Nurix Therapeutics

Blazing a New Path in Medicine

Inhibitors of the E3 Ubiquitin Ligase CBL-B Promote Potent T and NK Cell Mediated Anti-Tumor Response

17th Annual Drug Discovery Chemistry
April 19th, 2022

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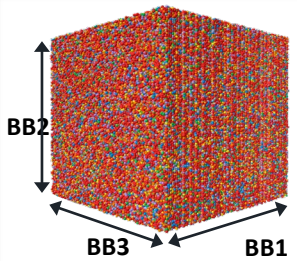
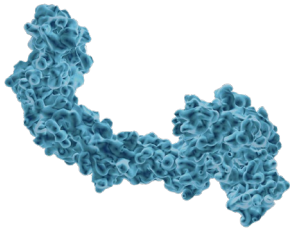
Nurix's DELigase Platform: Leading the Industry in DNA-Encoded Libraries for Targeted Protein Modulation

- DELigase™ is a versatile drug discovery platform comprised of massive DNA-encoded libraries (DEL) now containing over 5 billion compounds
- Nurix can rapidly screen an expanded universe of E3 ligases and proteins previously thought to be undruggable
- Nurix can modulate specific protein levels up or down with its drug discovery platform

DELigase Protein Modulation Platform



Proprietary DNA-Encoded Libraries, > $5x10^9$ compounds



>30 E3 ligases currently in discovery

Chimeric Targeting Molecules (CTMs) ***Decrease*** **specific protein levels**

Ligase Inhibitors ***Increase*** **specific protein levels**

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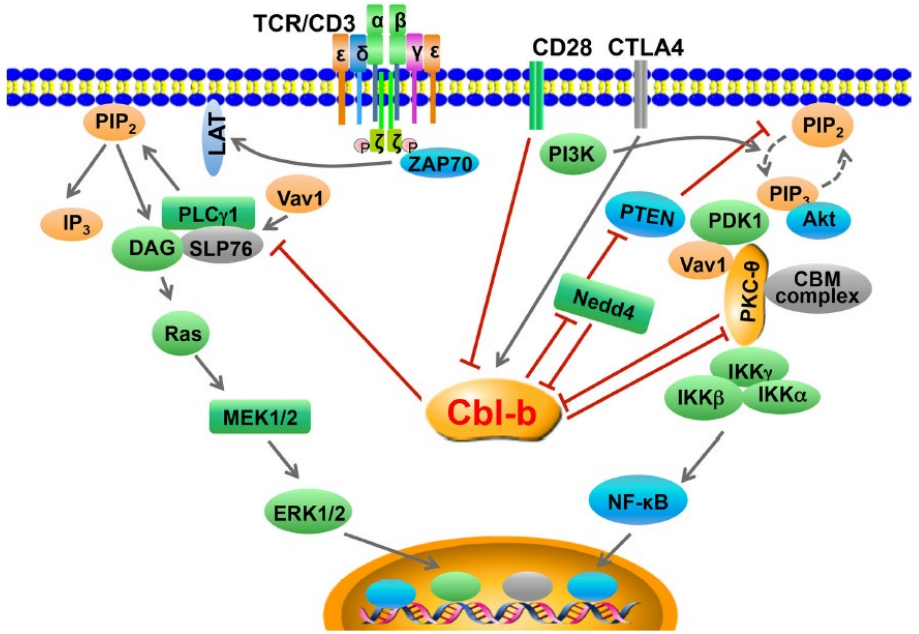
CBL-B: A Modulator of T Cell Activation and a Novel Target for Immuno-oncology

- CBL-B is an E3 ubiquitin ligase that is expressed in and regulates immune cells, including T, B, NK and dendritic cells
- In T cells, CBL-B limits cell activation following TCR engagement, enforcing the need of CD28 co-stimulation
- Inhibition or deletion of CBL-B increases IL-2 production in T cells upon stimulation and enhances immune response
- Mice deficient in CBL-B demonstrate enhanced signal dependent T cell activation and robust T and NK cell dependent anti-tumor activity
- Inhibiting CBL-B with a small molecule represents a novel immunotherapy target opportunity to overcome checkpoint resistance and reduce effects of the suppressive tumor microenvironment



Cellular Immunology
Volume 340, June 2019, 103878

CBL-B inhibition

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

Synergy with anti-PD-1

NX-1607: Optimized CBL-B inhibitor for oral delivery. Developing as an oral intracellular checkpoint inhibitor for treating solid tumors.

NX-0255: Optimized CBL-B inhibitor for *ex vivo* use. Developing in conjunction with autologous T cell therapies including TIL and CAR T.

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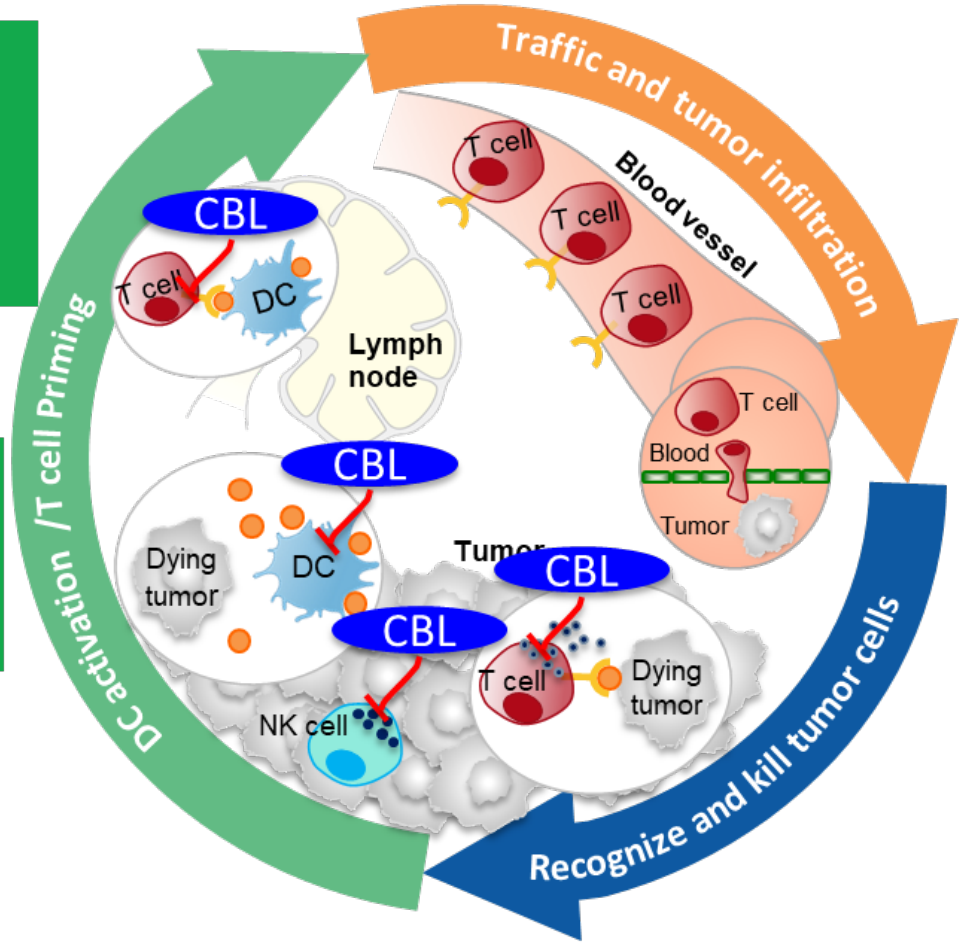
Opportunities for Oral NX-1607 Treatment to Enhance Cancer Immunity Cycle

