nurix

Leader in Targeted Protein Modulation

First Targeted Protein Degrader for Hematologic Malignancies

NX-2127

Promega TPD Symposium
Madison, WI
September 20, 2022

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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)

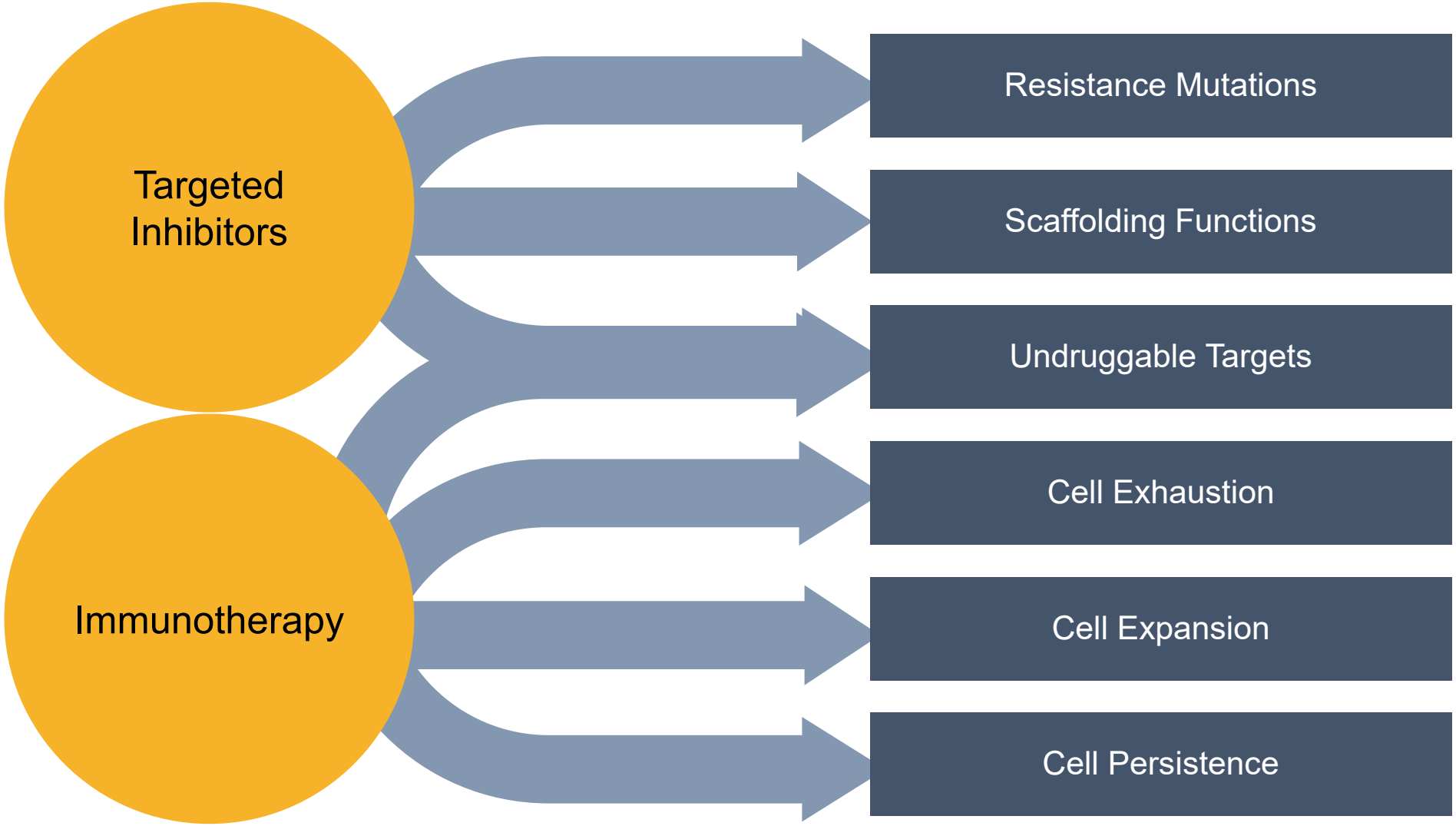
Inhibit ligases to increase specific protein levels

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

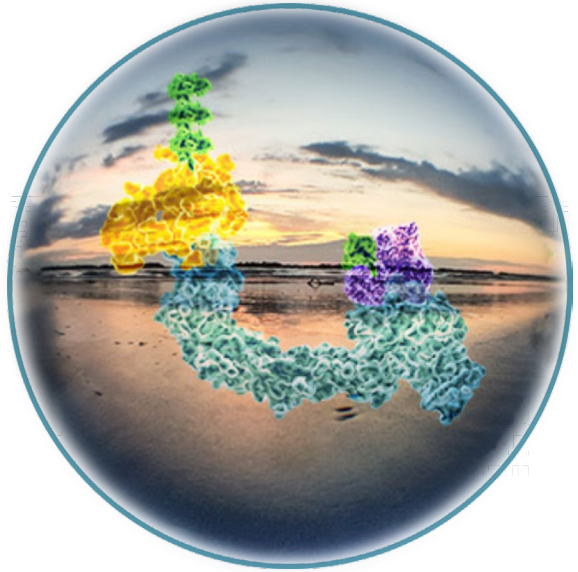
Nurix' Targeted Protein Modulation Pipeline Addresses Key Limitations of Leading Cancer Therapy Modalities



A First-In-Class Franchise of BTK Degraders: NX-2127 & NX-5948

BTK DEGRADATION & IMMUNOMODULATION NX-2127 (Oncology)

- Robust BTK degradation and immunomodulatory activity observed across all dose levels to date
- Positive clinical activity in all CLL patients, including responses in double-refractory patients with BTK or BCL2 mutations
- Initiated cohort expansion for CLL patients
- Dose exploration is ongoing for patients with NHL

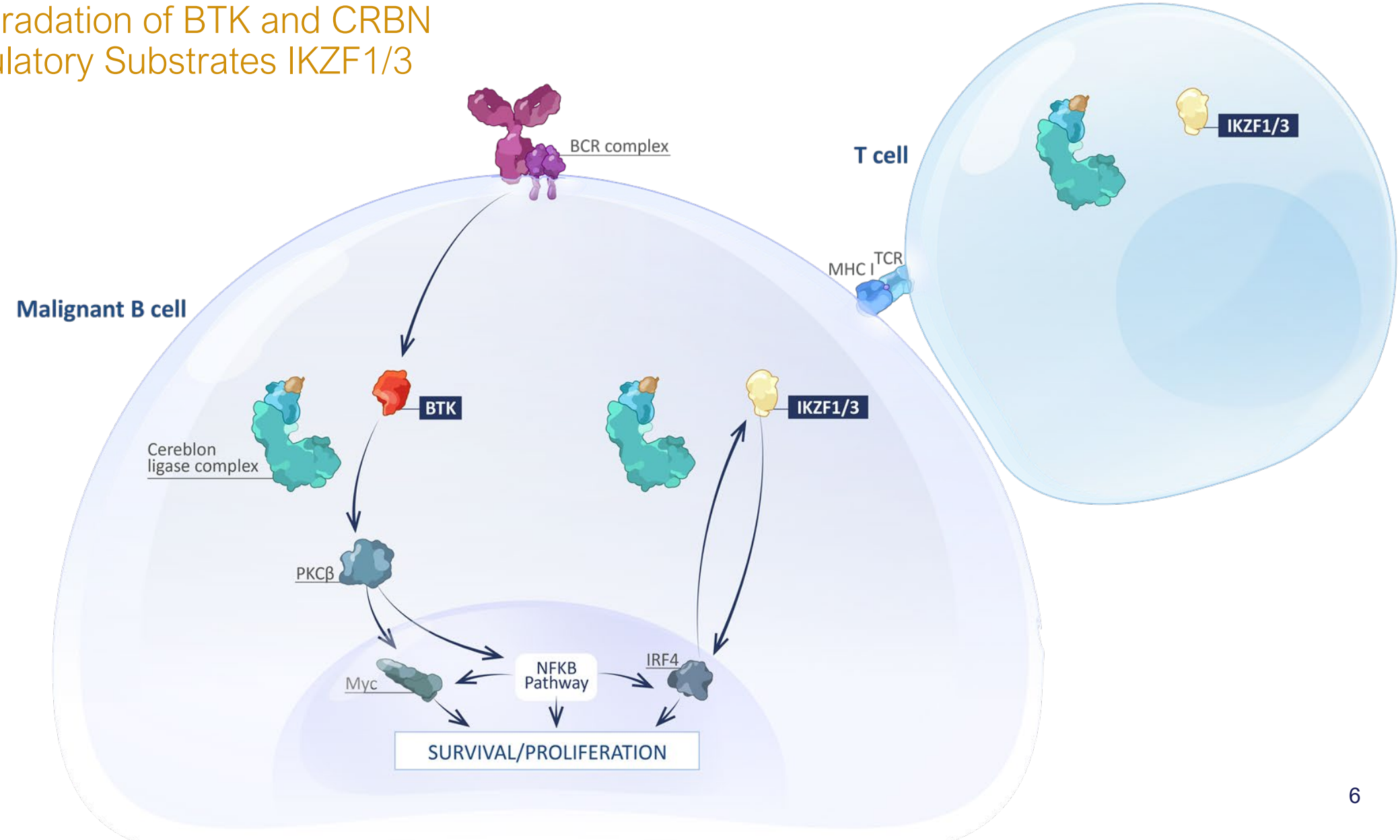


BTK DEGRADATION NX-5948 (Oncology & Autoimmune)

- Active against multiple BTK inhibitor-resistant mutations
- Crosses blood brain barrier and degrades BTK in brain-resident lymphoma cells and microglia in animal models
- Activity in multiple models of autoimmune disease
- First patient dosed in Phase 1a dose escalation trial

