Chemistry @Nurix: Protein Modulation for Drug Discovery

Bay Area Chemistry Symposium

Berkeley, CA

November 10th, 2022

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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

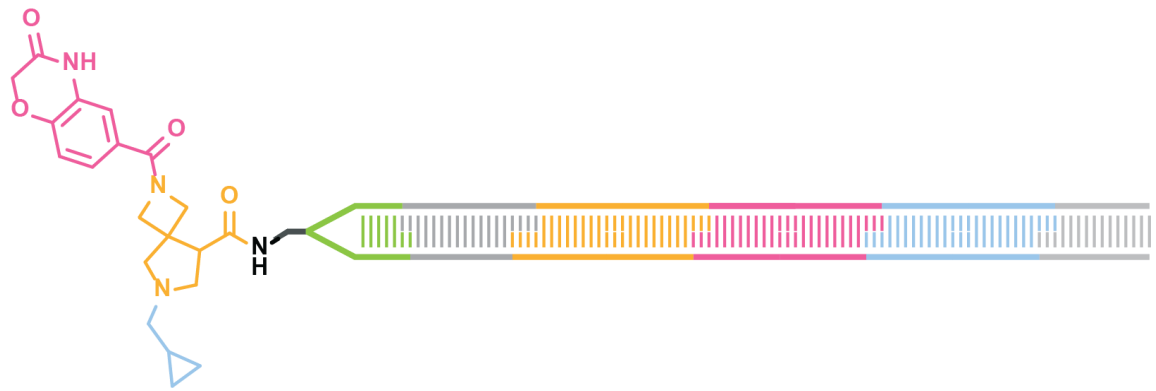
Nurix Is Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

MOA	Drug Program	Target/ Delivery	Therapeutic Area	Pre-Clinical	Phase 1	Phase 2	Phase 3
TPD	**NX-2127** Degrader	BTK-IKZF *Oral*	B-Cell Malignancies				
TPD	**NX-5948** Degrader	BTK *Oral*	B-Cell Malignancies				
TPE	**NX-1607** Inhibitor	CBL-B *Oral*	Immuno-Oncology				
TPE	**DeTIL-0255** Cell Therapy	Adoptive Cell Therapy *Ex vivo CBL-B Inhibition*	Gynecologic Malignancies				
TPM	Wholly owned	5 targets	Multiple				
TPD	Gilead Sciences	5 targets	Multiple				
TPD	Sanofi	5 targets	Multiple				

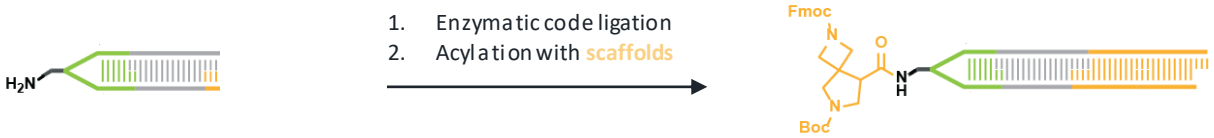
DNA-Encoded Libraries (DEL):
Anatomy of a DEL Molecule

Small molecule

DNA



DNA-Encoded Libraries (DEL):
Synthesis of a DEL Molecule



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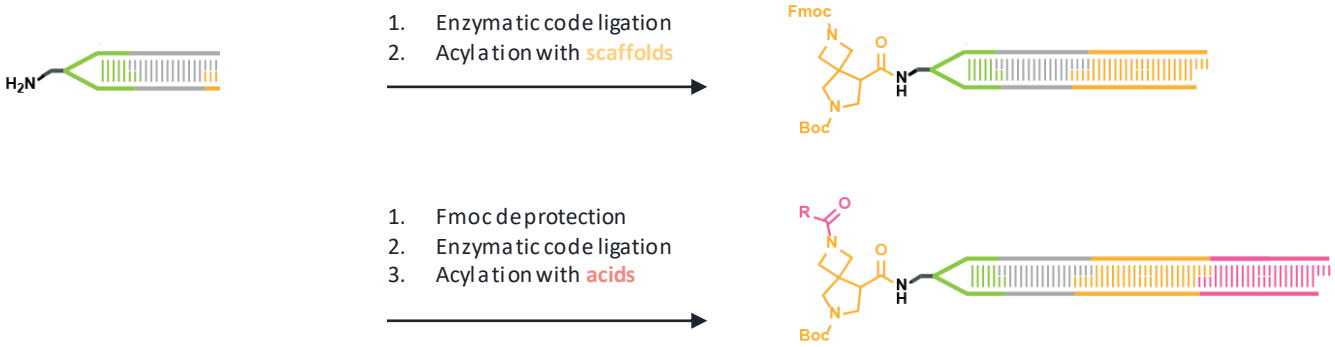

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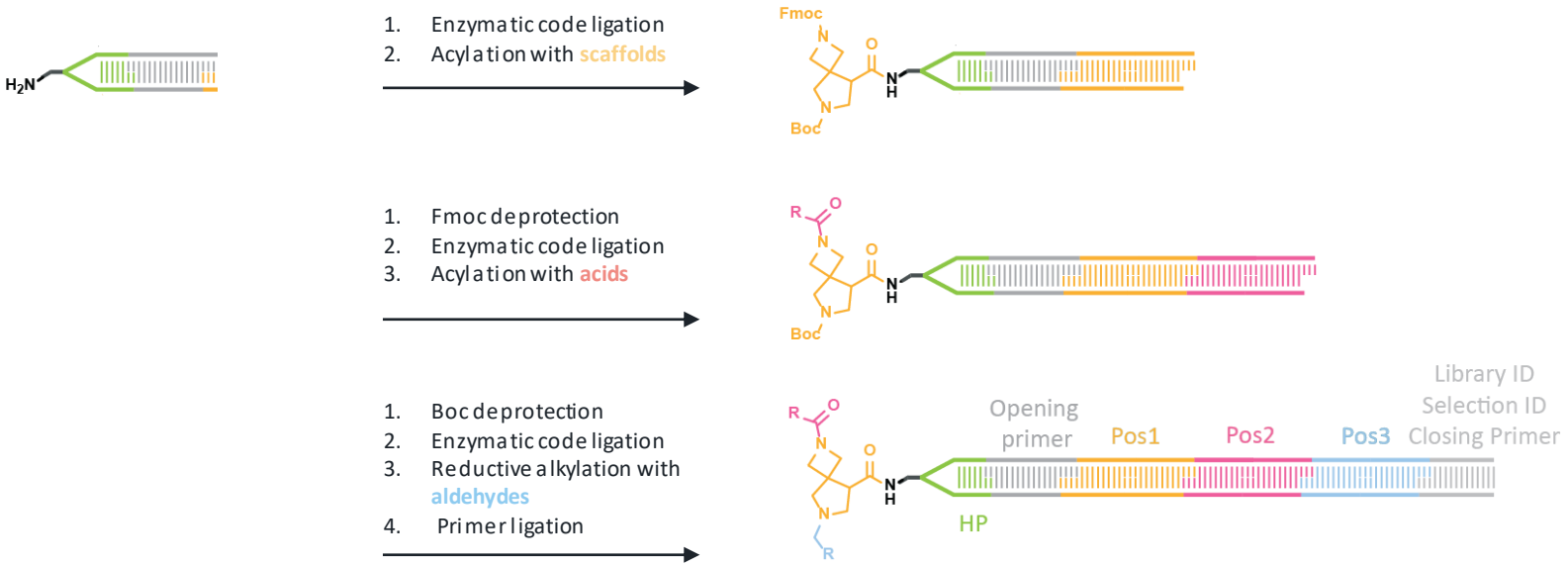
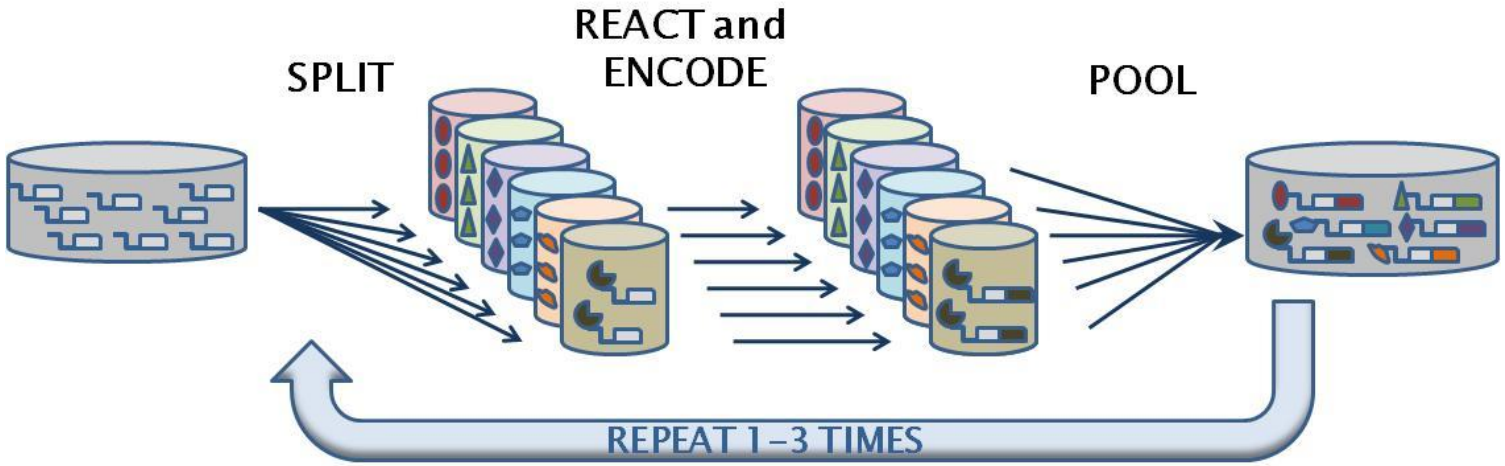


Switching the order of acylation vs alkylation doubles the size of the library from the same building blocks

