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Leader in Targeted Protein Modulation

Targeted Protein Degradation of BTK for Hematological Malignancies and Autoimmune Disease:
Preclinical and Initial Phase 1a PK/PD Data for NX-5948

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4th Protein Degradation & Targeting Undruggables Congress
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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 Degradation (TPD)

Harness ligases to decrease specific protein levels

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

Targeted Protein Elevation (TPE)

Inhibit ligases to increase specific protein levels

Nurix Is Advancing Three Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

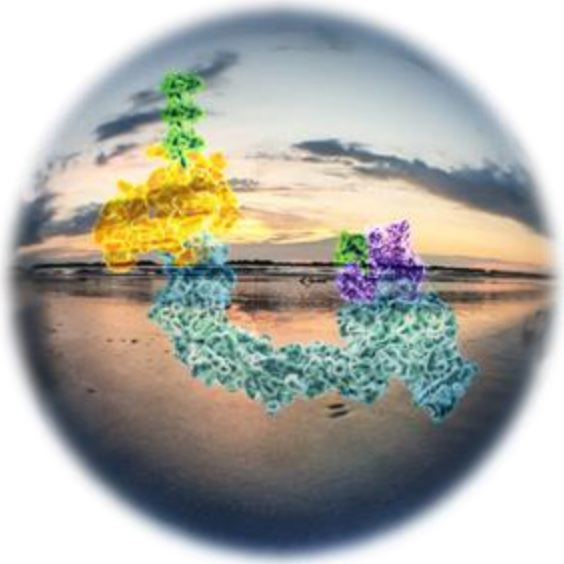
MOA	Drug program	Target/delivery	Therapeutic area	Preclinical	Phase 1a	Phase 1b
TPD	**NX-2127** Degrader	BTK-IKZF *Oral*	B-cell malignancies			
TPD	**NX-5948** Degrader	BTK *Oral*	B-cell malignancies			
TPE	**NX-1607** Inhibitor	CBL-B *Oral*	Immuno-Oncology			
TPM	Wholly owned	5 targets	Multiple			
TPD	Gilead Sciences & Sanofi	10 targets	Multiple			

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

NX-5948

BTK DEGRADATION

- Clinical evidence of potent BTK degradation in all patients tested
- Active against BTK inhibitor-resistant mutations in vitro
- Crosses blood brain barrier and degrades BTK in microglia and brain-resident lymphoma cells preclinically
- Phase 1a dose escalation trial ongoing in U.K. and IND accepted in the U.S.
- Preclinical activity in models of autoimmune disease



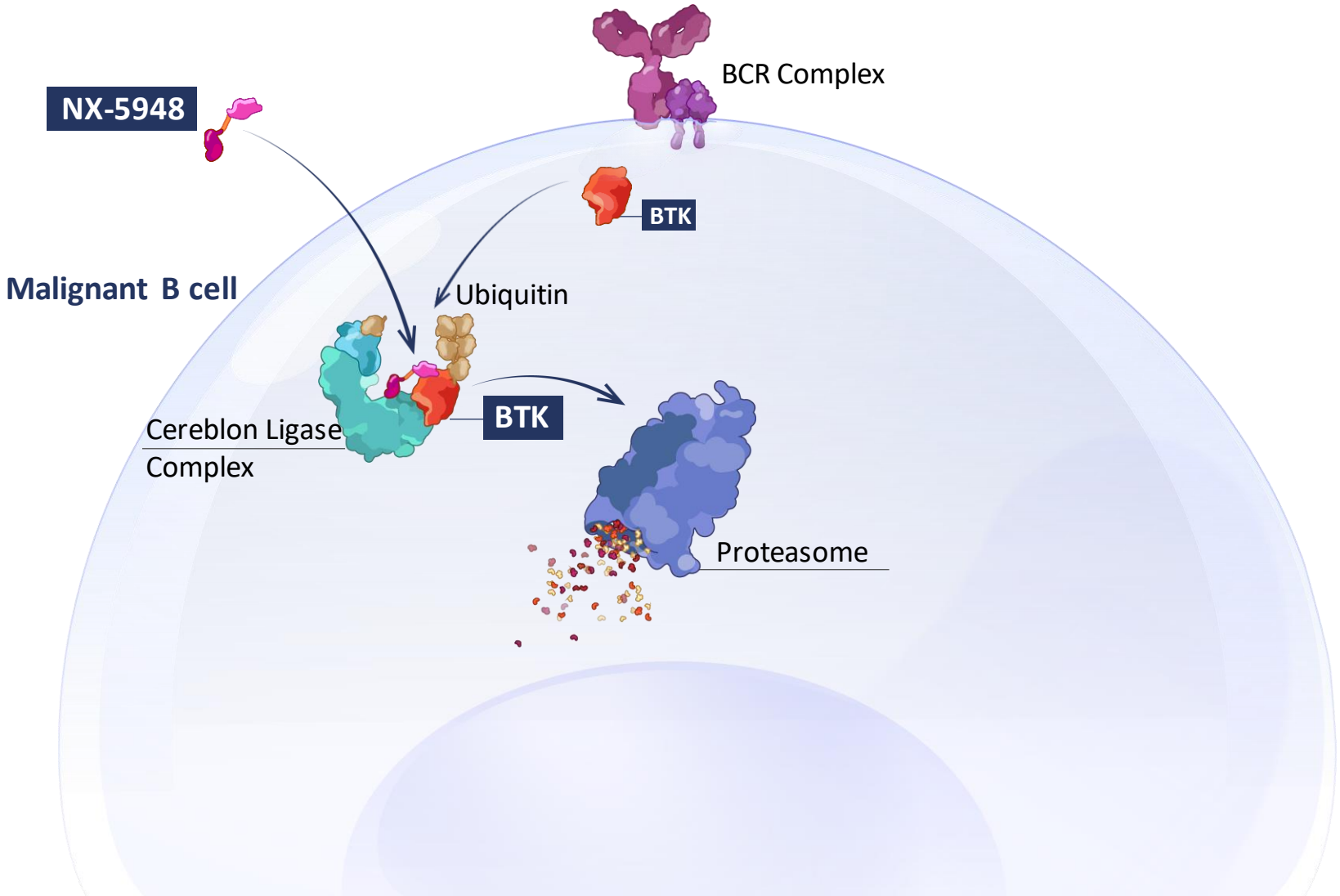
NX-2127

BTK DEGRADATION
& IMMUNOMODULATION

- Positive clinical activity in CLL patients, including responses in patients with BTK or BCL2 mutations
- Active in the clinic against BTK inhibitor-resistant mutations
- Complete response observed in a patient with DLBCL
- Phase 1b cohort expansion for CLL patients is ongoing
- Dose exploration is ongoing for patients with NHL

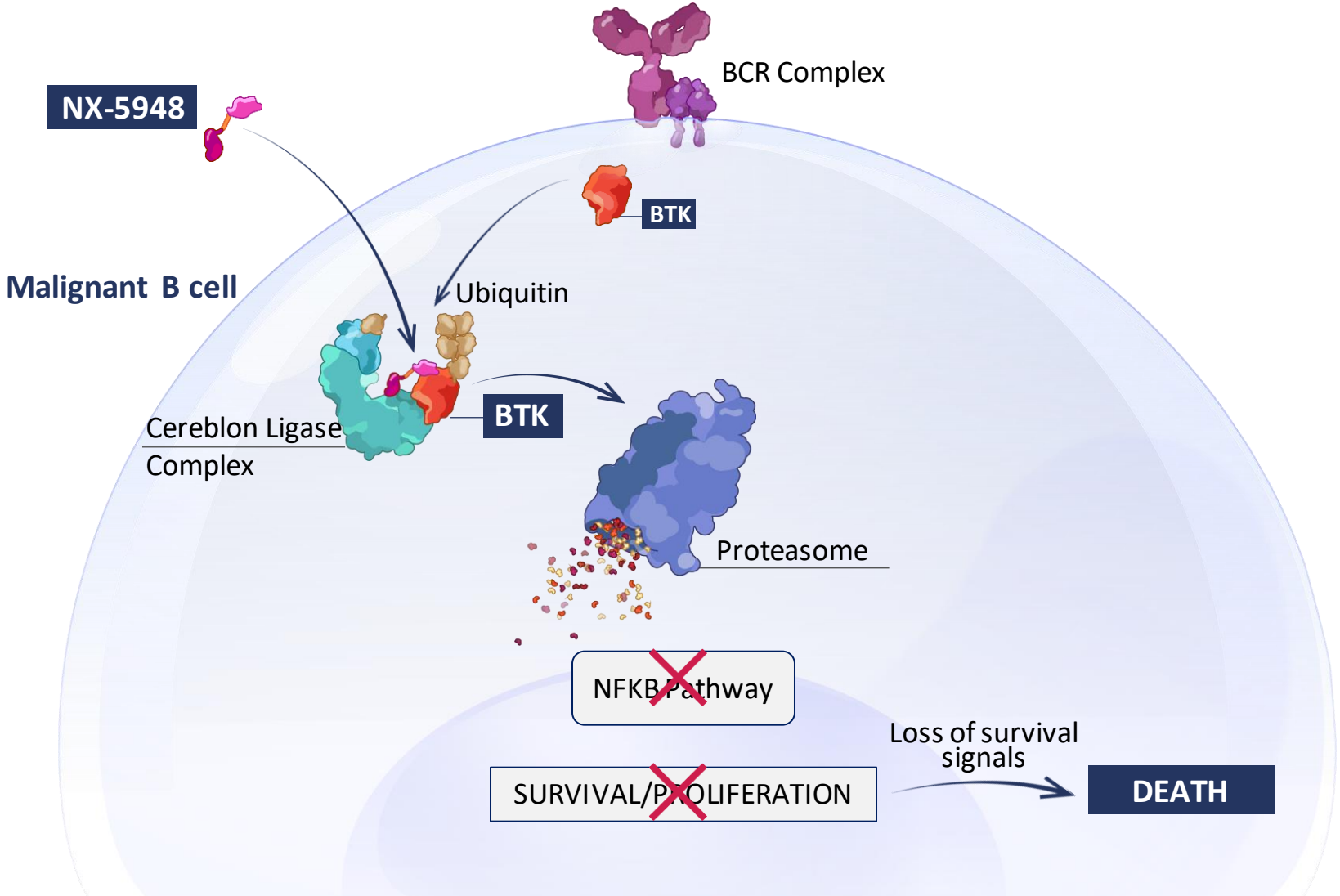
NX-5948 is a potent and selective degrader of BTK

Targeted degradation of Bruton's Tyrosine Kinase

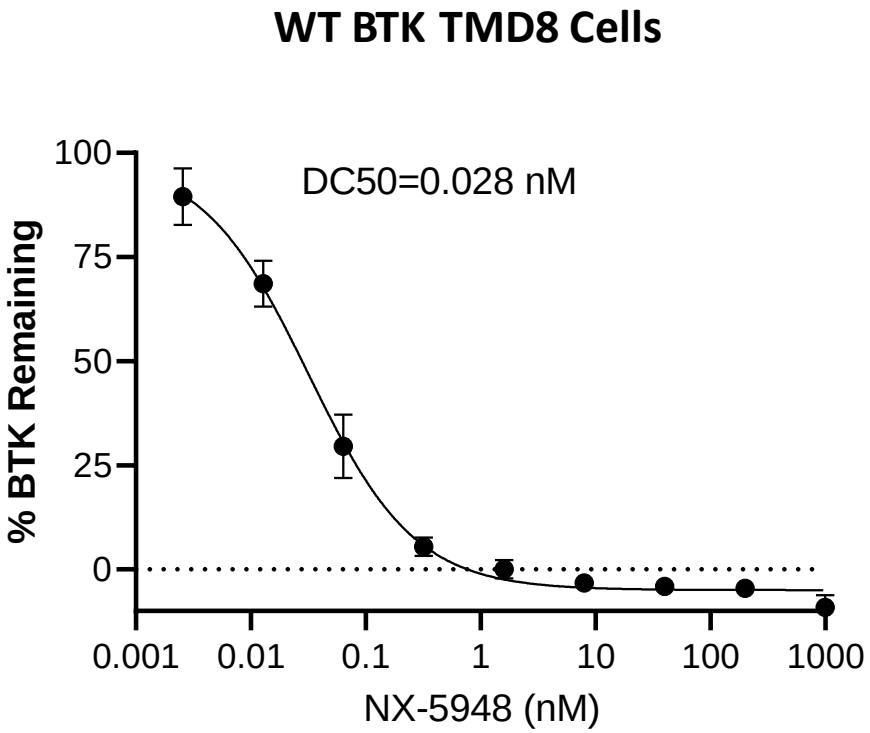


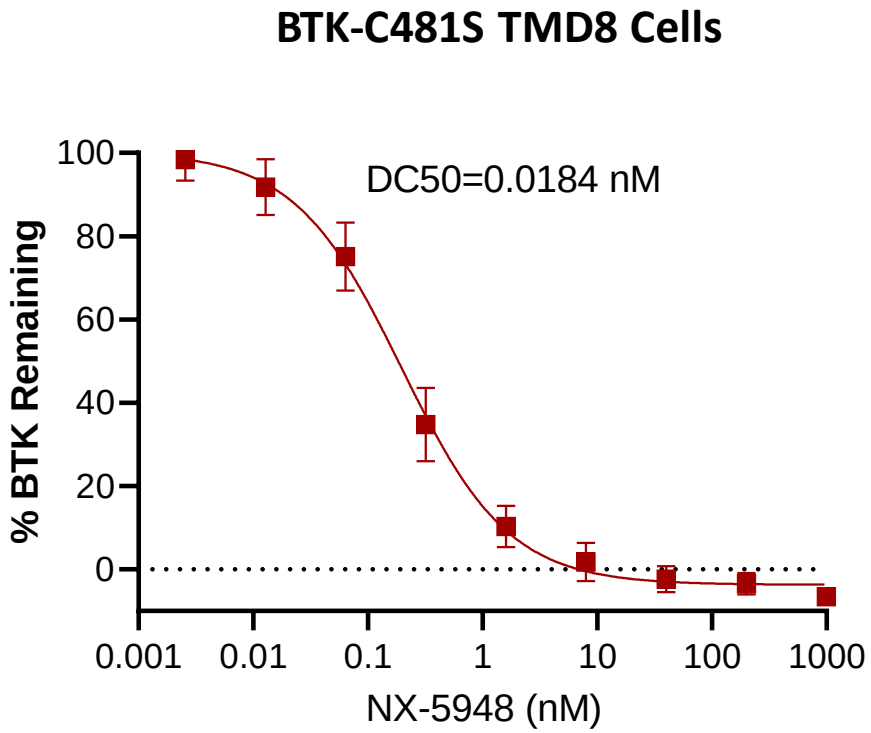
NX-5948 is a potent and selective degrader of BTK

