nurix

Leader in Targeted Protein Modulation

Exploring Success with Targeting a Novel E3 Ligase with a Small Molecule Inhibitor

NX-1607: A first-in-class CBL-B inhibitor in the clinic

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3rd Annual Ligase Targeting Drug Development

Boston, MA

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Nurix Drugs Engage Ligases for the Treatment of Cancer

Targeted Protein Modulation: TPM = TPD + TPE

A Powerful Cellular System

Targeted Protein Elevation (TPE)

Inhibit ligases to increase specific protein levels

Harness ligases to decrease specific protein levels

Targeted Protein Degradation (TPD)

Ubiquitin is ligated to target proteins to tag them for degradation by the proteasome

Nurix is Advancing a Pipeline of Propriety and Partnered Programs in Oncology and Inflammatory Diseases

MOA	Drug program	Target/delivery	Therapeutic area	Discovery	IND enabling	Phase 1a	Phase 1b
TPD	**NX-2127** Degrader	BTK-IKZF *Oral*	B-cell malignancies				
	NX-5948 Degrader	BTK *Oral*	B-cell malignancies				
	NX-0479 / GS-6791 Degrader	IRAK4 *Oral*	Rheumatoid arthritis and other inflammatory diseases			GILEAD	
TPE	**NX-1607** Inhibitor	CBL-B *Oral*	Immuno-Oncology				
TPM	Wholly owned & partnered	14 targets	Multiple				

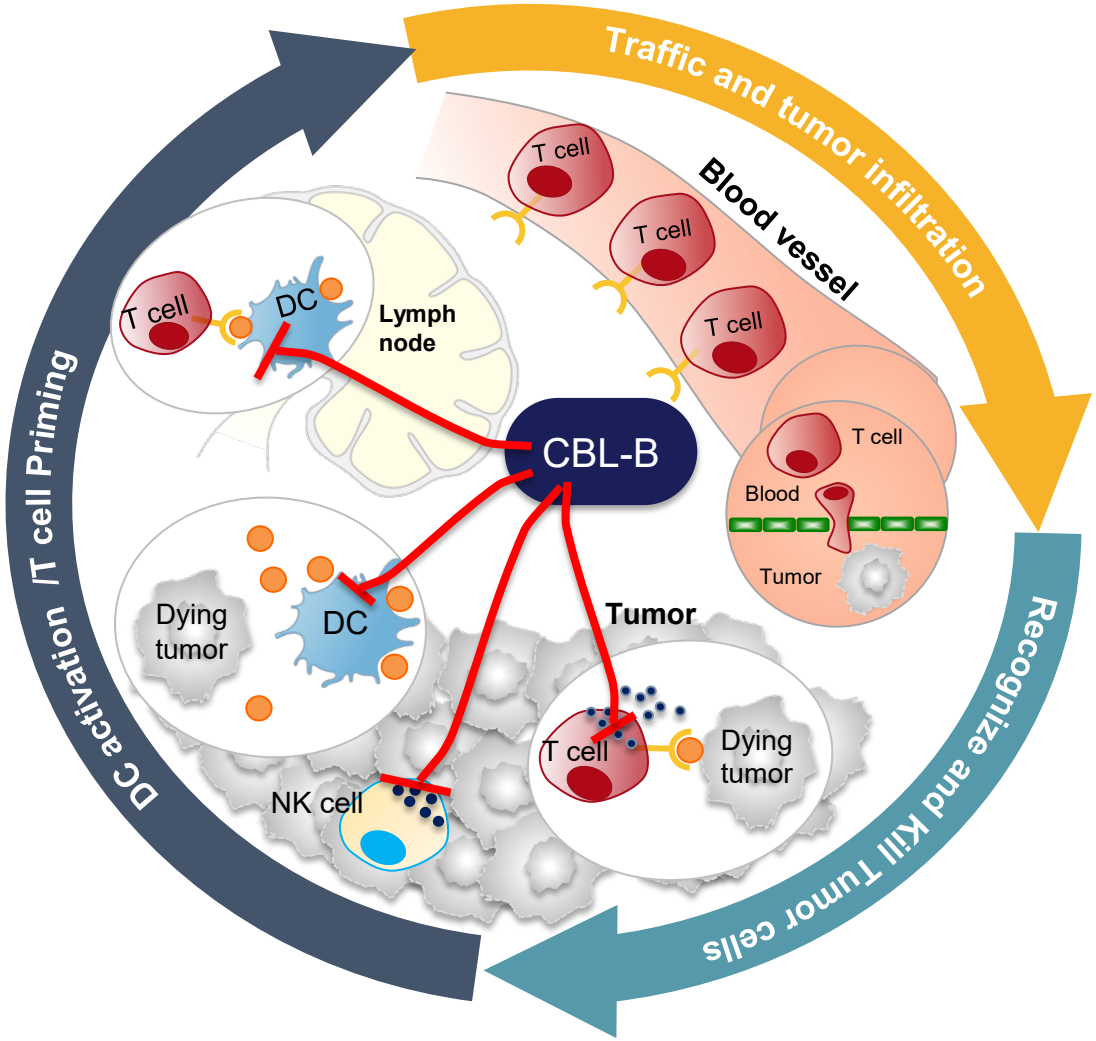
Targeting CBL-B Enhances Antitumor Response

A Master Orchestrator of the Immune System

CBL-B mediated mechanisms strongly restrains a productive anti-tumor response

CBL-B inhibition increases:

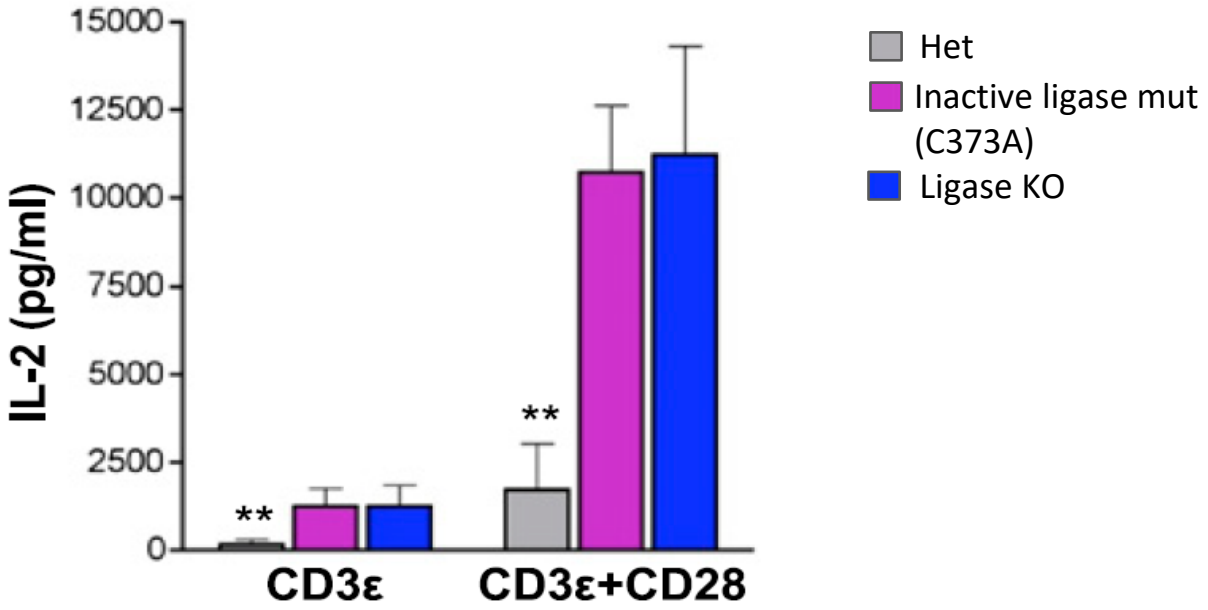
- DC and NK infiltration and function
- T cell priming
- Cytotoxic T cells function
- Ability of T cells to resist tumor immunosuppressive mechanisms: Treg, MDSC, and TGF-β



CBL-B is a Master Orchestrator of Immune Cell Activation

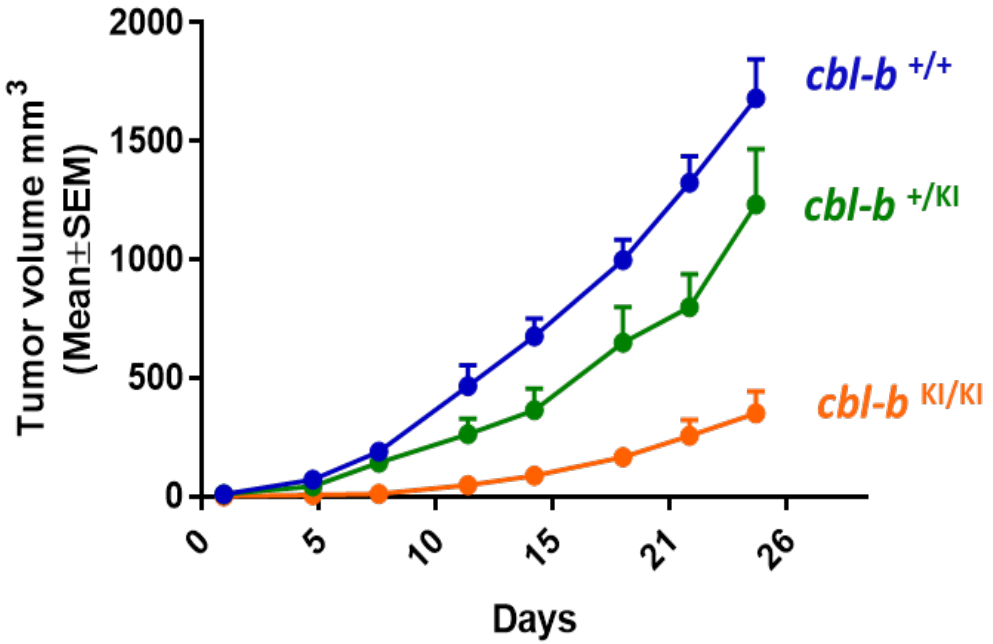
Loss of CBL-B ligase activity results in hyperactive T cells that can reject tumors

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



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).



