Nurix Therapeutics

Blazing a New Path in Medicine

Application of DNA-Encoded Libraries to Discover Small Molecules for E3 Ligase Modulation

2nd Annual Ligase Targeting Drug Development
April 28th, 2022

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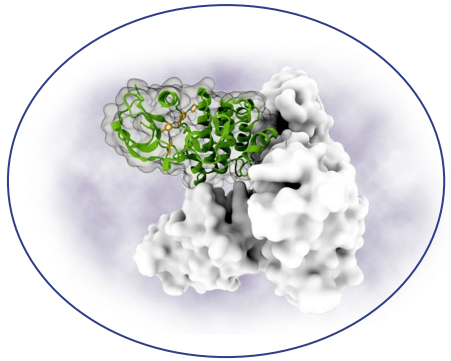
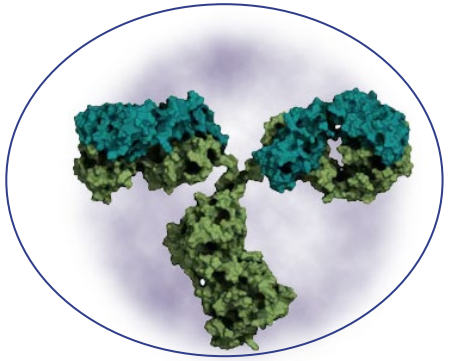
Working to Create a New Category of Medicine

Evolution of new therapeutic modalities

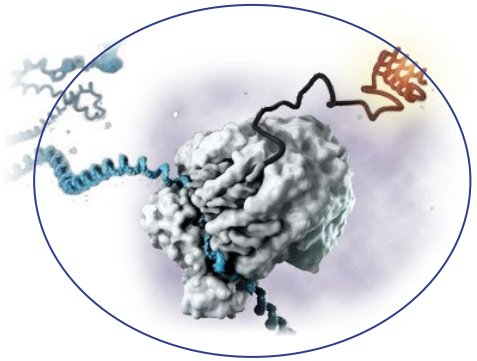


Small Molecule Inhibitors

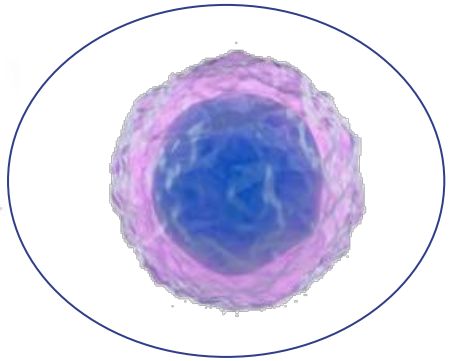


Antibodies

Therapeutic Proteins

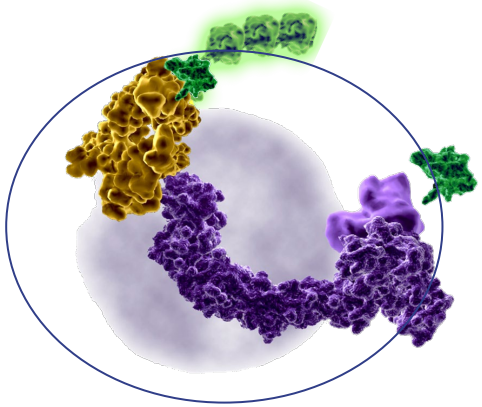


Nucleic Acid-Based Therapies:
Antisense, RNAi
Gene Therapy
CRISPR



Adoptive Cell Therapy

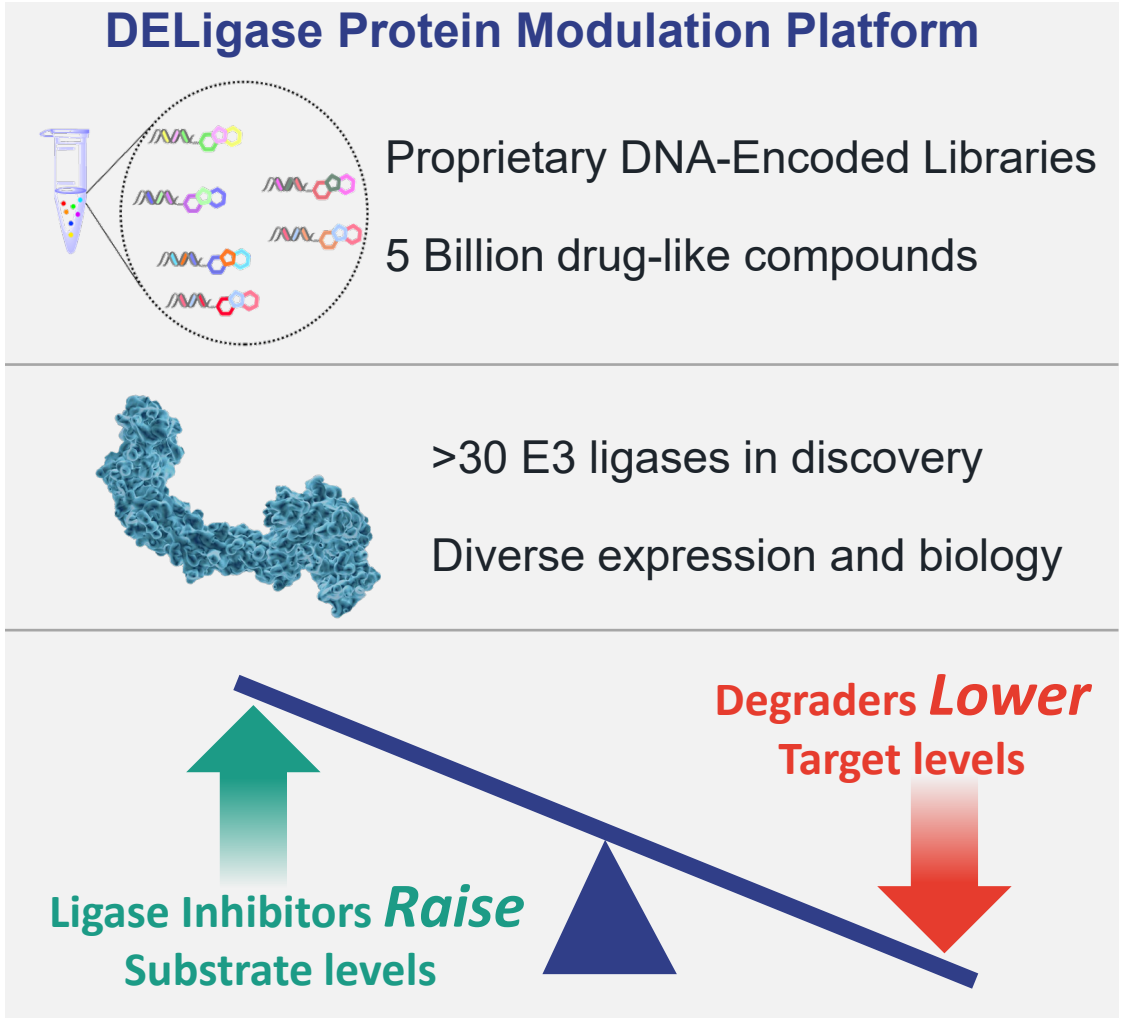
DeTIL



Nurix Protein Modulation Drugs to *Increase* or *Decrease* Specific Protein Levels

