nurix

Leader in Targeted Protein Modulation

Discovery and Optimization of CBL-B Inhibitors

ACS Fall Meeting

Chicago, IL

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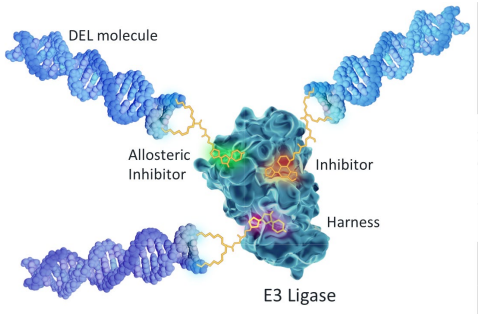
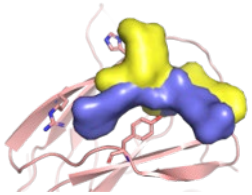
Nurix's DELigase Protein Modulation Discovery Platform

DEL Discovery



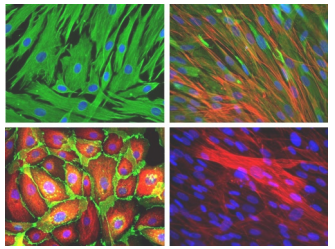
> 5 billion drug-like compounds that can be easily screened against hundreds of proteins to identify starting points therapeutic discovery

Rational and Empirical Chemistry



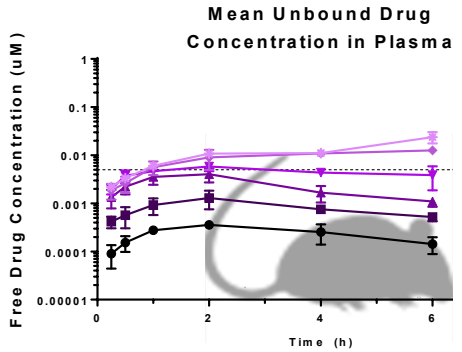
Structure Based Drug Design combined with chemistry automation enables broad exploration of lead-like chemical space for each program

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	**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				

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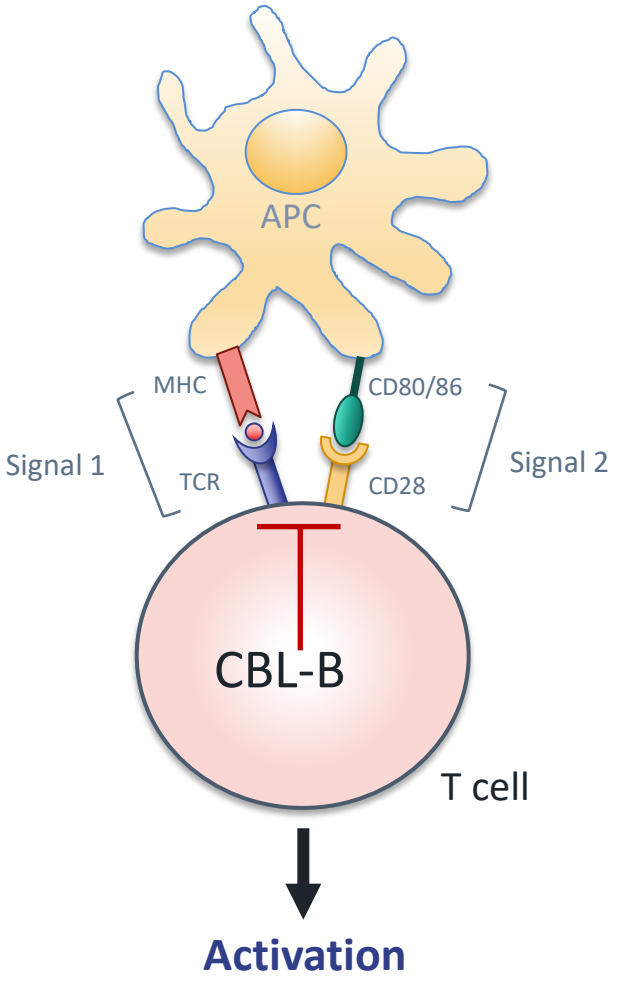
Gwenn Hansen
Cristiana Guiducci

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

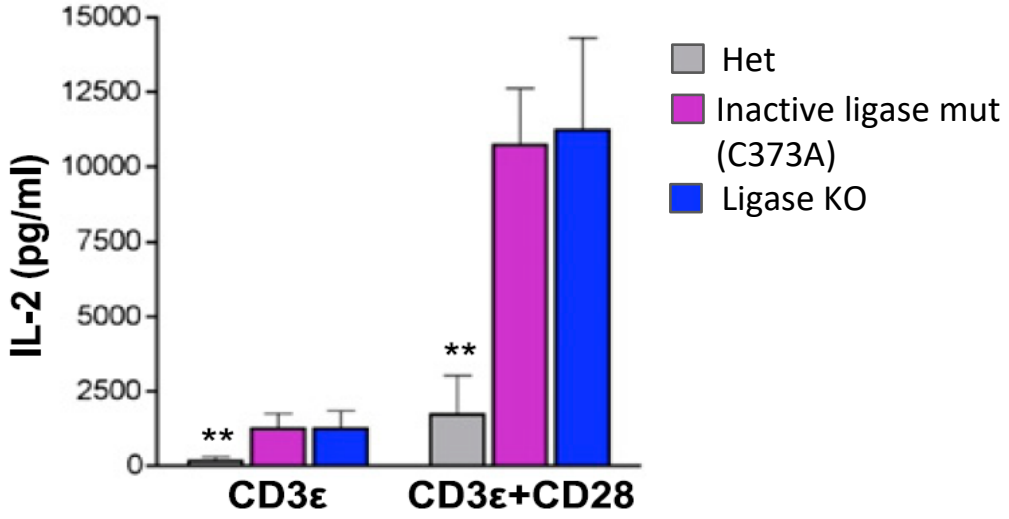
- IL-2 production
- Proliferation
- Central memory phenotype
- Anti-tumor activity
- Threshold of activation
- T cell exhaustion

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.

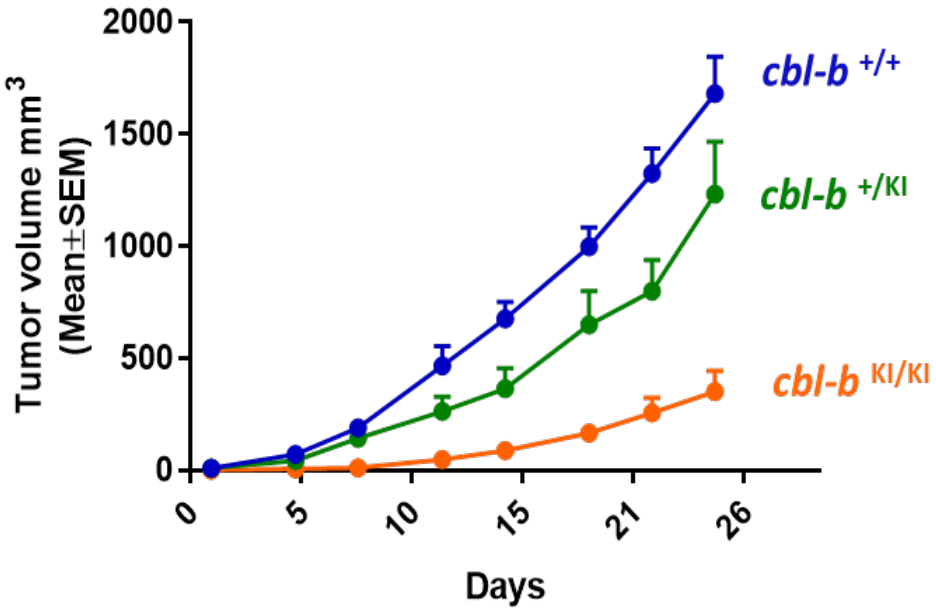
IL-2 secretion in KO and ligase inactive T cells *ex vivo*



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

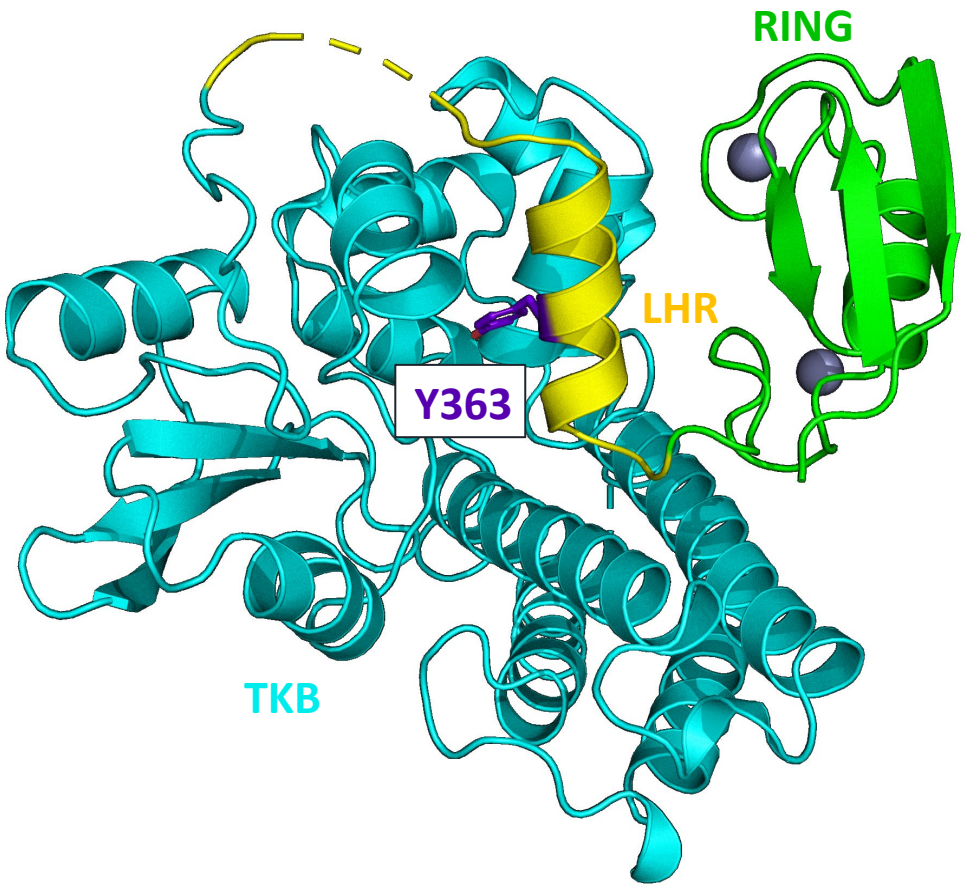
Ligase-dead or KO exhibit enhanced and equivalent response to either single- or double stimulation