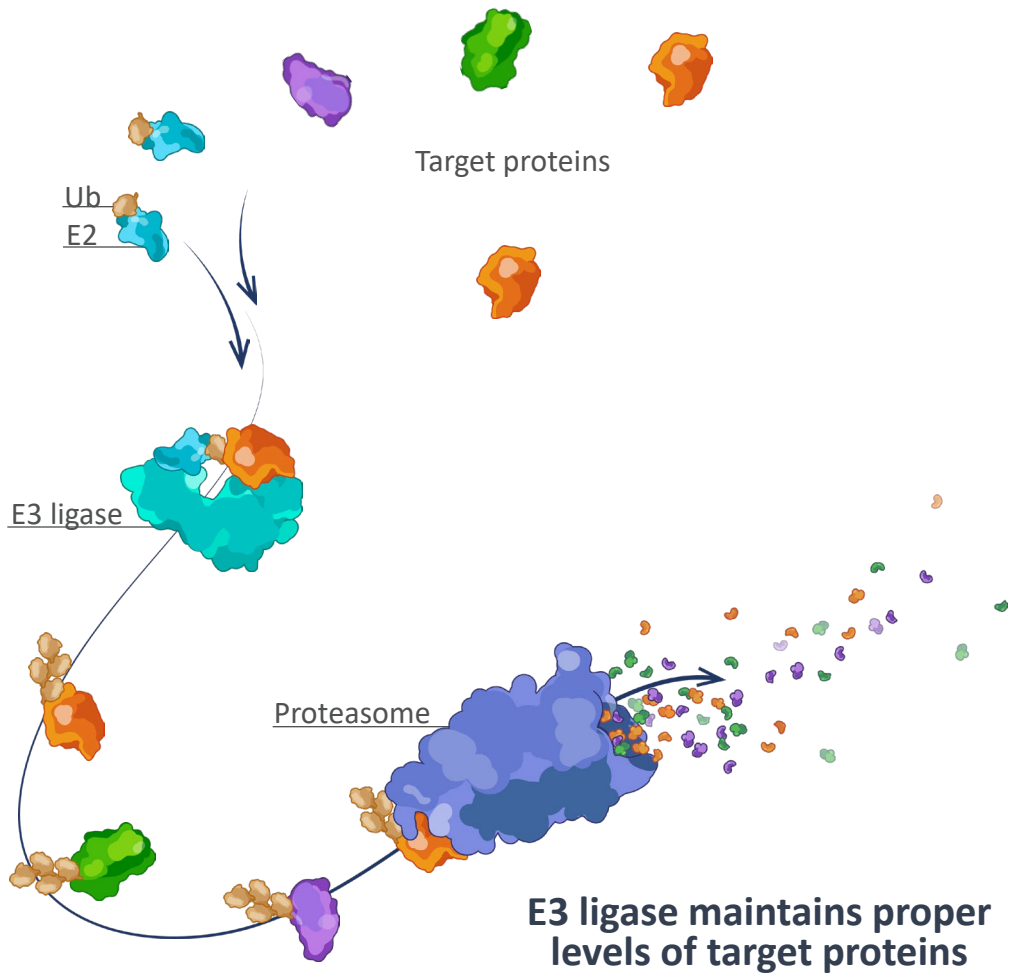
Paolino et. al. *J. Immunology*, 2011

Nurix Data

Targeted Protein Elevation

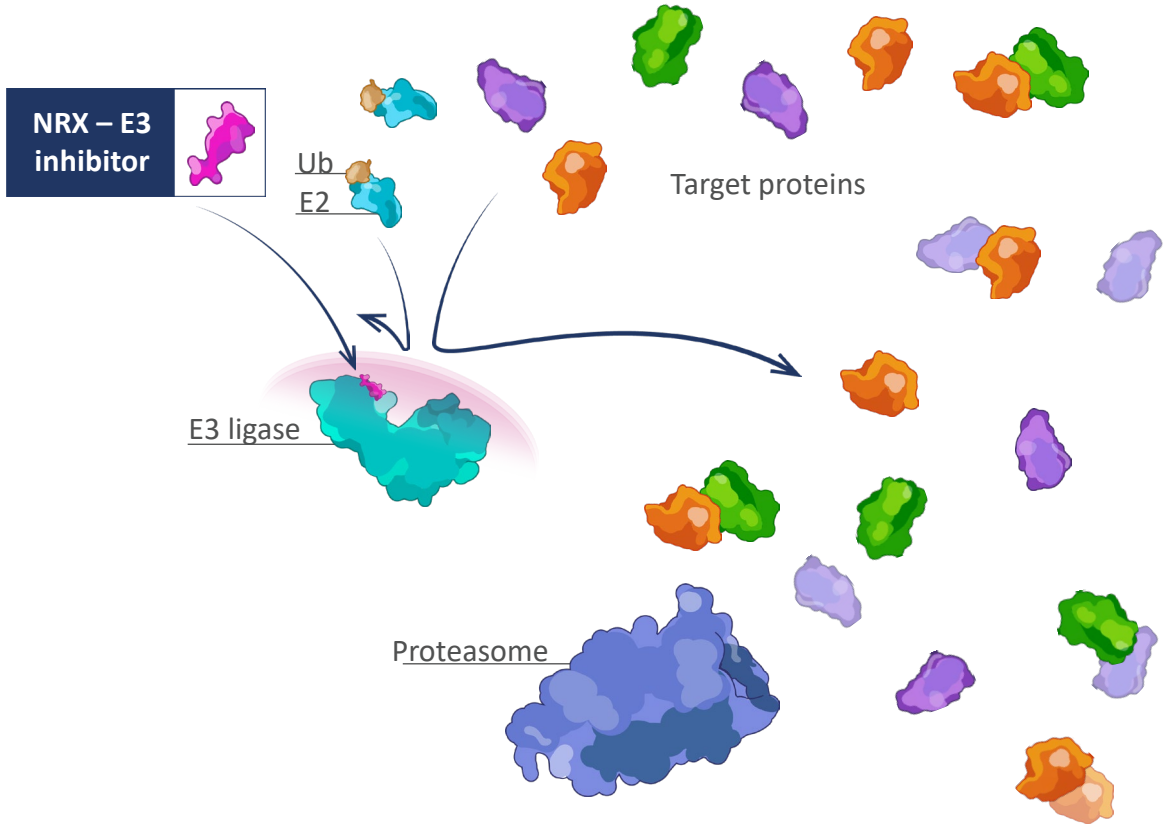
E3 Ligase Inhibition Raises Substrate Levels

Native State: Normal Levels of Target



E3 ligase maintains proper levels of target proteins

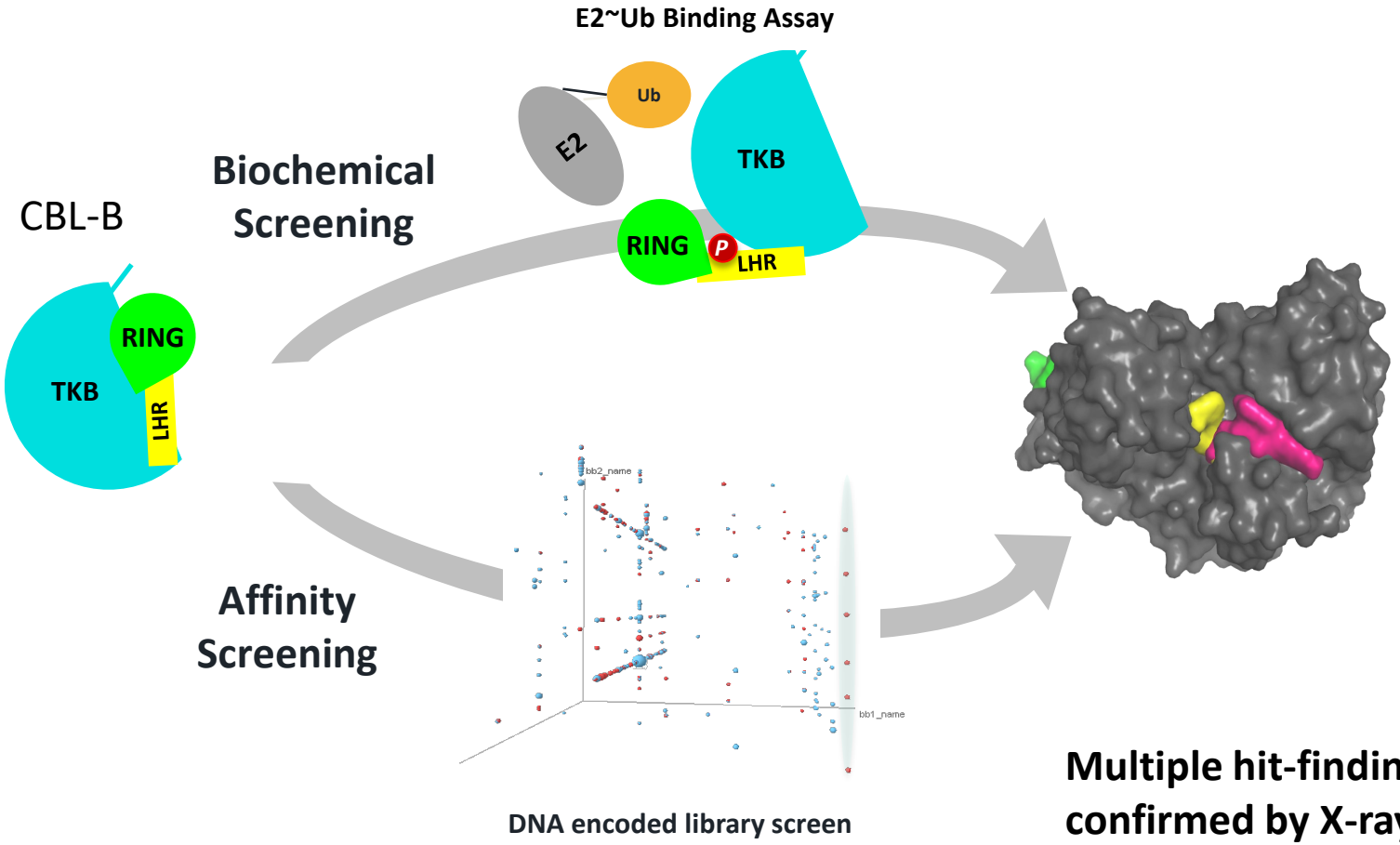
Ligase Inhibition: Increased Target Abundance



E3 Ligase Inhibition leads to Elevated levels of target proteins

E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; NRX, Nurix; Ub, ubiquitin

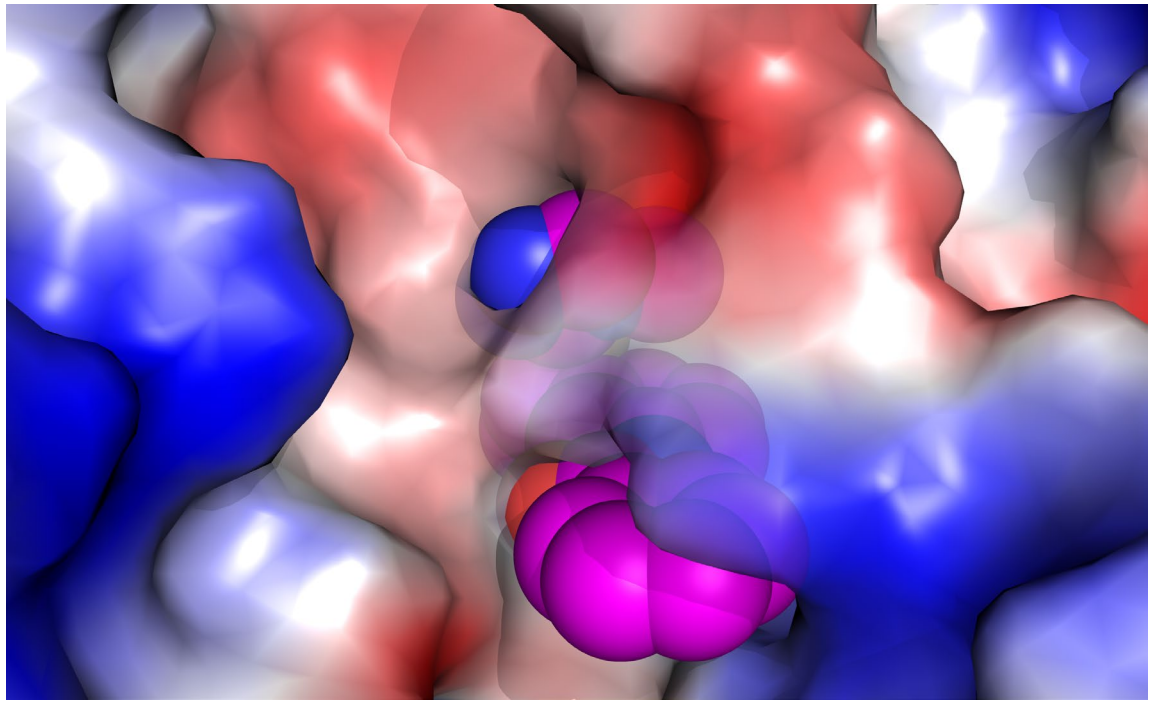
Multiple Screening Methodologies Yielded Chemical Matter for CBL-B