Enhance T cell priming by lowering threshold of T cell activation

Enhance DC proliferation, differentiation and maturation



Increase T Cell effector function and confer resistance to TGF-β, MDSC, and Tregs

Enhance NK function

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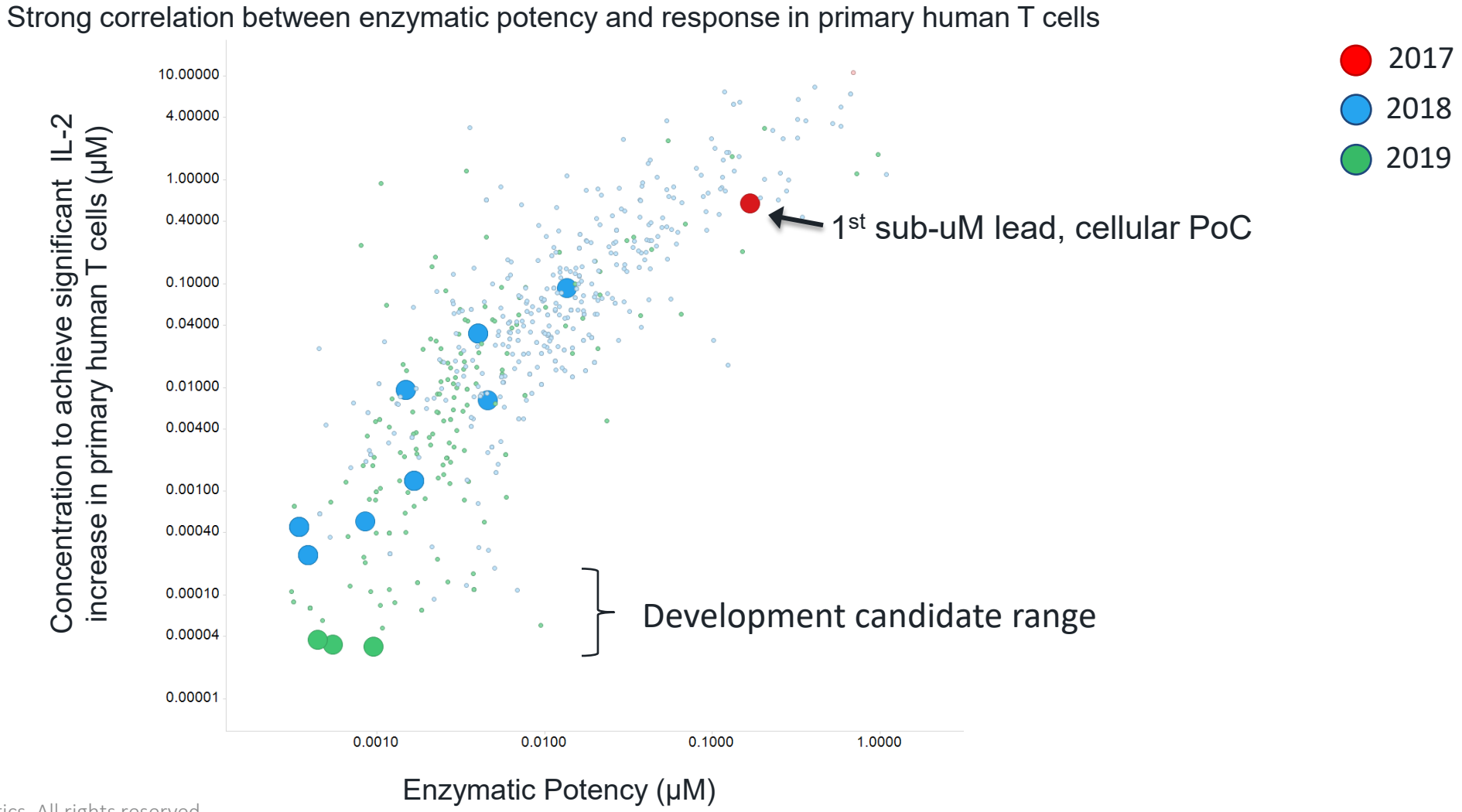
Medicinal Chemistry Efforts Led to Potency and Molecular Property Improvement for the Selection of Potent CBL-B Inhibitors



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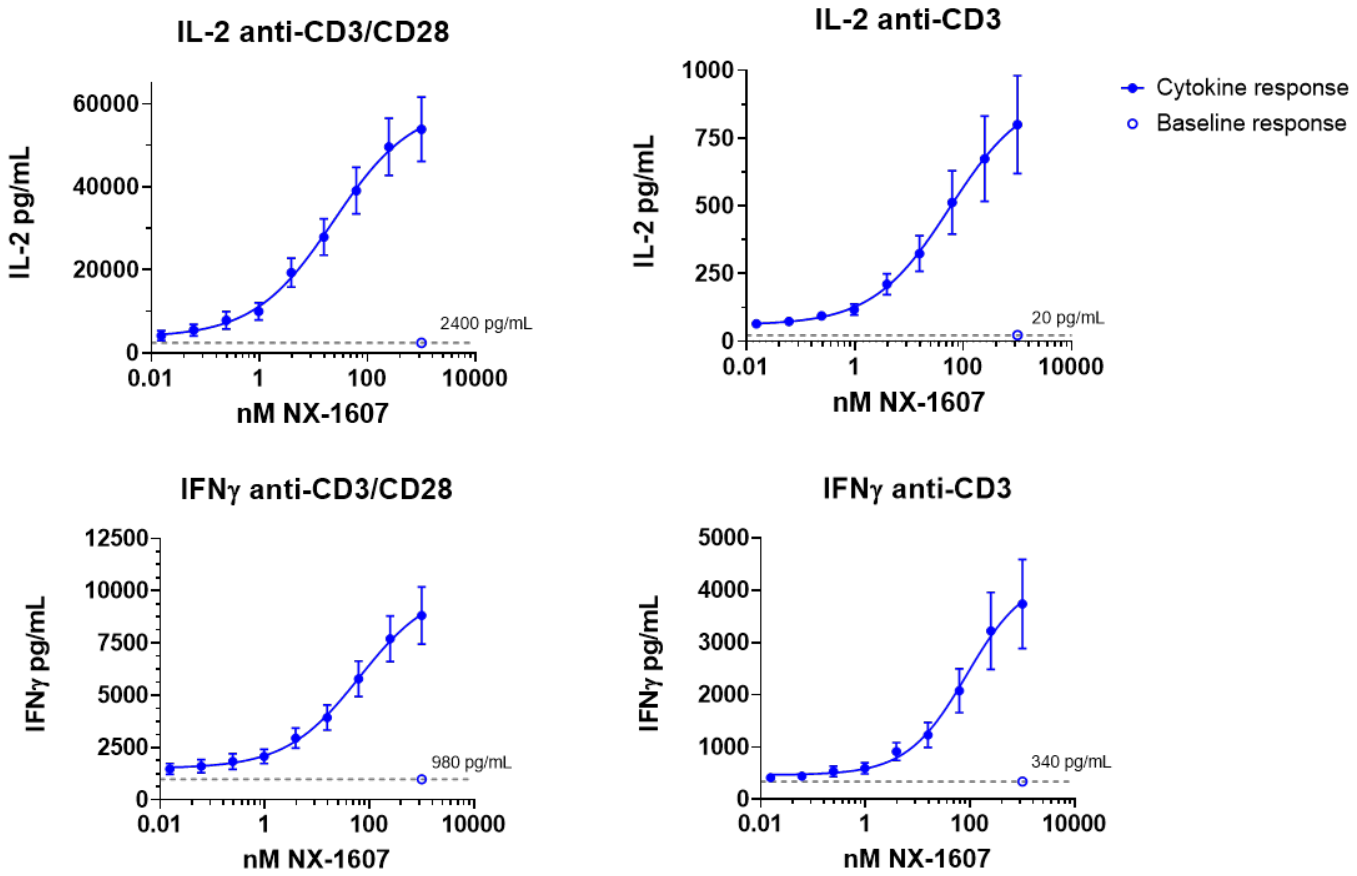
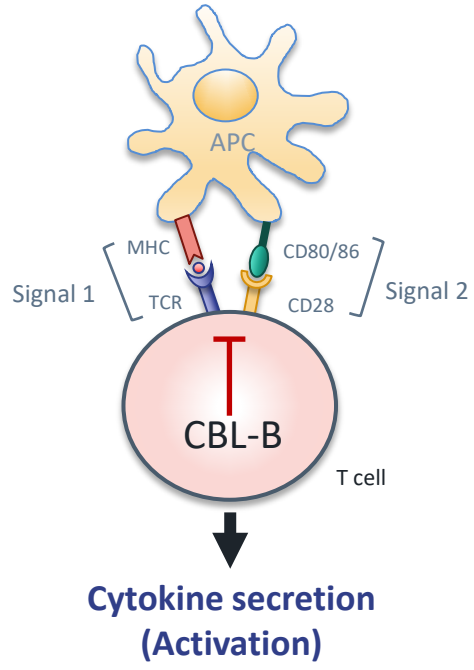
CBL-B Inhibitor NX-1607 Enhances IL-2 and IFN-γ Secretion in TCR Stimulated Primary Human T Cells