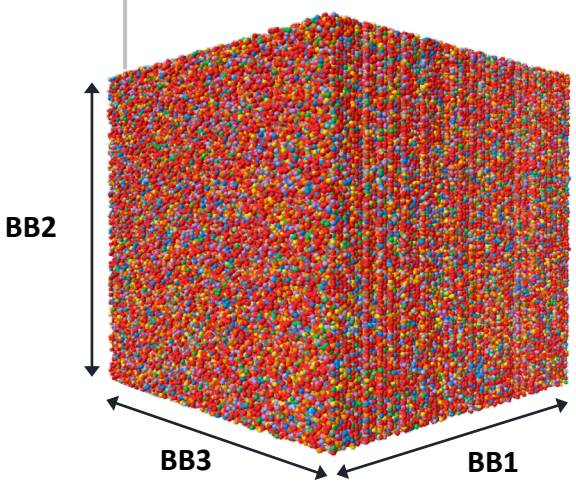
Nurix's DELigase Platform: Leading the Industry in Application of DEL for Targeted Protein Modulation

- DELigase™ is a versatile drug discovery platform utilizing DNA-encoded libraries (DEL) that represent over 5 billion drug-like compounds
- Nurix can find binders for proteins previously thought to be undruggable, particularly E3 ligases
- By inhibiting or harnessing E3 ligases, Nurix uses its discovery platform to modulate the levels of Target or substrate proteins



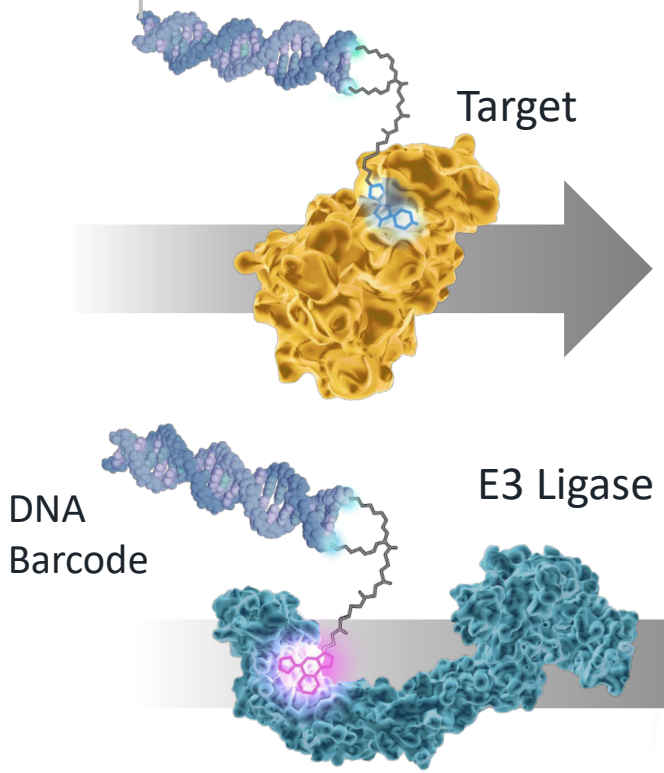
DELigase® Enables Efficient Degrader Discovery and Design

1 Billions of proprietary DNA-Encoded Library (DEL) compounds

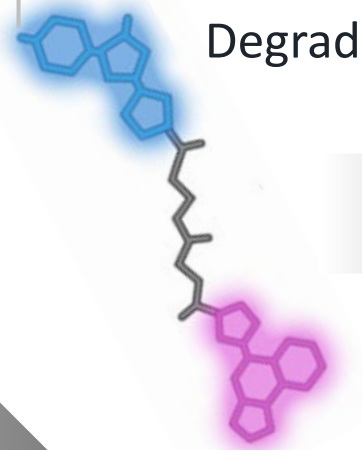


BB = Chemical Building Blocks

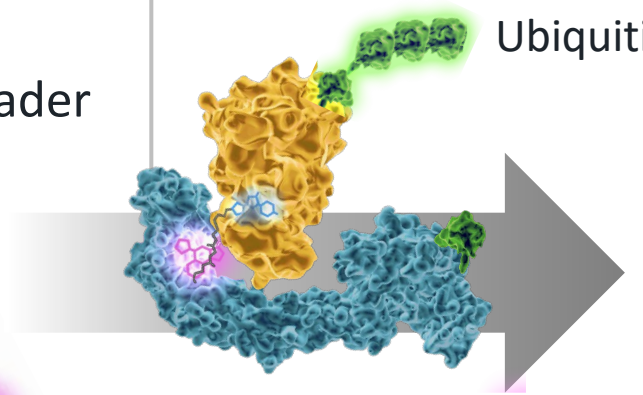
2 Target proteins and E3 ligases are screened using DEL



3 Binders from DEL are joined via a linker to construct degraders

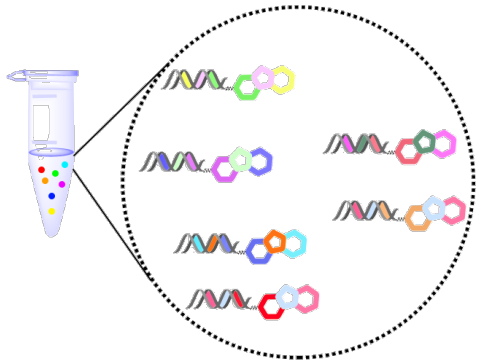


4 Degrader recruits E3 ligase to target protein, triggering ubiquitin transfer and degradation



Nurix DEL Discovery Platform

DE Library



- > 1 billion compounds represented in DEL “cube”
- Combinatorial 3D matrix of >1,000 building blocks
- Allows massively parallel screening
- Identifies novel binders to both ligases and target proteins

