



Nurix Therapeutics

Blazing a New Path in Medicine

Applying DEL Discovery to Protein
Modulation

17th Annual Drug Discovery Chemistry

April 19th, 2022

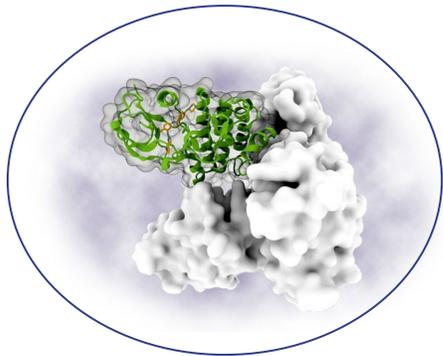
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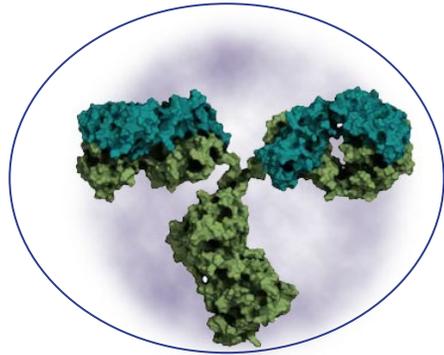
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Working to Create a New Category of Medicine

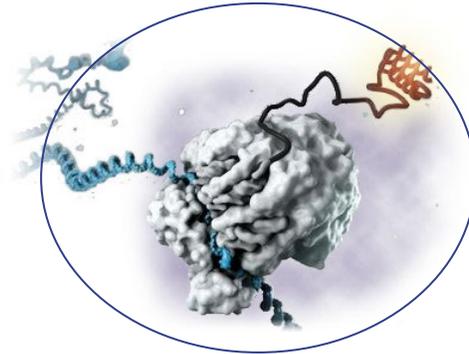
Evolution of new therapeutic modalities



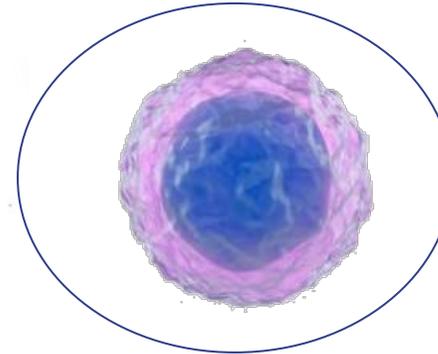
**Small Molecule
Inhibitors**



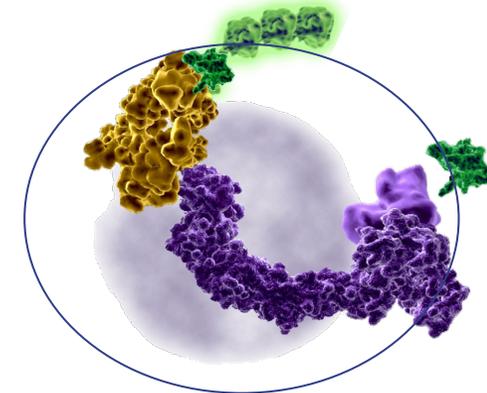
**Antibodies
Therapeutic
Proteins**



**Nucleic Acid-Based Therapies:
Antisense, RNAi
Gene Therapy
CRISPR**



**Adoptive Cell
Therapy
DeTIL**



**Nurix Protein
Modulation Drugs
to Increase or
Decrease Specific
Protein Levels**

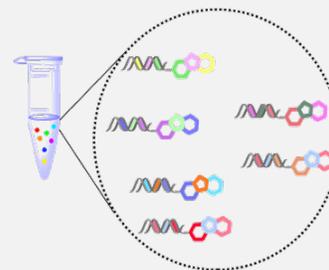
Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

Drug Program	Target / Delivery	Therapeutic Area	Discovery	IND enabling	Phase 1	Phase 2	Phase 3
<u>NX-2127</u> Degradar	BTK + IMiD activity <i>Oral</i>	B-cell Malignancies					
<u>NX-5948</u> Degradar	BTK <i>Oral</i>	B-cell Malignancies and Autoimmune Diseases					
<u>NX-1607</u> Inhibitor	CBL-B <i>Oral</i>	Immuno-oncology					
<u>DeTIL-0255</u> Cell therapy	Adopted cell therapy with <i>Ex vivo CBL-B inhibition</i>	Gynecologic malignancies					
Discovery pipeline							
Wholly owned	Degraders and inhibitors of multiple targets including E3 ligases, T cell kinase, hematology & oncology drivers, and viral proteins						
Gilead Sciences	5 targets						
Sanofi	5 targets						

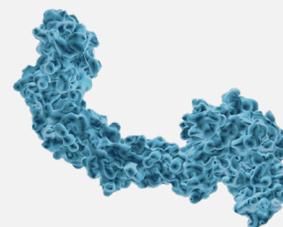
Nurix's DELigase Platform: Leading the Industry in Application of DEL for Targeted Protein Modulation

- DELigase™ is a versatile drug discovery platform utilizing DNA-encoded libraries (DEL) that represent over 5 billion drug-like compounds
- Nurix can find binders for proteins previously thought to be undruggable, particularly E3 ligases
- By inhibiting or harnessing E3 ligases, Nurix uses its discovery platform to modulate the levels of Target or substrate proteins

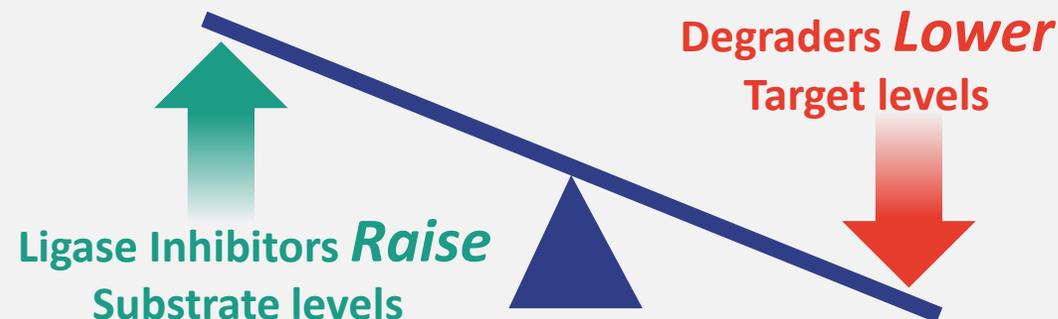
DELigase Protein Modulation Platform



Proprietary DNA-Encoded Libraries
5 Billion drug-like compounds



>30 E3 ligases in discovery
Diverse expression and biology



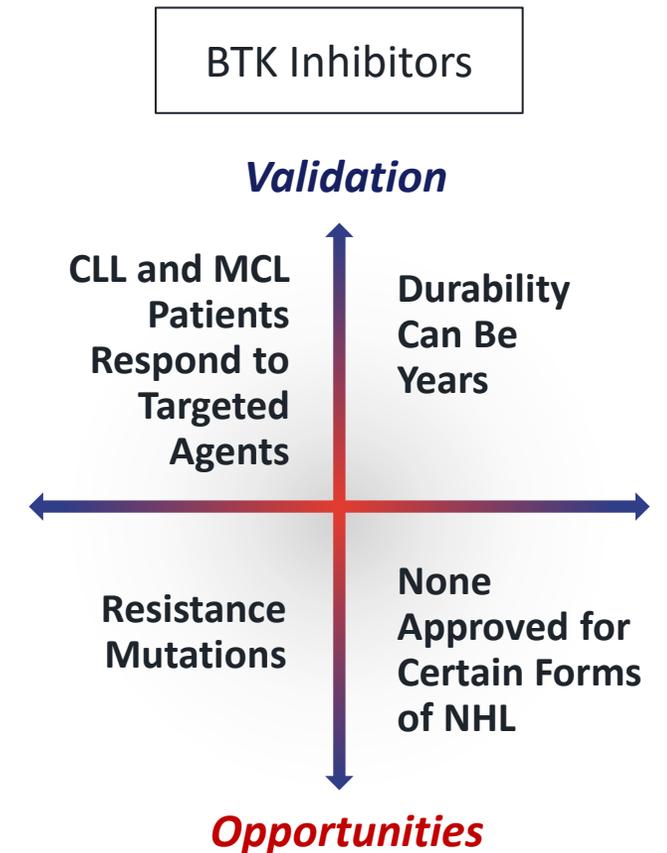
NX-2127: Targeted Degradator of BTK

Nurix's BTK Degradator Portfolio: Addressing Unmet Needs for BTK-driven Malignancies

- **BTK inhibitors are standard of care target however mutational escape represents a major unmet need**
 - BTK inhibitors are approved for CLL/SLL, mantle cell lymphoma, Waldenstrom's macroglobulinemia, marginal zone lymphoma, with estimated 2021 sales ~ \$8.5 billion
 - Next generation BTK inhibitors continue to be susceptible to mutational escape
- **Opportunities to meet unmet need with BTK degraders differentiated action**
 - Catalytic nature of targeted protein degraders provide a new MOA with fundamentally different PK/PD from inhibitors
 - Unique dual activity: NX-2127 combines the activities of BTK degradation and IMiDs which may be beneficial across a range of hematologic malignancies

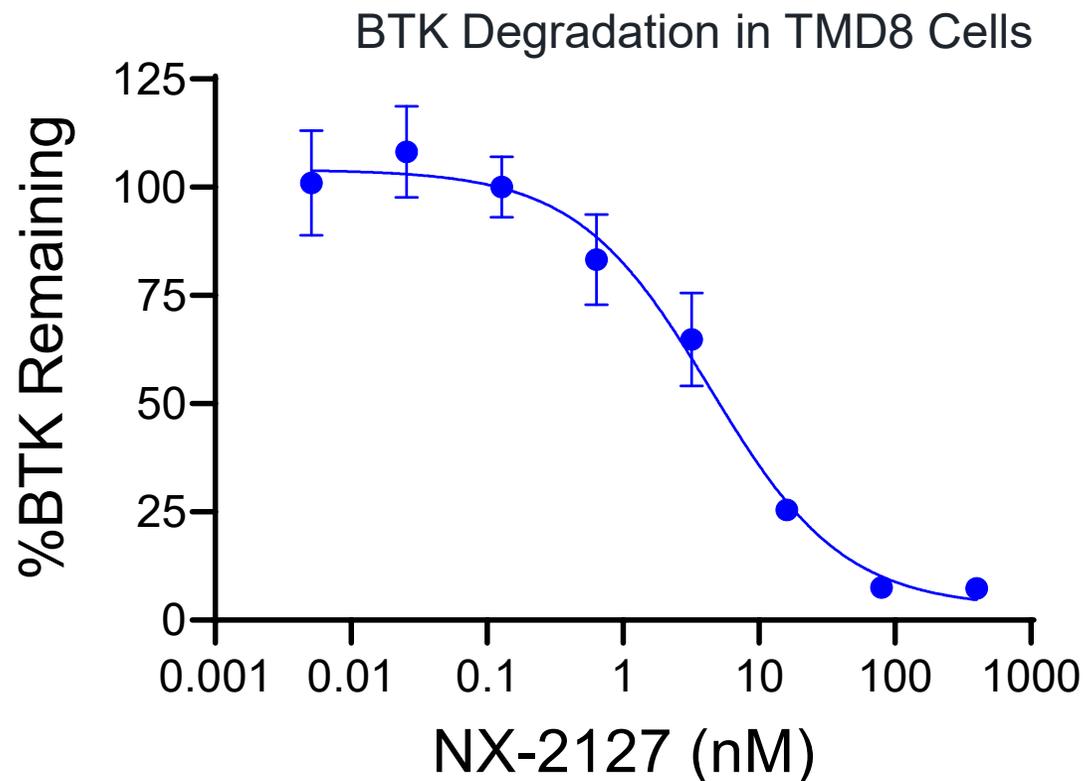
NX-2127: BTK degrader with IMiD activity. Developing across multiple B-cell malignancies (CLL, MCL, WM, MZL, DLBCL, FL)