Data represents 8 individual donors
Avg ± SEM

- NX-1607 increases stimulation-dependent production IL-2 and IFN-g
- NX-1607 has no impact in the absence of T cell stimulation measured by proliferation, activation markers or cytokine release

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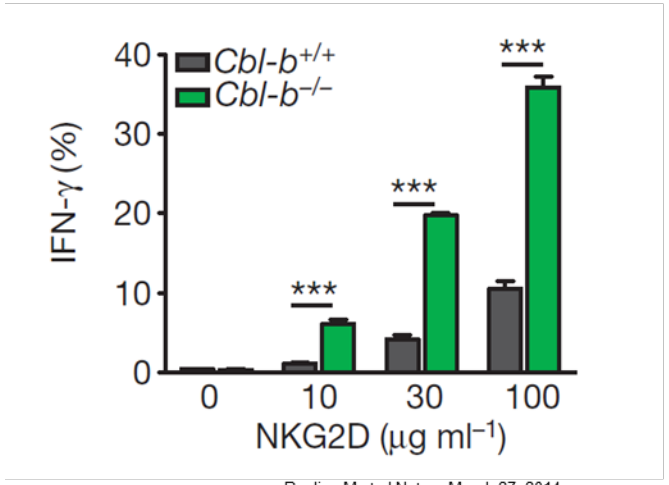
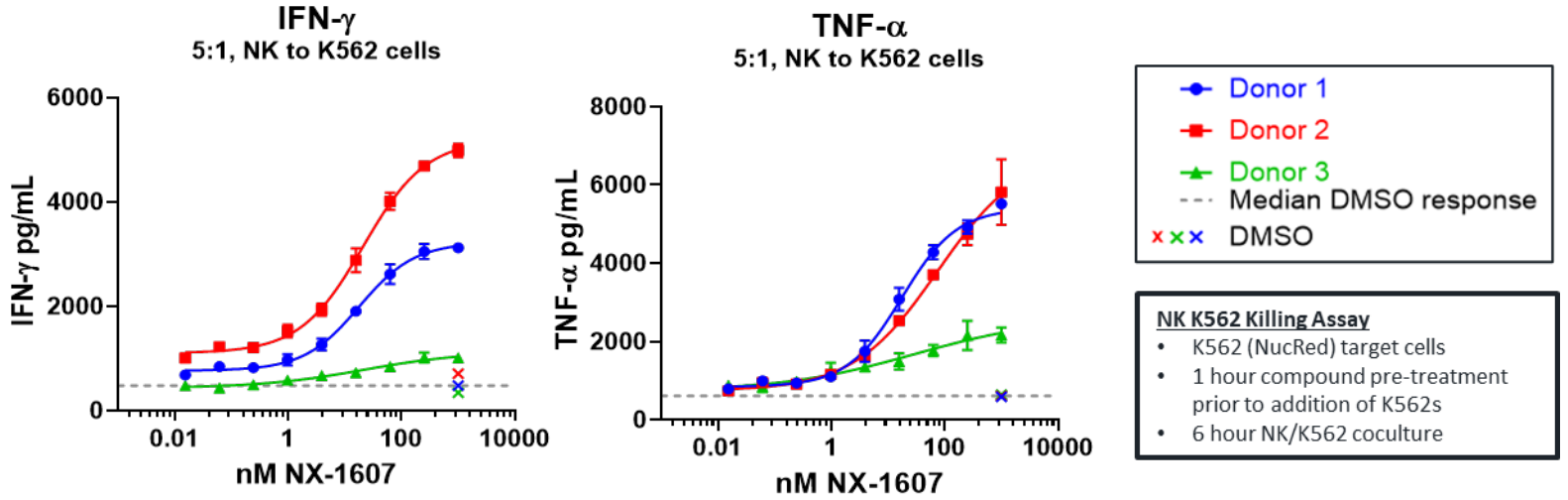
CBL-B Inhibitors Increase Secretion of Pro-Inflammatory Cytokines in Human NK cells

CBL-B KO NK cell activity



Paolino M et al Nature March 27, 2014

Primary human NK cell pharmacology



- TAM receptor signaling phosphorylates CBL-B leading to degradation of LAT1 which is required for NK cell activation signaling
- CBL-B inhibitors increase cytokine response in stimulated primary human NK cell
- CBL-B knockout enhances NK cell function responses *in vitro* and anti-tumor activity *in vivo* in a T-cell/B-cell deficient tumor model