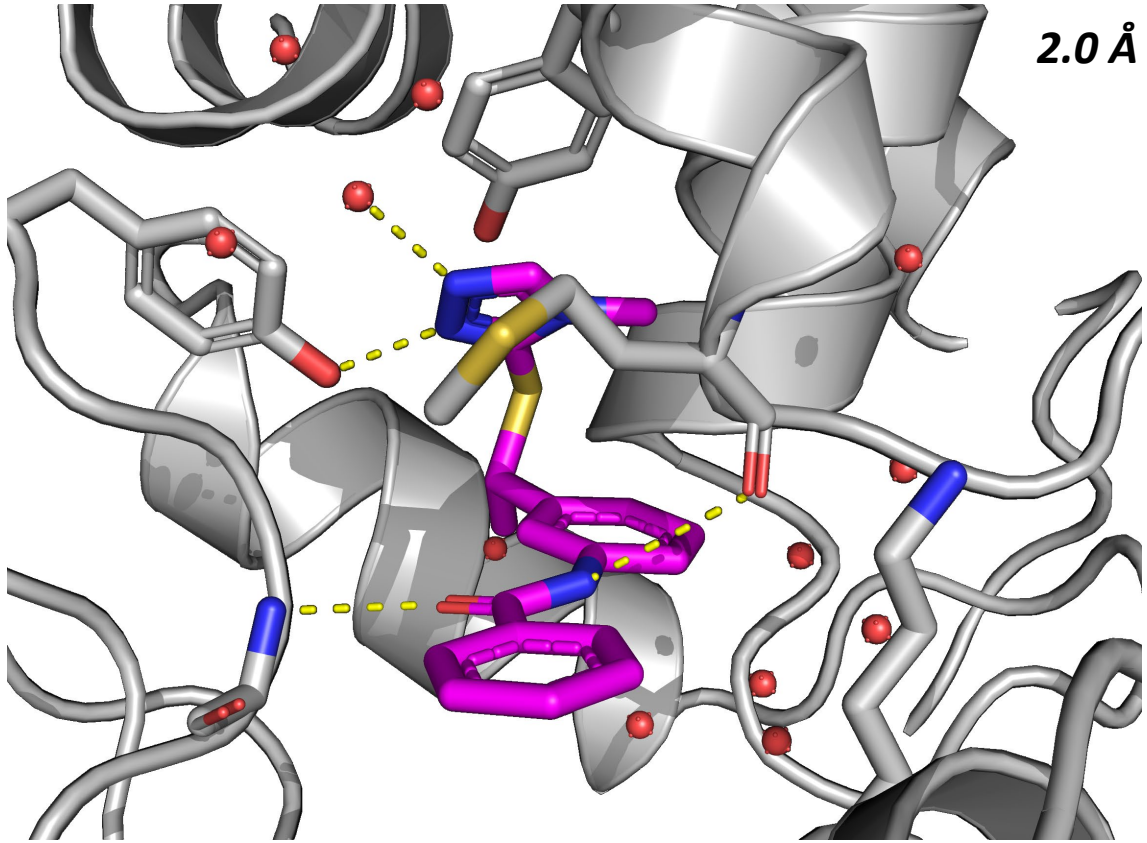


	HTS	DEL	Fragment
Lib size	300K	$1X10^9$	1600
# of Series	1	2	1
Hit Affinity	28 uM	2.4 uM	1800 uM
Hit mwt	338	537	211
Hit LE	0.27	0.22	0.33

Multiple hit-finding techniques yielded starting points that were confirmed by X-ray crystallography as well as biochemical and biophysical assays.

Crystal Structure Confirms Binding Mode as Intramolecular Glue

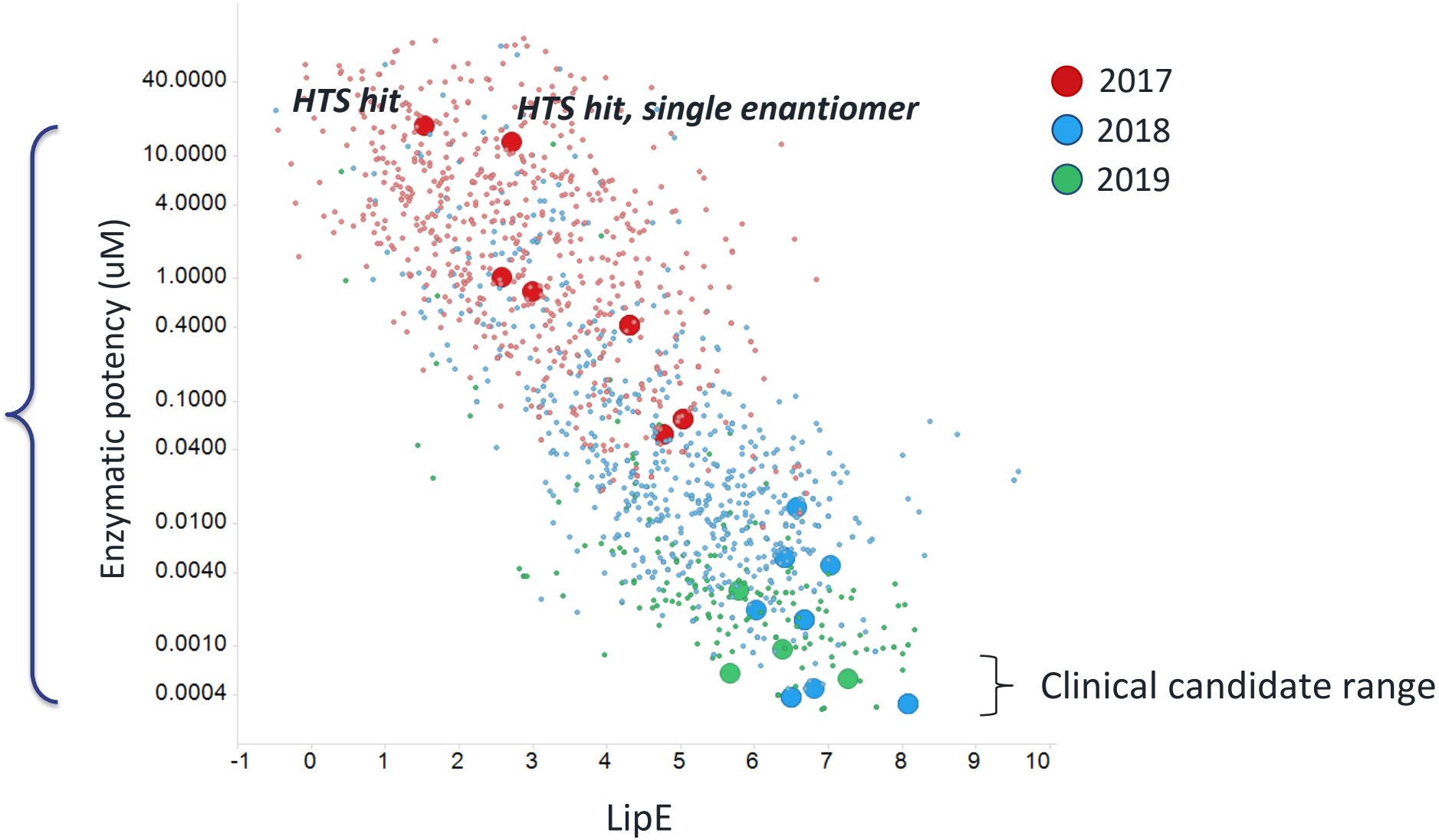




Nurix CBL-B inhibitors bind to closed-state conformation of E3 ligase and prevents phosphorylation

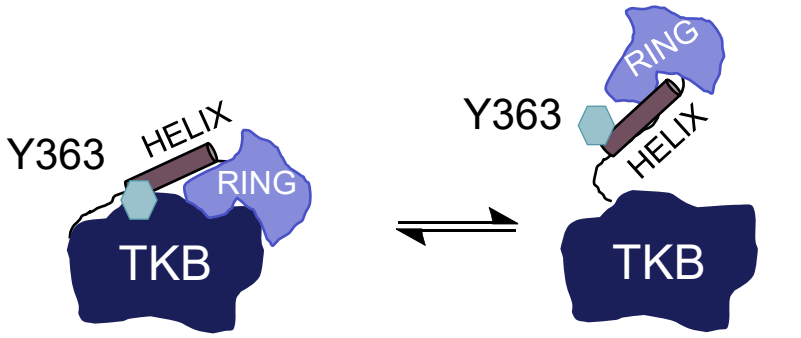
Over 10,000-fold Enzymatic Potency Improvement Achieved While Improving Molecular Properties

~ 10,000x potency improvement



NX-1607 Mechanism of Action: Intramolecular Glue

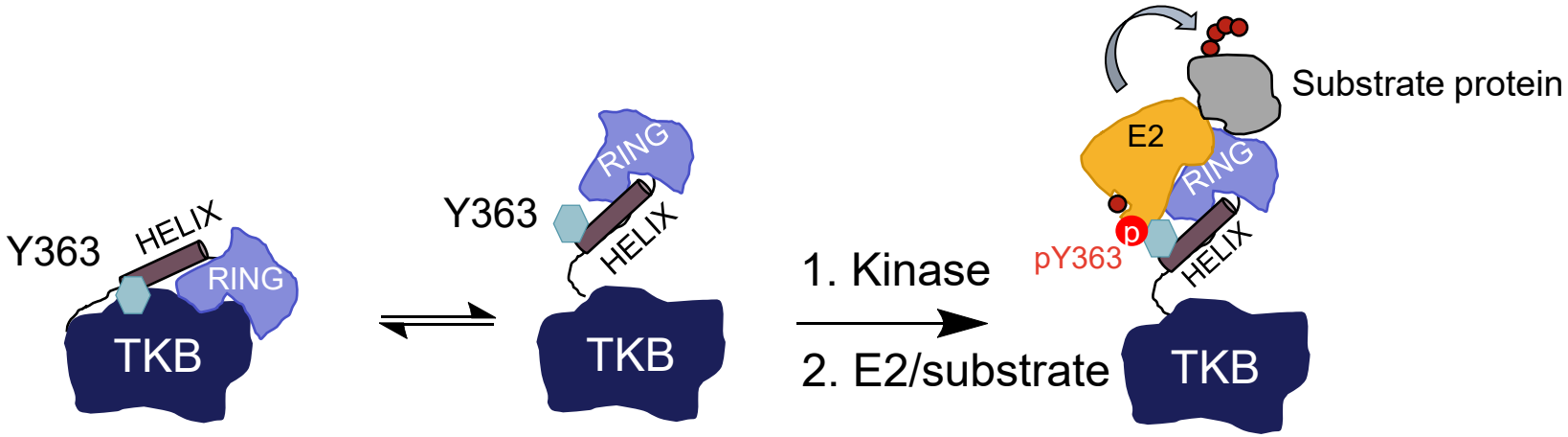
CBL-B is in Equilibrium Between Closed and Opened State