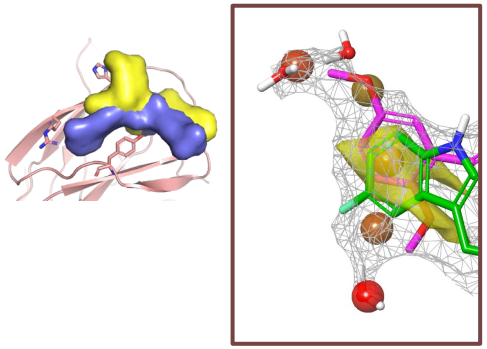
Selection

- Screening complex mixtures without a biochemical assay
- Highly multiplexed analysis of multiple protein isoforms & off-targets
- Assays run under multiple conditions to find competitive inhibitors, allosteric inhibitors, and binders

Data Analysis

- SAR rich output available for lead optimization
- Hit ID is agnostic of binding location
- Hit ID guided by structural similarity, scrutiny of matrixed selection results
- Artificial intelligence used to identify hits outside of our library

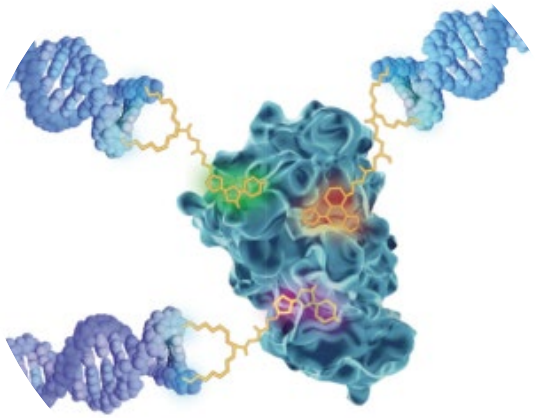
Hit Optimization



- DEL identifies multiple chemical series with varying affinities
- Leverage DEL SAR to drive optimization
- Parallel library driven hit optimization
- Structure Guided Design to improve affinity

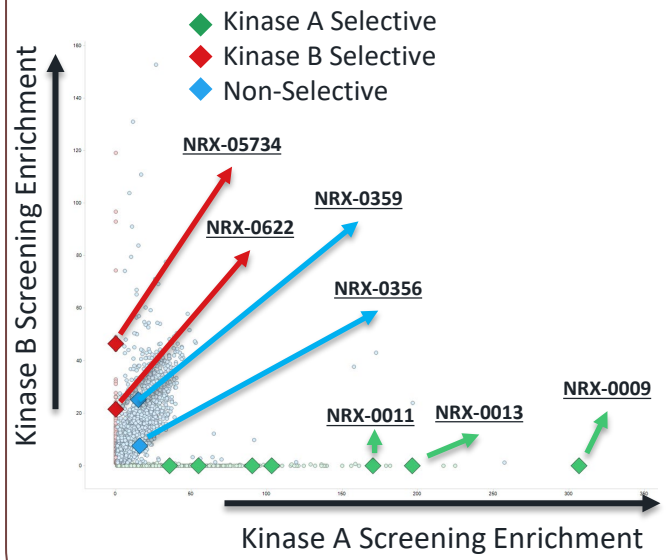
Integrated Platform Enabling Novel Drug Discovery

Binders can span the surface of the protein

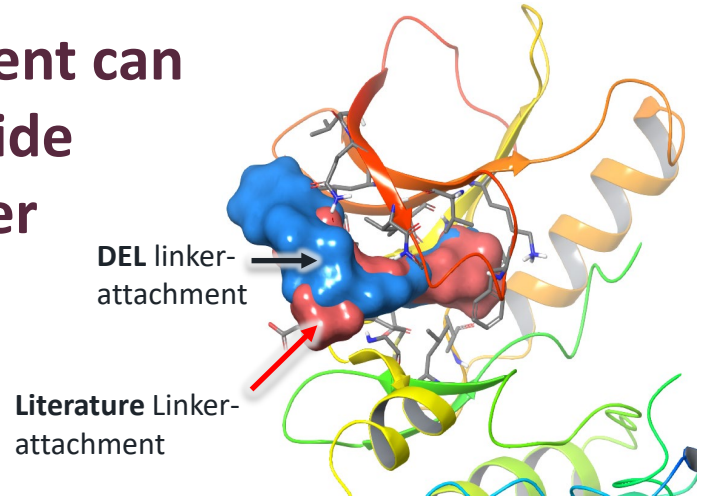


Parallel screening conditions enable identification of competitive inhibitors, allosteric inhibitors, and binders

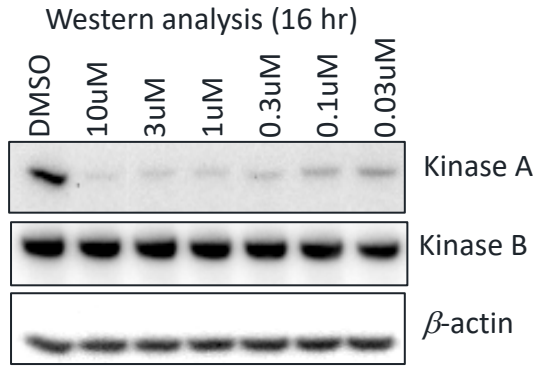
Parallel screening enables identification of selective binders or inhibitors



DNA attachment can be used to guide degrader linker placement



Potent selective degrader



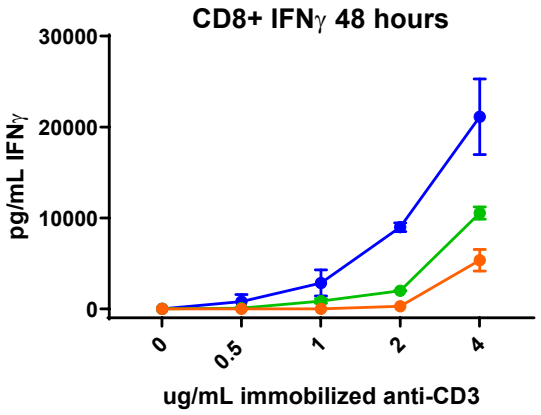
Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

Drug Program	Target / Delivery	Therapeutic Area	Discovery	IND enabling	Phase 1	Phase 2	Phase 3
NX-2127 Degrader	BTK + IMiD activity *Oral*	B-cell Malignancies					
NX-5948 Degrader	BTK *Oral*	B-cell Malignancies and Autoimmune Diseases					
NX-1607 Inhibitor	CBL-B *Oral*	Immuno-oncology					
DeTIL-0255 Cell therapy	Adopted cell therapy with *Ex vivo CBL-B inhibition*	Gynecologic malignancies					
Discovery pipeline							
Wholly owned	Degraders and inhibitors of multiple targets including E3 ligases, T cell kinase, hematology & oncology drivers, and viral proteins						
Gilead Sciences	5 targets						
Sanofi	5 targets						

