nurix

Leader in Targeted Protein Modulation

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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Discovery on Target

Boston

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Nurix Drugs Engage Ligases for the Treatment of Cancer

Targeted Protein Modulation: TPM = TPD + TPE

A Powerful Cellular System

CBL-B Inhibitor NX-1607 Targeted Protein Elevation (TPE)

Inhibit ligases to increase specific protein levels

Harness ligases to decrease specific protein levels

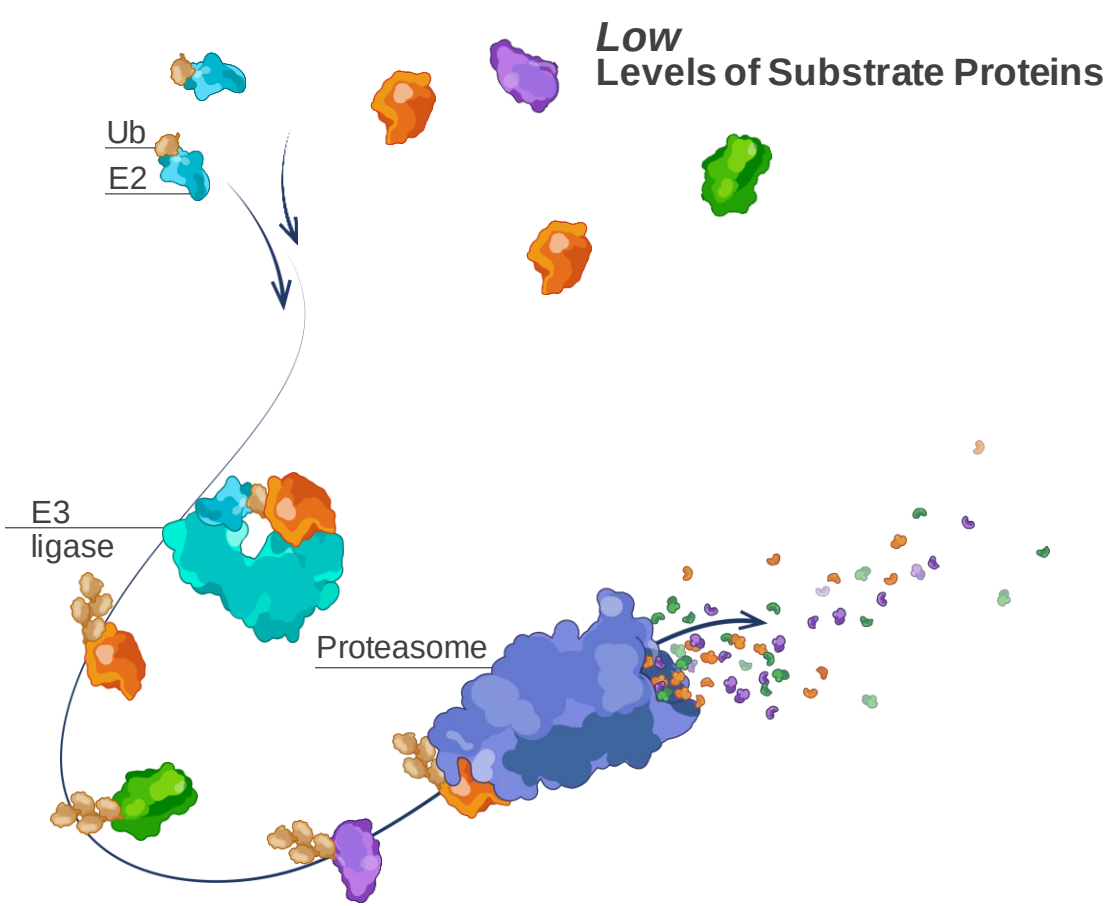
Targeted Protein Degradation (TPD) BTK degraders

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

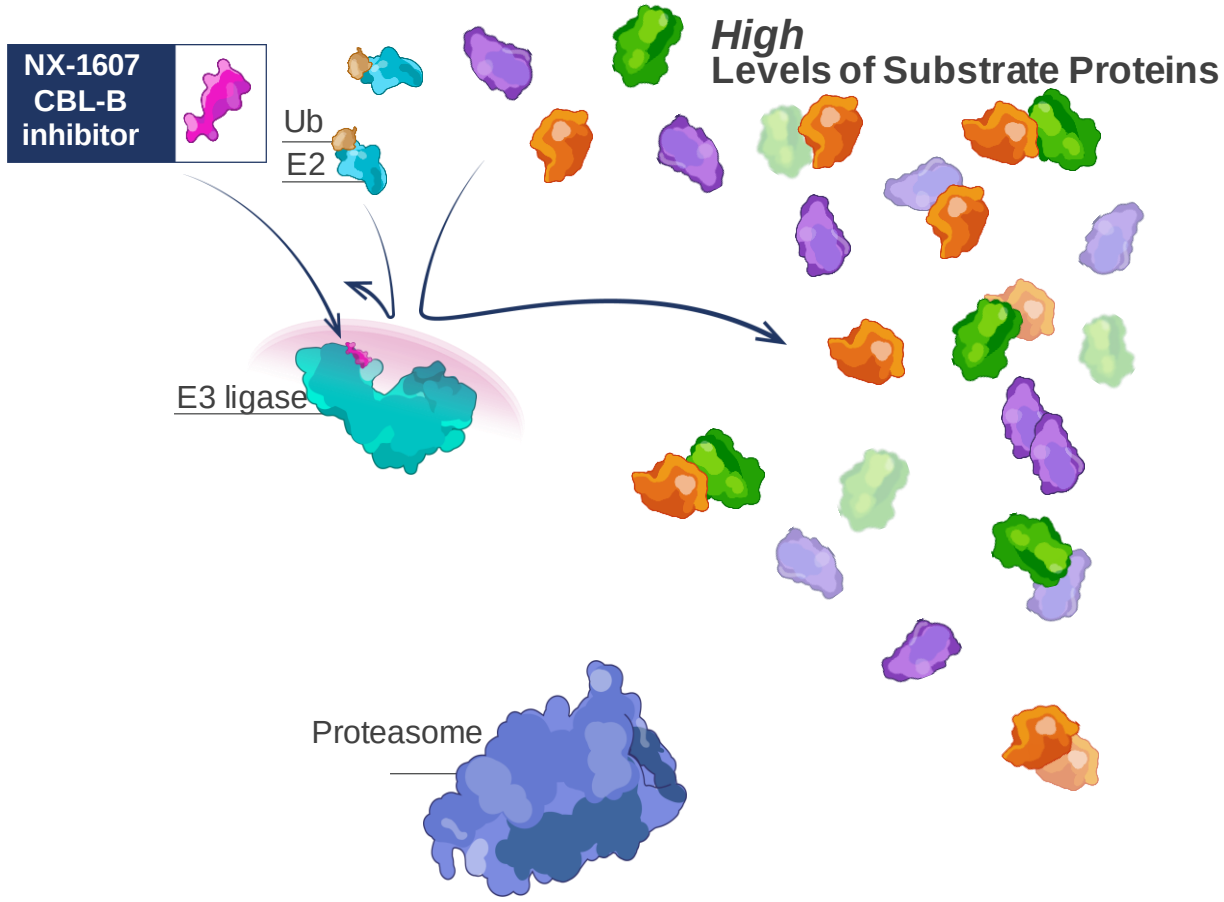
Targeted Protein Elevation

The Journey of CBL-B Inhibitor Discovery

CBL-B is an E3 ligase that restrains the levels of substrate proteins necessary for optimal anticancer response



CBL-B inhibition leads to elevated levels of substrate proteins which can restore cancer immunity



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

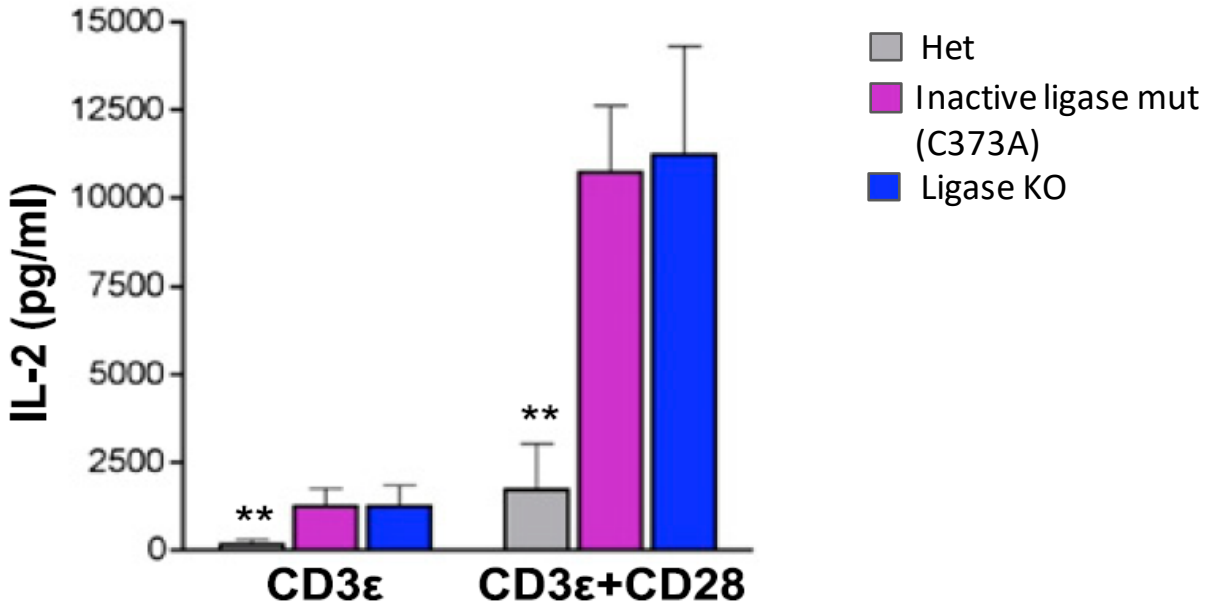
A CBL-B Inhibitor Could Revolutionize Cancer Treatment