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



Nurix Data

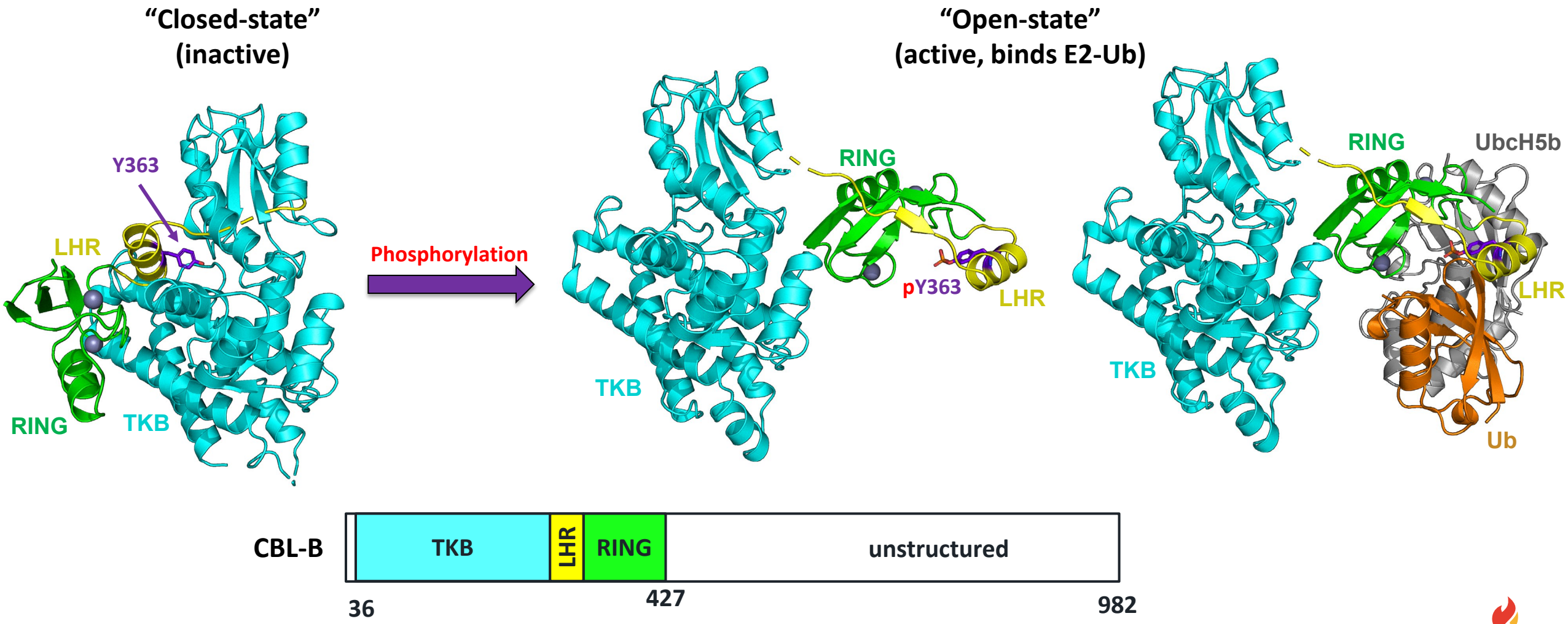
Inactive CBL-B is Autoinhibited



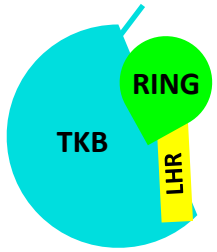
- When Y363 of CBL-B is not phosphorylated, the helix of the LHR domain packs against the TKB domain
- Incapable of binding Ub-E2
- Phosphorylation of Y363 requires dissociation of LHR-RING from TKB

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

Active CBL-B Binds Ub-loaded E2 Ligases

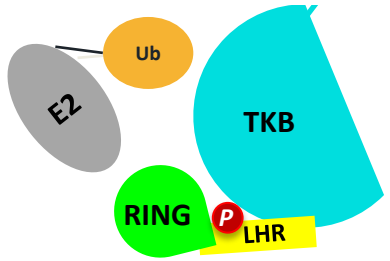


Multiple Lead-Finding Approaches Afforded CBL-B Binders

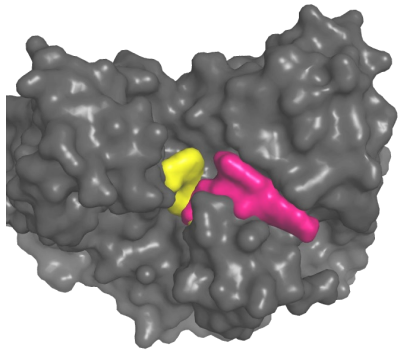


Biochemical Screening

SRC kinase



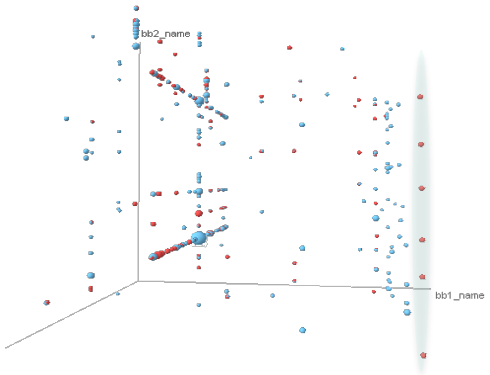
E2~Ub Binding Assay



Affinity Screening

DEL or Fragments

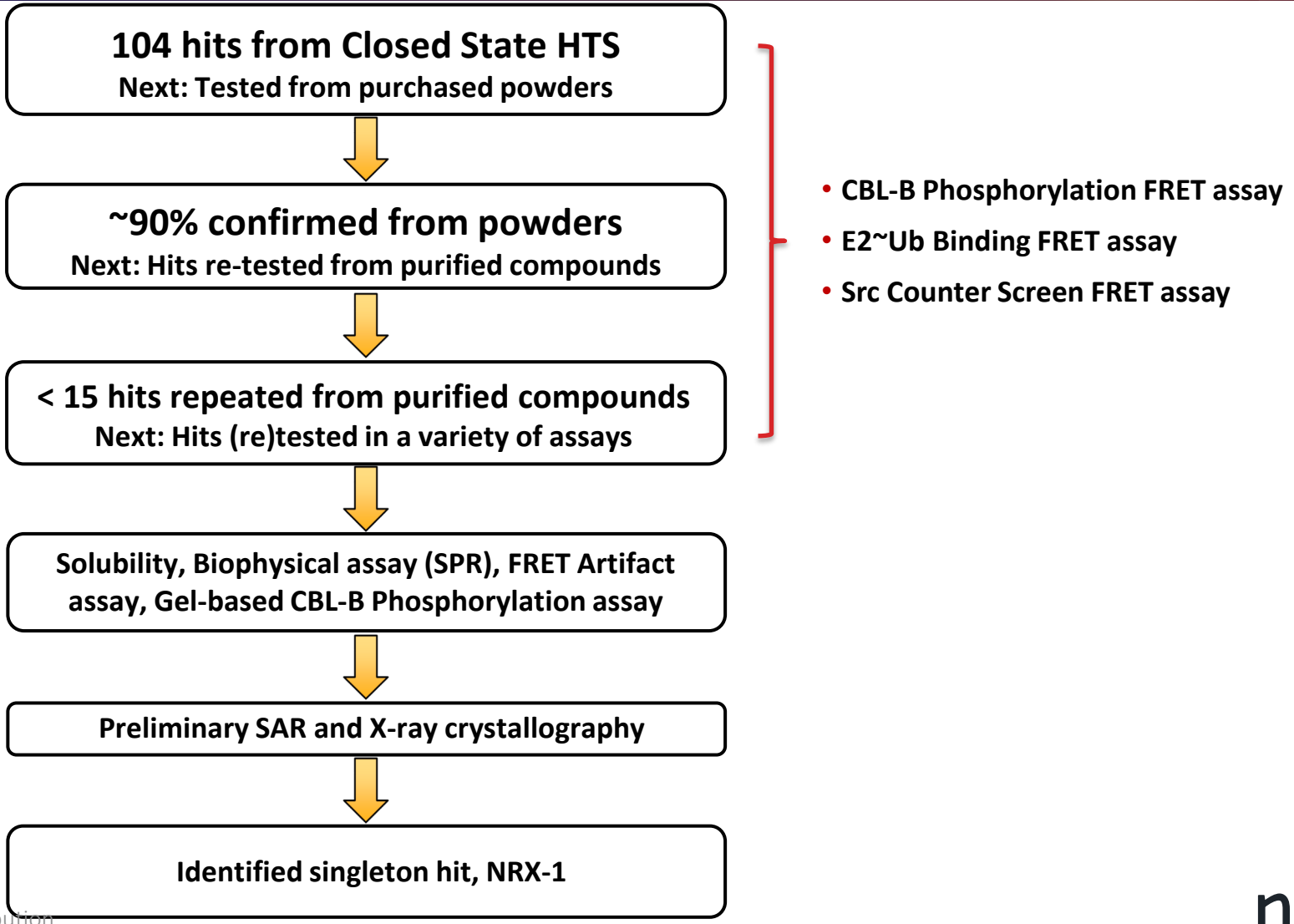
DEL Ligand Cube Plot



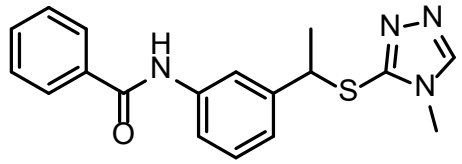
	HTS	DEL	Fragment
Lib size	300K	$1X10^9$	1600
# of Series	1	2	1
Hit Affinity	28 μM	2.4 μM	1800 μM
Hit mwt	338	537	211
Hit LE	0.27	0.22	0.33