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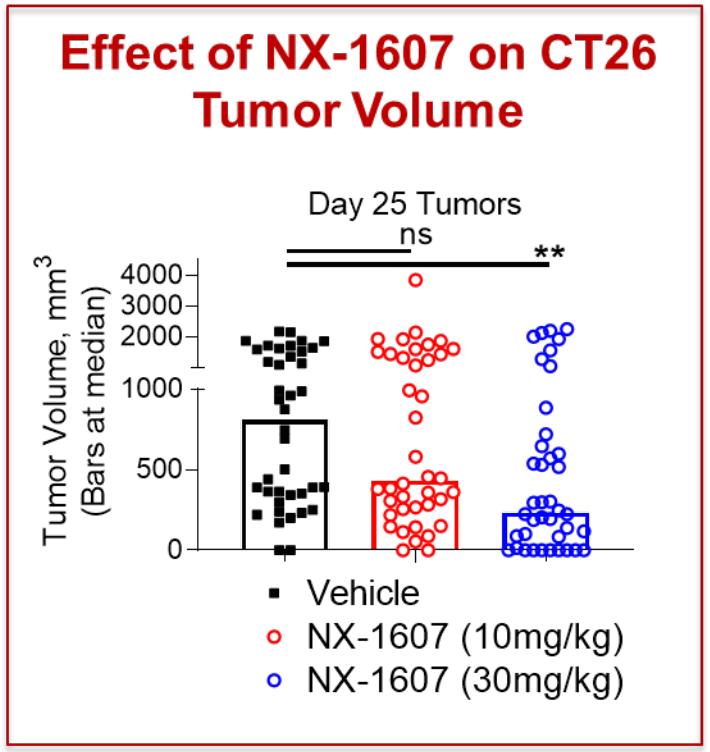
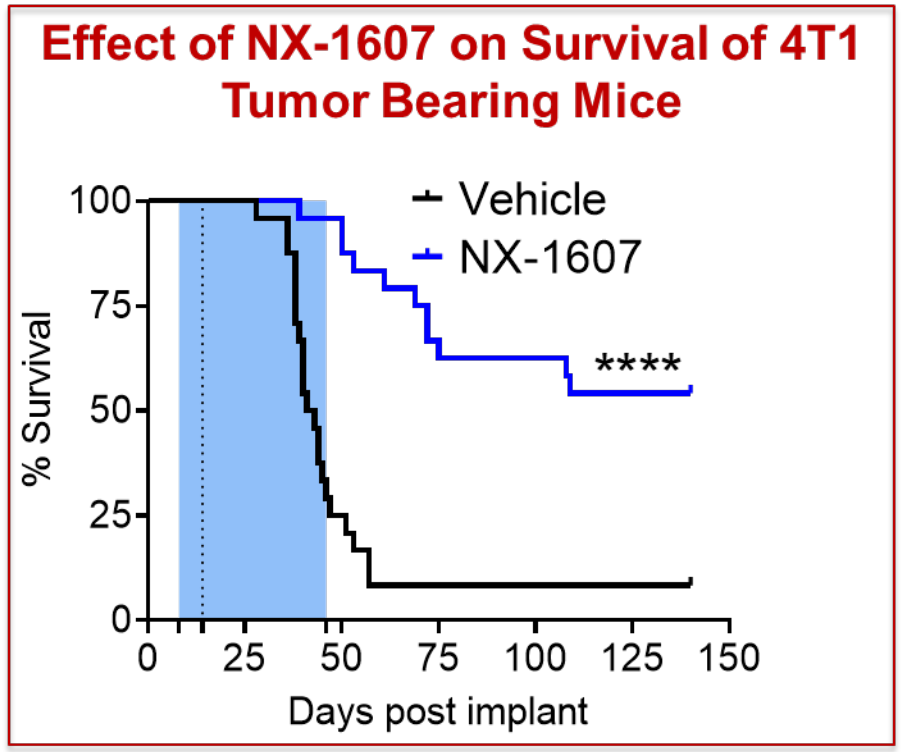
Single-Agent NX-1607 Induces Dose Dependent Antitumor Response in Multiple Models

Colorectal



Mice bearing tumors on their left and right flanks were treated from day 7 to day 32 with oral NX-1607 at 10 mg/kg (red circles) or 30 mg/kg (blue circles) or Vehicle (black squares).

Triple-negative breast



Mice were treated PO with NX-1607 at 30 mg/kg from day 7 to day 46 (shaded area). 4T1 primary tumors were surgically removed on day 15 (dotted line).

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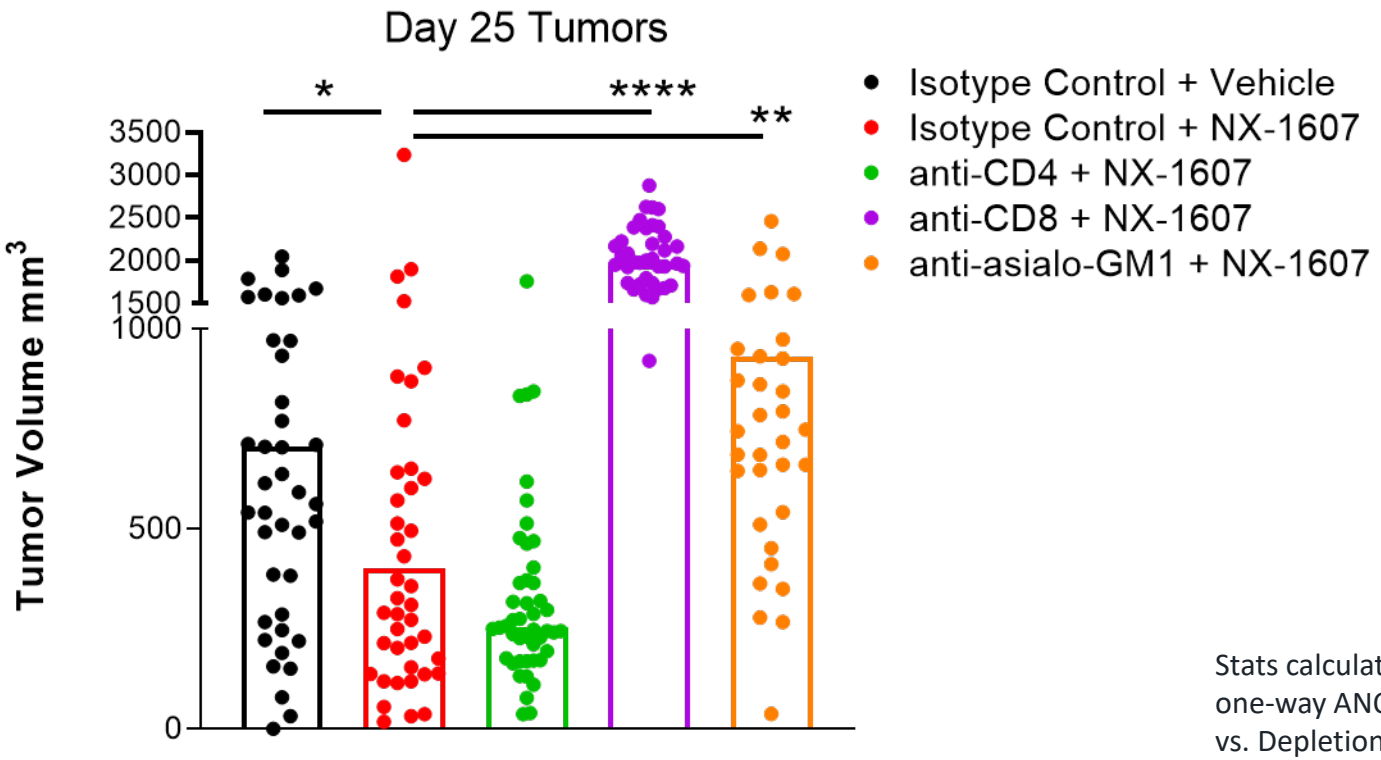
NX-1607 Antitumor Efficacy is Dependent on CD8+ T or NK Cell Activity



Stats calculated with Mann-Whitney (Vehicle vs. NX-1607) or one-way ANOVA with Dunn's multiple comparisons test (NX-1607 vs. Depletion groups); * $P \leq 0.05$, ** $P \leq 0.01$, **** $P \leq 0.0001$.

