



Leader in Targeted Protein Modulation

# Discovery and Optimization of CBL-B Inhibitors

ACS Fall Meeting

Chicago, IL

August 23, 2022

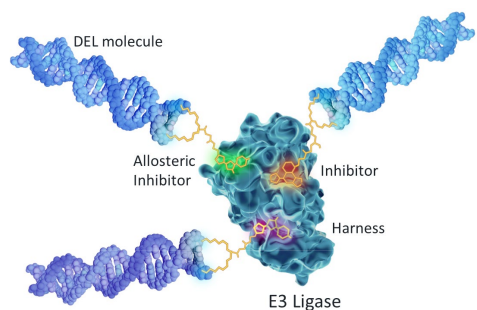
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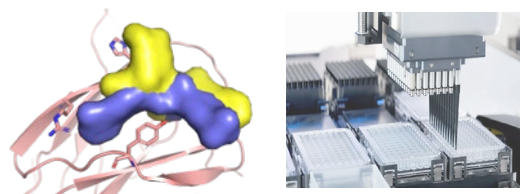
# Nurix's DELigase Protein Modulation Discovery Platform

## DEL Discovery



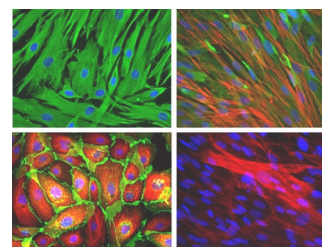
> 5 billion drug-like compounds that can be easily screened against hundreds of proteins to identify starting points therapeutic discovery

## Rational and Empirical Chemistry



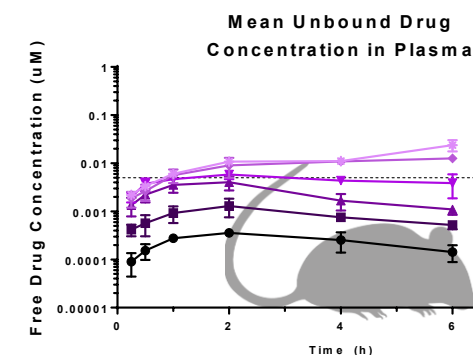
Structure Based Drug Design combined with chemistry automation enables broad exploration of lead-like chemical space for each program

## Direct-to-Cell Biology Capabilities



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

## Scaled Screening for in vivo exposure



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

# 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	<b>NX-2127</b> Degradar	BTK-IKZF <i>Oral</i>	B-Cell Malignancies				
	<b>NX-5948</b> Degradar	BTK <i>Oral</i>	B-Cell Malignancies				
TPE	<b>NX-1607</b> Inhibitor	CBL-B <i>Oral</i>	Immuno-Oncology				
	<b>DeTIL-0255</b> Cell Therapy	Adoptive Cell Therapy <i>Ex vivo CBL-B Inhibition</i>	Gynecologic Malignancies				
TPM	Wholly owned	5 targets	Multiple				
TPD	Gilead Sciences	5 targets	Multiple				
TPD	Sanofi	5 targets	Multiple				

# Acknowledgements

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## Chemistry

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Chenbo Wang  
Hiroko Tanaka  
Jose Leighton  
Oliver McConnell  
Jeff Mihalic  
Christoph Zapf

## Drug Discovery Technologies

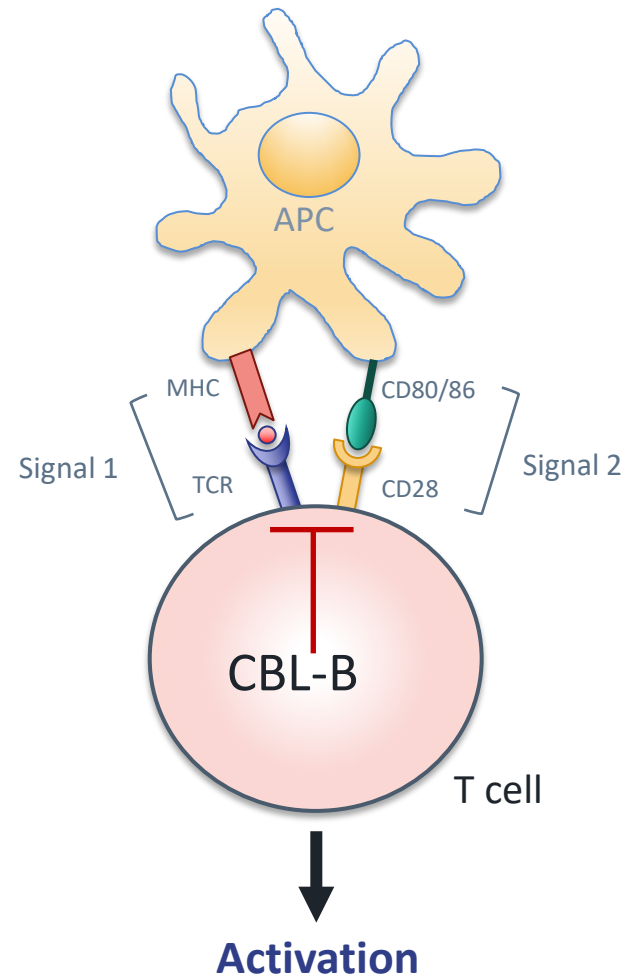
Eileen Ambing  
Jose Santos  
Morgan Lawrenz  
Dahlia Weiss  
Mario Cardozo  
Matt Clifton  
Stefan Gajewski  
Brandon Bravo  
Nichole O'Connell  
Paul Novick  
Tania Silva  
Andrew Sawayama

## Nurix Leadership

Arthur Sands  
Pierre Beurang  
Gwenn Hansen  
Cristiana Guiducci

# 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

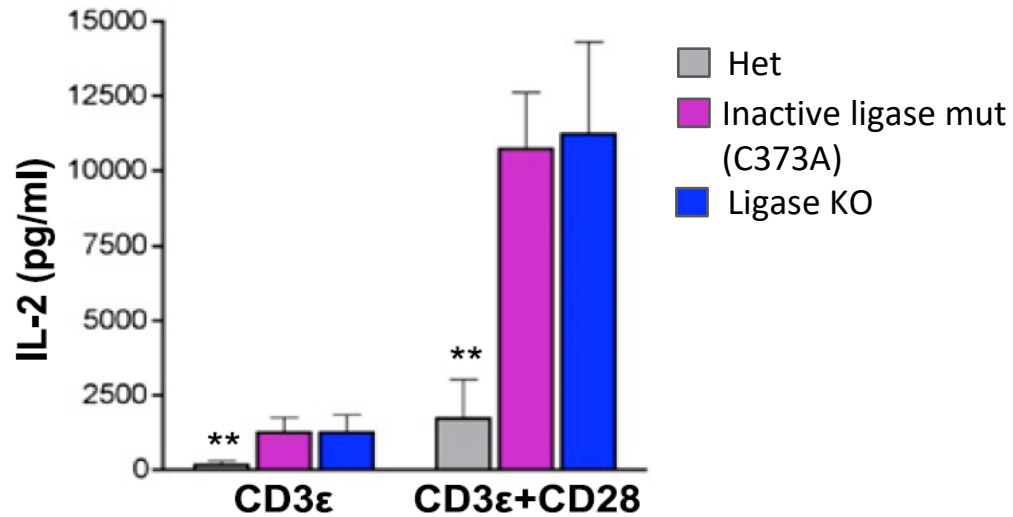
- ↑ IL-2 production
- ↑ Proliferation
- ↑ Central memory phenotype
- ↑ Anti-tumor activity
- ↓ Threshold of activation
- ↓ T cell exhaustion

***Synergy with anti-PD-1***

# 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.

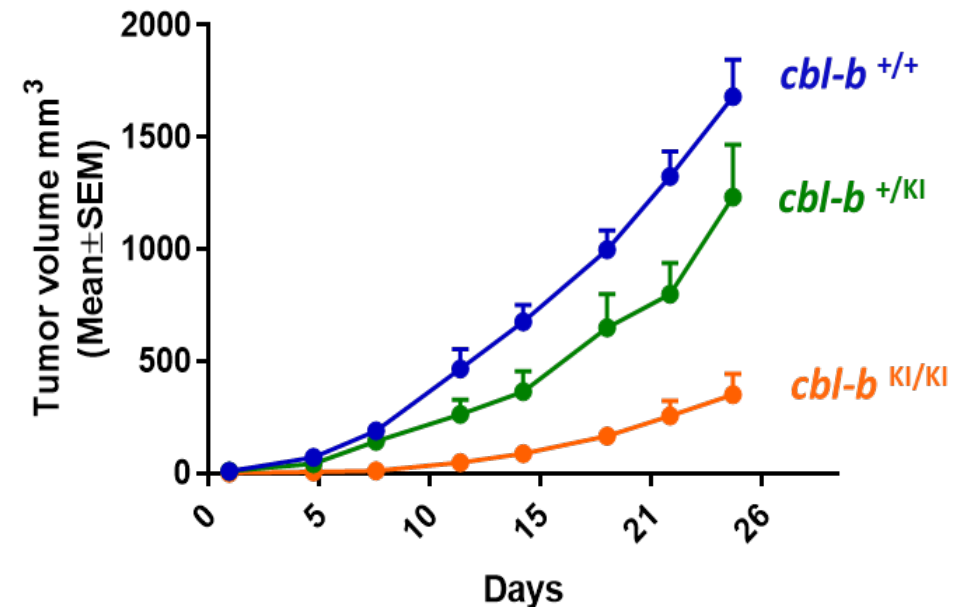
IL-2 secretion in KO and ligase inactive T cells *ex vivo*