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

CBL-B HTS Triage Revealed a Singleton Hit



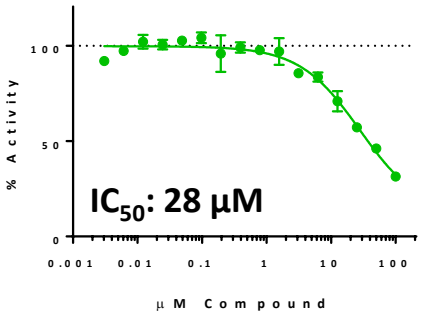
HTS Reveals a Singleton Hit



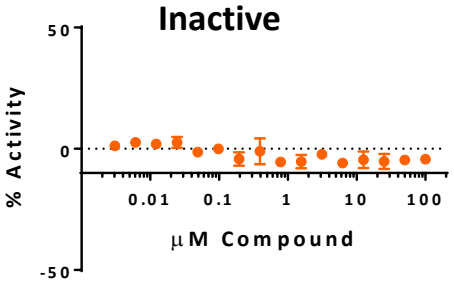
NRX-1
(racemic)

mwt = 338
K_{sol} 280 µM
cLogP 3.46
PSA 60

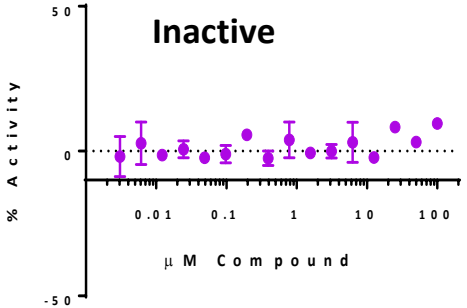
E2 binding FRET, Orthogonal



Src Counter Screen FRET

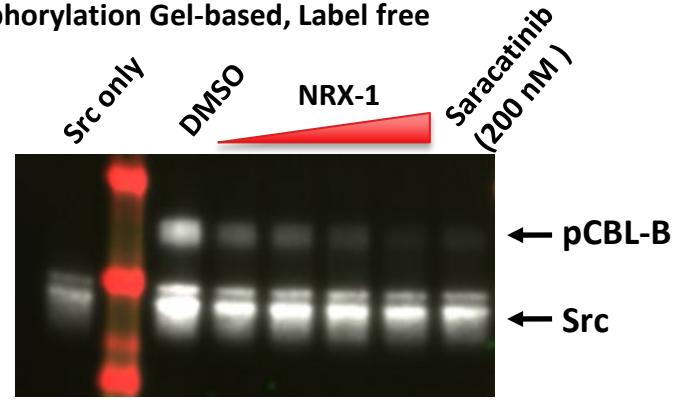


FRET Artifact Assay



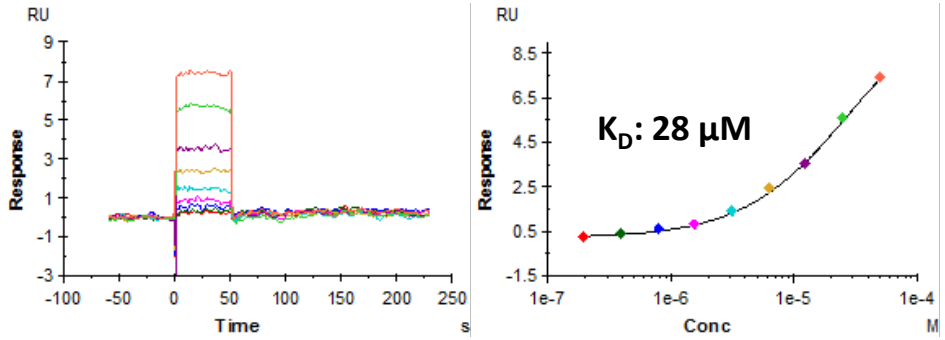
E2 binding assay and counter assays to examine Src activity or FRET artifacts indicate that **NRX-1** is a CBL-B inhibitor

CBL-B Phosphorylation Gel-based, Label free



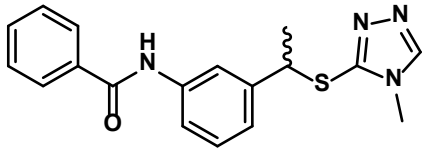
Compound titration (µM): 12.5, 25, 50, 100

Compound Binding to CBL-B by SPR

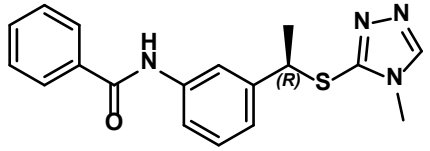


- SPR confirms **NRX-1** binding affinity and stoichiometry to CBL-B
- SPR binding affinity and biochemical potency in close agreement