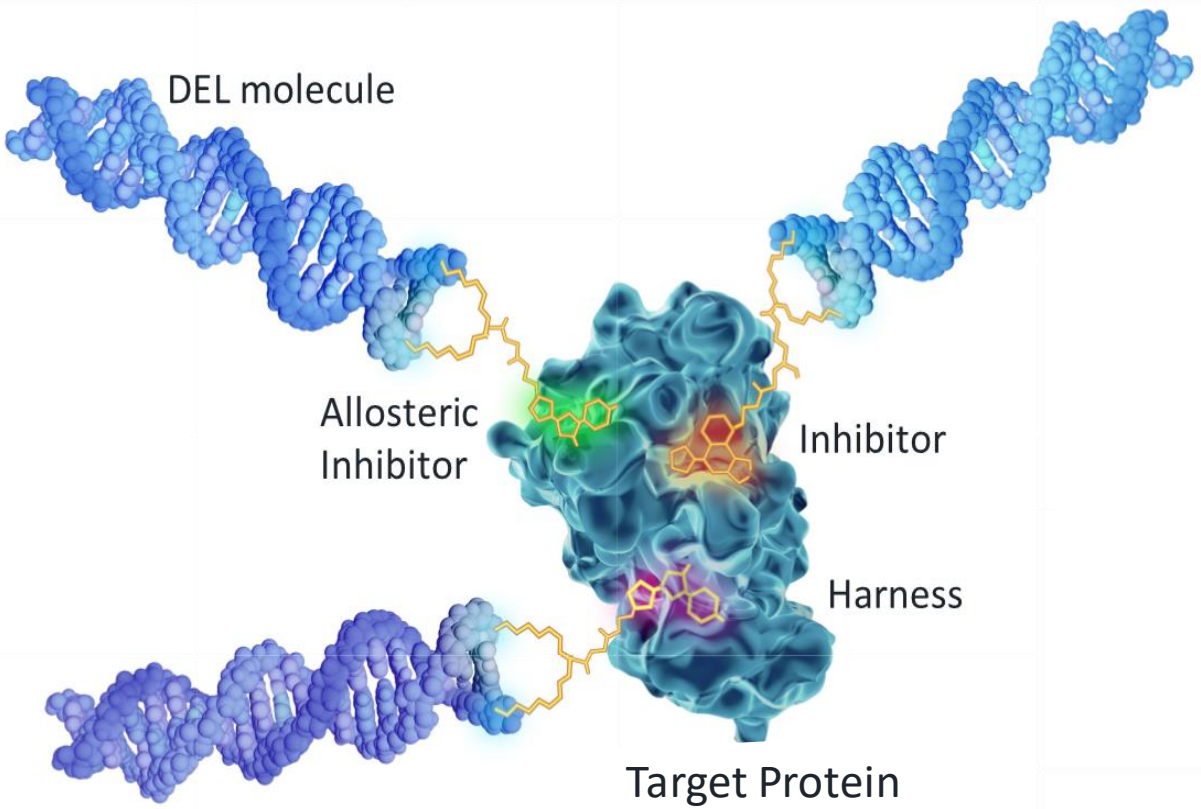
DNA-Encoded Libraries (DEL)
Massive Diversity in a Single Tube



Cycles of Chemistry	BBs Step 1	BBs Step 2	BBs Step 3	Library Size
1	100			100
2	100	1000		100,000
3	100	1000	1000	100,000,000

Current Nurix library contains >5 billion unique compounds

DEL Screening for *Binders*



- 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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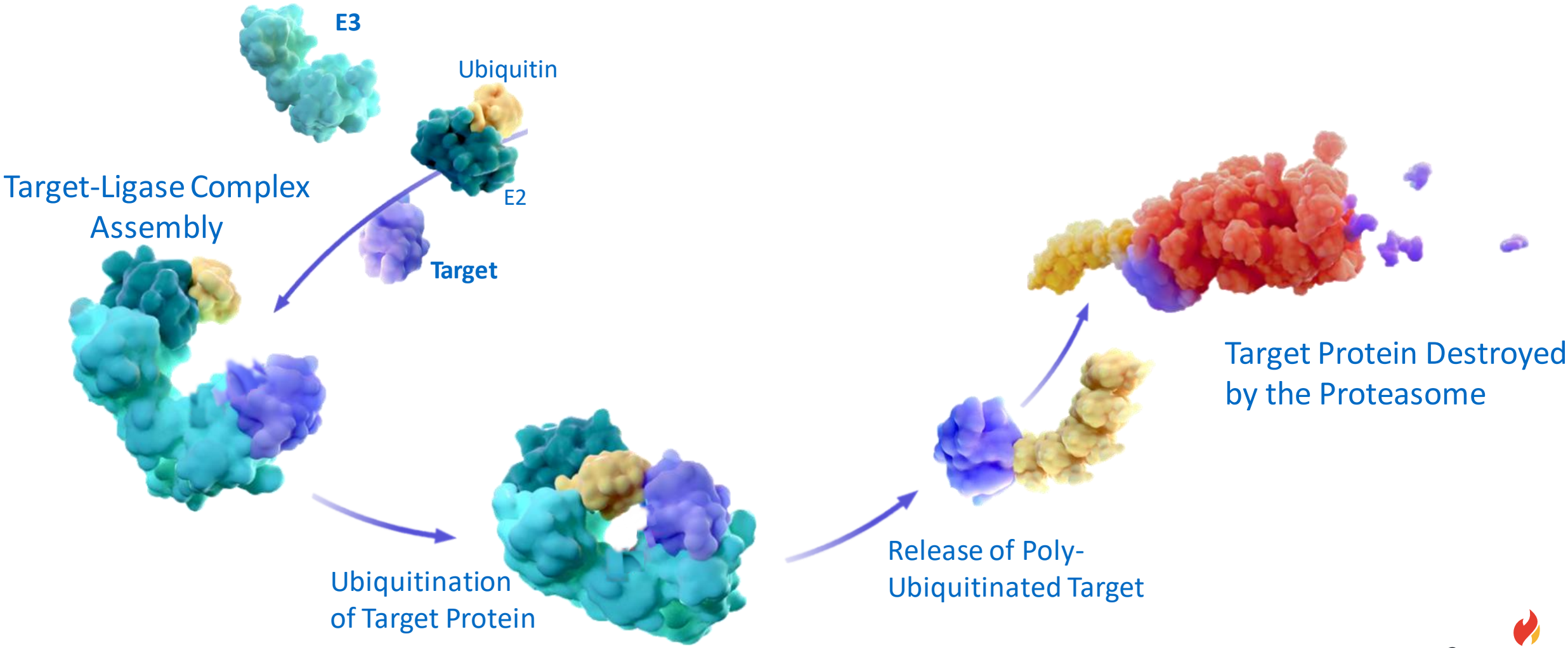
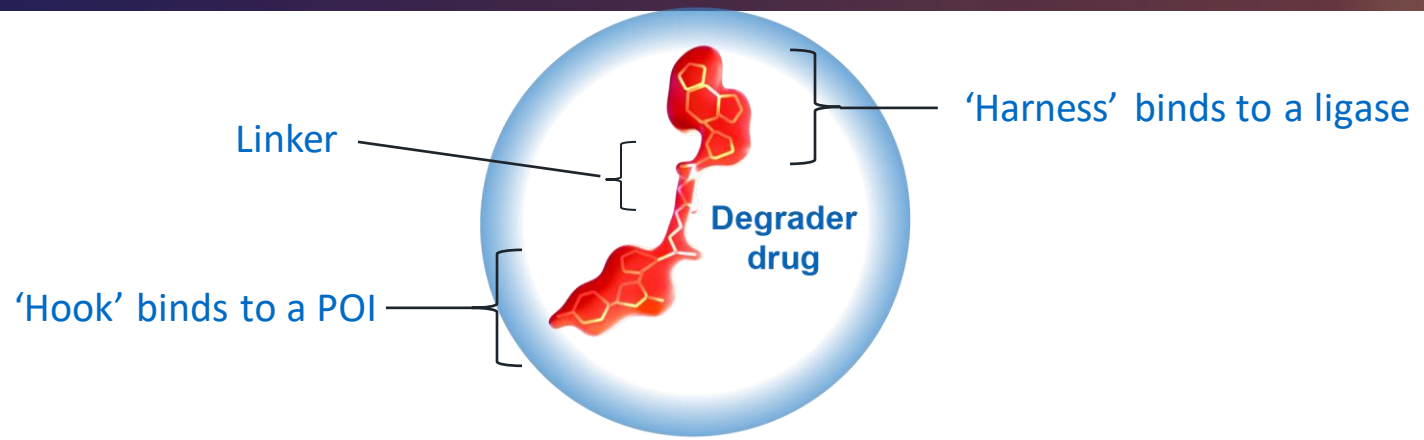
What is Targeted-Protein Degradation (TPD)?

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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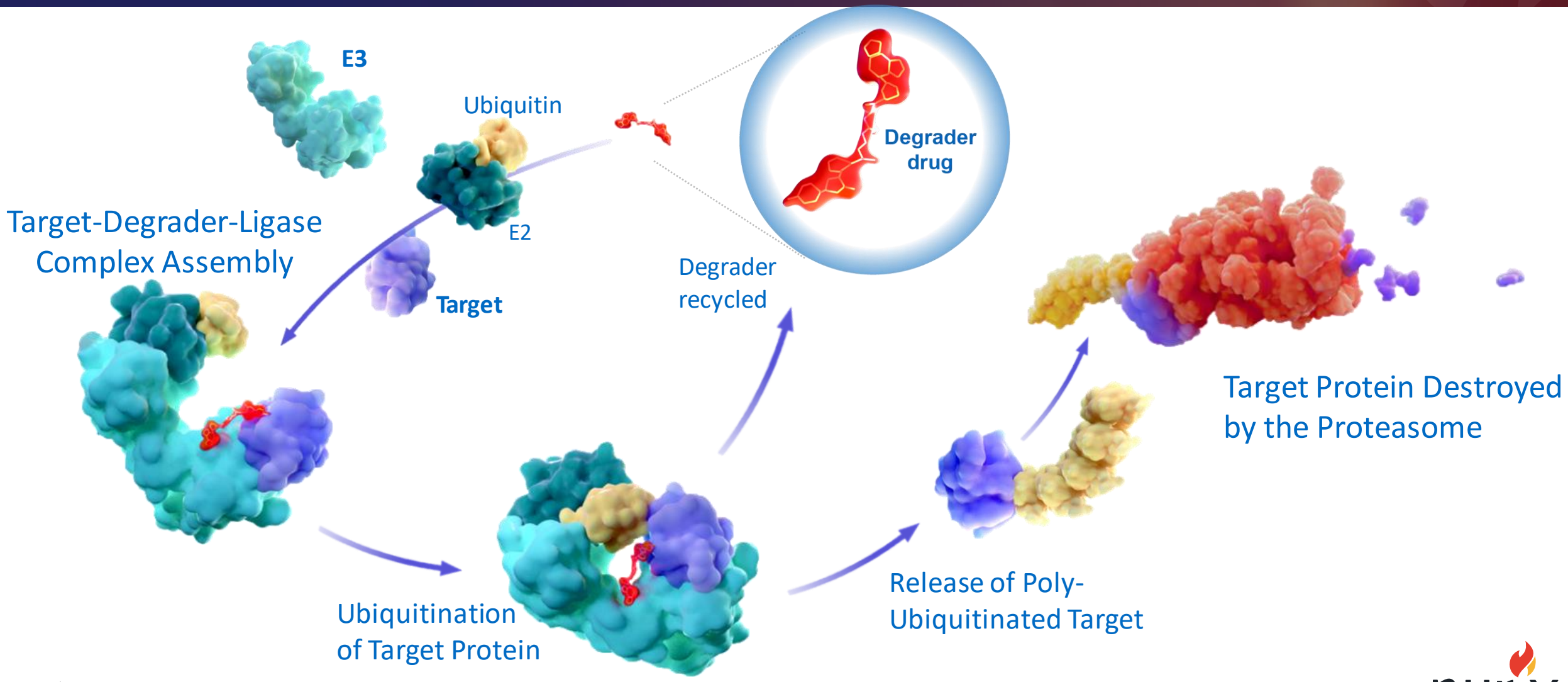

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Advantages of TPD over Inhibitors

1. Drugging the undruggable

   Some targets, such as structural proteins or transcription factors, are not amenable to inhibitors

2. Catalytic degradation

   One degrader can eliminate many protein molecules

3. Prolonged activity

   Degradation of the target protein requires re-synthesis to regain its function

4. Complete elimination of target function

   Certain targets have multiple functions and degradation would eliminate all protein functions, recapitulating a genetic knock-out

