



# Discovery and Characterization of CBL-B Intramolecular Glue Inhibitors That Increase T Cell Activation and Suppress Tumor Growth

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## Frederick Cohen

I have the following relevant financial relationships to disclose:

Employee of: Nurix Therapeutics, Inc.

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# Disclosure Information

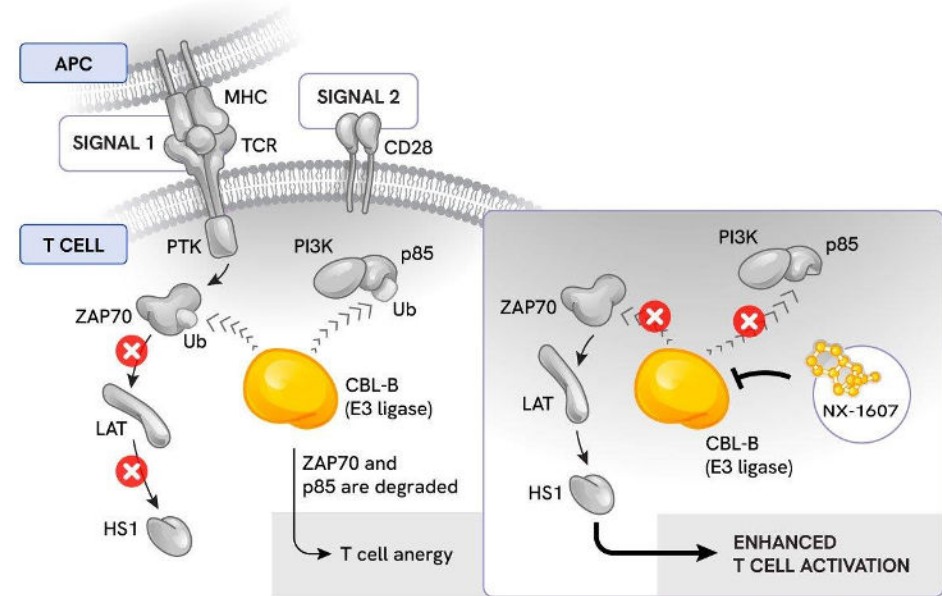


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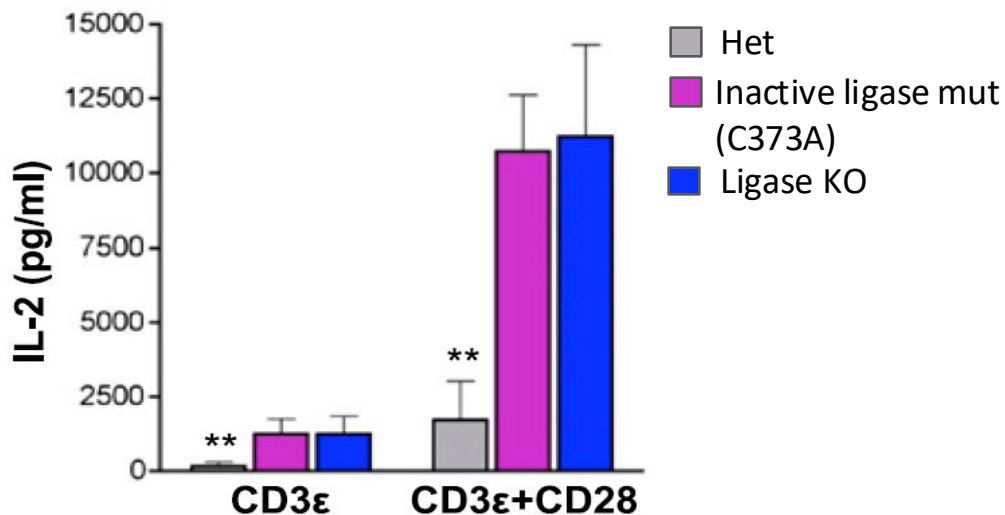
# CBL-B is a Master Modulator of Immune Cell Activation