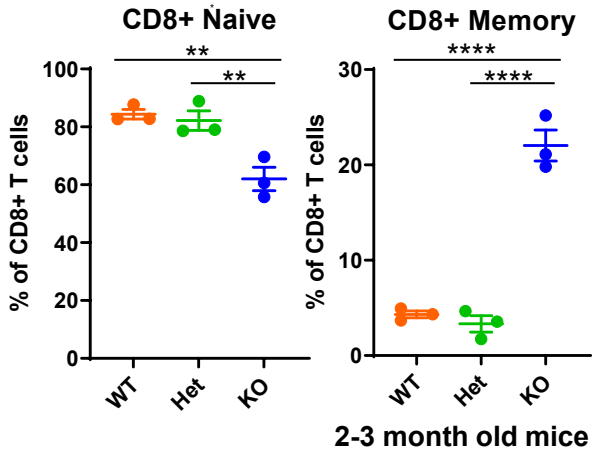
Pellino1 is an Immuno-Oncology Target

- 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

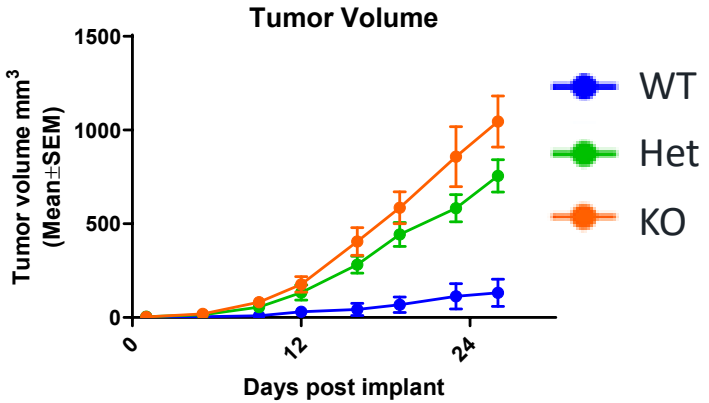
Enhanced Cytokine Secretion



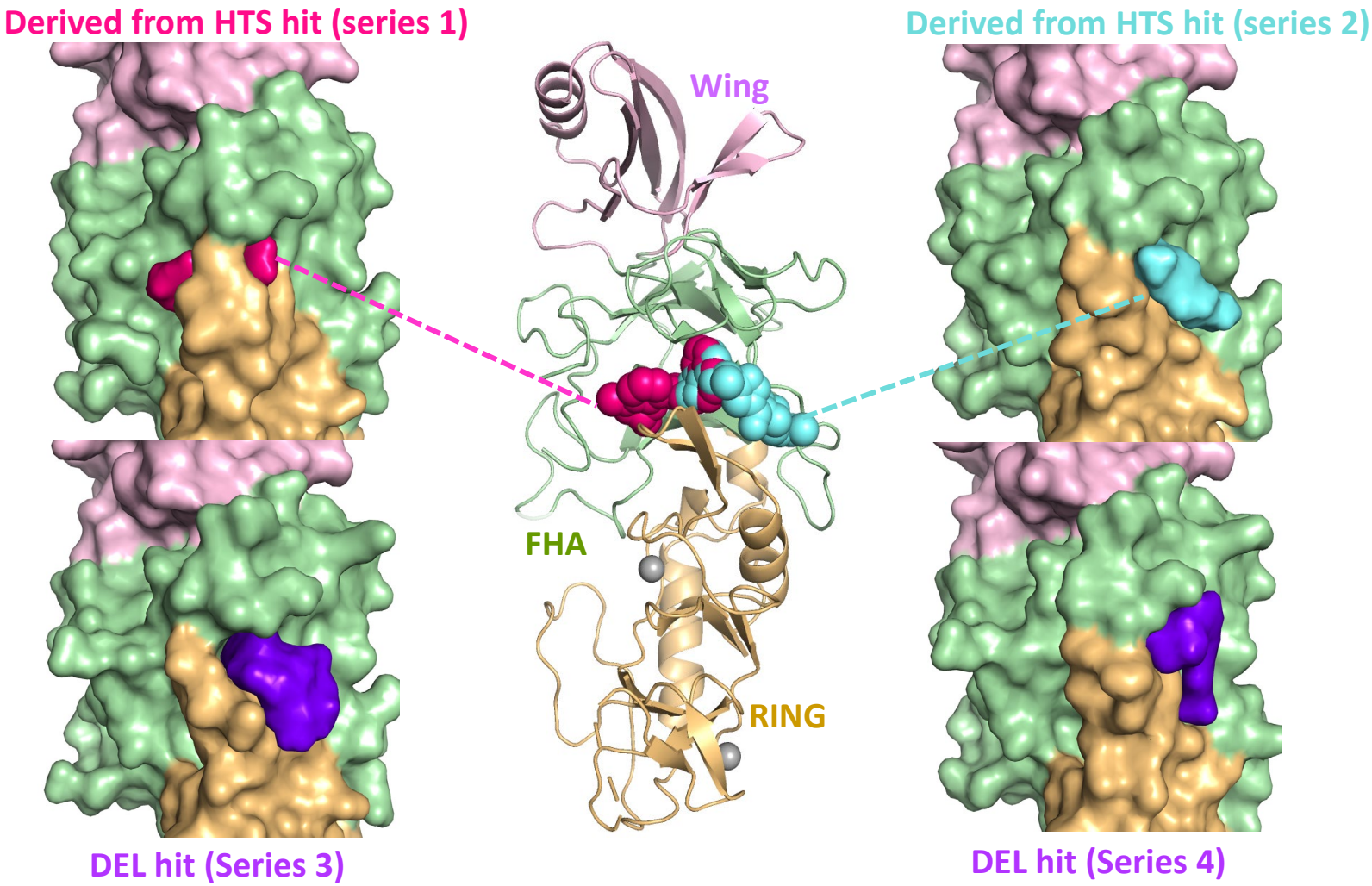
Increased Memory T Cells



Tumor Growth Inhibition

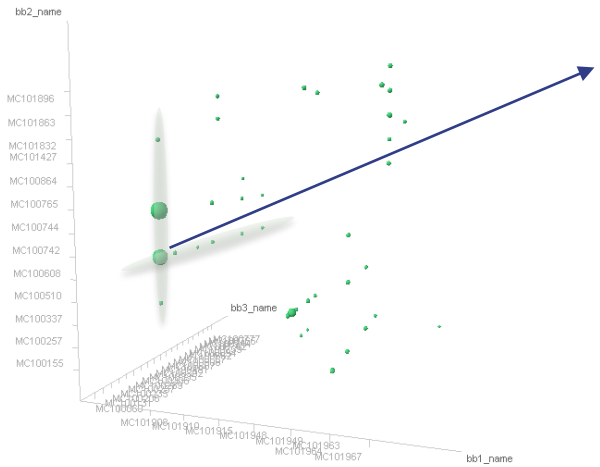


Multiple Hit Finding Approaches Yield Pellino1 Binders



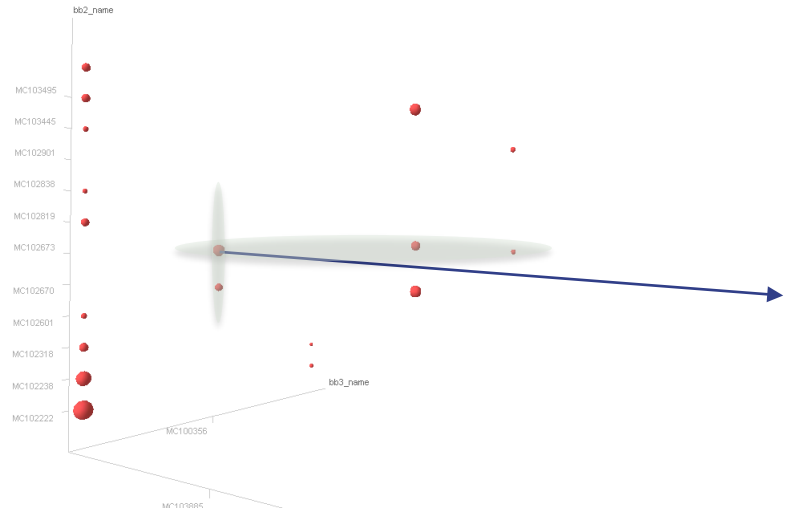
Two Series Confirmed as Pellino1 Binders from DEL Screen

DEL Screen Affinity Plot



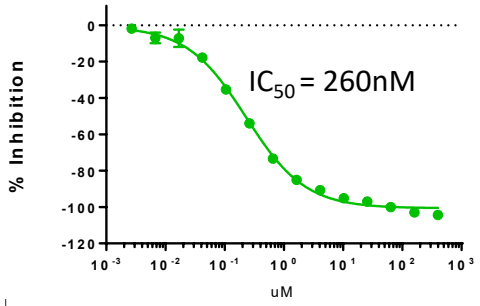