Closed State
INACTIVE

Opened State

NX-1607 Mechanism of Action: Intramolecular Glue



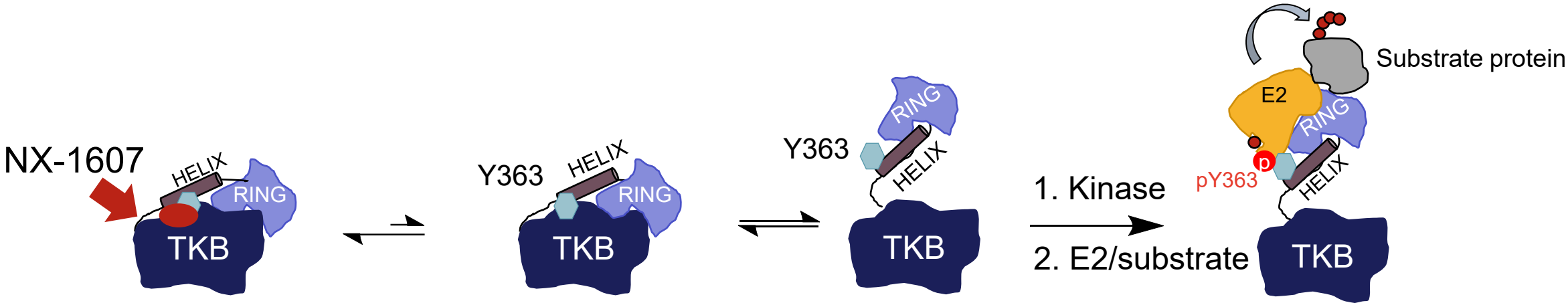
Closed State
INACTIVE

Opened State

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

Immune Response

NX-1607 Mechanism of Action: Intramolecular Glue



NX-1607 acts as an intramolecular glue forcing CBL-B in its folded **INACTIVE** state

Closed State **INACTIVE**

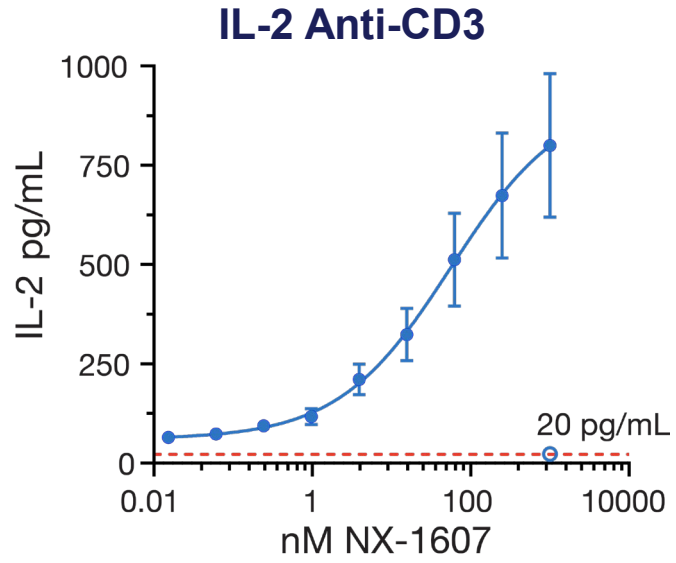
Opened State

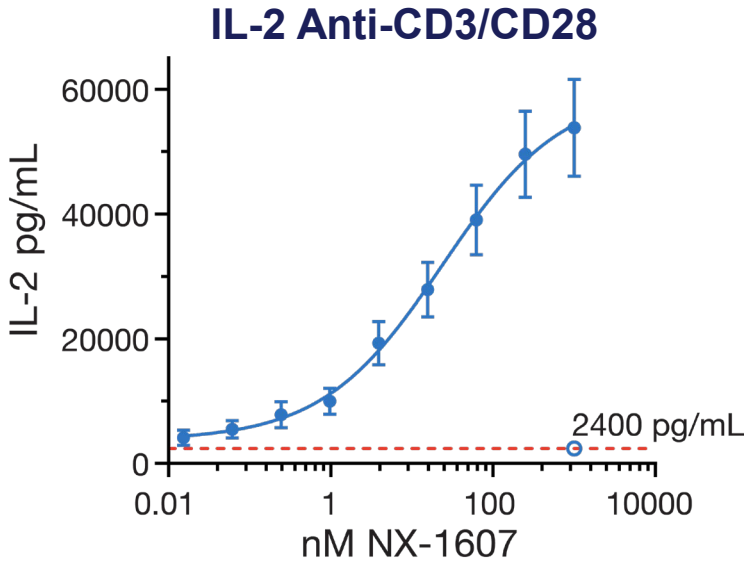
Phosphorylation locks CBL-B in the **ACTIVE** Conformation

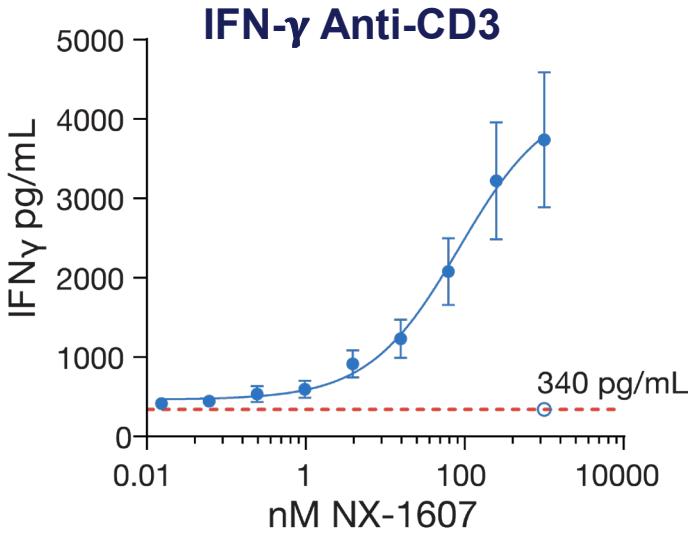
Immune Response

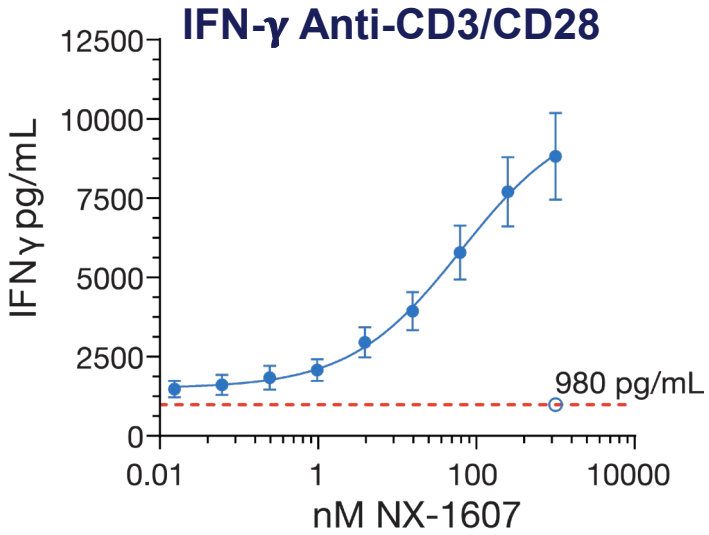
Immune Response

NX-1607 Increases IL-2 and IFN-γ Secretion in TCR Stimulated Primary Human T cells







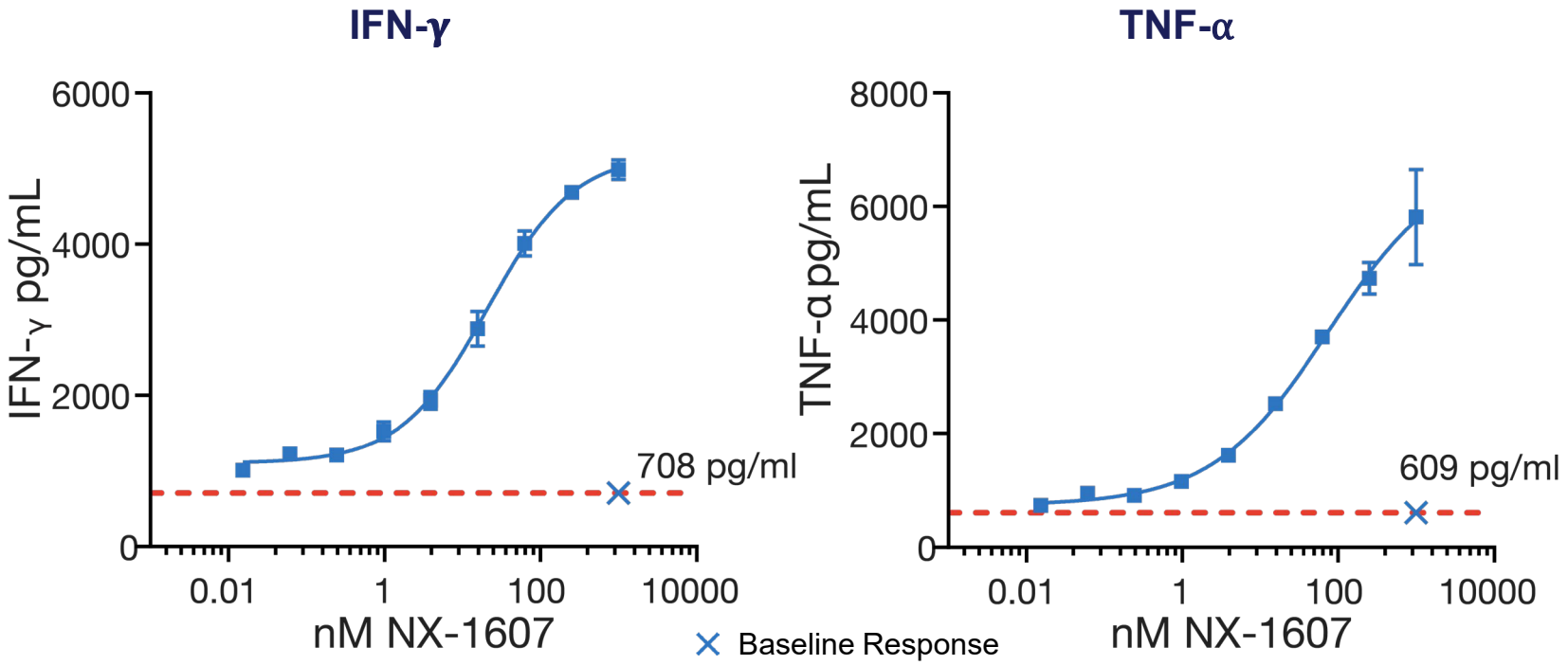


NX-1607 increases TCR stimulation-dependent production of IL-2 and IFN-γ in primary human T cells