NRX-3 is a Specific Inhibitor of CBL-B

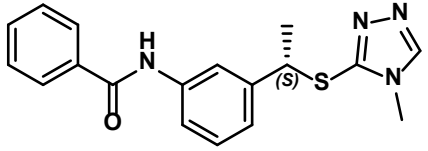


Chiral SFC



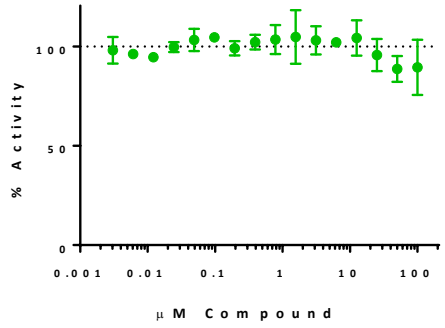
NRX-2

NRX-1
HTS Screening hit

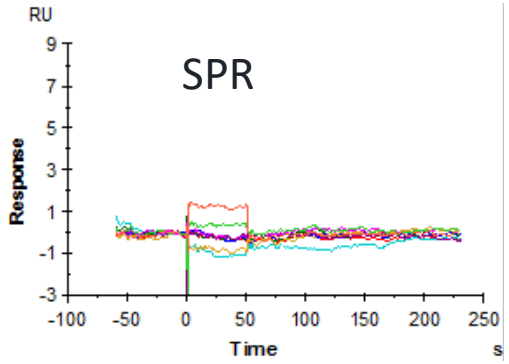


NRX-3
Resolved Screening hit
E2-Ub: IC_{50} = 12 µM
mwt = 338; LE = 0.29

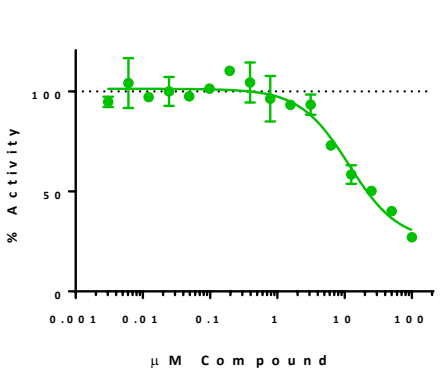
E2-Ub binding

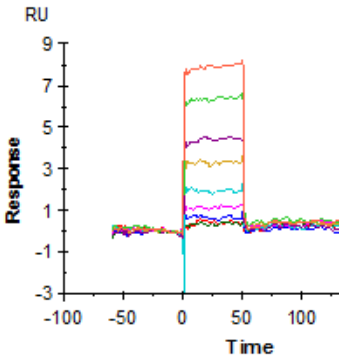


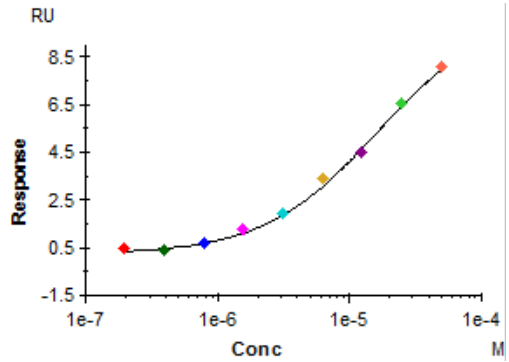
SPR



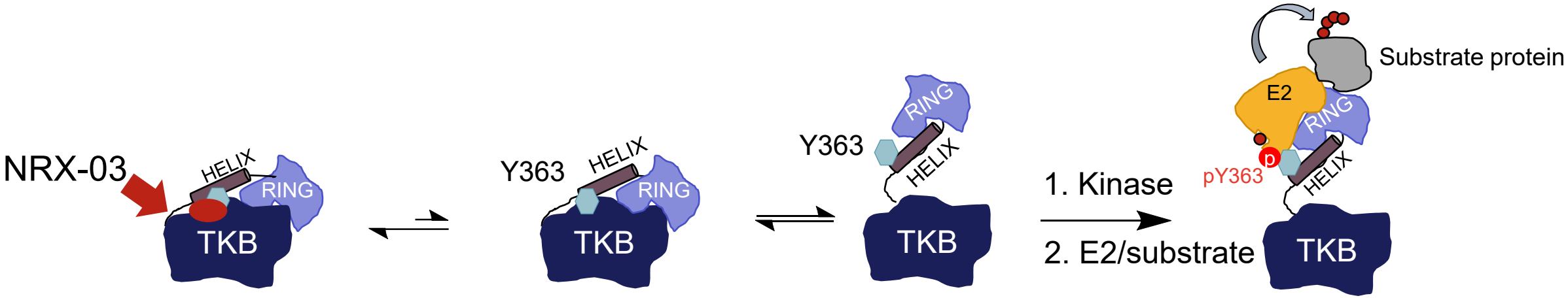
K_D: 16 µM







NRX-3 is an Intramolecular Glue



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

Closed State **INACTIVE**

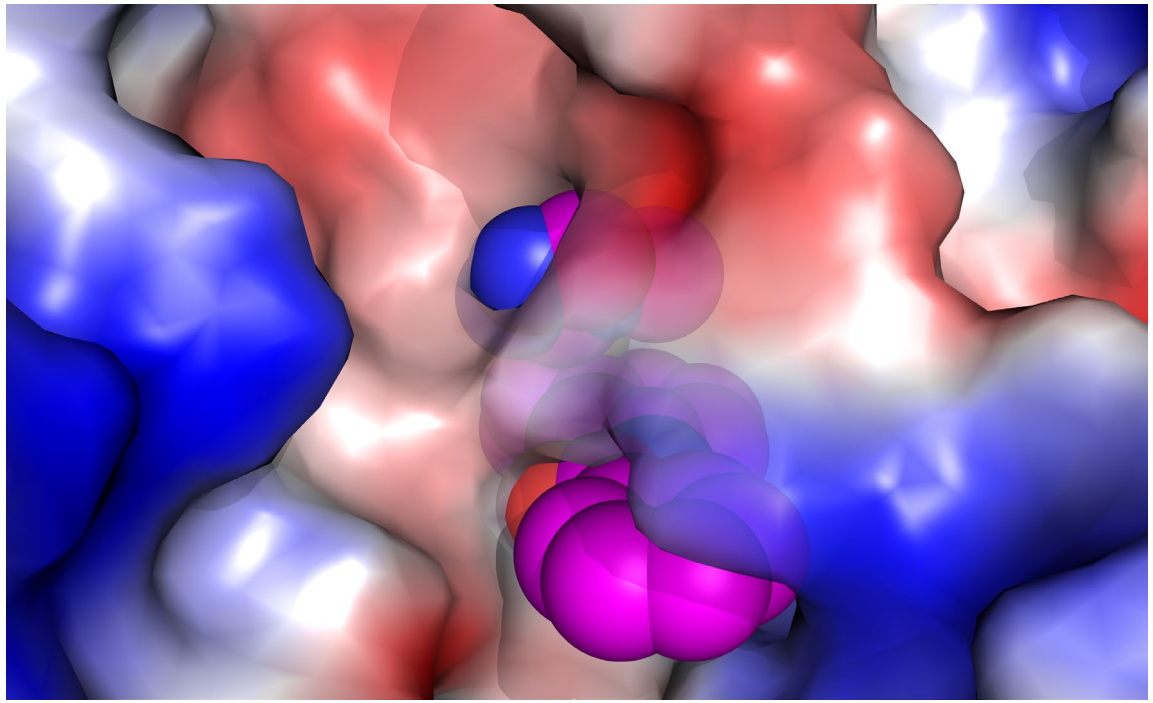
Opened State

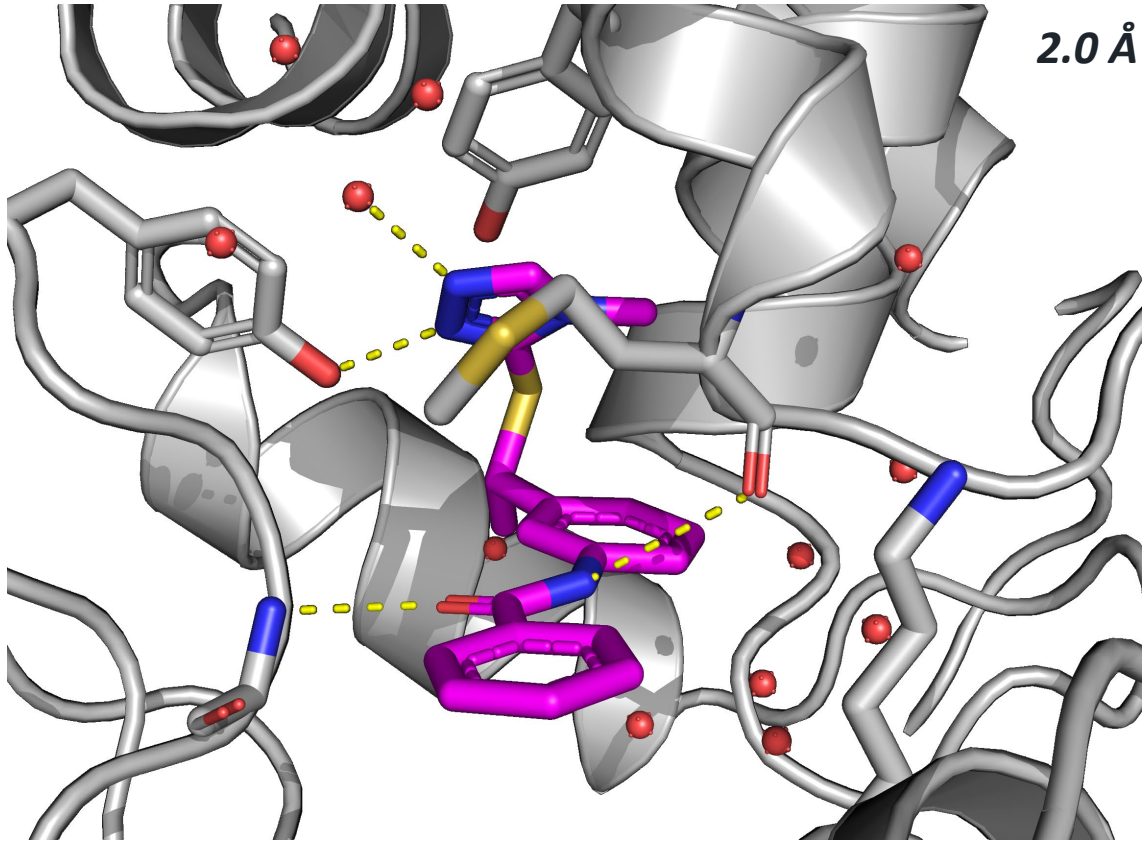
Phosphorylation locks CBL-B in the **ACTIVE** Conformation

Immune Response

Immune Response

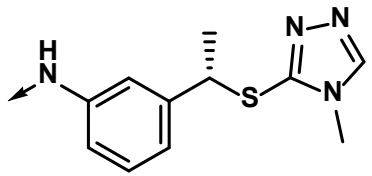
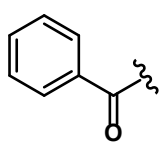
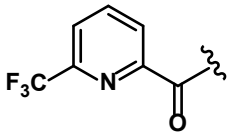
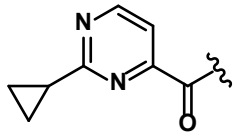
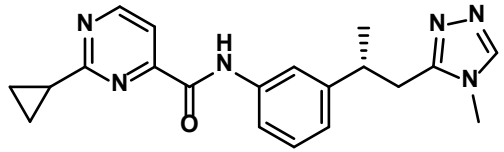
Crystal Structure Confirms Binding Mode as Intramolecular Glue





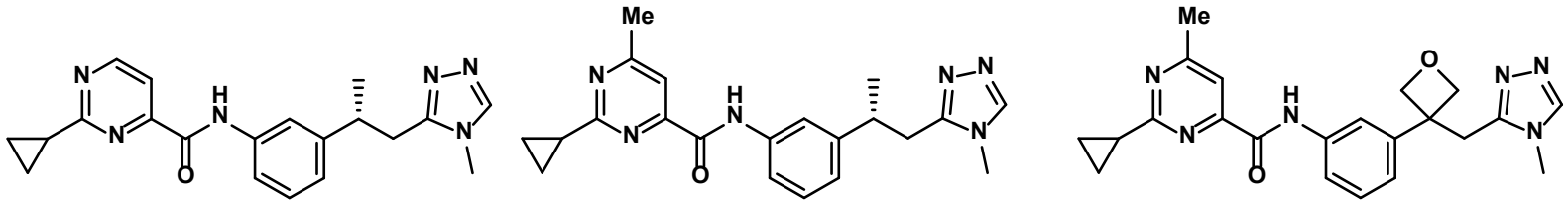
NRX-3 binds to closed-state CBL-B and prevents phosphorylation

Early SAR: Focus on Affinity and Properties

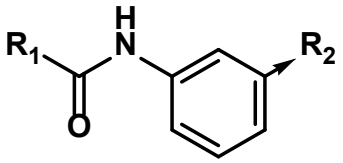
	NRX-3	NRX-4	NRX-5	NRX-6
E2-Ub: IC_{50} (μM)	12	0.23	0.092	0.088
Ligand Efficiency	0.29	0.33	0.36	0.37
Cellular Substrate Ub IC_{50} (μM)		7	3	1.7
Microsomes h/m Cl_{int} (mL/min/kg)		20/360	-/500	30/73
Plasma stability m/r $T_{1/2}$ (min)		-	140/-	280/-
Papp MDCK (MDR1) A→B/B→A ratio		26/1	33/1	9/6
Ksol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