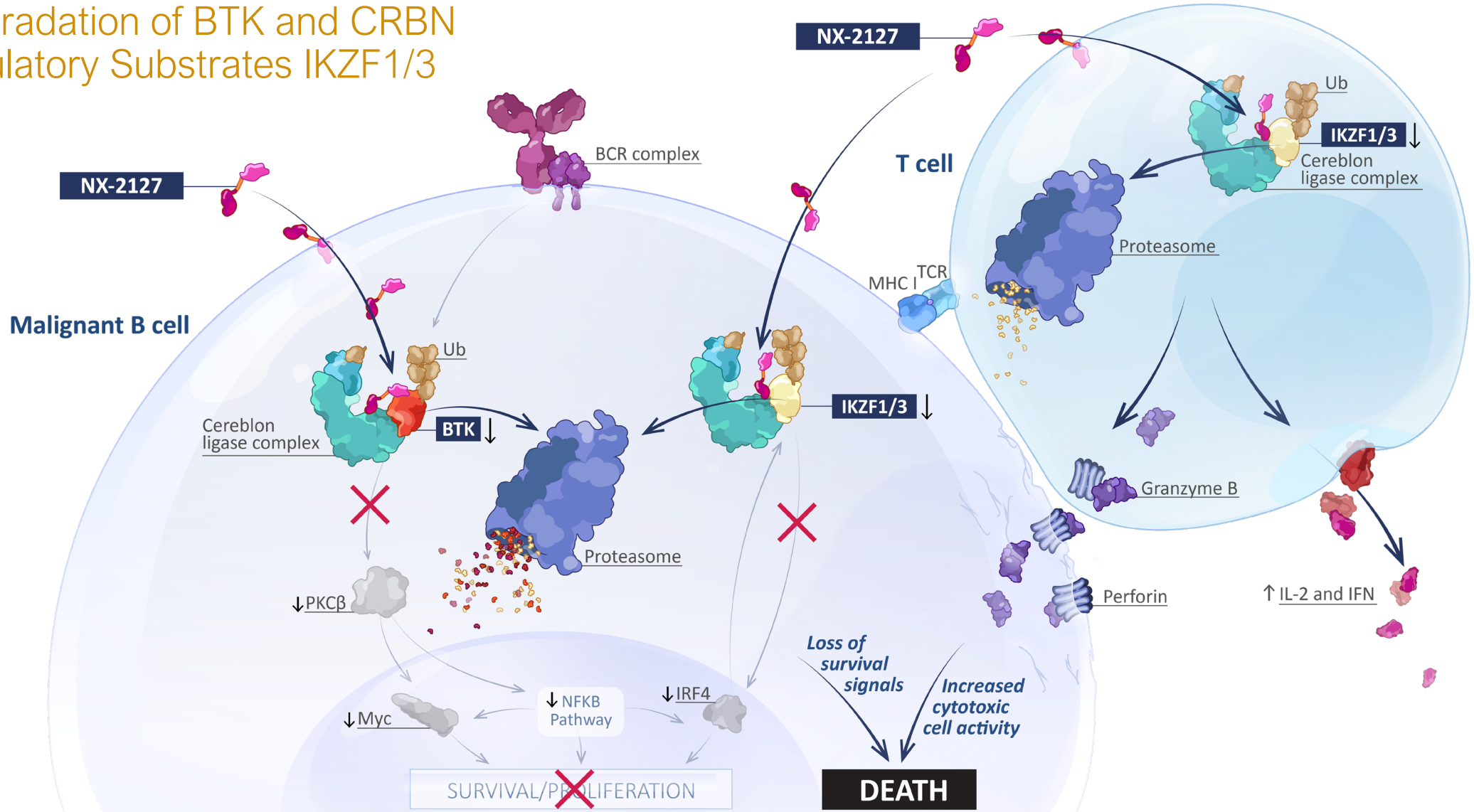
NX-2127 Dual Mechanism of Action

Targeted Degradation of BTK and CRBN Immunomodulatory Substrates IKZF1/3

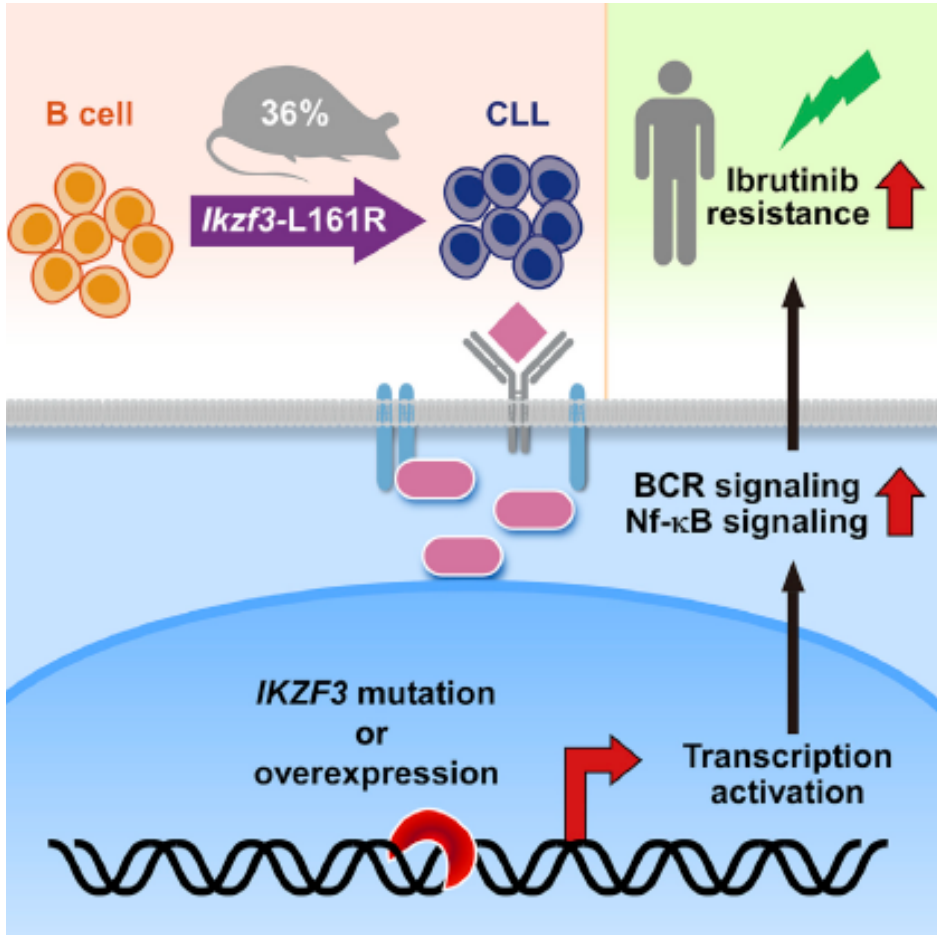


NX-2127 Dual Mechanism of Action

Targeted Degradation of BTK and CRBN Immunomodulatory Substrates IKZF1/3



Aiolos (IKZF3) Overexpression Drives BTK Inhibitor Resistance in CLL, a Rationale for a Combination Strategy



Article

Cancer Cell

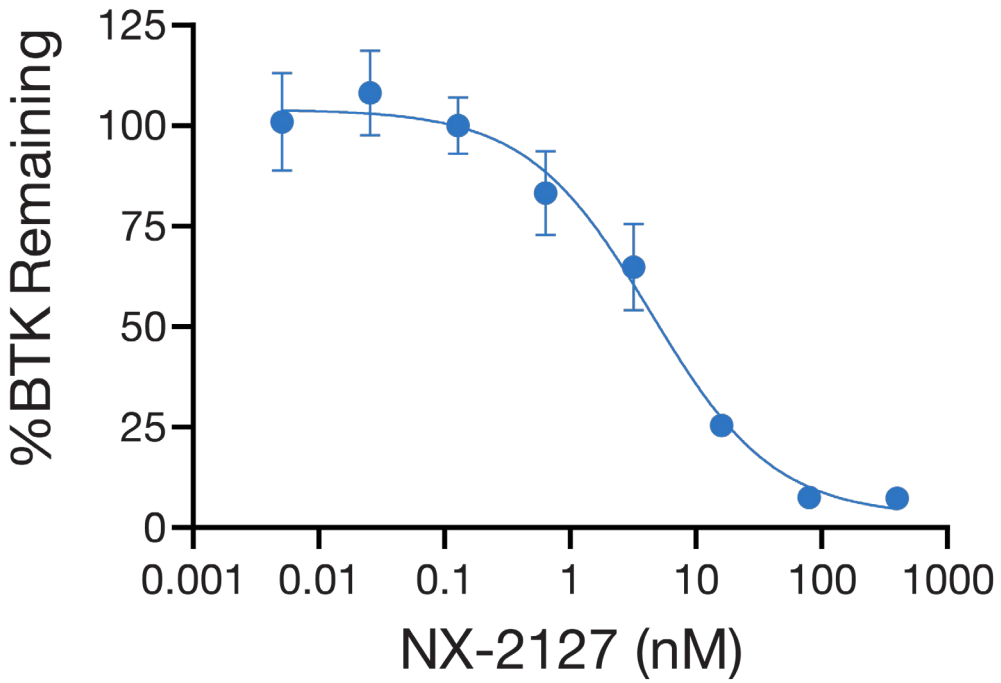
A hotspot mutation in transcription factor *IKZF3* drives B cell neoplasia via transcriptional dysregulation

"Our results thus highlight IKZF3 oncogenic function in CLL via transcriptional dysregulation and demonstrate that this pro-survival function can be achieved by either somatic mutation or overexpression of this CLL driver. This emphasizes the need for combinatorial approaches to overcome IKZF3-mediated BCR inhibitor resistance."

Source: Lazarian et al; Cancer Cell 39, 380–393, March 8, 2021

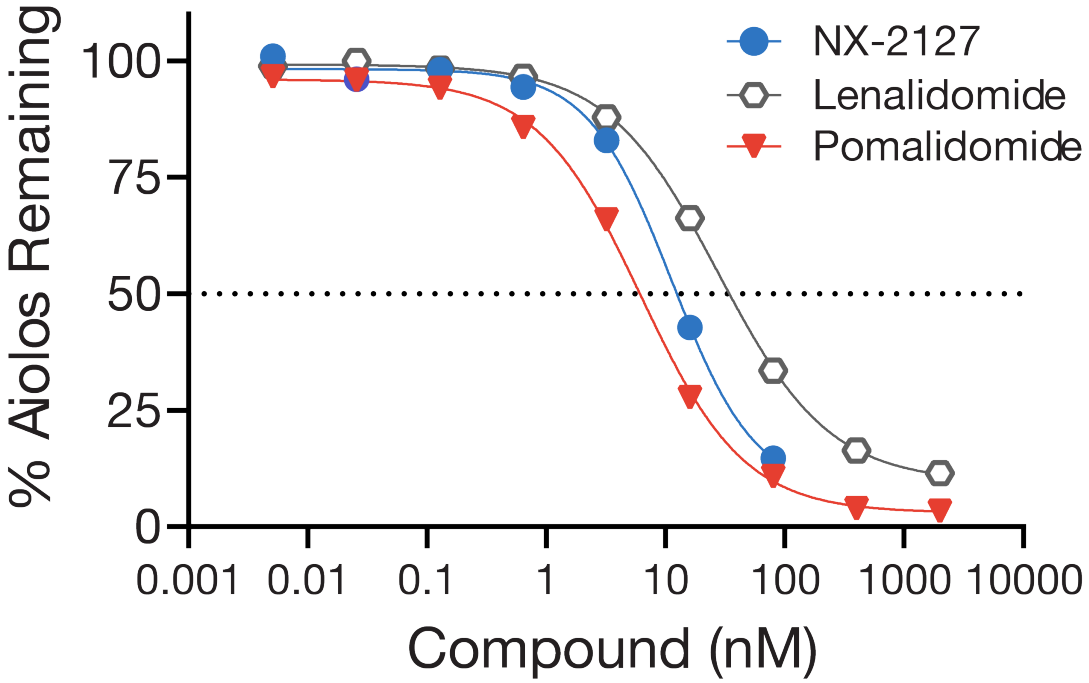
NX-2127 Degrades Both BTK and Immunomodulatory Cereblon Neosubstrate Aiolos