Targeted degradation of Bruton's Tyrosine Kinase



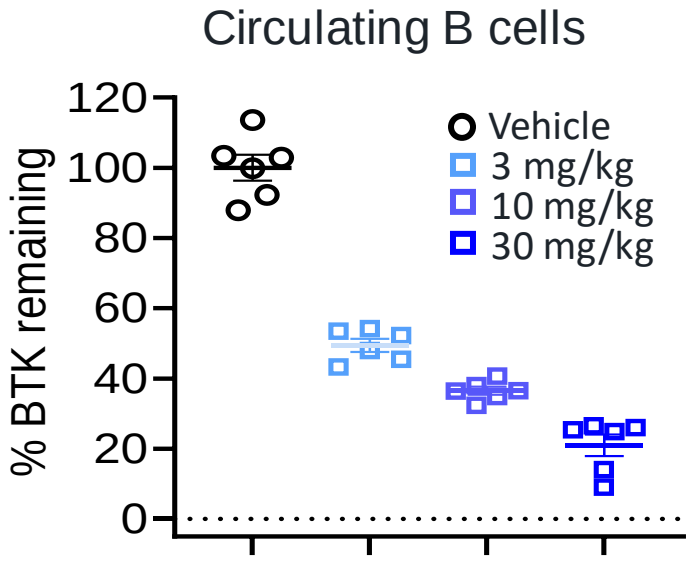
NX-5948 was Designed for Potent and Rapid Degradation of Wildtype and C481S-Mutated BTK

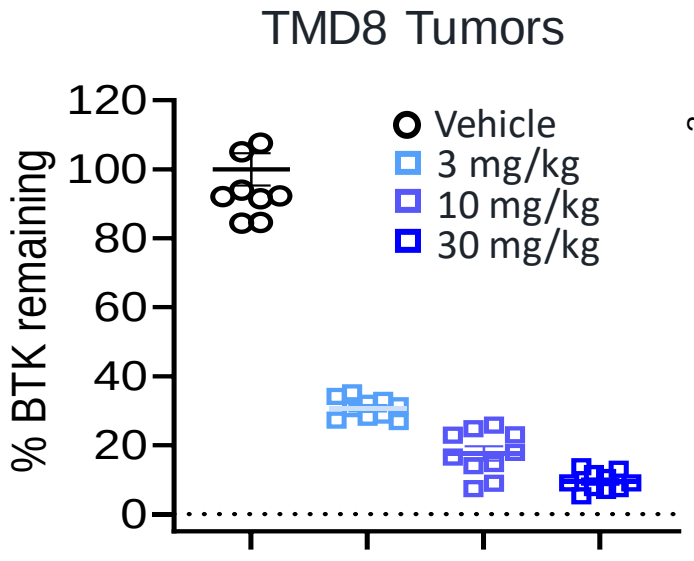


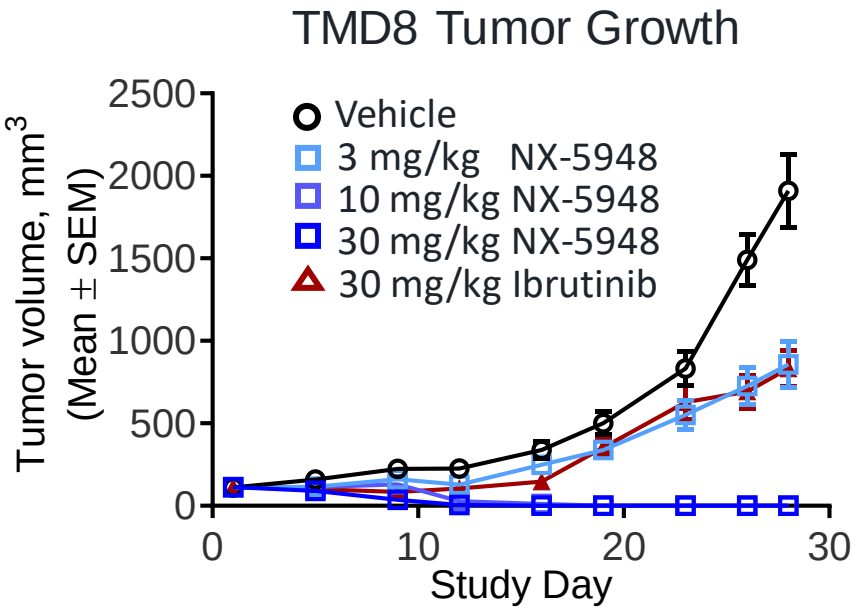


TMD8 cells harboring WT BTK or a knock-in BTK mutation (C481S) were incubated with NX-5948 for 24 hours, and BTK degradation was assessed by flow cytometry.

Degradation of BTK by NX-5948 Correlates with Significant Tumor Growth Inhibition





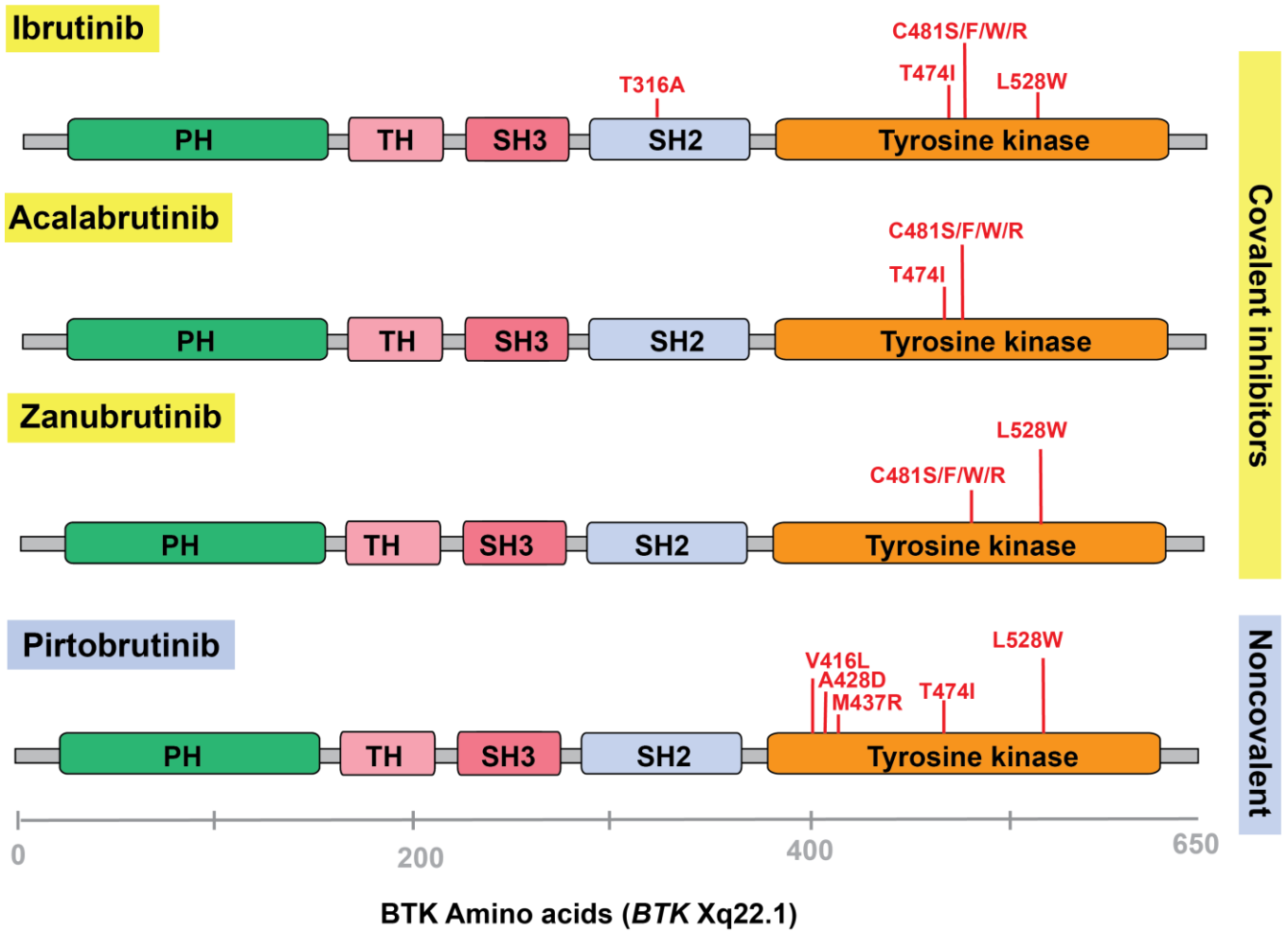


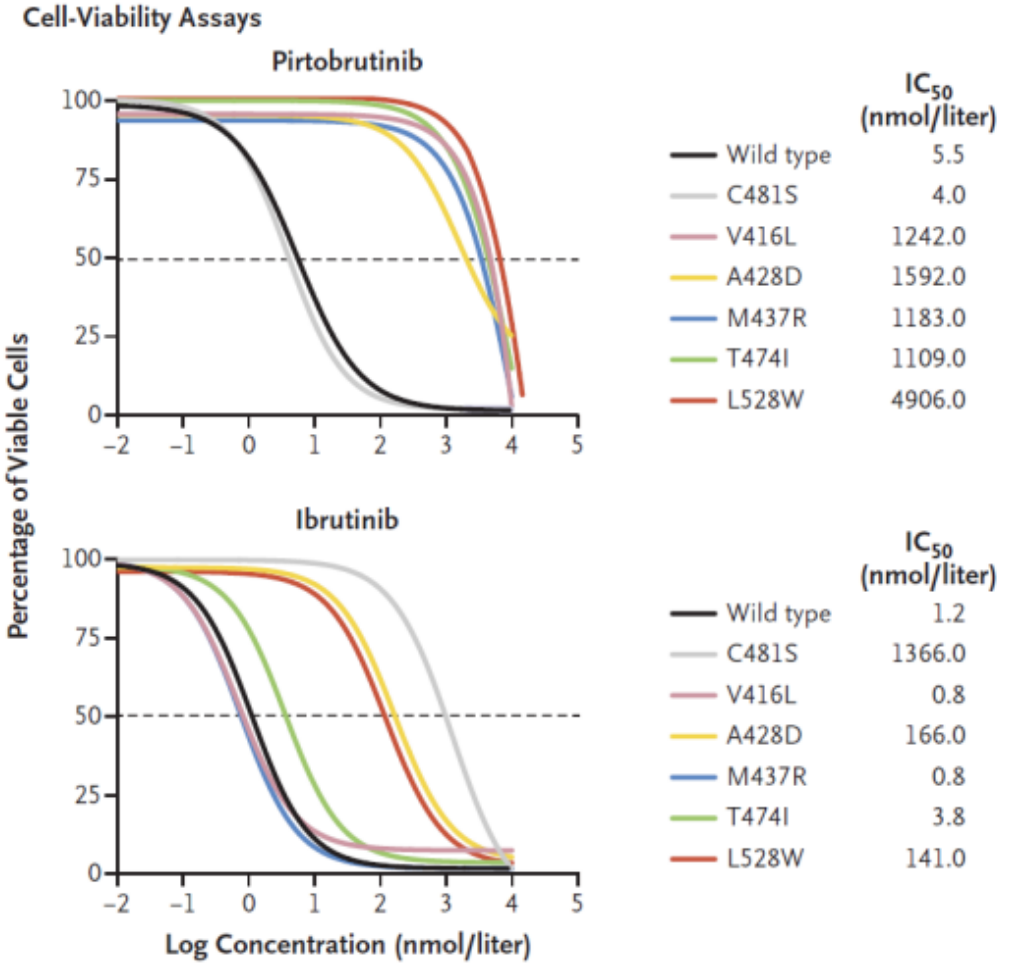
Treatment	Oral gavage dose (mg/kg)	% BTK degradation in circulating B cells	% BTK degradation in TMD8 tumor tissue	% TGI vs Vehicle (Day 26)	*P* value vs Vehicle
Vehicle	0	0.0±3.7	0.0±4.7	N/A	N/A
NX-5948	3	50.5±1.9	69.2±0.9	54%	0.0025
	10	63.5±1.1	82.4±2.1	100%	<0.0001
	30	79.0±3.1	90.5±0.5	100%	<0.0001
Ibrutinib	30	N/A	N/A	57%	0.0015

N/A: Not applicable; TGI: tumor growth inhibition.
P values determined on tumor volume by mixed-effect analysis with Dunnett's multiple comparisons test