5. Activity against resistance mutations

   Inhibitors require high affinity binding and are susceptible to mutations which degraders can overcome

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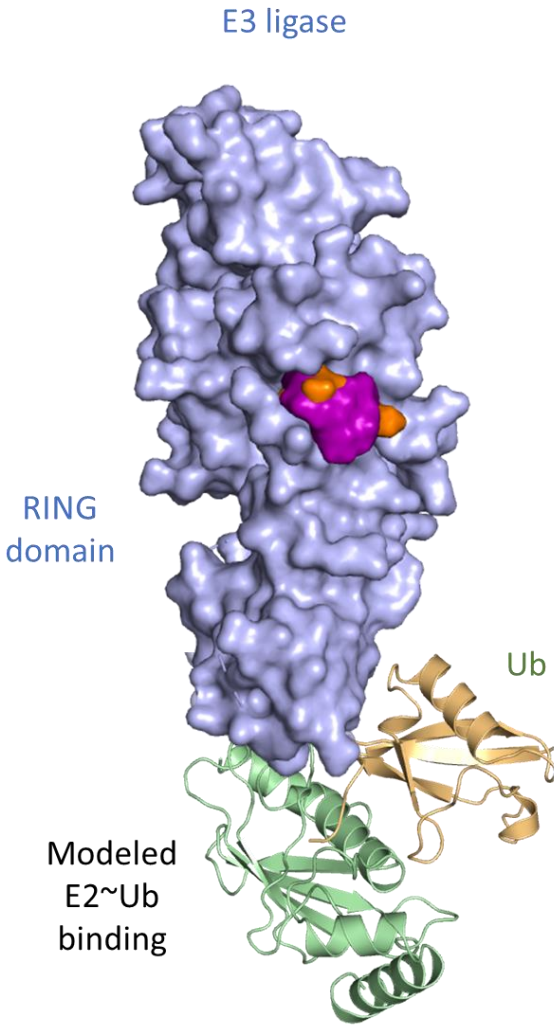
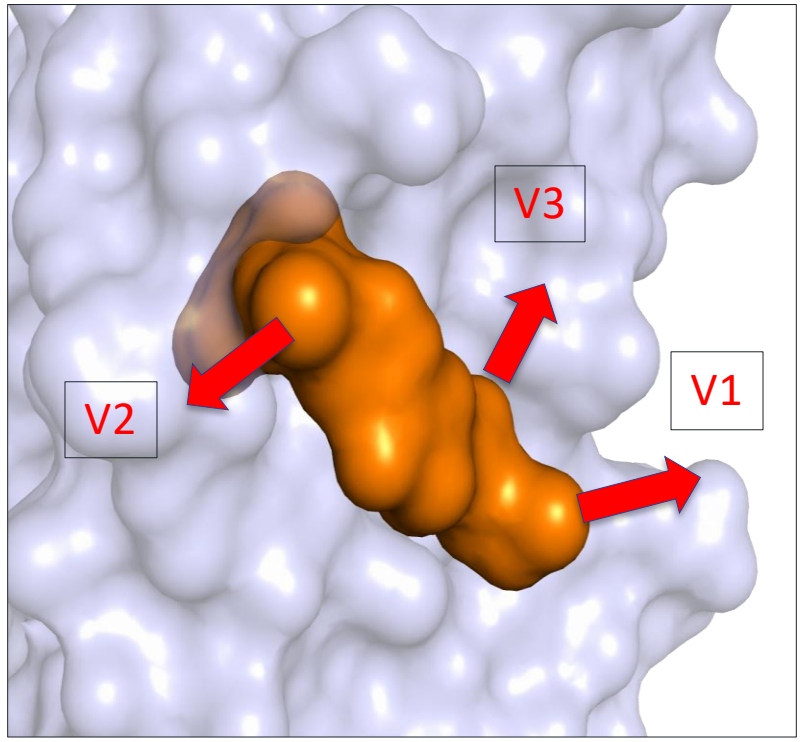
Putting it All Together: Discovery of Degraders of Pellino1, an E3 Ligase

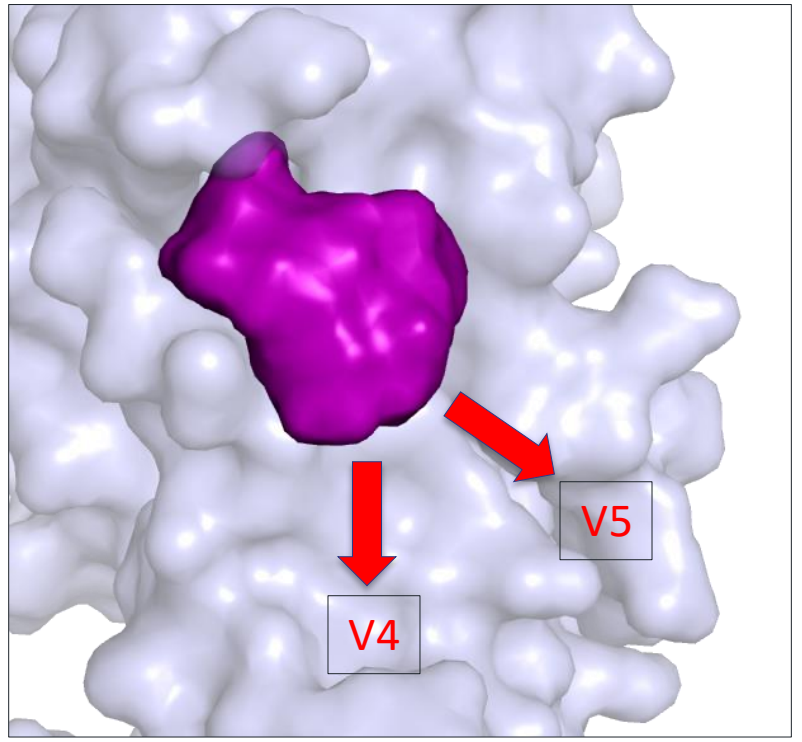


Optimized HTS series



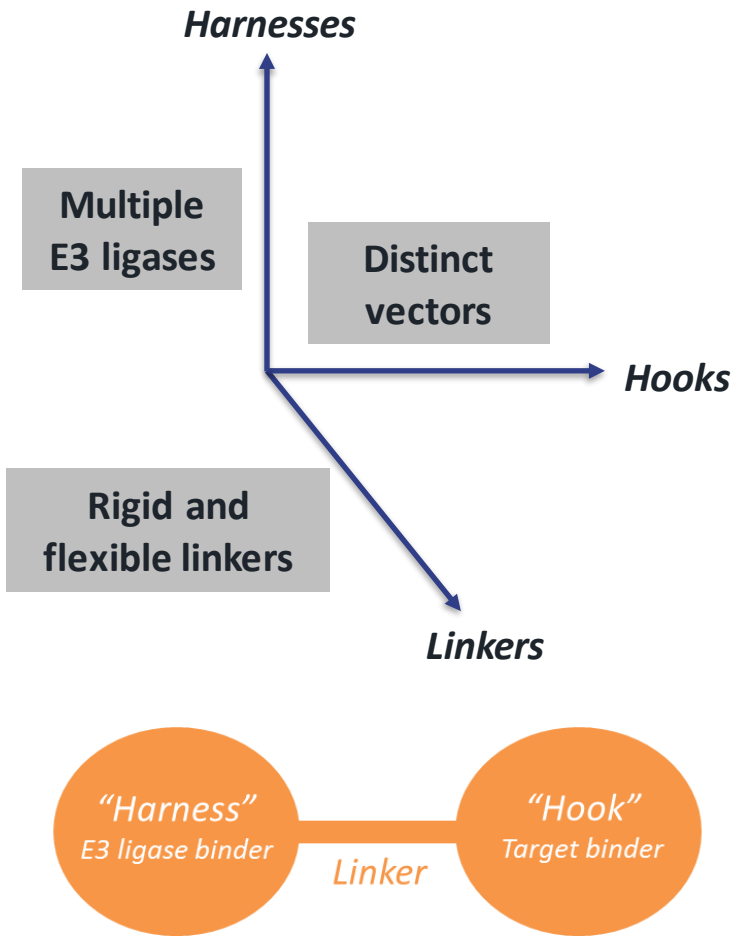
IC_{50} = 2 nM

Unoptimized DEL series



IC_{50} = 260 nM

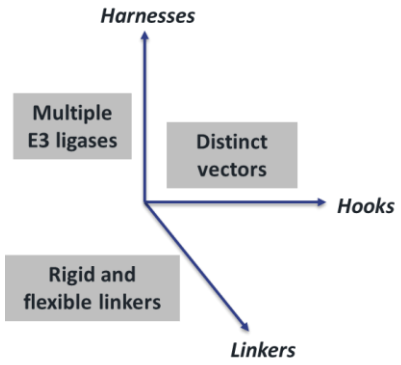
Matrix Approach to Degrader Hit Identification and Optimization

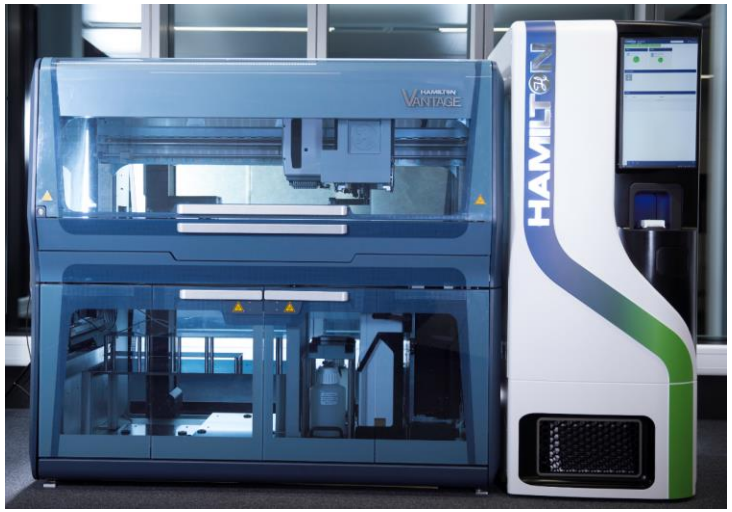


Key Goals of Matrix Strategy for Degrader Identification:

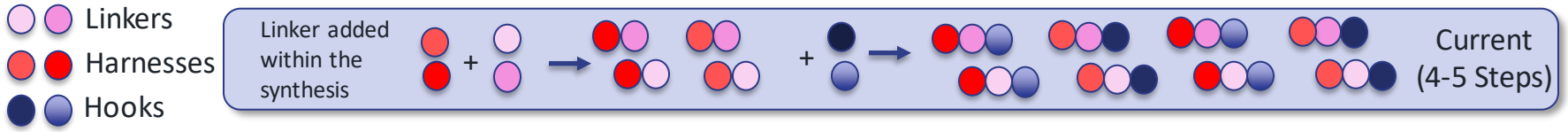
1) Identify productive ligase(s) for degradation of target protein
2) Prioritize hook/harness ligands which give most productive target protein degradation
   - Required ligand affinity for ligase/target protein
   - Binding site(s) which lead to productive ternary complex formation for degradation
3)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