BTK Degradation in TMD8 Cells



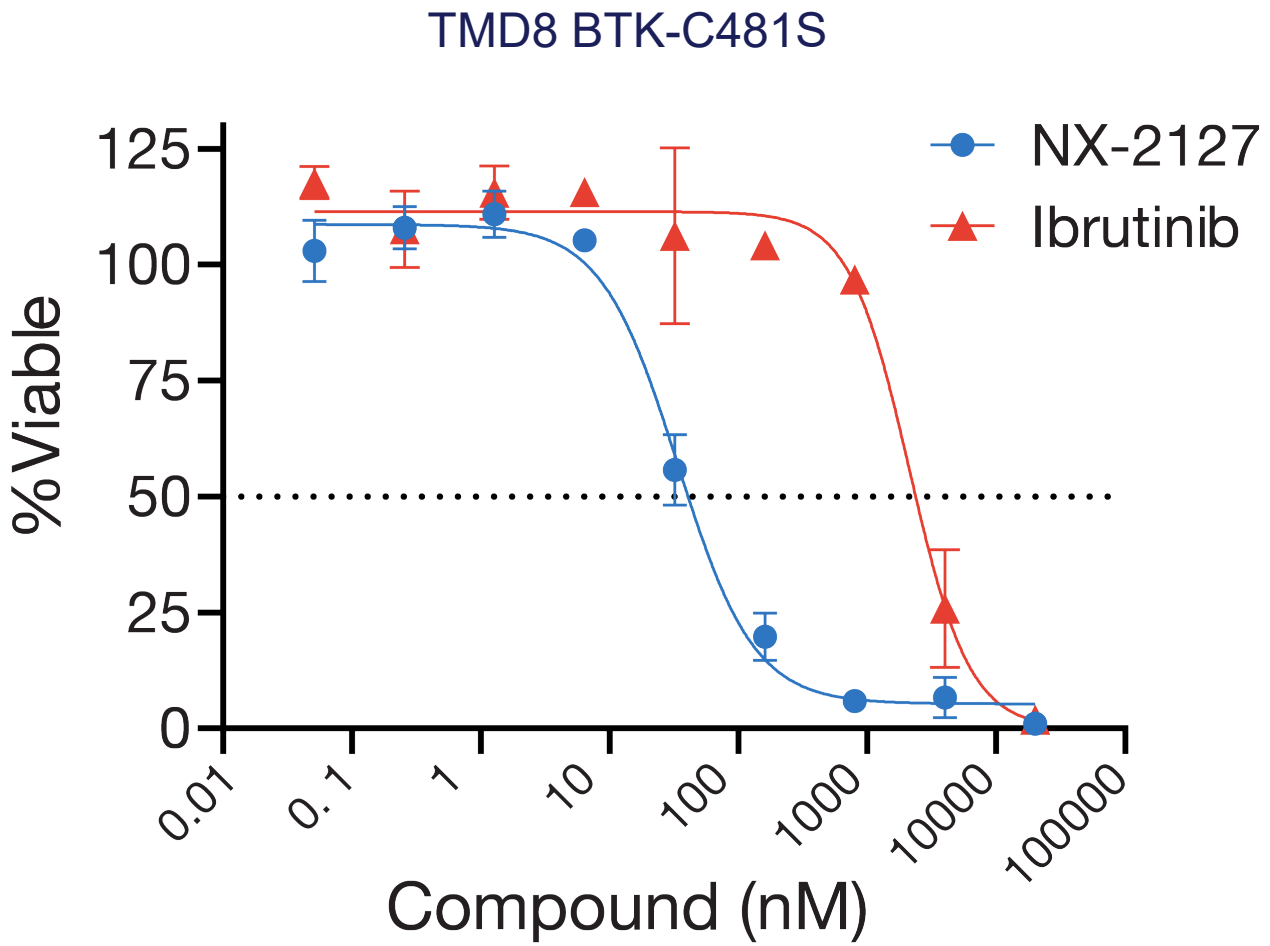
NX-2127 shows potent BTK degradation in TMD8 cells (human DLBCL cell line)

Aiolos Degradation in T Cells



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

NX-2127 Is Active Against Ibrutinib-Resistant Tumor Cell Lines

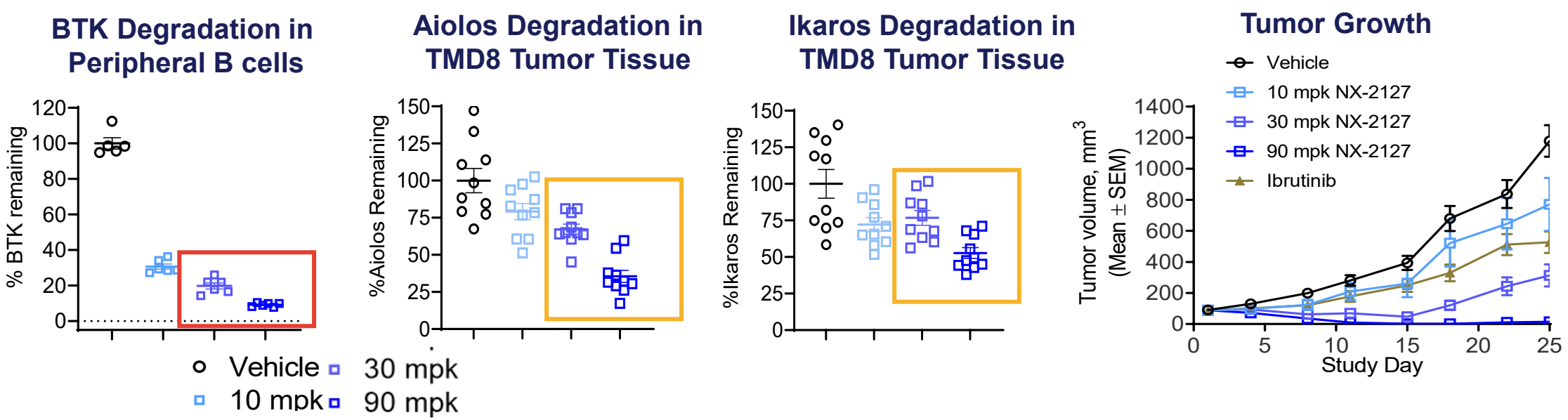


BTK-C481 mutations are the most common resistance mutations to ibrutinib and other covalent BTK inhibitors

NX-2127 may offer a therapeutic option for patients with resistance to BTK inhibitors

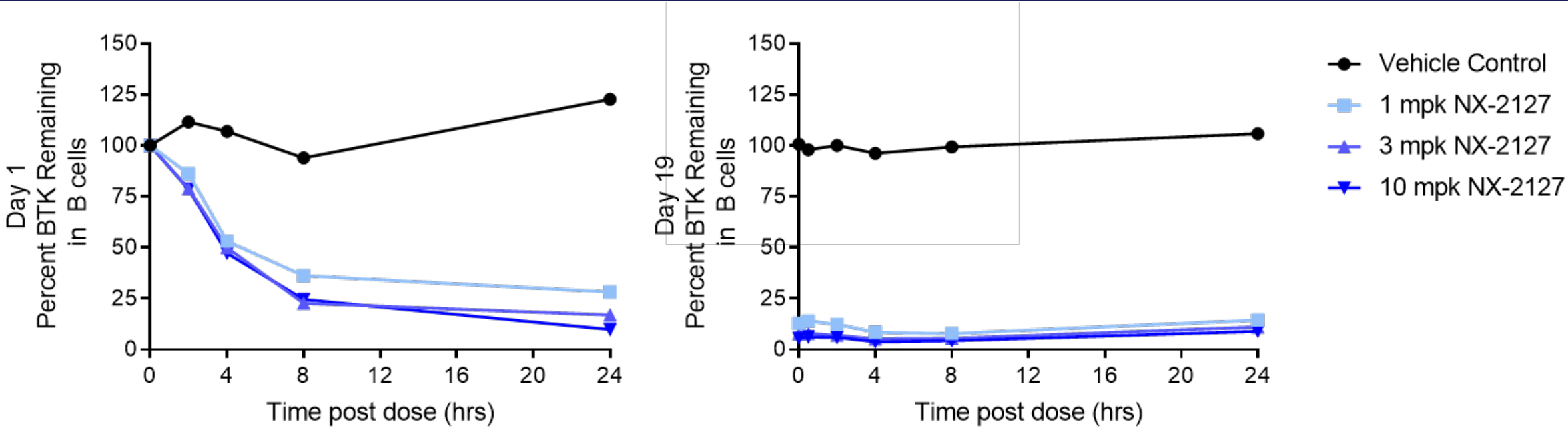
BTK Degradation of 80%+ Drives Potent Anti-tumor Activity in Preclinical Models

Ikaros and Aiolos degradation also achieve target range at therapeutic doses



Oral dose of NX-2127 (mg/kg)	10	30	90
% BTK degradation in peripheral B cells	69%	80%	91%
% Aiolos degradation in tumor tissue	21%	33%	64%
% Ikaros degradation in tumor tissue	28%	23%	47%
% Tumor growth inhibition vs Vehicle(Day 24)	58%	74%	100%