- CT26 tumor on left and right flanks treated from Day 9 to Day 25 with oral NX-1607 at 30 mg/kg, PO QD in the presence of depleting antibodies for CD4+ cells, CD8+ cells, or NK cells (anti-asialo-GM1)

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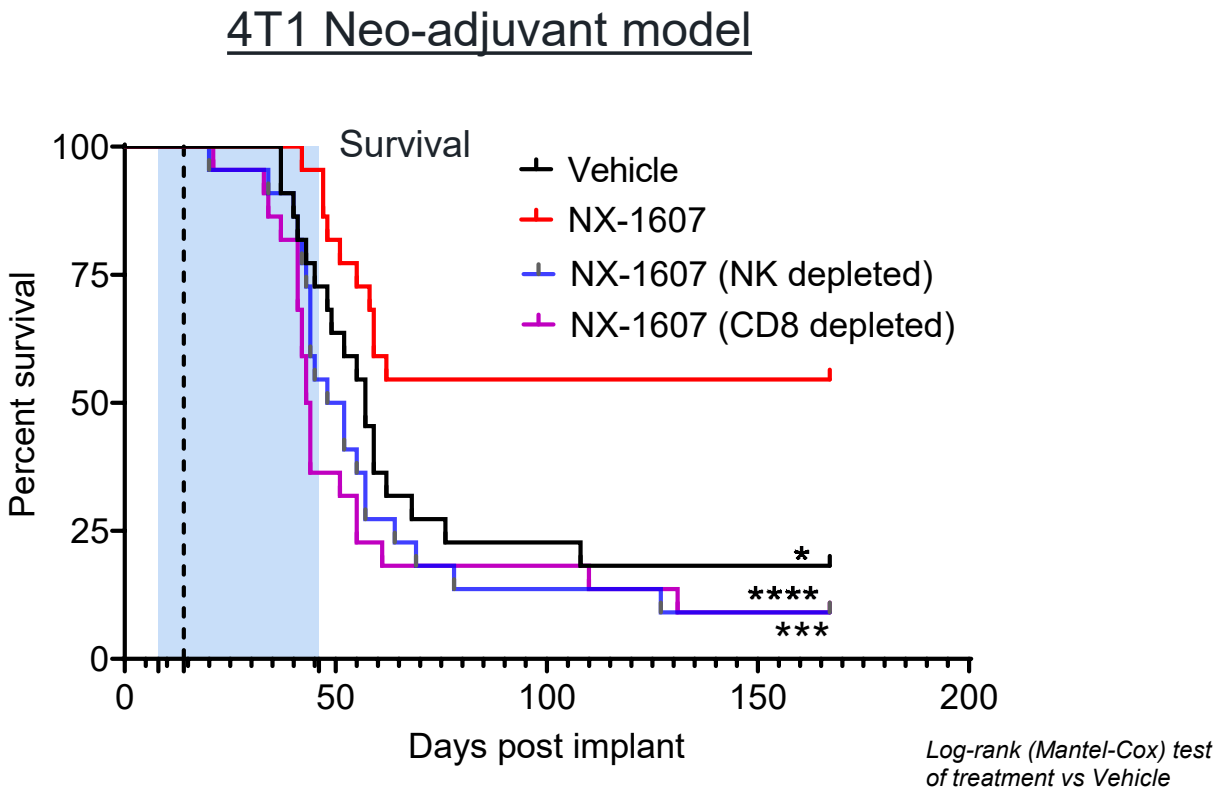
Single-Agent NX-1607 Induces Long Term Survival in Metastatic, Triple Negative, Breast Cancer Model

- Once daily oral dosing of NX-1607
- Tumors implanted at Day 0
- Surgical removal of primary tumor at Day 15
- NX-1607 was given before the surgery from Day 7 to Day 15 (neo-adjuvant phase) and continued after surgery (adjuvant phase) until Day 46



- NX-1607 exhibits single agent efficacy in the 4T1 neo-adjuvant model (p=0.0286)
- NX-1607 efficacy is abrogated by NK depletion

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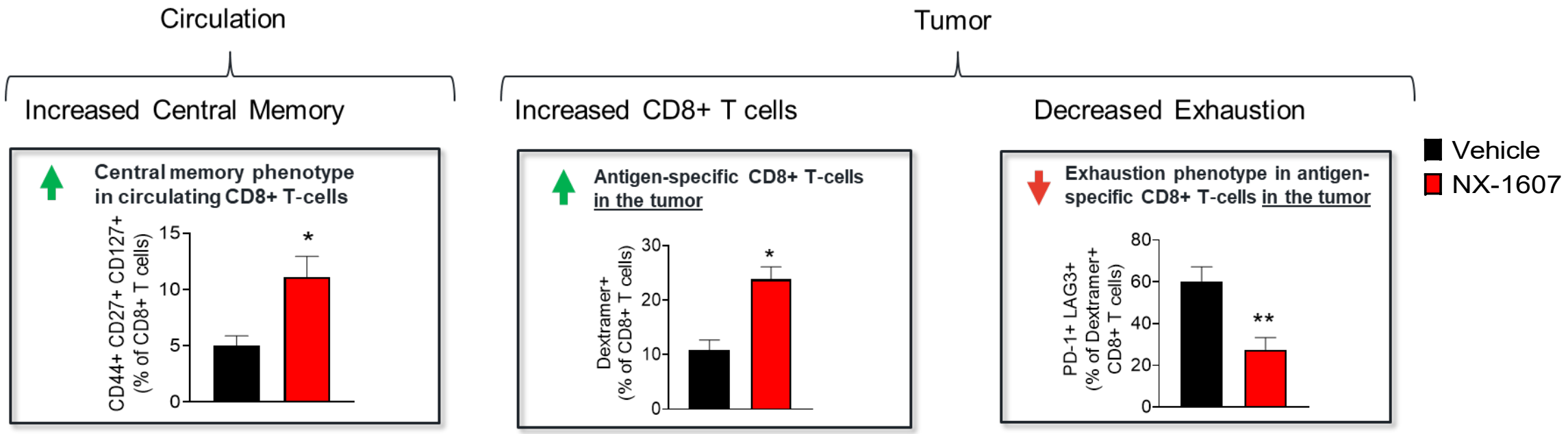
NX-1607 Treatment Increases Tumor Antigen Specific Response in a Metastatic Triple Negative Breast Cancer Tumor Model