- 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

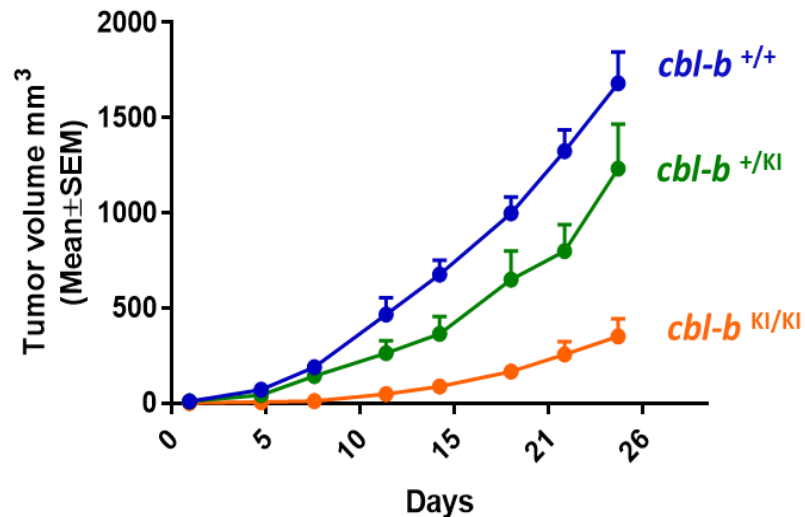


# Inactivation of CBL-B Leads to Enhanced T Cell Activation

IL-2 secretion in knock-out (KO) and ligase inactive T cells *ex vivo*



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



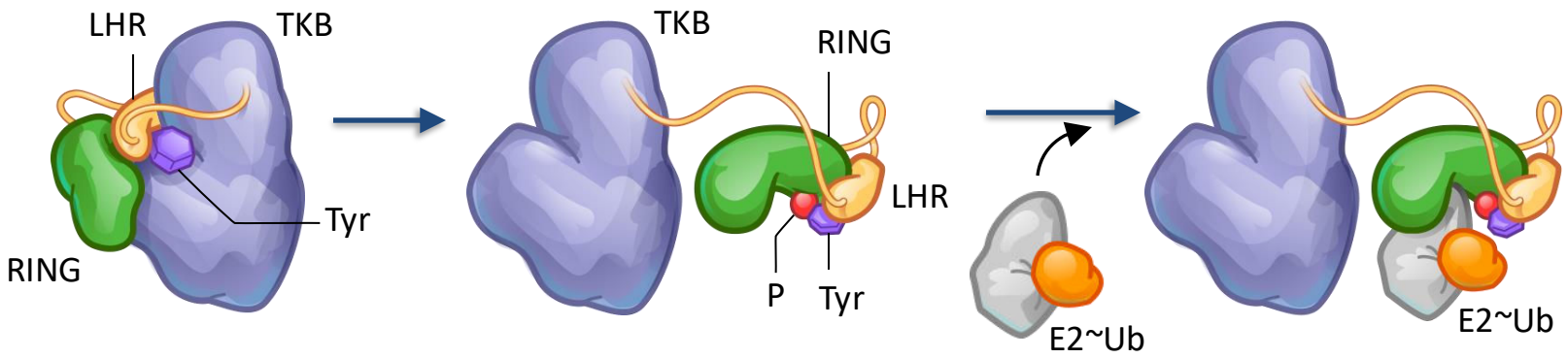
Ligase-dead or KO exhibit similar enhancement of T cell activation in response to TCR stimulation

Nurix Data

# CBL-B is Regulated Through Conformational Change and Phosphorylation

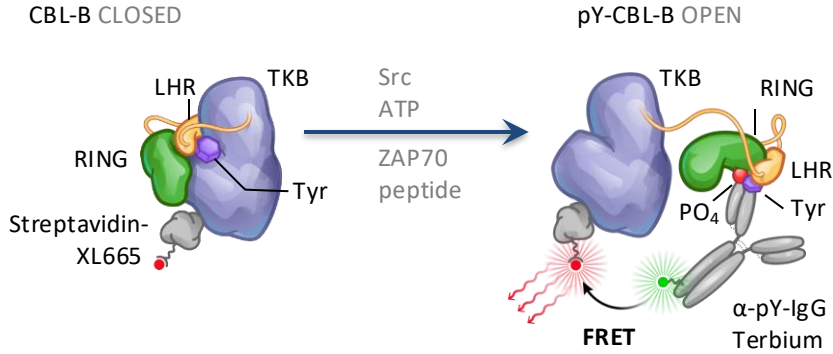
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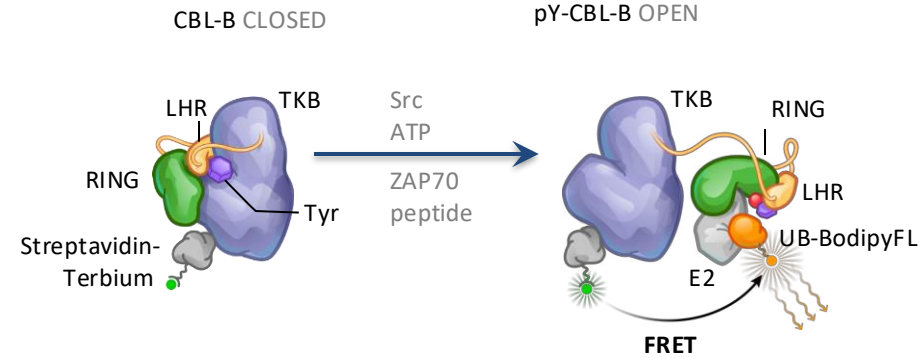


# Mechanism-Agnostic Screening Assays Guided by CBL-B Biology

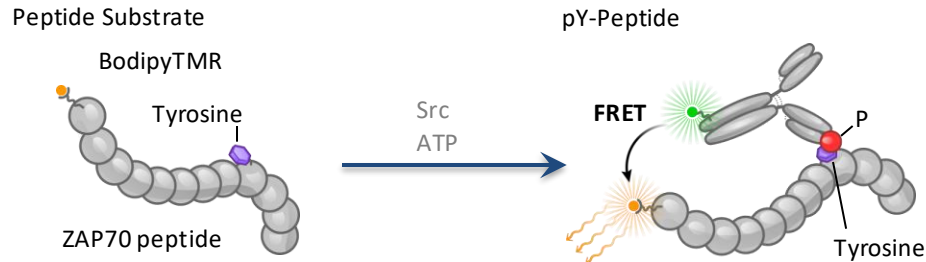
## Phospho-CBL-B Assay



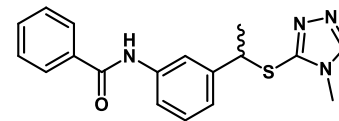
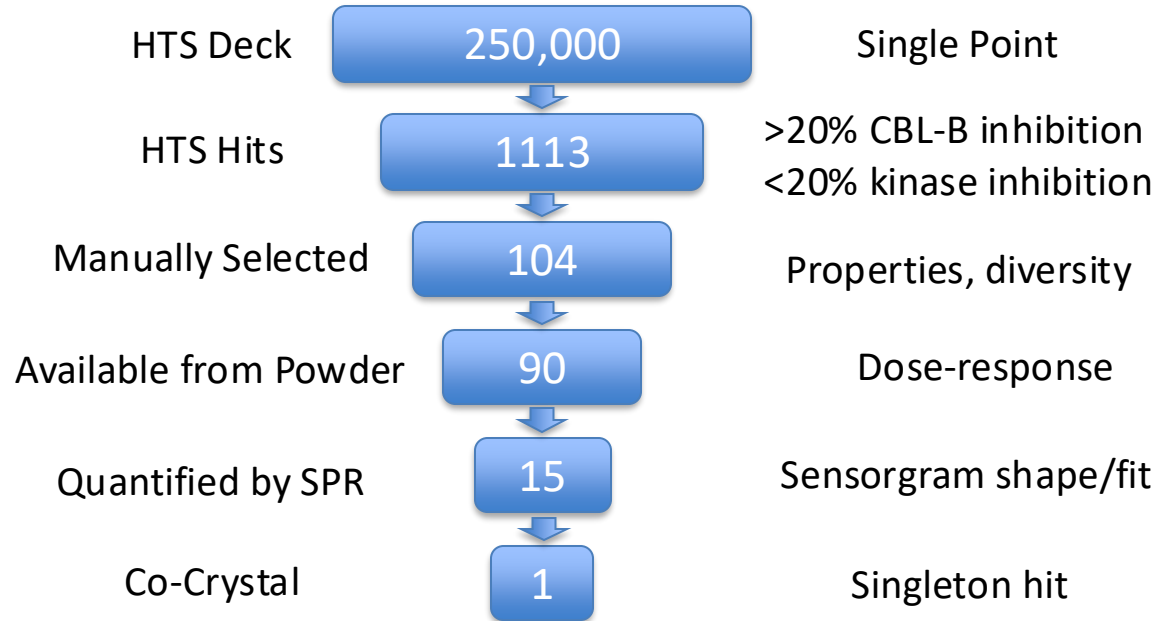
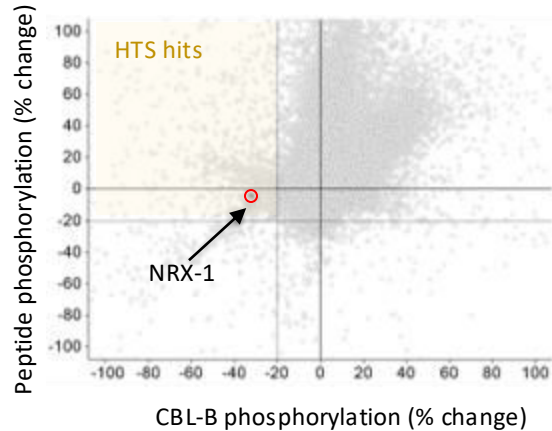
## E2-Ub Binding Assay