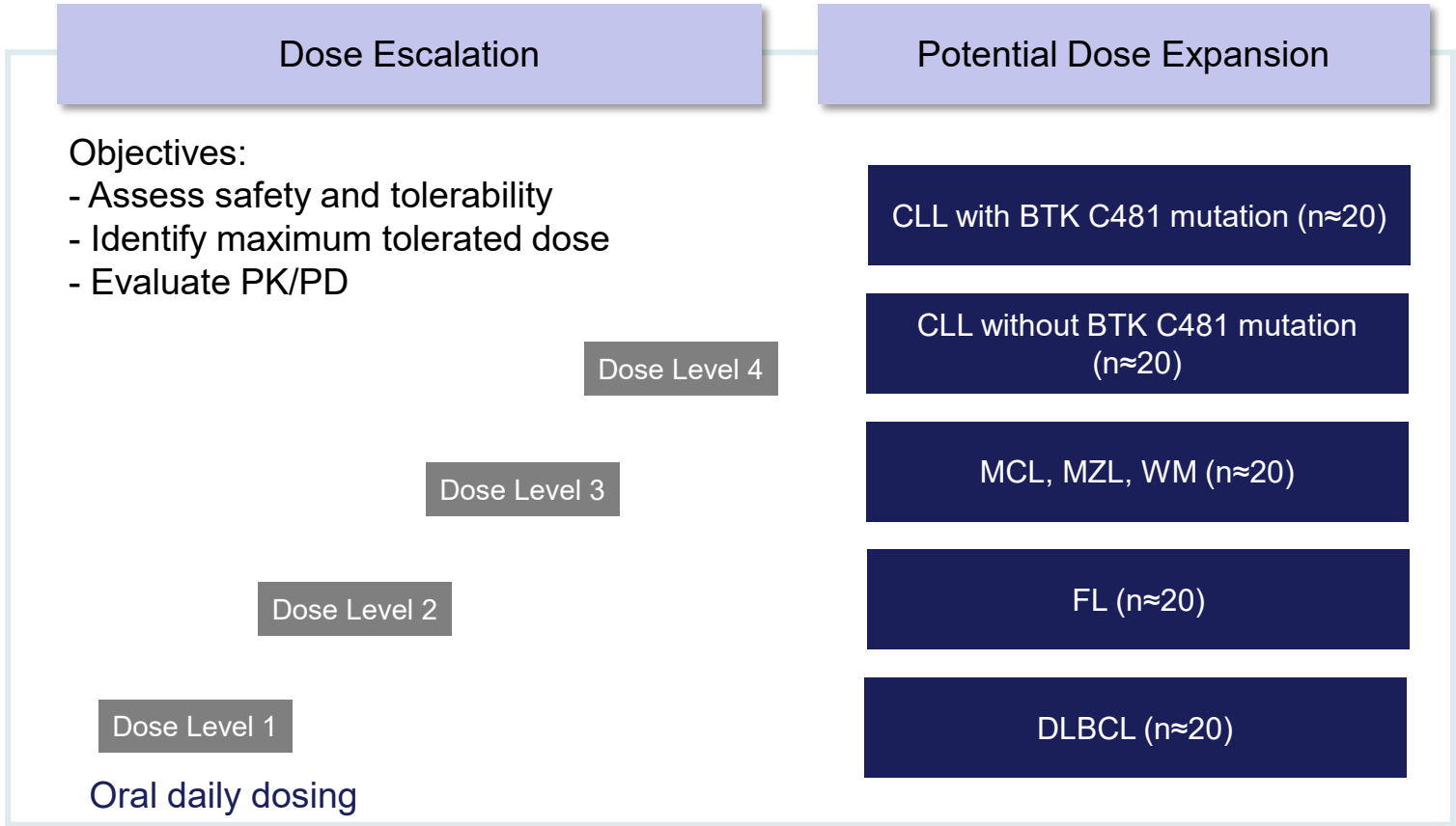
Oral Dosing of NX-2127 Degrades BTK in Non-Human Primates



- 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
Trial Design and Active Sites



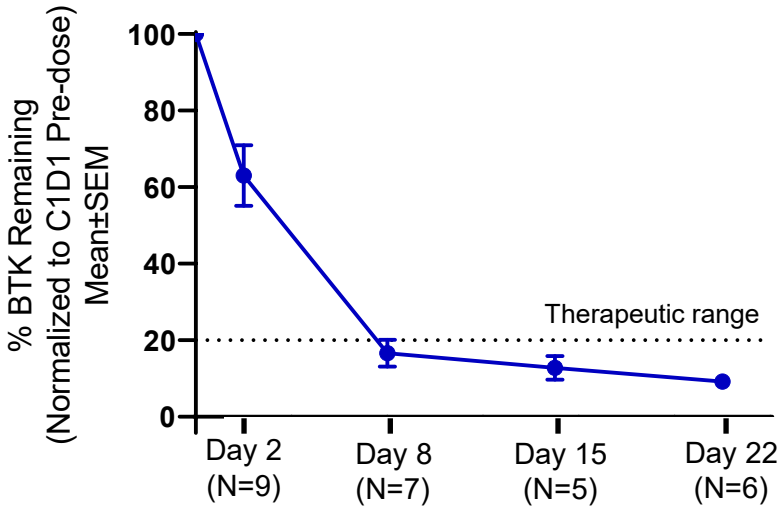
CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenstrom's macroglobulinemia.

- Memorial Sloan Kettering Cancer Center
- MD Anderson Cancer Center
- City of Hope: Duarte, California
- National Institutes of Health Clinical Center
- Sarah Cannon Research Institute
  - Colorado Blood Cancer Institute
  - Florida Cancer Specialists
  - Tennessee Oncology
- University of California, San Francisco
- University of California, Irvine
- OSU Wexner Medical Center
- Swedish Cancer Institute, Seattle
- University of Cincinnati Medical Center

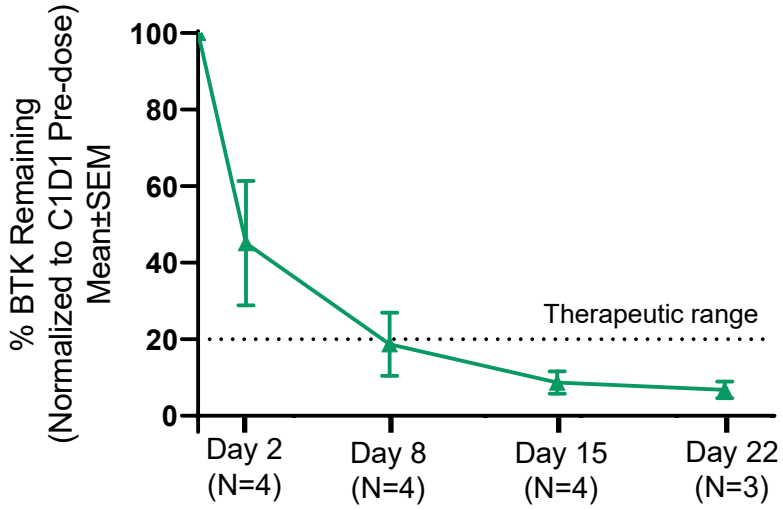
Robust BTK Degradation Observed with NX-2127 Across All Dose Levels and Malignancies

NX-2127-001

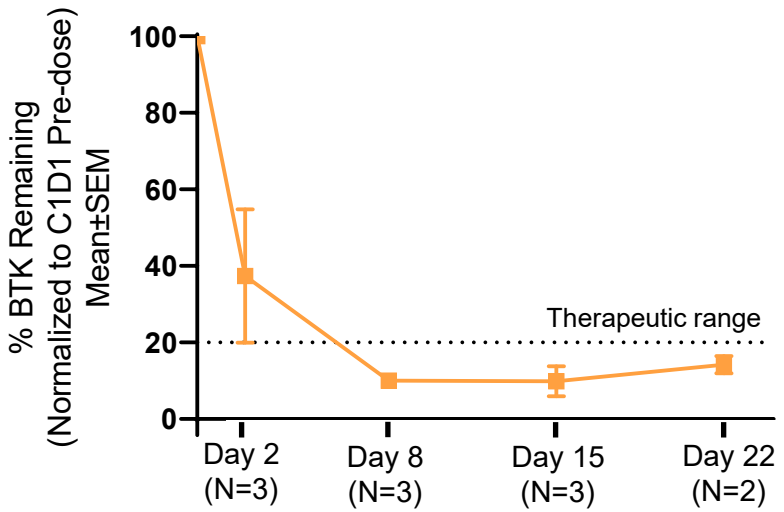
Cohort 1-100 mg
% BTK remaining in CD19+ B cells



