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

Non-Small Cell Lung Cancer Drug Development Summit

Boston, MA
Sept 21st, 2022
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Targeted Protein Modulation: \( TPM = TPD + TPE \)

**Targeted Protein Degradation (TPD)**

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

**Harness ligases to decrease specific protein levels**

**Targeted Protein Elevation (TPE)**

Inhibit ligases to increase specific protein levels.

**A Powerful Cellular System**

Nurix Drugs Engage Ligases for the Treatment of Cancer
E3 Ligase Inhibition Results in Targeted Protein Elevation (TPE)

Native E3 Ligase activity –
Maintains target proteins at low levels

Inhibited E3 Ligase –
Target proteins elevated

E2, ubiquitin-conjugating enzyme; E3, ubiquitin ligase; NRX, Nurix; Ub, ubiquitin
Nurix Is Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

<table>
<thead>
<tr>
<th>MOA</th>
<th>Drug Program</th>
<th>Target/ Delivery</th>
<th>Therapeutic Area</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
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<td>TPM</td>
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MOA, Mechanism of action; TPD, Targeted Protein Degradation; TPE, Targeted Protein Elevation; TPM, Targeted Protein Modulation
CBL-B is an E3 ubiquitin ligase that is expressed in and regulates immune cells, including T, B, NK and dendritic cells.

Mice deficient in CBL-B demonstrate enhanced signal-dependent T cell activation and robust T and NK cell dependent anti-tumor activity.

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 the immune response.

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.

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.
Targeting CBL-B Enhances Antitumor Response

A Master Orchestrator of the Immune System

CBL-B mediated mechanisms strongly restrain 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
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NX-1607 Mechanism of Action: Intramolecular Glue

CBL-B is in Equilibrium Between Closed and Opened State
NX-1607 Mechanism of Action: Intramolecular Glue

1. Kinase
2. E2/substrate

Phosphorylation locks CBL-B in the ACTIVE Conformation

CBL-B target proteins at low levels

Immune Response
NX-1607 Mechanism of Action: Intramolecular Glue

1. Kinase
   Phosphorylation locks CBL-B in the ACTIVE Conformation

2. E2/substrate
   NX-1607 acts as an intramolecular glue forcing CBL-B in its folded INACTIVE state

NX-1607

opened state

pY363

E2

Substrate protein

Immune Response

CBL-B target proteins elevated (TPE)

Immune Response

CBL-B target proteins at low levels
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

[Graphs showing the effect of NX-1607 on IL-2 and IFN-γ production]
NX-1607 Increases Secretion of Pro-Inflammatory Cytokines in Human NK cells

**NK K562 Killing Assay**

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

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

**NX-1607 Reduced Tumor Volume**
- Colorectal (CT26)

**NX-1607 Prolonged Survival**
- Triple-Negative Breast (4T1)

**NX-1607 Reduced Tumor Volume**
- B Cell Lymphoma (A20)

**NX-1607**
- 30 mg/kg day 7 to 46
- 30 mg/kg day 16 to 28

Shaded area indicates dosing period

Day 25 Tumors

<table>
<thead>
<tr>
<th>Tumor Volume, mm³ (Bars at Median)</th>
<th>Vehicle</th>
<th>NX-1607 (10mg/kg)</th>
<th>NX-1607 (30mg/kg)</th>
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**Tumor Volume mm³ (Mean ± SEM)**

- **NX-1607**
- **Vehicle**

P<0.0001
**NX-1607 Antitumor Efficacy is Dependent on CD8+ T Cells or NK Cell Activity**

- CT26 colorectal 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).

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 ≤ 0.05, ** P ≤ 0.01, **** P ≤ 0.0001.

![Graph showing tumor volume comparison](image-url)
NX-1607 Treatment Induces Dose Dependent T and NK Cell Intratumoral Infiltration and Enhanced Function

CT26 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 Increases Tumor Antigen Specific Response in a Metastatic Triple Negative Breast Cancer Tumor Model

- 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.

4T1 breast cancer model. ANOVA test with post-hoc Dunn’s multiple comparisons test * p<0.05; **p<0.01
NX-1607 and Anti-PD-1 Synergize to Enhance Anti-tumor Effects and Survival of Mice in Multiple Tumor Models

Colorectal (CT26) Long-Term Survival

Colorectal (MC38) Long-Term Survival

Triple-Negative Breast (4T1) Tumor Volume

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

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.
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 Raji Tumor Cells

NX-1607-mediated NK activation potentiates rituximab antitumor activity

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

**Percentage of Survival**

![Graph showing survival rates over time with different treatment groups.](image)
Dose Dependent Increases of CBL-B Proximal Biomarker Correlates with Antitumor Effects of NX-1607

Pharmacodynamic relationship in mice following NX-1607 dosing

Antitumor activity in mice

NX-1607

A20 - B cell lymphoma model
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

Objectives:
• Assess safety and tolerability
• Identify maximum tolerated dose
• Evaluate PK/PD including proprietary biomarkers

Oral daily dosing

Dose Escalation

Cohort Expansion

Checkpoint resistant tumors
Immunosuppressive microenvironment
Poorly immunogenic tumors

Melanoma
Squamous Cell Carcinoma of the Head and Neck (HNSCC)
Non-small Cell Lung Cancer (NSCLC)
Platinum Resistant Epithelial Ovarian Cancer (EOC)
Gastric Cancer
Metastatic Castration Resistant Prostate Cancer (mCRPC)
Mixed Solid Tumor Cohort
Diffuse Large B-cell Lymphoma with Richter Transformation (DLBCL-RT)
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 microenvironment

• 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
Thank you