NX-1607 has no impact in the absence of T cell stimulation as measured by proliferation, activation, or cytokine release

Cytokine Response
Baseline Response

NX-1607 Increases Secretion of Pro-Inflammatory Cytokines in Human NK cells



NX-1607 increases stimulation-dependent production of IFN-γ and TNF-α in primary human NK cells

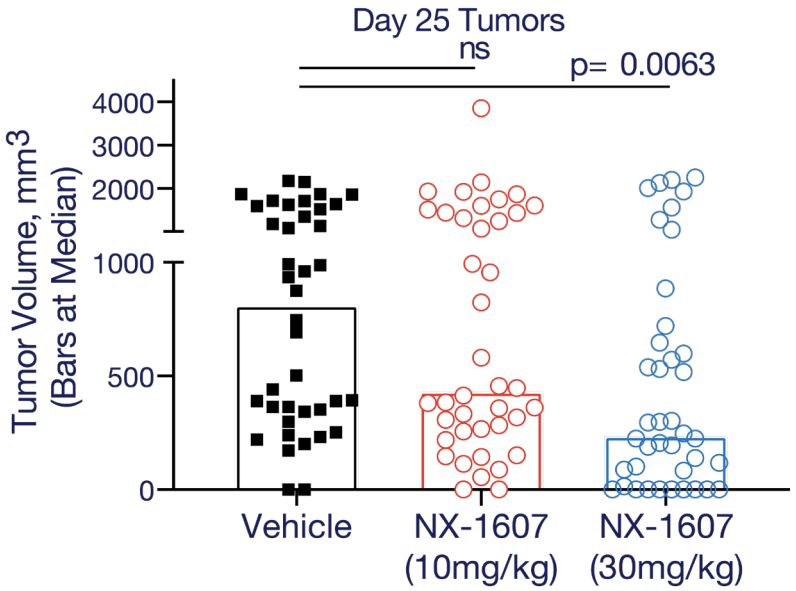
NX-1607 has no impact in the absence of NK cell stimulation, as measured by cytokine release

NK K562 Killing Assay

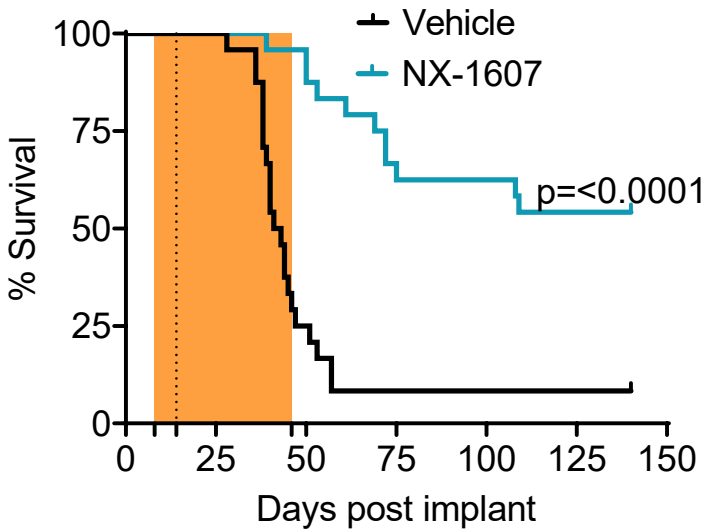
- 1 hour compound pre-treatment prior to addition of K562s target cells
- 6 hour NK/K562 coculture

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

NX-1607 Reduced Tumor Volume
Colorectal

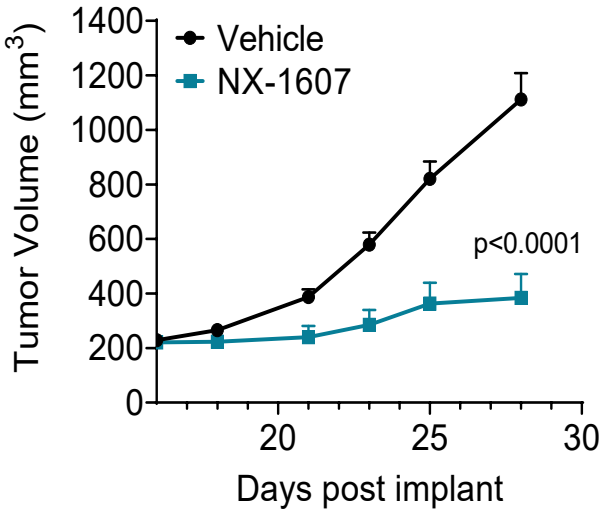


NX-1607 Prolonged Survival
Triple-Negative Breast



NX-1607 30 mg/kg day 7 to 46

NX-1607 Reduced Tumor Volume
B Cell Lymphoma

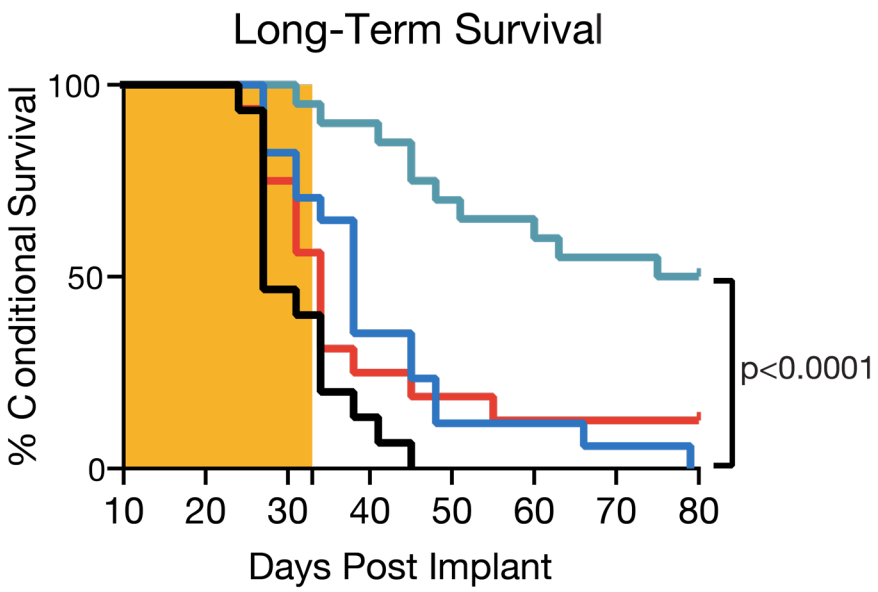


NX-1607 30 mg/kg day 16 to 28

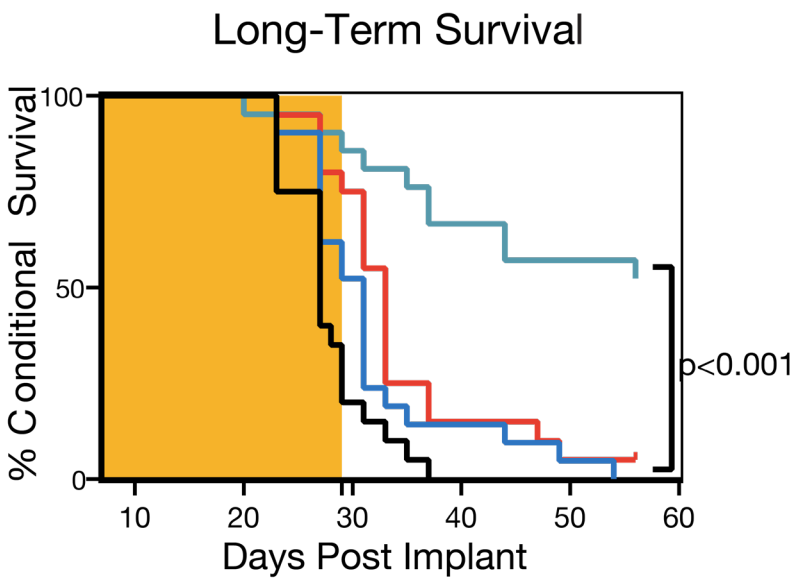
Shaded area indicates dosing period

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

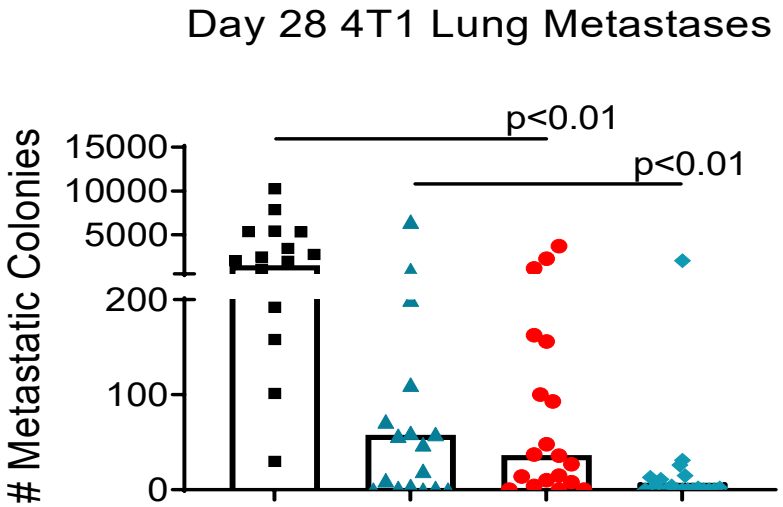
Colorectal (CT26)



Colorectal (MC38)