- The ultimate goal of cancer immunotherapy is to generate a coordinated immune system response against cancer associated antigens
- Immune checkpoint agents such as anti-PD-1/PD-L1 have demonstrated impressive long-lasting responses in only a subset of patients
- Resistance mechanisms prevent most patients from responding:
  - ⇢ Low antigen presenting cells and NK cells within the tumor
  - ⇢ Tumor microenvironment not permissive to T cell trafficking in the tumor
  - ⇢ Excessive T cell exhaustion from chronic antigen stimulation
  - ⇢ Downregulation of MHC Class I
- CBL-B inhibitors are optimal next generation IO agents: act on multiple immune cells, addressing multiple resistance mechanisms

CBL-B is a Master Orchestrator of Immune Cell Activation

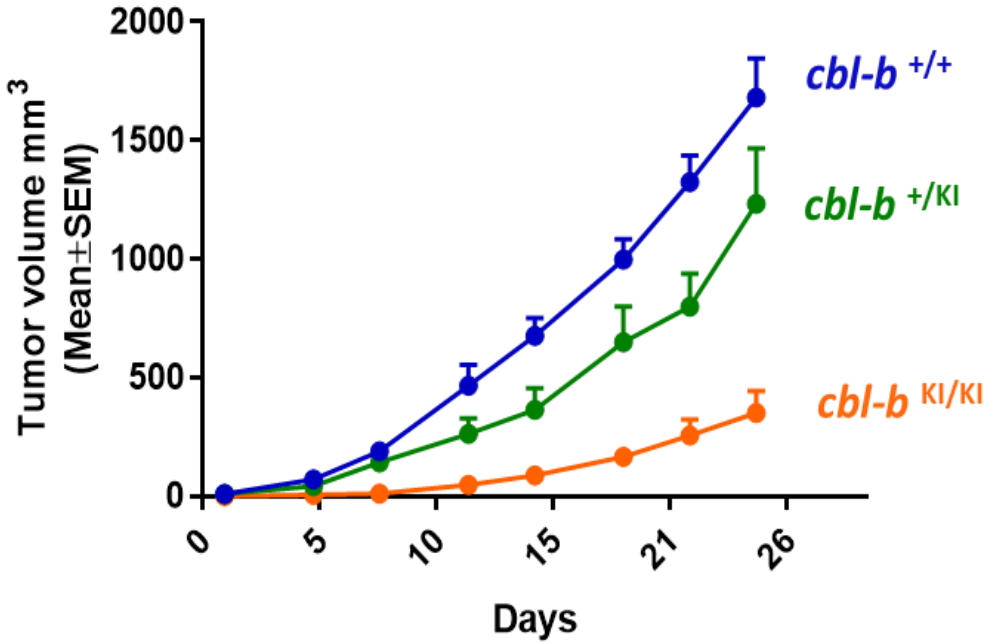
Loss of CBL-B ligase activity results in hyperactive T cells that can reject tumors

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

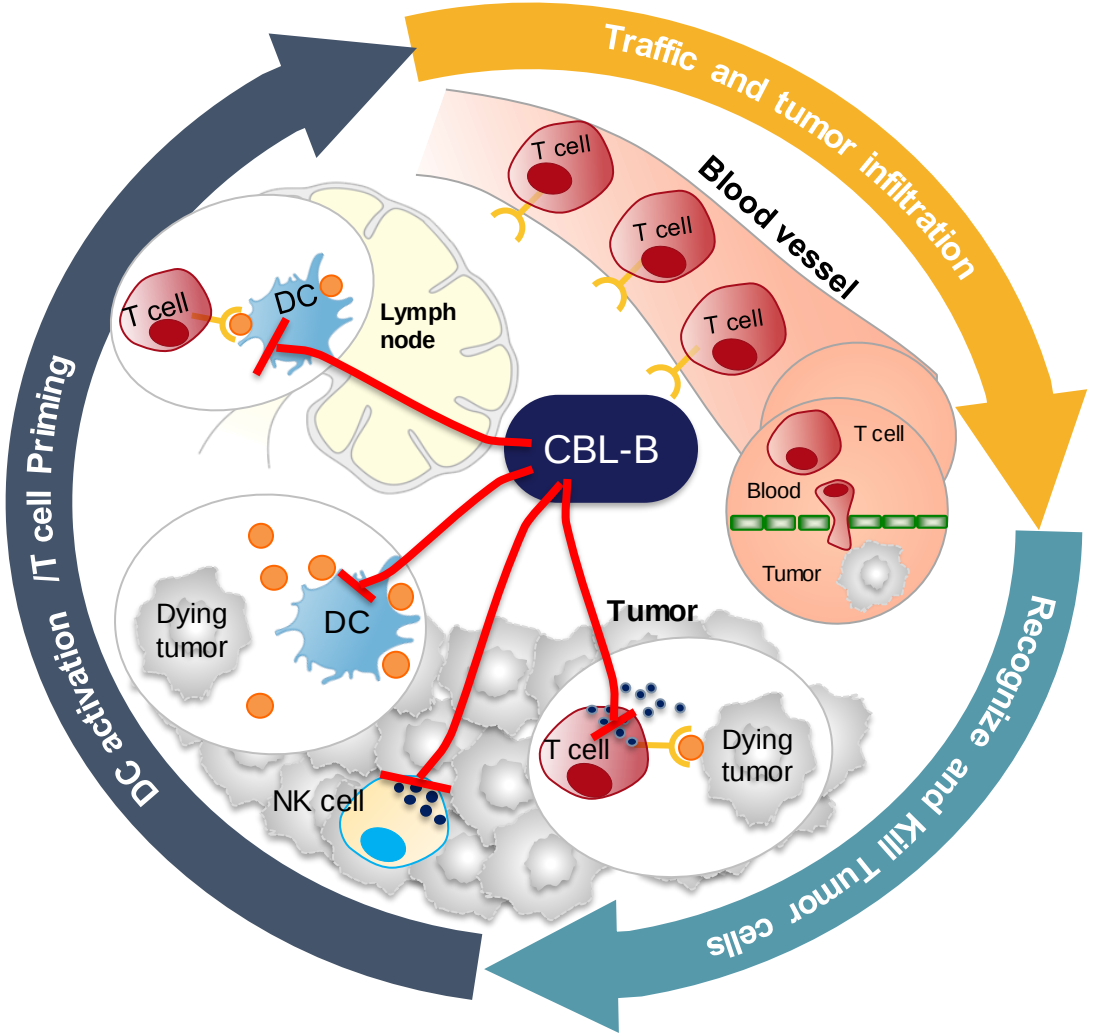
Targeting CBL-B Enhances Antitumor Response

A Master Orchestrator of the Immune System

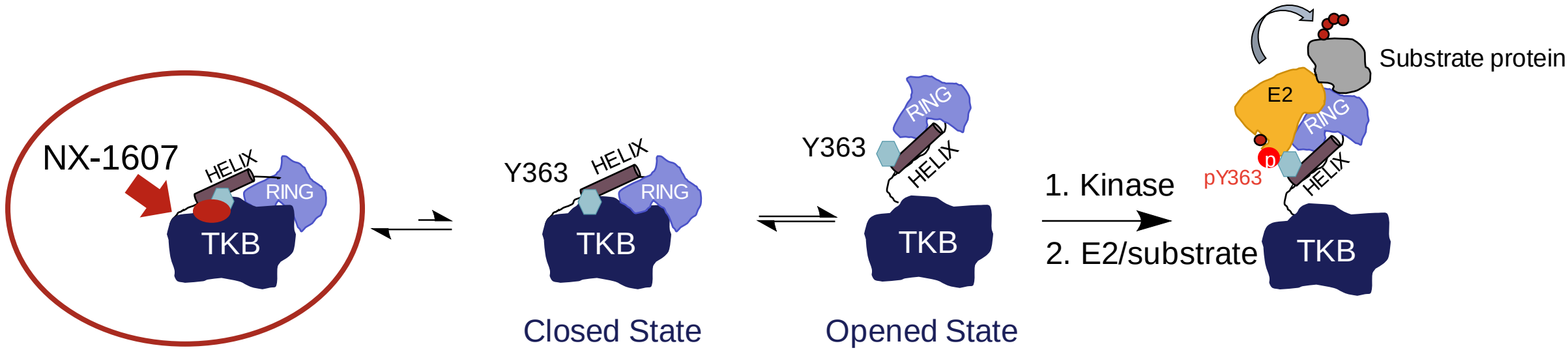
CBL-B is an E3 ubiquitin ligase that strongly restrains a productive anti-tumor response

NX-1607, a CBL-B inhibitor, acts as an intramolecular glue & 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