Matrix Approach to Degrader Hit Identification and Optimization



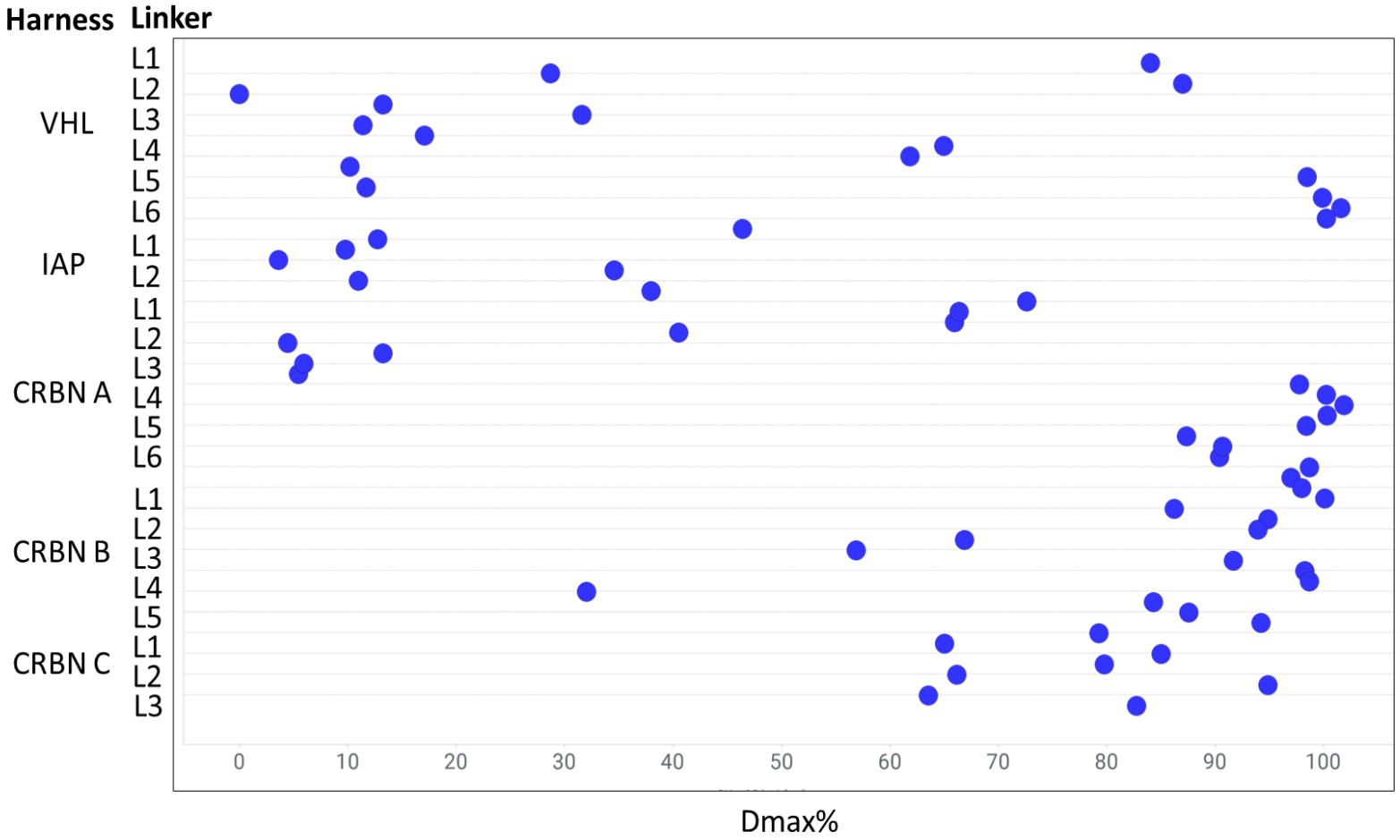


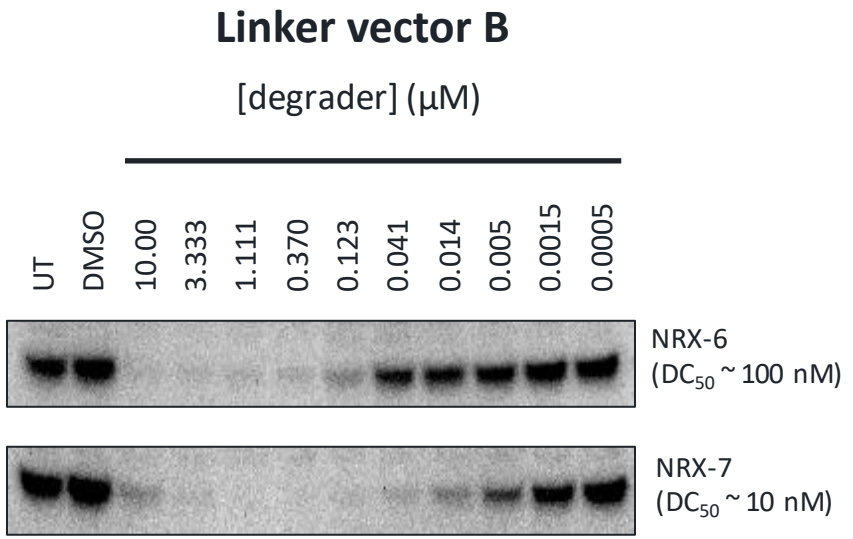
- One compound/well combinatorial libraries
- Up to 5 steps before purification
- Typically, 200-400 degrader compounds made over 4-6 weeks



Diverse combinatorial libraries synthesized

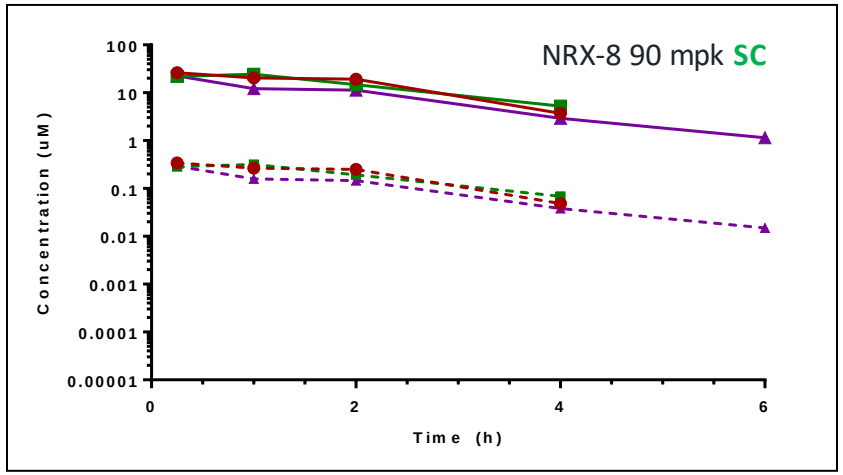
Putting it All Together: Discovery of Degraders of Pellino1, and E3 Ligase

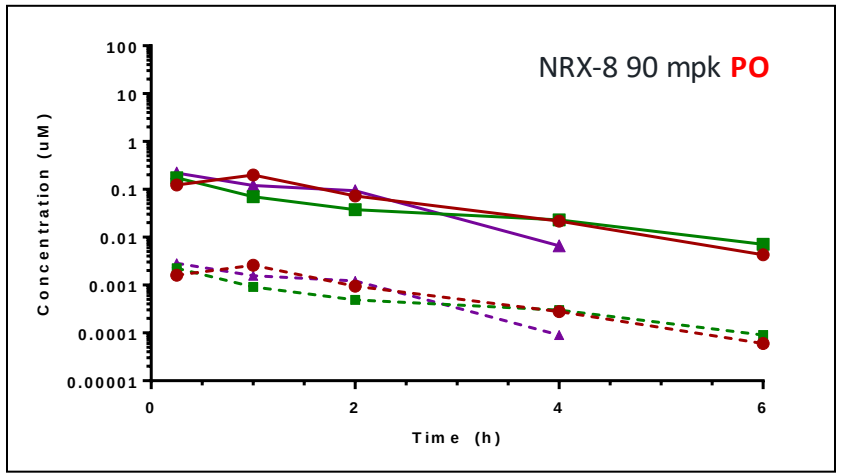


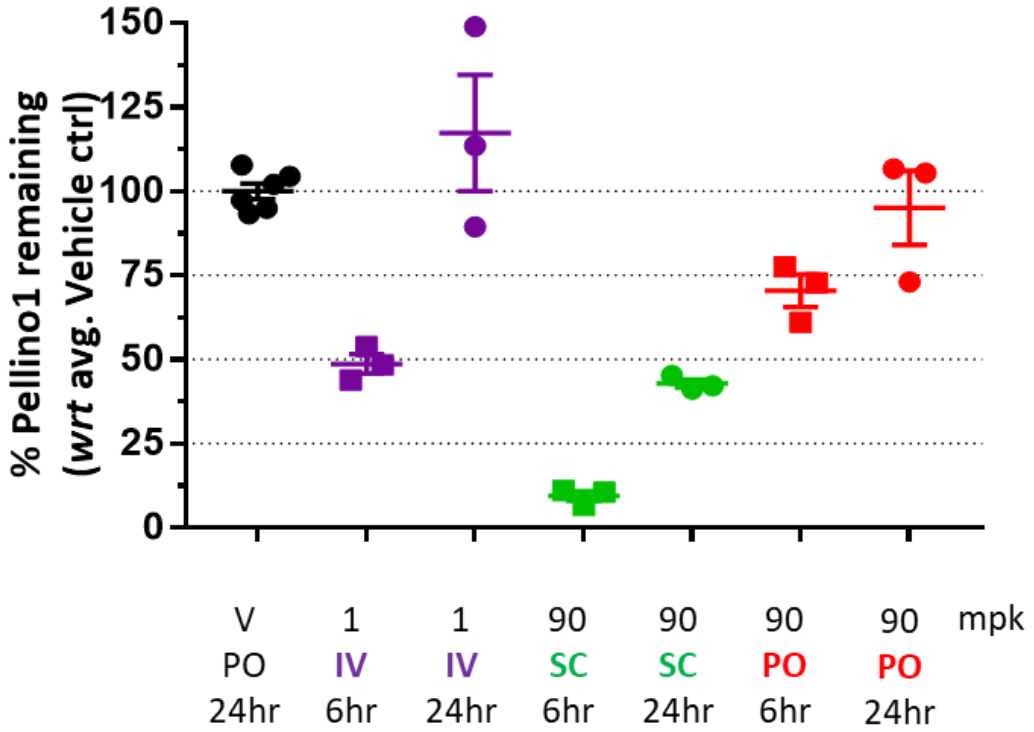


Pellino1 degradation plot highlights the impact of scanning both ligase and linker space, rapidly identifying a broad spectrum of potent degraders early in a program

Putting it All Together: Discovery of Degraders of Pellino1, and E3 Ligase







- Rapid discovery of tool compounds for in vivo biology
- Further optimization (Medicinal Chemistry) for compounds effective by PO dosing

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Nurix Drugs Engage Ligases for the Treatment of Cancer

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Harness ligases to decrease specific protein levels