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

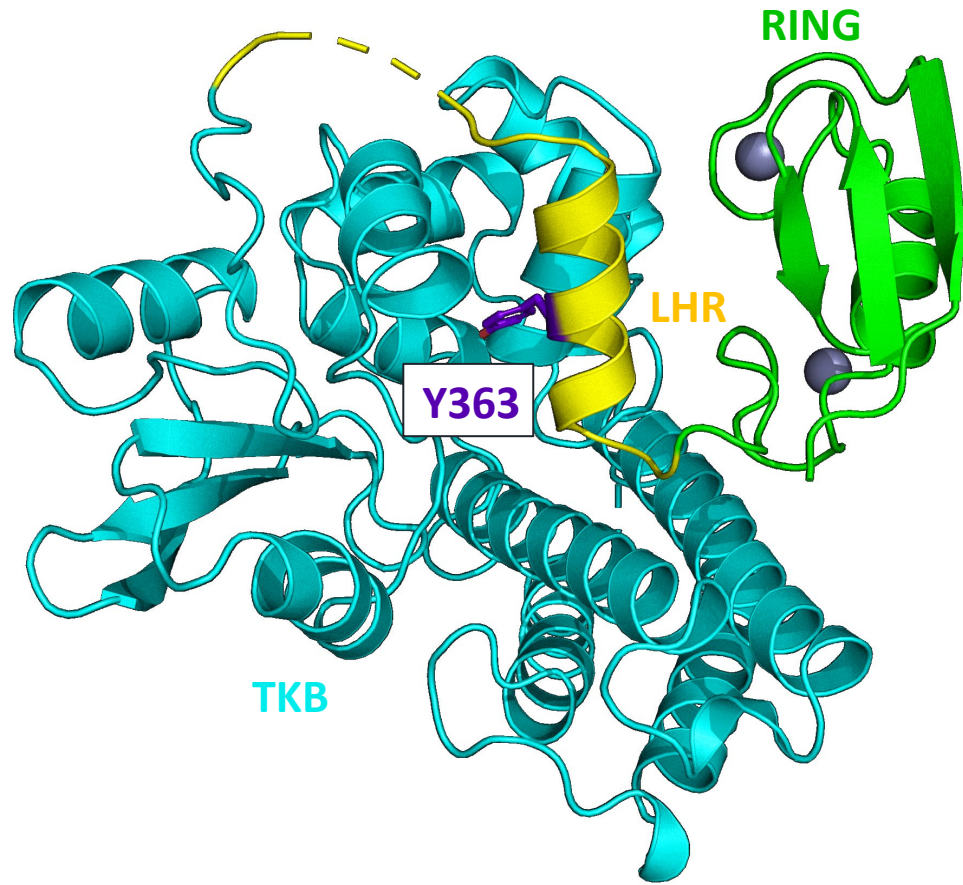
Ligase-dead or KO exhibit enhanced and equivalent response to either single- or double stimulation

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



Nurix Data

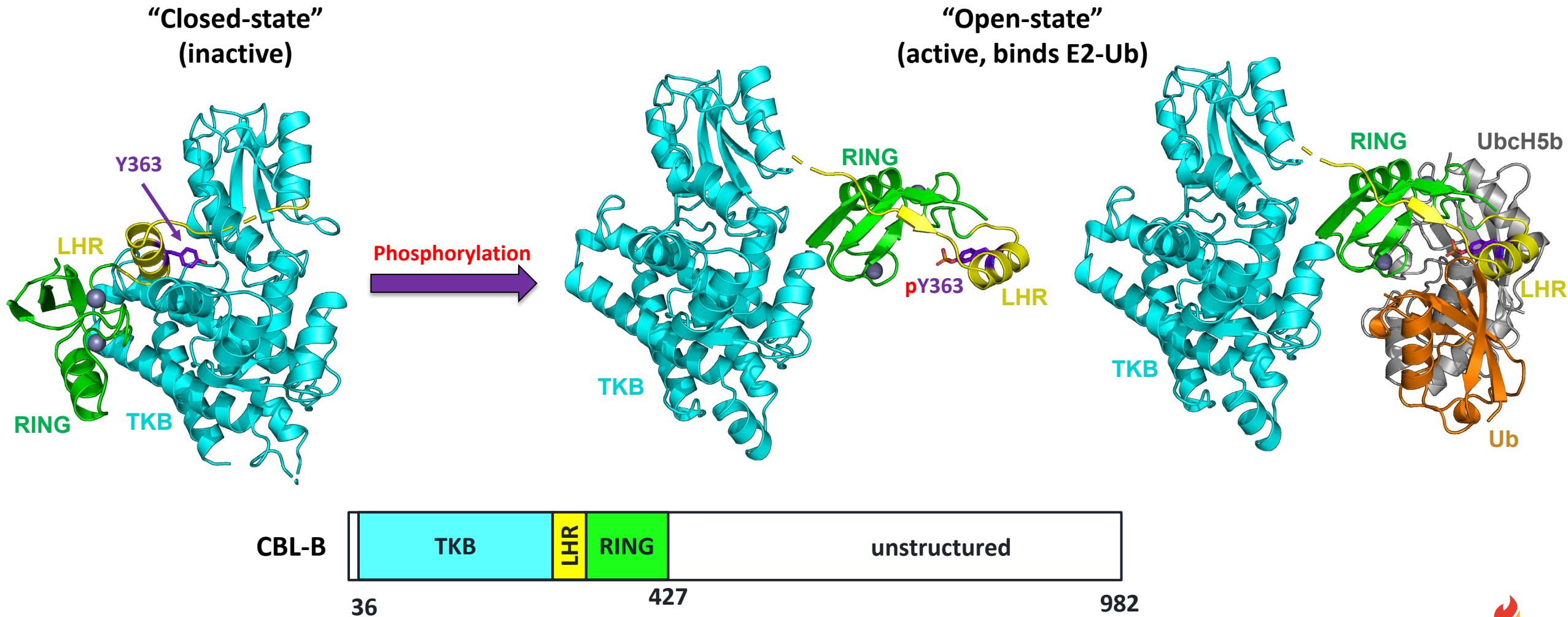
# Inactive CBL-B is Autoinhibited



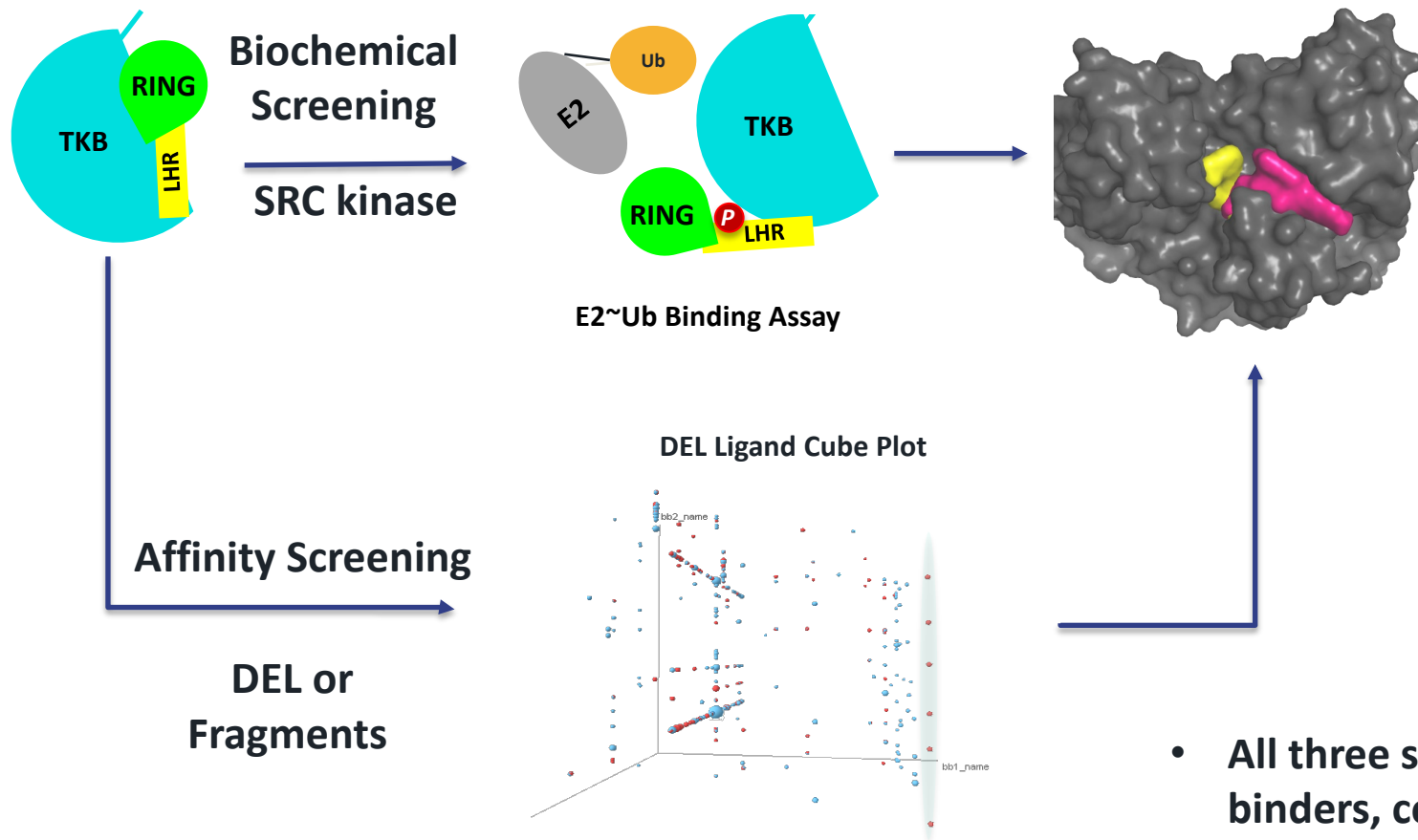
- When Y363 of CBL-B is not phosphorylated, the helix of the LHR domain packs against the TKB domain
- Incapable of binding Ub-E2
- Phosphorylation of Y363 requires dissociation of LHR-RING from TKB