NX-1607 Mechanism of Action: Intramolecular Glue



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

Leading to Enhanced Immune Response

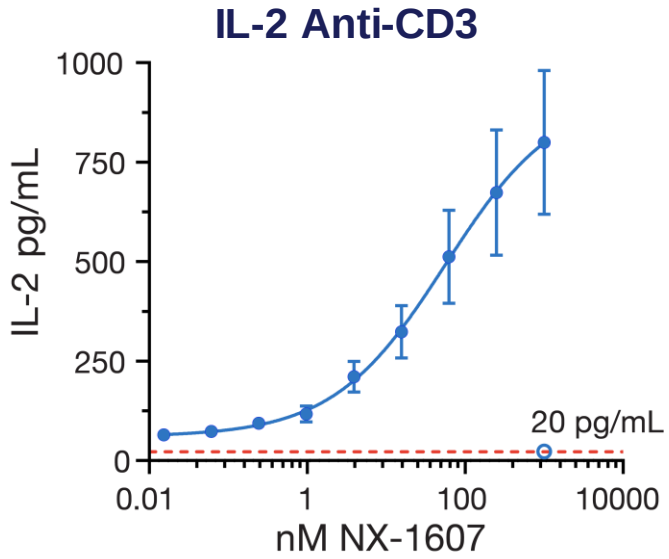
Closed State
INACTIVE

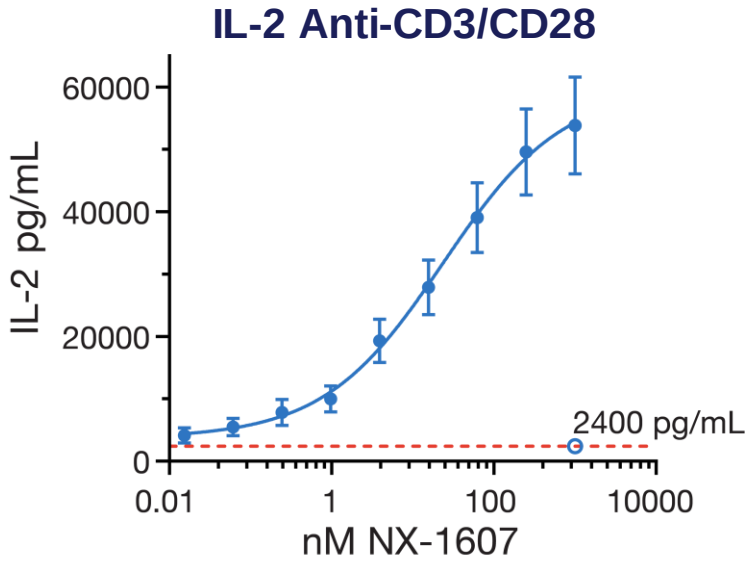
Opened State

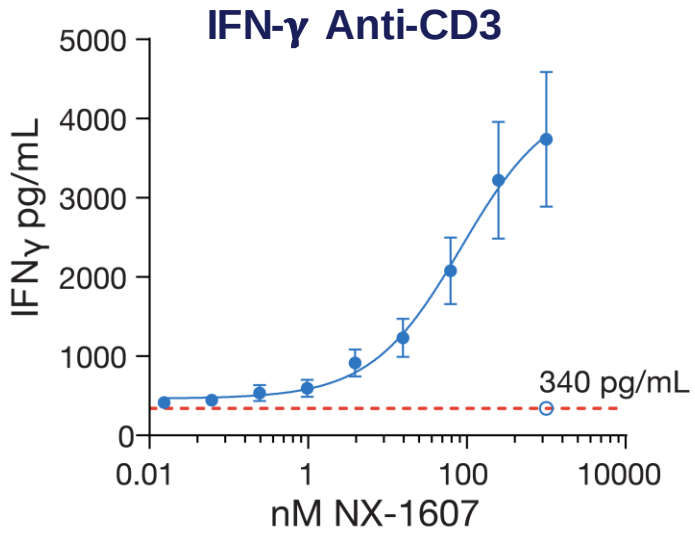
Phosphorylation locks CBL-B in the **ACTIVE** Conformation

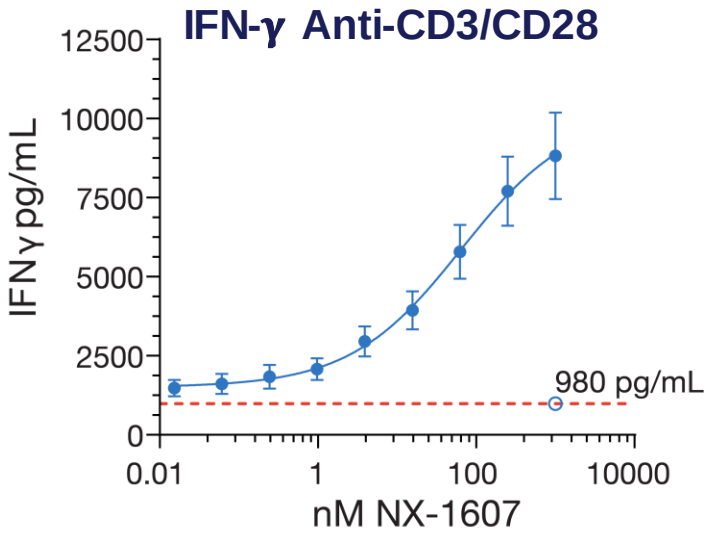
Decreased Immune Response

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









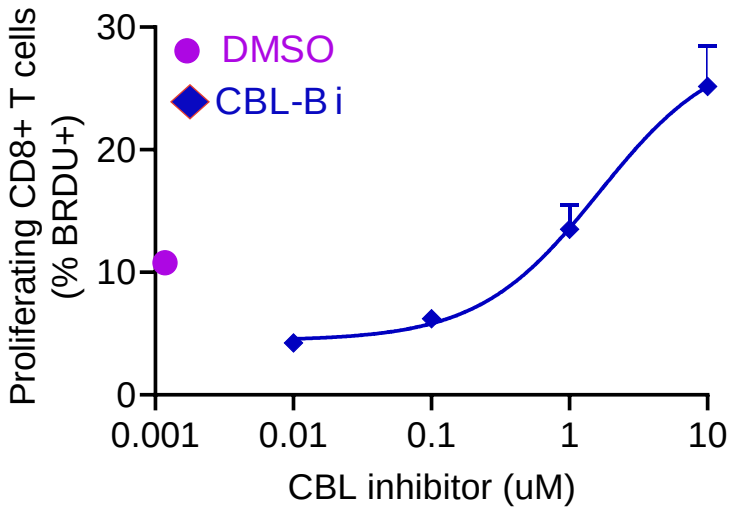
NX-1607 increases TCR stimulation-dependent production of IL-2 and IFN-γ in primary human T cells

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

Cytokine Response
Baseline Response

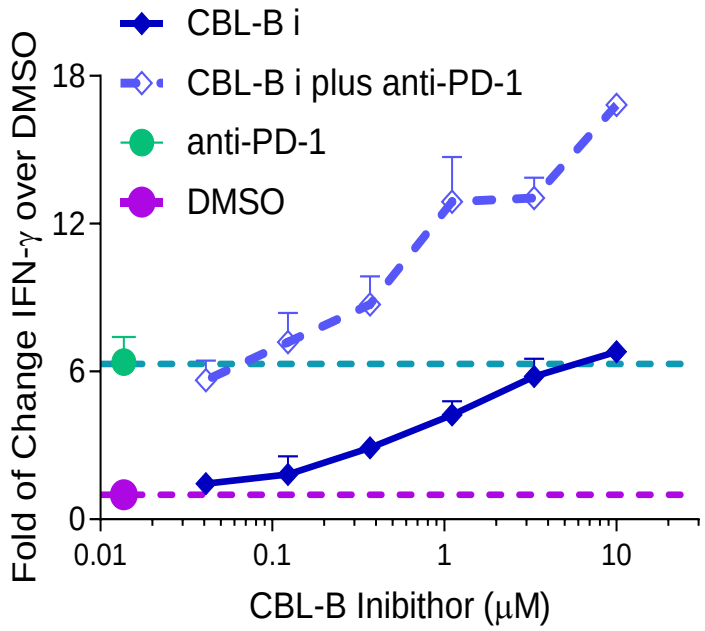
CBL-B Inhibition Enhances T Cell Proliferation and Function

CBL-B inhibition enhances antigen recall



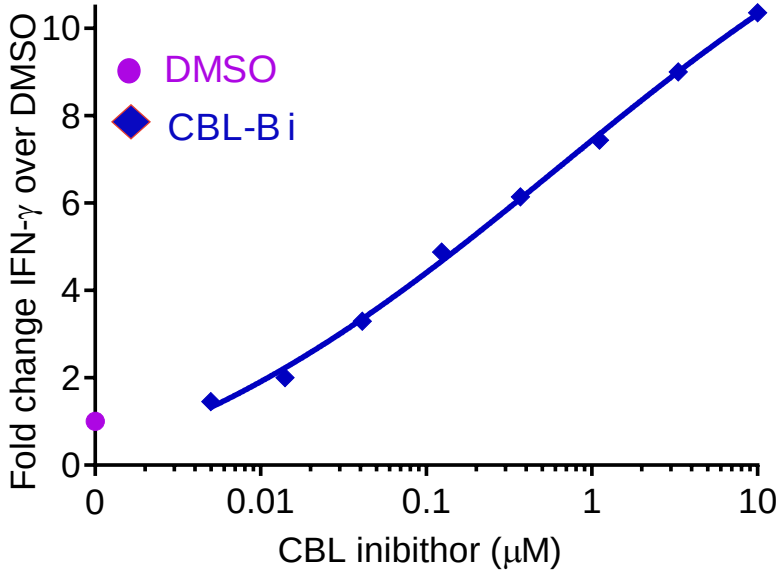
Human PBMC stimulated with CMV antigen for 120 hr in presence or absence of CBL inhibitor

CBL-B inhibition enhances exhausted T cell function



Human exhausted T cells were re-stimulated in presence of CBL-Bi or anti-PD-1 or a combination of the two.