Cohort 2-200 mg
% BTK remaining in CD19+ B cells



Cohort 3- 300 mg
% BTK remaining in CD19+ B cells

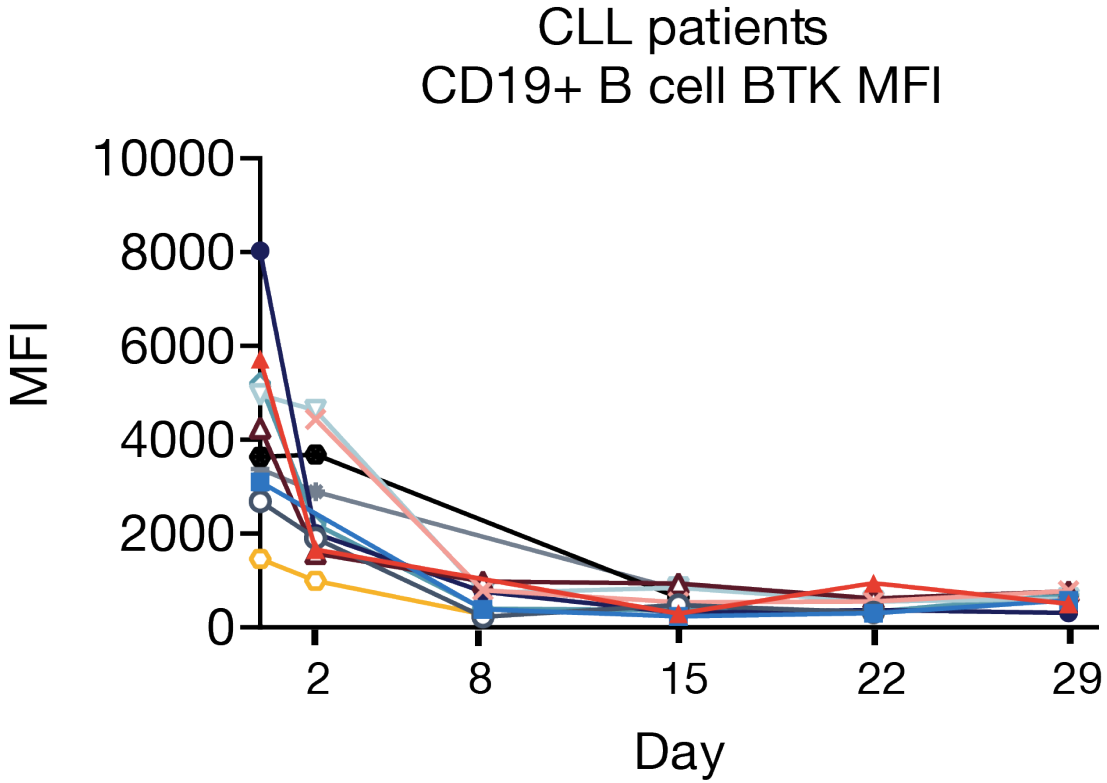


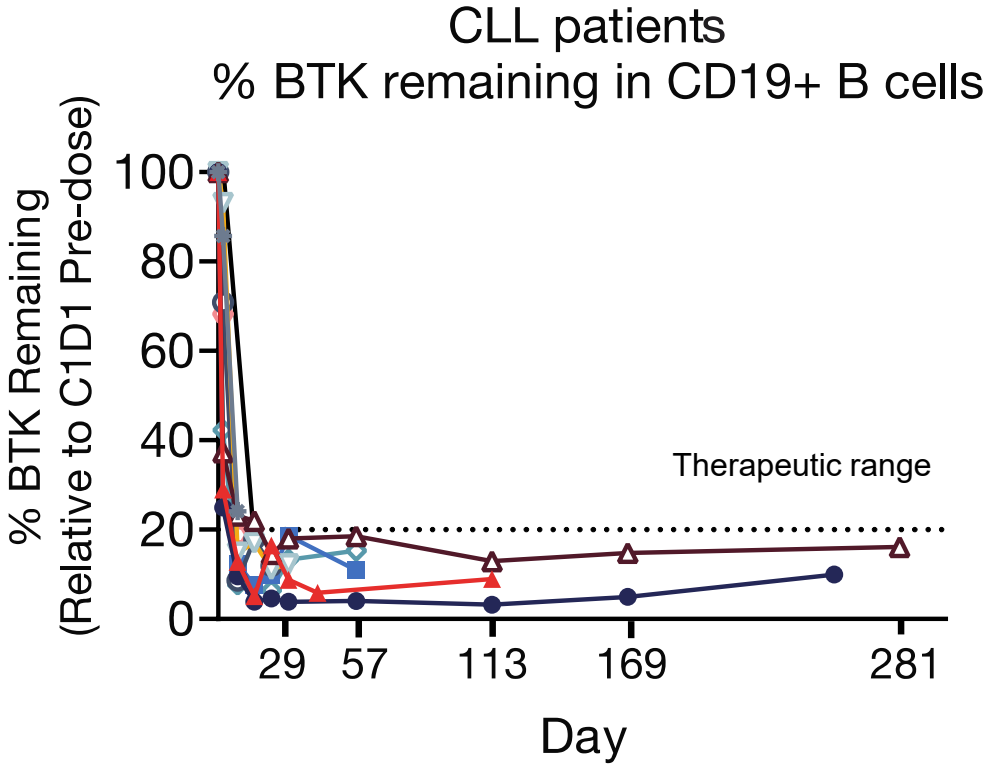
Dose	% BTK Degraded (Average trough)				
	Baseline	Day 2	Day 8	Day 15	Day 22
100 mg	0	37	83	87	90
200 mg	0	55	81	91	93
300 mg	0	63	90	90	86¥

¥ Includes 1 patient who was dose-reduced from 300mg to 100mg mid-cycle.

Rapid and Sustained Degradation of BTK in Patients with CLL

NX-2127-001





Target BTK degradation achieved by Day 15 (steady state) for all starting BTK levels

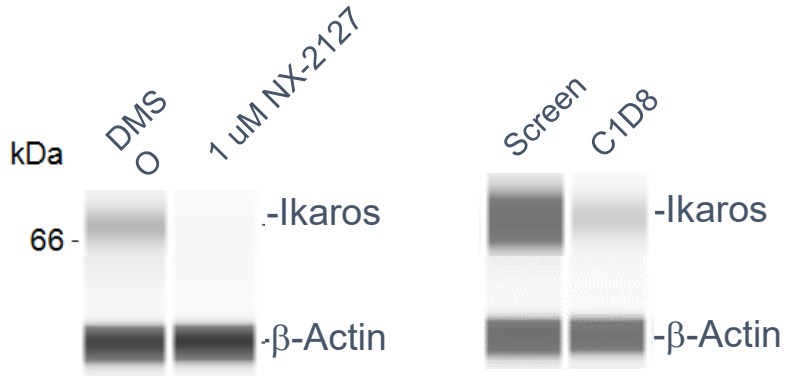
BTK degradation is sustained

NX-2127 Demonstrates Greater Ikaros Degradation, Consistent with Cereblon Immunomodulatory Activity

NX-2127-001

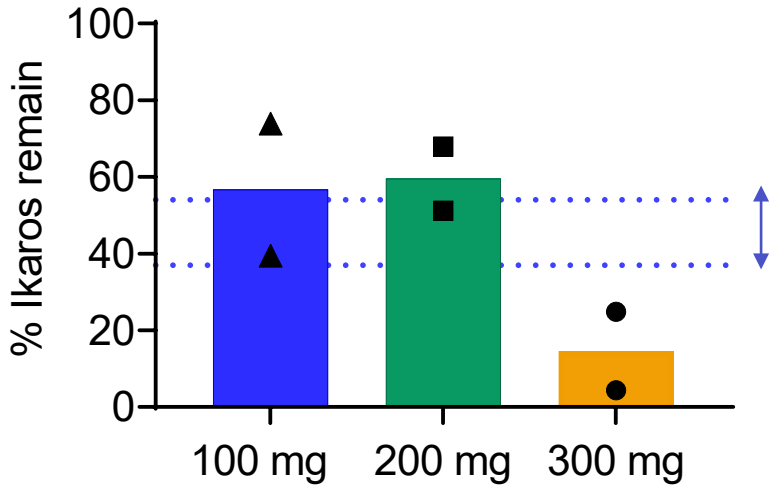
Healthy Donor
(ex vivo positive control)

Example 100 mg
CLL Patient



Ikaros protein was detected from PBMC cell lysate from healthy donor or patient in NX-2127-001 trial

% Ikaros Remaining
at C1D8



Range of Ikaros decrease seen with lenalidomide

Franssen et al; 2018

- Degradation of cereblon neo-substrate Ikaros confirmed by Western Blot
- Ikaros degradation is sustained on treatment
- Ikaros degradation consistent with published reports for immunomodulatory drugs

Case Study: Clinical Response Observed in First Patient

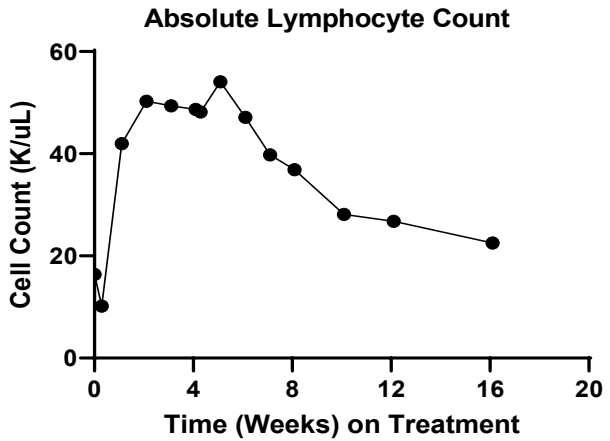
Patient in response and on therapy for more than 12 months*

Patient History:
78-year-old male with stage IV CLL

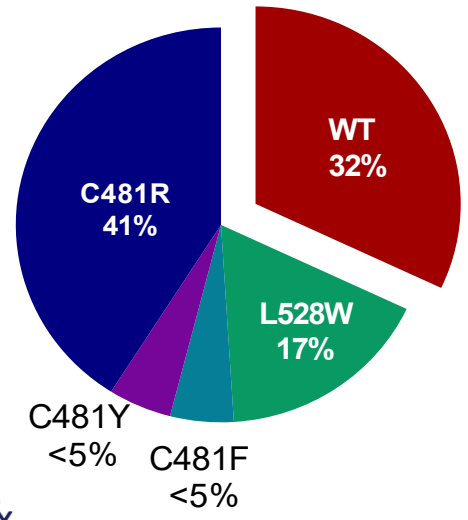
Prior Treatments:
1. Rituximab, 2015
2. Ibrutinib, 2015-2021

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

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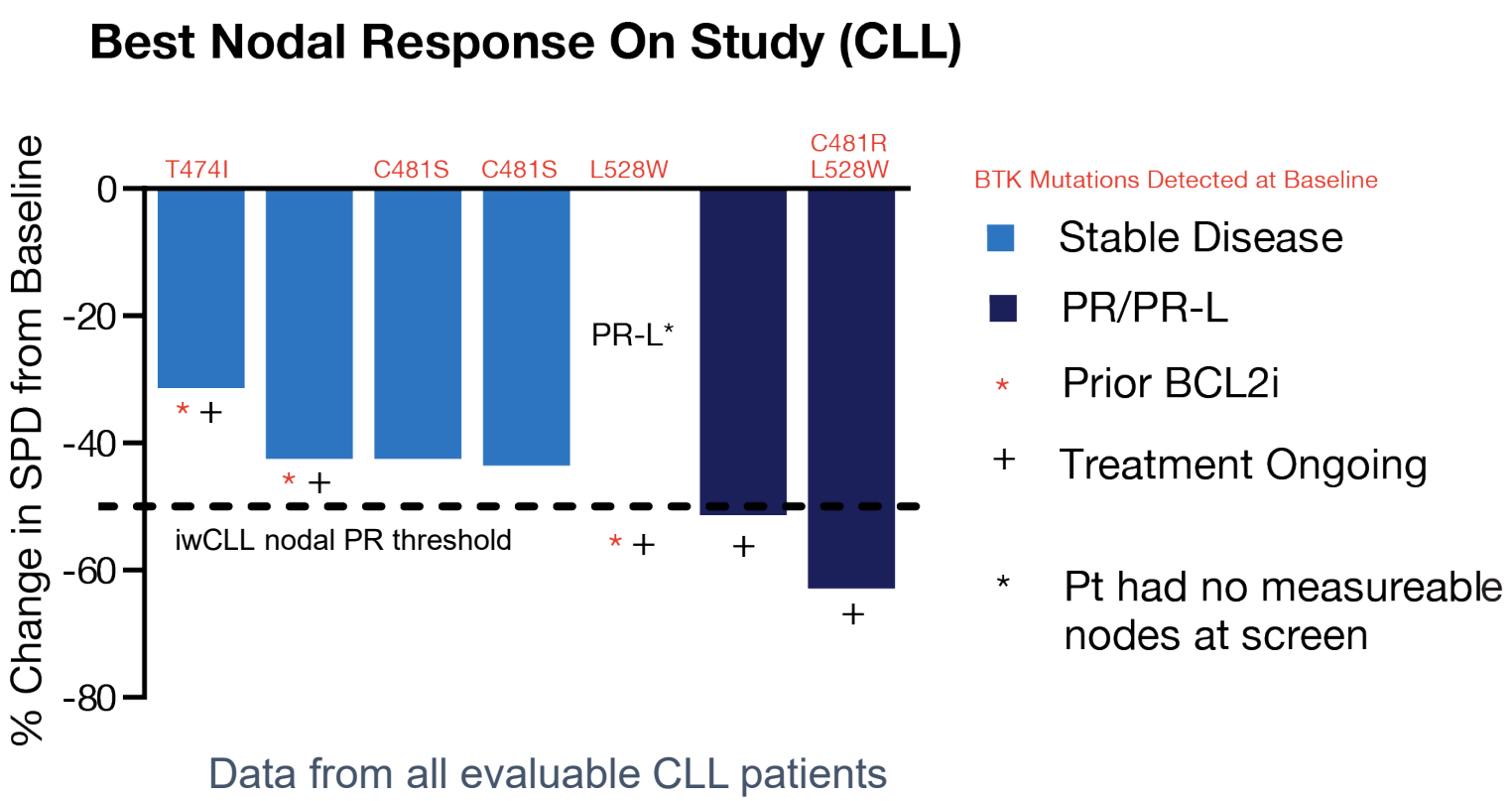
* Data Cut April 8, 2022

NX-2127-001 Phase 1a: Positive Initial Findings in CLL Support Expansion at 100 mg