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

- NX-1607 treatments result in immune cell phenotypic changes, both in the tumor microenvironment (TME) and in peripheral blood in animal models.
- Similar changes have been associated with extended survival and better prognosis in cancer patients

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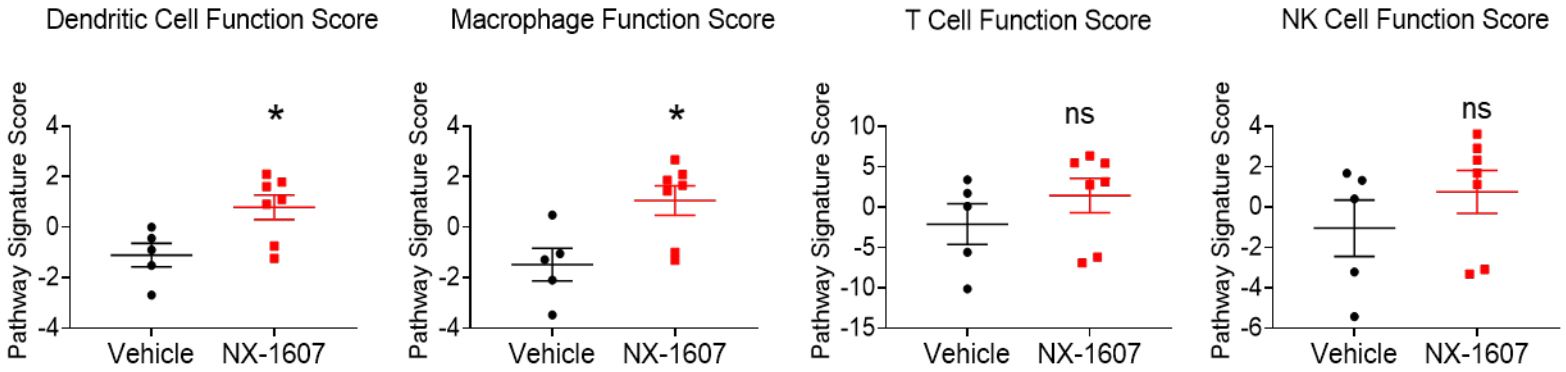
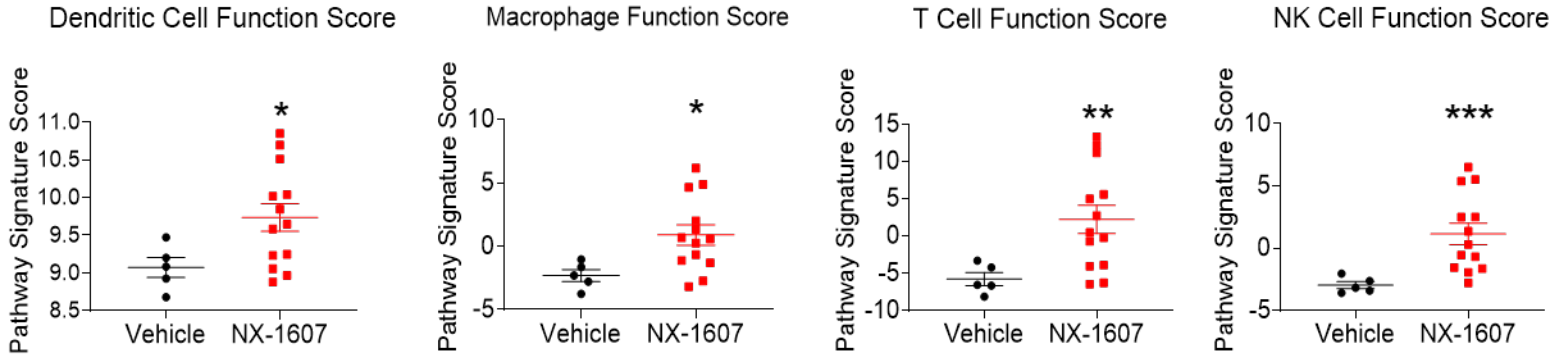
NX-1607 Promotes Infiltration of CT26 Tumors with Activated T and NK Cells

4 Doses NX-1607



19 Doses NX-1607



Statistics used Mann-Whitney test (* $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$)

- Orally administered NX-1607 effects on TIL in CT26 tumors after 4 or 19 doses of NX-1607 at 30 mg/kg, PO QD
- NanoString nCounter PanCancer Mouse Immune Profile panel analysis

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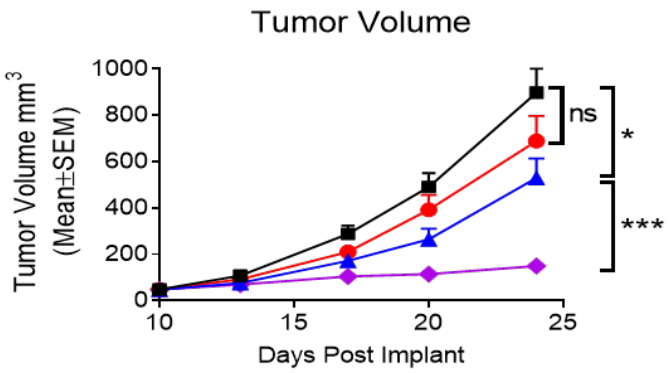
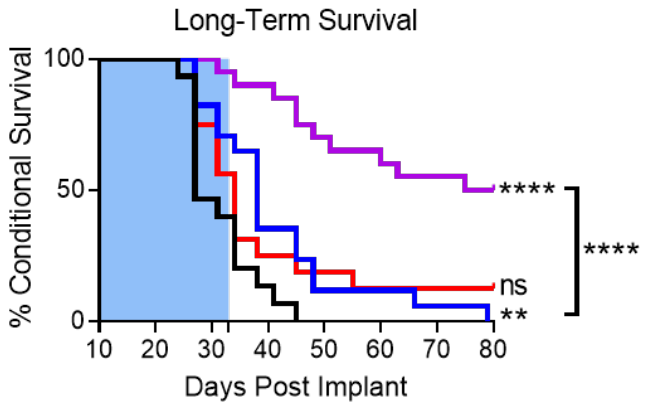
NX-1607 and Anti-PD-1 Synergize to Enhance Anti-Tumor Effects and Survival of Mice in Multiple Tumor Models

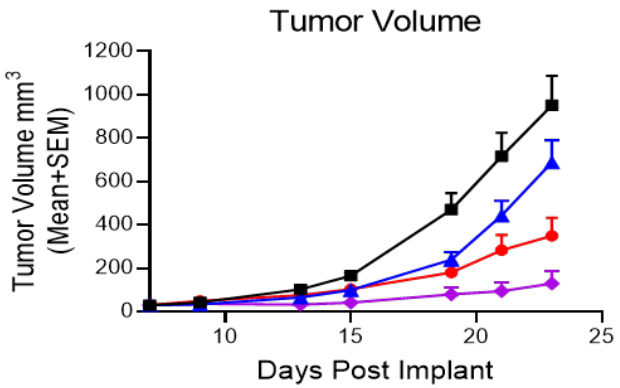
Vehicle NX-1607 Anti-PD-1 NX-1607 + Anti-PD-1