## Kinase Counter-Screen

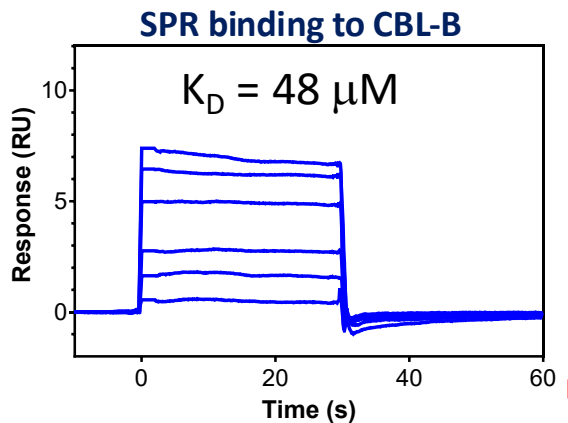
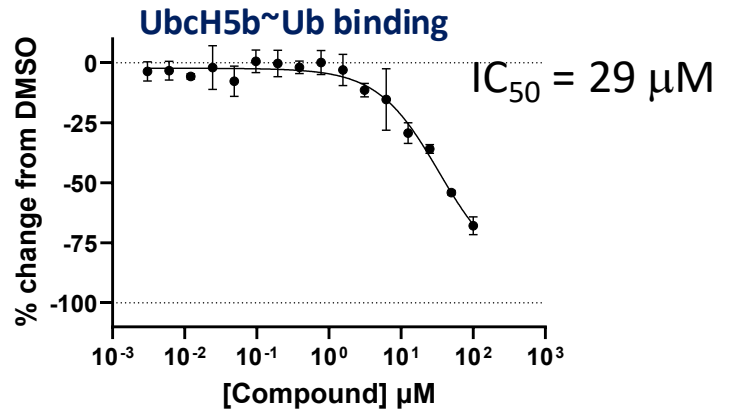
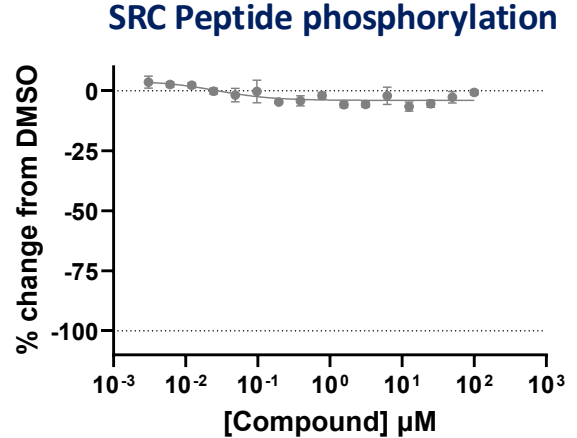
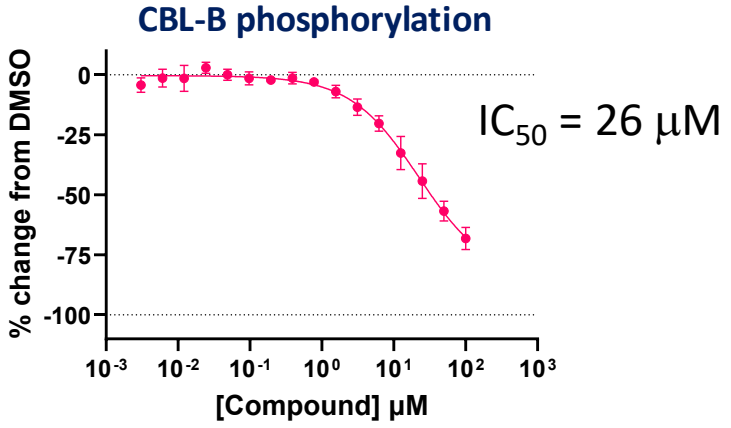


# HTS and Confirmation Affords a Singleton Hit



NRX-1

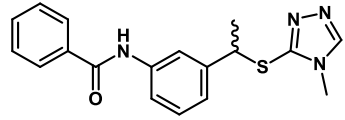
# HTS and Confirmation Affords a Singleton Hit



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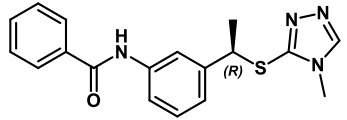
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# NRX-3 is a Specific Inhibitor of CBL-B