NX-5948: BTK degrader without IMiD activity. Developing for targeted B-cell malignancies and autoimmune diseases

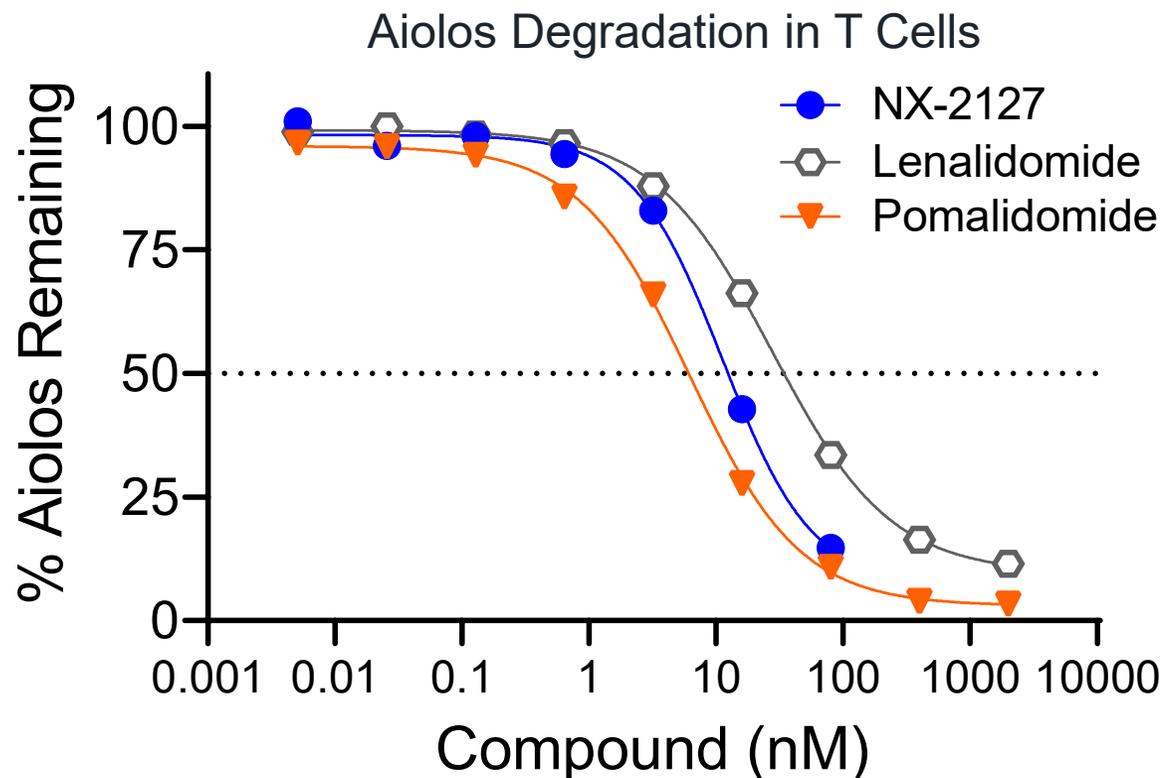


BTK, Bruton tyrosine kinase; IMiD, Immunomodulatory imide drugs; DLBCL, Diffuse large B cell lymphoma; CLL, Chronic lymphocytic leukemia, SLL, small lymphocytic lymphoma; MCL, Mantle cell lymphoma; WM, Waldenstrom's macroglobulinemia; MZL, Marginal zone lymphoma; FL, Follicular lymphoma; NHL, non-Hodgkin lymphoma

NX-2127 Degrades Both BTK and CRBN Neosubstrate Aiolos

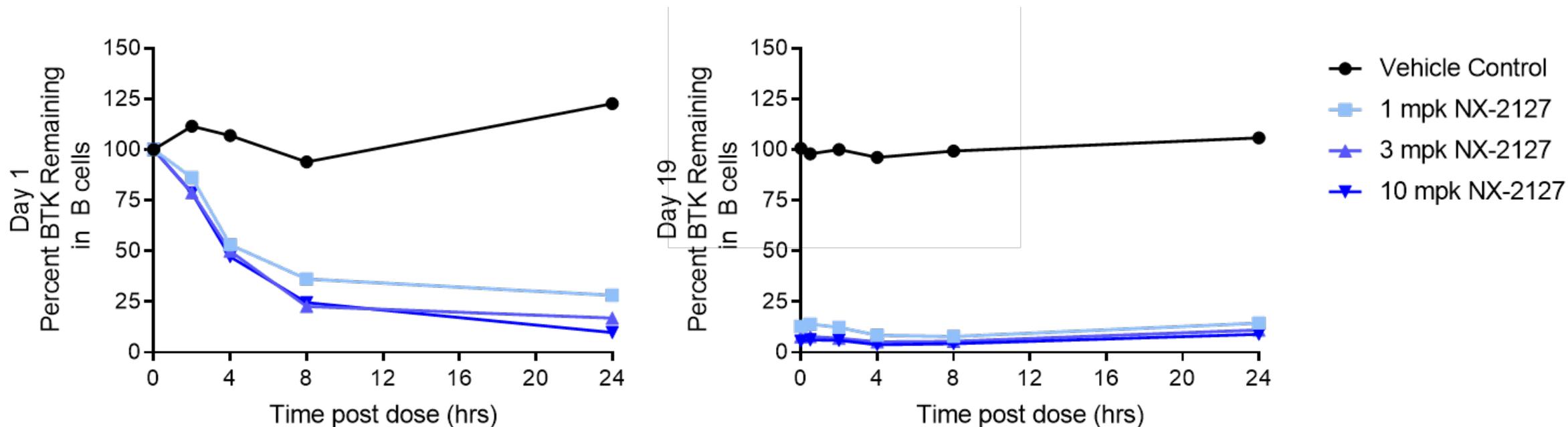


NX-2127 shows potent BTK degradation in TMD8 cells (human DLBCL cell line)



NX-2127 degradation of Aiolos in human T cells occurs at a similar potency to lenalidomide and pomalidomide

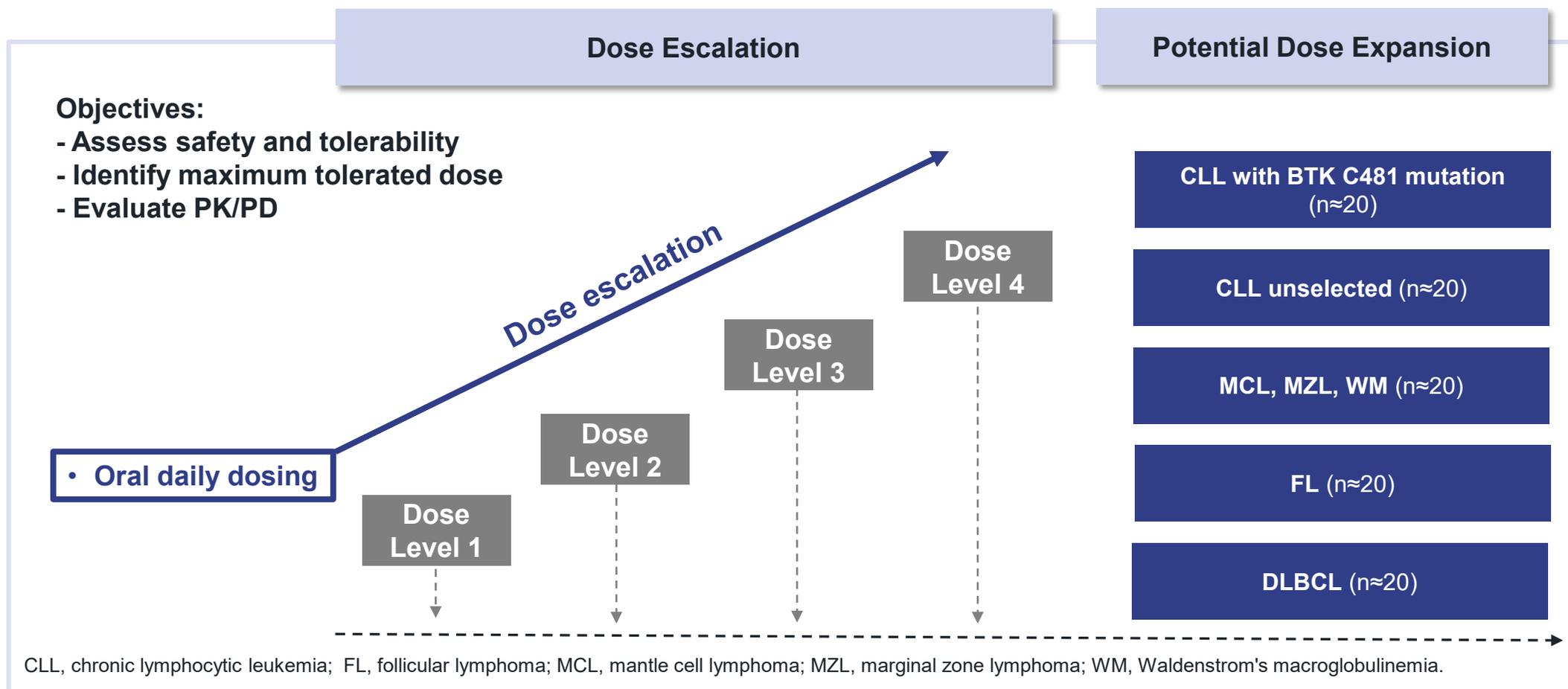
Oral Dosing of NX-2127 Degrades BTK in NHPs