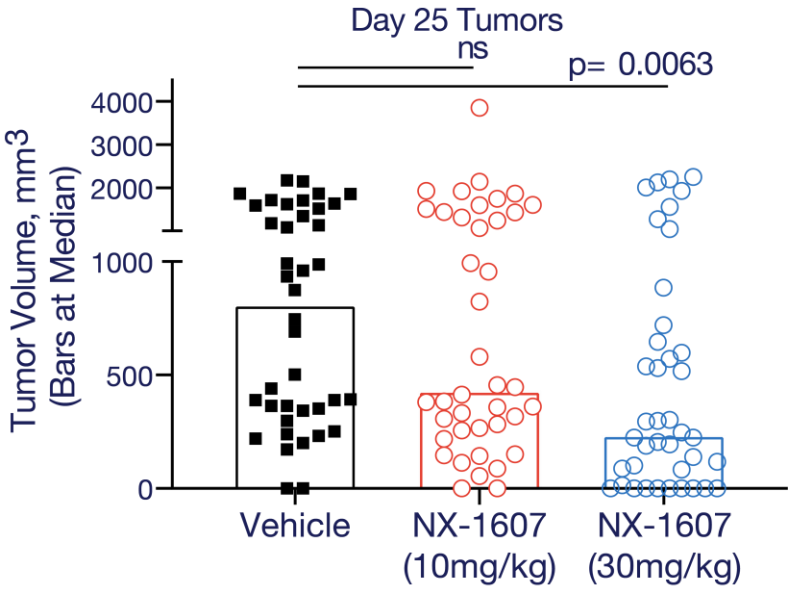
CBL-B inhibition enhances anergic T cell function



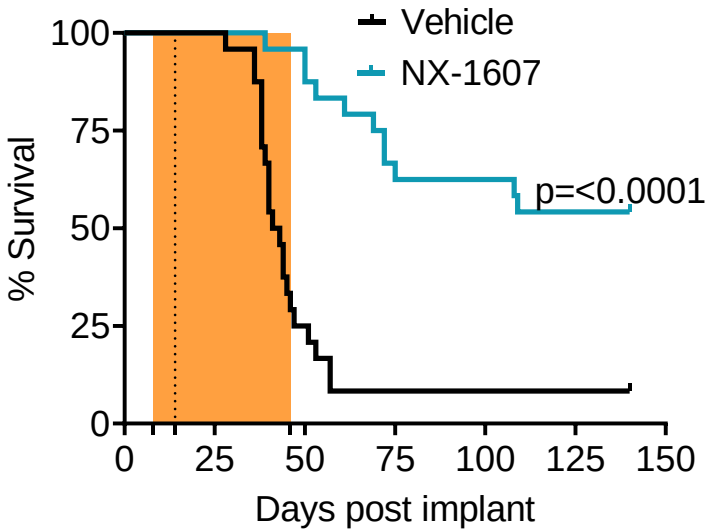
Anergic human T cells were restimulated with CD3/CD28 for 48 hr in presence or absence of CBL inhibitor

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

NX-1607
Reduced Tumor Volume
Colorectal

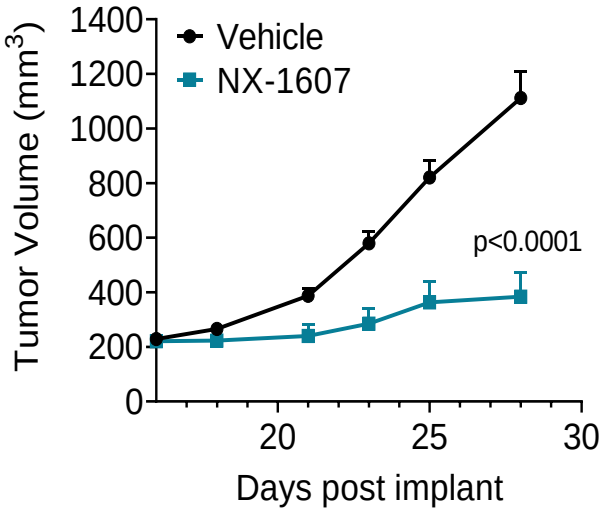


NX-1607
Prolonged Survival
Triple-Negative Breast



NX-1607 30 mg/kg day 7 to 46

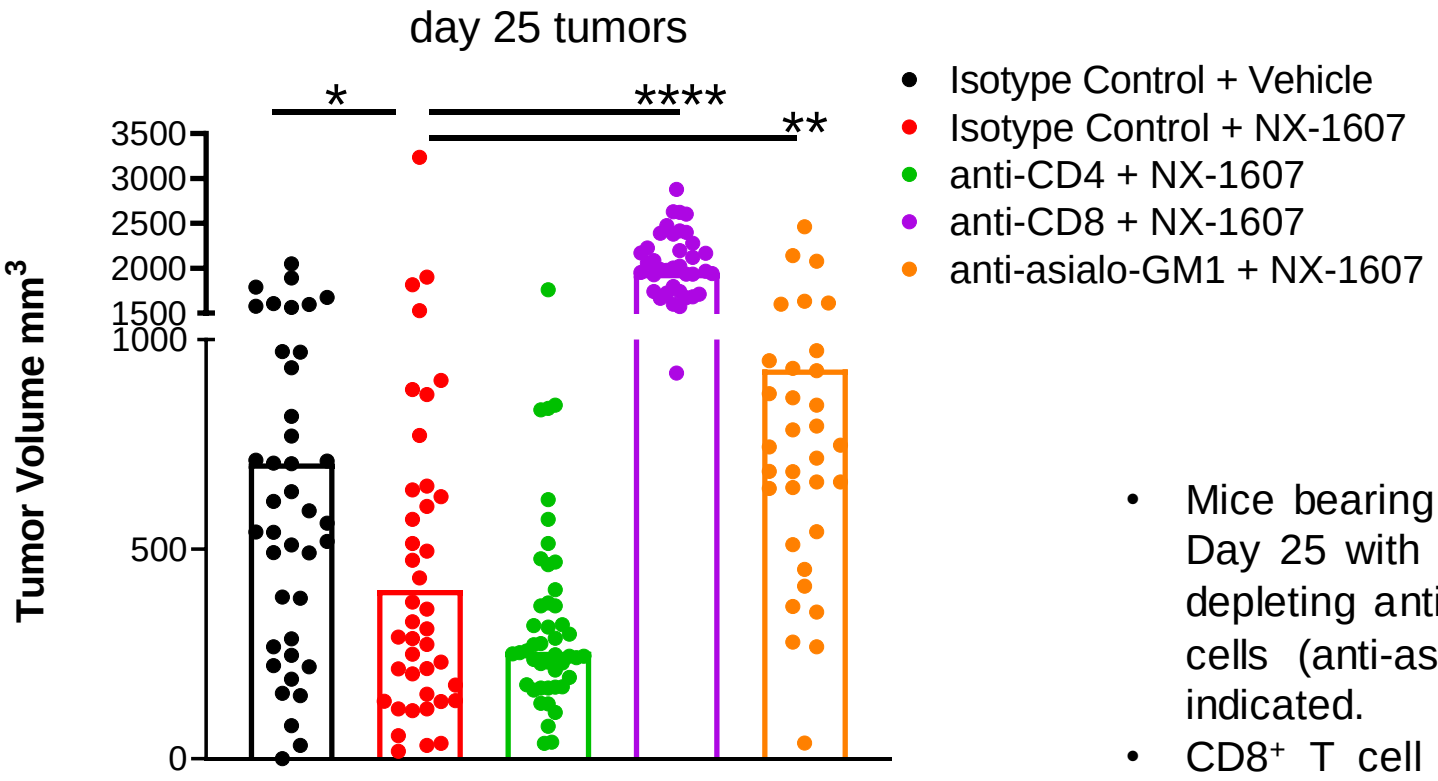
NX-1607
Reduced Tumor Volume
B Cell Lymphoma



NX-1607 30 mg/kg day 16 to 28

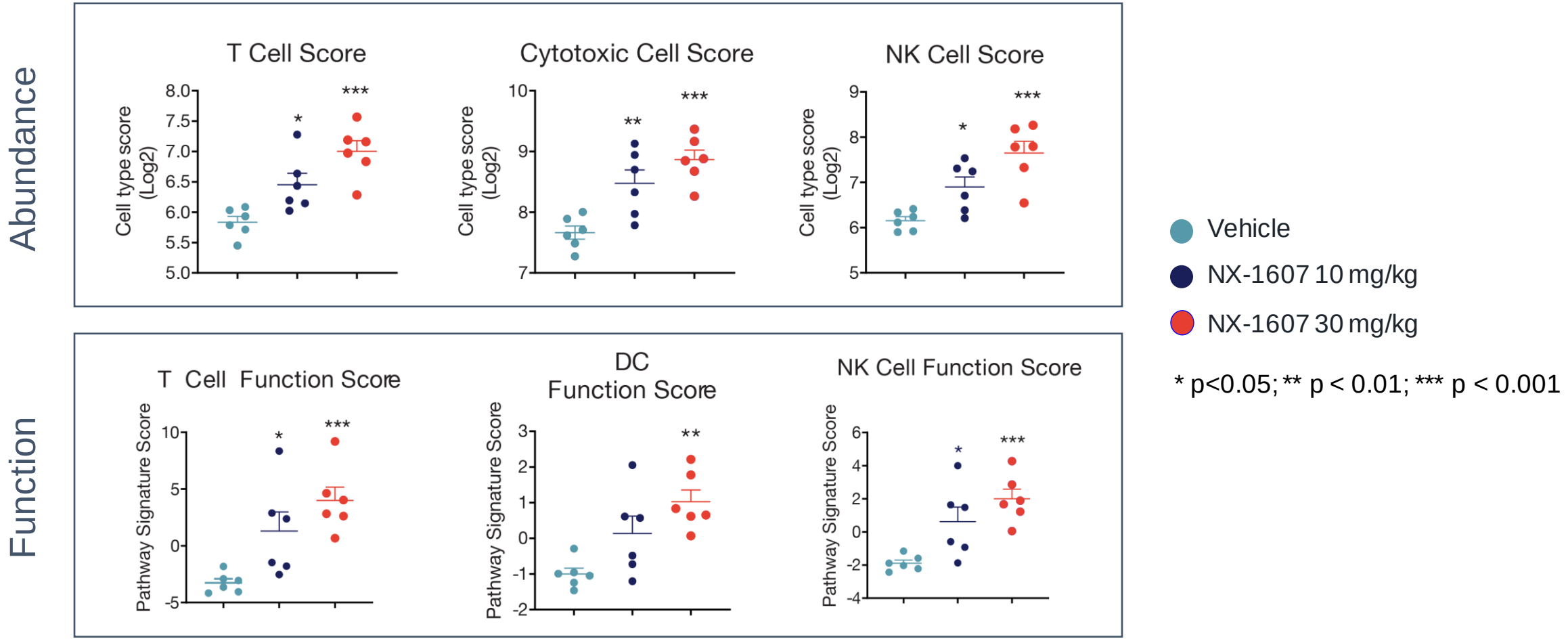
Shaded area indicates dosing period

NX-1607 Antitumor Efficacy is Abrogated by CD8+ T or NK Cell Depletion



- Mice bearing CT26 tumors were treated from Day 9 to Day 25 with oral NX-1607 at 30 mg/kg in presence of depleting antibodies for CD4+ cells, CD8+ cells, or NK cells (anti-asialo-GM1). Tumor volume at Day 25 is indicated.
- $CD8^+$ T cell or NK cell depletion abrogates NX-1607 activity.