Rountree et al., TPD 2022

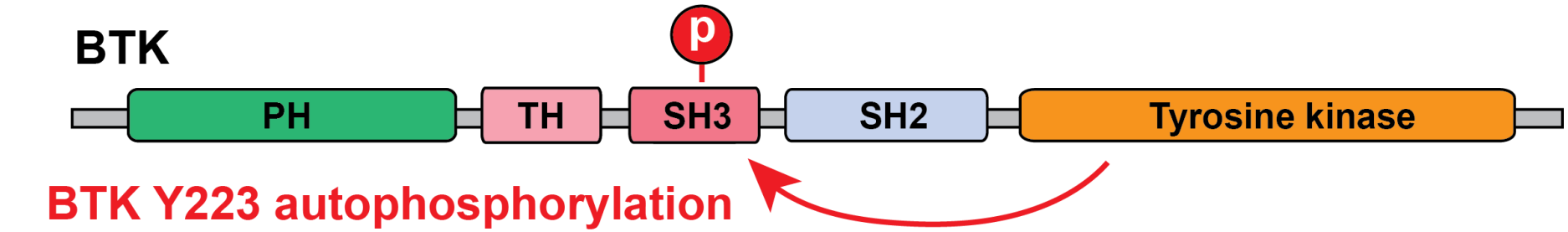
Increasing Use of BTK Inhibitors in the Clinic have Revealed a Growing Spectrum of Treatment-Emergent Resistance Mutations

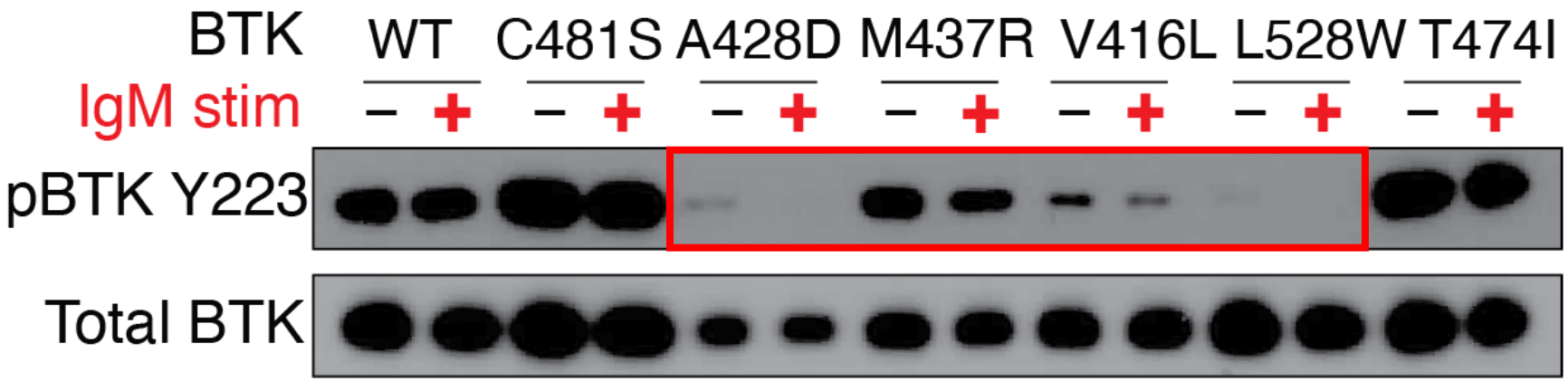




Wang, Mi, Thompson, et al. NEJM 2022

Drug Induced Mutations in BTK Render this Protein Target "Undruggable"

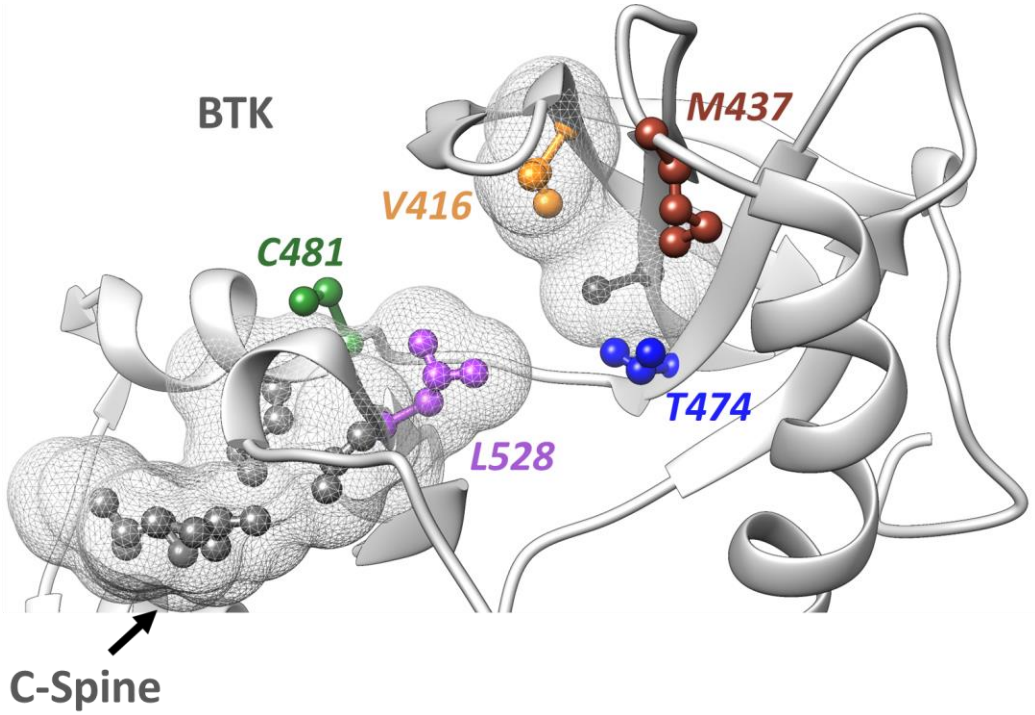




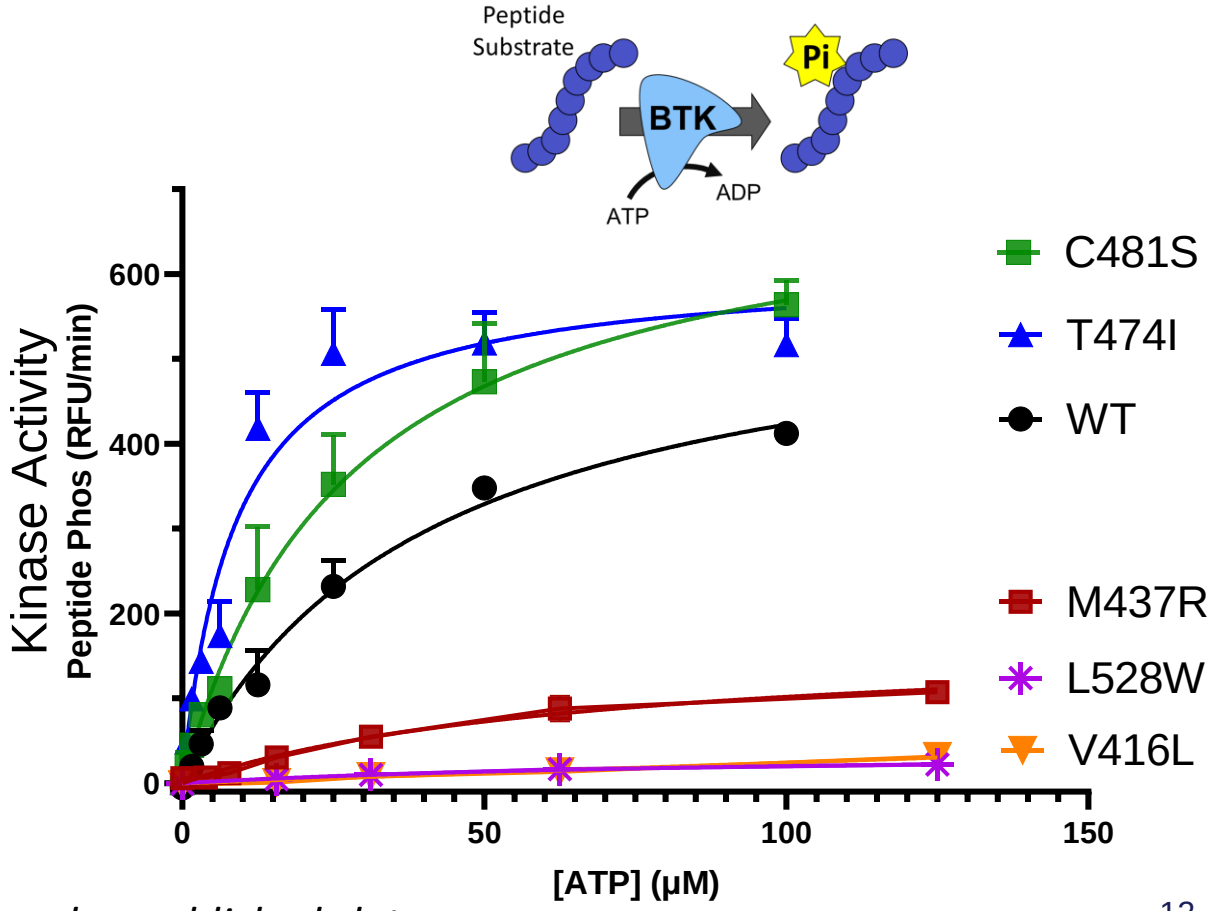
Wang, Mi, Thompson, et al. NEJM 2022

Structural and Enzymatic Studies of New BTKi-Resistant Mutations Confirms BTK Scaffolding Function

Mutations revealed by non-covalent inhibitors interrupt the catalytic C-spine of kinase domain

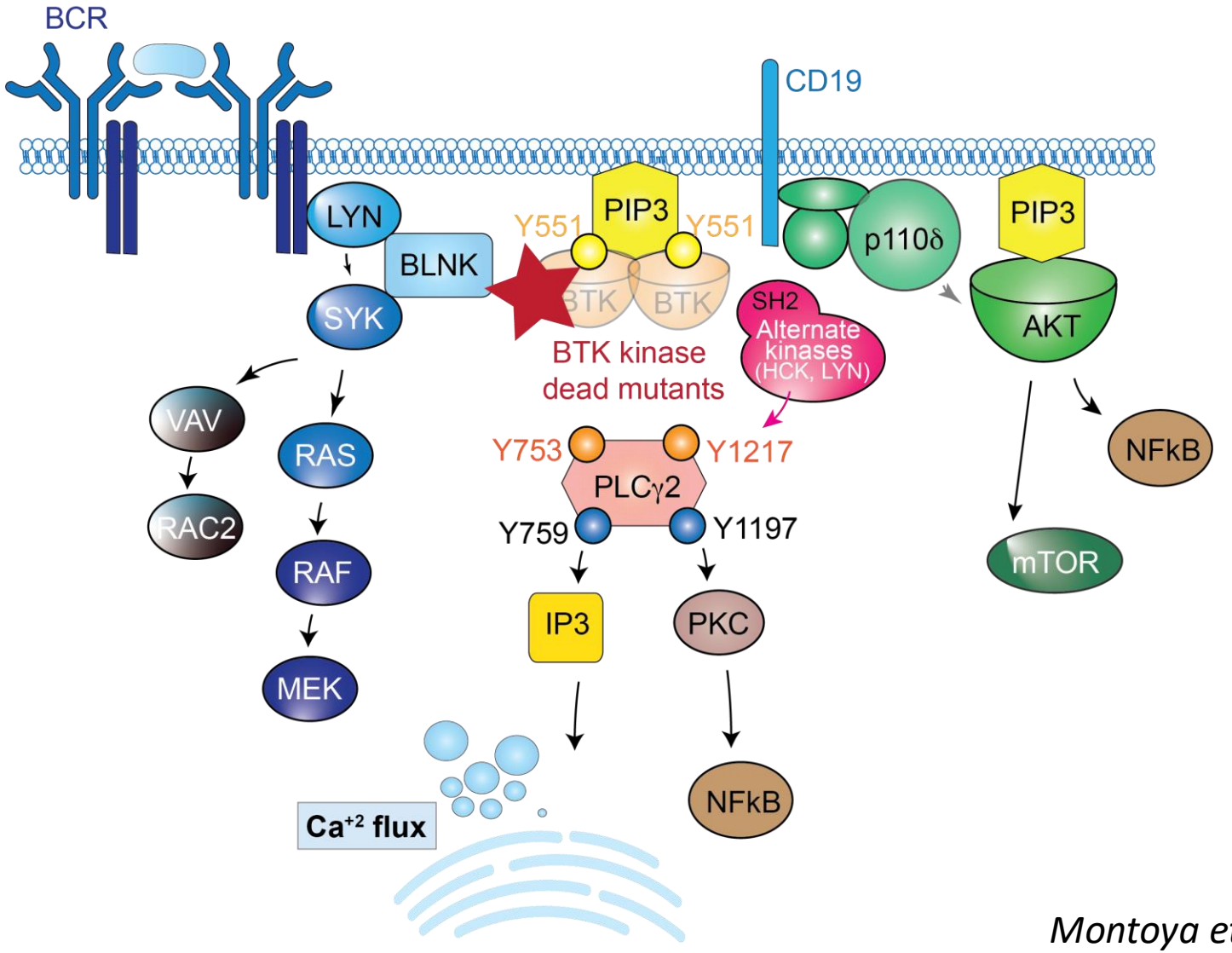


Some mutations that confer resistance to BTKis lack kinase activity yet still potentiate BCR signaling