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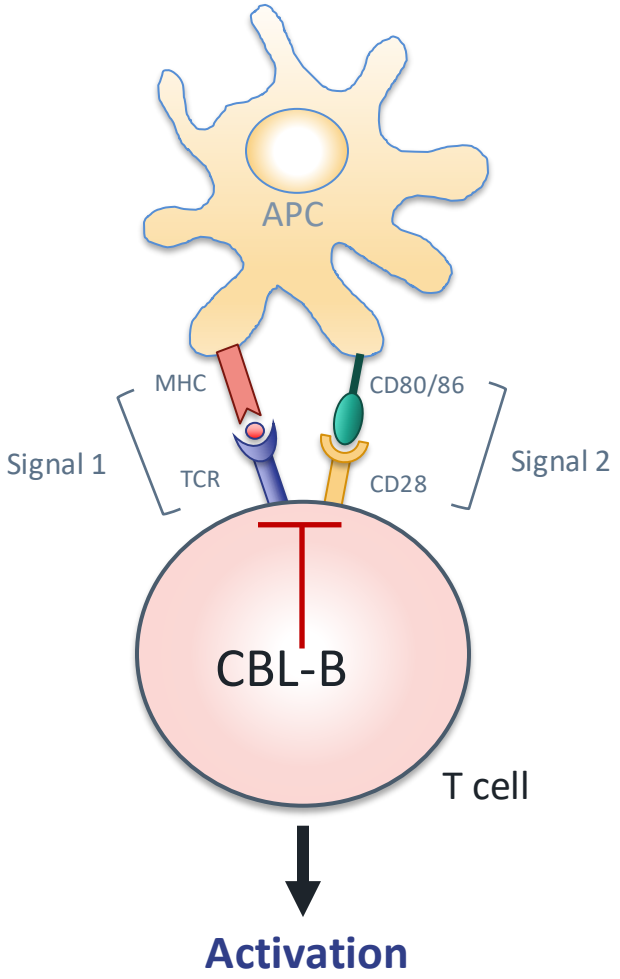
Targeted Protein Elevation (TPE)

Inhibit ligases to increase specific protein levels

CBL-B is a Modulator of Immune Cell Activation

- CBL-B is an E3 ubiquitin ligase highly expressed in cells of the immune system
- CBL-B regulates T, B, and NK cell activation
- Blocking CBL-B removes a brake on the immune system
- *cbl-b* deficient mice demonstrate robust T cell and NK cell-mediated antitumor immunity



CBL-B inhibition

- IL-2 production
- Proliferation
- Central memory phenotype
- Anti-tumor activity
- Threshold of activation
- T cell exhaustion

Synergy with anti-PD-1

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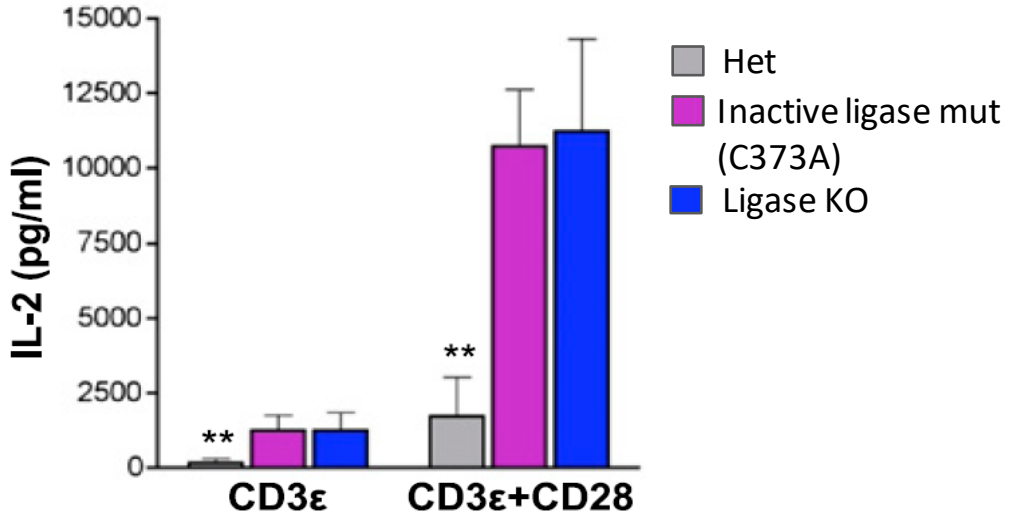
CBL-B is a Modulator of Immune Cell Activation

Inactivation or deletion of CBL-B results in hyperactive T cells and inhibition of tumor growth.

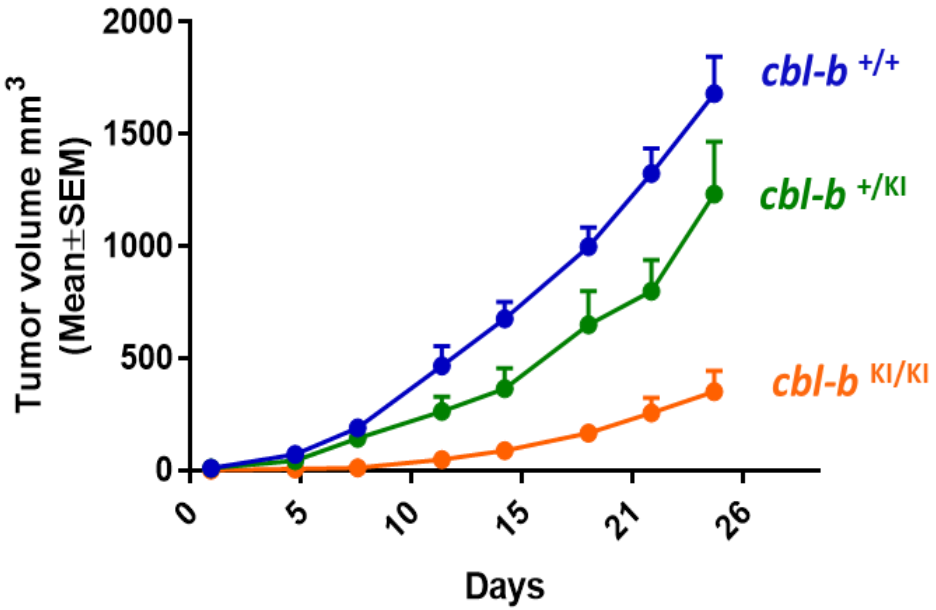
IL-2 secretion in KO and ligase inactive T cells *ex vivo*



Paolino et. al. *J. Immunology*, 2011

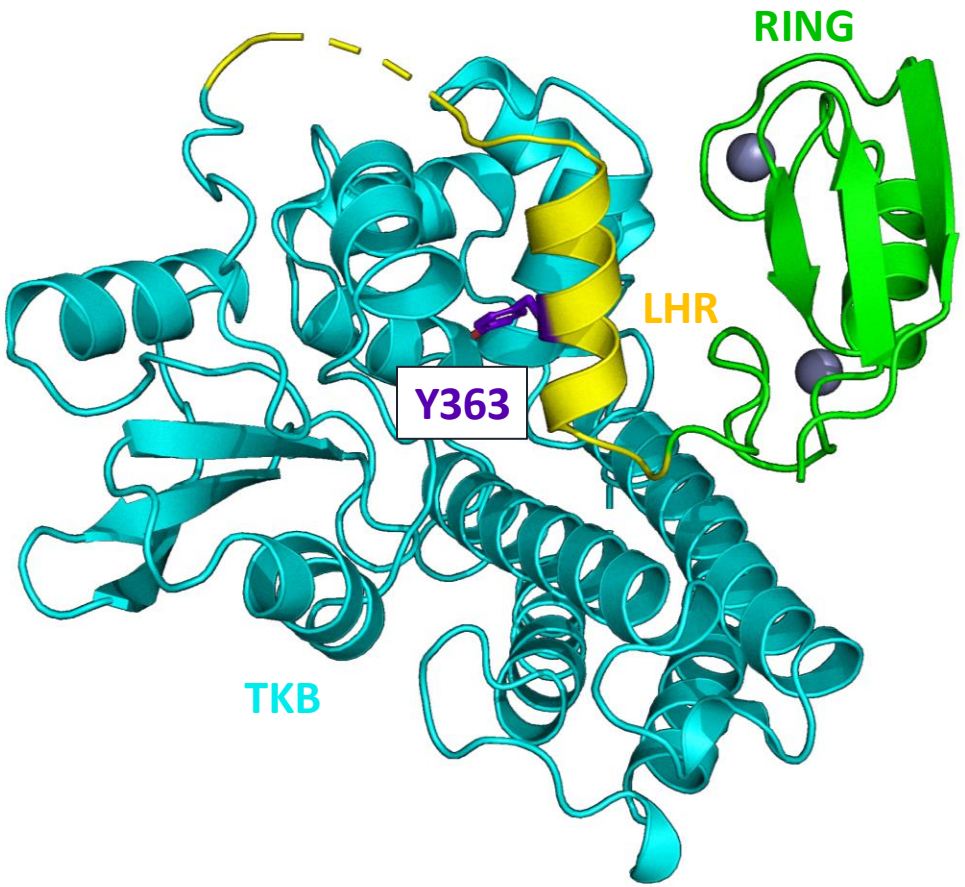
Ligase-dead or KO exhibit enhanced and equivalent response to either single- or double stimulation

Ligase-inactive *cbl-b* knock-in mice inhibit tumor growth (TC-1 syngeneic model).



Nurix Data

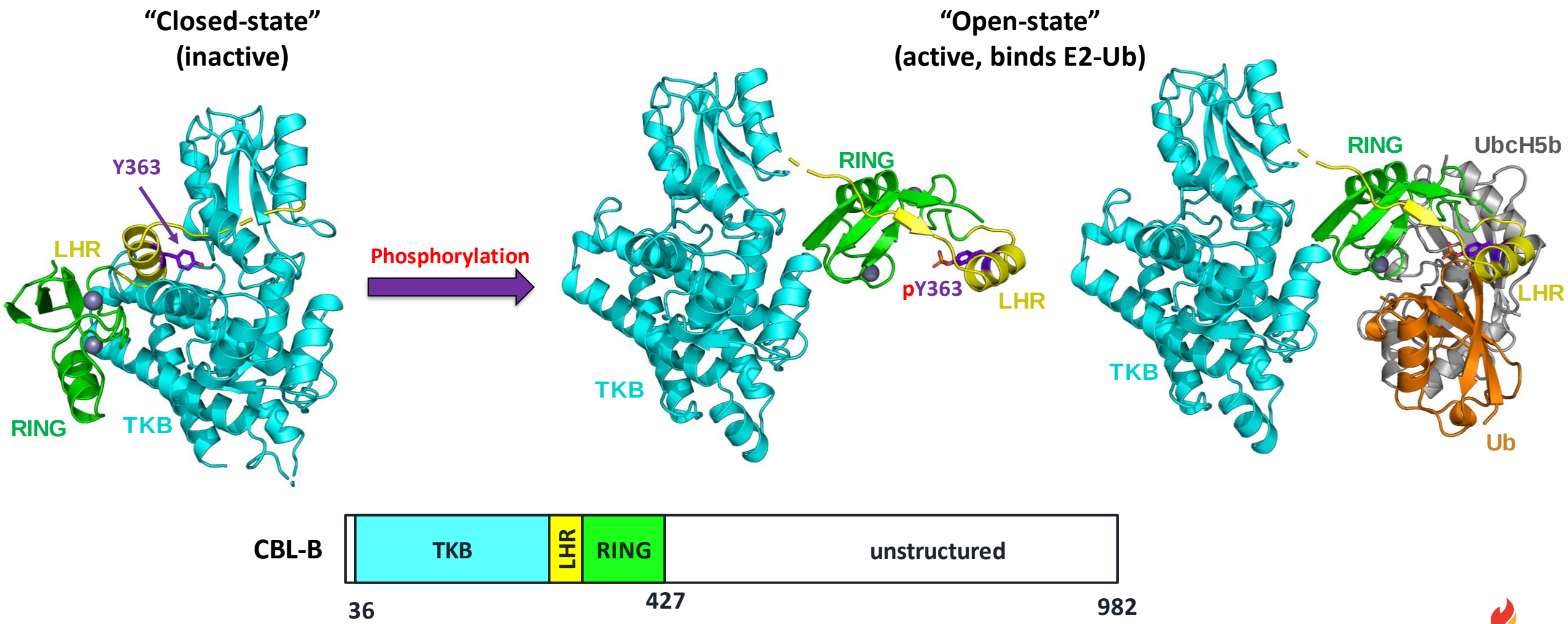
Inactive CBL-B is Autoinhibited



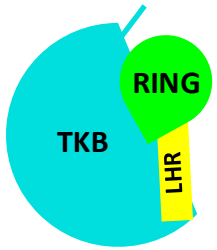
- When Y363 of CBL-B is not phosphorylated, the helix of the LHR domain packs against the TKB domain
- Incapable of binding Ub-E2
- Phosphorylation of Y363 requires dissociation of LHR-RING from TKB