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.

NX-1607 Treatment Results in Immune Cell Phenotypic Changes, Both in the Tumor Microenvironment (TME) and in Peripheral Blood in Animal Models

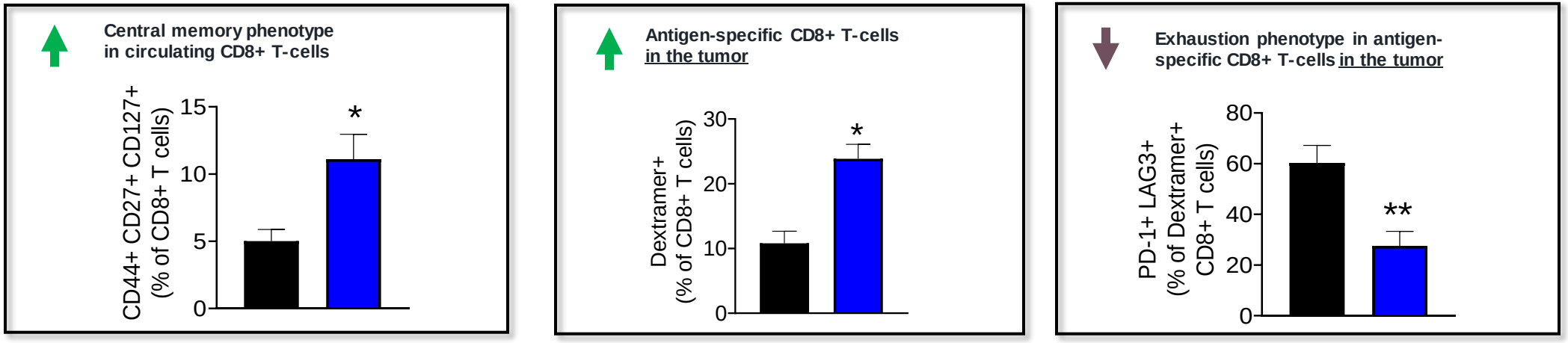
Circulation

Increased Central Memory

Tumor

Increased CD8+ T cells

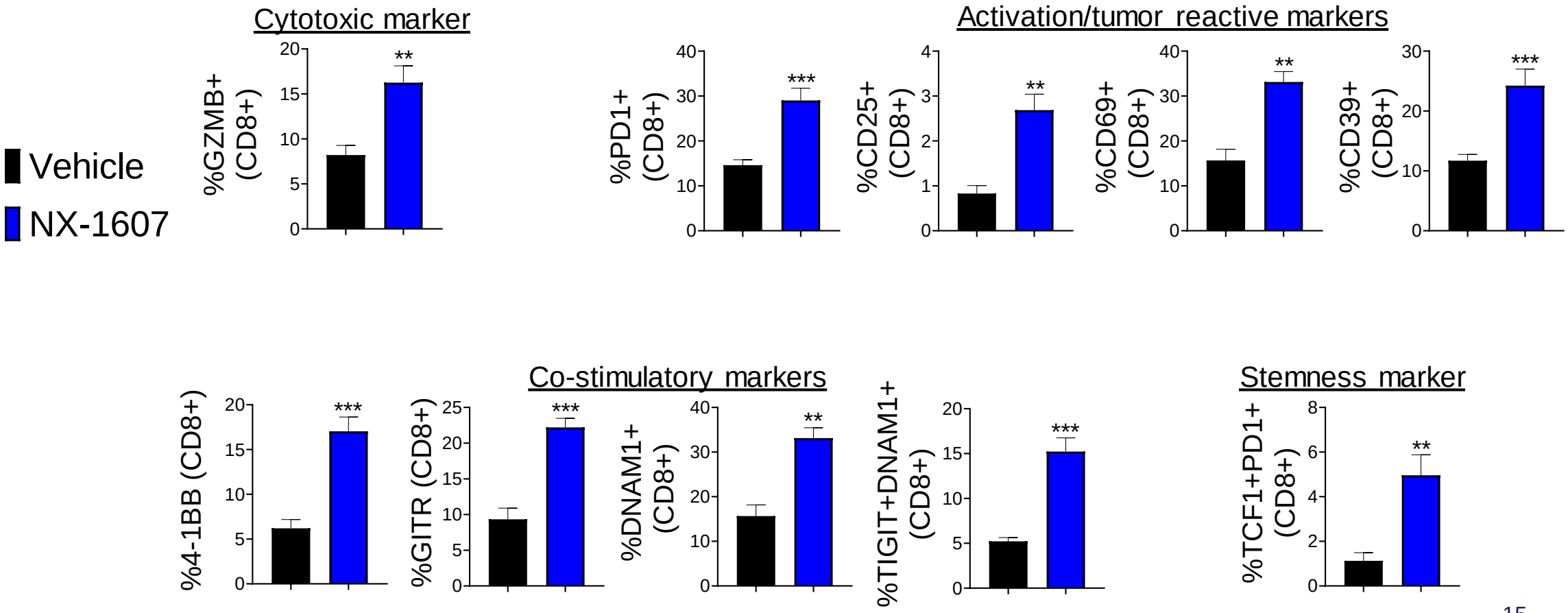
Decreased Exhaustion



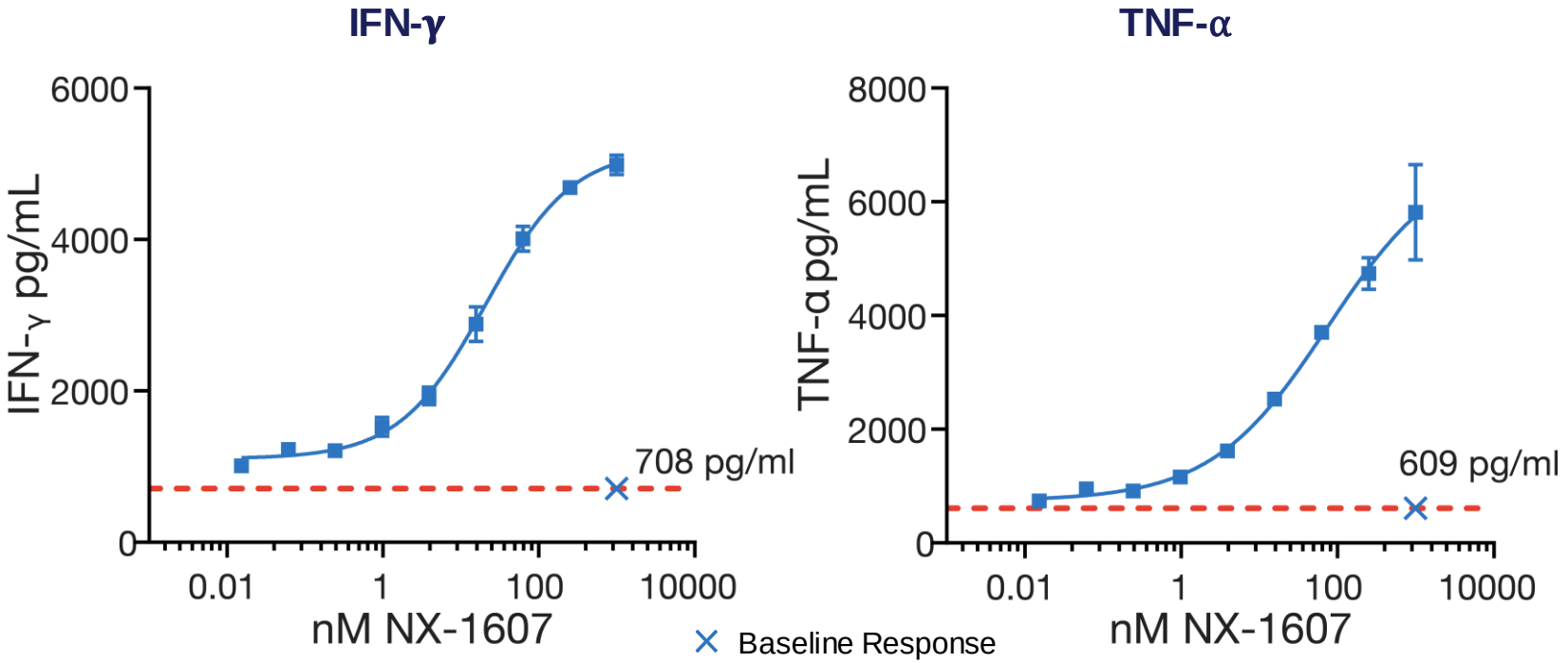
4T1 breast cancer model. ANOVA test with post-hoc Dunn's multiple comparisons test * $p<0.05$; ** $p<0.01$

Response to NX-1607 is Associated with Tumor CD8+ T Cell Subsets Characterized by High Expression of Cytotoxic, Activation and Co-Stimulatory Markers

Tumor Infiltrating Lymphocyte phenotype:



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

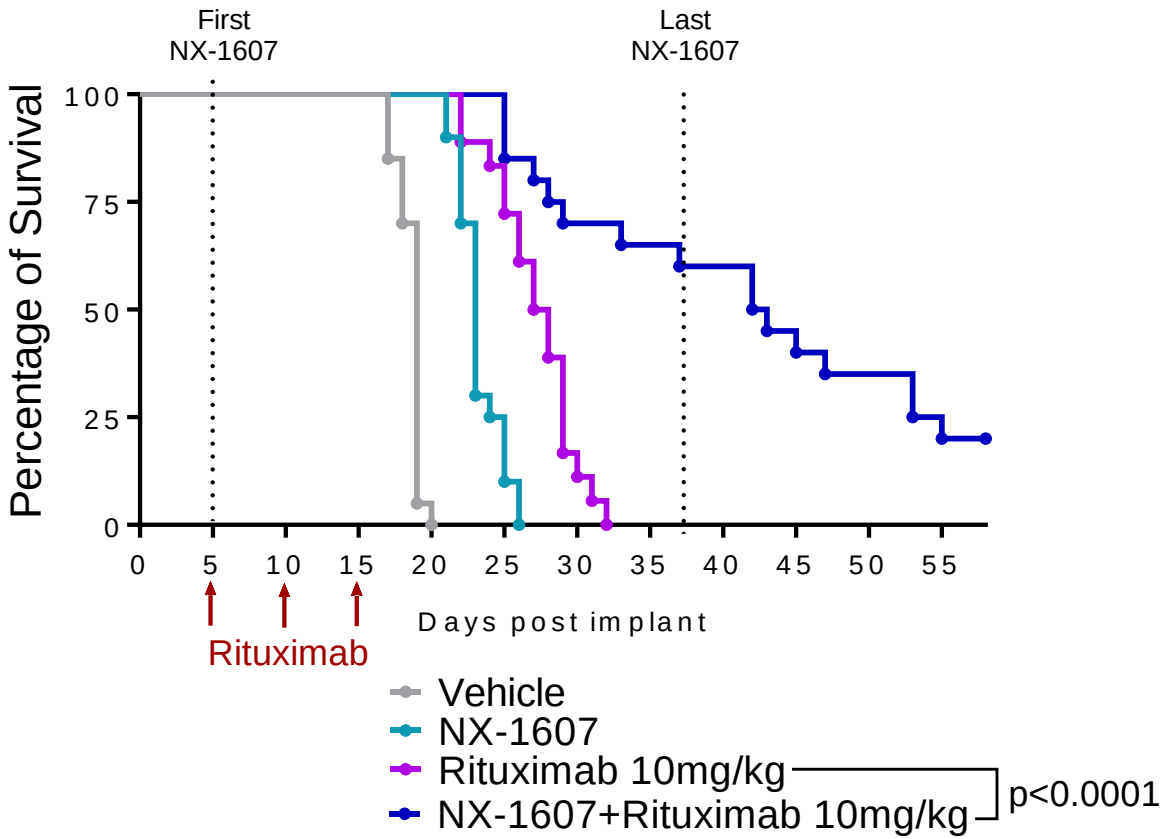
NK K562 Killing Assay

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

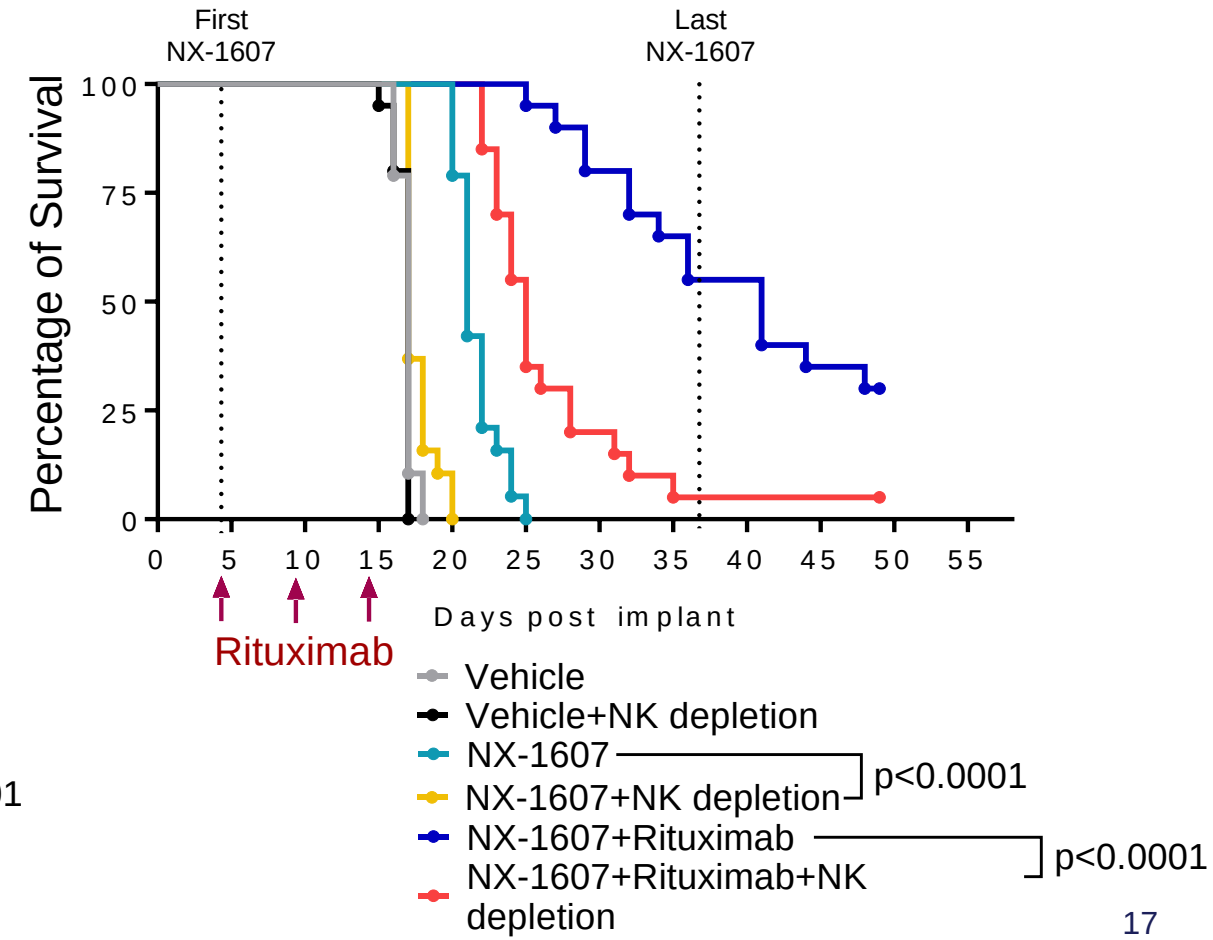
Combination of NX-1607 and Rituximab Enhances Anti-tumor Activity in a Human NHL Animal Model

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

NX-1607-mediated NK activation potentiates rituximab antitumor activity

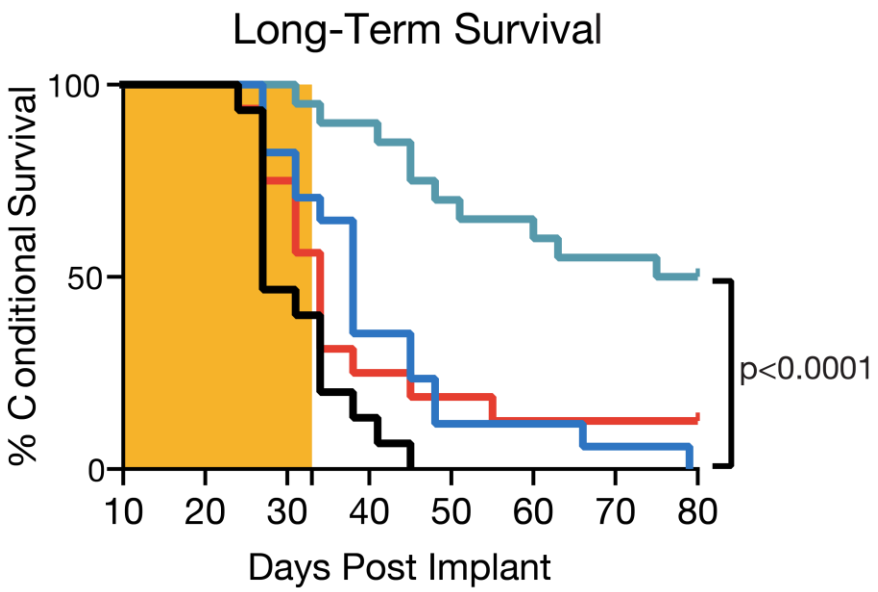


NK depletion abrogates NX-1607 and NX-1607 + Rituximab antitumor activity

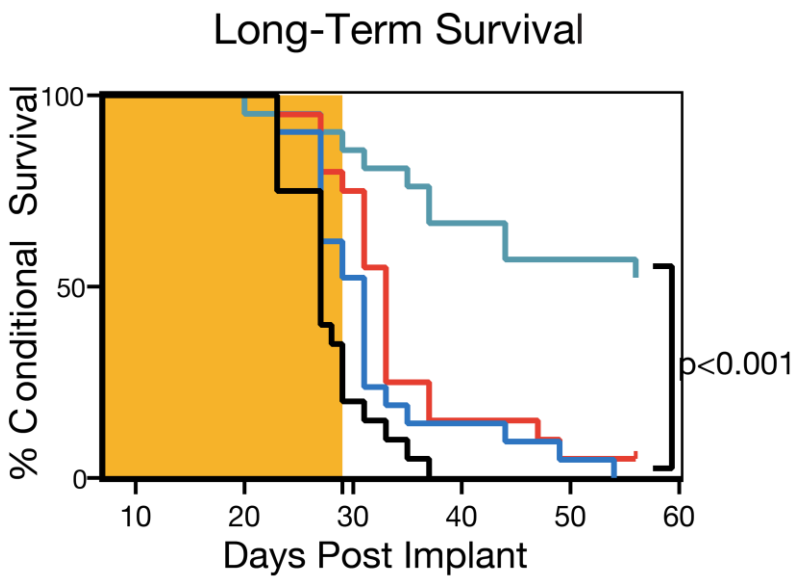


NX-1607 and Anti-PD-1 Synergize to Enhance Anti-tumor Effects and Survival of Mice in Multiple Tumor Models