NRX-1
MW = 542.6
cLogP = 2.1
LE = 0.24
LipE = 4.8

DEL Screen Affinity Plot

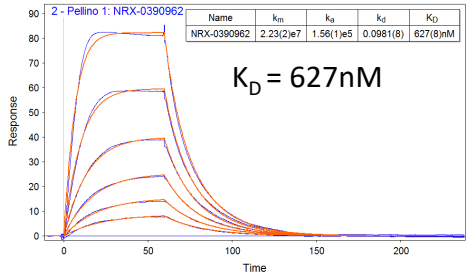


NRX-2
MW = 472.6
cLogP = 3.6
LE = 0.25
LipE = 2.7

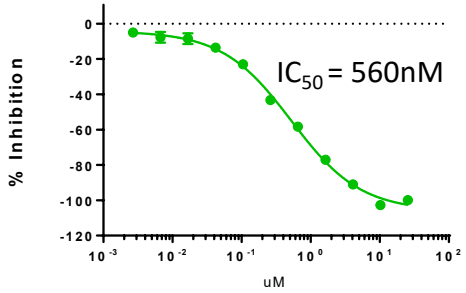
Peptide Binding Inhibition (FRET EC_{30})



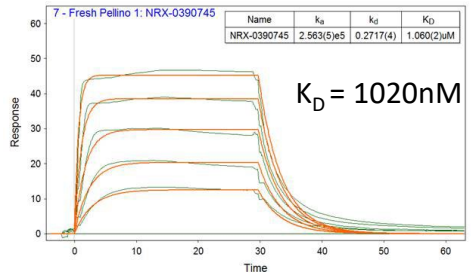
Surface Plasmon Resonance



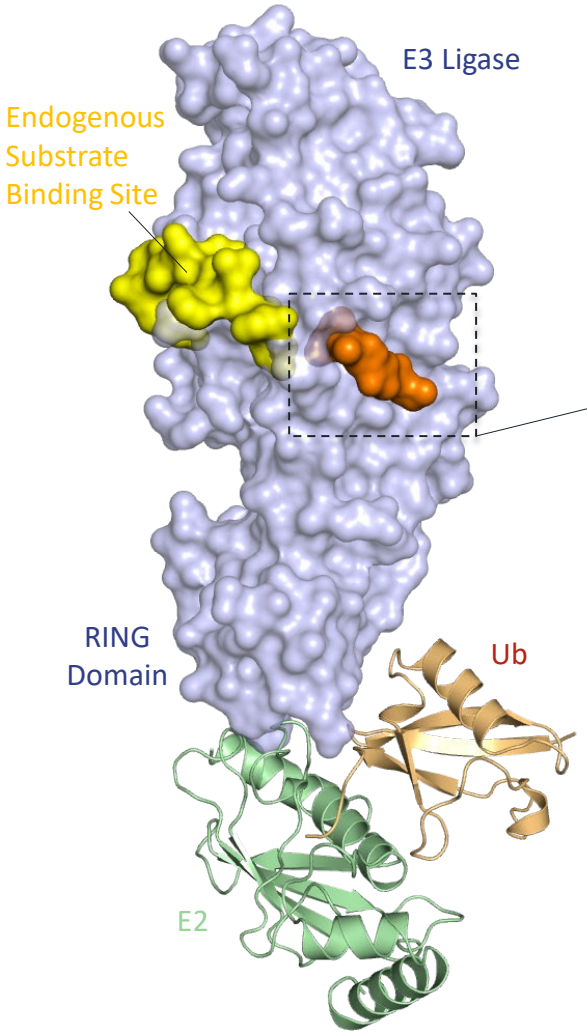
Peptide Binding Inhibition(FRET EC_{30})



Surface Plasmon Resonance



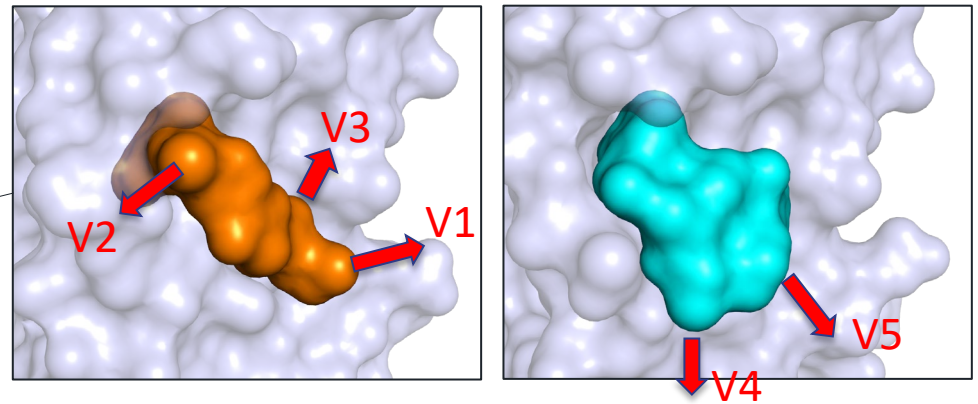
Multiple Linker Vectors Identified from Pellino1 Binders