# Active CBL-B Binds Ub-loaded E2 Ligases



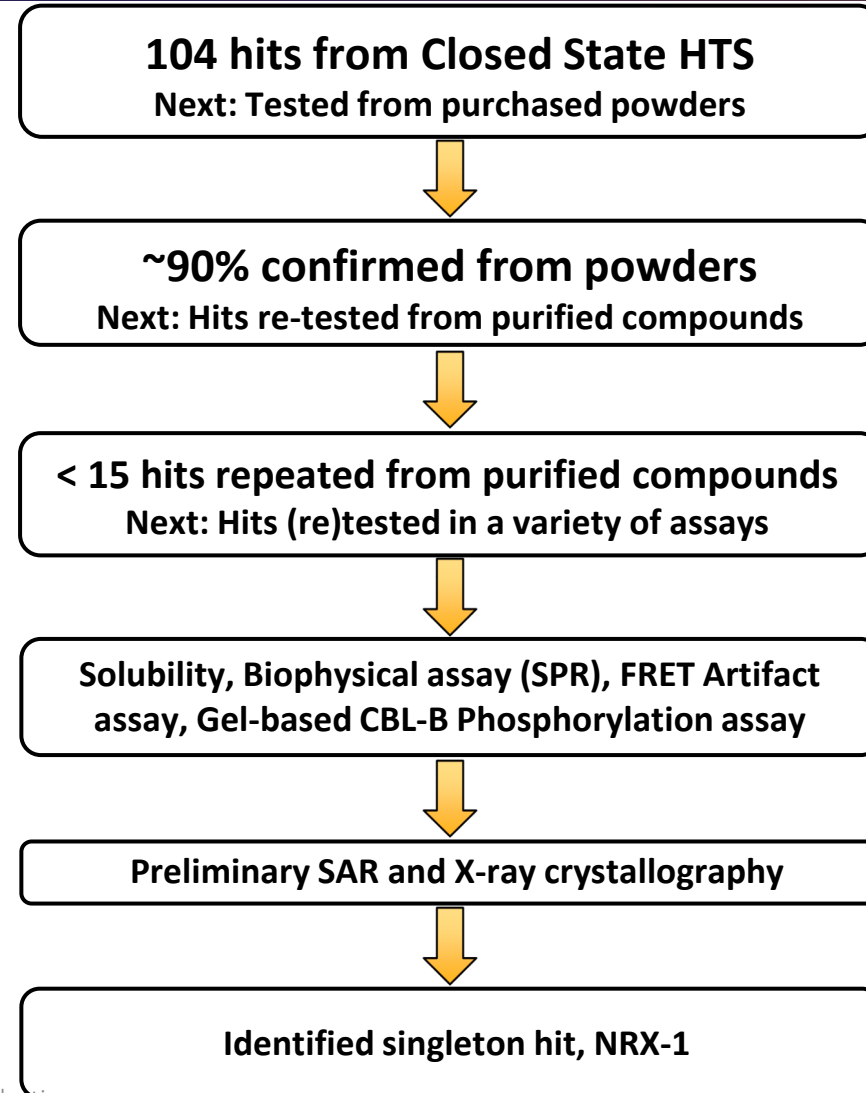
# Multiple Lead-Finding Approaches Afforded CBL-B Binders



	HTS	DEL	Fragment
Lib size	300K	1X10 <sup>9</sup>	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

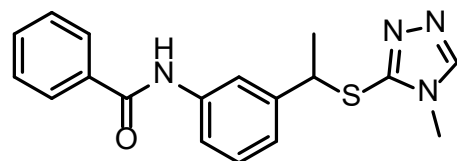
- All three screening techniques afforded validated binders, confirmed by X-ray crystallography.

# CBL-B HTS Triage Revealed a Singleton Hit



- CBL-B Phosphorylation FRET assay
- E2~Ub Binding FRET assay
- Src Counter Screen FRET assay

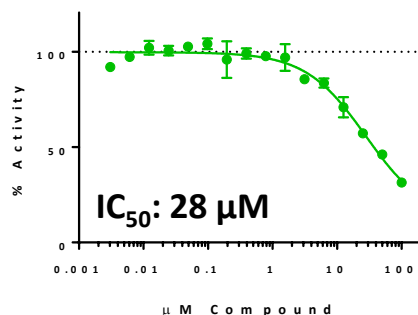
# HTS Reveals a Singleton Hit



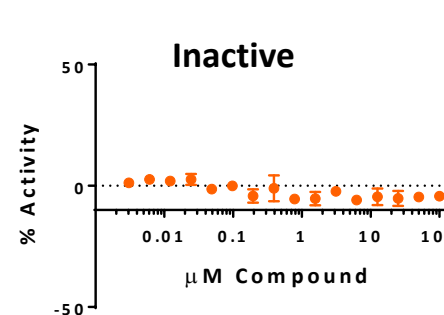
**NRX-1**  
(racemic)

mwt = 338  
 $K_{sol}$  280  $\mu$ M  
 cLogP 3.46  
 PSA 60

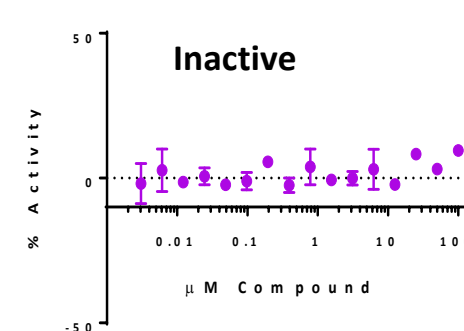
**E2 binding FRET, Orthogonal**



**Src Counter Screen FRET**

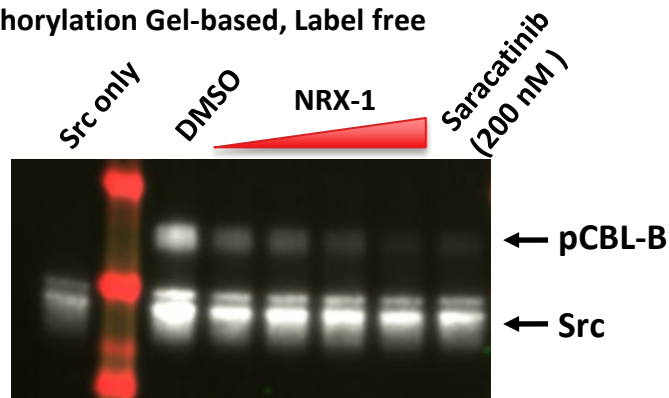


**FRET Artifact Assay**



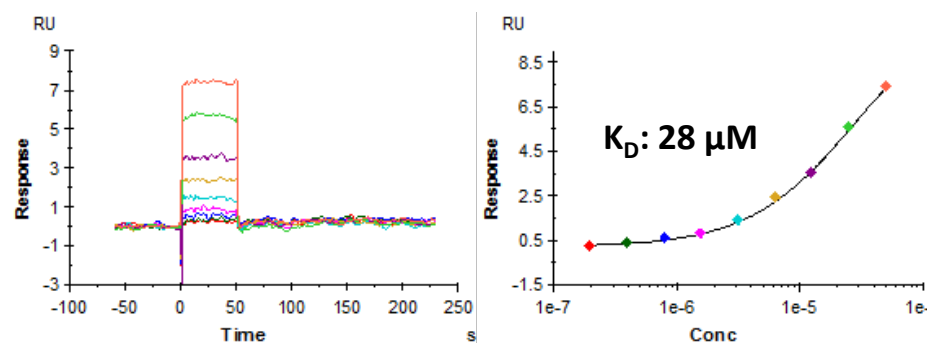
E2 binding assay and counter assays to examine Src activity or FRET artifacts indicate that **NRX-1** is a CBL-B inhibitor

**CBL-B Phosphorylation Gel-based, Label free**



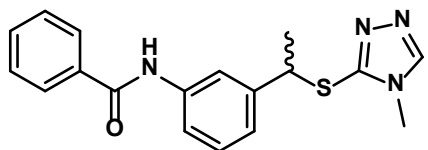
Compound titration ( $\mu$ M): 12.5, 25, 50, 100

**Compound Binding to CBL-B by SPR**



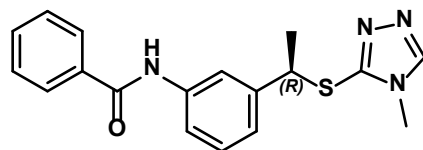
- SPR confirms **NRX-1** binding affinity and stoichiometry to CBL-B
- SPR binding affinity and biochemical potency in close agreement