Early SAR: Focus on Affinity and Properties

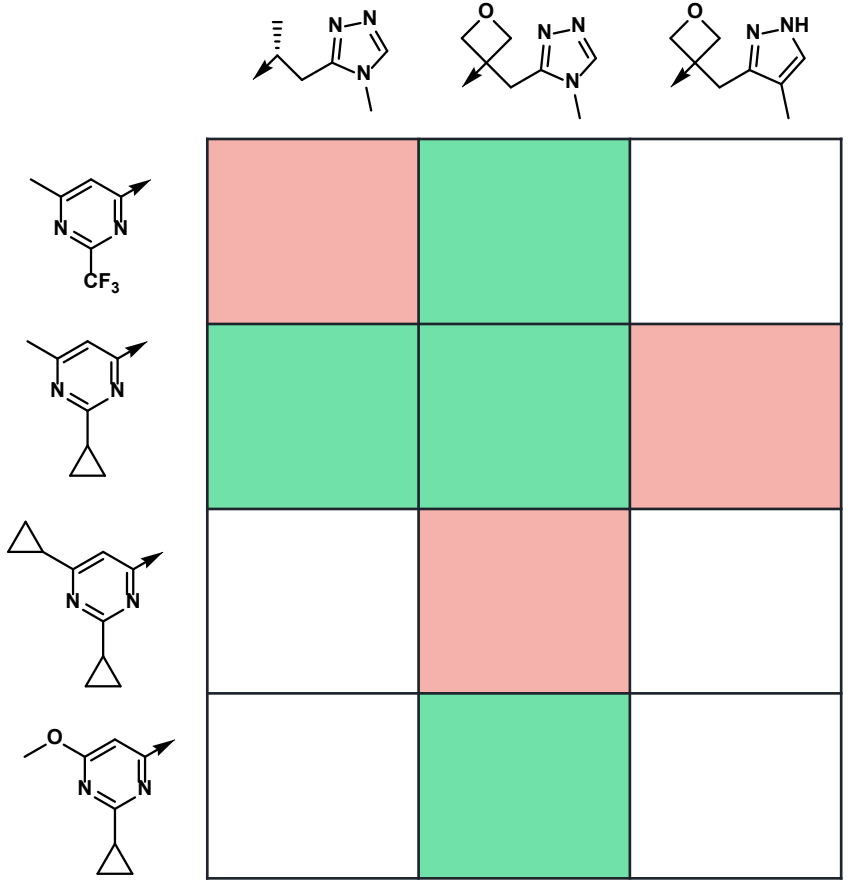


	NRX-6	NRX-7	NRX-8
E2-Ub: IC_{50} (μM)	**0.088**	**0.038**	**0.021**
Ligand Efficiency	**0.37**	**0.37**	**0.36**
Cellular Substrate Ub IC_{50} (μM)	**1.7**	**0.78**	**0.79**
Microsomes h/m Cl_{int} (mL/min/kg)	**30/73**	**-/67**	**7/26**
Plasma stability m/r $T_{1/2}$ (min)	**280/-**	**>1000/163**	**>1000/>1000**
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**

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

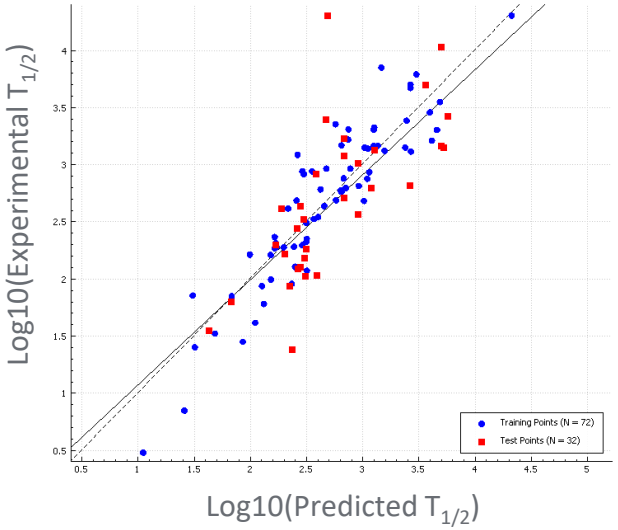
First observed with low recovery in PPB assays

Machine Learning Model for Rat Plasma Stability

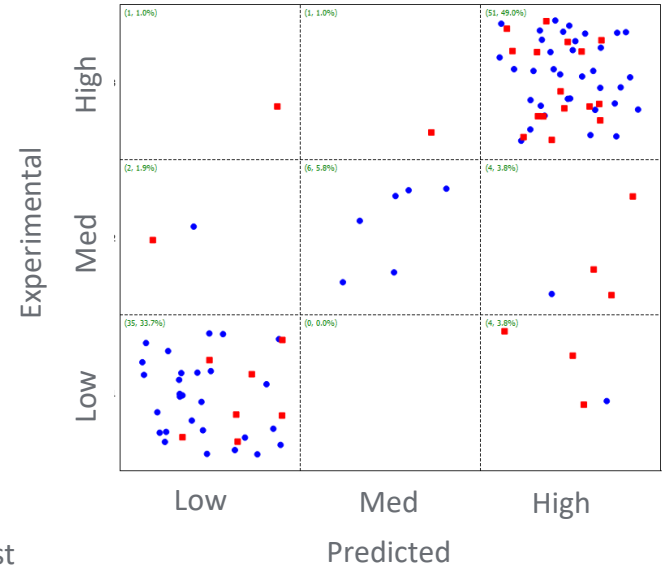
To assist with lead optimization, models were built based on the 104 experimental plasma stability data points available at the time.