Modeled E2~Ub binding

Series 1: Optimized Series Derived from HTS

Series 3: Unoptimized DEL Series

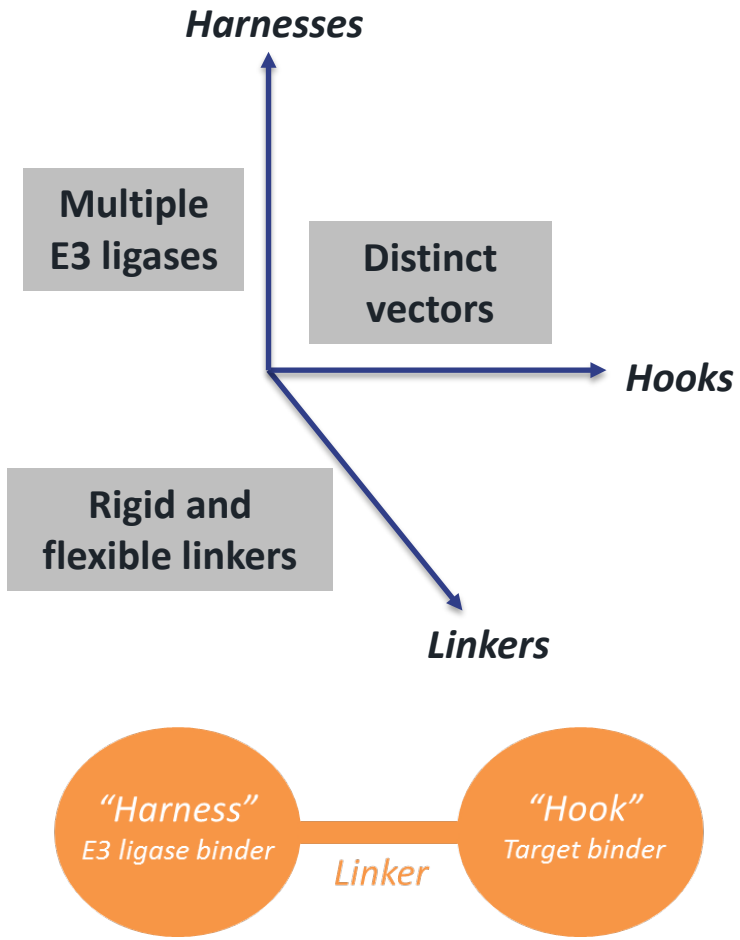


IC_{50} = 2nM

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

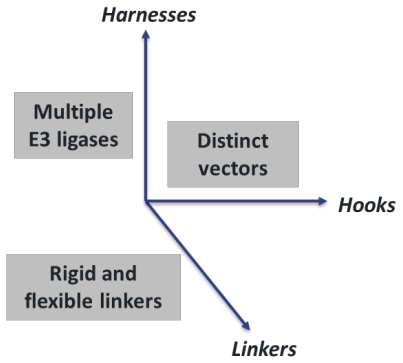
Matrix Approach to Degrader Hit Identification and Optimization

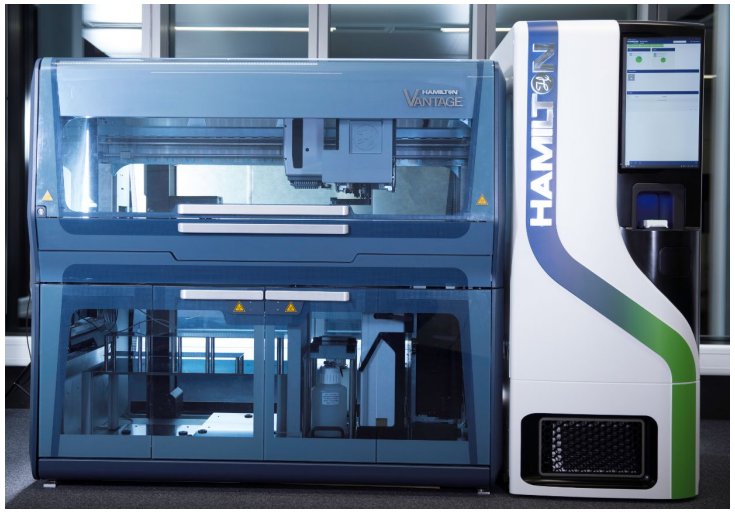


Key Goals of Matrix Strategy for Degrader Identification:

1) Identify productive ligase(s) for degradation of target protein
2) Prioritize hook/harness ligands which give most productive target protein degradation
   - Required ligand affinity for ligase/target protein
   - Binding site(s) which lead to productive ternary complex formation for degradation
3) Select hook/harness linker vector(s) for further exploration and optimization