- Significant degradation of BTK in 4 hours and more than 90% degradation through 24 hours post dosing at the highest dose level
- Once daily, oral dosing of NX-2127 maintains suppression of BTK protein levels throughout the 19-day duration of the study (NX-2127 PK $t_{1/2}$ = 5.4 h)

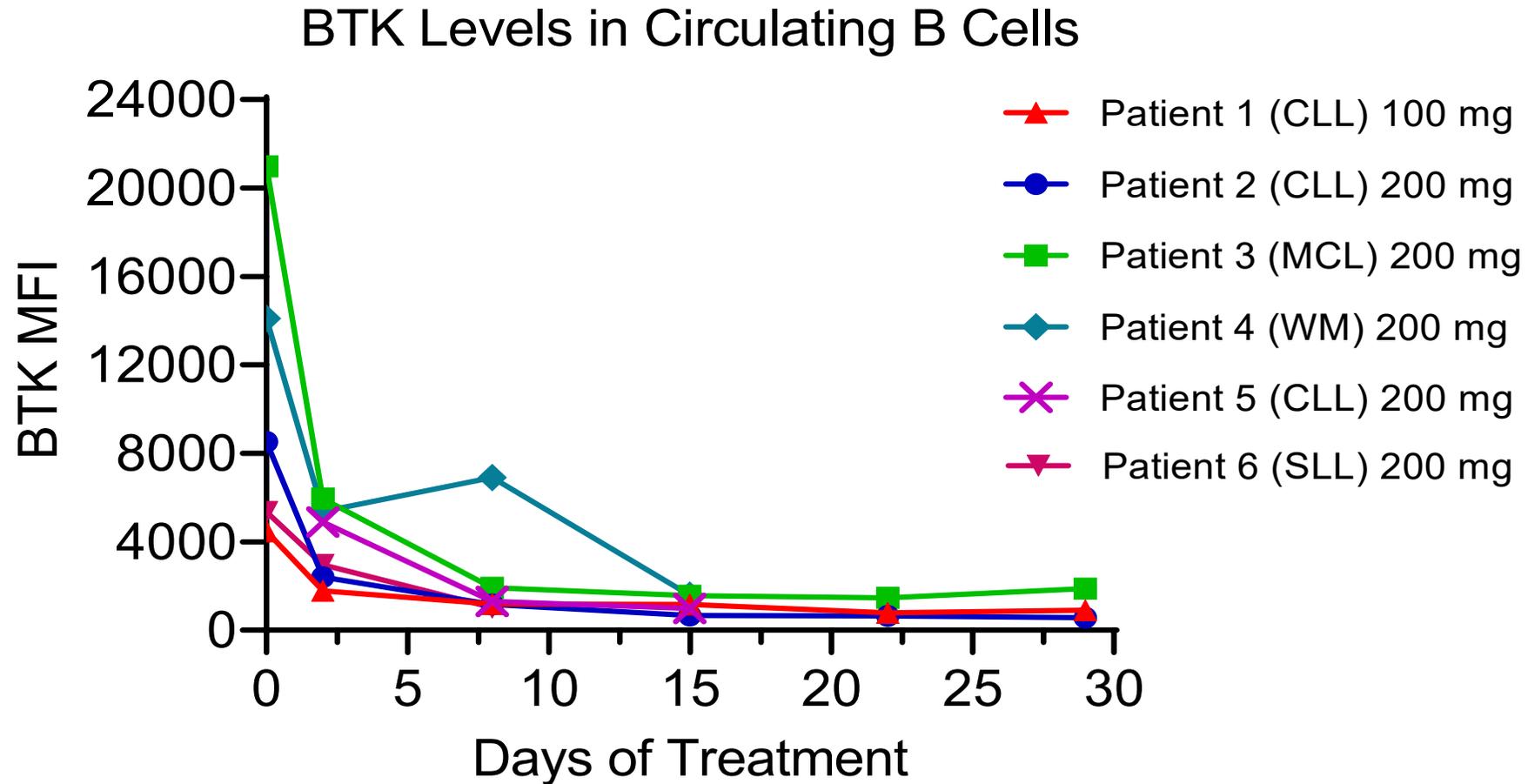
NX-2127-001: Phase 1 First-in-Human Clinical Trial Design

Two-Part Phase 1 Monotherapy Trial of NX-2127 in Relapsed or Refractory B-Cell Malignancies



Robust BTK Degradation Observed in All Patients Dosed Regardless of Baseline BTK Protein Levels

- Oral daily treatment of NX-2127 induced a rapid and significant decrease in BTK levels that was sustained throughout dosing
- Patients have varying levels of BTK in B cells at the start of treatment



MFI: geometric mean fluorescence intensity in circulating CD19+ B cells.

Clinical Response Observed in First Patient

Patient History:

78-year-old male with stage IV CLL

Prior Treatments:

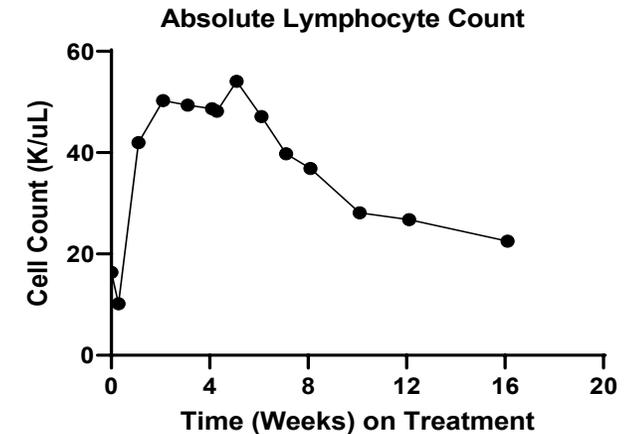
1. Rituximab, 2015
2. Ibrutinib, 2015-2021

Disease at Study Entry:

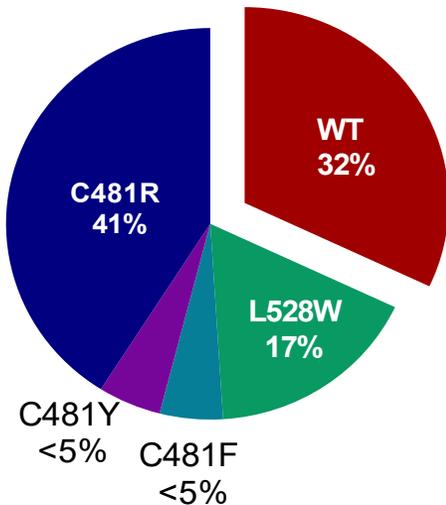
Bone Marrow Involvement: 85.4%
Spleen: Enlarged (15.7 cm)
Nodal Lesions: Several, largest 4.2 cm
Multiple resistance mutations

Safety

Exposure	No dose interruptions or modifications
DLT's	None
SAE's	None
Grade 3 or > AE	Neutropenia (ANC = 860), resolved without intervention



Up to 68% of Leukemia Cells with BTK Mutations



Disease Assessment

Time Point	Hgb (g/dL)	Plt (K/uL)	ALC (K/uL)	Spleen (cm)	Spleen % change ^a	Lymph Node SPD (cm ²)	Nodal SPD % Change	Response ^b
Baseline	14.3	112	16.4	15.7	---	27.1	---	----
Week 8	13.2	133	36.9	14.8	-33%	13.4	-51%	Stable Disease ^c
Week 16	14.1	114	22.5	14.2	-56%	10.8	-60%	Partial remission with lymphocytosis

^a Spleen % change is the percent change to a reference "normal" of 13 cm.

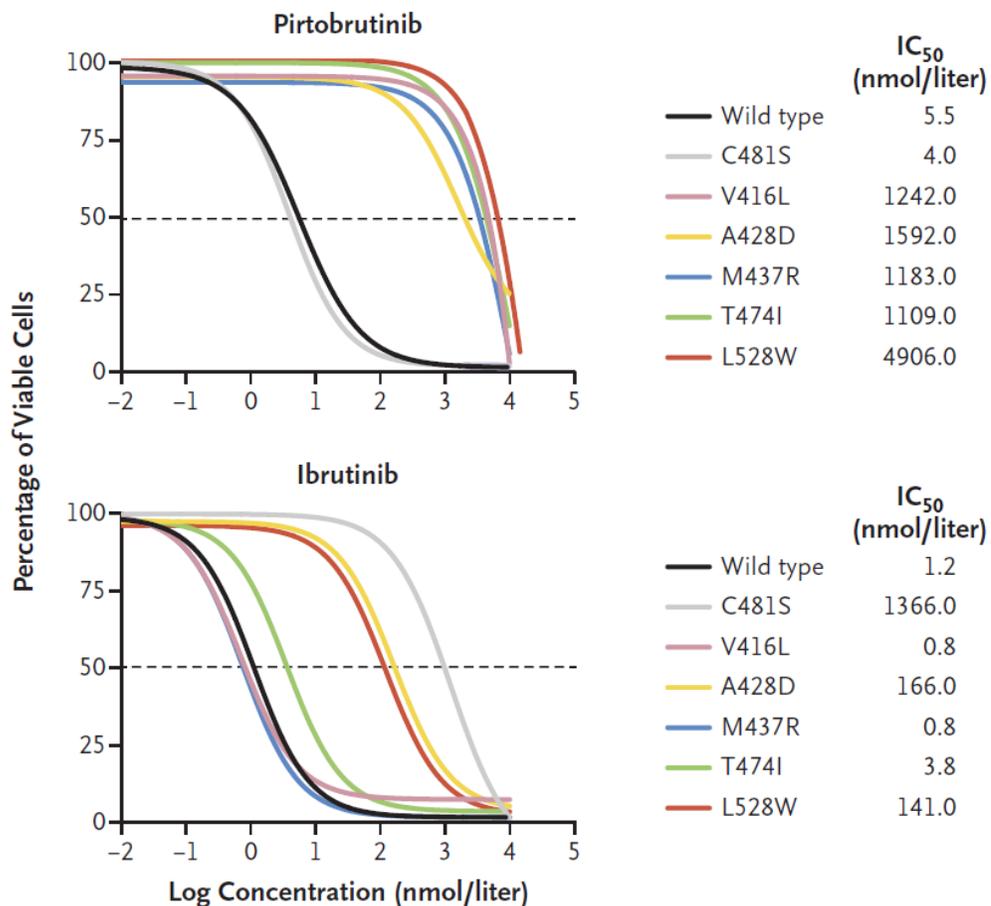
^b Response for this patient as per International working group on chronic lymphocytic leukemia (iwCLL)

^c Listed as partial remission in database.