Montoya et al., ASH 2022 and unpublished data

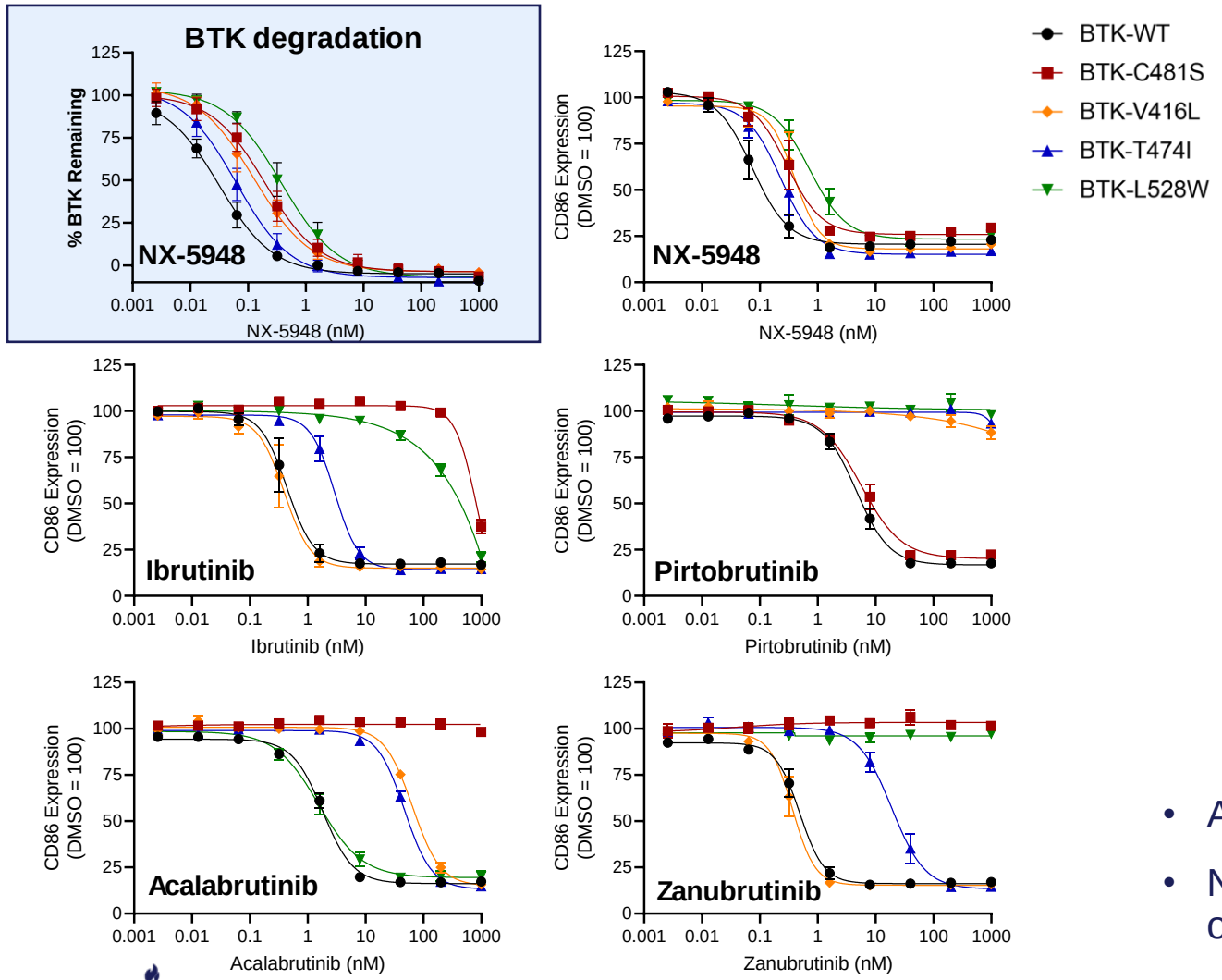
Can Targeted Protein Degradation Address the Scaffolding Function of Mutant BTK?



Montoya et al., ASH 2022

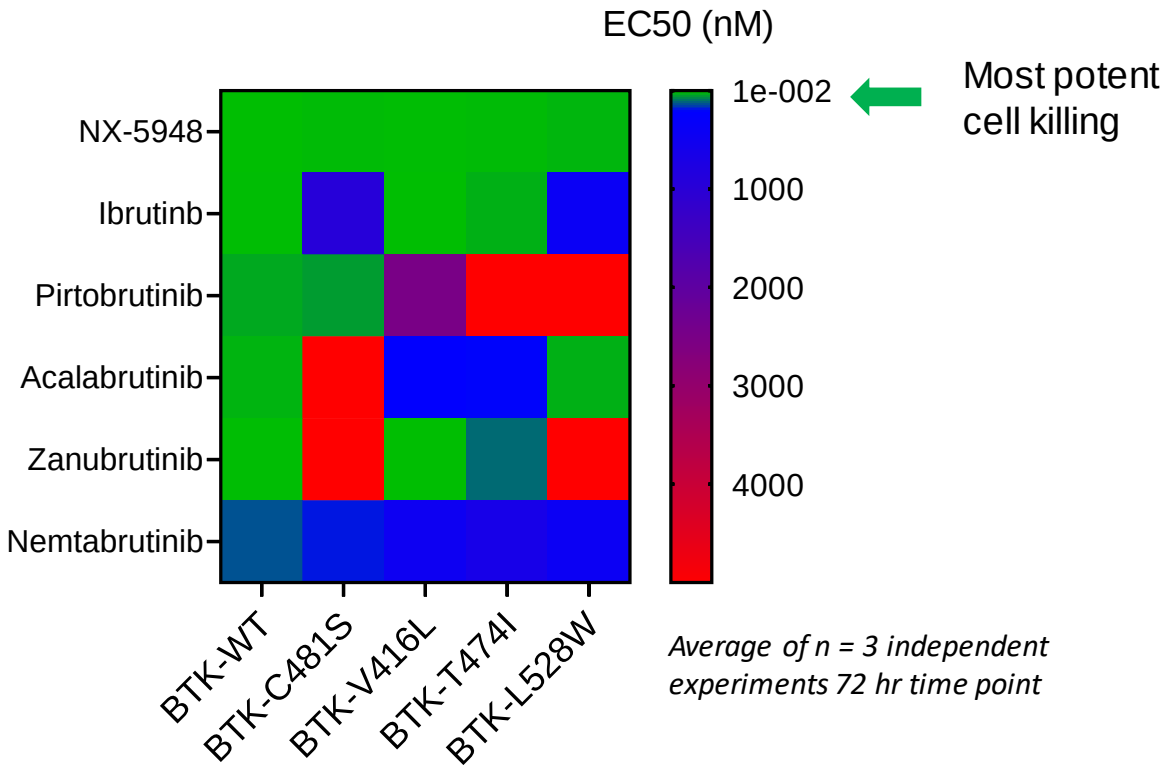
NX-5948 is More Potent and Broadly Active Than All BTK Inhibitors Tested

BTK degradation and activation marker suppression in TMD8 tumor cells



Average of n = 3 independent experiments +/- SEM

TMD8 tumor cell killing

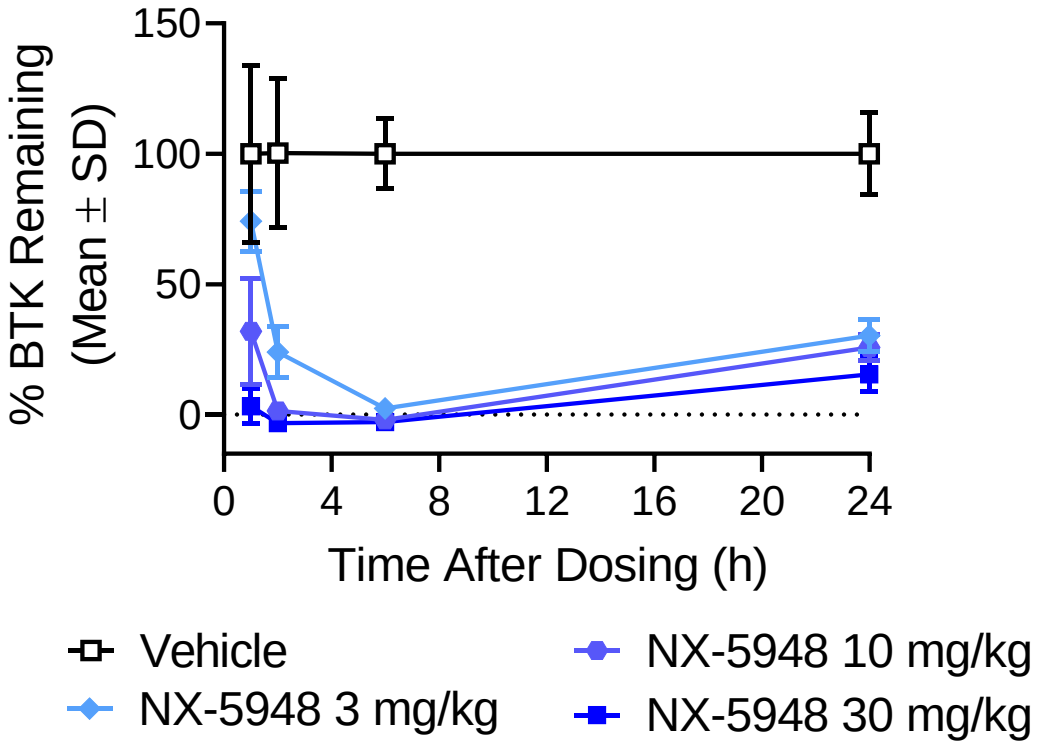


Average of n = 3 independent experiments 72 hr time point

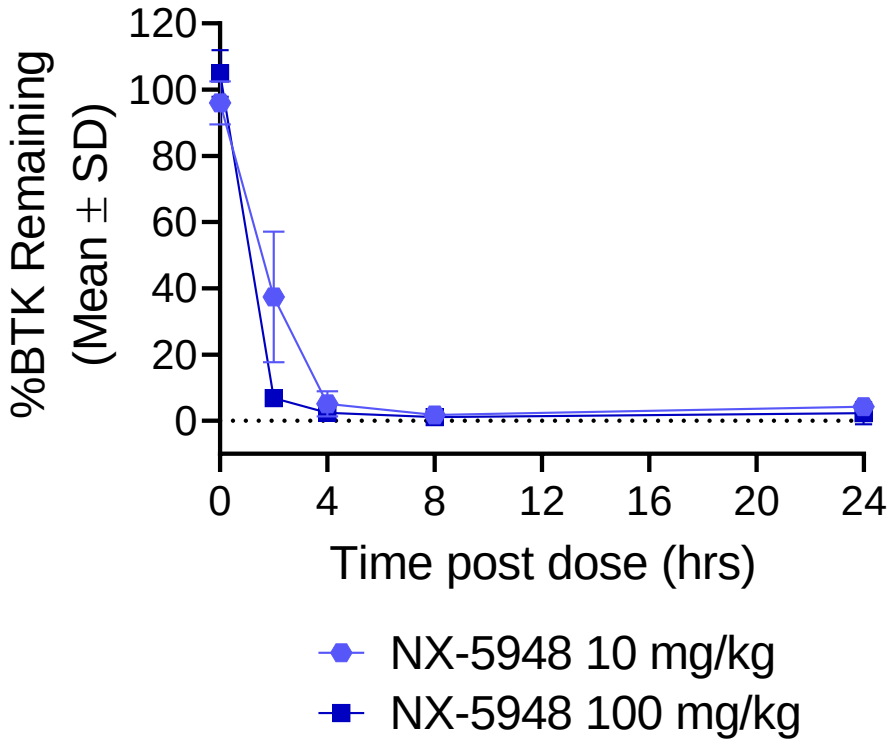
- All inhibitors have resistance mutation liabilities
- NX-5948 displays potent cell killing and maintains suppression of CD86 in the context of key resistance mutations

A Single Oral Dose of NX-5948 Promotes Rapid and Complete BTK Degradation in Mouse and Primate B cells

BTK Levels in Mouse Circulating B Cells



BTK Levels in Cyno Circulating B Cells

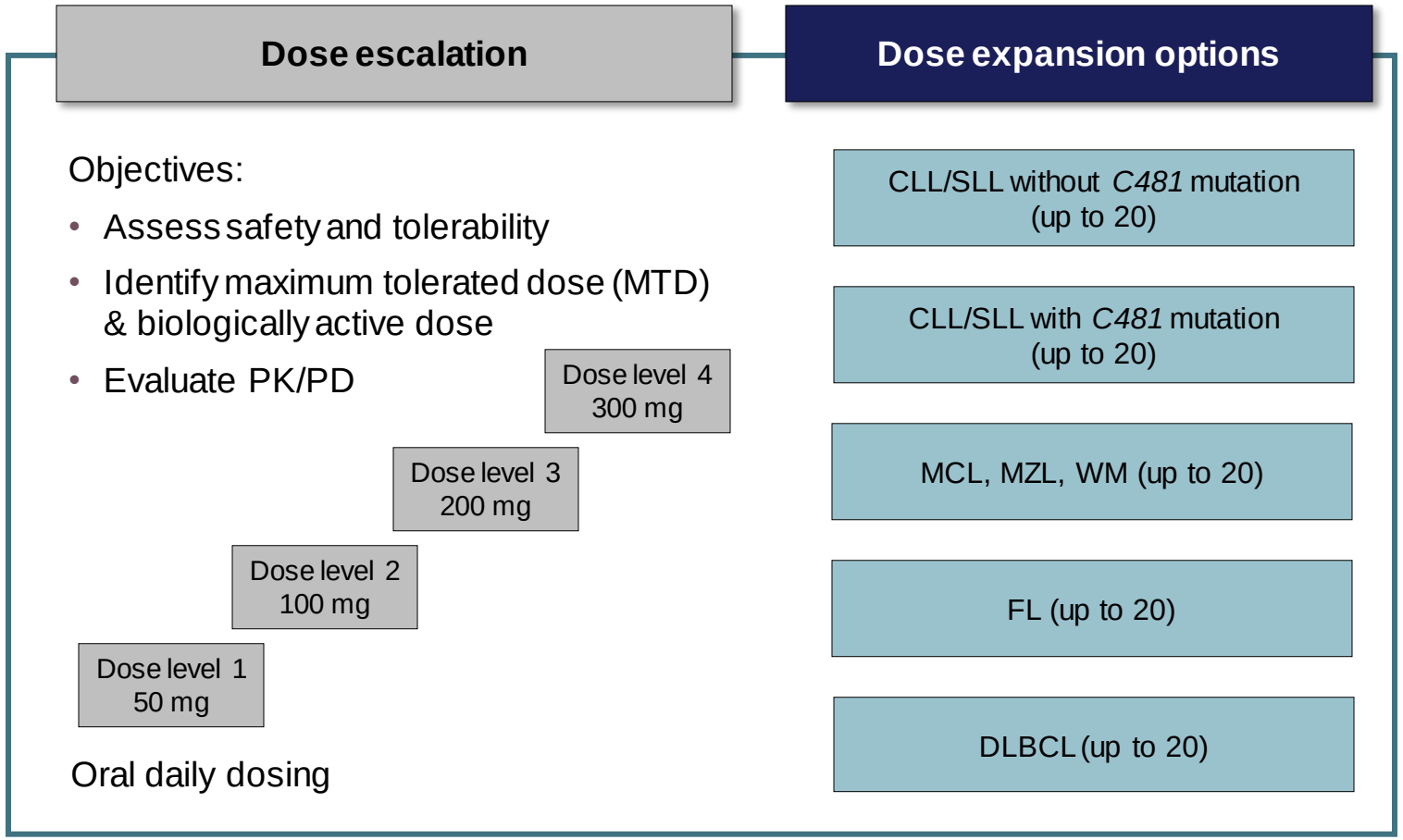


- In mice, BTK levels increased 24 hours after dosing from BTK resynthesis
- In cynomolgus monkeys, BTK levels remained suppressed at 24 hours