Matrix Approach to Degrader Hit Identification and Optimization



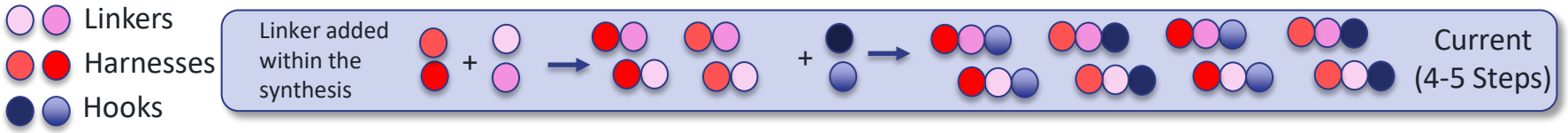


Binders from DEL and HTS
Affinity < 1 µM

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

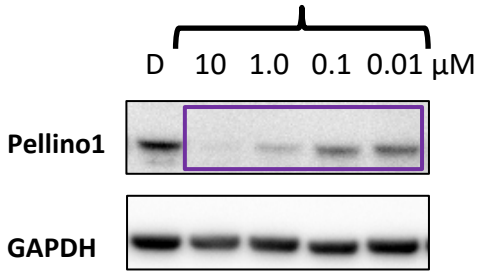


Diverse combinatorial libraries synthesized

Multiple E3 Ligases Enable Pellino1 Degradation

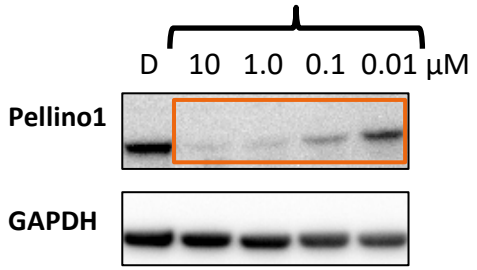
VHL

VHL-based degrader



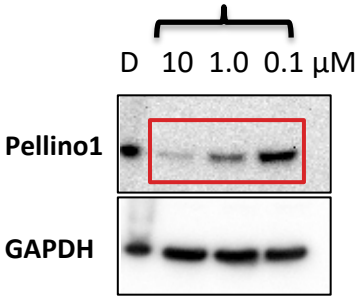
CRBN

CRBN-based degrader



IAP

IAP-based degrader

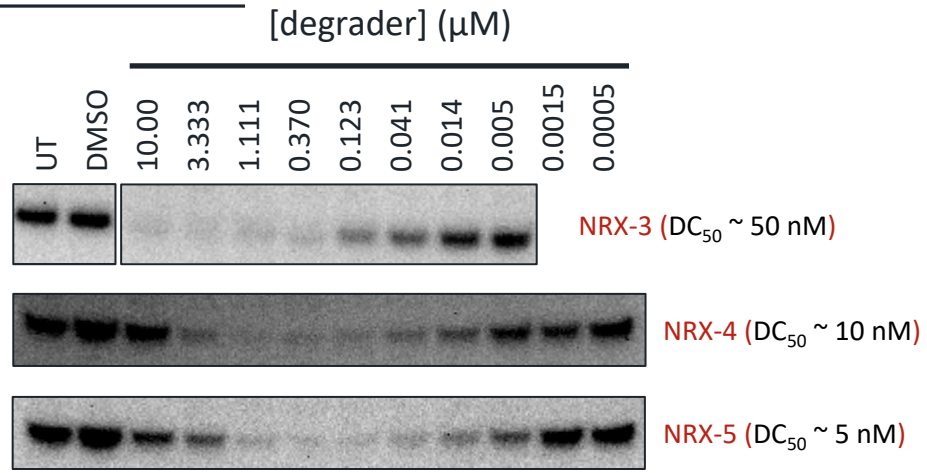


- Multiple ligases identified as being active for Pellino1 degradation
- CRBN-based degraders selected for further exploration

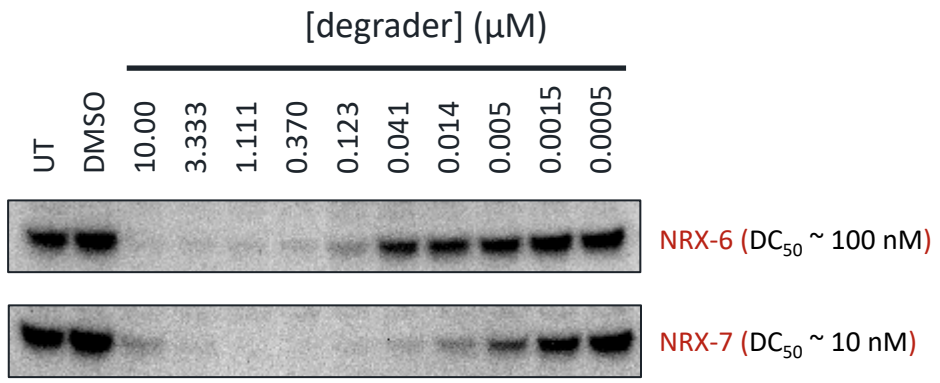
Unstimulated Jurkat cells treated with compound for 24 hours

Pellino1 Degradation Observed with Multiple Linker Vectors

Linker Vector A



Linker Vector B

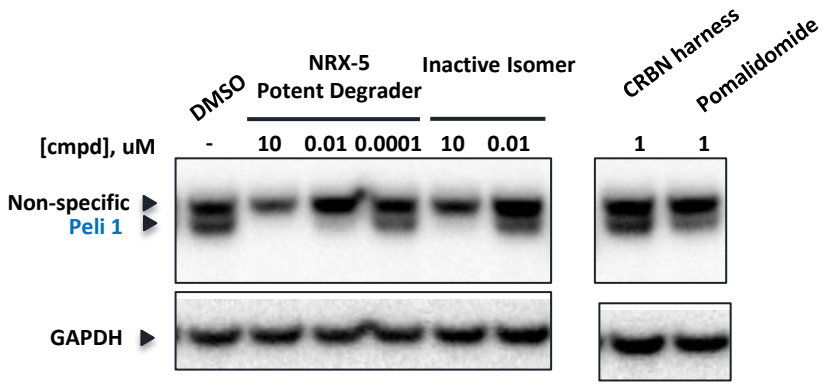


- Multiple linker vectors identified which enable potent degradation of Pellino1
- Most potent degraders identified with Linker Vector A
- Other linker vectors resulted in inactive cellular degraders

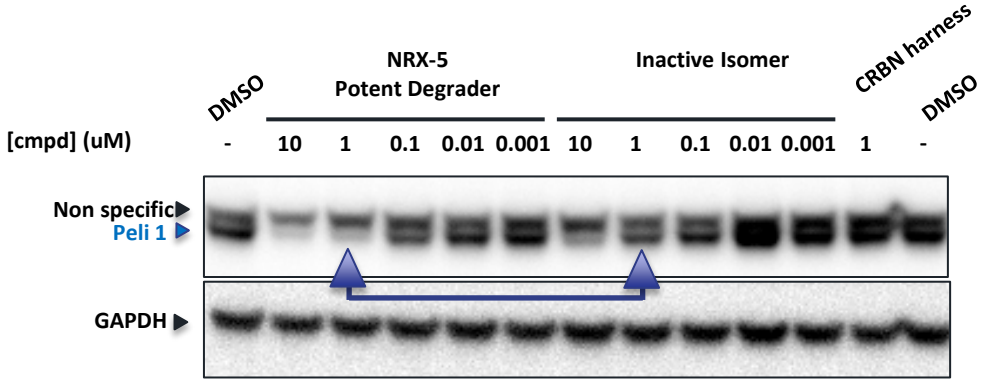
Degradation in Jurkat Cells (24hr)

