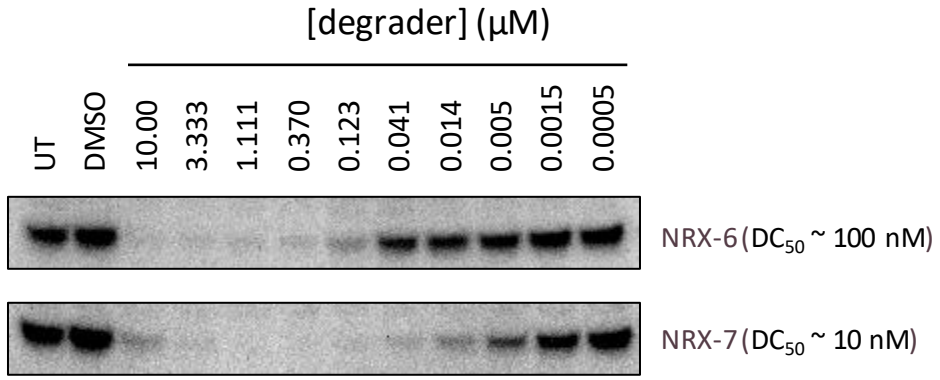
Unstimulated Jurkat cells treated with compound for 24 hours

Pellino1 Degradation Observed with Multiple Linker Vectors

Linker Vector A



Linker Vector B

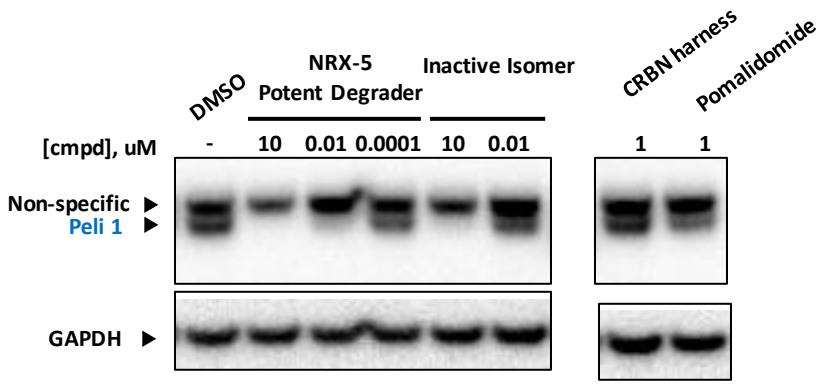


- Multiple linker vectors identified which enable potent degradation of Pellino1
- Most potent degraders identified with Linker Vector A
- Other linker vectors resulted in inactive cellular degraders
- Degradation confirmed to be Ubiquitin, NEDD8 and proteasome dependent

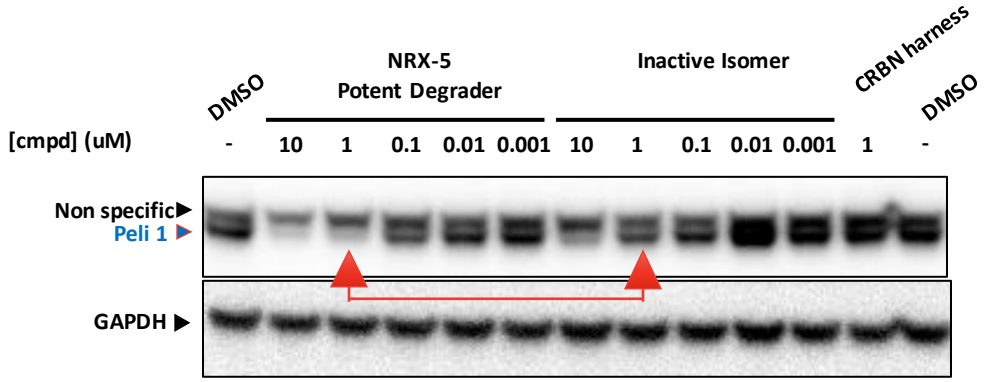
Degradation in Jurkat Cells (24hr)