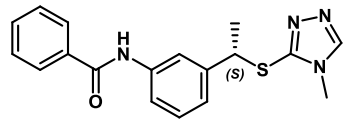


**NRX-1**  
HTS Screening hit

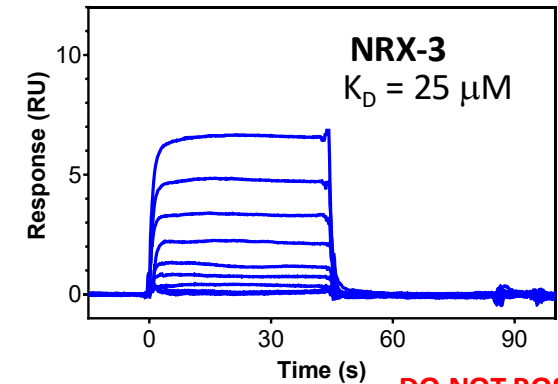
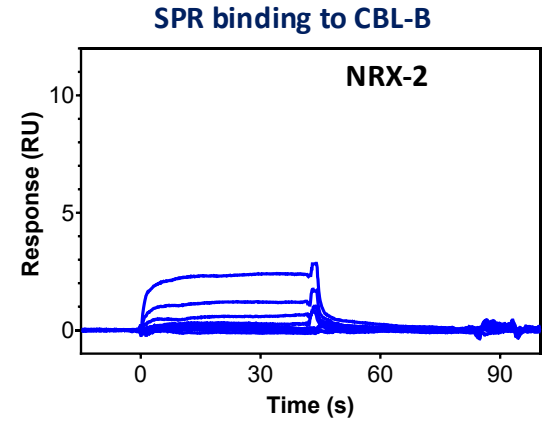
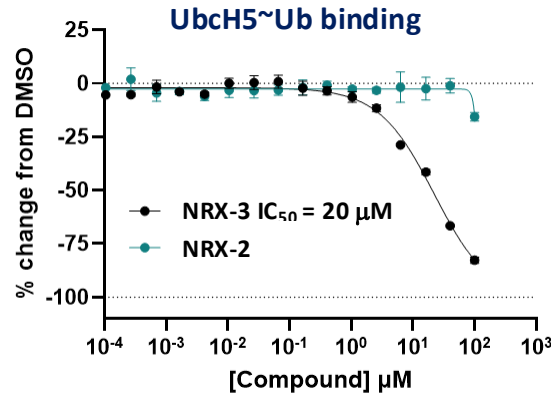
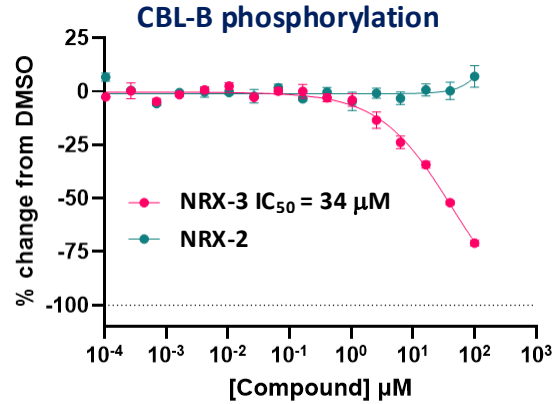
Chiral SFC ↓



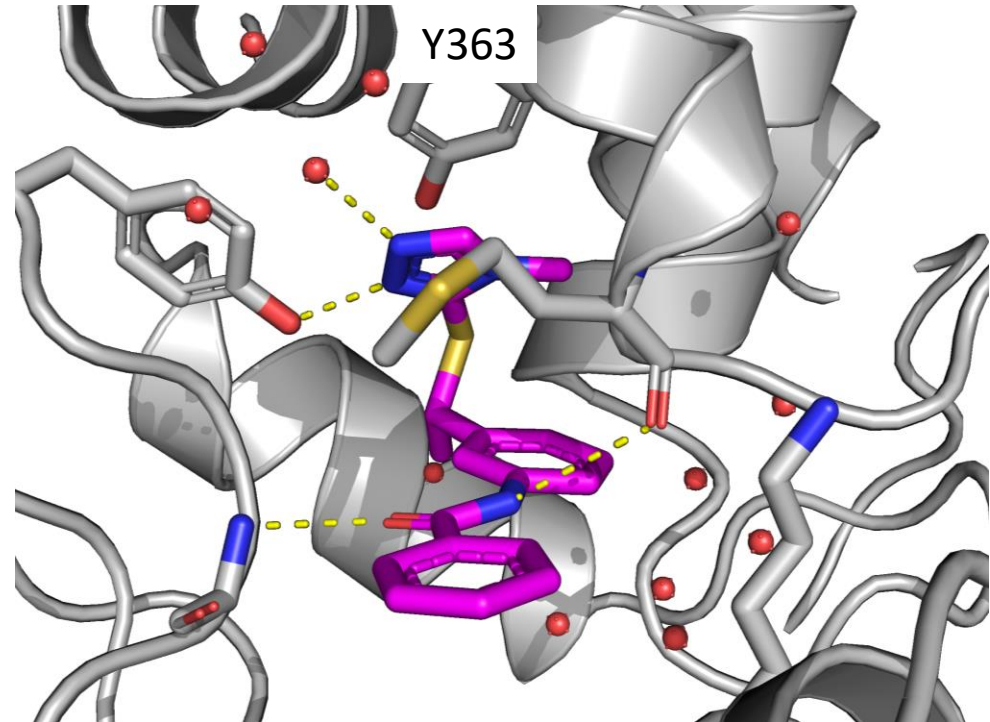
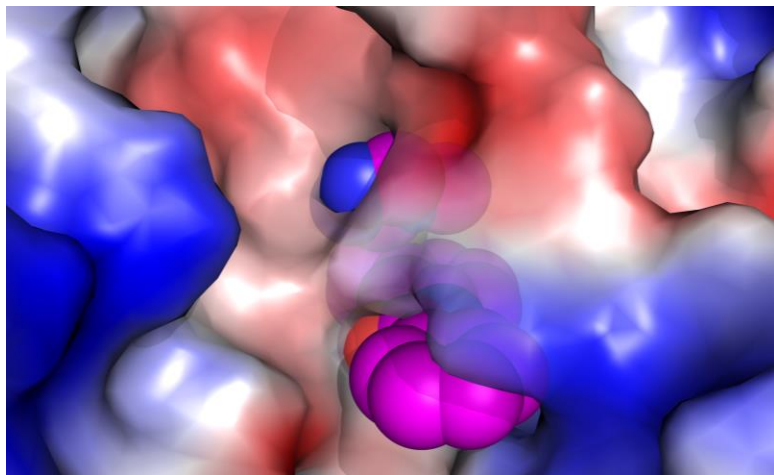
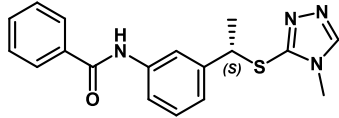
**NRX-2**