# NRX-3 is a Specific Inhibitor of CBL-B

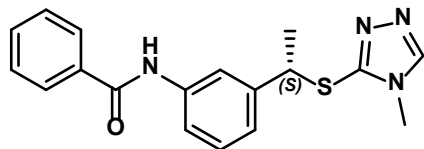


**NRX-1**  
HTS Screening hit

Chiral SFC

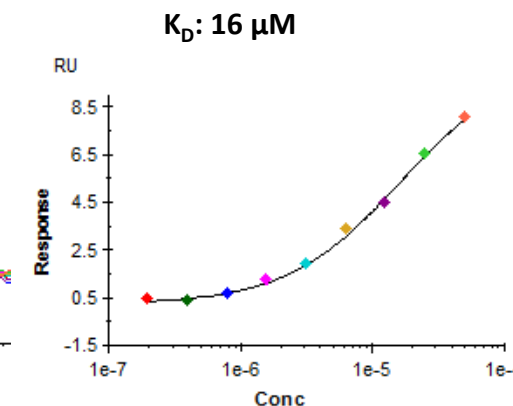
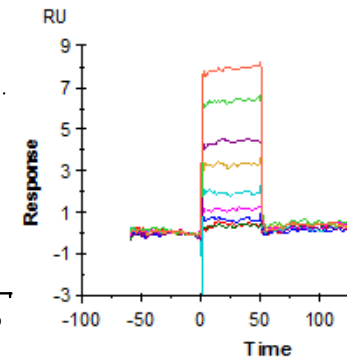
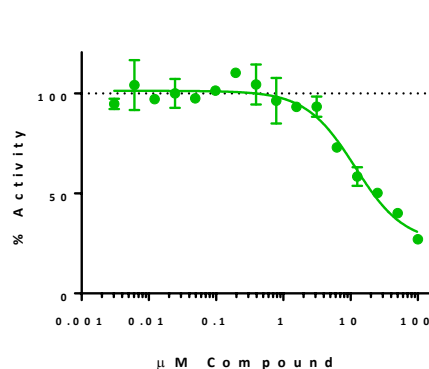
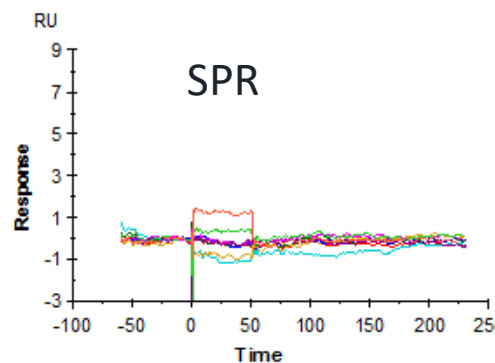
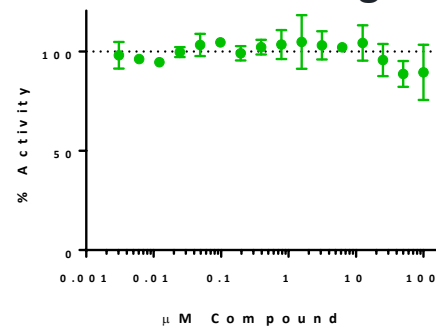


**NRX-2**

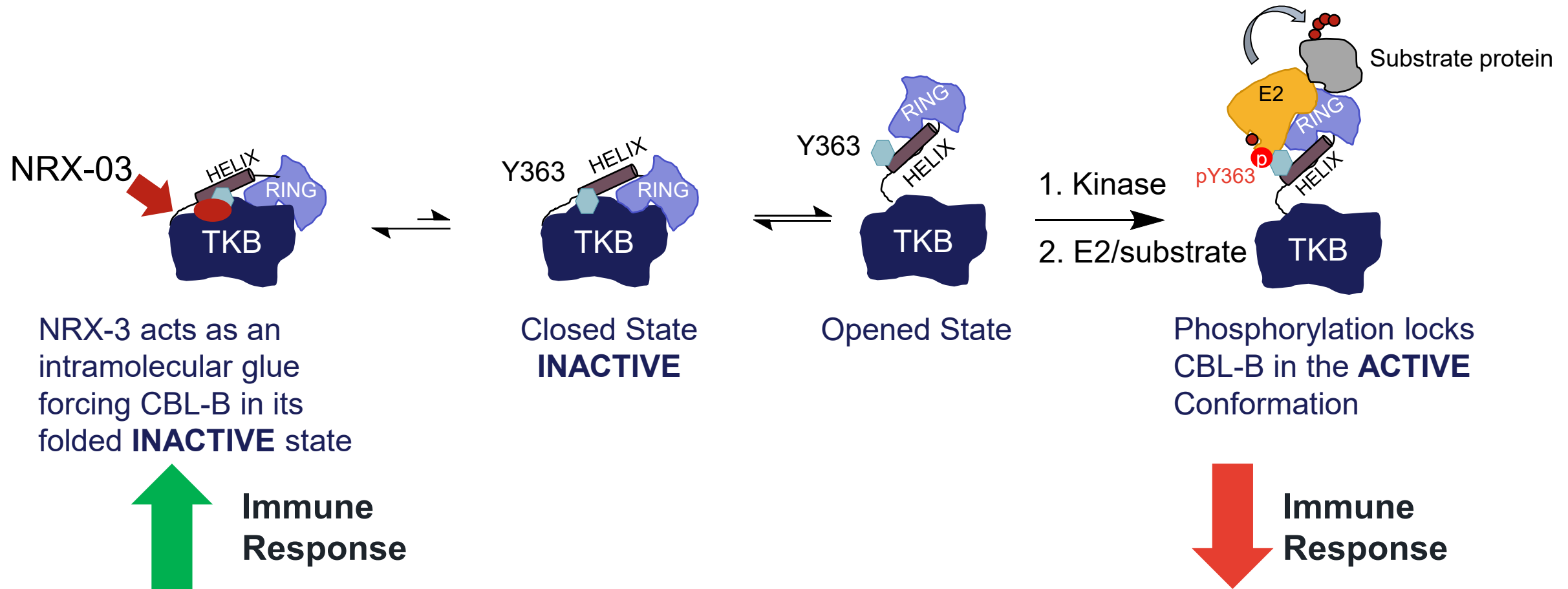


**NRX-3**  
Resolved Screening hit  
E2-Ub:  $IC_{50} = 12 \mu M$   
mwt = 338; LE = 0.29

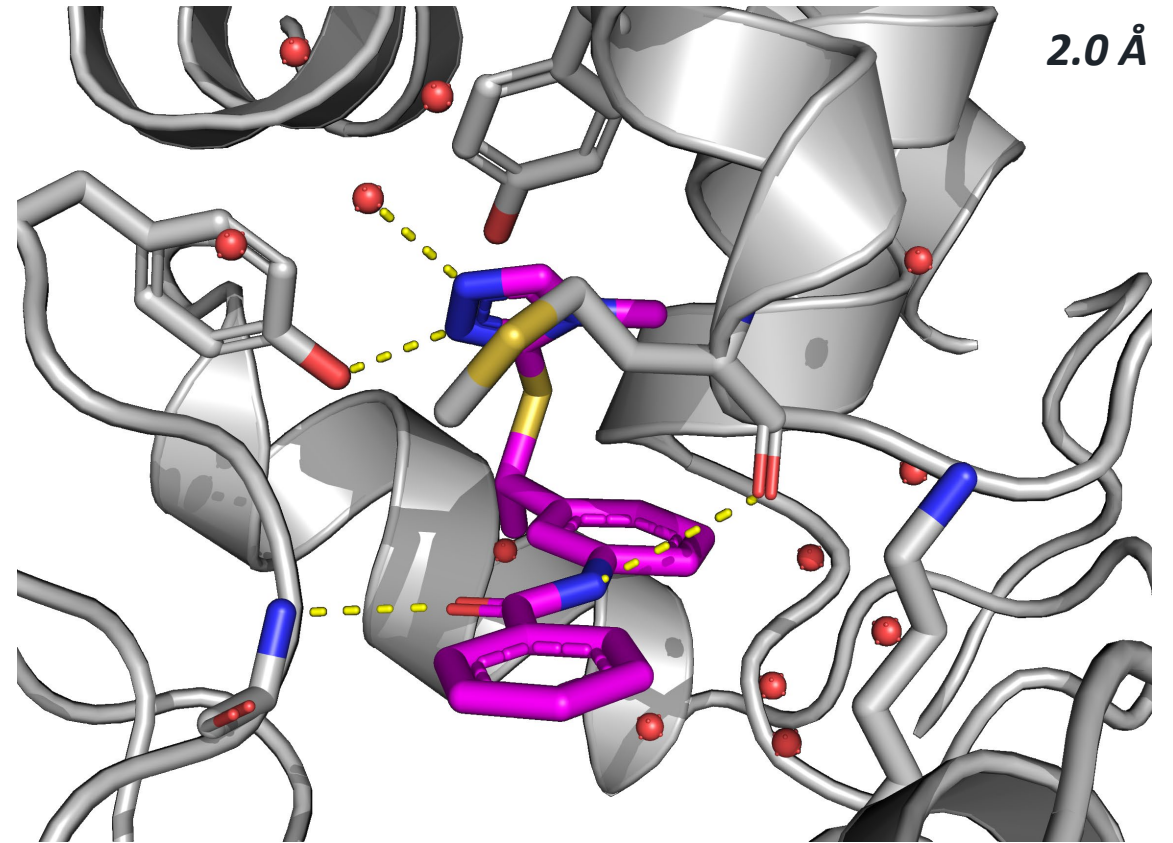
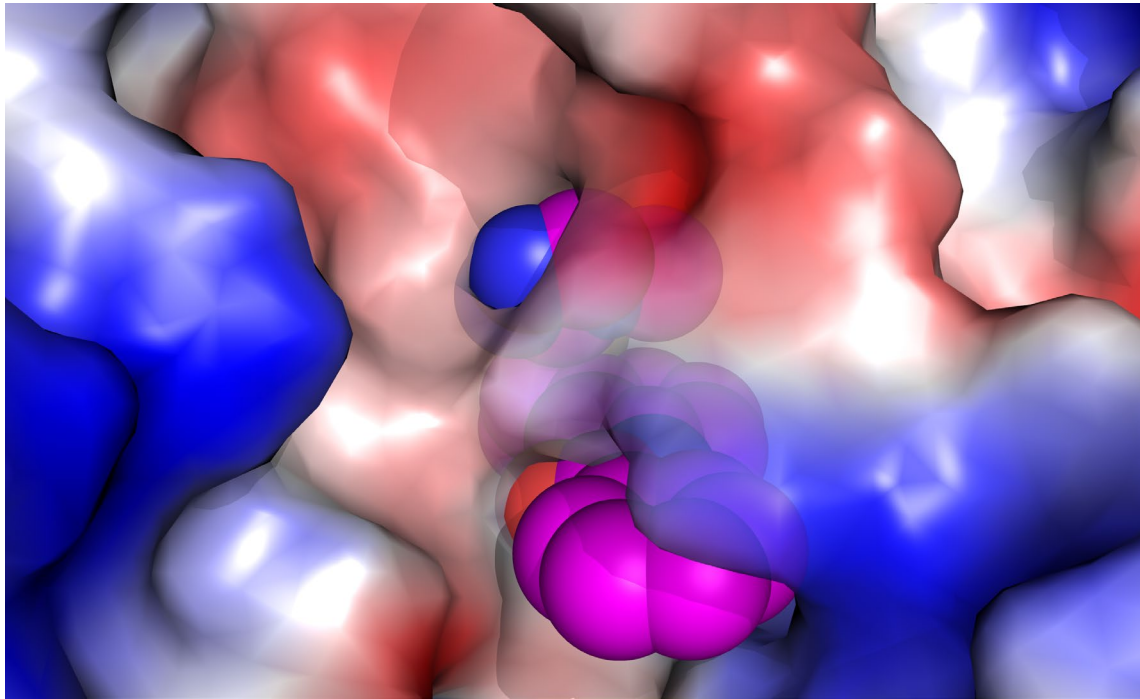
E2-Ub binding