Dou, et. al., Nature Structural & Molecular Biology volume 19, pages184–192 (2012)

Active CBL-B Binds Ub-loaded E2 Ligases

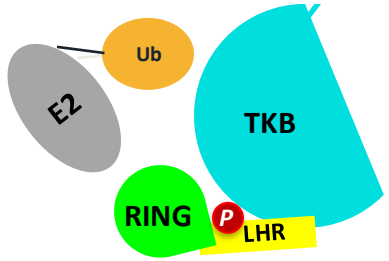


Multiple Lead-Finding Approaches Afforded CBL-B Binders

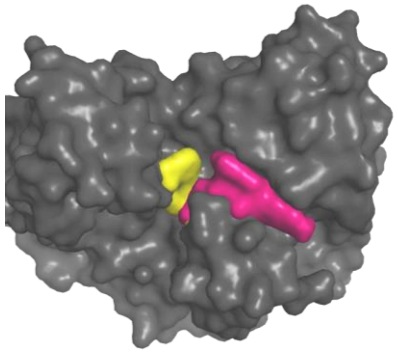


Biochemical Screening

SRC kinase



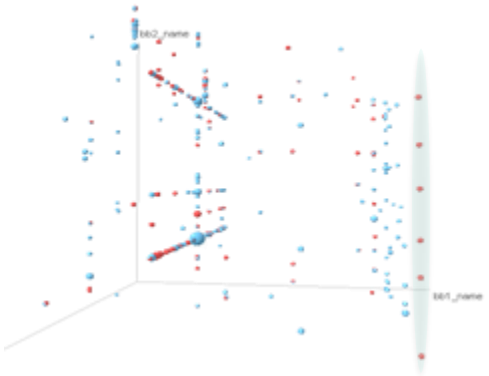
E2~Ub Binding Assay



Affinity Screening

DEL or Fragments

DEL Ligand Cube Plot



	HTS	DEL	Fragment
Lib size	300K	$1X10^9$	1600
# of Series	1	2	1
Hit Affinity	28 μM	2.4 μM	1800 μM
Hit mwt	338	537	211
Hit LE	0.27	0.22	0.33

- **All three screening techniques afforded validated binders, confirmed by X-ray crystallography.**

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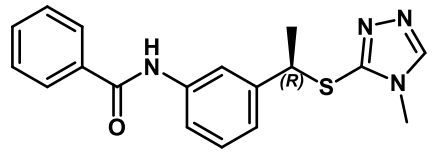
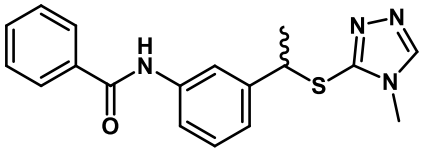
NRX-3 is a Specific Inhibitor of CBL-B

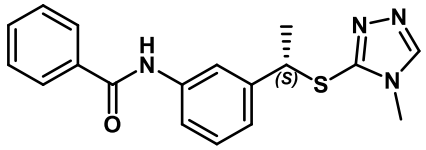


NRX-2



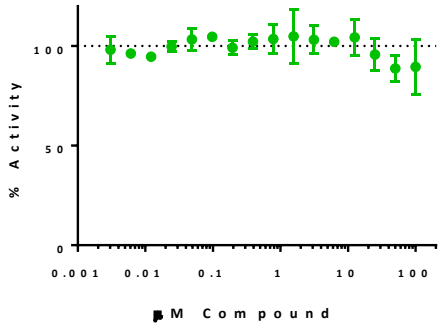
Chiral SFC

NRX-1
HTS Screening hit

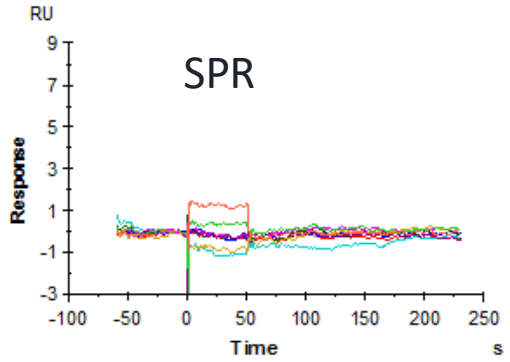


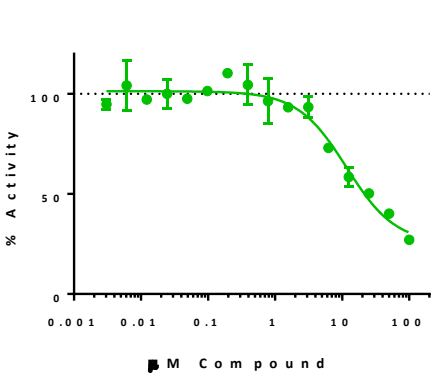
NRX-3
Resolved Screening hit
E2-Ub: IC_{50} = 12 µM
mwt = 338; LE = 0.29

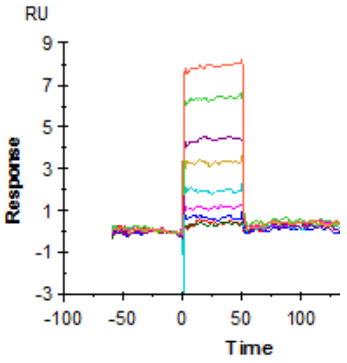
E2-Ub binding



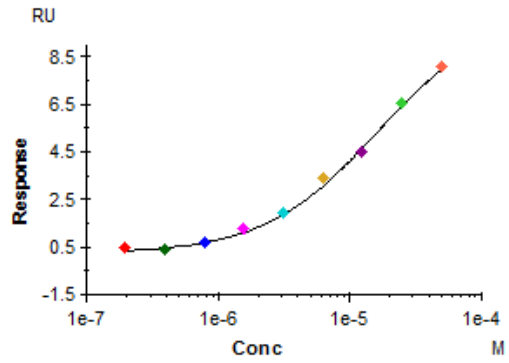
SPR



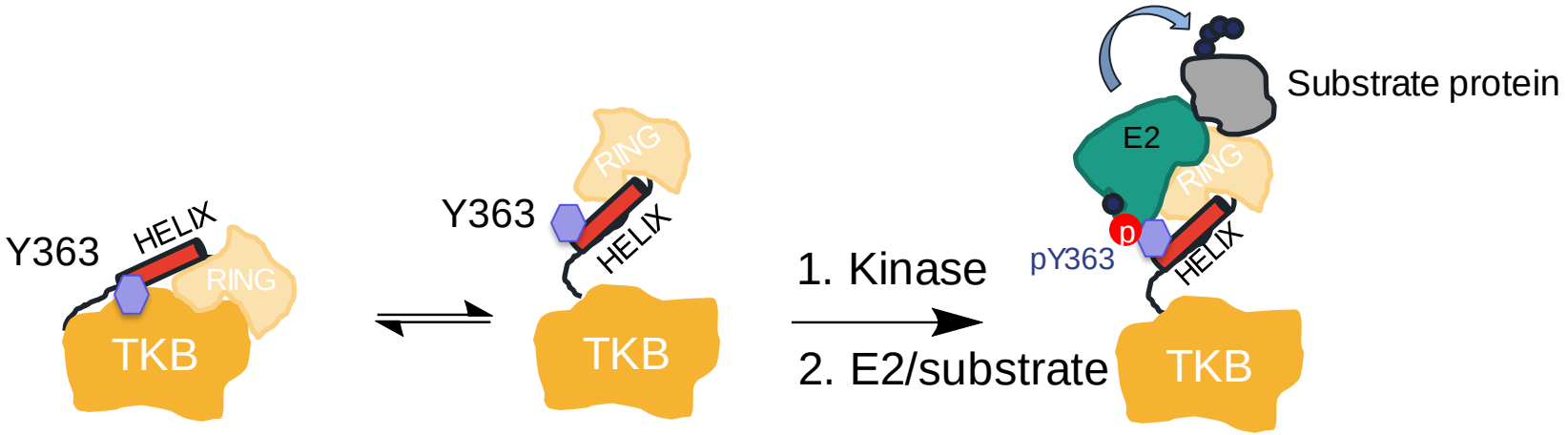




K_D: 16 µM



NRX-3 is an Intramolecular Glue



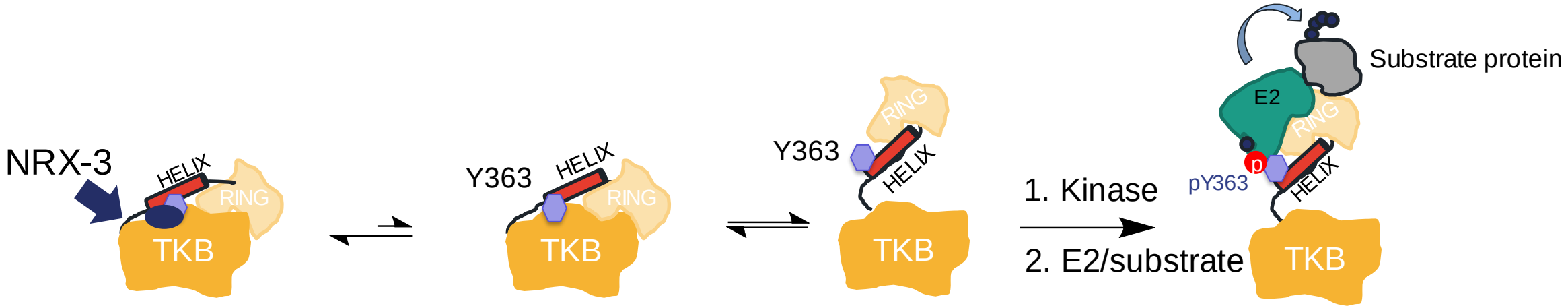
Closed State
INACTIVE

Opened State

Phosphorylation locks CBL-B in the **ACTIVE** Conformation

Immune Response

NRX-3 is an Intramolecular Glue



NRX-3 acts as an intramolecular glue forcing CBL-B in its folded **INACTIVE** state