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

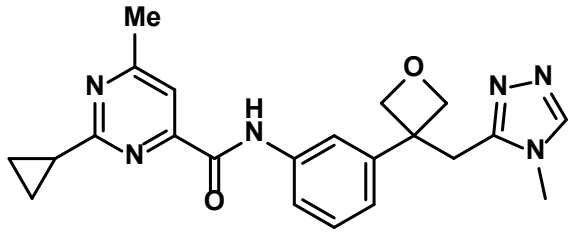
Regression ANN Model



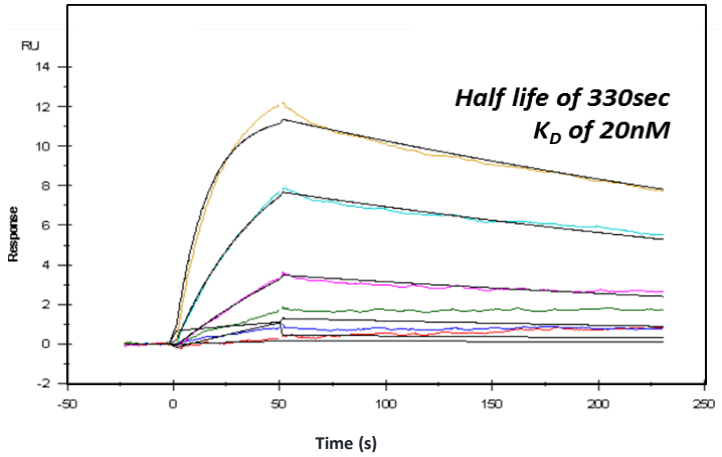
Classification SVM Model



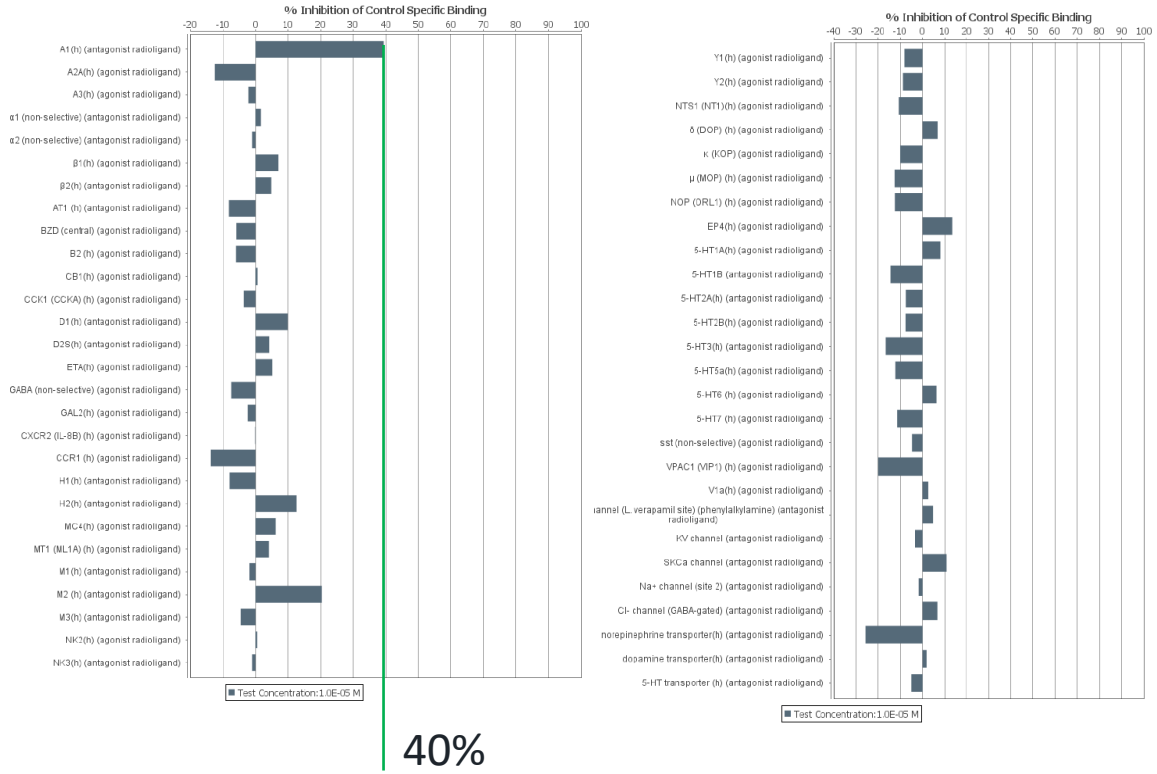
NRX-8 Is a Specific Inhibitor of CBL-B



CBL-B SPR characterization

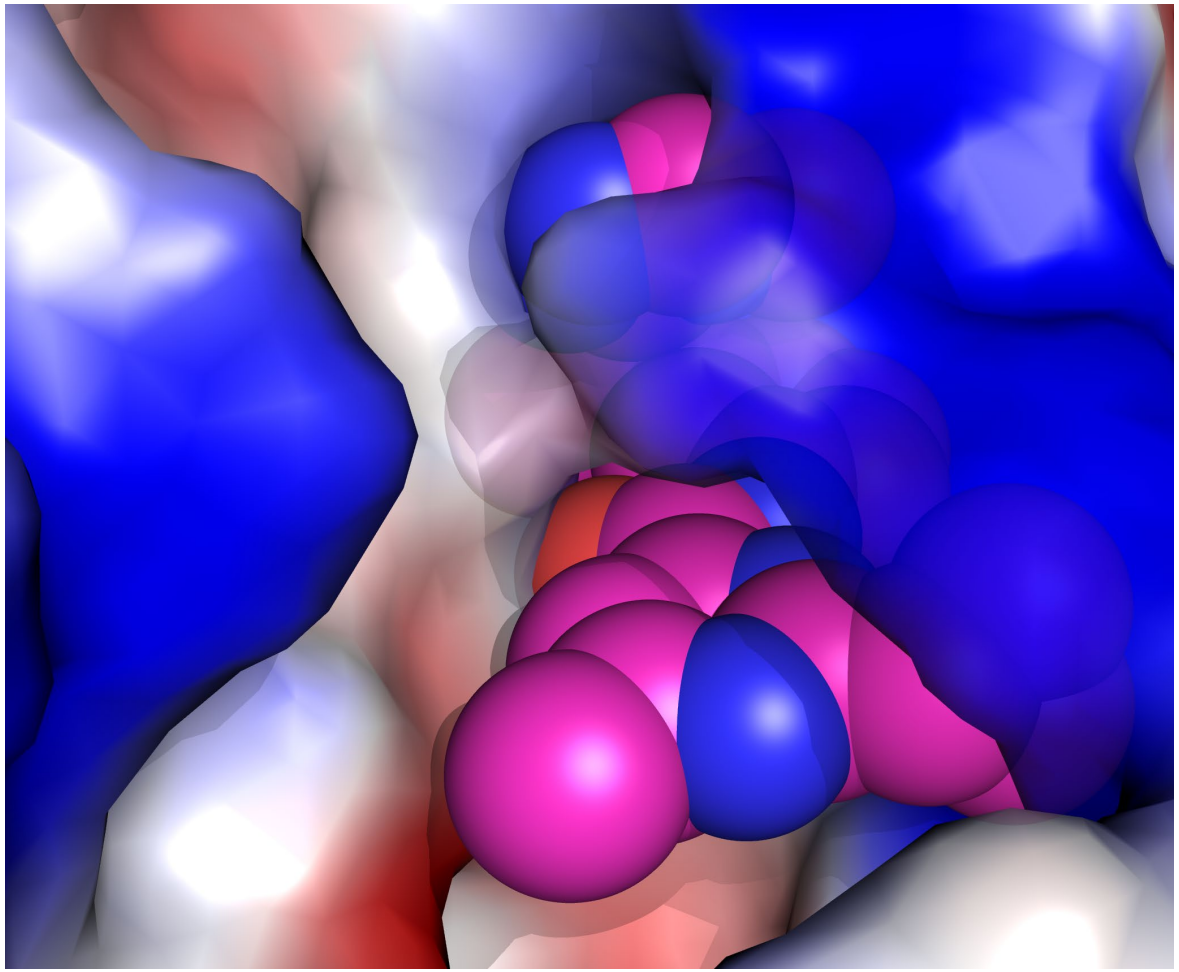


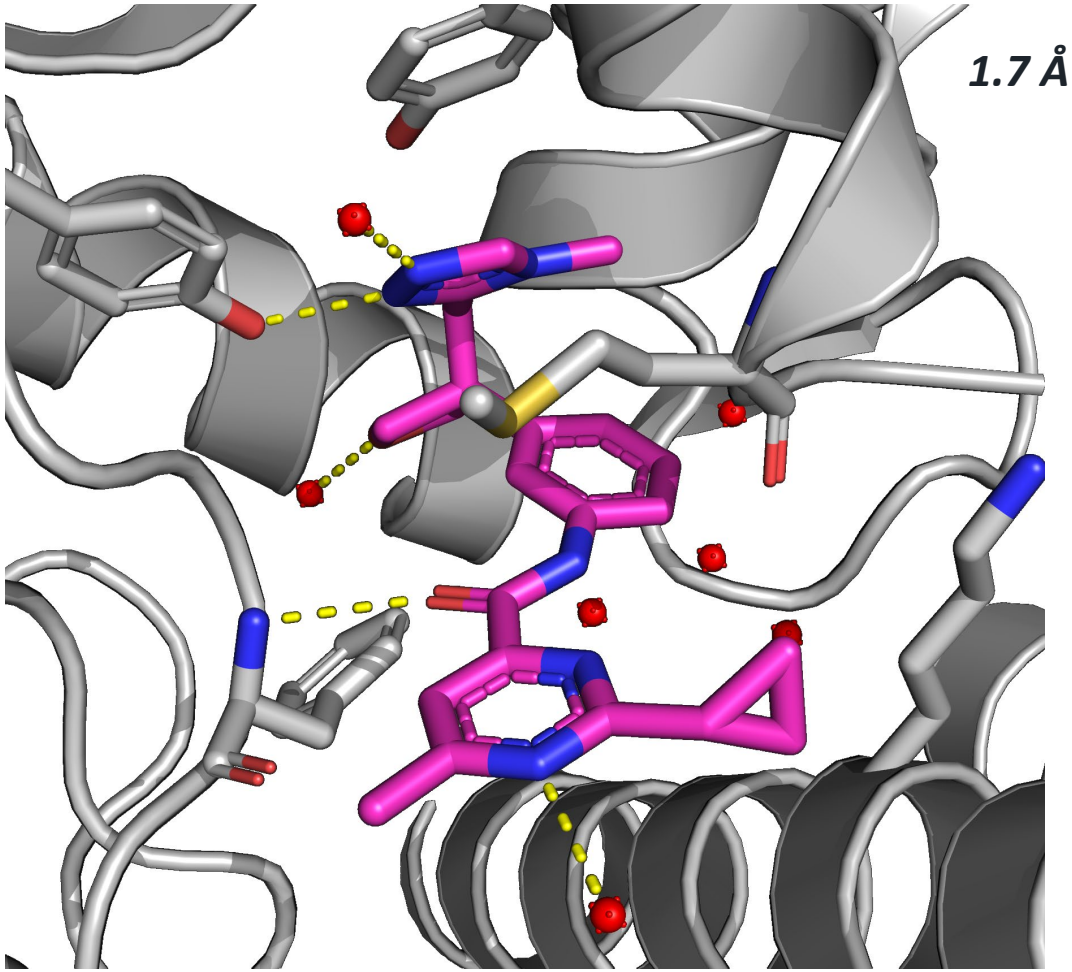
CEREP Panel, <40% activity at 10 μM (N = 52)



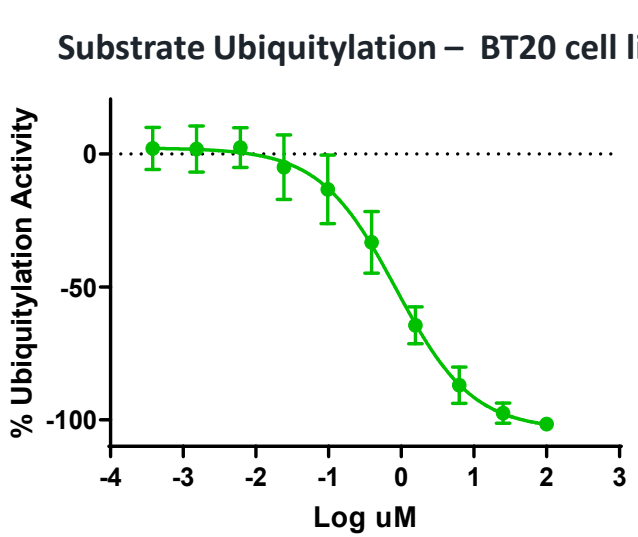
NRX-8 displays clean 1:1 binding stoichiometry with CBL-B and is clean in off-target screening.