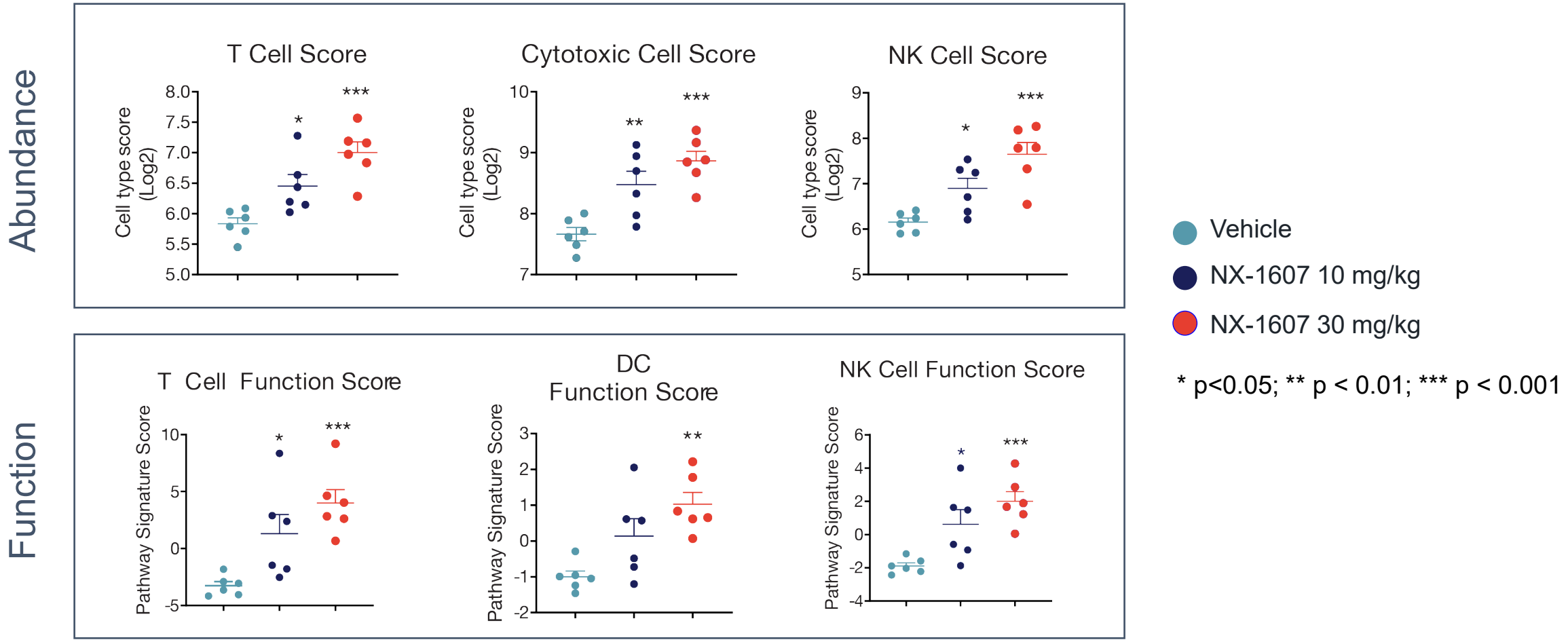
Triple-Negative Breast (4T1)



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

NX-1607 Treatment Induces Dose Dependent T and NK Cell Intratumoral Infiltration and Enhanced Function

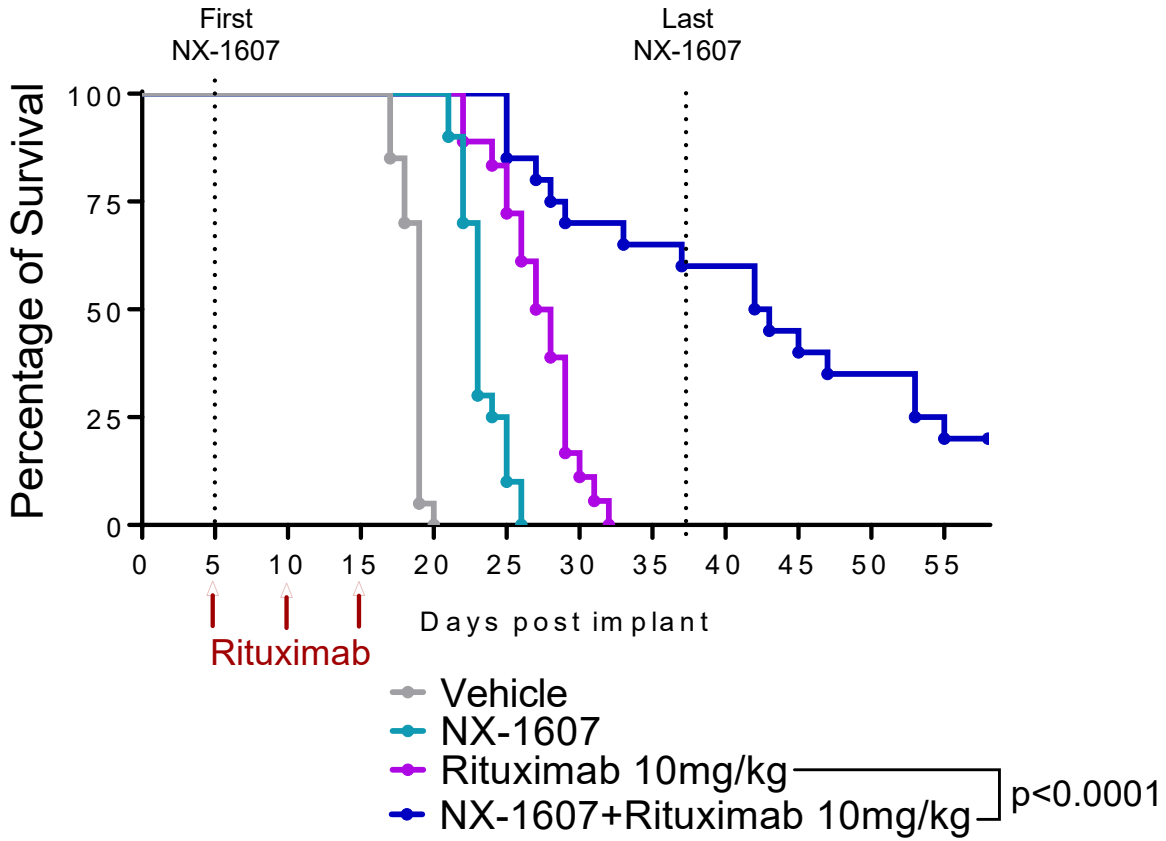


Tumor-bearing mice treated for 18 days with NX-1607 at 10 or 30 mg/kg. Tumor microenvironment profiled using NanoString technology.

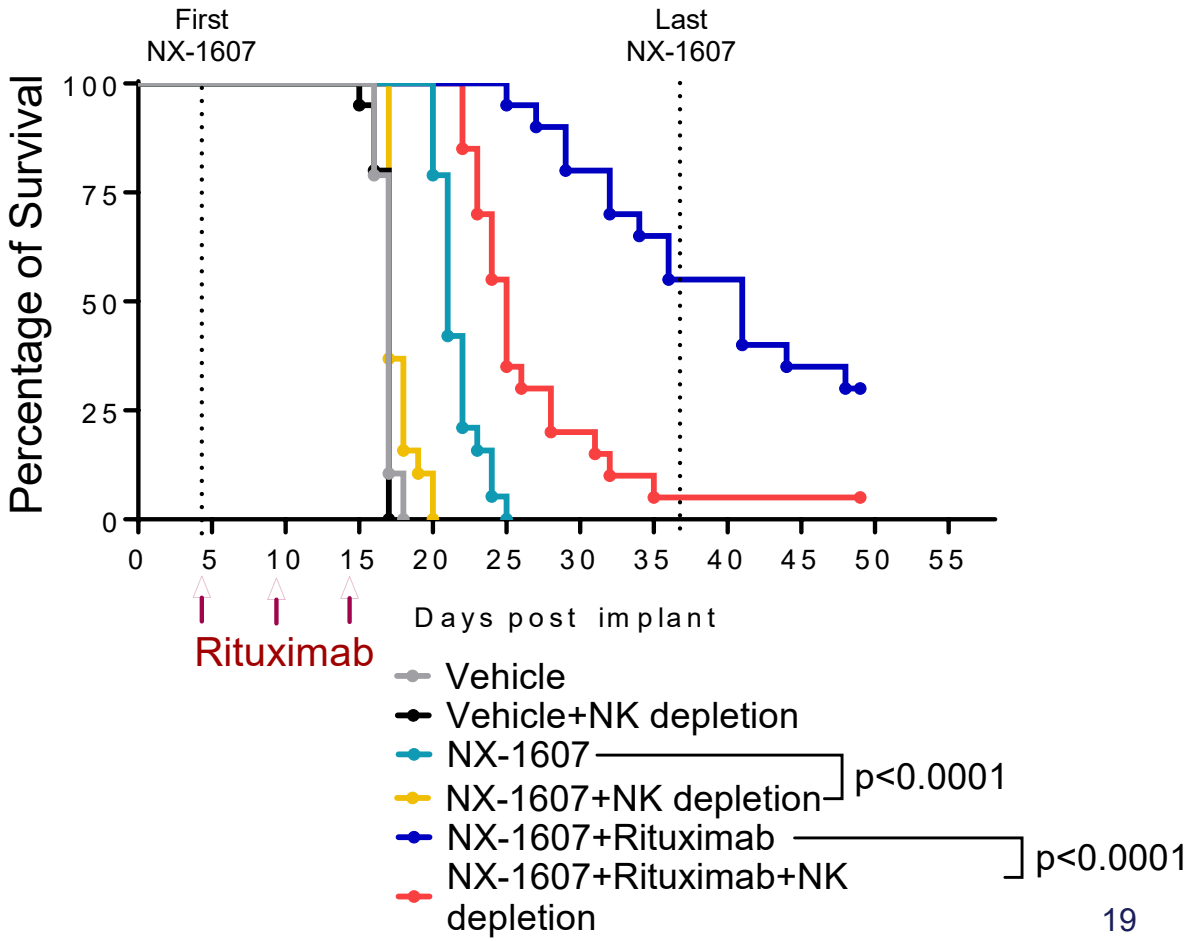
Combination of NX-1607 and Rituximab Enhances Anti-tumor Activity in a Human NHL Animal Model