Closed State **INACTIVE**

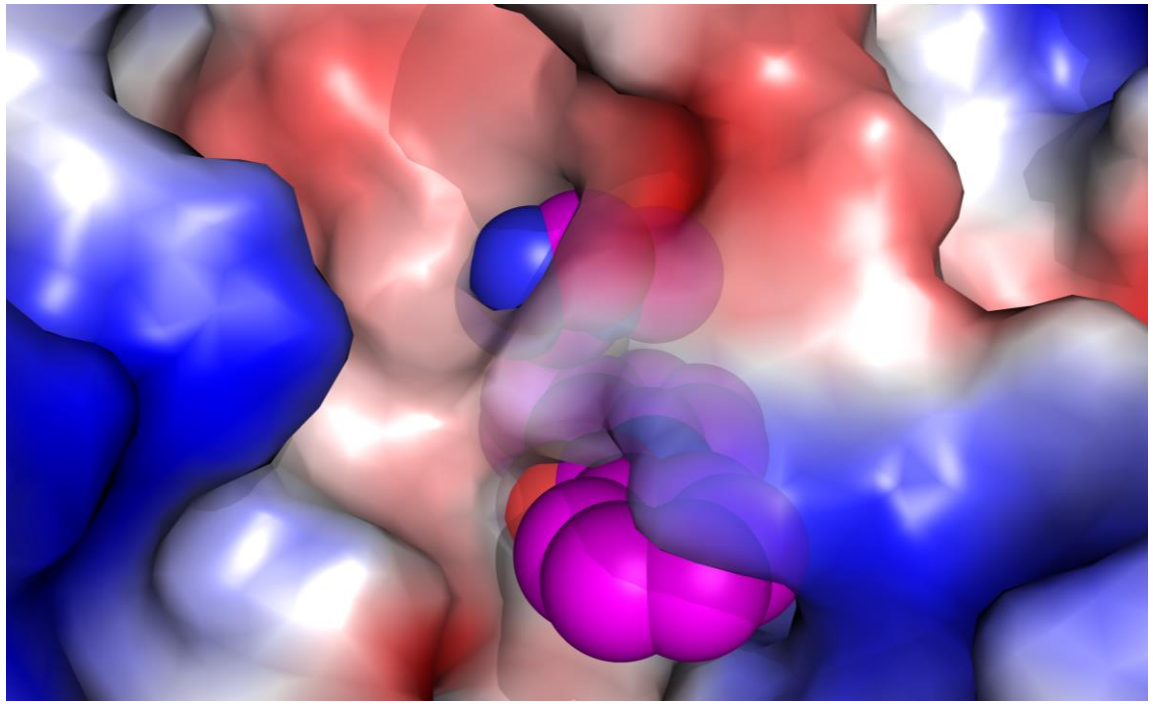
Opened State

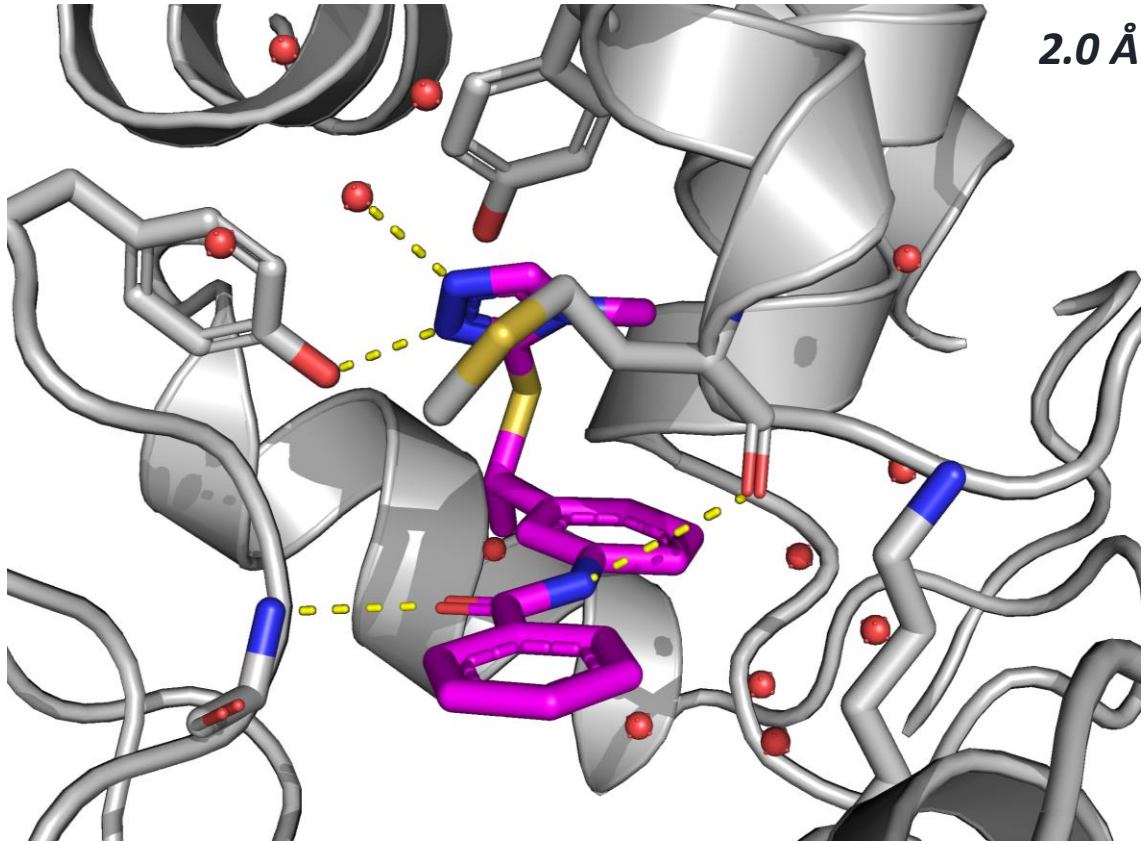
Phosphorylation locks CBL-B in the **ACTIVE** Conformation

Immune Response

Immune Response

Crystal Structure Confirms Binding Mode as Intramolecular Glue





NRX-3 binds to closed-state CBL-B and prevents phosphorylation

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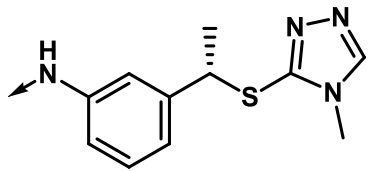
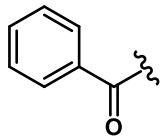
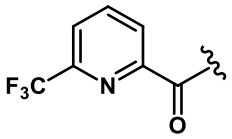
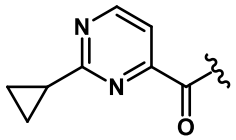
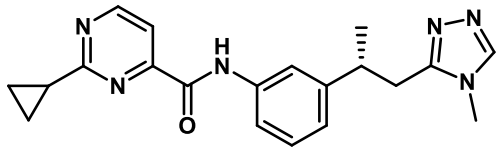
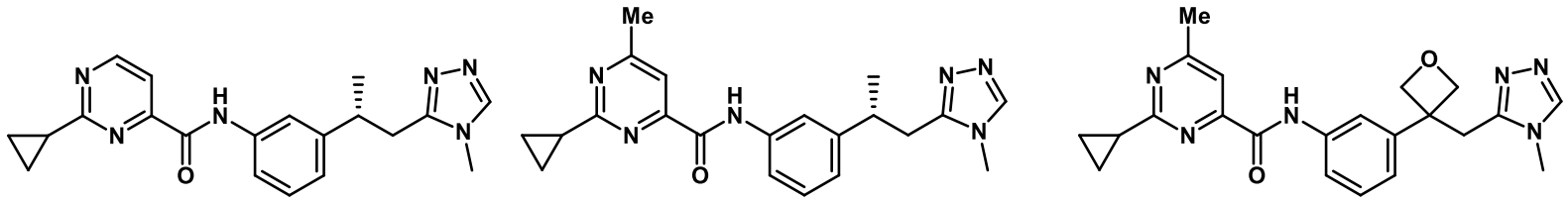
Early SAR: Focus on Affinity and Properties

	NRX-3	NRX-4	NRX-5	NRX-6
E2-Ub: IC_{50} (μM)	12	0.23	0.092	0.088
Ligand Efficiency	0.29	0.33	0.36	0.37
Cellular Substrate Ub IC_{50} (μM)		7	3	1.7
Microsomes h/m Cl_{int} (mL/min/kg)		20/360	-/500	30/73
Plasma stability m/r $T_{1/2}$ (min)		-	140/-	280/-
Papp MDCK (MDR1) A→B/B→A ratio		26/1	33/1	9/6
Ksol (μM)		250	300	270
$LogD_{7.4}$		2.6	2.3	1.9

Early SAR: Focus on Affinity and Properties



	NRX-6	NRX-7	NRX-8
E2-Ub: IC_{50} (μM)	**0.088**	**0.038**	**0.021**
Ligand Efficiency	**0.37**	**0.37**	**0.36**
Cellular Substrate Ub IC_{50} (μM)	**1.7**	**0.78**	**0.79**
Microsomes h/m Cl_{int} (mL/min/kg)	**30/73**	**-/67**	**7/26**
Plasma stability m/r $T_{1/2}$ (min)	**280/-**	**>1000/163**	**>1000/>1000**
Papp MDCK (MDR1) A→B/B→A ratio	**9/6**	**7/7**	**2/14**
Ksol (μM)	**270**	**260**	**300**
$LogD_{7.4}$	**1.9**	**2.4**	**1.7**