**NRX-3**  
Resolved Screening hit  
mw = 338;  
LE = 0.27

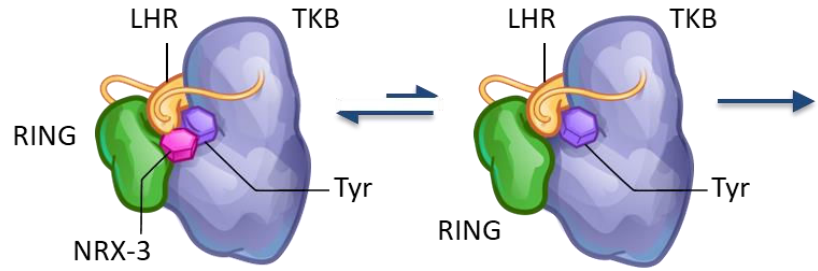


# Crystal Structure Confirms Binding Site of NRX-3

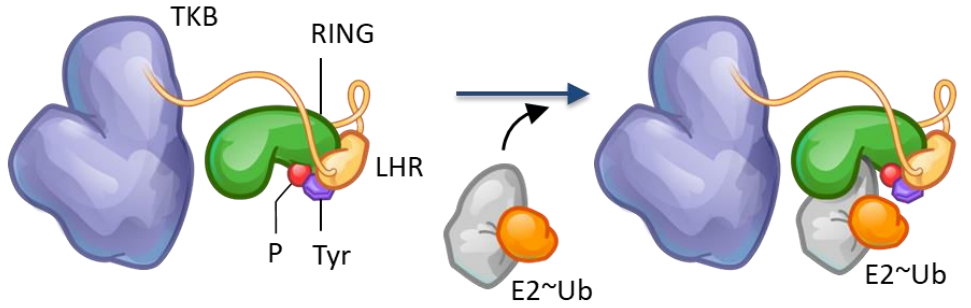


# NRX-3 Acts as an Intra-Molecular Glue Inhibitor of CBL-B

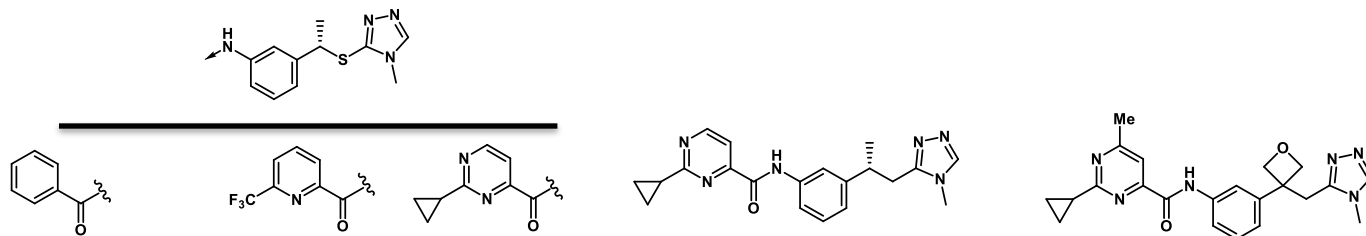
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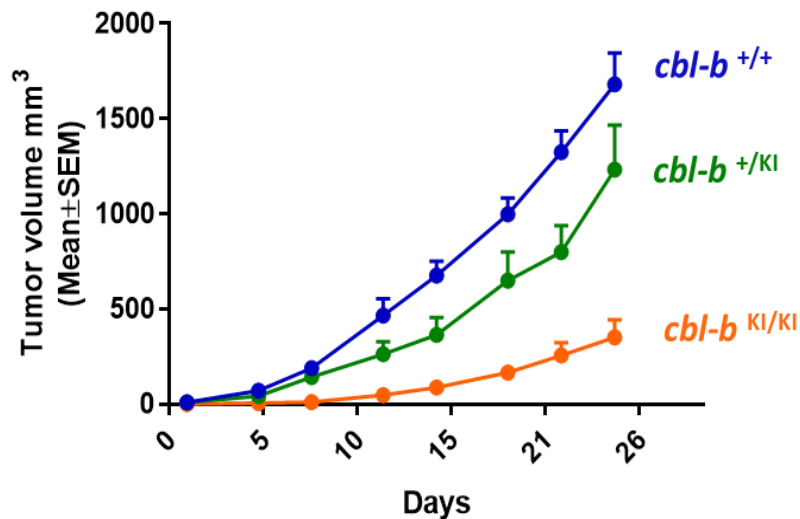
# Early SAR: Focus on Affinity and Properties



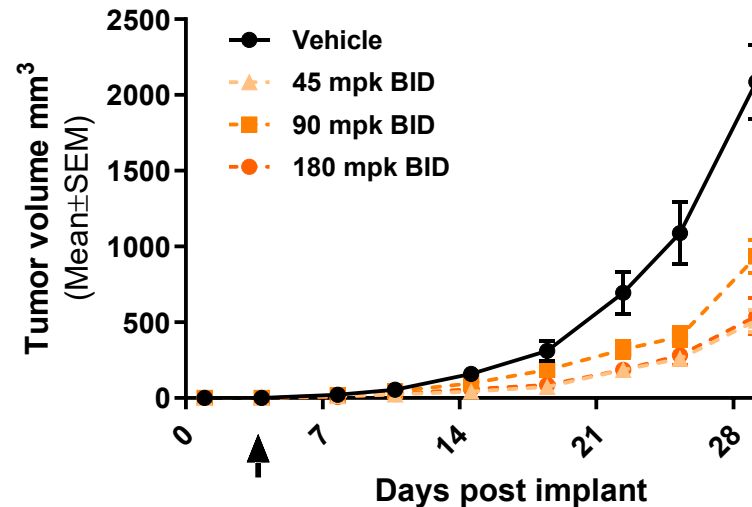
	NRX-3	NRX-4	NRX-5	NRX-6	NRX-8766
E2-Ub: IC <sub>50</sub> (μM)	~20	0.23	0.092	0.088	0.021
LipE (pIC <sub>50</sub> -CLogP)	1.7	2.8	2.3	3.4	6.4
Cellular Substrate Ub IC <sub>50</sub> (μM)		7	3	1.7	0.79