NX-1607 Strongly Potentiate Rituximab-Directed NK Cell ADCC Against Tumor Cells

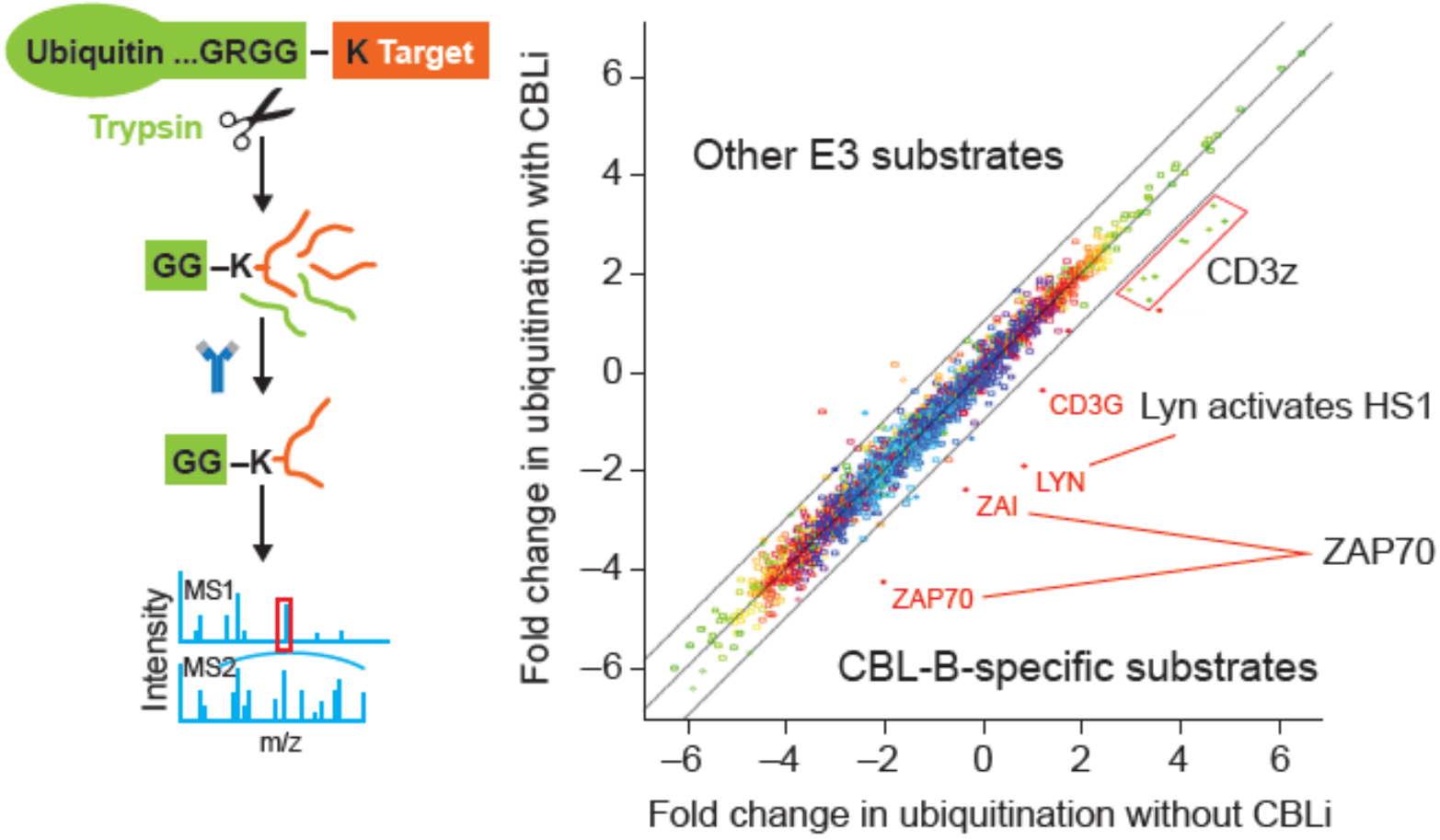
NX-1607-mediated NK activation potentiates rituximab antitumor activity



NK depletion abrogates NX-1607 and NX-1607 + Rituximab antitumor activity



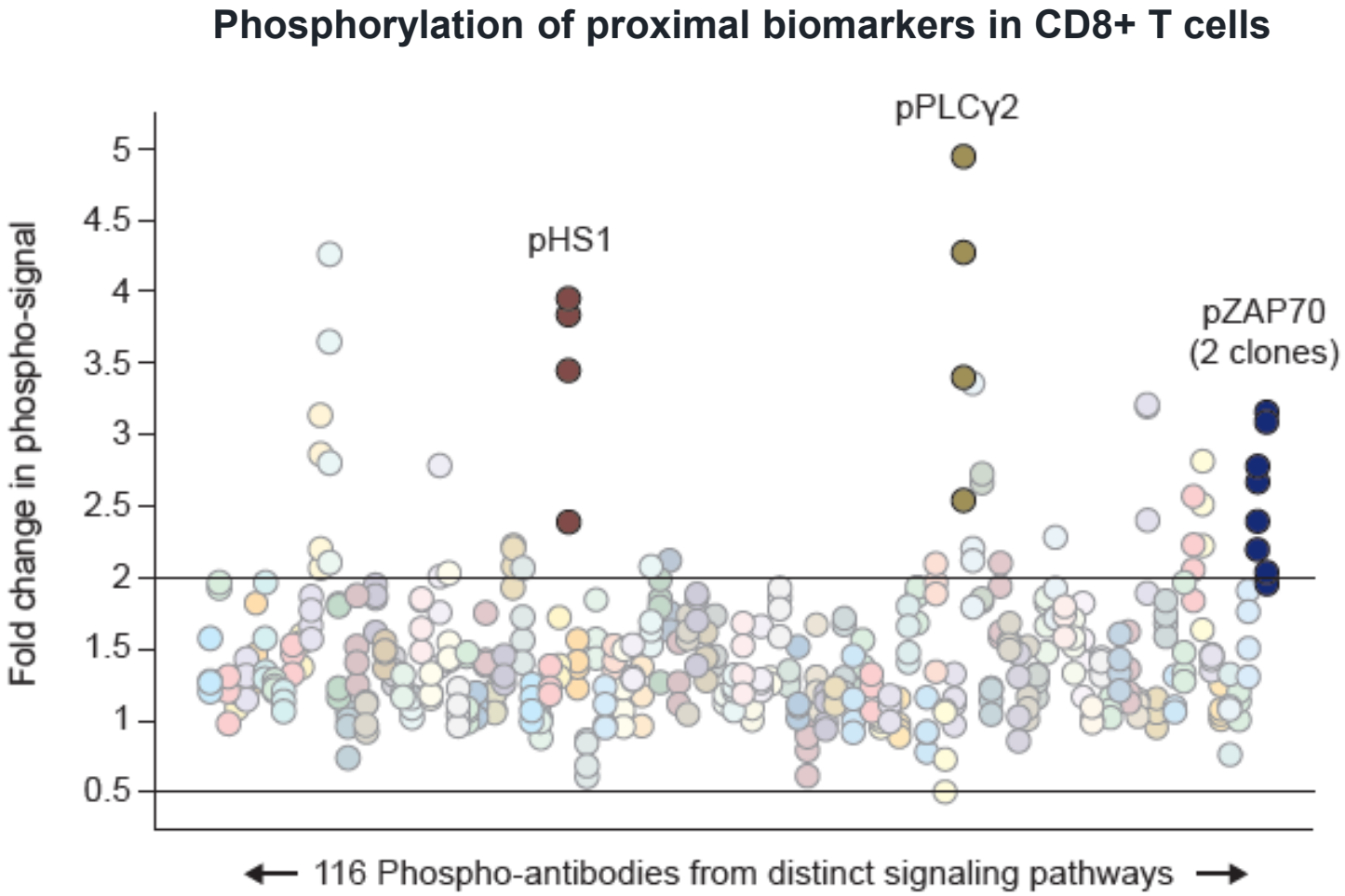
UbiScan Identified Direct CBL Substrates Within the T Cell Receptor (TCR) Signaling Cascade



Decreased signal represents direct substrates ubiquitinated by CBL-B ligase activity

Inhibiting CBL-B decreases ubiquitination of important T Cell receptor signaling molecules

Phospho-Protein Flow Cytometry Assay Identified Proximal Biomarkers



- Human PBMCs were stimulated with or without CBL-B inhibition
- Expression levels were determined for phospho-proteins downstream the TCR signaling
- Overlapping results from orthogonal assays (Ubiscan) provided confidence in proximal biomarker signals

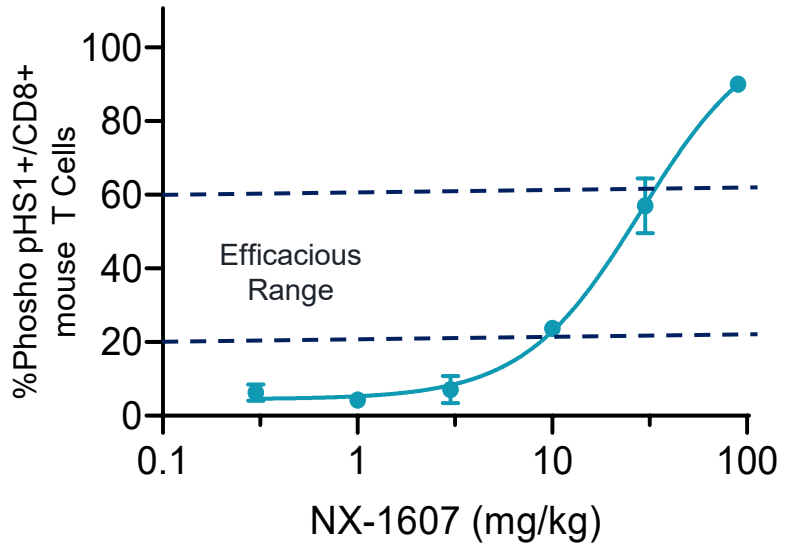
HS1: Substrate of LYN receptor, and an essential adaptor protein at the immune synapse, via VAV1

PLCγ2: Expressed in both T cells and B cells; associates with LAT and SLP-76 & becomes phosphorylated upon TCR stimulation

ZAP70: Key organizer of downstream TCR signaling

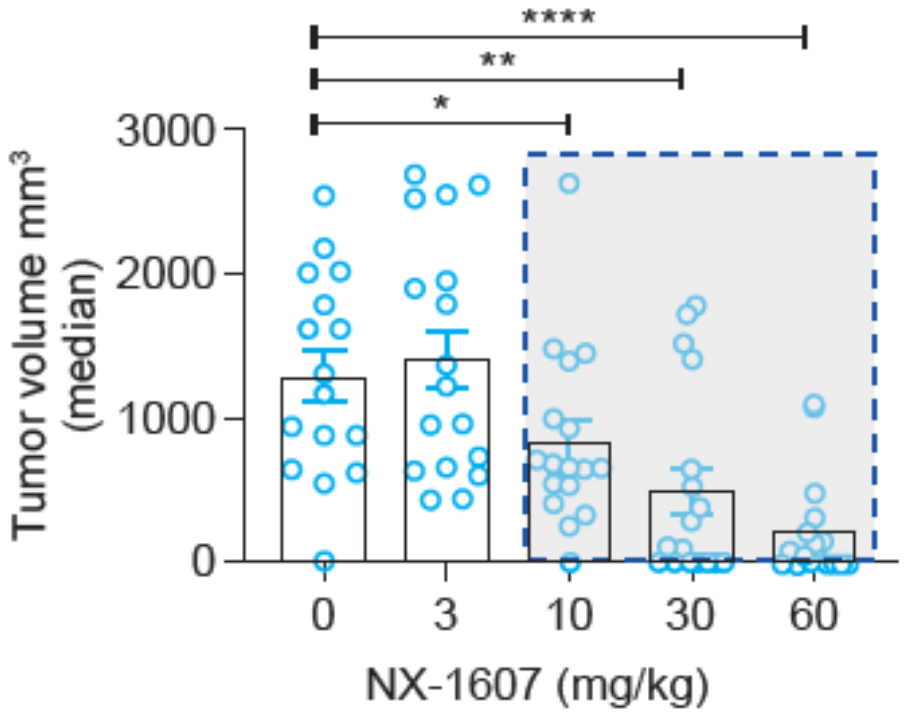
Dose Dependent Increases of CBL-B Proximal Biomarker Correlates with Antitumor Effects of NX-1607