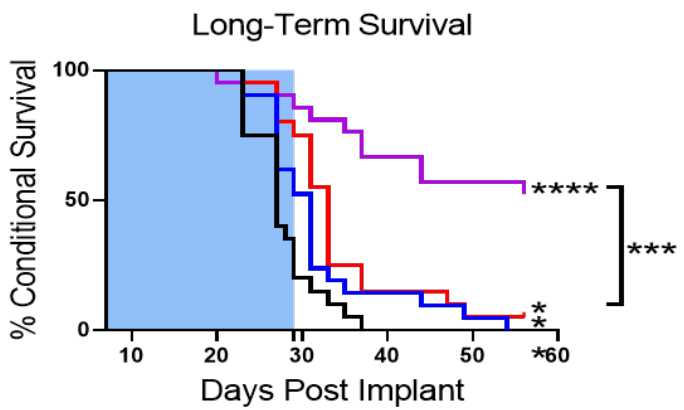
Colorectal (CT26)



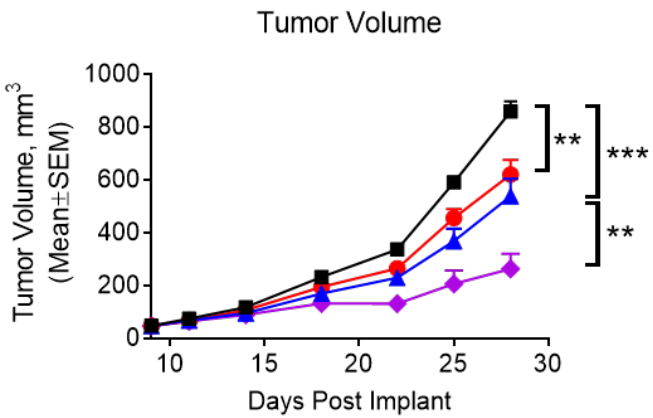


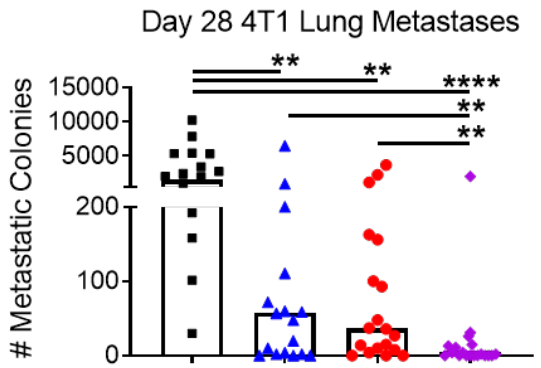
Colorectal (MC38)





Triple-negative breast (4T1)





NX-1607 antitumor efficacy is abrogated by CD8+ T or NK cell depletion (data not shown)

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.

Statistical analysis used one- or two-way ANOVA with corrections for multiple groups or Log-rank tests for survival curves.

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Summary NX-1607

- Pharmacological inhibition of CBL-B with NX-1607 recapitulates the anti-tumor effects observed in the genetic model of ligase inhibition
- NX-1607 exerts potent single agent anti-tumor activity which is dependent on CD8+ T cells and NK cells
- NX-1607 promotes infiltration of activated T cells with a lower exhausted phenotype in the tumor microenviroment
- NX-1607 strongly synergizes with PD-1 blockade to increase the rate of complete rejection and long-term survival of tumor bearing mice
- A Phase 1a clinical trial of NX-1607 is currently on going

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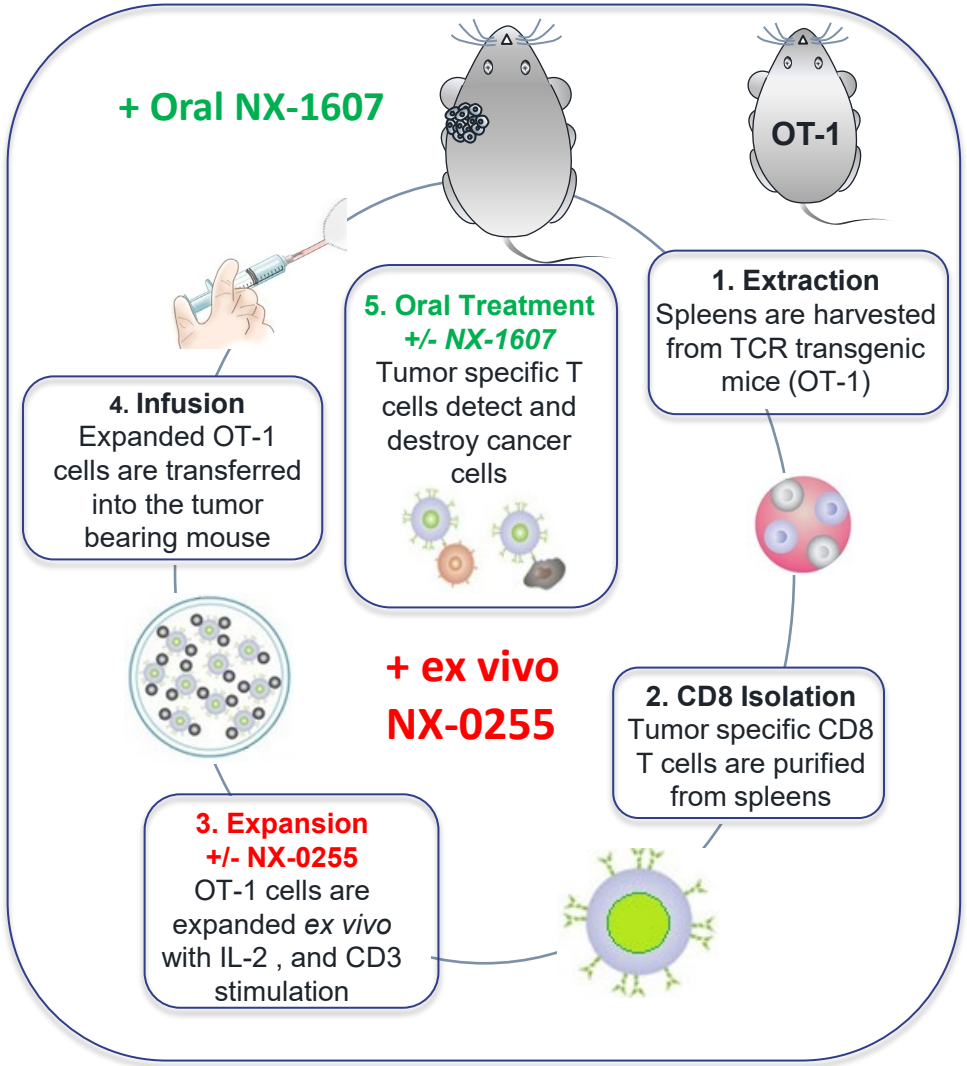
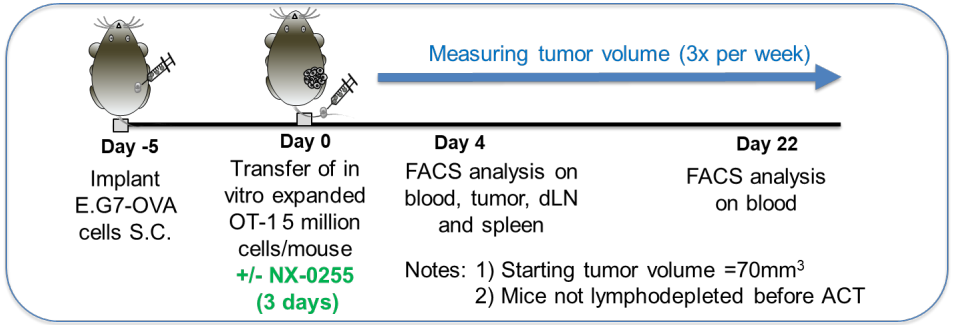
Model of Drug Enhanced Adoptive Cell Therapy