DLT: dose limiting toxicity; SAE: serious adverse event; AE: adverse event; ANC: absolute neutrophil count; Hgb: hemoglobin, Plt: platelet count, ALC: absolute lymphocyte count, SPD: sum of product diameters

L528W is Among Several Newly Identified Mutations that Confer Resistance to Noncovalent BTK Inhibitors

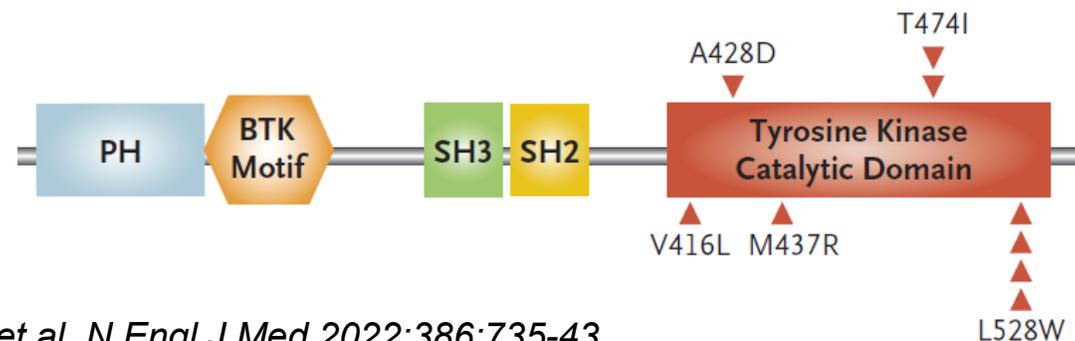
Cell-Viability Assays



The NEW ENGLAND
JOURNAL of MEDICINE

“Our data suggest potential new therapeutic approaches to overcome the newly described BTK inhibitor resistance mechanisms. For example, these data provide a rationale for therapies aimed at addressing the potential scaffold function of BTK rather than inhibiting BTK kinase activity.”

Locations of BTK Mutations



Source: Wang et al, N Engl J Med 2022;386:735-43

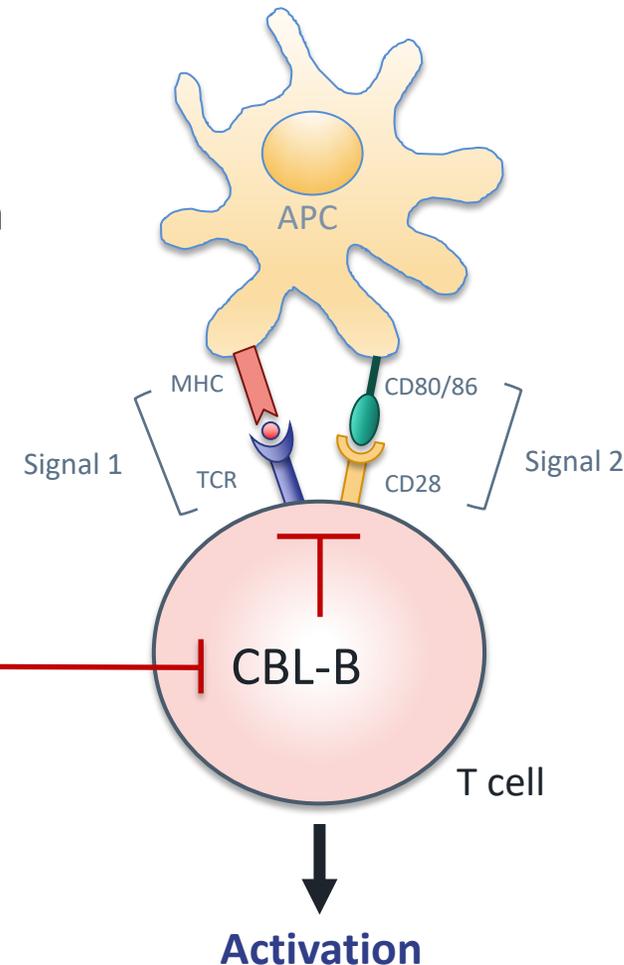
NX-1607: Inhibitor of CBL-B Ligase

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

- CBL-B is an E3 ligase that regulates the immune system by specifically ubiquitinating proteins involved in signaling through the T cell antigen receptor
- Blocking CBL-B removes a brake on the immune system enhancing both T cell and NK cell responses
- CBL-B function is supported by mouse and human genetics

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.

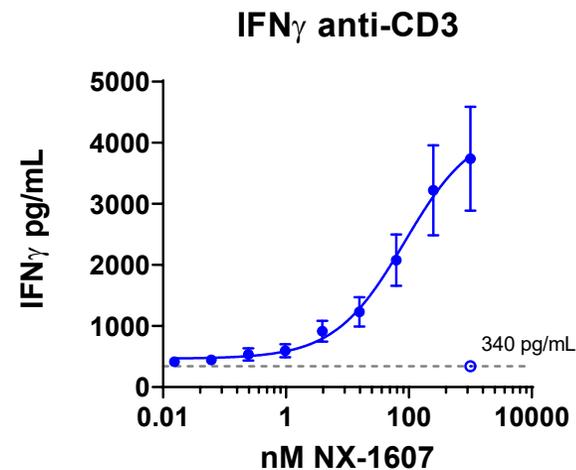
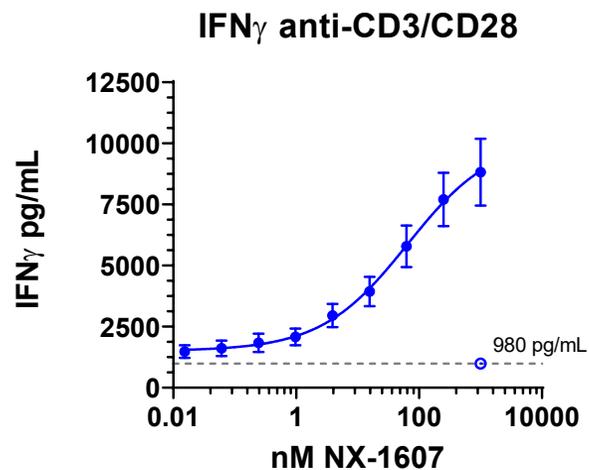
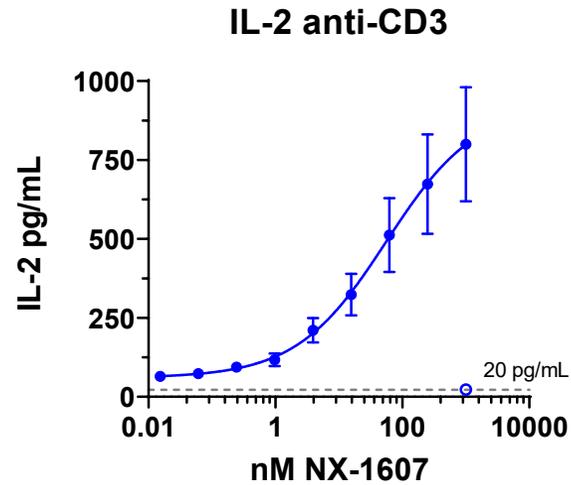
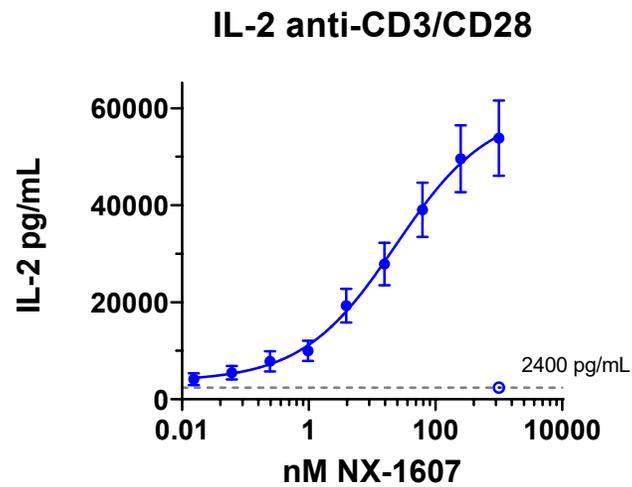


CBL-B inhibition

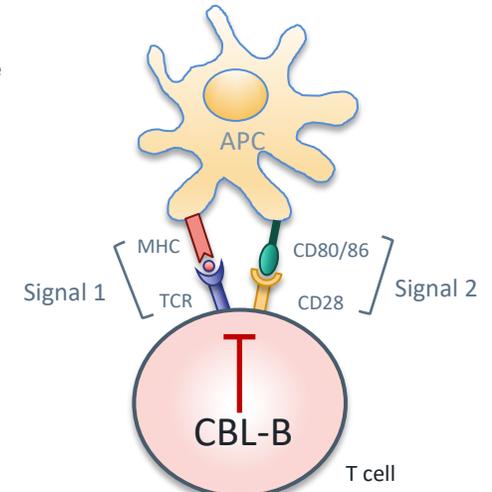
- ↑ IL-2 production
- ↑ Proliferation
- ↑ Central memory phenotype
- ↑ Anti-tumor activity
- ↓ Threshold of activation
- ↓ T cell exhaustion

Synergy with anti-PD-1

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



● Cytokine response
○ Baseline response



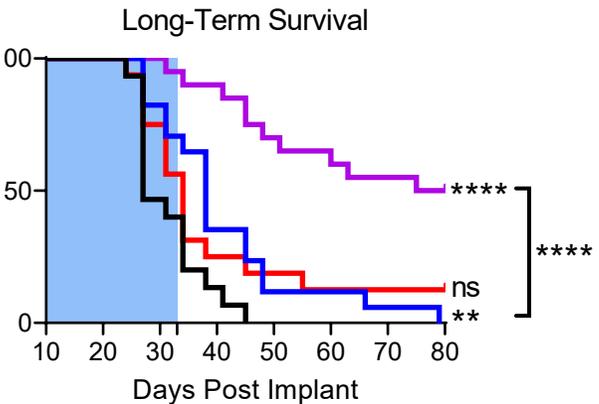
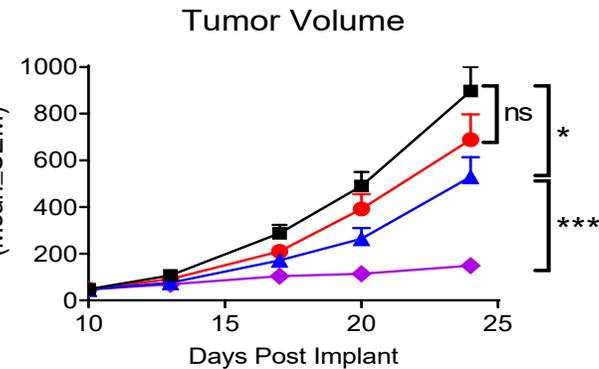
**Cytokine secretion
(Activation)**