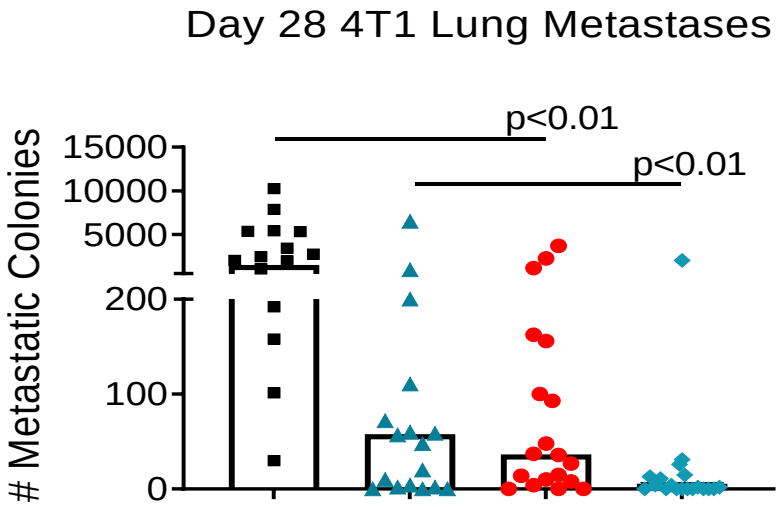
Colorectal (CT26)



Colorectal (MC38)



Triple-Negative Breast (4T1)

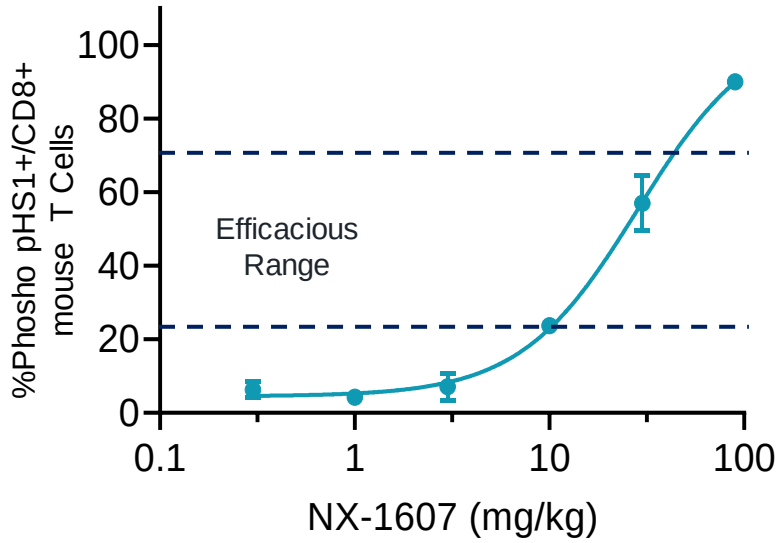


Vehicle NX-1607 anti-PD-1 NX-1607+anti-PD-1

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

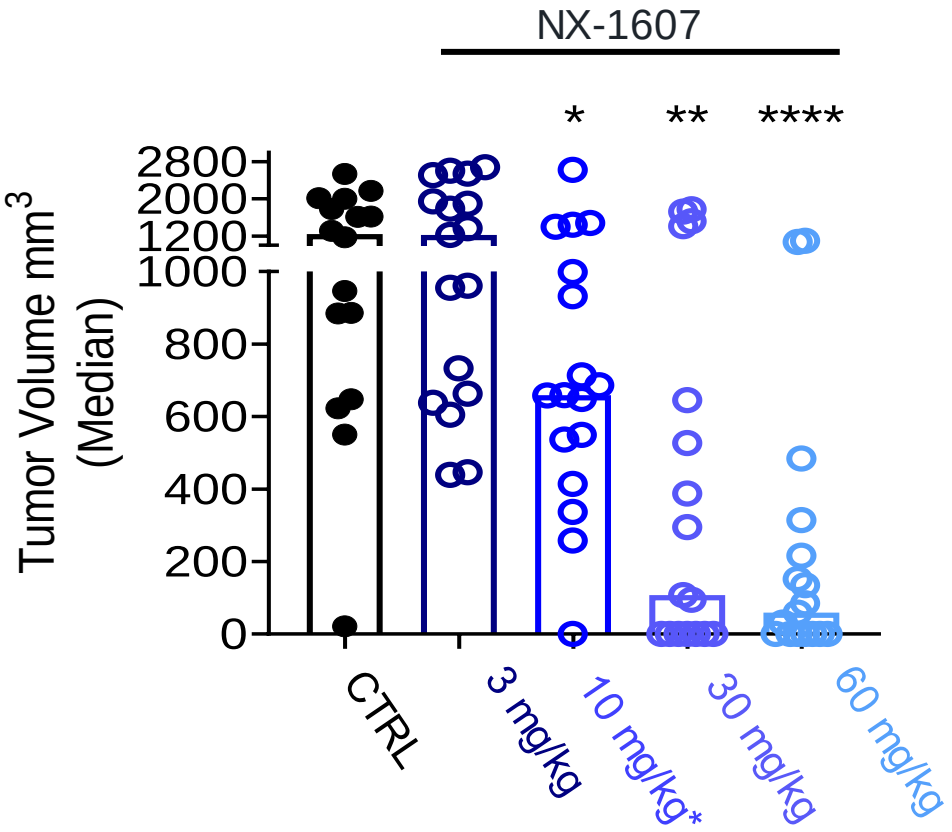
Dose Dependent Increases of CBL-B Proximal Biomarker Correlates with Antitumor Effects of NX-1607

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

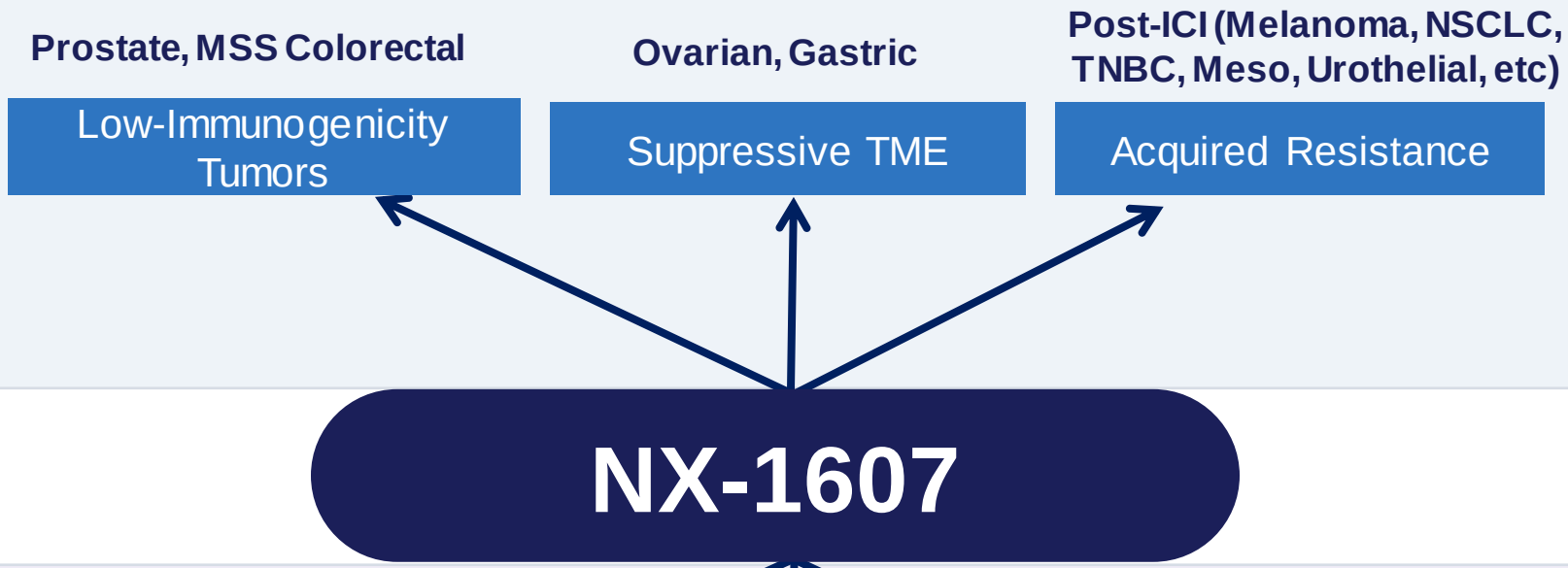
Antitumor activity in mice



A20 - B cell lymphoma model

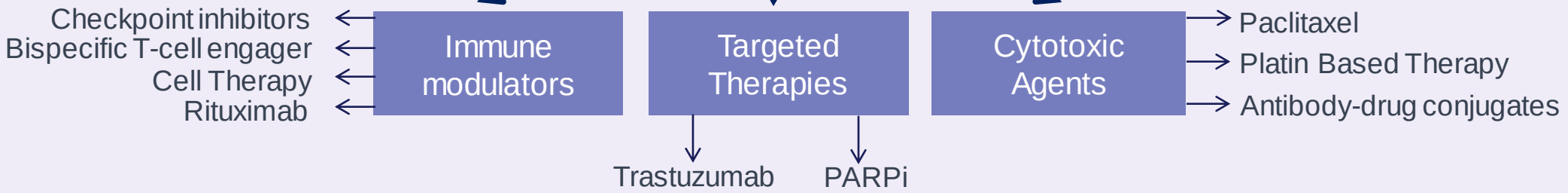
CBL-B Inhibition: Multiple Hypotheses to Be Tested in the Clinic