SPD, sum of the product of diameters; iwCLL, international Workshop on CLL

- Meaningful clinical benefit in CLL patients with a median of 6 prior lines of therapy
- Biologic activity including nodal reductions and/or lymphocytosis observed in all patients treated
- Responses in patients with resistance mutations to covalent and non-covalent BTK inhibitors
- Responses include a double-refractory patient who had prior BCL2 inhibitor therapy

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

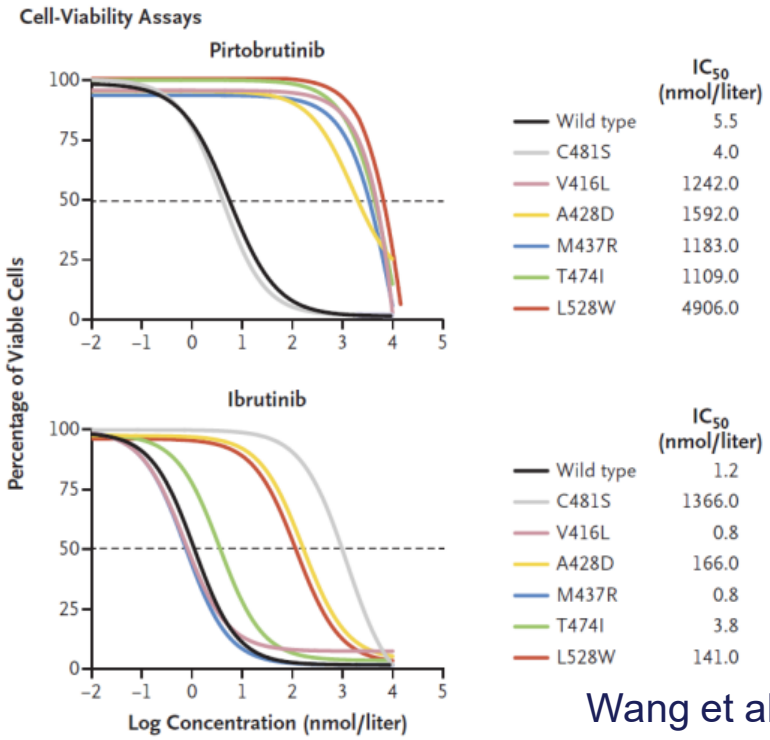
Phase 1a continues in NHL and Phase 1b CLL cohort initiated at 100mg

	Dose Escalation (Phase 1a)
Indications	CLL, MCL, MZL, WM, FL, DLBCL
Line of Therapy	Third line or later (Waldenstrom patients second line or later)
Dose Range*	50mg – 300mg oral once daily
Status	CLL: 100mg expansion dose selected MCL, MZL, WM, DLBCL: Dose escalation ongoing

	Cohort Expansion (Phase 1b)
Initiated	**CLL (n≈40)** Failed 2 or more prior treatments including a BTK inhibitor and regardless of baseline BTK mutation status
Potential	**MCL, MZL, WM (n≈20)** **FL (n≈20)** **DLBCL (n≈20)**

*50mg dose added as per project Optimus guidance

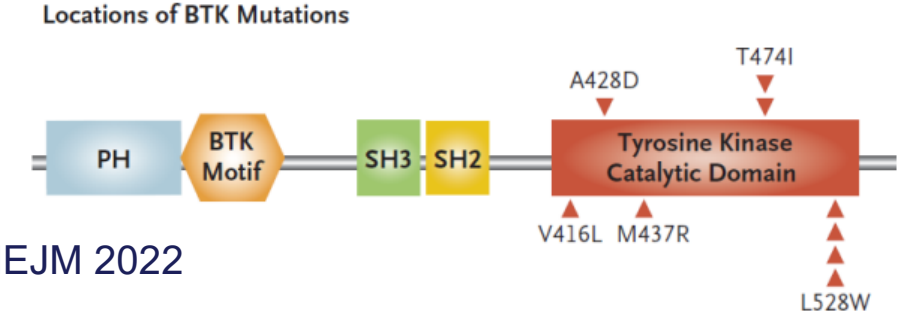
Emerging BTK mutations confer resistance to covalent and non-covalent BTK inhibitors



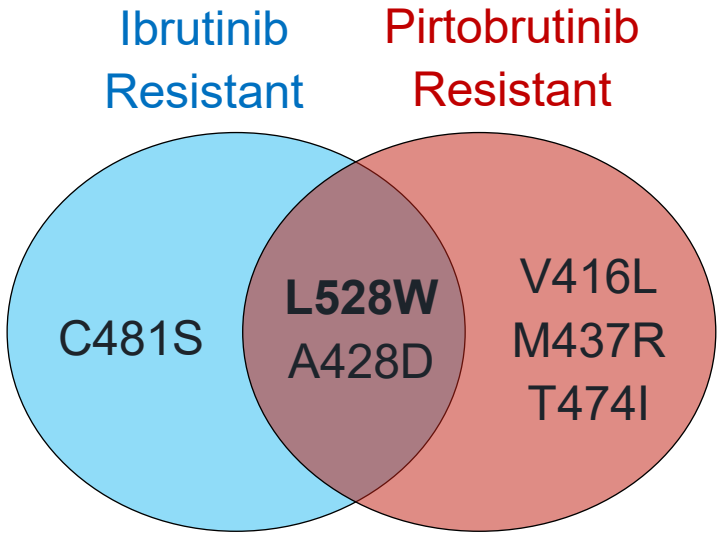
	Pirtobrutinib IC_{50} (nmol/liter)	Ibrutinib IC_{50} (nmol/liter)
Wild type	5.5	1.2
C481S	4.0	1366.0
V416L	1242.0	0.8
A428D	1592.0	166.0
M437R	1183.0	0.8
T474I	1109.0	3.8
L528W	4906.0	141.0

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."

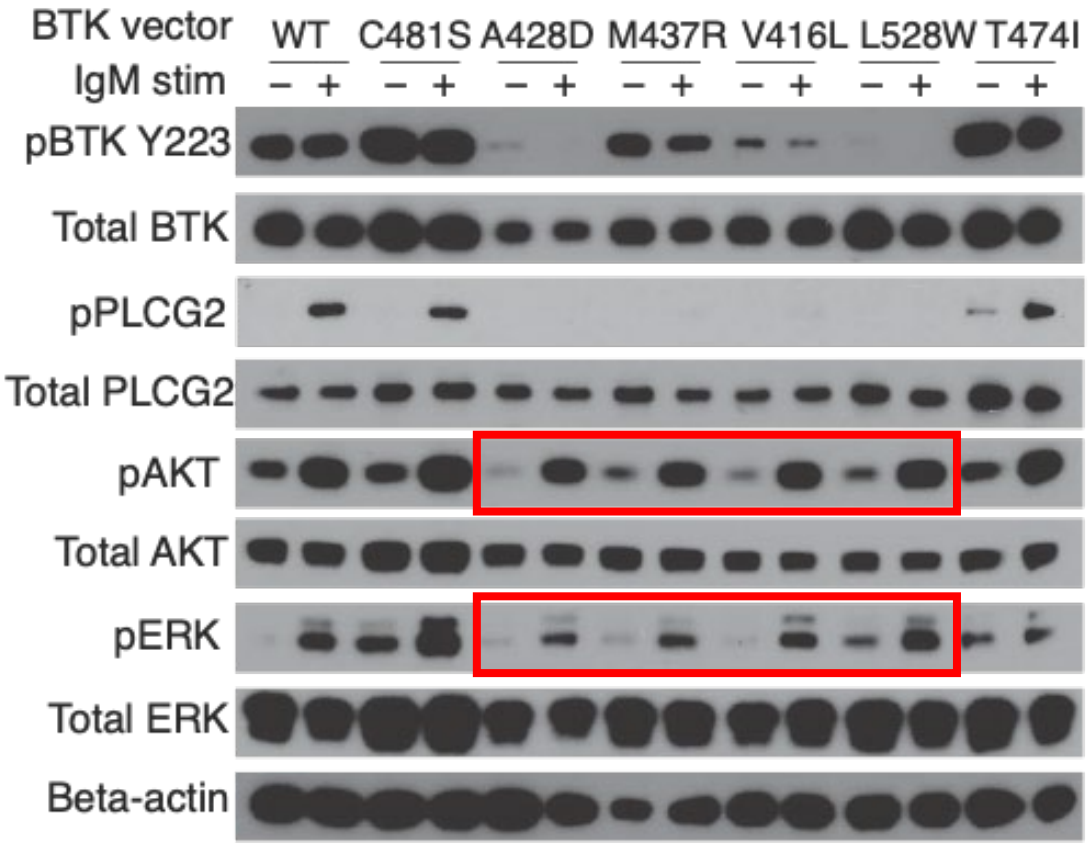


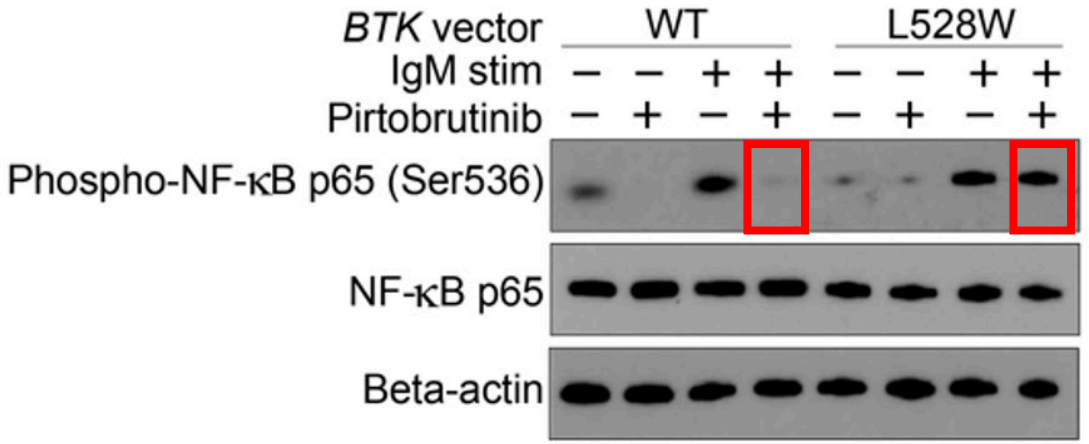
Wang et al. NEJM 2022



- C481S mutation confers resistance to ibrutinib but not pirtobrutinib
- M437R, V416L, and T474I mutations confer resistance to pirtobrutinib but not ibrutinib
- L528W and A428D mutations confer resistance to both ibrutinib and pirtobrutinib
- L528W is the most common pirtobrutinib resistance mutation observed in the clinic

Upon IgM Stimulation, Kinase Dead BTK Mutants Still Capable of AKT, ERK, and NF-κB Activation