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

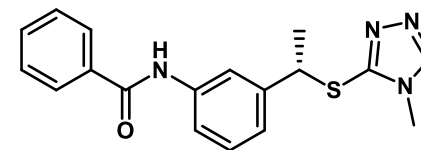
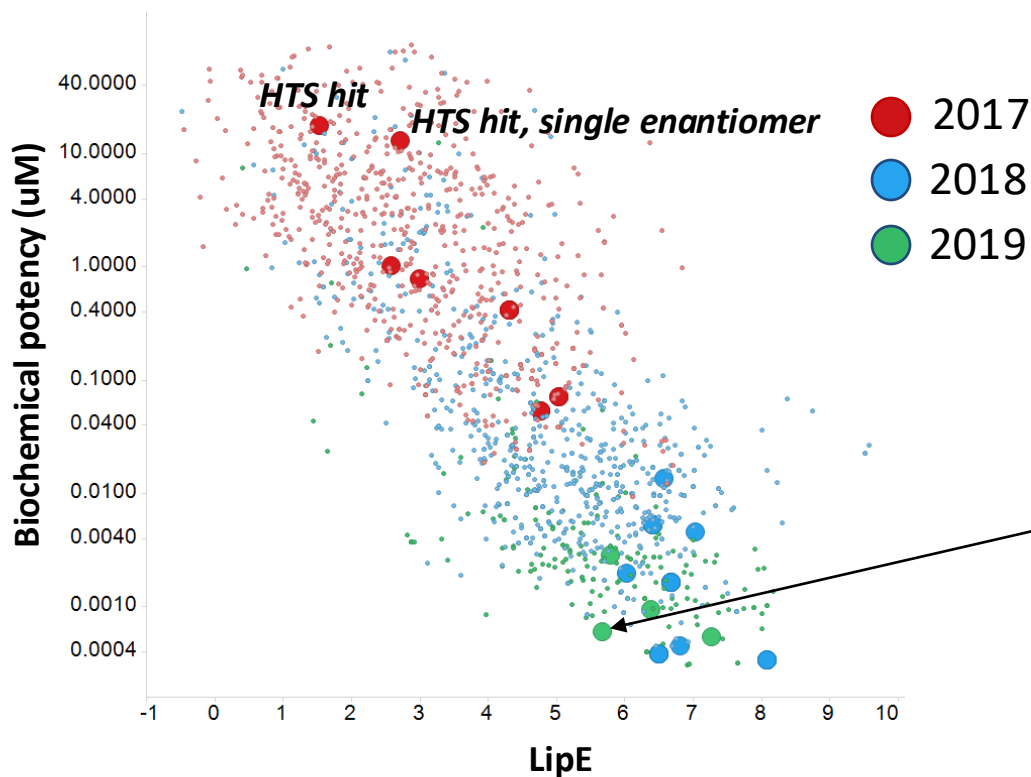
Ligase-inactive *cbl-b* knock-in mice inhibit tumor growth in the TC-1 syngeneic model



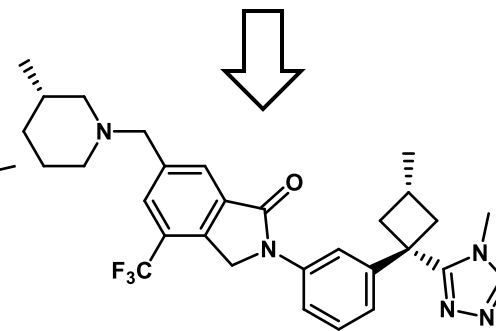
Pharmacologic Inhibition of CBL-B inhibits tumor growth in the CT26 Syngeneic Model



# Optimization Leads to NX-1607

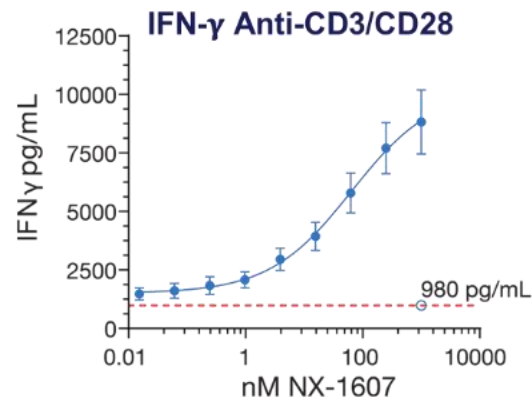
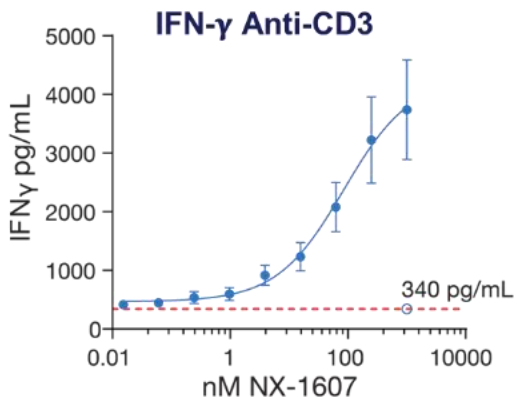
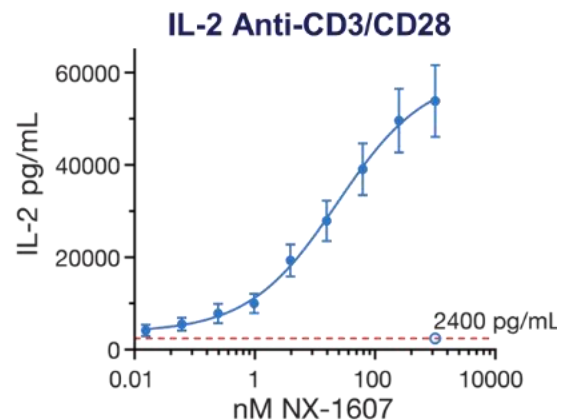
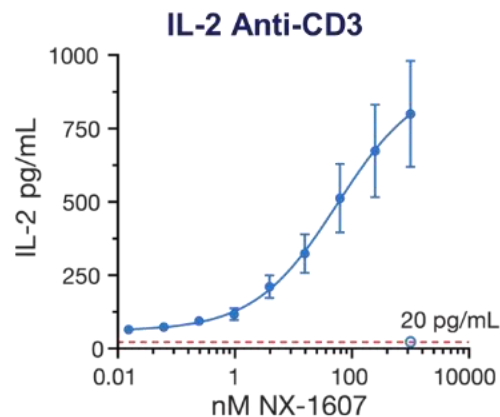