Data represents 8 individual donors
Avg \pm SEM

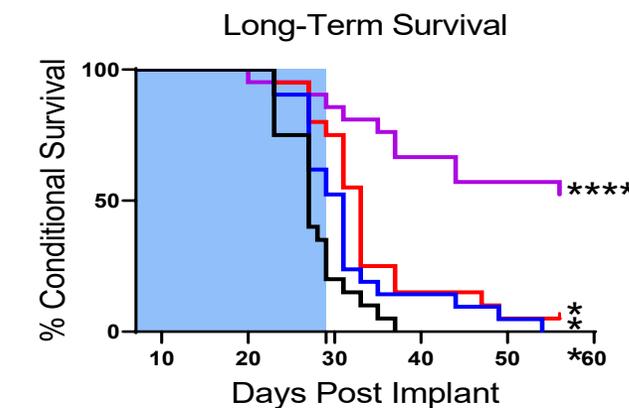
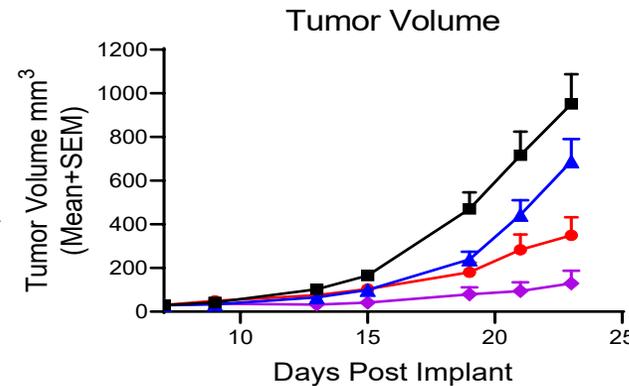
NX-1607 and Anti-PD-1 Synergize to Enhance Anti-tumor Effects and Survival of Mice in Multiple Tumor Models

■ Vehicle ▲ NX-1607 ● Anti-PD-1 ◆ NX-1607 + Anti-PD-1

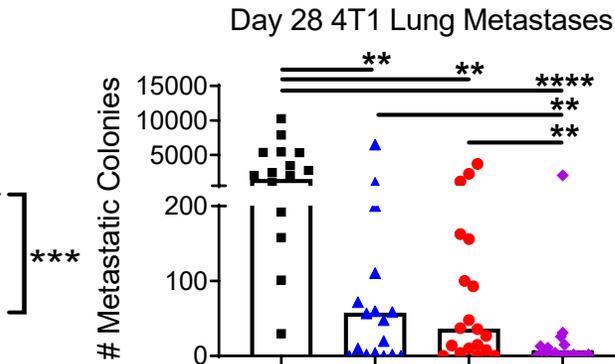
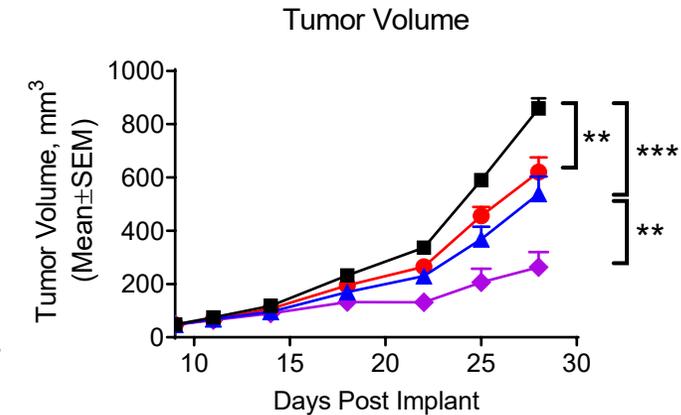
Colorectal (CT26)



Colorectal (MC38)



Triple-negative breast (4T1)



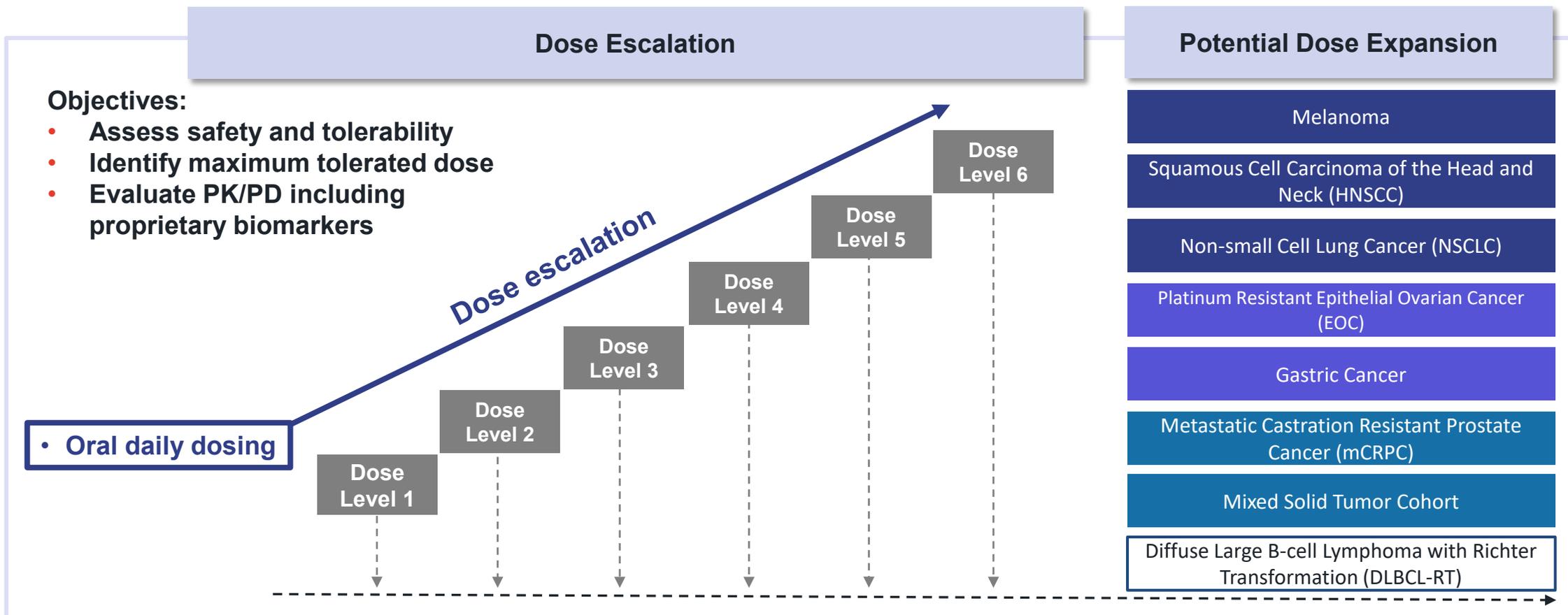
NX-1607 antitumor efficacy is abrogated by CD8+ T or NK cell depletion (data not shown)

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.

NX-1607-101: Phase 1 First-in-Human Clinical Trial Design

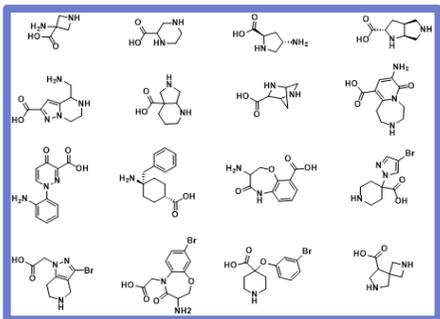
Two-Part Phase 1 Monotherapy Trial of NX-1607 in Relapsed or Refractory Tumors



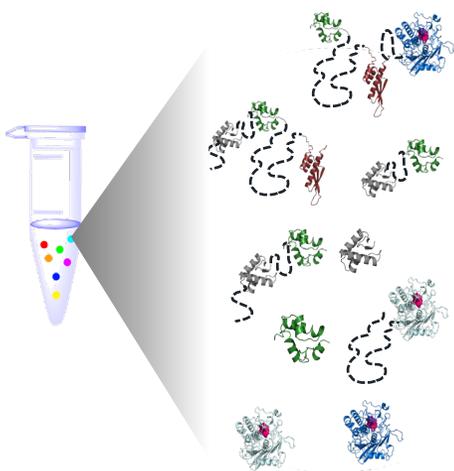
- Checkpoint resistant tumors
- Immunosuppressive microenvironment
- Poorly immunogenic tumors

Expanding our Discovery Pipeline using DELigase

How We're Implementing DEL for Protein Modulation

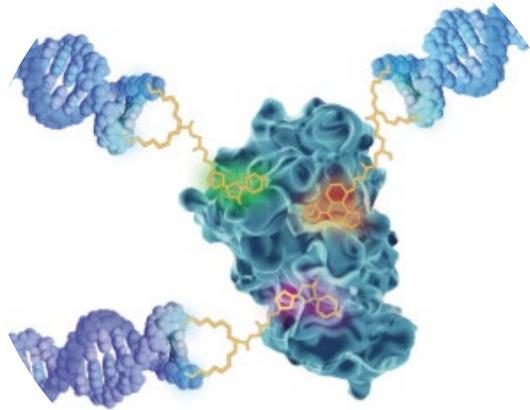


- Proprietary DEL scaffold libraries are unique to Nurix; custom scaffold DELs are distinct in the field and afford more chemical novelty vs other collections
- Extensive in-house protein chemistry and affinity selection expertise to tackle difficult targets and protein complexes
- Broader, on average, scope of screening to address “plastic” surfaces as well as the potential for mutation-specific conformations, protein complexes and conformational change
- On-DNA synthesis and ASMS for thorough hit-finding; investigation of library synthetic routes; increased capture of rare hits; better translation to ML
- Large repertoire of covalent warheads



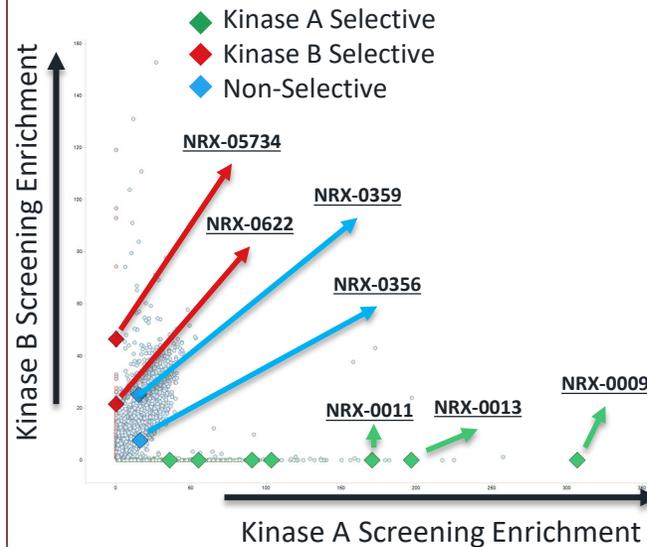
Integrated Platform Enabling Novel Drug Discovery