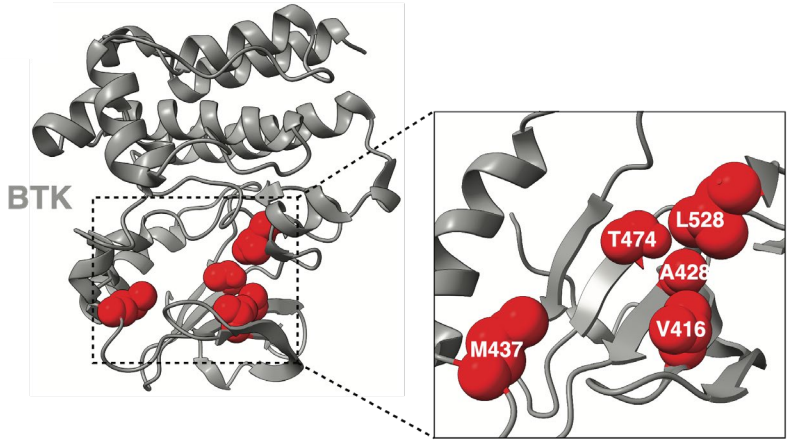




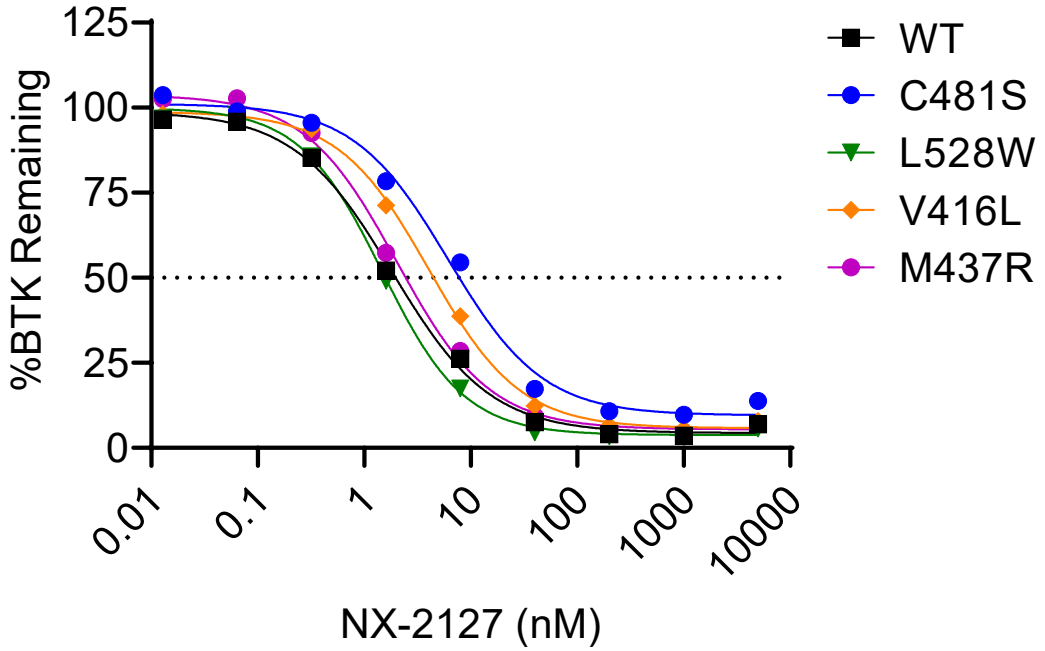
Wang E*, Mi X*, Thompson MC*… Mato, AR*, Taylor J*, Abdel-Wahab O*, NEJM 2022

Nurix Degraders Directly Address Emerging Resistance Mutations and BTK Scaffolding Activity

Treatment with noncovalent BTK inhibitors are changing the resistance landscape



NX-2127 is capable of degrading not only C481x, but also the novel BTK mutations observed post treatment with pirtobrutinib



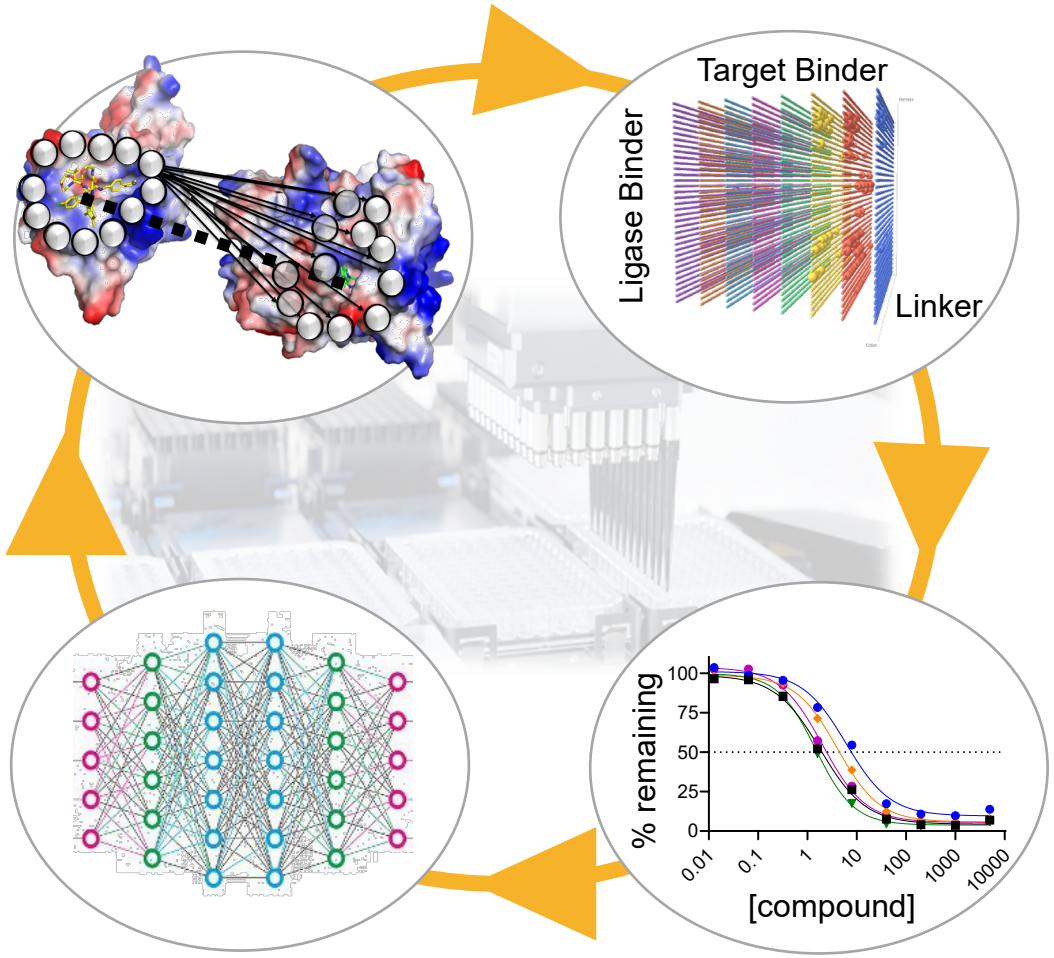
Wang E*, Mi X*, Thompson MC*… Mato, AR*, Taylor J*, Abdel-Wahab O*, NEJM 2022

A Transition from Empiricism to Informed Design Will Require Learning Degrader Design Rules

Challenge: Identifying and optimizing degraders remains largely an empirical process

DESIGN SCOPE

Theoretical range of degrader chemical space more fortuitous than rational



SYNTHESIZE AT SCALE

Automation enables Nurix to sample unprecedented chemical space

WRITE THE RULEBOOK

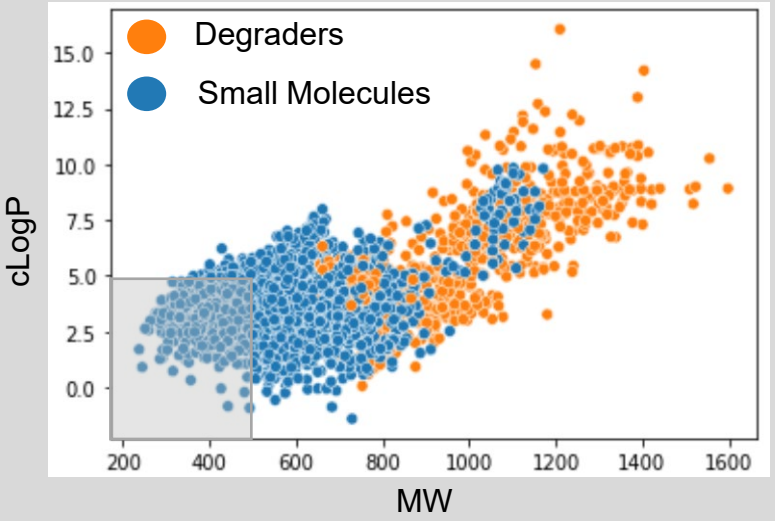
Machine Learning transforms large datasets into degrader rulebook for improved design

DISCOVER LEADS

Empirical cell-based and animal data reveals degraders with optimal performance

Future Directions: Predicting Solubility in Unique Chemical Space with Machine Learning

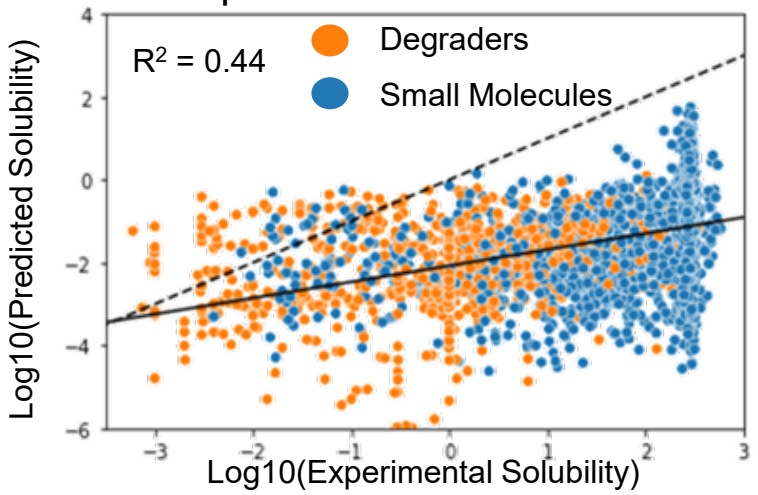
Problem:
Degraders occupy non-traditional chemical space



- Common approaches for property prediction fail for these classes of compound
- Lack of intuition introduces inefficiency in Lead Optimization campaigns