Degradation of Pellino1 in Human and Mouse T Cells

Human CD8 T cells



Mouse Total T cells



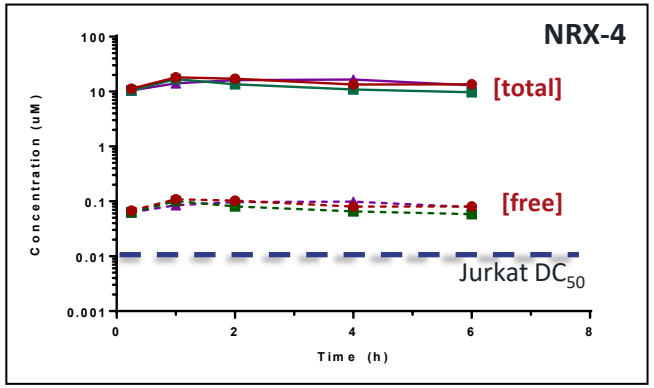
- Pellino1 degradation conserved in primary human CD8 T cells and mouse T cells

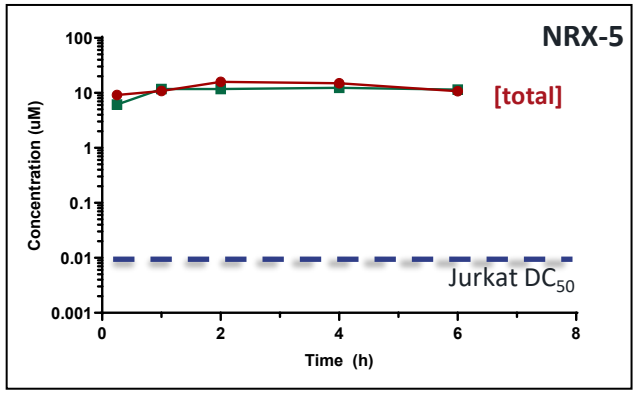
In Vivo Degradation of Pellino1 in Mice

NRX-5

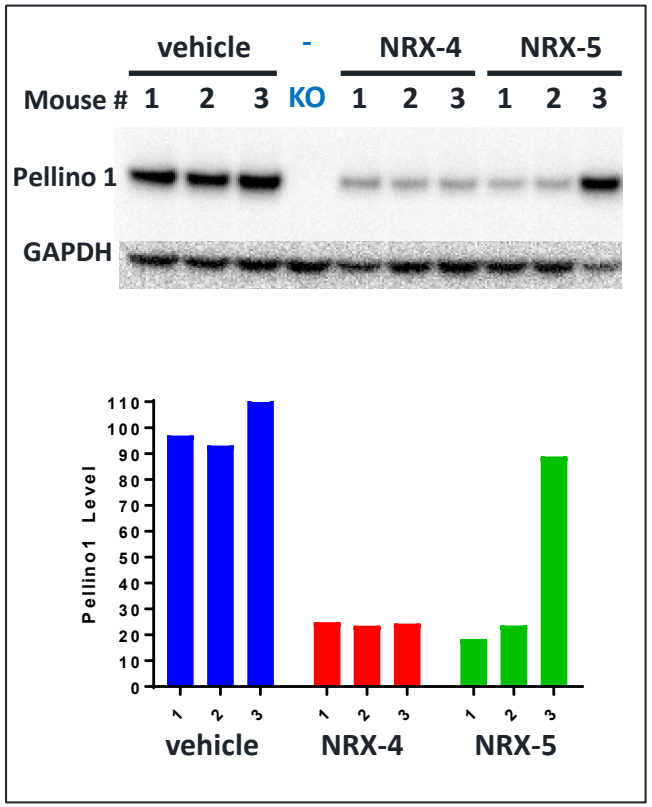
MW = 881
LogD (pH 7.4) = 3.0
Solubility = 1.4 µM
Pellino1 DC_{50} = 10 nM

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

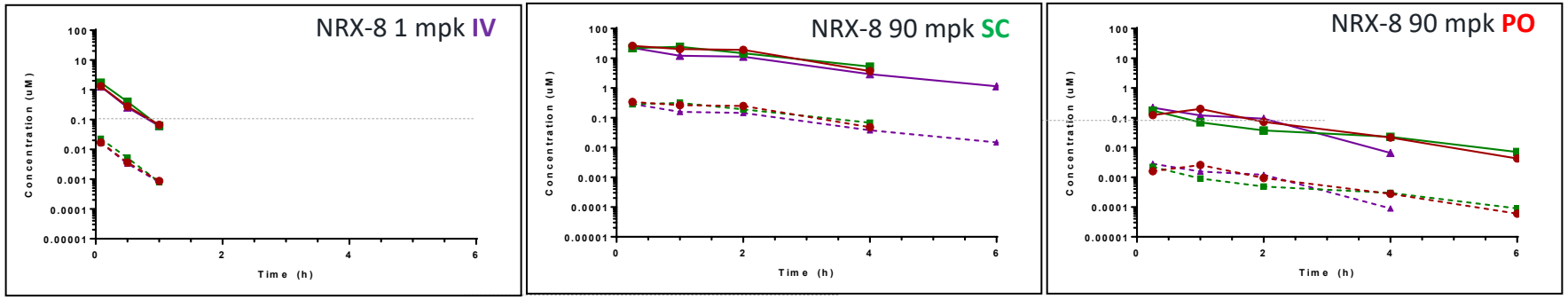




Pellino1 Levels in Mouse Splenocytes (6 hours post single 90 mg/kg IP dose)

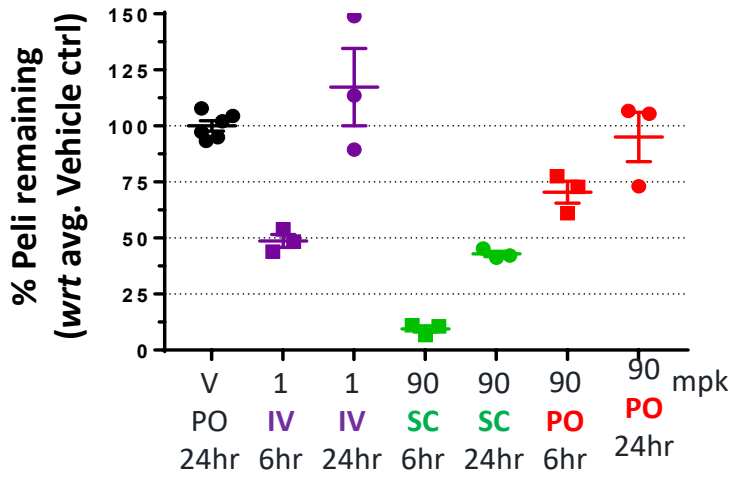


Oral Dosing of NRX-8 Demonstrates Pellino1 Degradation



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 immunooncology applications
  - Potent cellular degradation of Pellino1 demonstrated with $DC_{50} < 0.1$ µM
  - Cellular degradation preserved across human cell lines, primary human cells and primary mouse cells
  - *In vivo* degradation of Pellino1 demonstrated in mouse

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