Binders can span the surface of the protein

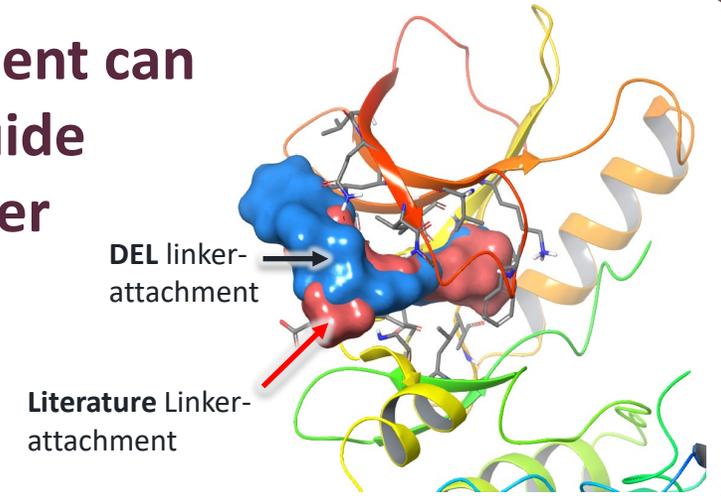


Parallel screening conditions enable identification of competitive inhibitors, allosteric inhibitors, and binders

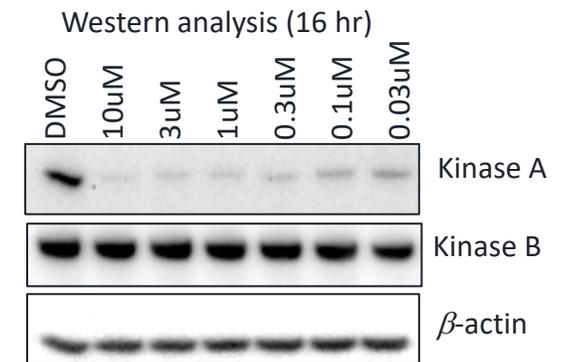
Parallel screening enables identification of selective binders or inhibitors



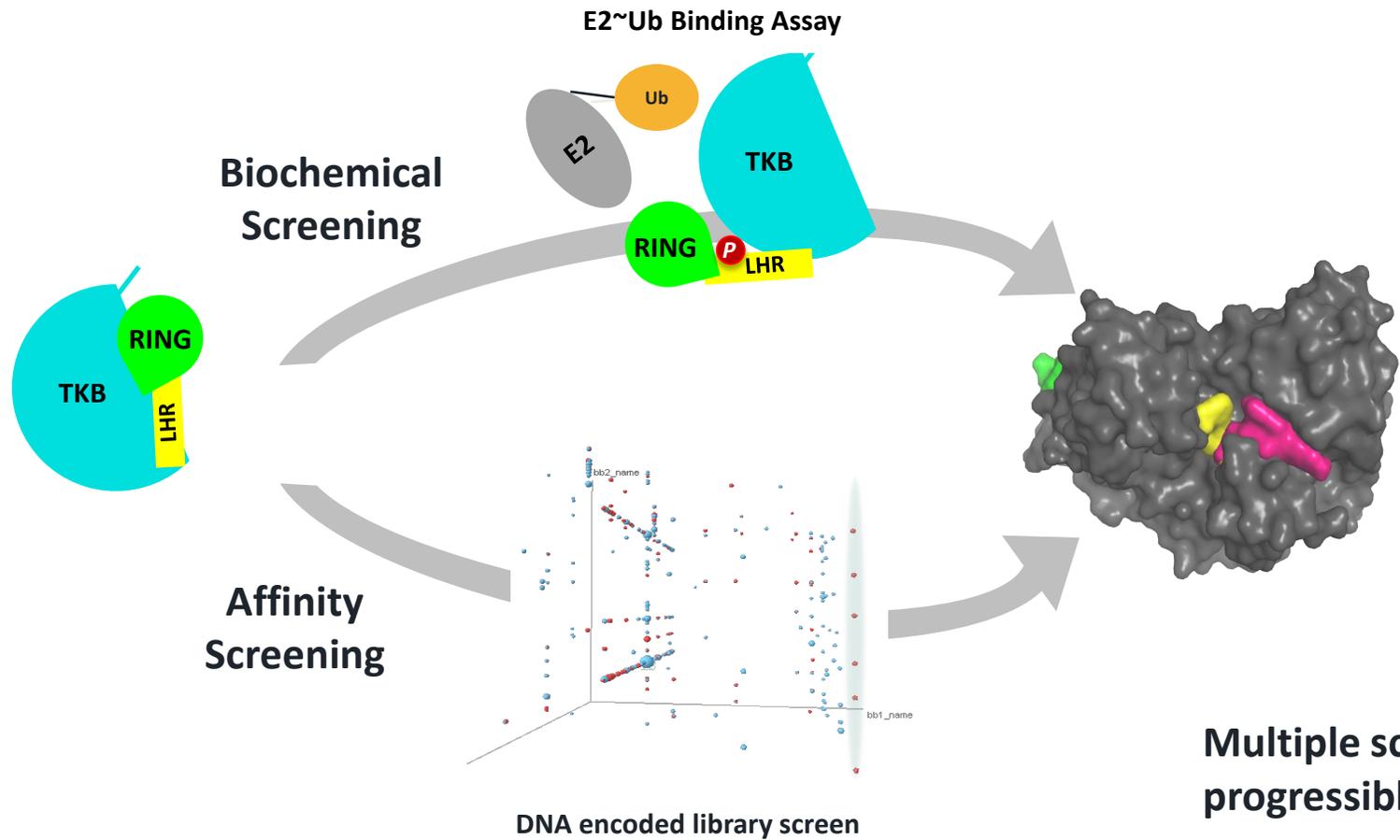
DNA attachment can be used to guide degrader linker placement



Potent selective degrader



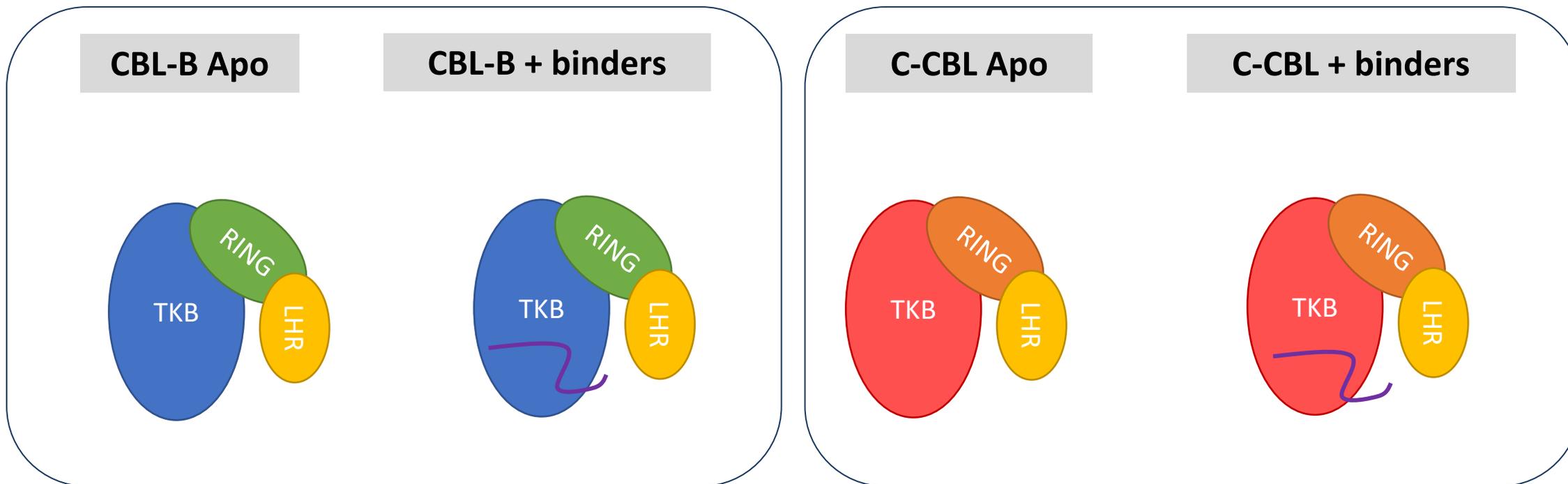
Multiple Chemical Series Identified Through Different Screening Approaches



	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 screening techniques yielded validated and progressible series confirmed by X-ray crystallography.

Over 30 Binding Conditions Applied to Interrogate CBL

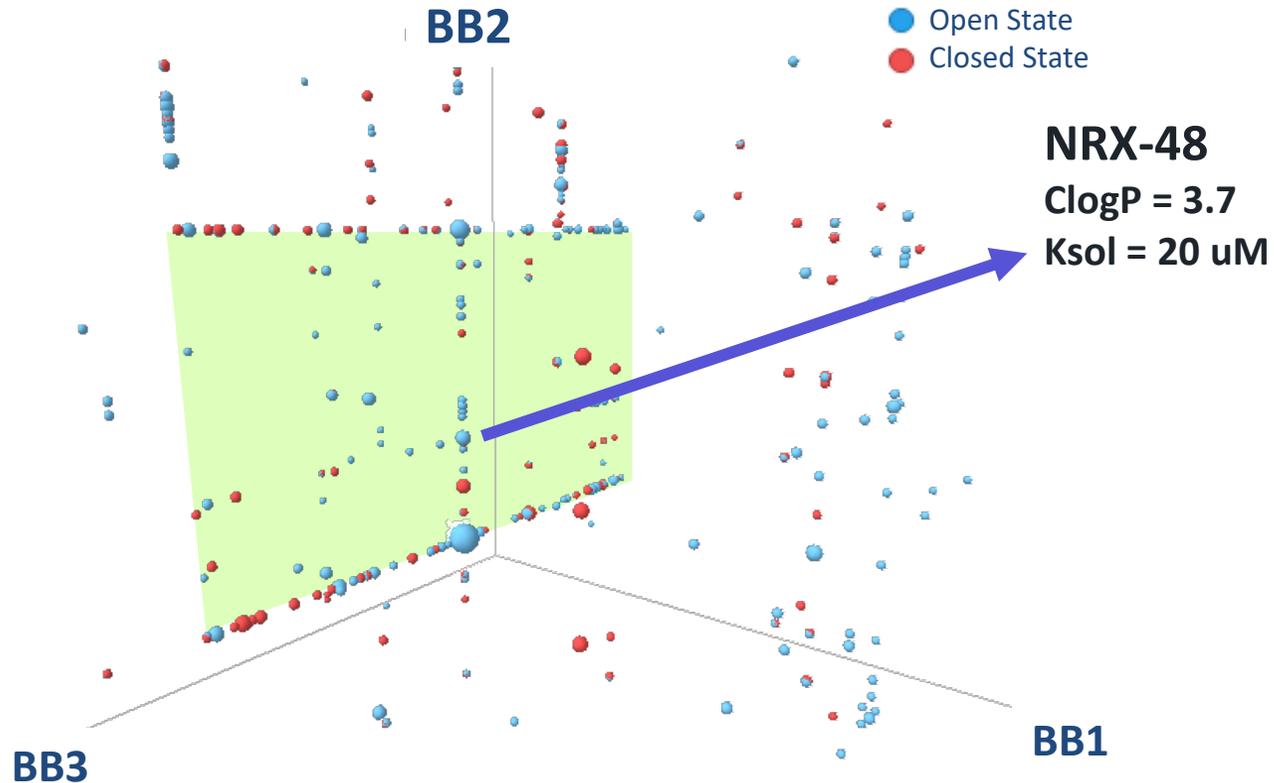


Identify novel chemical matter for CBL-B while differentiating known versus novel binding pockets