Degradation of Pellino1 in Human and Mouse T Cells

Human CD8 T cells



Mouse Total T cells



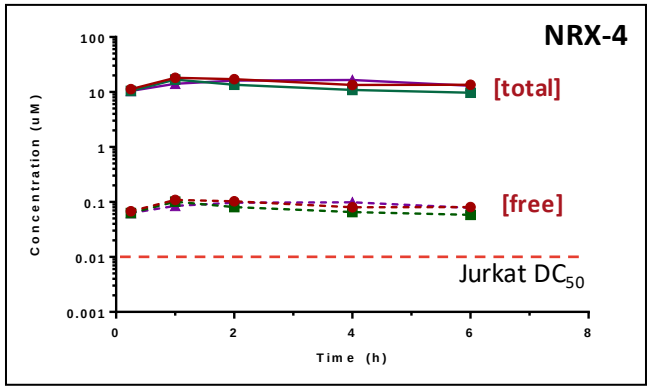
- Pellino1 degradation conserved in primary human CD8 T cells and mouse T cells

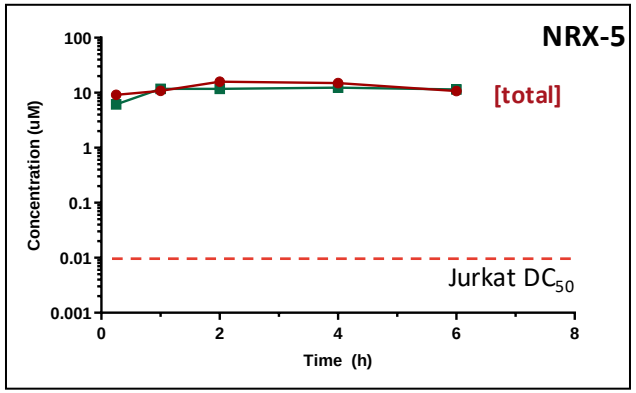
In Vivo Degradation of Pellino1 in Mice

NRX-5

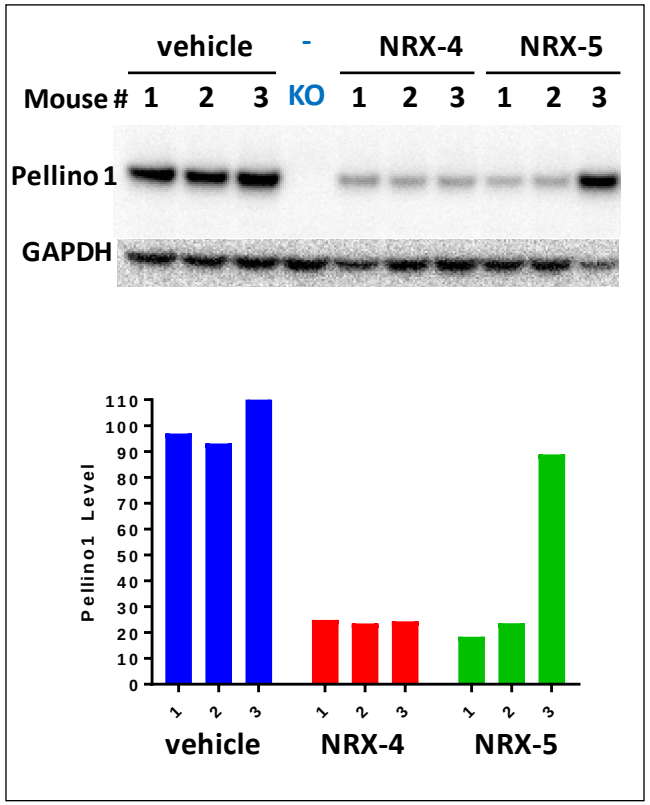
MW = 881
LogD (pH 7.4) = 3.0
Solubility = 1.4 µM
Pellino1 DC_{50} = 10 nM