Rountree et al., TPD 2022

NX-5948-301: Trial design

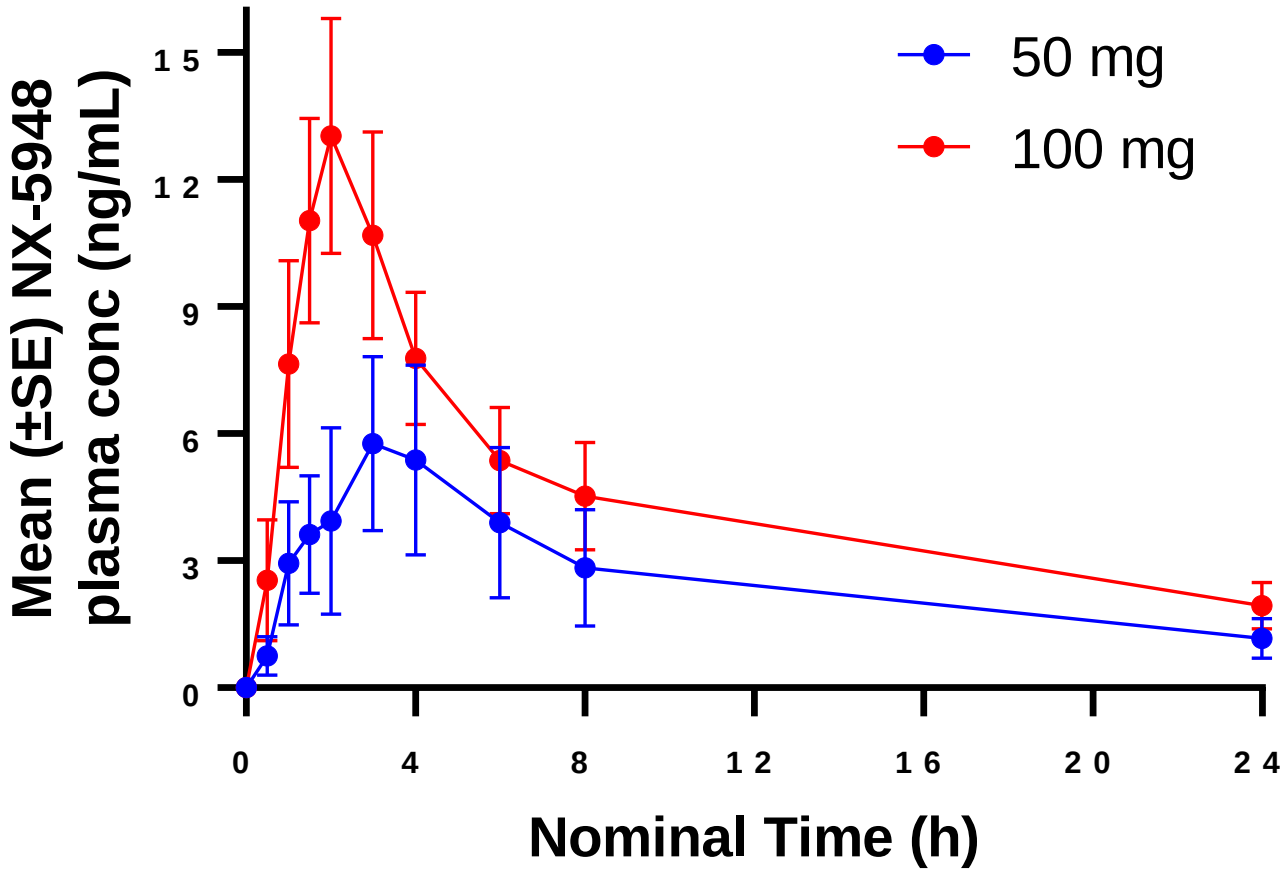
Phase 1 trial in adults with relapsed/refractory B-cell malignancies



- Phase 1a dose escalation is ongoing at clinical sites in the U.K.
- Plans to initiate U.S. sites in early 2023

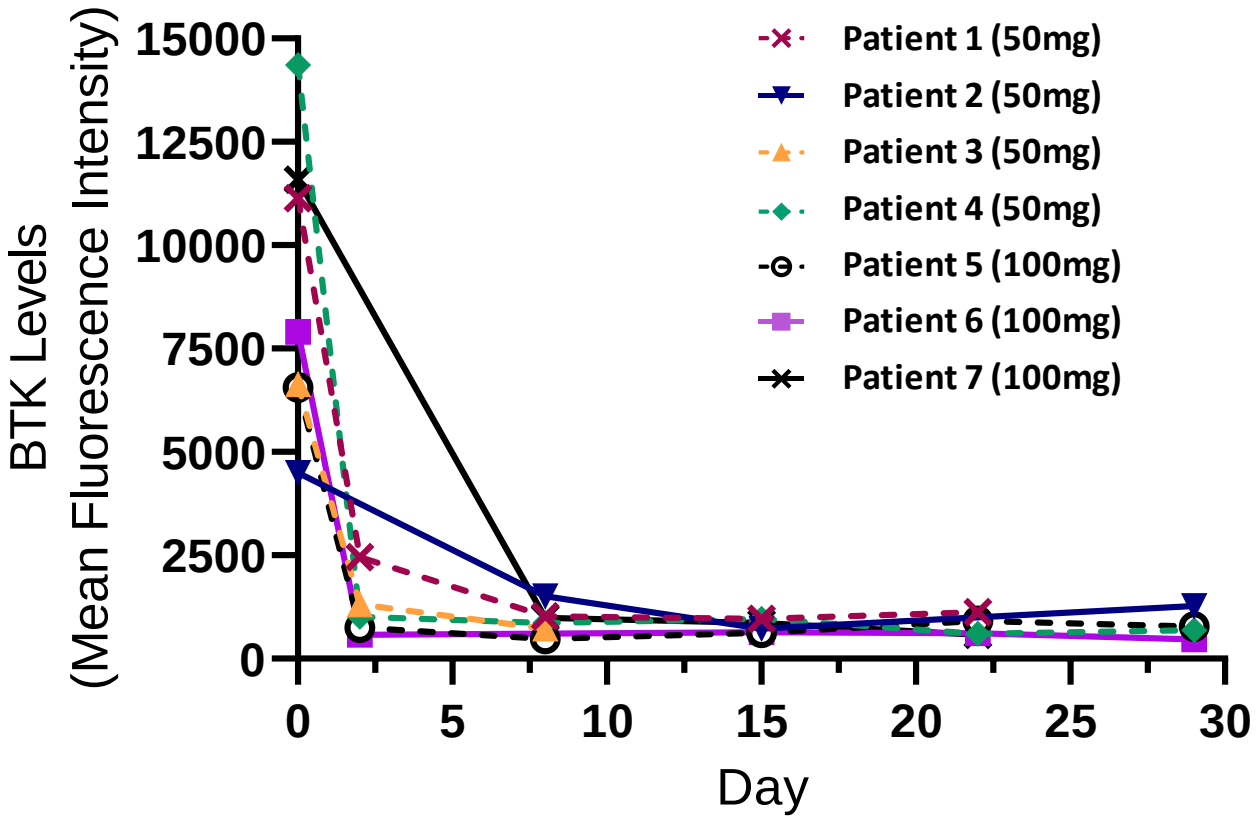
CLL, chronic lymphocytic leukemia; **DLBCL**, diffuse large B-cell lymphoma; **FL**, follicular lymphoma; **MCL**, mantle cell lymphoma; **MZL**, marginal zone lymphoma; **PD,** pharmacodynamics; **PK,** pharmacokinetics; **WM**, Waldenstrom's macroglobulinemia

Preliminary Data Suggests NX-5948 Exhibits Linear PK and Supports Daily Dosing



- Half-life ~12 hours
- T_{max} of 2-3 hours
- Exposures (both AUC and C_{max}) increase linearly with dose

NX-5948: Rapid, Robust and Sustained BTK Degradation



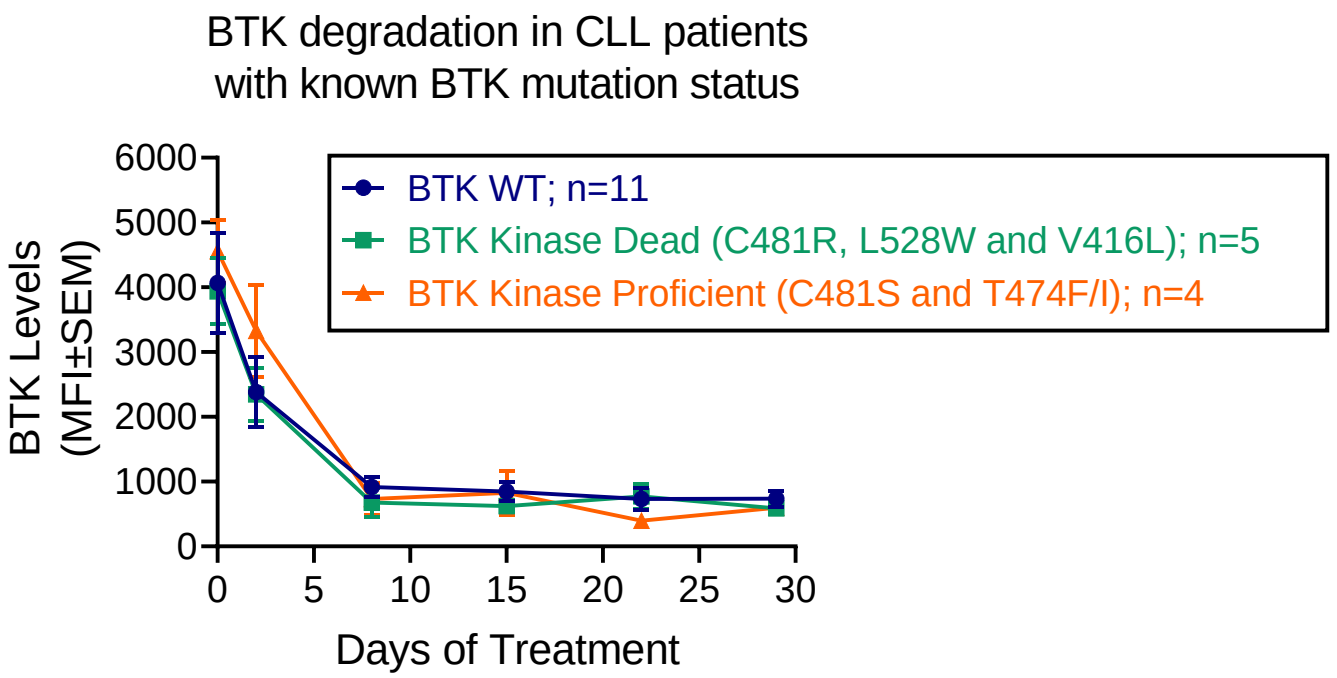
BTK levels are evaluated in real time in a FACS-based assay on whole blood from patients treated with NX-2127

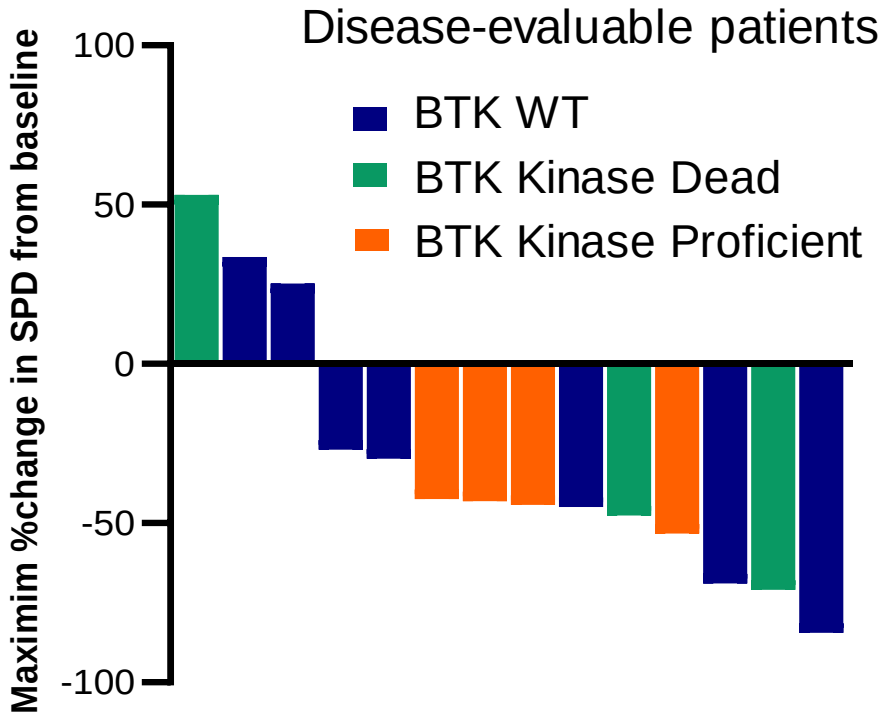
Initial proof of mechanism

- Rapid and sustained degradation of BTK
- Robust BTK degradation observed in all patients tested to date
- Dose escalation ongoing in patients with relapsed/refractory B cell malignancies