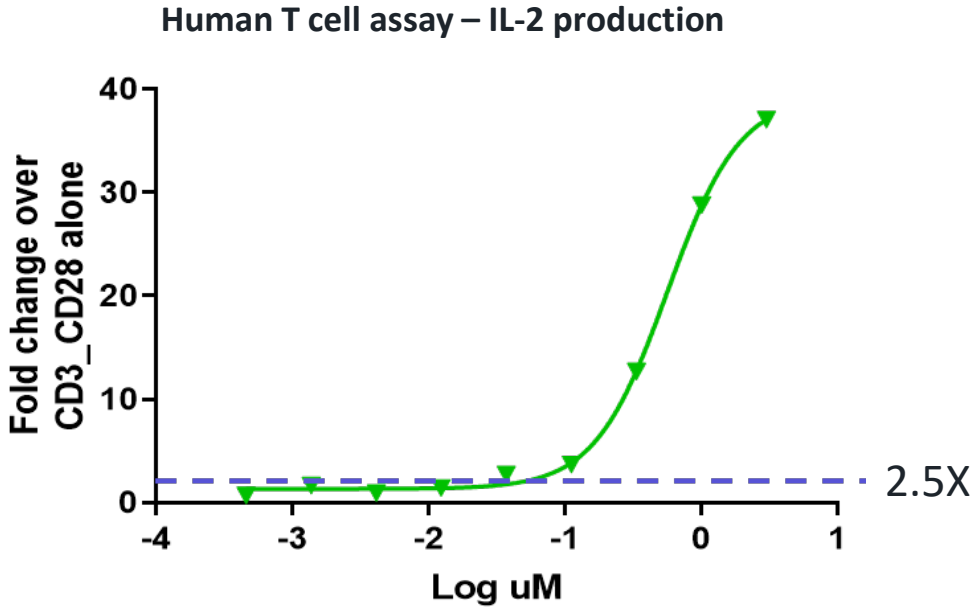
NRX-8 Maintains Original Hit Binding Mode





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

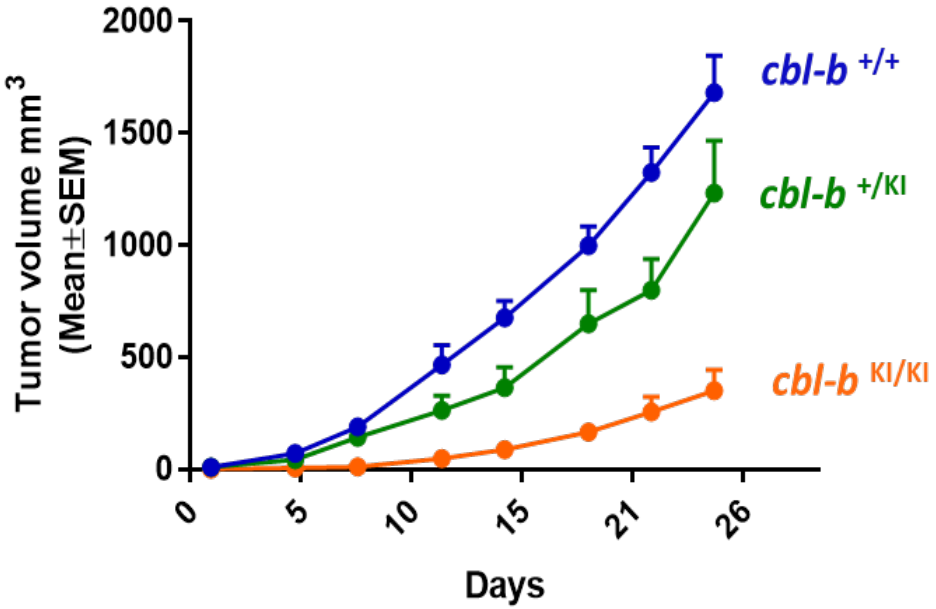




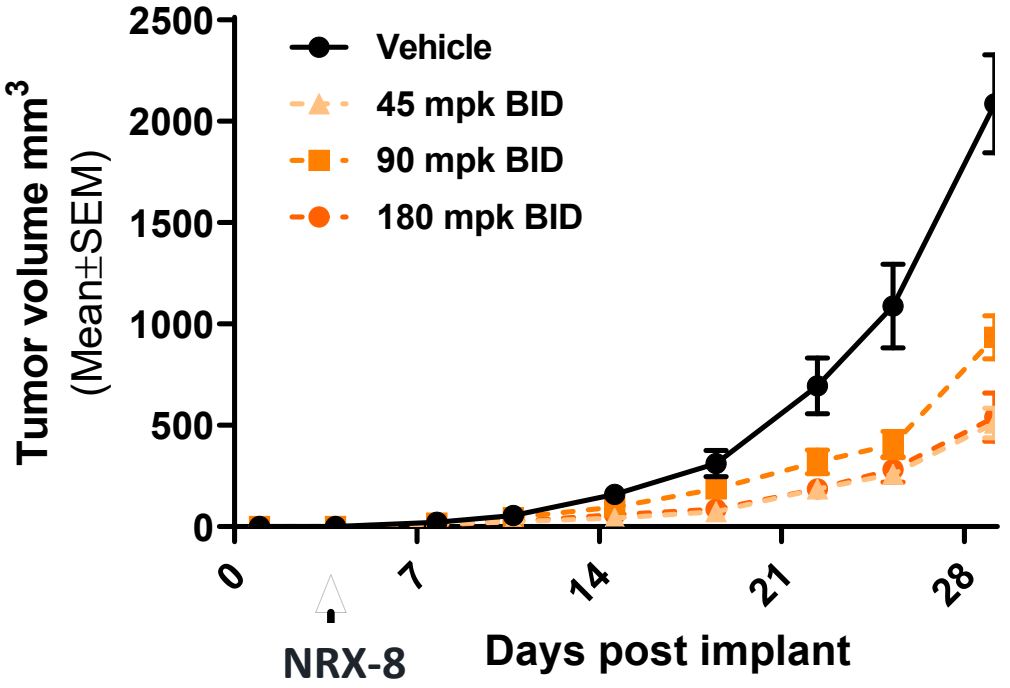
	NRX-8
IL-2 (2.5X over baseline response)	80 nM
Cellular Ubiquitylation of substrate (BT20 – MSD assay)	850 nM

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

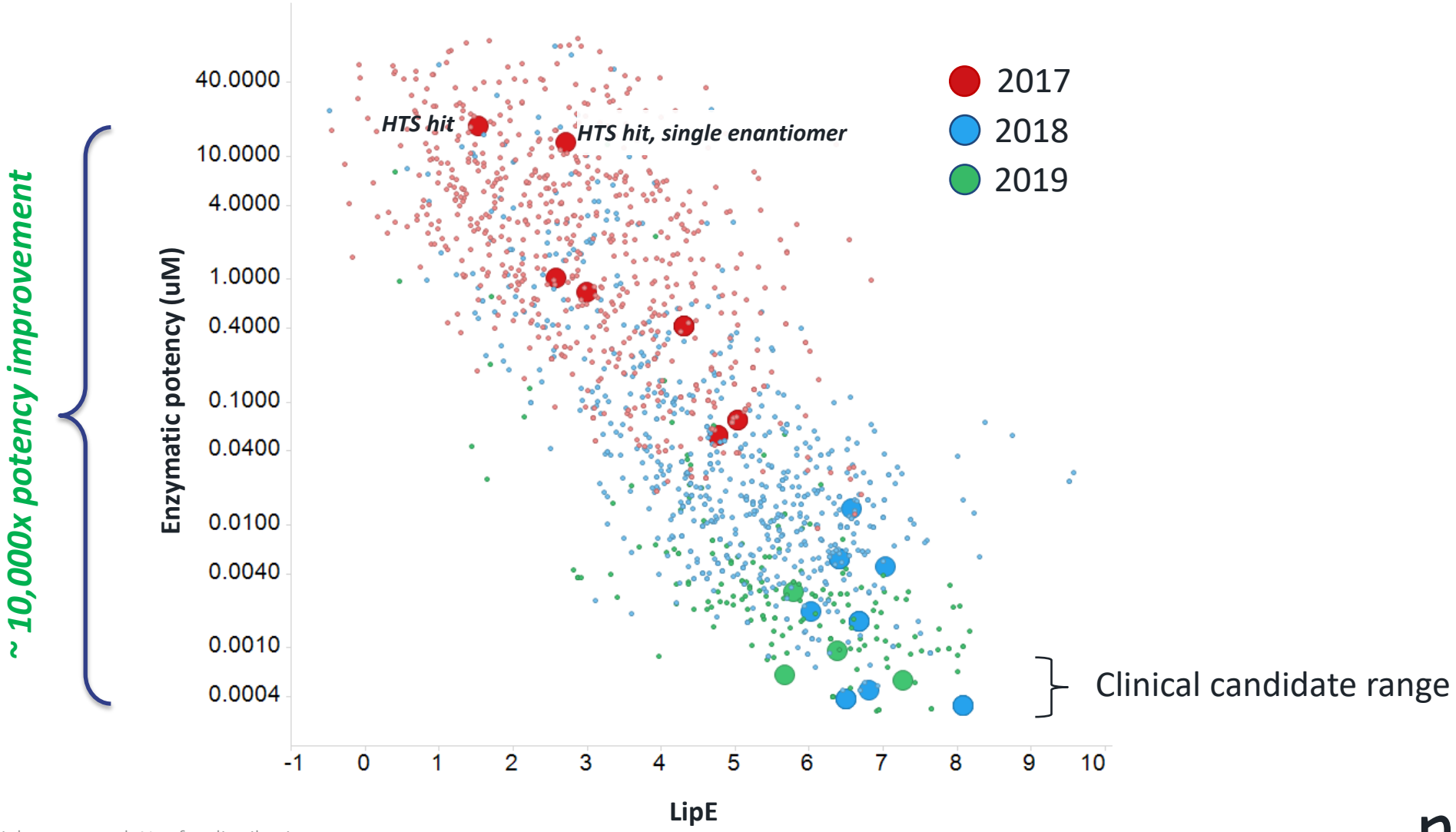
Ligase-inactive *cbl-b* knock-in mice inhibit tumor growth in TC1 Syngeneic Model