Single 90 mg/kg IP dose in C57BL/6 Mice

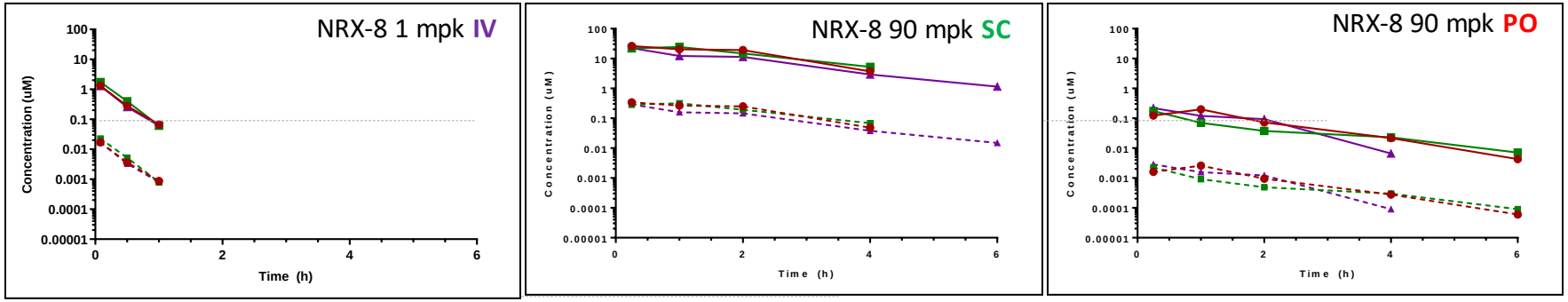




Pellino1 Levels in Mouse Splenocytes (6 hours post single 90 mg/kg IP dose)

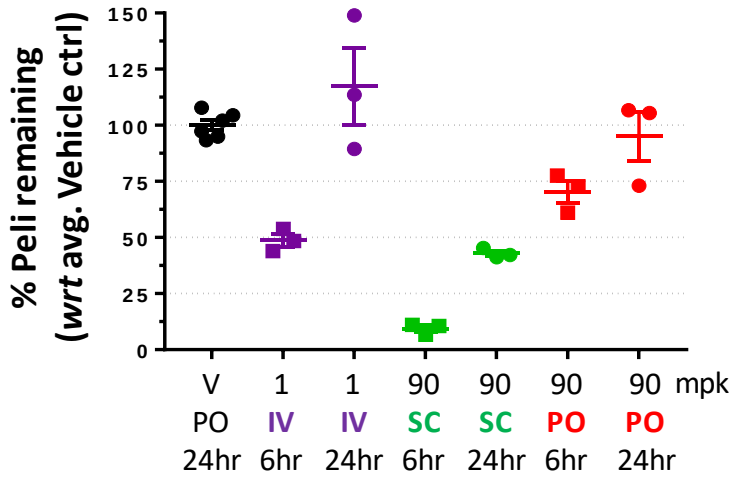


Oral Dosing of NRX-8 Demonstrates Pellino1 Degradation



NRX-8

MW = 701
LogD (pH 7.4) = 3.4
Solubility = 7.4 µM
Pellino1 DC_{50} = 2.7 nM



Summary

- Nurix's DELigase platform enables the discovery of potent binders to difficult-to-drug ligase targets with good physicochemical properties

- Matrix approach to identification of active cellular degraders can rapidly yield hit degraders for further optimization

- DELigase platform enabled degradation of Pellino1, an E3 ligase target for immuno-oncology applications
  - Potent cellular degradation of Pellino1 demonstrated with DC50 < 0.1 µM
  - Cellular degradation preserved across human cell lines, primary human cells and primary mouse cells
  - In vivo degradation of Pellino1 demonstrated in mouse

Thank You

Nurix Therapeutics

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