Treatment with Nurix's NX-2127 Degrader Leads to BTK Degradation and Clinical Response Irrespective of Mutation Status

- BTK degradation of 80% was achieved in CLL patients, including those harboring BTK C481, T474, L528, and V416 resistance mutations





Patients with kinase dead mutations are classified as kinase dead regardless of co-occurrence of kinase proficient mutations

NX-5948: BTK Degrader Demonstrates Rapid and Sustained BTK Degradation With Early Signs of Differentiated Safety

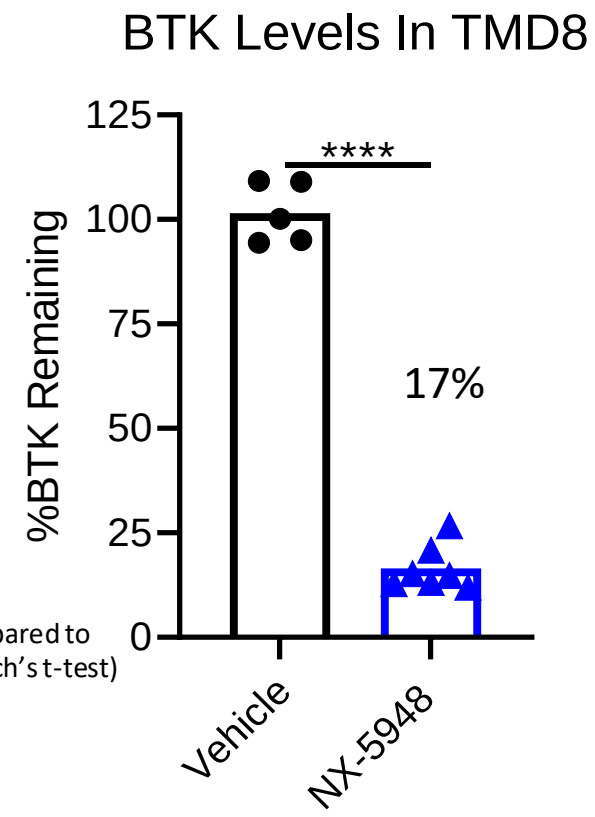
Phase 1a Dose Escalation

- Early evidence of target engagement
- Rapid and sustained BTK degradation in all patients
- No evidence of immunomodulatory associated adverse events

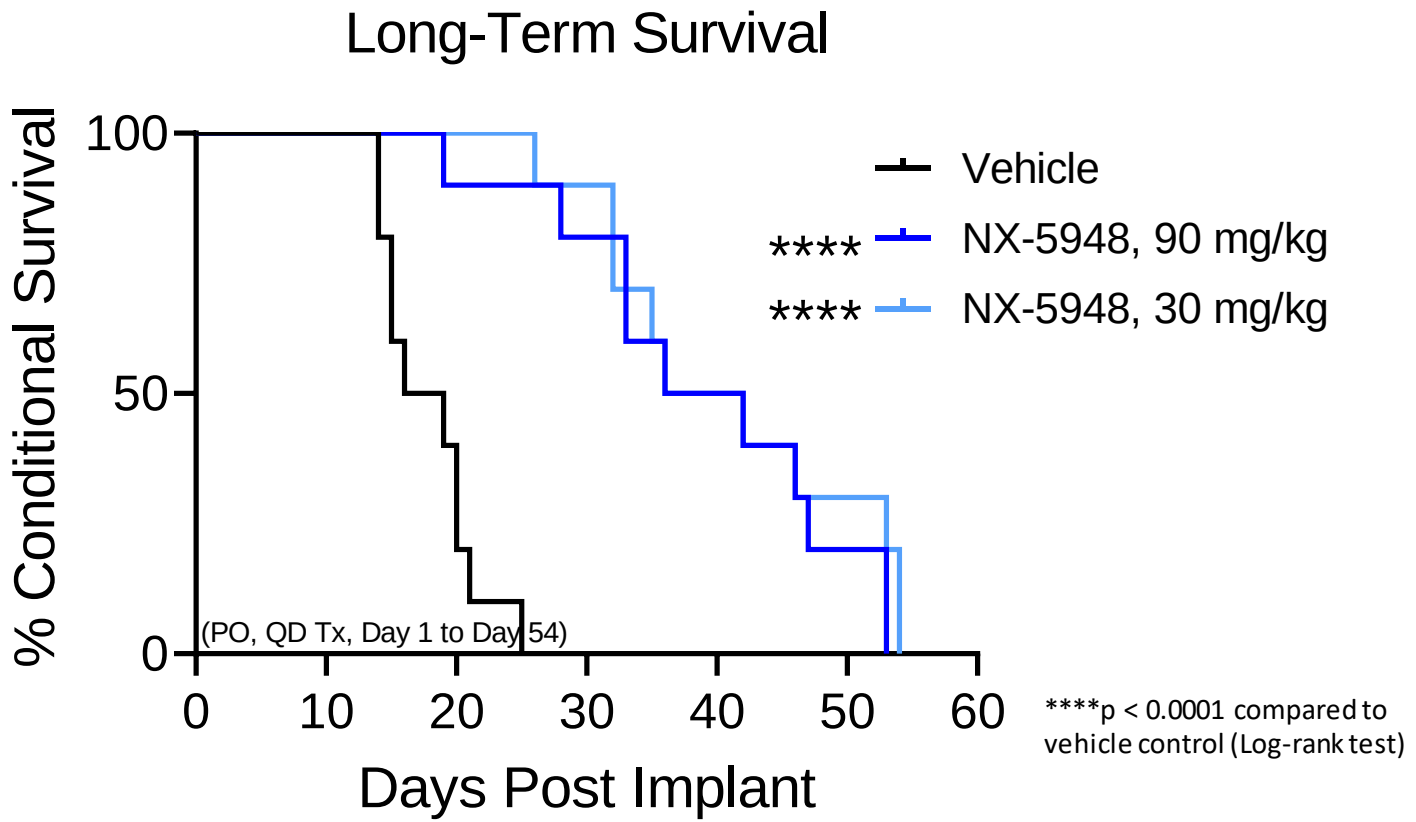
Next steps:

- Initiate clinical sites in the U.S.
- Identify Phase 1b expansion dose
- Select indications for cohort expansion with initial focus likely in CLL

Oral Administration of NX-5948 Degrades BTK in Tumor Cells and Prolongs Survival in a Mouse Model of CNS Lymphoma



****p < 0.0001 compared to vehicle control (Welch's t-test)

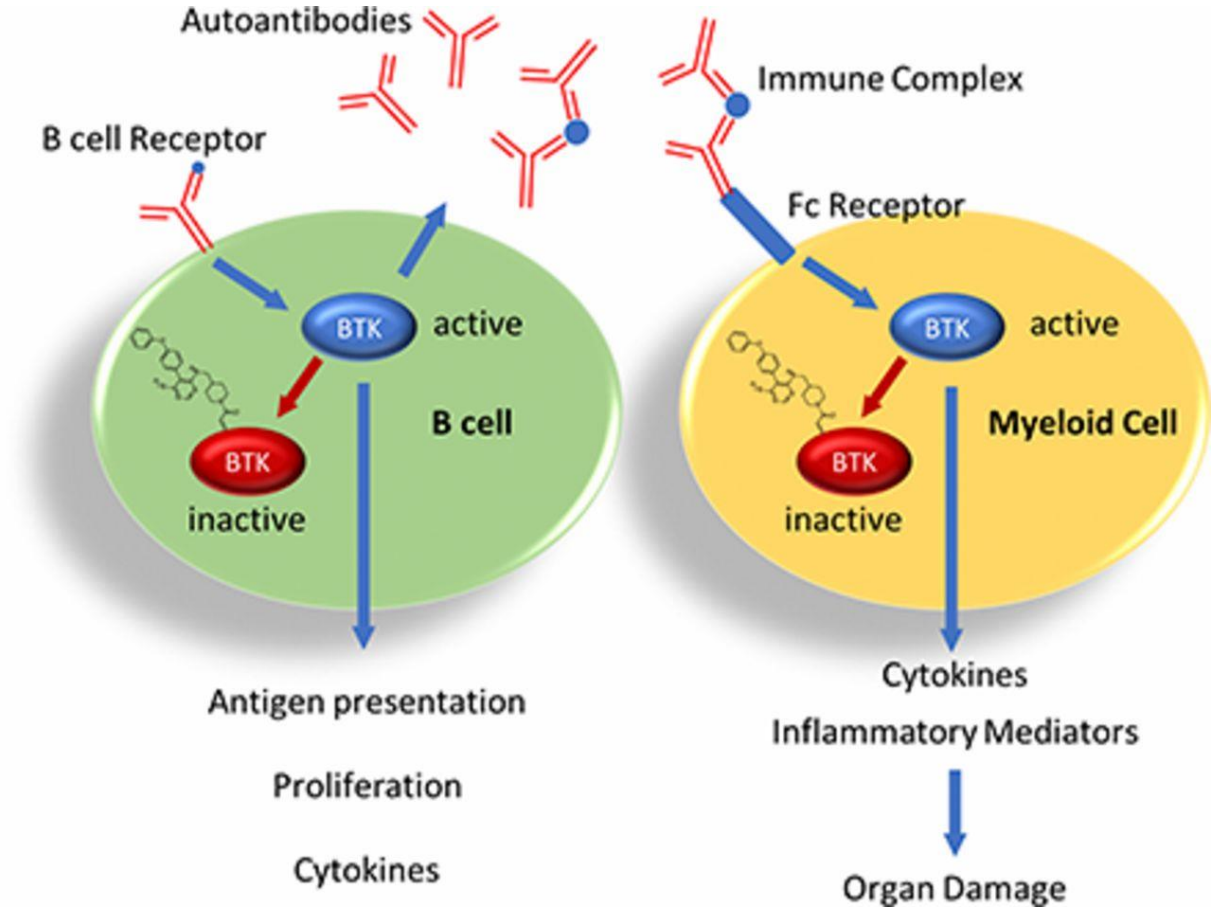


****p < 0.0001 compared to vehicle control (Log-rank test)

5 x 10e^5 TMD8 cells implanted by intracranial injection on Day 0
NX-5948 administered orally QD Days 1-11 (left) or Days 1-54 (right)
BTK levels assessed 24 h after the 11th dose by flow cytometry

Rountree et al., TPD 2022

BTK Regulates Signaling Pathways in B cells and Myeloid Cells that Contribute to Autoimmunity

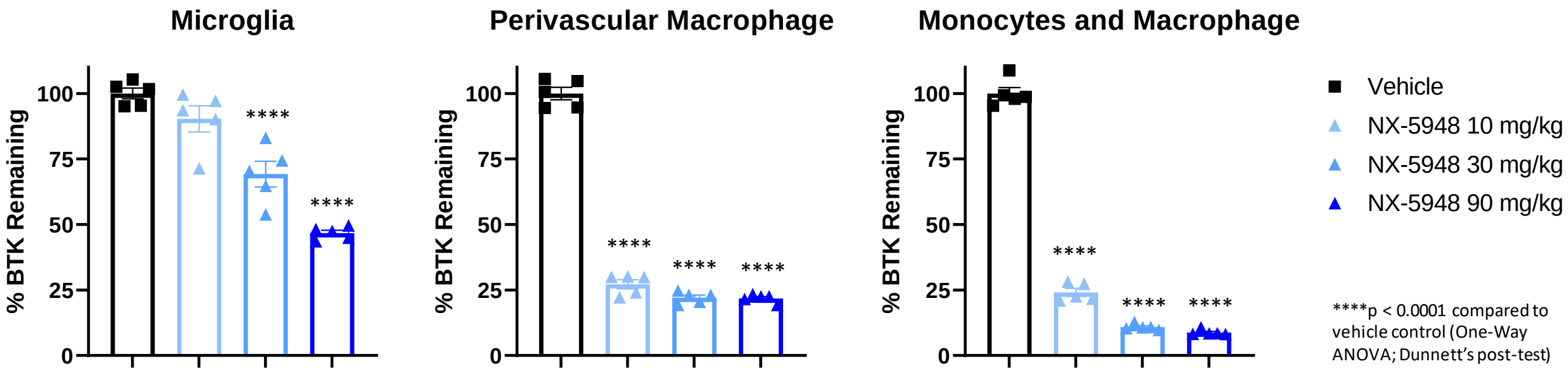


Haselmayer, JI, 2019

- BTK transduces signals downstream of the B cell receptor, toll-like receptors, and Fc receptors in B cells and myeloid cells
- BTK regulates B cell maturation, autoantibody production, and antigen presentation to T cells
- BTK regulates immune-complex mediated activation of myeloid cells which directly damages tissues

NX-5948 Degrades BTK in Microglia and Macrophage in Brains of Naïve Mice

- NX-5948 drives dose-dependent BTK degradation in cells isolated from brains
- Magnitude of BTK degradation depends on dose and cell type