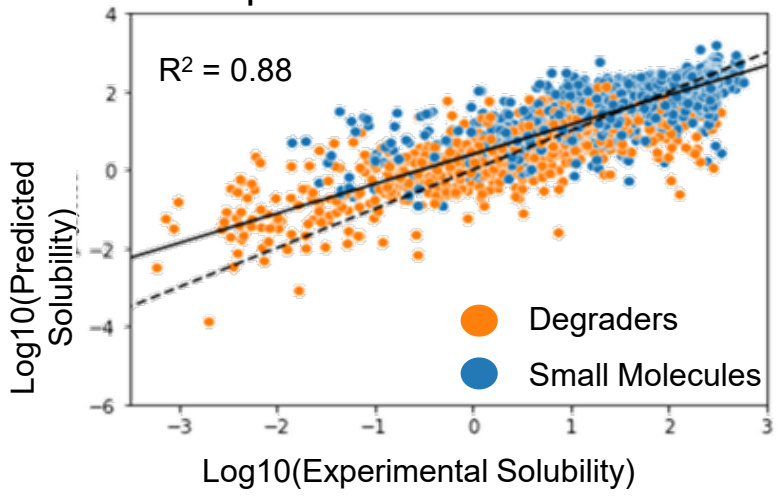
Leading Chem-informatics Software

Experiment vs Prediction:



Nurix's Machine Learning Models

Experiment vs Prediction:

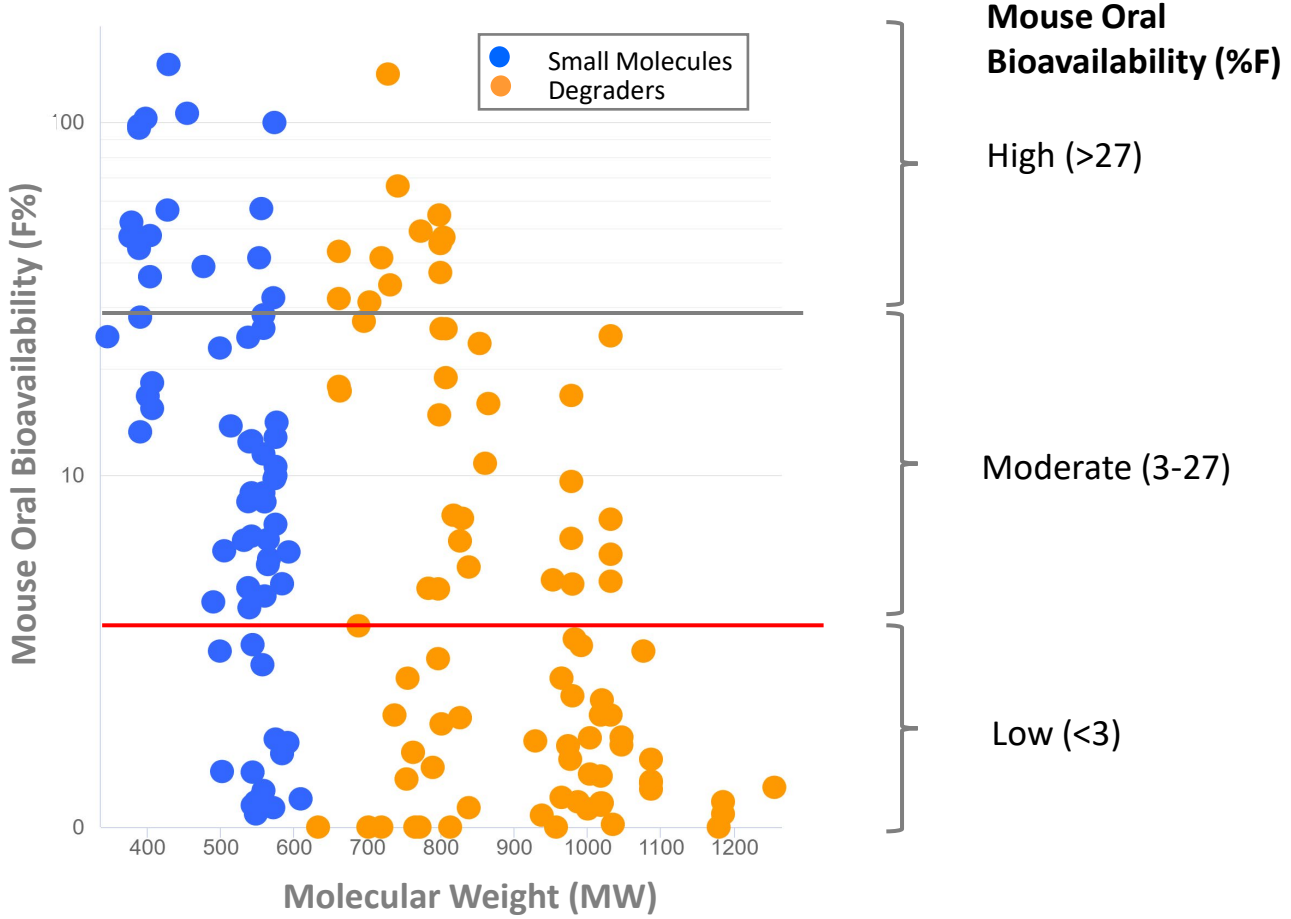


Solution:
Application of modern machine learning frameworks improve our understanding of structure-to-property relationships, enabling better hit selection and more efficient degrader design and optimization

Future Directions: Predicting Bioavailability

Moderate bioavailability is achievable for Nurix compounds with MW up to ~1,000 daltons

- Data set = 168 compounds (small molecules and bi-functional degraders) from several programs with mouse oral bioavailability
- Oral bioavailability for Nurix degraders demonstrate moderate to high bioavailability (F% > 3) is achievable for compound MWs up to ~1,000 daltons



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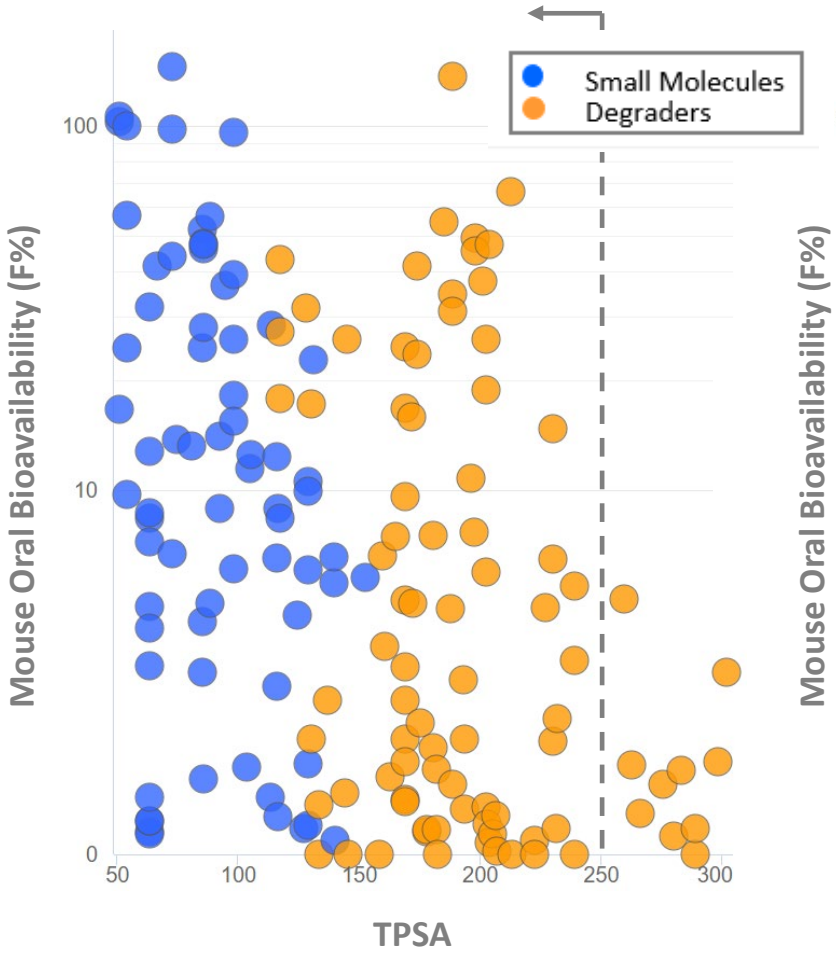
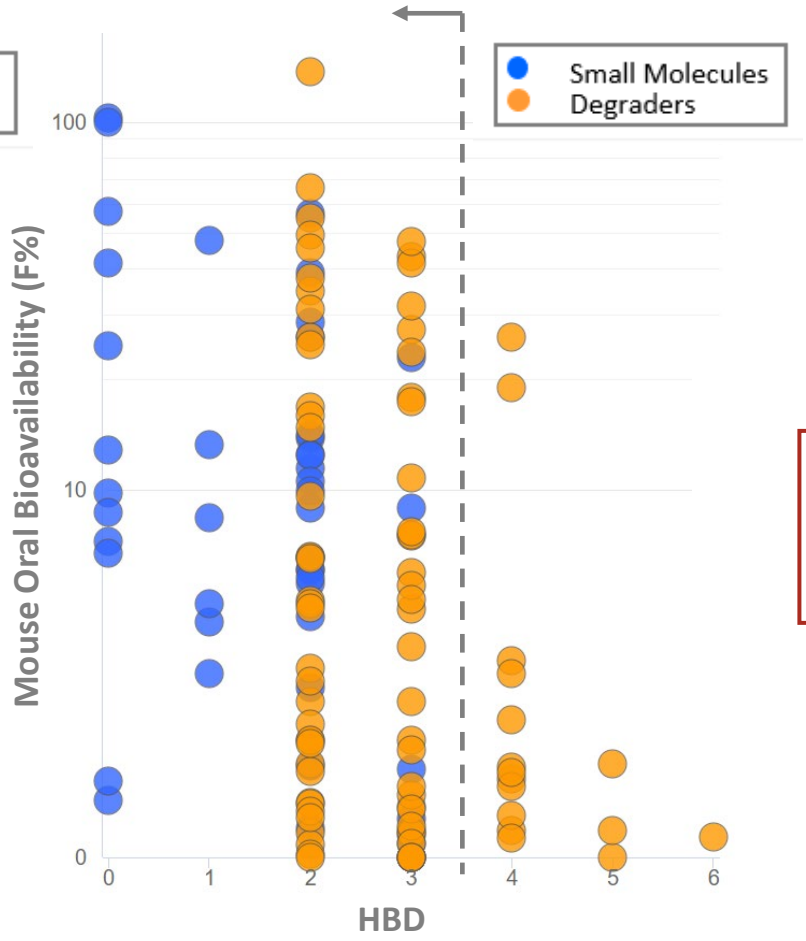
Future Directions:

Nurix Bro5 property guidelines extend property range except for HBD count

Topological polar surface area (TPSA)



Hydrogen-bond donors (HBD)



Compound property guideline comparison

	Lipinski[1] Ro5	Veber[2] Ro5	Nurix Bro5
MW	< 500		≤ 1,000
Lipophilicity	LogP < 5		LogD < 6
HBA	≤ 10		≤ 10
HBD	≤ 5		≤ 3
TPSA (Å)		< 140	< 250
RotB		≤ 10	≤ 11
ArRNG			≤ 5

[1]Lipinski, C.A. et al., *Adv. Drug Delivery Rev.* ***1997****, 23,* 3–25
[2]Veber, D. F. et al., *J. Med. Chem.* ***2002****, 45,* 12, 2615–2623

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Thank You