Protocol:



Analyses performed:

- Anti-tumor response monitored over time
- Cytokine production analysis
- Splenocyte re-stimulation with tumor antigen to measure the multifunctionality of the OT-1 CD8 T cells

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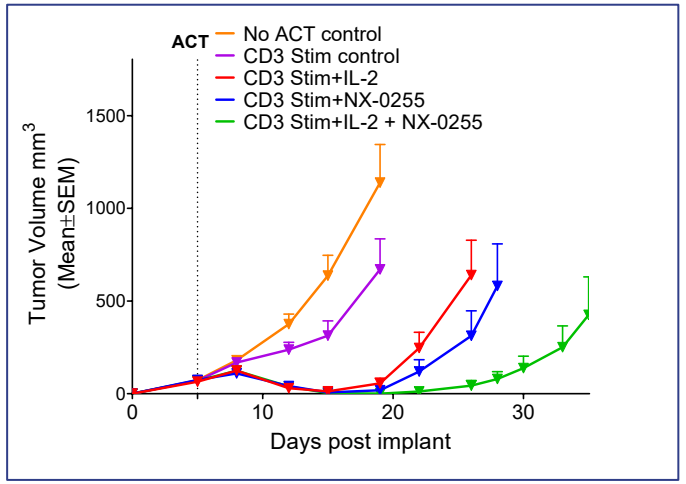
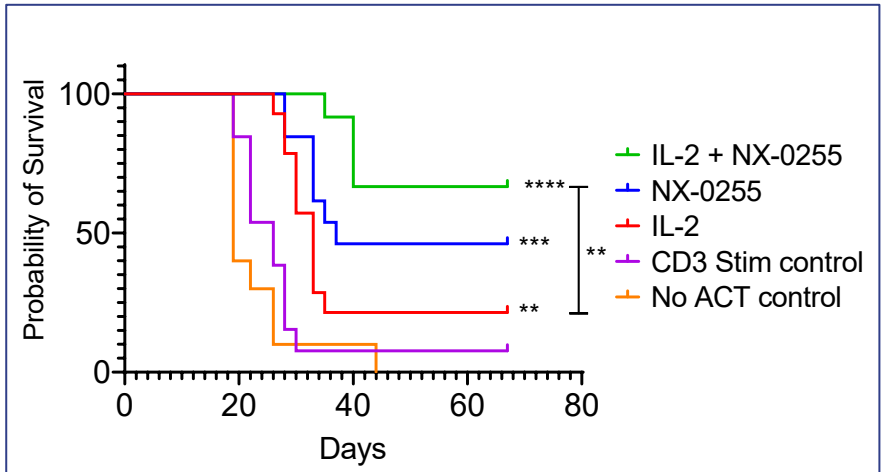
NX-0255 Expanded OT-1 Cells Differentiate into Potent Effectors Capable of Rejecting Established Tumors

- ✓NX-0255 expanded CD8+ T cells are more potent effectors than CD8+ T cells expanded in presence of IL-2.
- ✓Combination of IL-2 and NX-0255 synergize to exert deeper antitumor response.
- ✓NX-0255 expanded T cells have superior capacity for tumor infiltration, proliferation and cytokine production after antigen recall

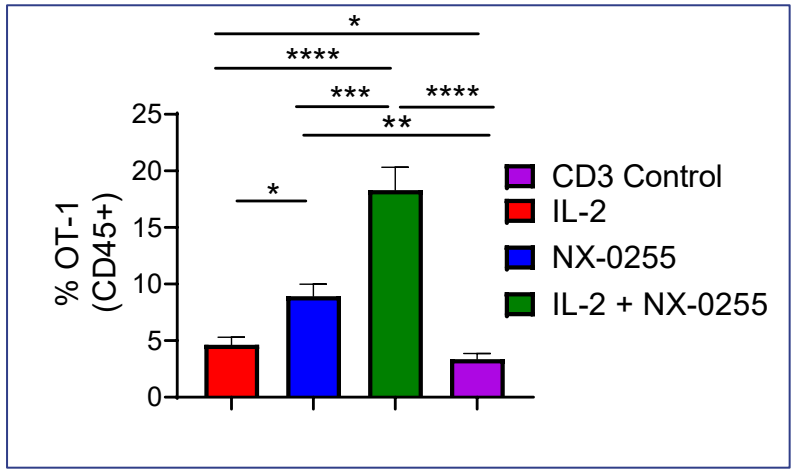
Tumor Volume



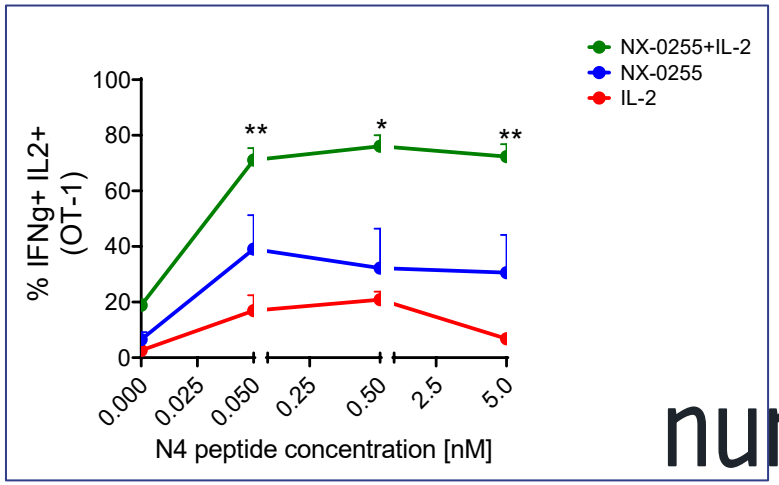
Survival



Freq of OT-1 cells in Tumors (4 days after ACT)



Freq of IFNg+IL-2+ OT-1 cells after peptide re-stimulation 1 year after primary rejection



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Summary NX-0255

- Treatment of CD3-stimulated tumor-specific CD8 T cells using NX-0255, a novel small molecule CBL-B inhibitor, is associated with increased anti-tumor activity in both OT-I models
- NX-0255 treated tumor-specific CD8+ T cells show increased expansion in tumor and blood, after adoptive transfer *in vivo*
- NX-0255+IL-2 treated OT-I cells differentiate into long-lived central-memory cells with superior polyfunctionality during the recall response
- These results support the rationale for the use of NX-0255 in the production of an investigational drug-enhanced TIL therapy, DeTIL-0255, which is currently in a Phase 1 clinical trial

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