# NRX-3 is an Intramolecular Glue

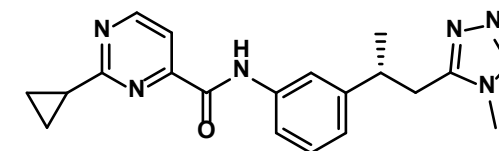
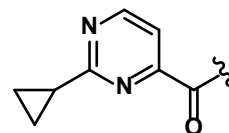
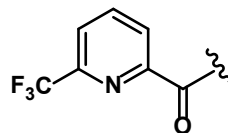
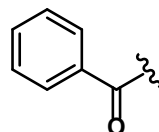
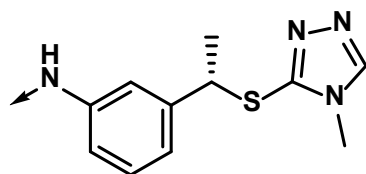


# Crystal Structure Confirms Binding Mode as Intramolecular Glue



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

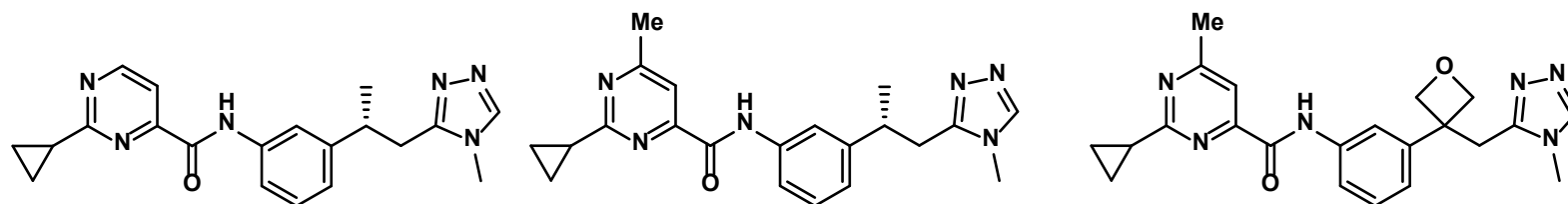
# Early SAR: Focus on Affinity and Properties



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

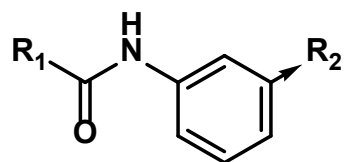


# Early SAR: Focus on Affinity and Properties



	NRX-6	NRX-7	NRX-8
E2-Ub: IC <sub>50</sub> (μM)	0.088	0.038	0.021
Ligand Efficiency	0.37	0.37	0.36
Cellular Substrate Ub IC <sub>50</sub> (μM)	1.7	0.78	0.79
Microsomes h/m Cl <sub>int</sub> (mL/min/kg)	30/73	-/67	7/26
Plasma stability m/r T <sub>1/2</sub> (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 <sub>7.4</sub>	1.9	2.4	1.7

# Complex SAR for Rat Plasma Stability



Rat Plasma  $T_{1/2}$  (min)  
**over/under** = 600 min



The SAR for rat plasma stability was not predictable by chemists

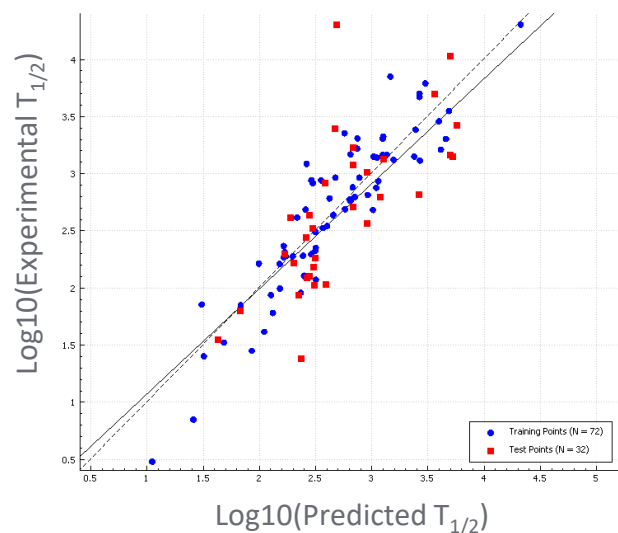
First observed with low recovery in PPB assays

# Machine Learning Model for Rat Plasma Stability

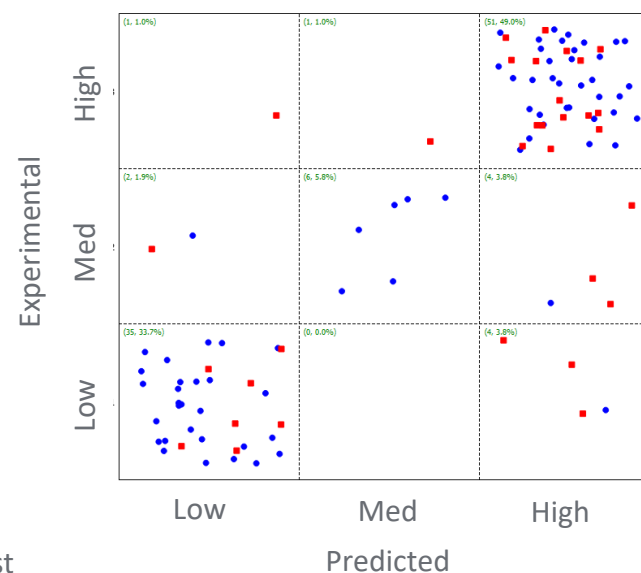
To assist with lead optimization, models were built based on the 104 experimental plasma stability data points available at the time.

Despite the low volume of data, both regression and classification models demonstrated high predictive power and provided key insights driving series progression

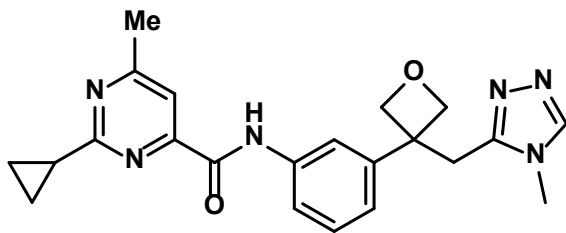
Regression ANN Model



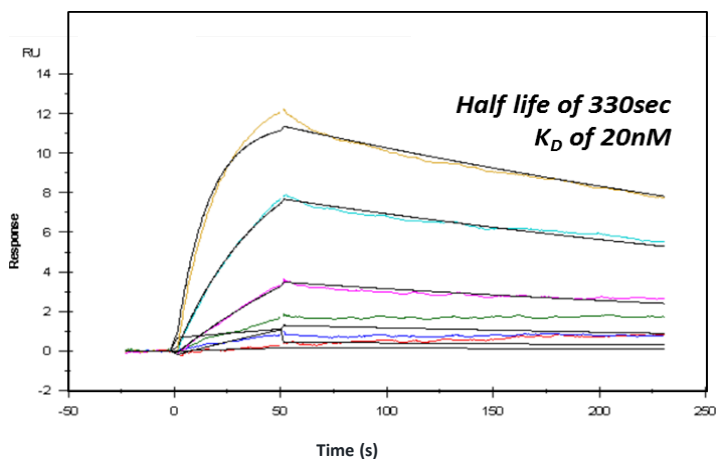
Classification SVM Model



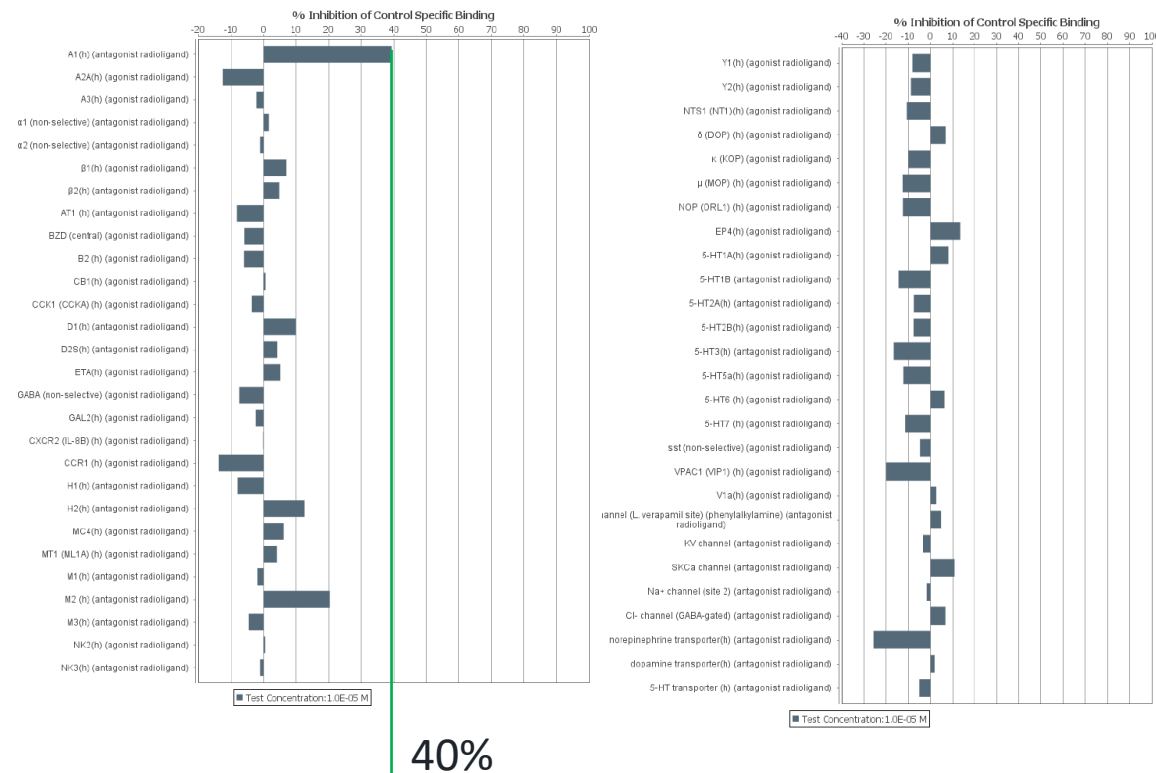
# NRX-8 Is a Specific Inhibitor of CBL-B