Differentiate CBL-B versus C-CBL binders

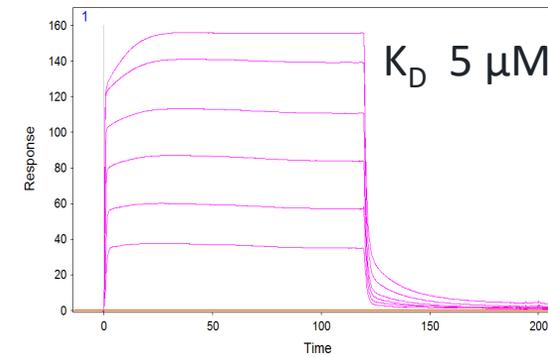
Selective Binder for CBL-B Identified

DEL Screen Affinity Plot

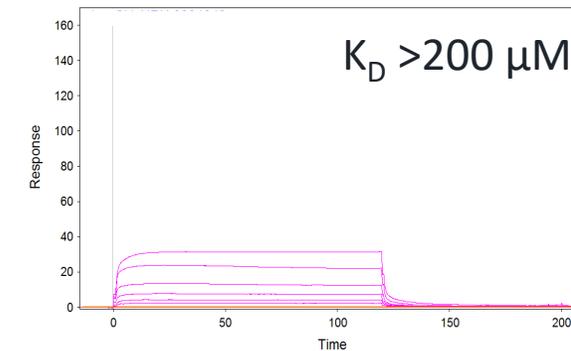


Biophysical assessment of NRX-48:

CBL-B SPR



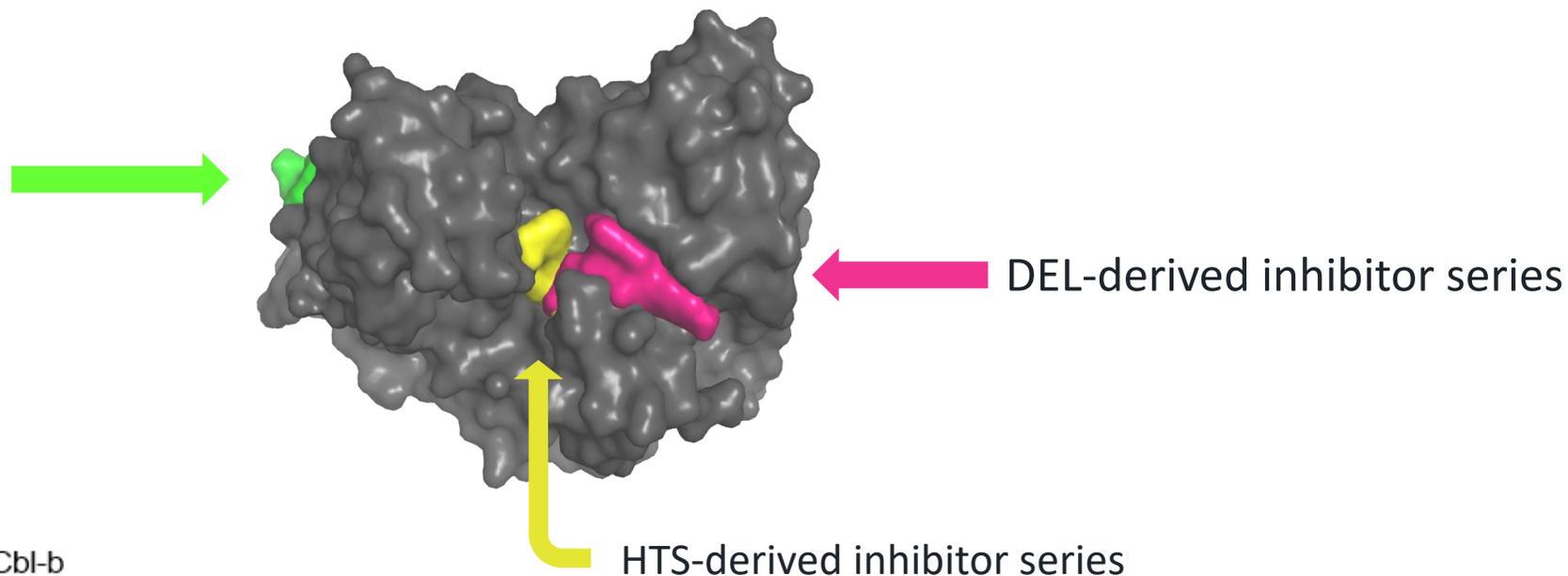
C-CBL SPR



DEL Screening Delivered Differentiated Chemical Matter, Unlocking Challenging Protein Target

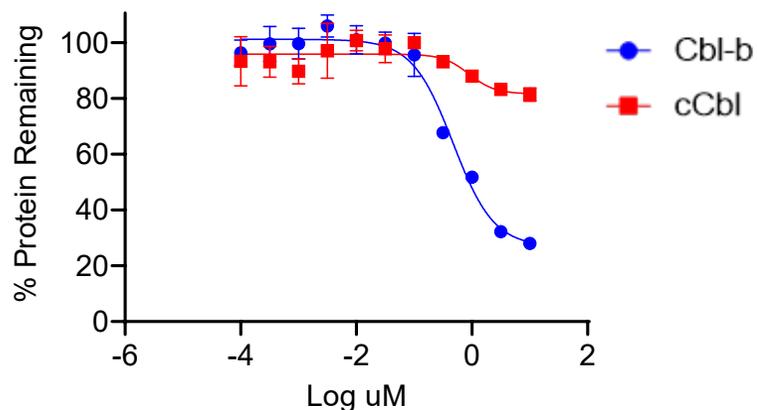
DEL-derived degrader series:

	CBL-B	C-CBL
DC ₅₀ (uM)	0.9	-
D _{max} (%)	72	19



CBL HiBit Assay

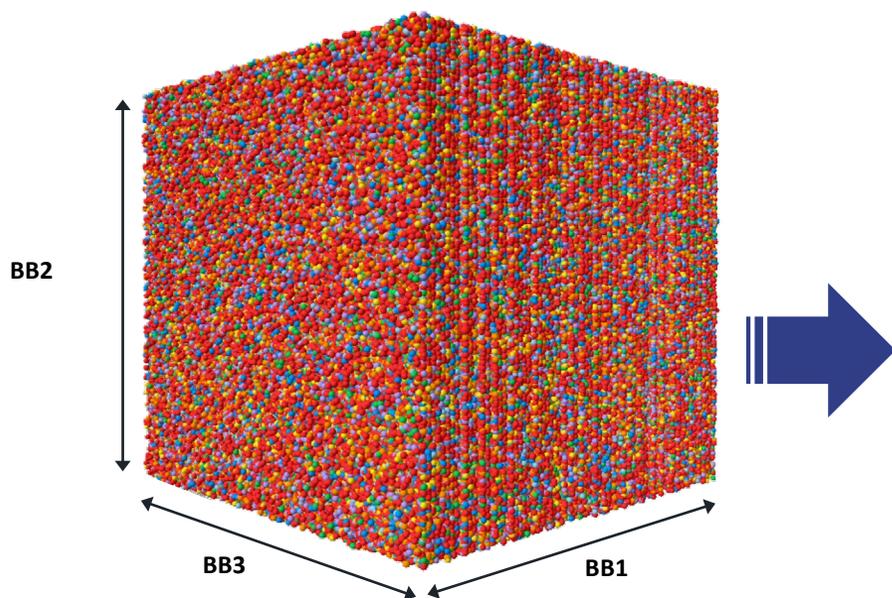
NRX-94



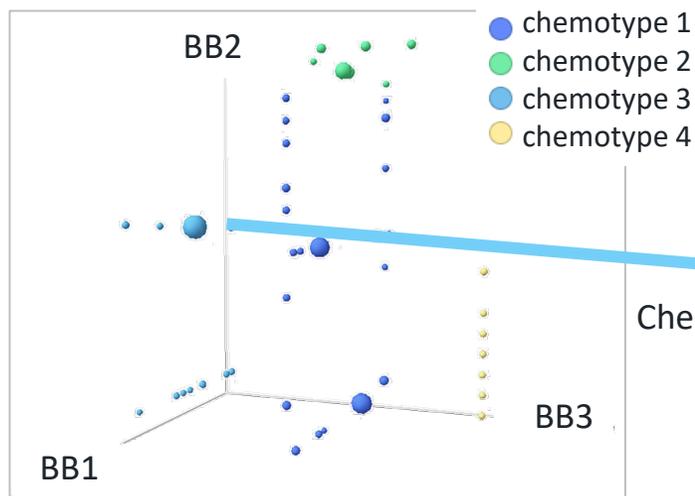
DEL enabled the identification of both binders and inhibitors of CBL-B without the need for an apriori understanding of this intractable target

Potent SARS Binder Directly from DELigase Platform

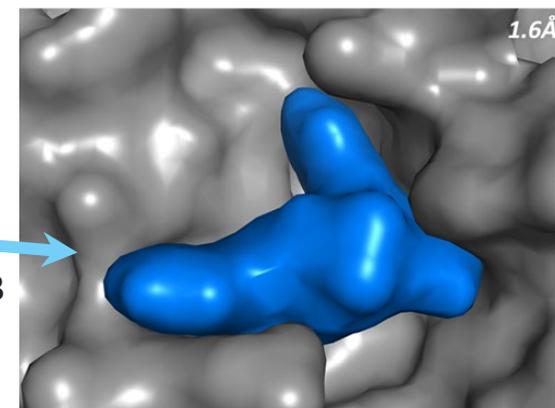
Nurix DELs consist of billions of DNA-barcoded compounds