NRX-3, screening hit  
 $IC_{50} = \sim 20 \mu M$



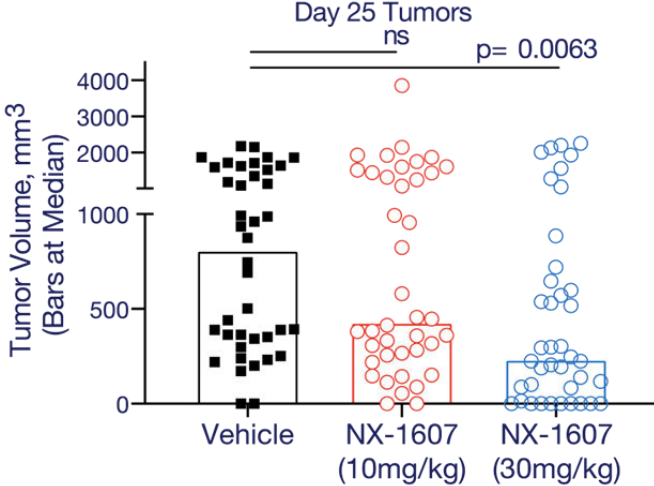
NX-1607  
 $K_D = 0.4 \text{ nM}$

# NX-1607 Increases IL-2 and IFN- $\gamma$ Secretion in Response to TCR Stimulation

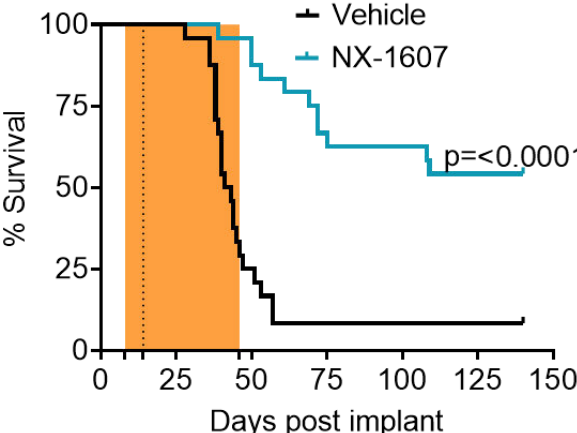


# Single-Agent NX-1607 Induces Anti-tumor Response in Multiple Models

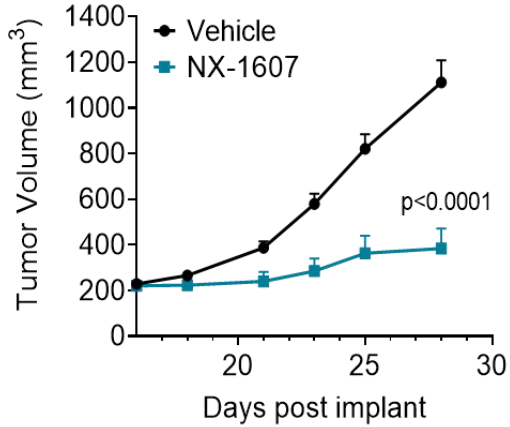
## Colorectal (CT26)



## Triple-Negative Breast (4T1)



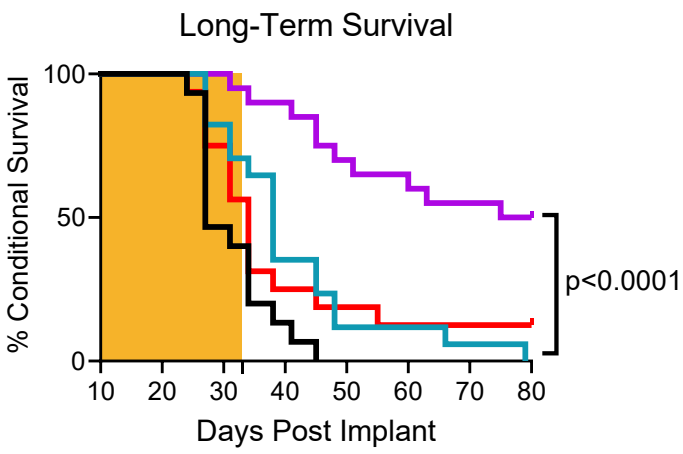
## B Cell Lymphoma (A20)



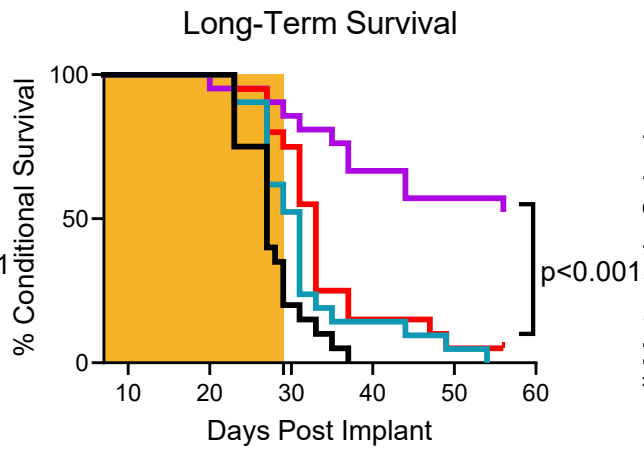
Shaded area indicates dosing period:  
NX-1607 (30 mg/kg, PO daily)

# NX-1607 and Anti-PD-1 Synergize to Enhance Survival in Multiple Models

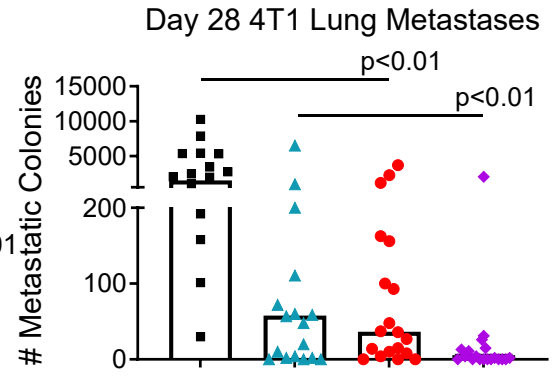
## Colorectal (CT26)