CT26 Syngeneic Model

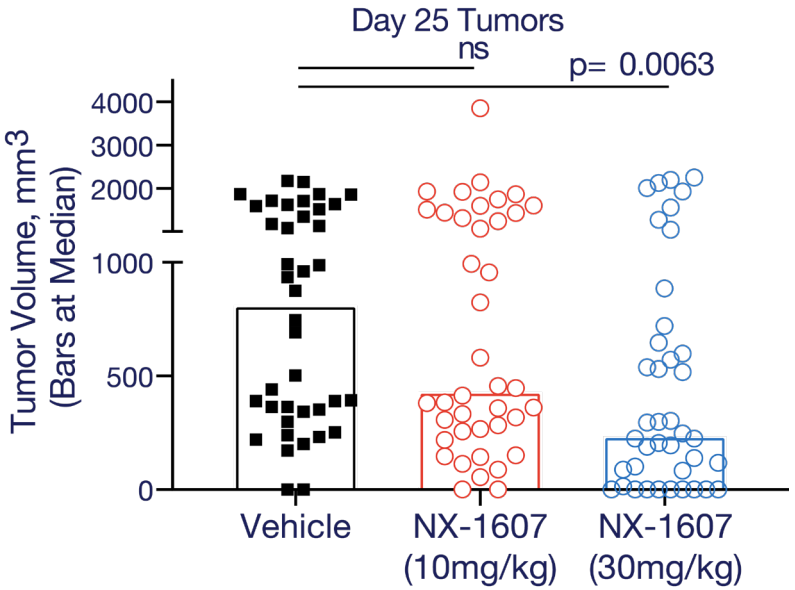


Over 10,000-fold Enzymatic Potency Improvement Achieved While Improving Molecular Properties

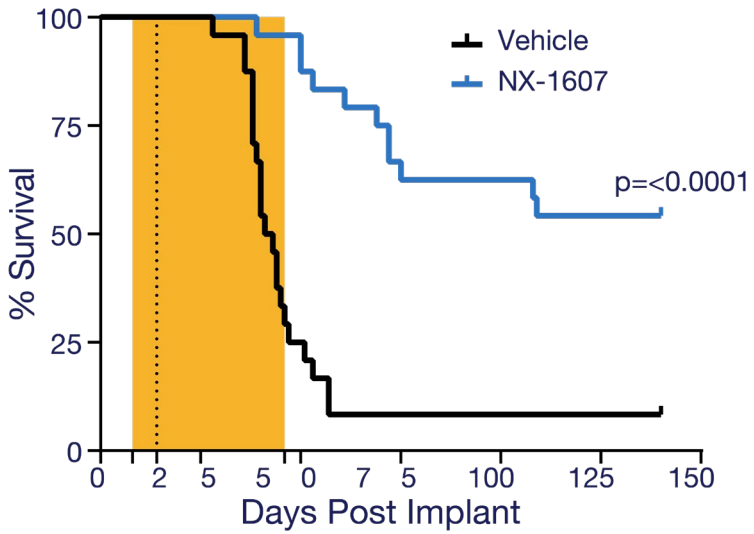


Single-Agent NX-1607 Induces Antitumor Response in Multiple Models

NX-1607
Reduced Tumor Volume
Colorectal

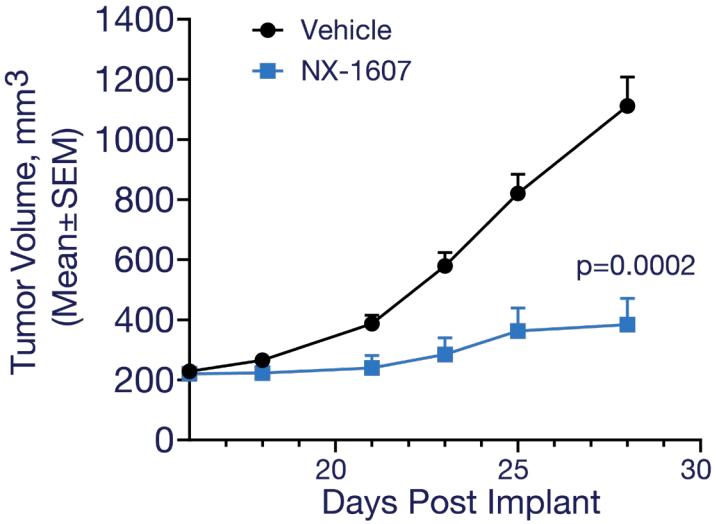


NX-1607
Prolonged Survival
Triple-Negative Breast



NX-1607 30 mg/kg day 7 to 46

NX-1607
Reduced Tumor Volume
B Cell Lymphoma

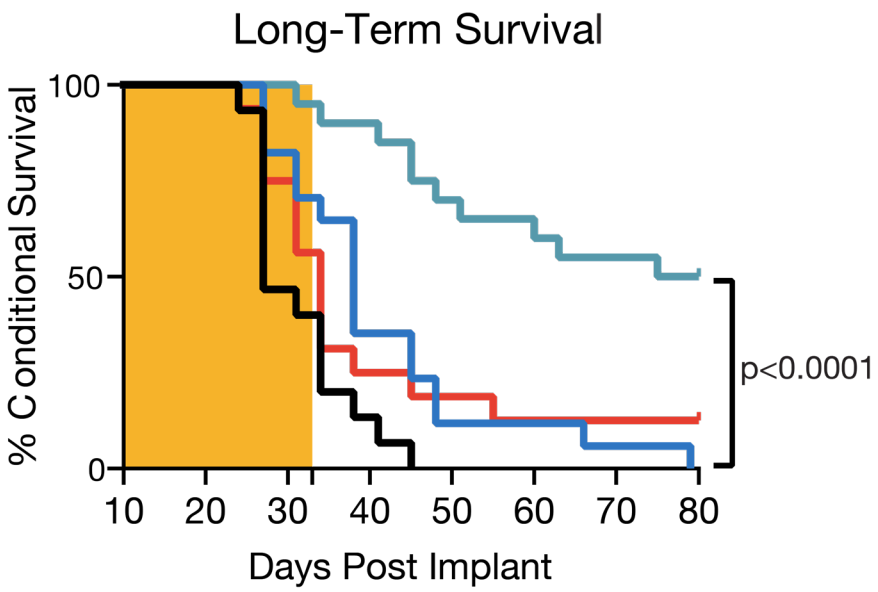


NX-1607 30 mg/kg day 16 to 28

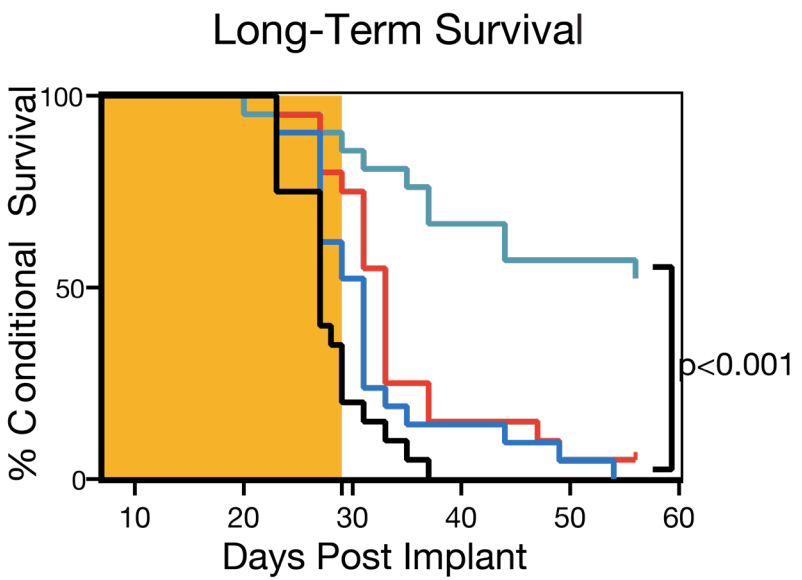
Shaded area indicates dosing period

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

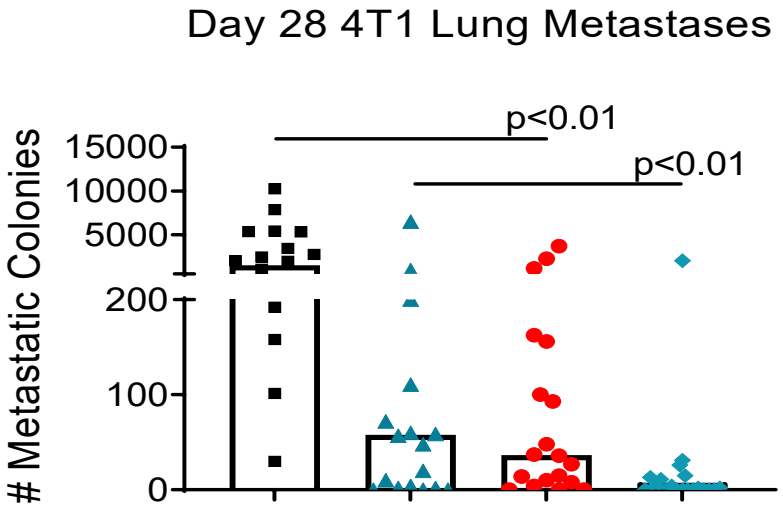
Colorectal (CT26)



Colorectal (MC38)



Triple-Negative Breast (4T1)



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