## CBL-B SPR characterization

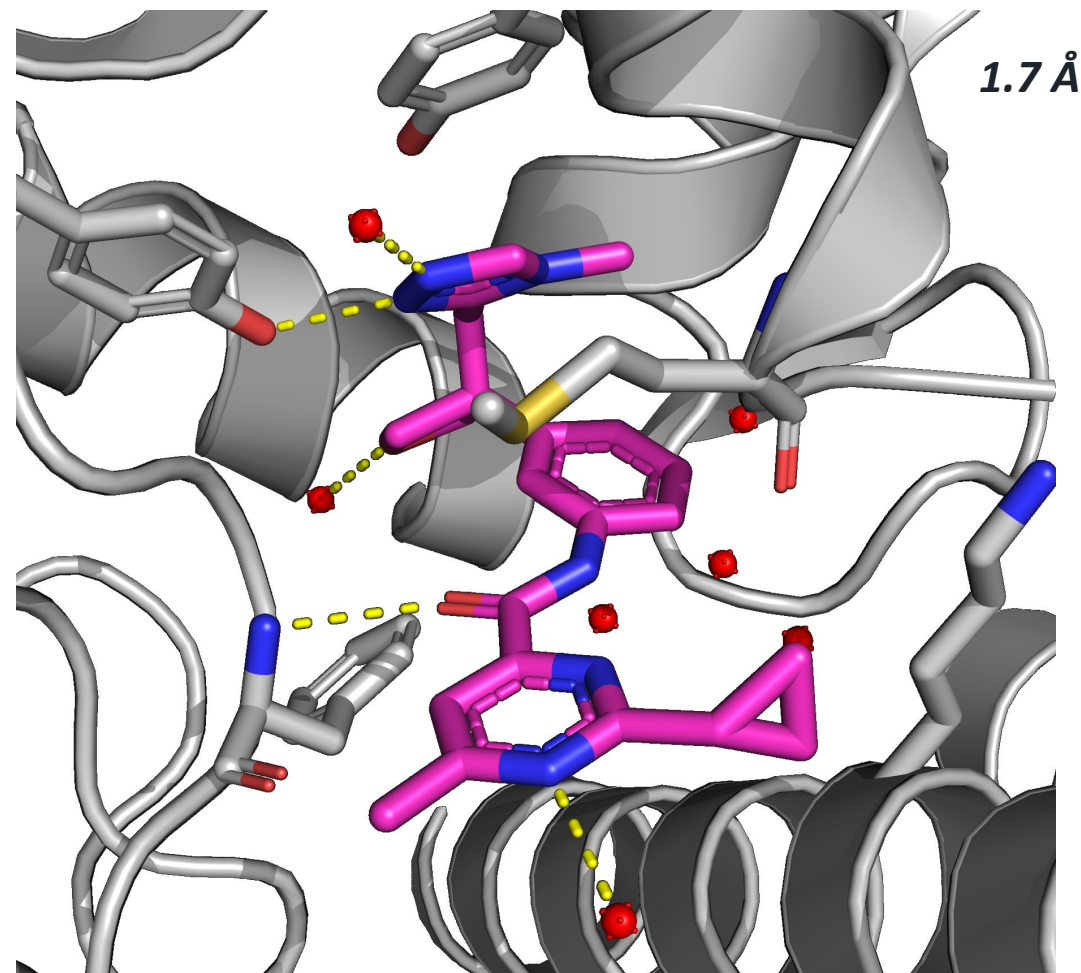
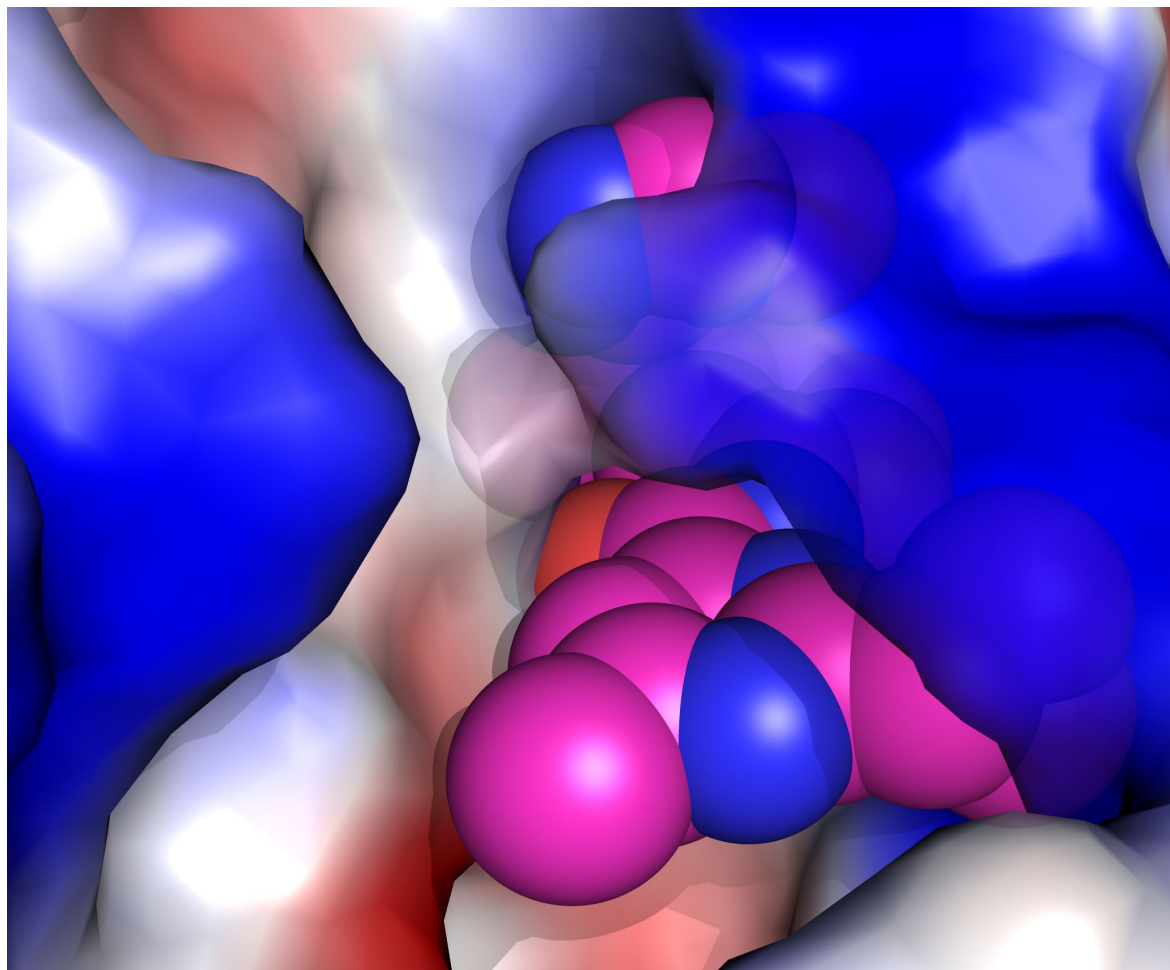


## CEREP Panel, <40% activity at 10 μM (N = 52)



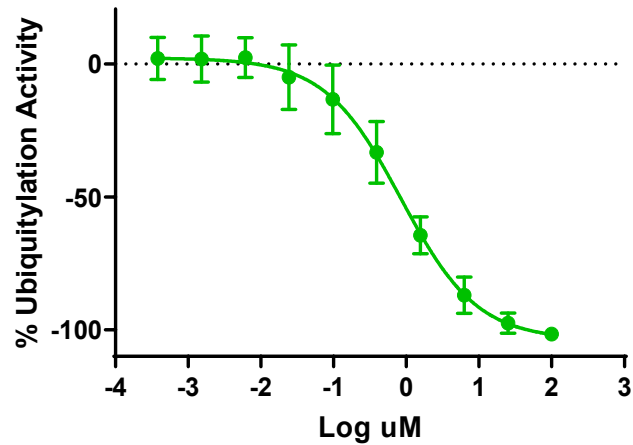
NRX-8 displays clean 1:1 binding stoichiometry with CBL-B and is clean in off-target screening.