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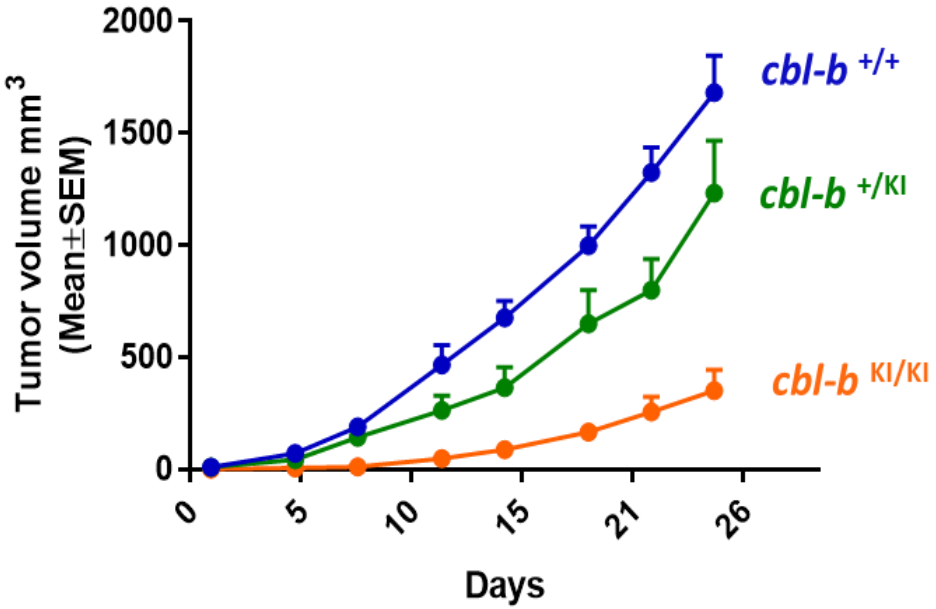
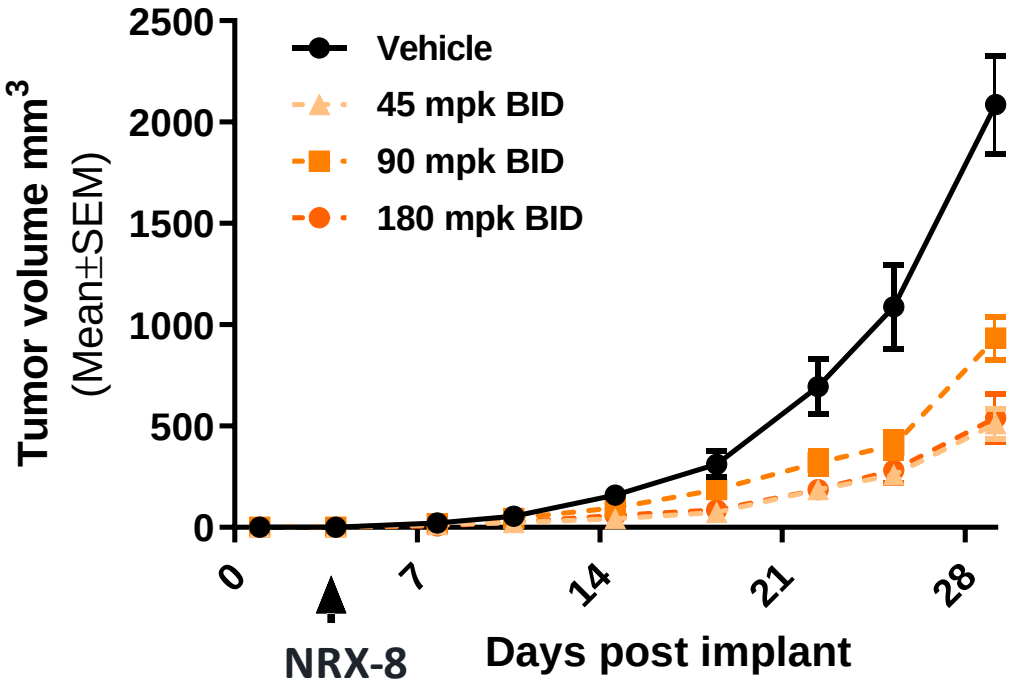
Pharmacologic Inhibition of CBL-B Recapitulates Anti-Tumor Effects of Genetic Model of Ligase Inhibition

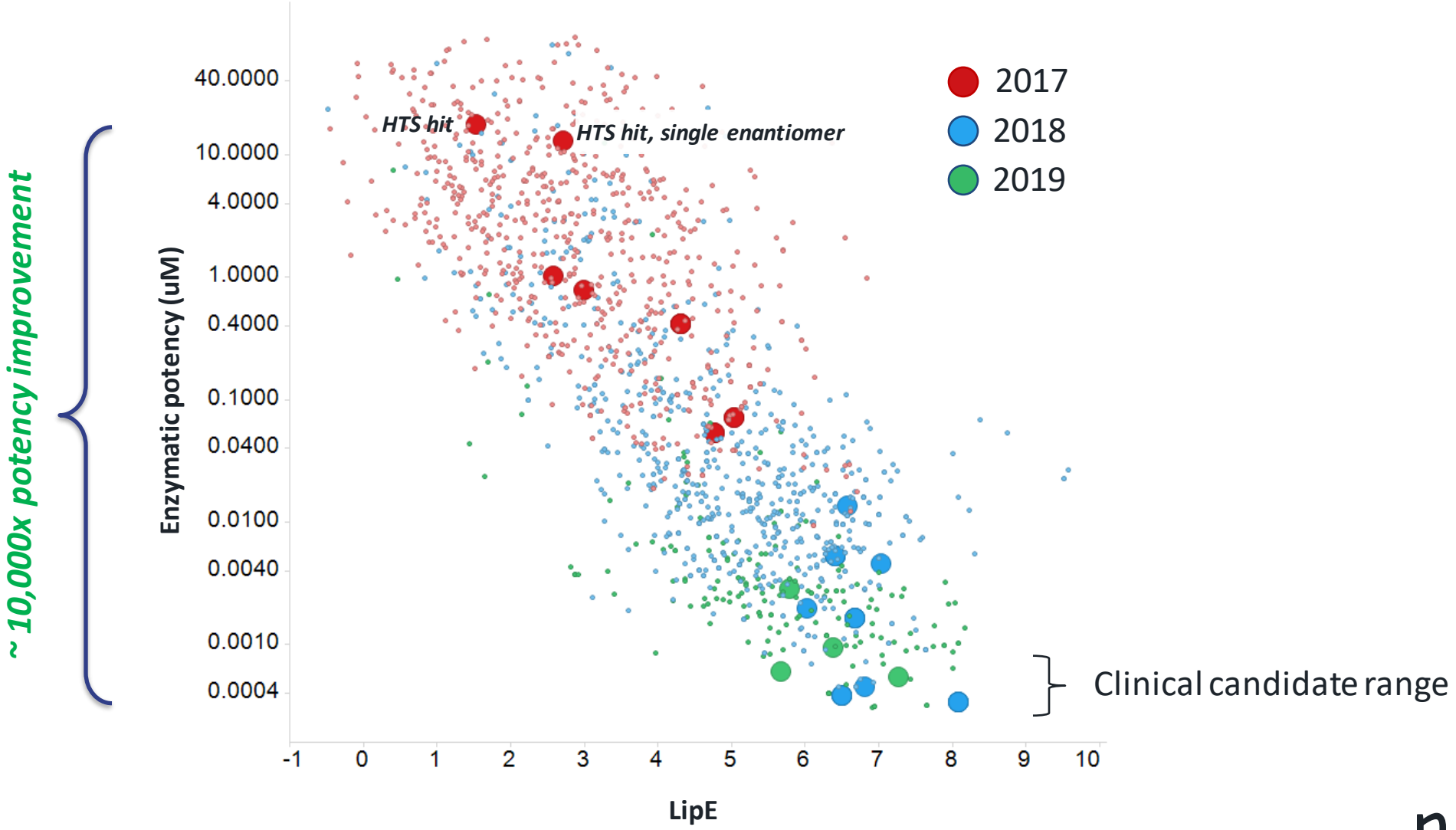
Ligase-inactive *cbl-b* knock-in mice inhibit tumor growth in TC1 Syngeneic Model



CT26 Syngeneic Model

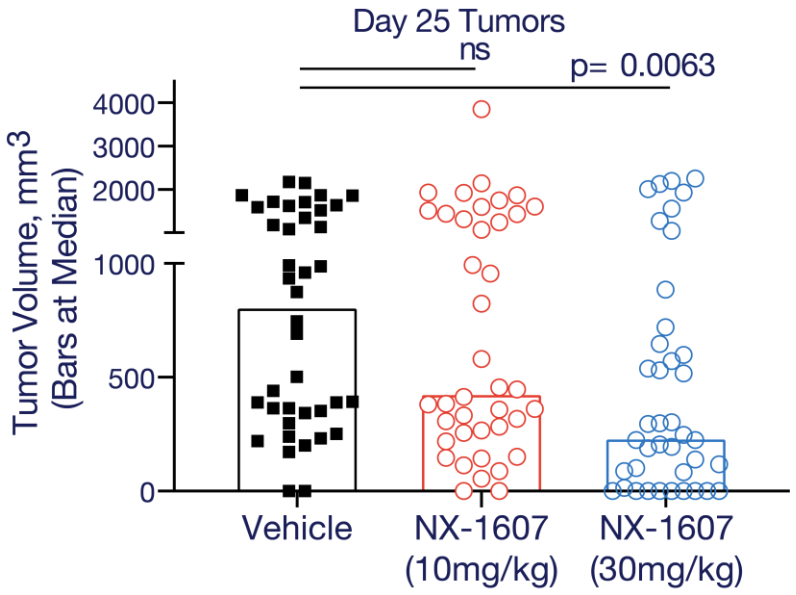


Over 10,000-fold Enzymatic Potency Improvement Achieved While Improving Molecular Properties

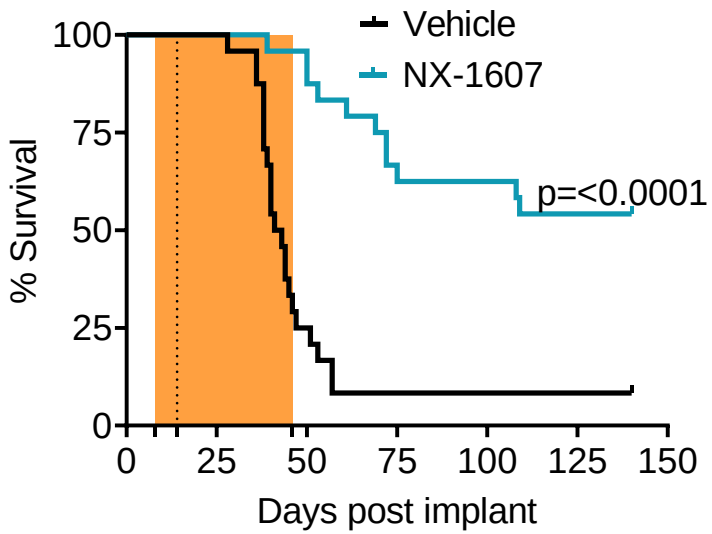


Single-Agent NX-1607 Induces Antitumor Response in Multiple Models

NX-1607
Reduced Tumor Volume
Colorectal

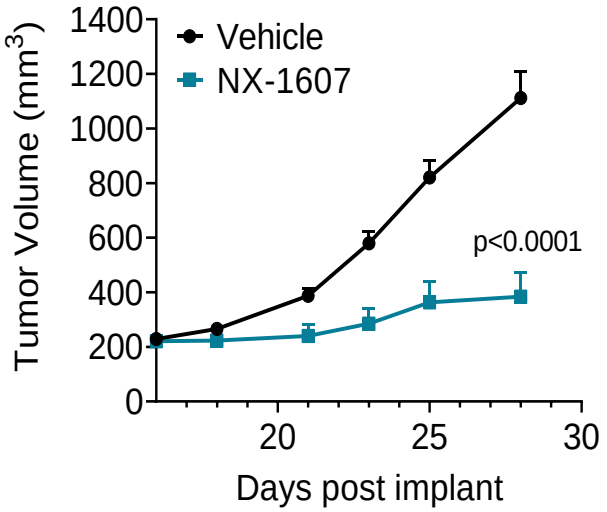


NX-1607
Prolonged Survival
Triple-Negative Breast



NX-1607 30 mg/kg day 7 to 46

NX-1607
Reduced Tumor Volume
B Cell Lymphoma



NX-1607 30 mg/kg day 16 to 28

Shaded area indicates dosing period

Thank you

Nurix Therapeutics