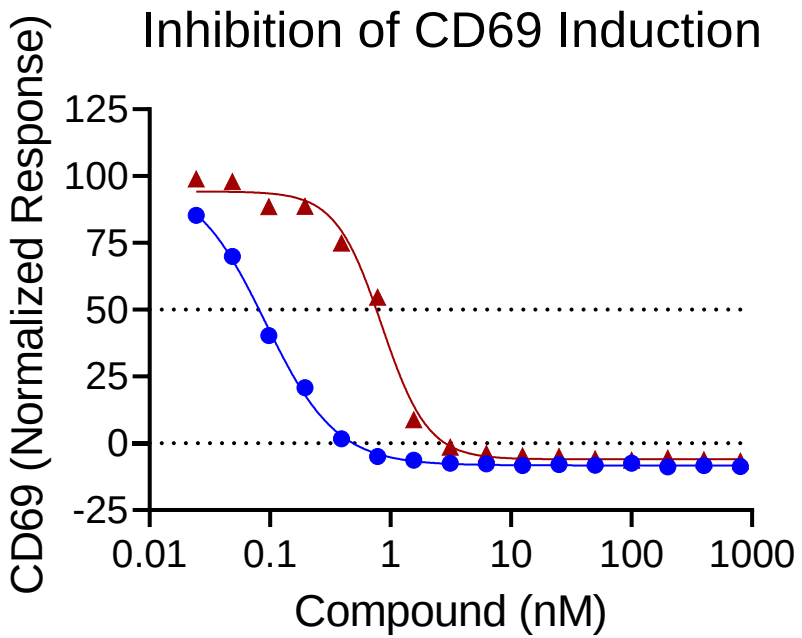


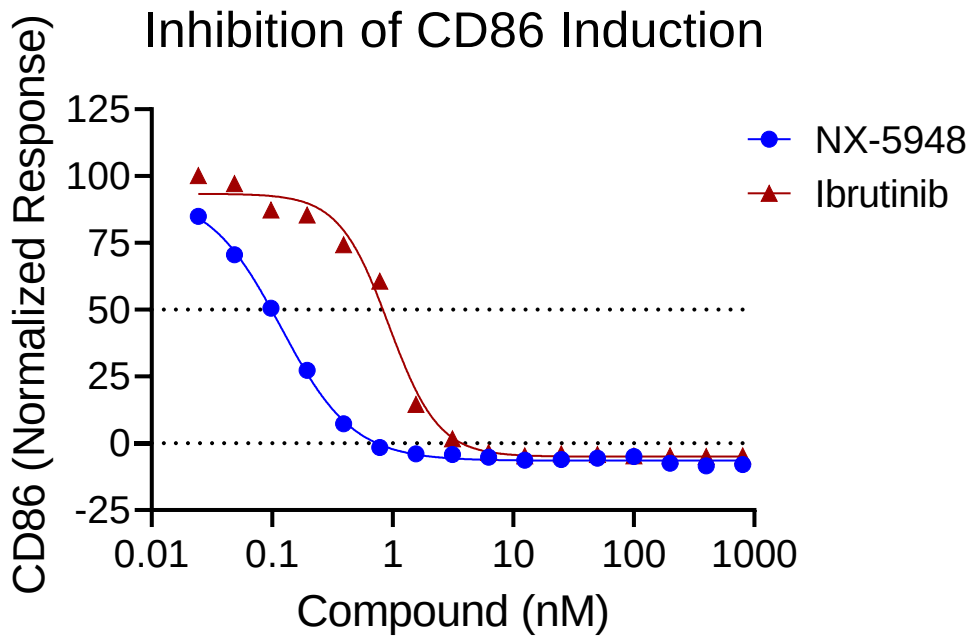
NX-5948 administered orally QD x 3 days to naïve C57BL/6J mice. BTK levels assessed 8 h after 3rd dose by flow cytometry.

Rountree et al., TPD 2022

NX-5948 is a Potent Inhibitor of Anti-IgM-Mediated B Cell Activation

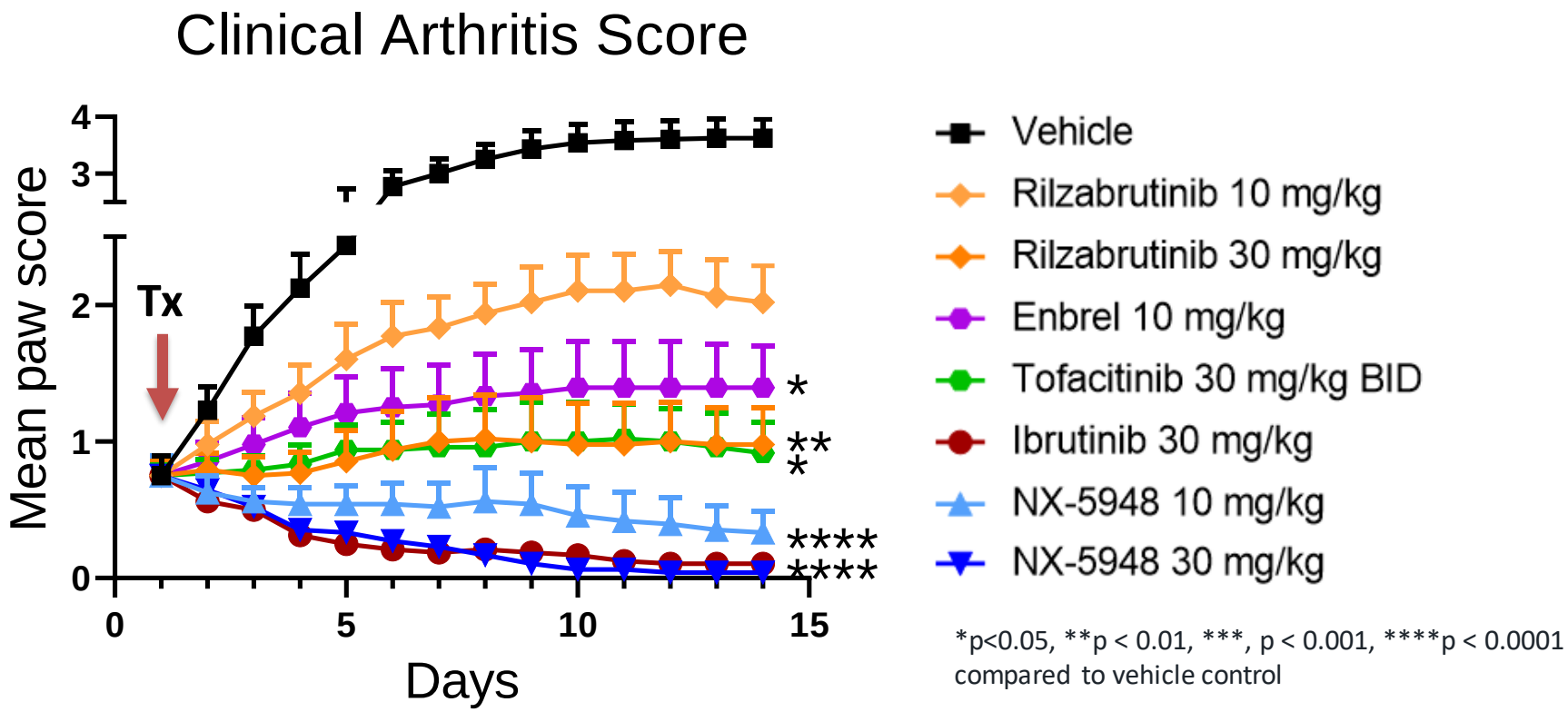
NX-5948 is more potent than ibrutinib at inhibiting B cell activation following BCR stimulation





N=1 donor
Data representative of 3 independent donors

NX-5948 Improves Arthritis Clinical Scores and Provides a Similar or Greater Benefit as BTKi or Standard of Care Agents



*p<0.05, **p < 0.01, ***, p < 0.001, ****p < 0.0001 compared to vehicle control

- 30 mg/kg NX-5948 resulted in complete resolution of symptoms in 10/12 mice
- 30 mg/kg ibrutinib resulted in complete resolution of symptoms in 7/12 mice
- Oral NX-5948 treatment resulted in lower mean clinical score than Rilzabrutinib, Tofacitinib, or Enbrel

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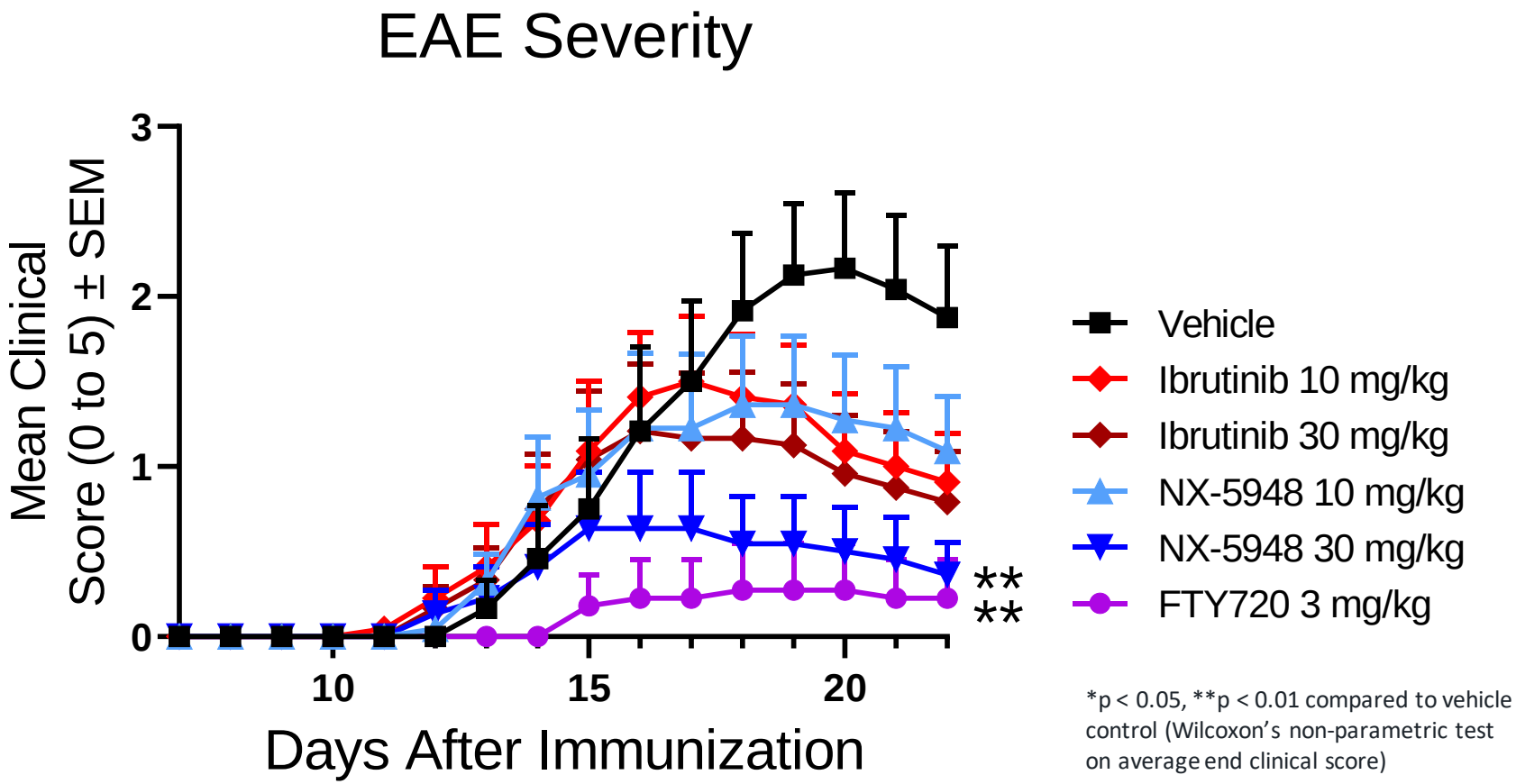
Rountree et al., 3rd B&T-cell Summit 2022

NX-5948 Improves EAE Clinical Scores and Provides More Benefit Than Ibrutinib



*p < 0.05, **p < 0.01 compared to vehicle control (Wilcoxon's non-parametric test on average end clinical score)

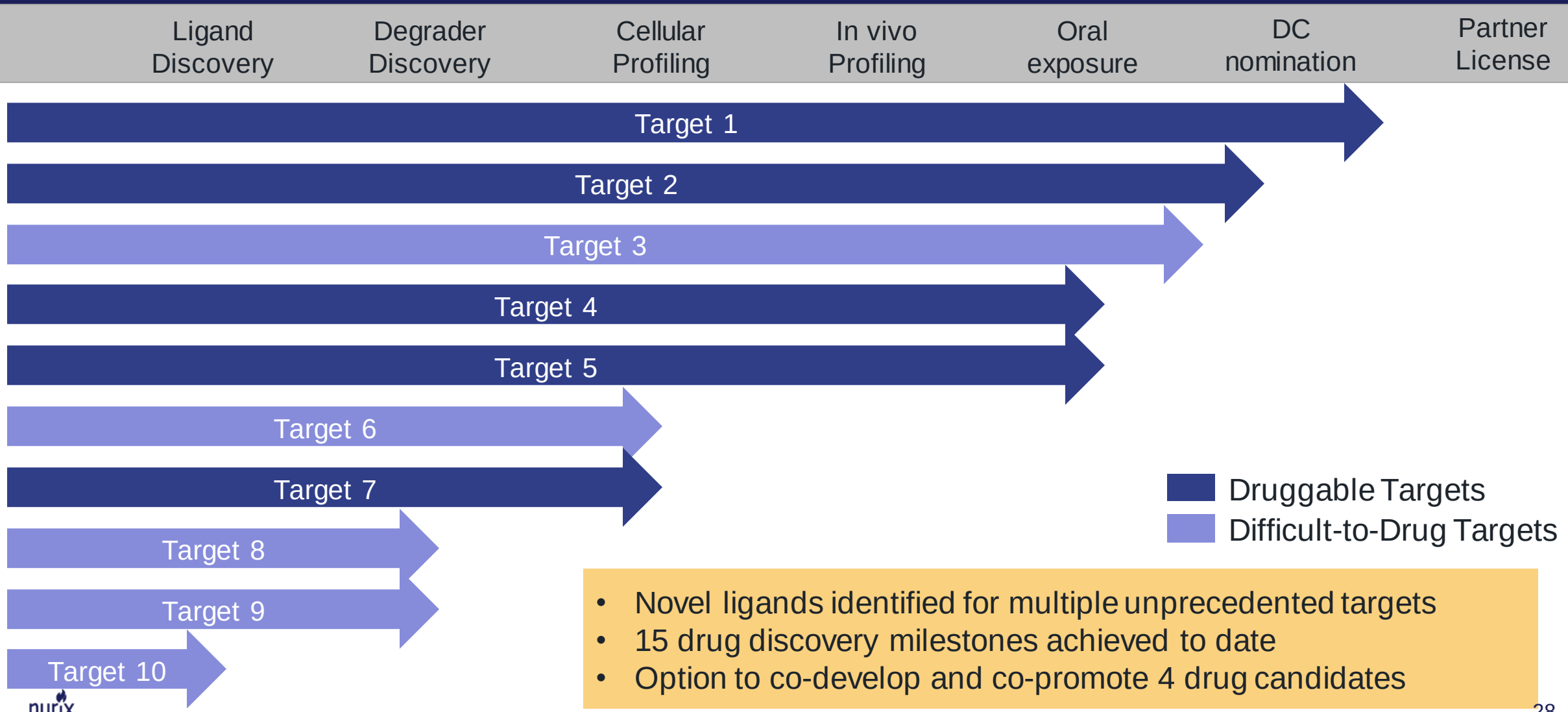
Rountree et al., 3rd B&T-cell Summit 2022