Pharmacodynamic relationship in mice following NX-1607 dosing



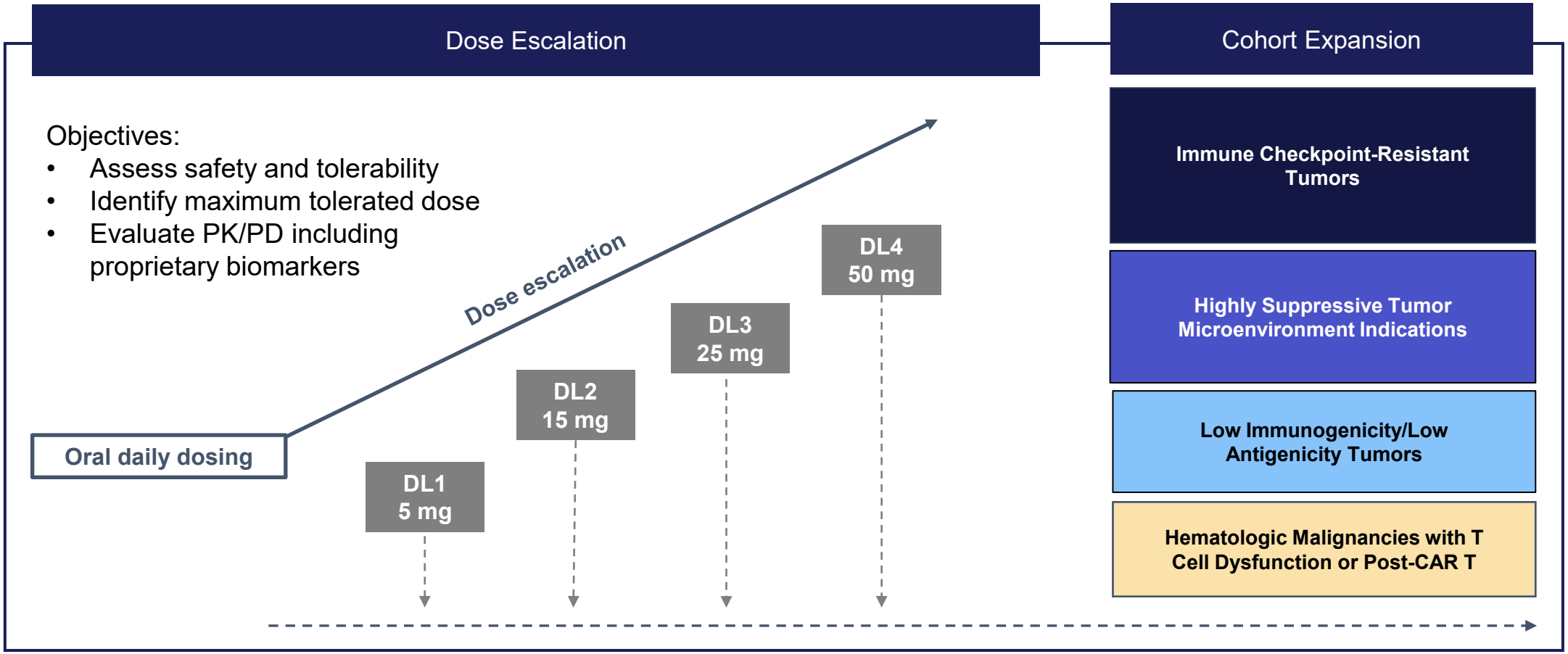
In vivo efficacy observed between 10-60 mpk which corresponds to ~20-60% pHS1+ CD8+ T Cells

NX-1607 reduced tumor volume



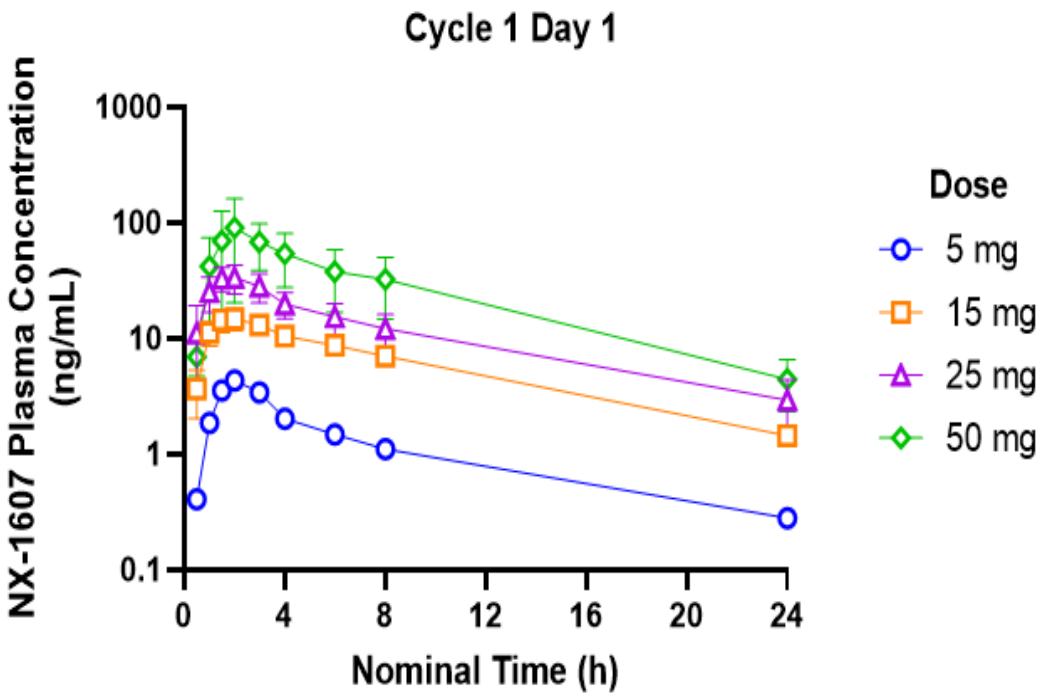
NX-1607-101: Phase 1 first-in-human clinical trial design

Two-Part Phase 1 Monotherapy Trial of NX-1607 in Relapsed or Refractory Tumors



NX-1607-101 Interim PK Results Suggest Linear PK

- Preliminary PK data suggest NX-1607 has dose-proportional exposures and a mean half-life of 6 to 8 hours at doses ranging from 5 to 50 mg



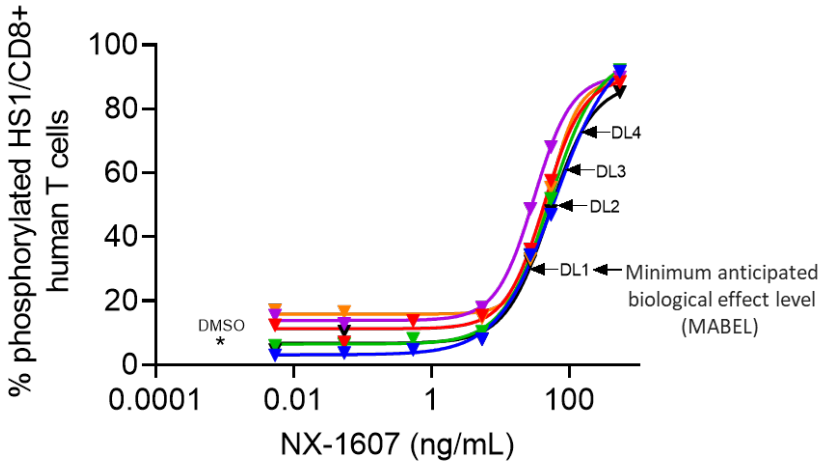
Dose	Cycle 1 Day 1			
	C_{max} (ng/mL)	$AUC_{0\text{-last}}$ (h*ng/mL)	T_{max} (h)	$t_{1/2}$ (h)
5 mg (n=1)	4.35	26.2	2.0	7.72
15 mg (n=9)	16.2 (38.5)	129 (33.4)	2.0 (1.5 - 6.0)	7.14 (19.8)
25 mg (n=6)	30.1 (109)	201 (103)	1.5 (1.0 - 3.0)	6.82 (27.5)
50 mg (n=2)	79.2 (134)	502 (113)	2.5 (2.0 - 3.0)	5.88 (7.7)

LLOQ = 0.05 ng/mL
Data extract date: Dec 7th, 2022

C_{max} and $AUC_{0\text{-last}}$ are presented as geometric mean (geometric %CV); T_{max} is presented as median (range); $t_{1/2}$ is presented as mean (%CV)

Characterization of a Novel Biomarker and First Evidence of Target Engagement for a CBL-B Inhibitor in the Clinic

Human whole blood and dose projection modeling

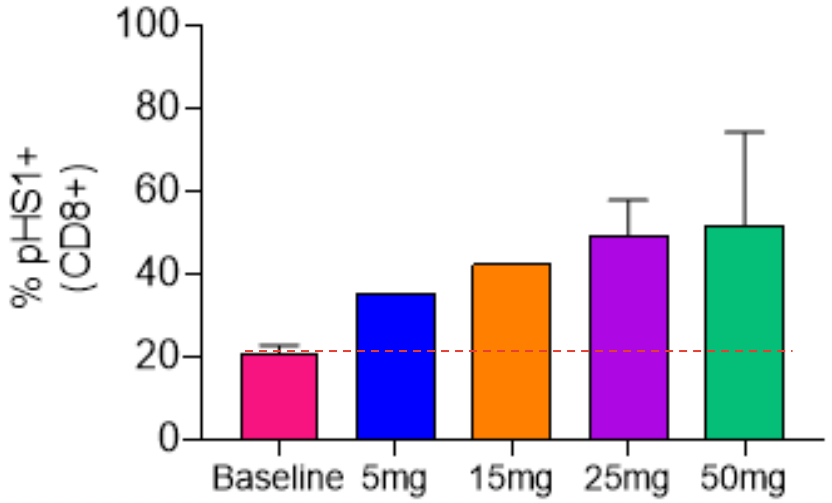


Proposed dose level[a]	NX-1607 dose (mg)	Estimated % HS1+/CD8+ T cells
-1	2.5	22.2
1[b]	5	30.0
2	15	49.7
3	25	60.6
4	50	74.0

[a]Dose levels in NX-1607-101.
[b]Minimum anticipated biological effect level (MABEL).

Clinical data

Maximal % pHS1+ expressing CD8+ T cells observed in C1D1



	Dose level 1 5mg	Dose level 2 15mg	Dose level 3 25mg	Dose level 4 50mg
Cycle 1, N:	1	1	6	2

NX-1607-101 Clinical Trial Status

- Dose escalation is ongoing
- Consistent with preclinical models, we are observing dose-dependent increases of proximal biomarkers
- Initial clinical data from Phase 1a is expected in H2 2023
- We expect to define Phase 1b dose for cohort expansion in H2 2023

Summary and Conclusions

- E3 Ligases like CBL-B can act as gate-keepers of signaling pathways, therefore they can be powerful therapeutic targets
- Inhibition of E3 ligases can raise the levels of many substrate proteins in a coordinated fashion, which can be desirable in a disease setting like cancer
- Nurix CBL-B inhibitors act as intra-molecular glues, locking CBL-B in an inactive conformation and preventing the phosphorylation and activation of this E3 Ligase
- Inhibition of CBL-B shows single agent anti-tumor activity and synergizes with Anti-PD1 to enhance anti-tumor effects and survival of mice in multiple tumor models
- A first-in-human phase 1 clinical trial was initiated for NX-1607. Early results show linear PK and evidence of target engagement using a novel biomarker representing a direct substrate of CBL-B.
- Initial Clinical data from this trial is expected later this year (2H 2023).

Thank You!