## Colorectal (MC38)



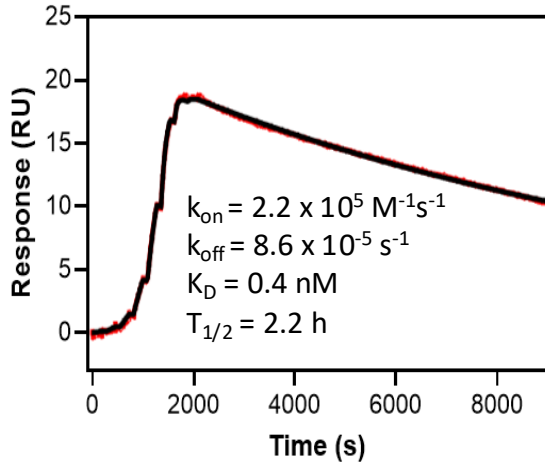
## Triple-Negative Breast (4T1)



■ 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)

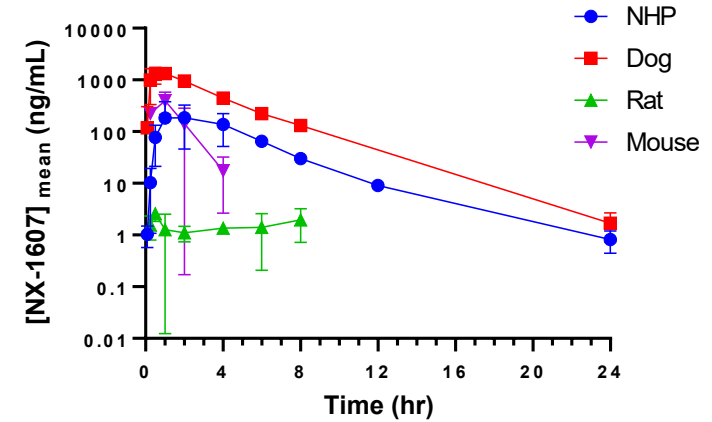
# NX-1607 Displays Favorable Preclinical Profile



SPR sensorgram for the binding kinetics and affinity measurements of NX-1607 to CBL-B.

The dark red curves are fitted curves generated from a 1:1 binding model.

NX-1607 Properties	
Parameter	Value
mw	537.6 amu
pKa/LogD <sub>7.4</sub>	8.3/3.5
Solubility (PBS, pH=7.4)	230 uM
K <sub>D</sub> CBL-B (nM) spr	0.4 nM
K <sub>D</sub> C-CBL (nM) spr	1.43 nM
CACO Permeability A-B(10 <sup>-6</sup> cm/sec)	18.3
B-A Ratio	2.3
hPPB	97.1 %
GSH trapping/TDI	Neg
Ames/MNT (+/- S9)	Neg

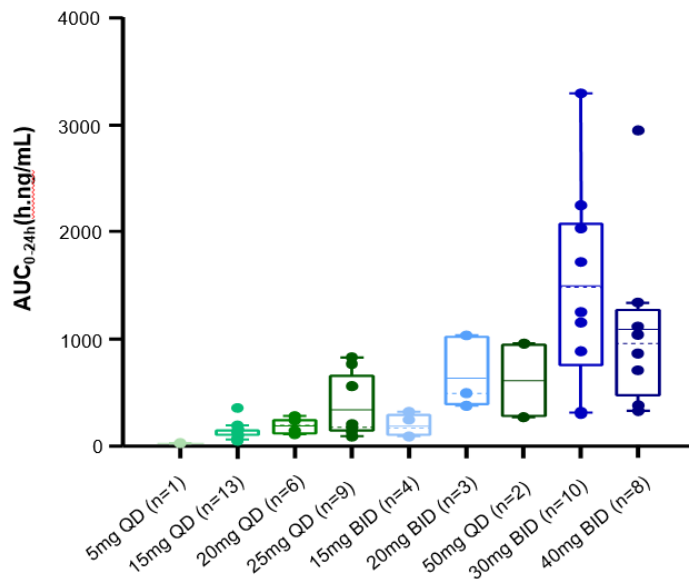


	Mouse	Rat	Dog	NHP
F (%)	25	0.23	48	7

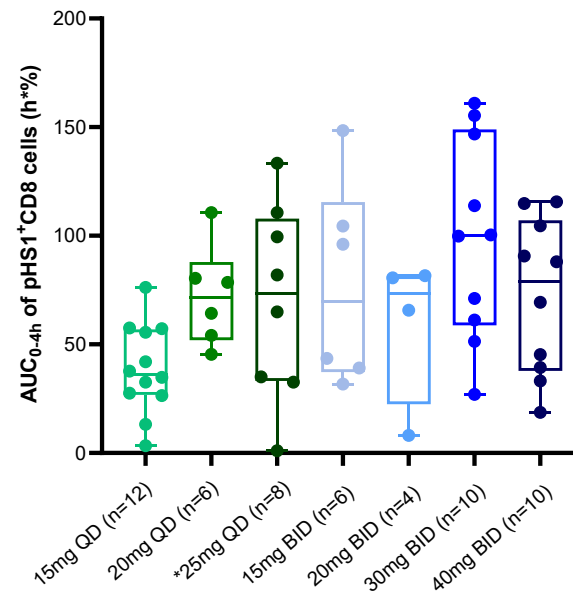
- NX-1607 CL is ~50% of LBF across preclinical species
- Is moderately bound to plasma

# NX-1607 Demonstrates Dose-Dependent PK and Modulation of Biomarker pHS1 in Patients

## Steady state pharmacokinetics



## Pharmacodynamic activity of pHS1 in CD8 T cells



- NX-1607 demonstrates dose-dependent pharmacokinetics.
- NX-1607 increases the percentage of pHS1-positive CD8 T cells from baseline across dose cohorts.

# Summary

- Deep understanding of CBL-B regulation allowed design of mechanism-agnostic screening assays
- HTS and careful follow-up afforded a singleton hit
- This series functions as an intra-molecular glue, stabilizing the closed, inactive state of CBL-B
- Optimization resulted in NX-1607, a potent and selective inhibitor of CBL-B
- Early clinical results show linear PK and modulation of proximal biomarkers