Single-Agent Monotherapy



NX-1607

Potential Combinations with FDA-Approved Agents



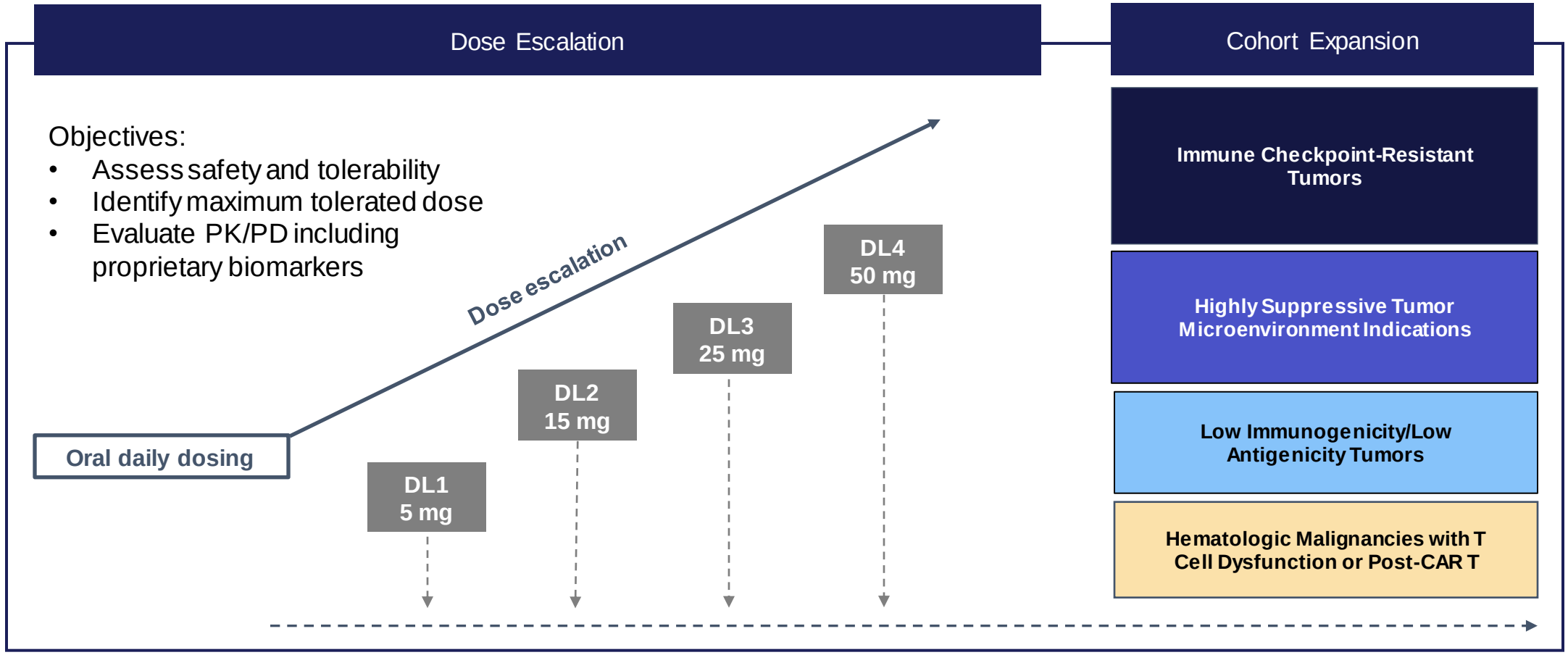
NX-1607-101

Phase 1 First-in-human Clinical Trial Design

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

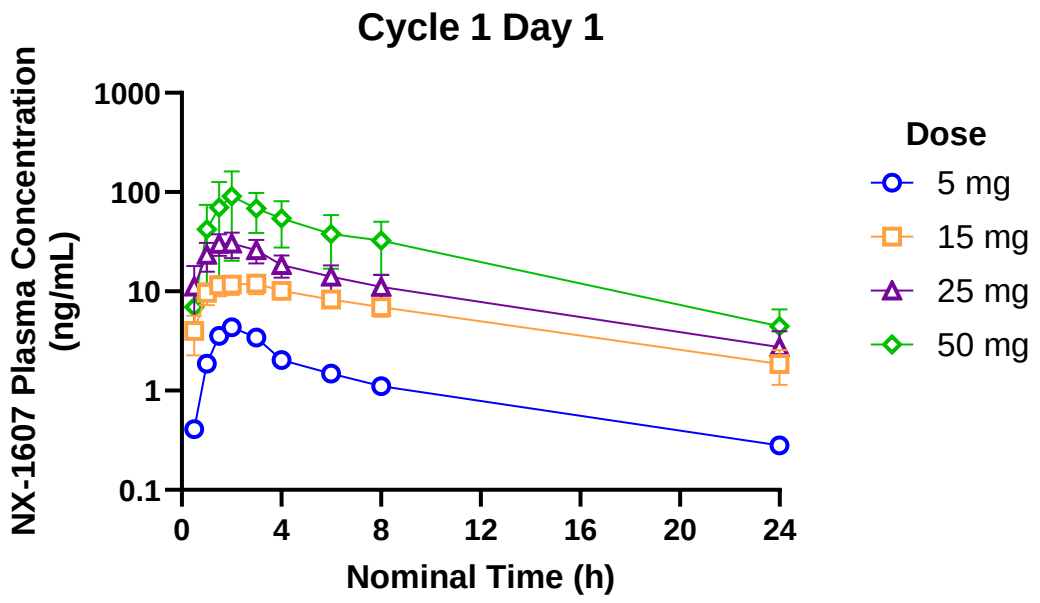
NX-1607-101: Phase 1 first-in-human clinical trial design

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 linear PK and a mean half-life of 6 to 8 hours at doses ranging from 5 to 50 mg, with little to no accumulation.



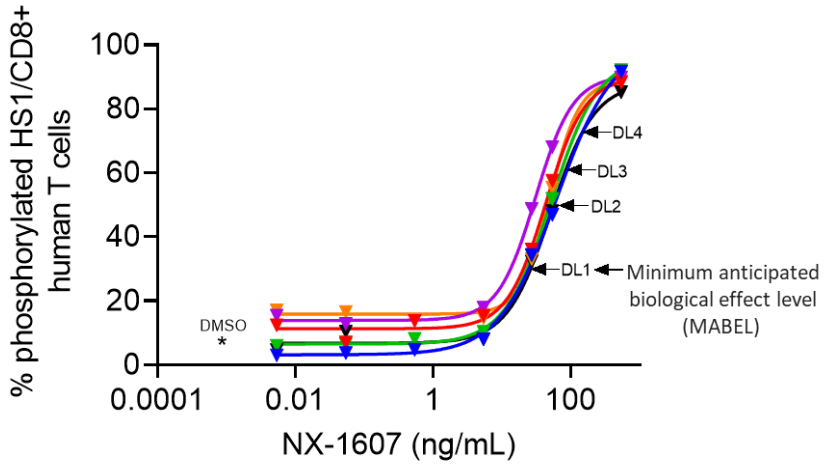
Dose	Cycle 1 Day 1					
	C_{max} (ng/mL)		$AUC_{0\text{-last}}$ (ng*hr/mL)		T_{max} (h)	$t_{1/2}$ (h)
	Estimated	Observed	Estimated	Observed		
5 mg (n=1)	9	4.35	40	26.2	2	7.72
15 mg (n=1)	28	13.6	119	86.8	2	6.29
25 mg (n=6)	47	30.1	199	201	1.5	6.82
50 mg (n=2)	94	79.2	398	502	2.5	5.88

LLOQ = 0.05 or 0.5 ng/mL

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

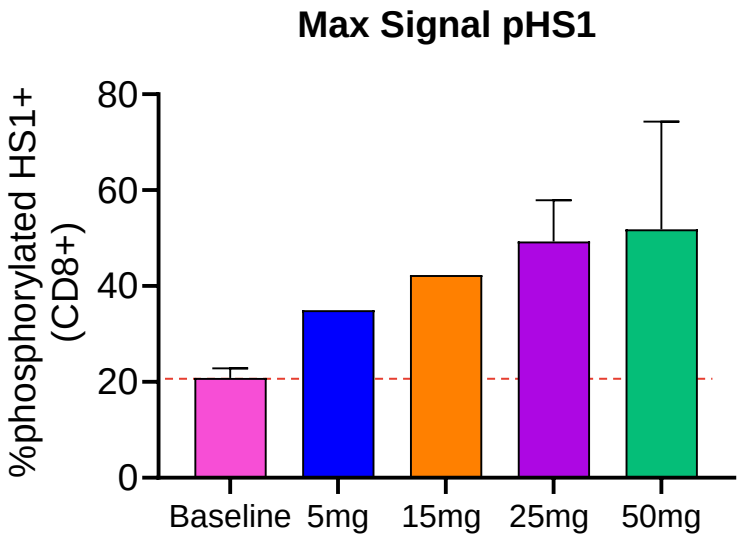
Interim Proximal PD Evaluation Demonstrates Dose-proportional Increases of pHS1 Consistent with Potent Anti-tumor Activity in Mouse Models

Human whole blood and dose projection modeling



Proposed dose level[a]	NX-1607 dose (mg)	Estimated %pHS1+/CD8+ T cells Cycle 1	Observed % pHS1/CD8+ T cells Cycle 1
-1	2.5	22	
1[b]	5	30	35
2	15	50	42
3	25	61	49
4	50	74	52

Clinical data C1D1



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

Summary and Conclusions

- The E3 ligase CBL-B acts as a major gate-keeper of immune signaling pathways, making it a powerful target for cancer immunotherapy.
- Nurix's CBL-B inhibitor, NX-1607, acts as an intra-molecular glue, locking CBL-B in an inactive conformation preventing the phosphorylation and activation of this E3 Ligase.
- Inhibition of CBL-B shows single agent anti-tumor activity and synergizes with anti-PD-1 to enhance anti-tumor effects and survival of mice in multiple tumor models.
- Tumors in NX-1607-treated mice displayed increased CD8+ T cell infiltration with enhanced cytotoxicity and stemness marker expression.
- A first-in-human phase 1 clinical trial was initiated for NX-1607. Early results show linear PK and evidence of proximal biomarkers increase

Thank You!