# NRX-8 Maintains Original Hit Binding Mode

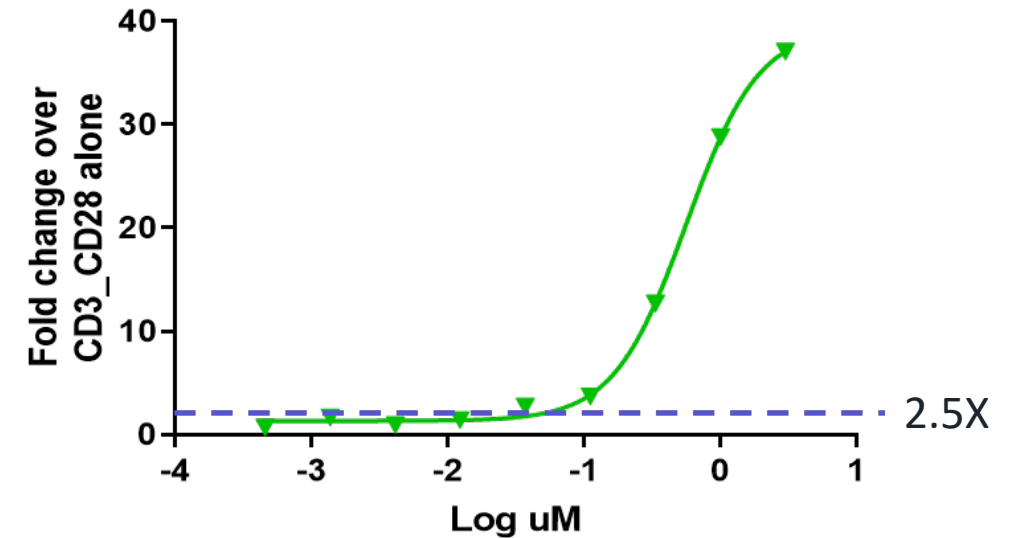


# NRX-8 Inhibits Substrate Ub and Stimulates IL-2 Induction

Substrate Ubiquitylation – BT20 cell line



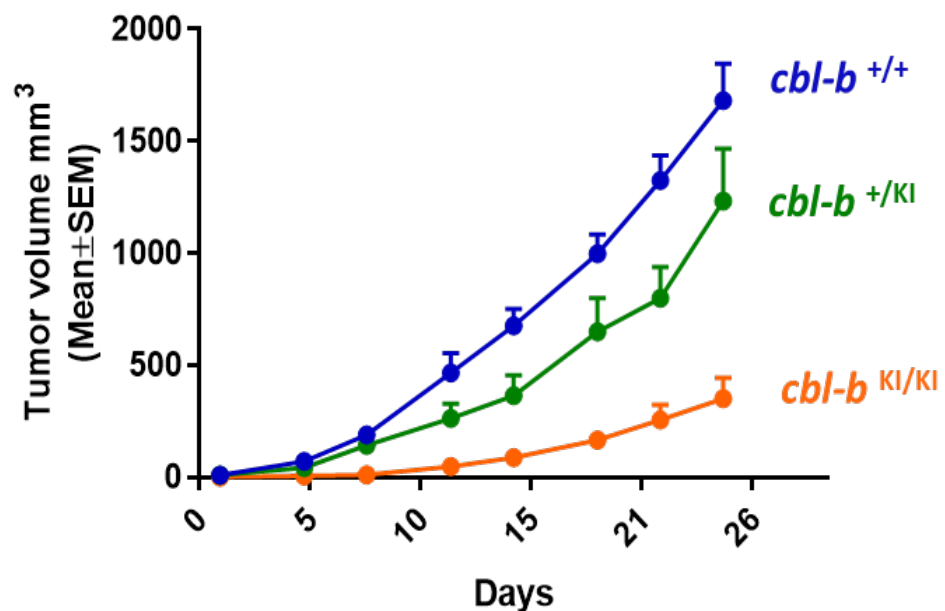
Human T cell assay – IL-2 production



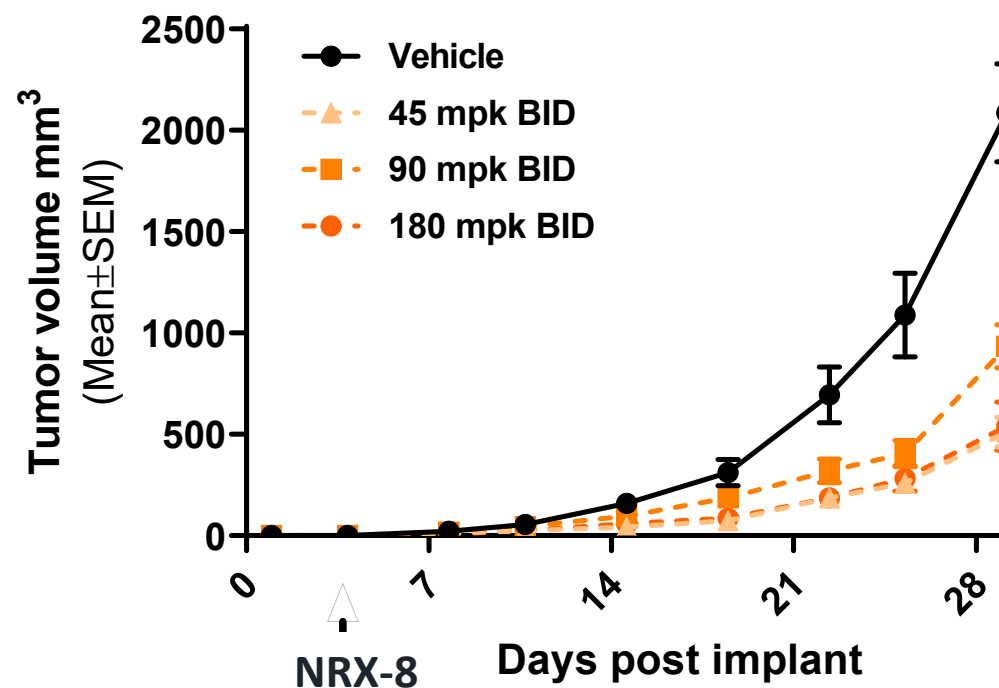
	NRX-8
IL-2 (2.5X over baseline response)	80 nM
Cellular Ubiquitylation of substrate (BT20 – MSD assay)	850 nM

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

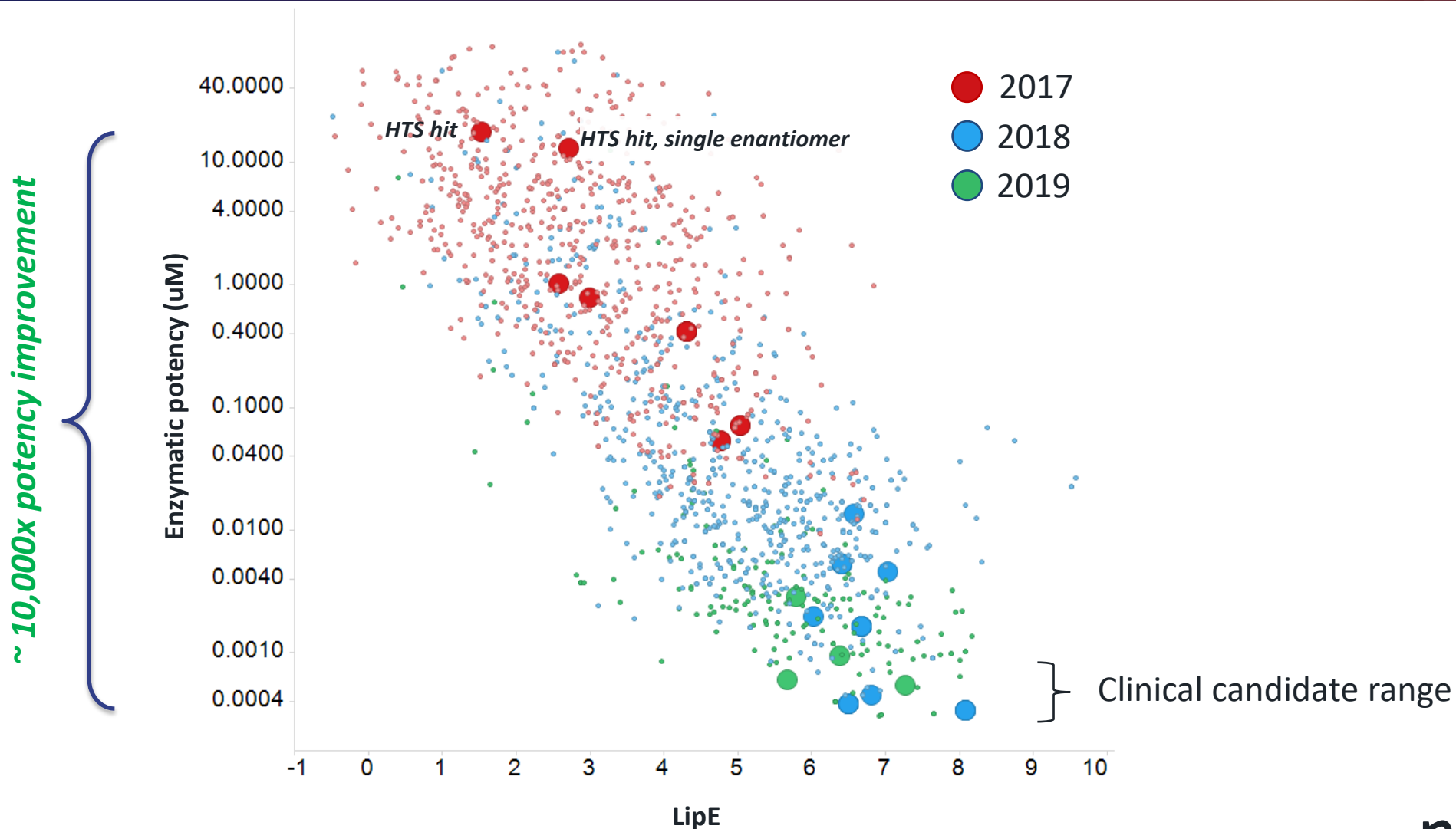
## Ligase-inactive *cbl-b* knock-in mice inhibit tumor growth in TC1 Syngeneic Model