Nurix's Clinical Experience with Targeted Protein Degradation Illustrates the Benefits of Novel Therapeutic Modalities

Catalytic modality of TPD can provide:

1. Increased target coverage
   - One degrader can degrade many protein molecules
2. Prolonged activity against a target
   - Protein synthesis rather than drug clearance is required to restore target
   - Ideally suited for non-daily delivery methodologies
3. Ability to address mutational resistance
   - Nurix's BTK degraders are potent against unanticipated BTK active site mutations
4. Ability to address novel and non-enzymatic targets
   - Degraders are agnostic to protein catalytic function; noncatalytic proteins can be targeted
   - Structured (e.g. transcription factors) and 'plastic' proteins can be addressed

Leveraging Early Success with BTK Degraders to Build a Broad Collaboration Pipeline that Includes Many Unprecedented and First-In-Class Targets



- Novel ligands identified for multiple unprecedented targets
- 15 drug discovery milestones achieved to date
- Option to co-develop and co-promote 4 drug candidates

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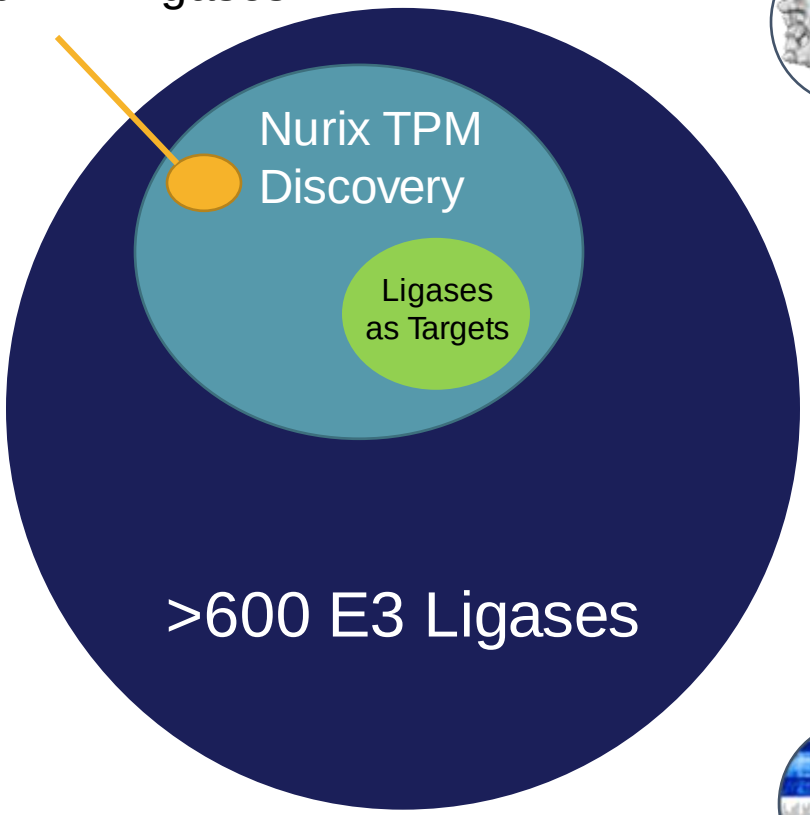
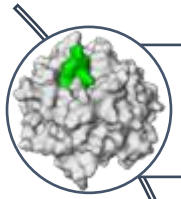
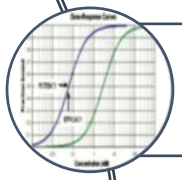
Unique TPM Opportunities Can Be Unlocked by Harnessing or Inhibiting Additional E3 Ligases

Precedented TPD ligases

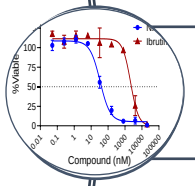




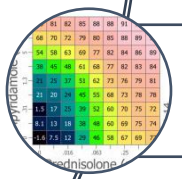
Unlock novel targets and pathways



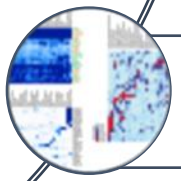
Improve target coverage and selectivity



Overcome inhibitor resistance



Neosubstrate synergy with target biology



Enhance selectivity through ligase specificity

Nurix Has a Comprehensive Degrader Discovery Pipeline

Ligand Discovery | Ligand Optimization | Degrader Profiling | DC nomination | Clinic

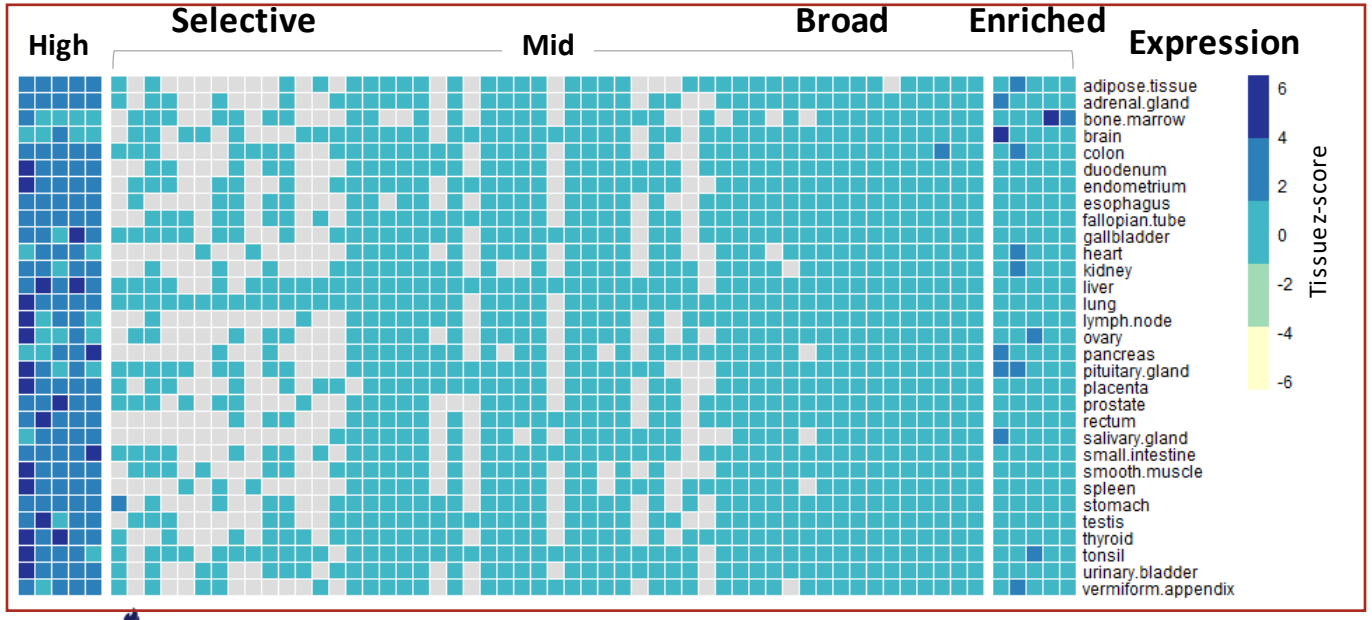
CBL Inhibitors and BTK Degraders

20 Ligases & UPS Targets

11 Ligases & UPS Targets

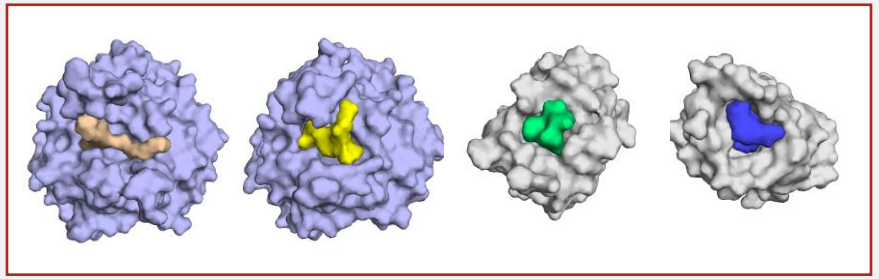
48 Targets

>70 Degradation Effectors in Discovery Pipeline



Human Normal Tissue Proteomics; Source: Expression Atlas E-PROT-29

Examples:



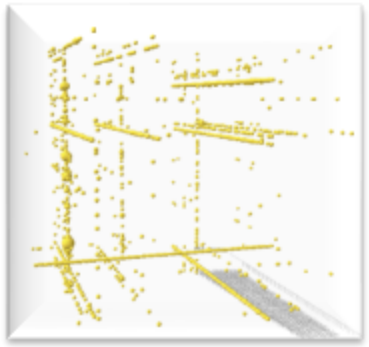
Multiple ligands identified for novel ligases with broad expression and high processivity in cancer and normal tissues

Nurix Has a Comprehensive Degrader Discovery Pipeline

Ligase prioritization

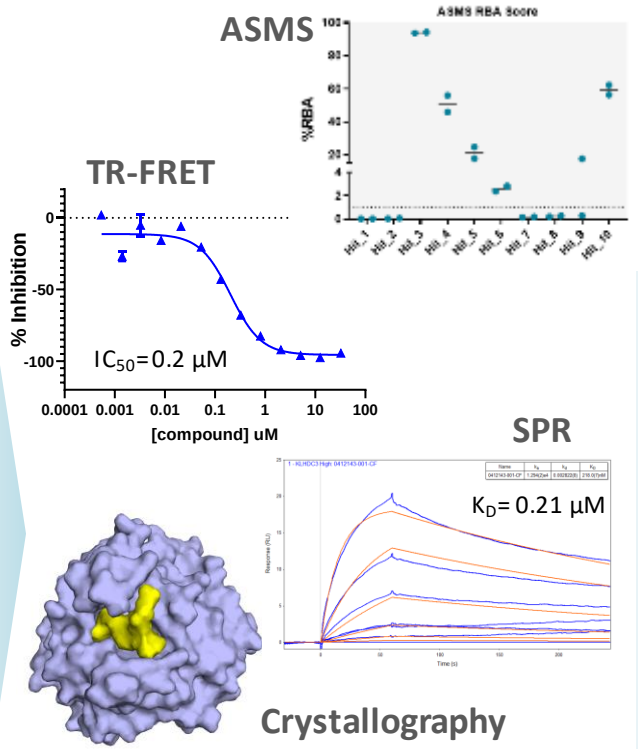
- Fn **Function**
- Ex **Expression**
- Ac **Activity**
- Tr **Tractability**

DEL screen for ligase binders



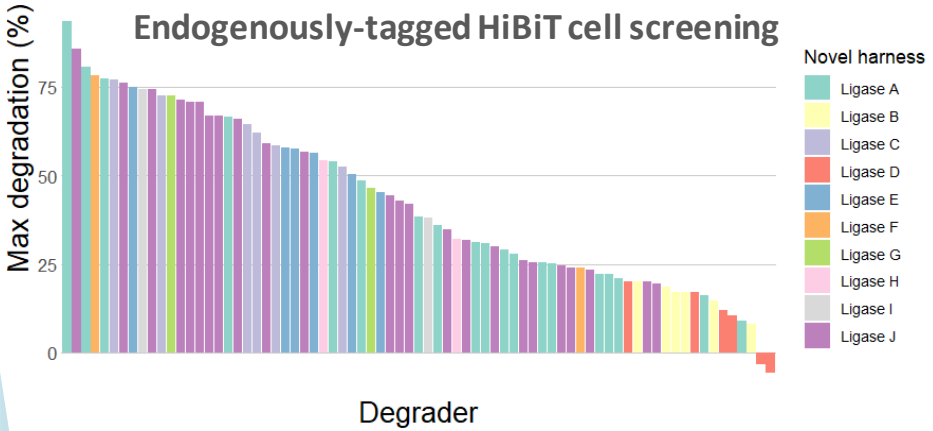
- Screening complex mixtures without a biochemical assay
- Highly multiplexed analysis of multiple conditions to identify substrate competitive and allosteric binders
- Internalization of published ligands

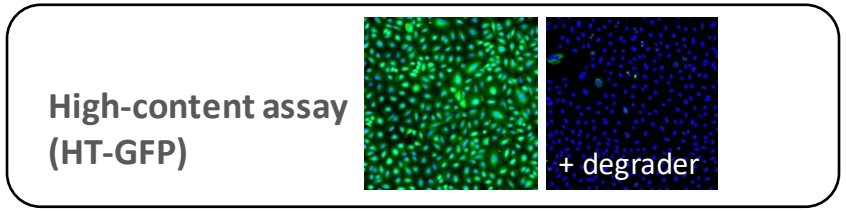
Harness optimization



- An array of biochemical, biophysical, and structure elucidation tools used to identify and optimize high affinity harnesses

Degrader activity characterization





- Automated synthesis of bivalent degrader library with validated target binders
- High-throughput cellular screen for active degraders
- Extensive panel of conditions to confirm ternary complex and UPS-driven MOA

Thank you!