1. Screen Nurix DEL collection against SARs COV-2 protein targets



2. Identify rare small molecule binders



SARs COV-2 Protein Target (gray)

3. Solve X-ray crystal structure; Evaluate for activity

Potent, Reversible M^{pro} Inhibitor Identified using DEL

NRX-1

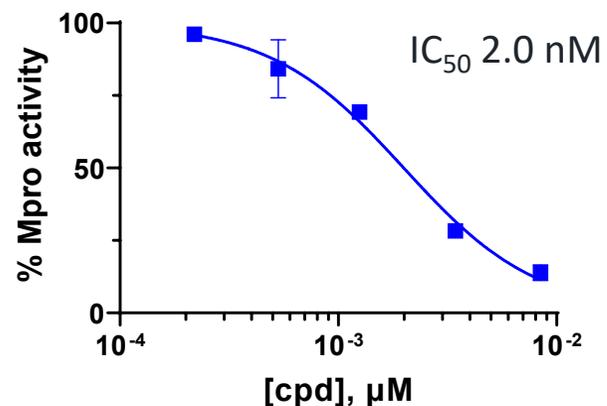
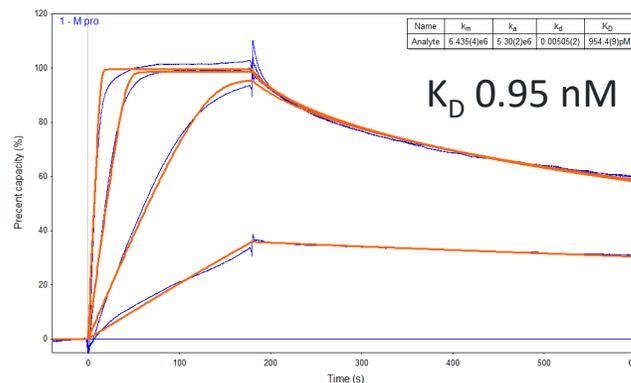
M^{pro} K_D = 1.1 nM (n=3)

M^{pro} IC₅₀ = 2.0 nM

MW <540

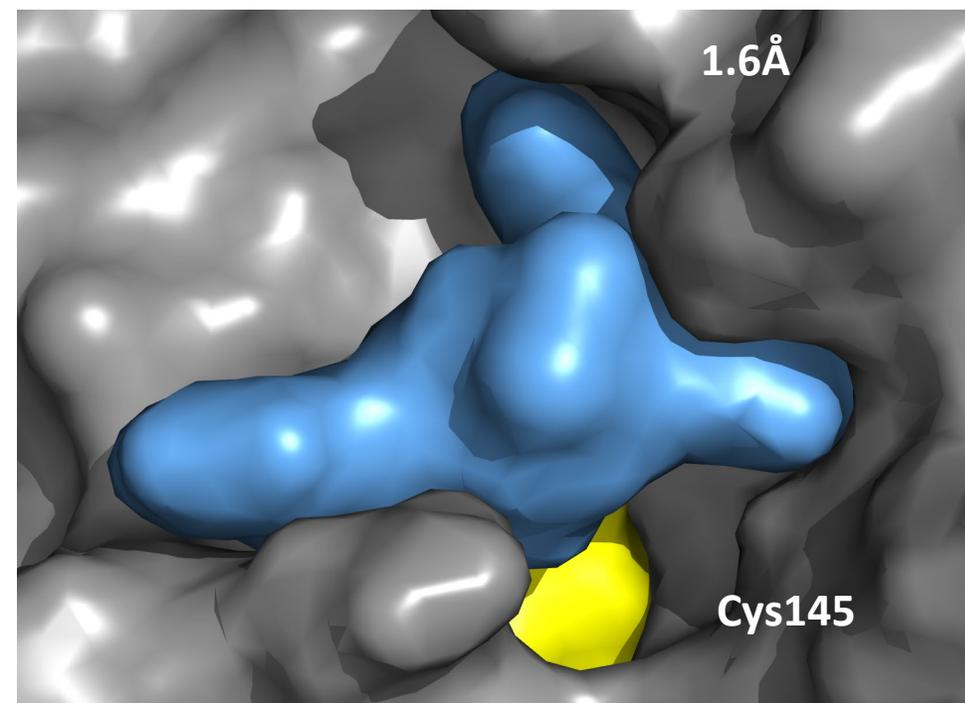
LE = 0.31

Solubility = 245 μM



- The initial DEL hit is the most potent, reversible M^{pro} ligand reported to date
- Ideal starting-point for development of an inhibitor and degrader

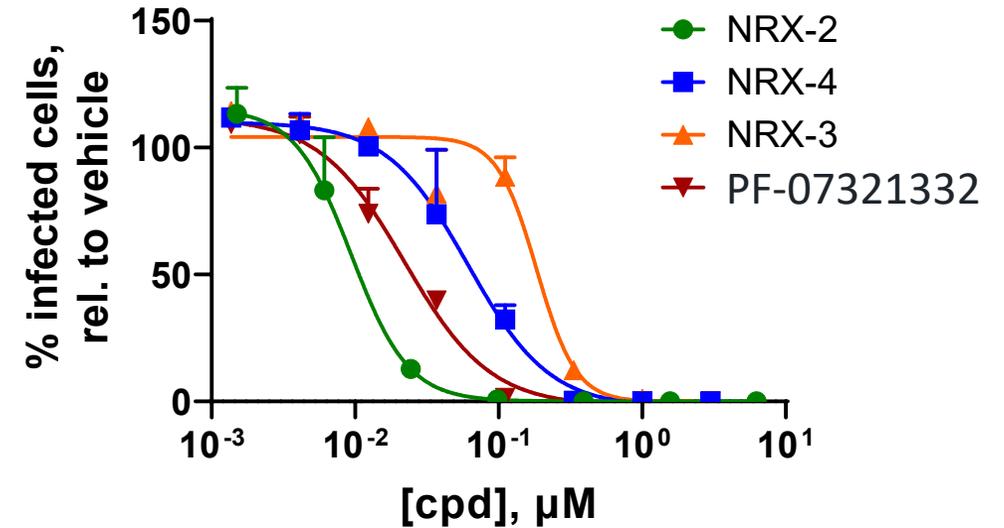
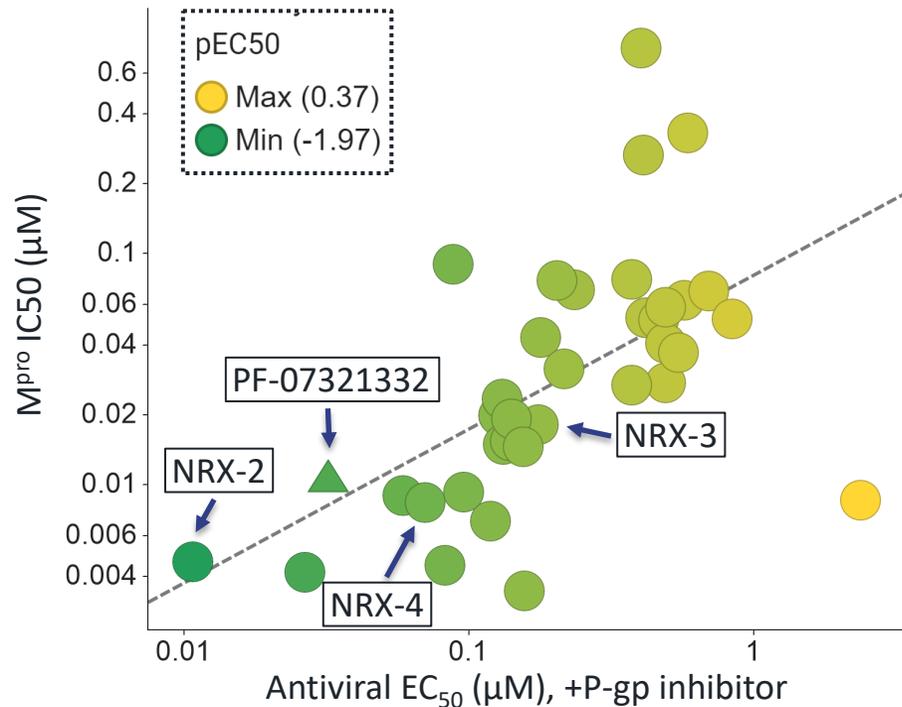
X-ray of NRX-1 bound to M^{pro}



- Structurally enabled, currently have 17 Nurix M^{pro} X-ray structures to guide design efforts

Nurix M^{pro} Inhibitors Demonstrate *in vitro* Antiviral Activity Comparable to Approved Agent

Compounds screened in a 2-day *in vitro* antiviral assay using SARS-CoV-2/WA1 in Calu-3 cells



Compound	EC ₅₀ , nM	EC ₉₀ , nM
NRX-2	11	28
NRX-4	70	221
NRX-3	174±68	353±234
PF-07321332	32±7	80±27

- Correlation established between the biochemical IC₅₀ and cellular EC₅₀ with approximately 10-fold cell to enzyme shift

NRX-4 Compares Favorably to Nirmatrelvir Across a Range of Parameters

		NRX-4	PF-07321332, nirmatrelvir
Chemical starting point		Custom scaffold DEL	Peptide substrate
Chiral centers		1	6
Mechanism		Non-covalent	Reversible-covalent
Clinical Status		Pre-clinical	Approved for emergency use, co-dosed with Ritonavir
Molecular weight/cLogP		<560/3.8	500/0.8
M ^{pro} biochemical IC ₅₀ (μM)		0.008	0.011
Calu-3 SARS-CoV-2 EC ₉₀ (μM)*		0.25	0.32
HLM Cl _{int} (μL/min/mg)		25.4	24.5 [†]
Mouse PK (1 mg/kg iv 10 mg/kg po)	Cl (mL/min/kg)	38	21
	AUC Inf (hr*μM)	2.1	4.7
	T _{1/2} (hr)	3.1	4.4
	Bioavailability, F%	26	29

* without co-treatment of P-gp efflux inhibitor

[†] Reported in Owen *et al.*, *Science* **374**, 1586-1593 (2021)

Advancing Our Pipeline to Multiple Clinical Milestones in 2022

NX-2127

- Initiate Phase 1b trial in mid-2022
- Present additional Phase 1a clinical results in H2 2022

NX-5948

- Dose first patient in Phase 1a trial in H1 2022
- Establish Phase 1a PK/PD in H2 2022

NX-1607

- Establish Phase 1a PK/PD in mid-2022

DeTIL-0255

- ✓ Dose first patient in Phase 1 trial in H1 2022
- Phase clinical update from safety run in H2 2022

Investor R&D day

- Planned for Q2 2022 (May 19 in NYC)

Note: All anticipated timing is based on calendar-year periods

Thank you

Nurix Therapeutics