## CT26 Syngeneic Model



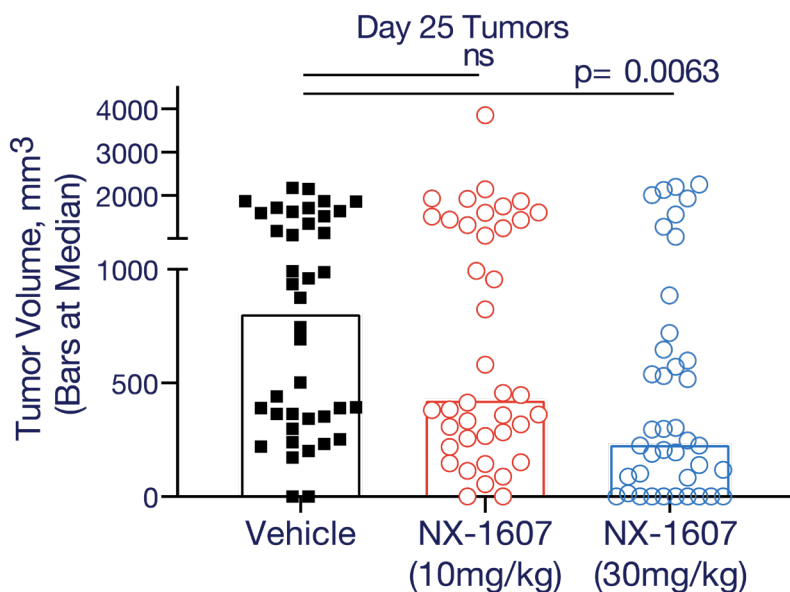
# Over 10,000-fold Enzymatic Potency Improvement Achieved While Improving Molecular Properties



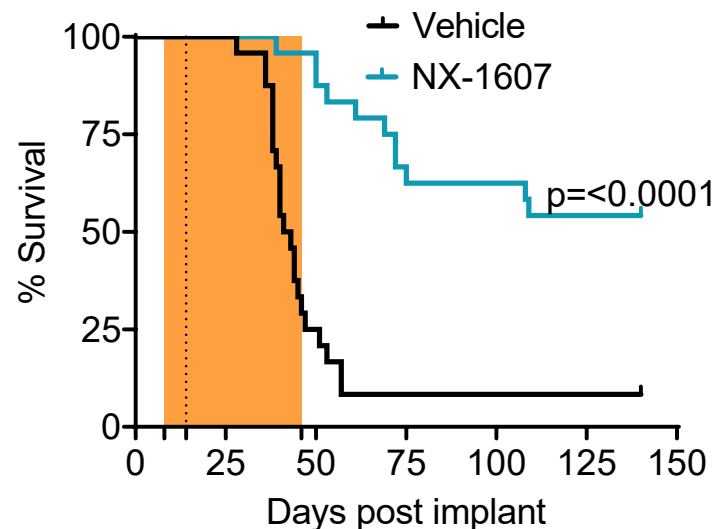


# Single-Agent NX-1607 Induces Antitumor Response in Multiple Models

**NX-1607  
Reduced Tumor Volume  
Colorectal**

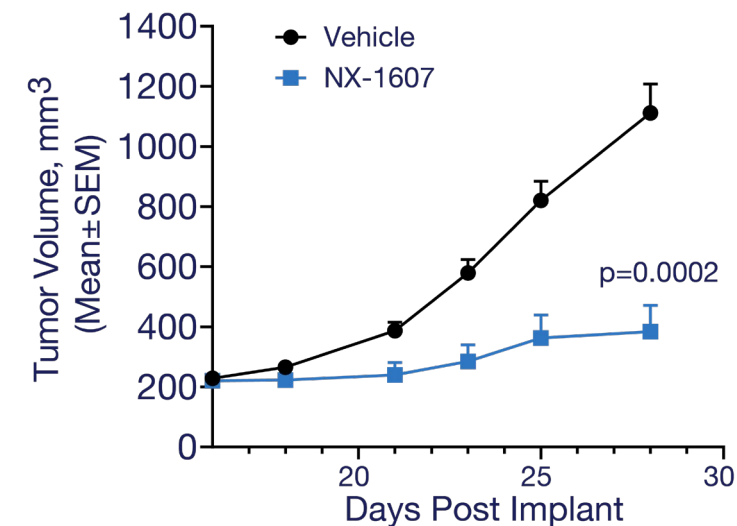


**NX-1607  
Prolonged Survival  
Triple-Negative Breast**



NX-1607 30 mg/kg day 7 to 46

**NX-1607  
Reduced Tumor Volume  
B Cell Lymphoma**



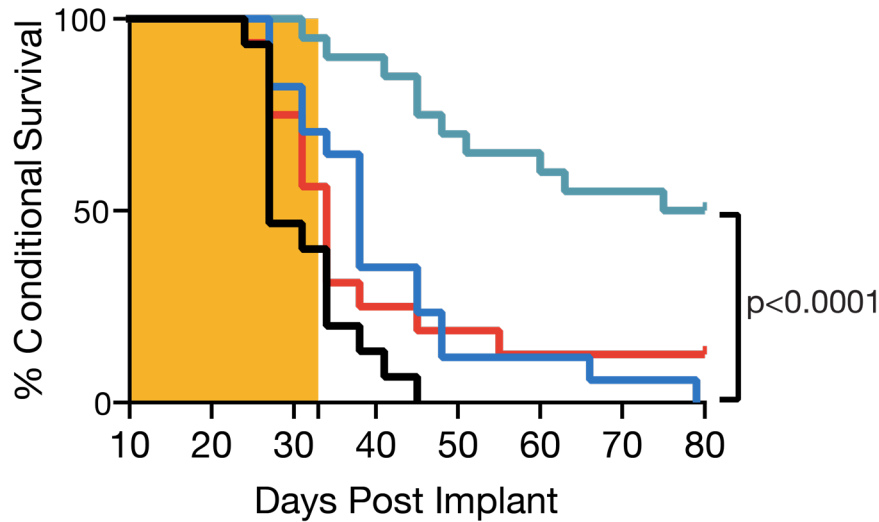
NX-1607 30 mg/kg day 16 to 28

Shaded area indicates dosing period

# NX-1607 and Anti-PD-1 Synergize to Enhance Anti-tumor Effects and Survival of Mice in Multiple Tumor Models

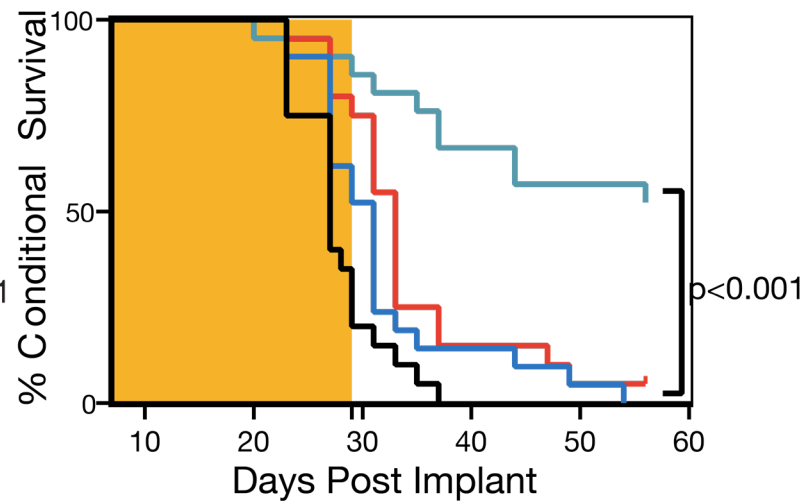
## Colorectal (CT26)

Long-Term Survival



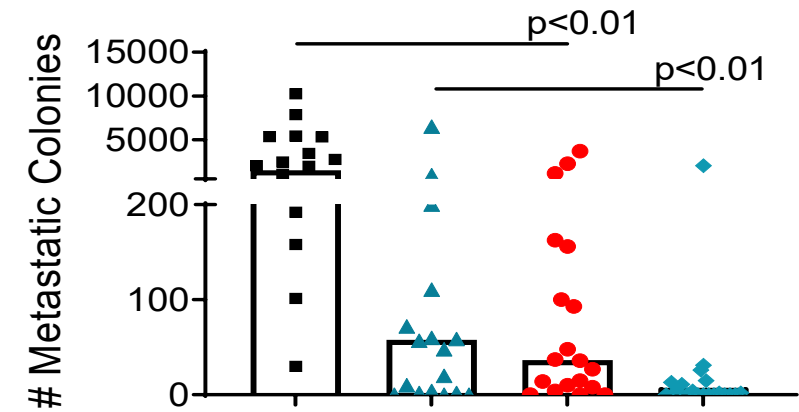
## Colorectal (MC38)

Long-Term Survival



## Triple-Negative Breast (4T1)

Day 28 4T1 Lung Metastases



■ Vehicle ▲ NX-1607 ● anti-PD-1 ◆ NX-1607+anti-PD-1

Shaded area indicates dosing period: NX-1607 (30 mg/kg, PO daily) and anti-PD-1 twice a week at 10 mg/kg dosing period

# Summary

- CBL-B regulates T, B, and NK cell activation
- Multiple screening approaches afforded validated binders to CBL-B
- Plasma instability may be an under-appreciated liability for amide-containing compounds
- Pharmacological inhibition of CBL-B recapitulates the anti-tumor effects of the genetic model of ligase inhibition
- NRX-8 specifically binds to CBL-B and 'glues' the protein in a closed state, preventing phosphorylation and E2-Ub binding
- Dosing of NRX-8 (45 mg/kg BID) inhibits tumor growth in mice
- Further optimization resulted in NX-1607 with sub-nM affinity and optimal in vivo anti-tumor activity
- Phase 1 clinical trial of NX-1607 in relapsed or refractory tumors is currently ongoing

# Thank you

Nurix Therapeutics

