nurix

Leader in Targeted Protein Modulation

First Disclosure of NX-5948, an Oral Targeted Degrader of Bruton's Tyrosine Kinase (BTK) for the Treatment of B-cell Malignancies

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American Chemical Society Conference

First Time Disclosures

San Francisco, CA

August 16, 2023

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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)

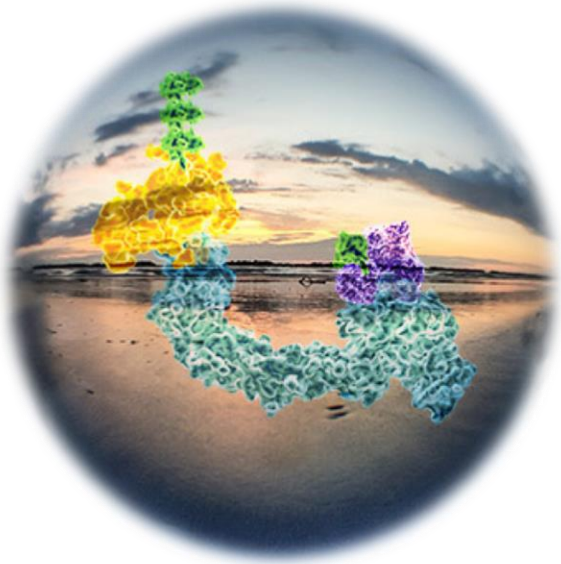
Inhibit ligases to increase specific protein levels

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

NX-5948

SELECTIVE
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
- Activity in multiple models of autoimmune disease
- Phase 1a dose escalation trial ongoing in U.K. and U.S.



NX-2127

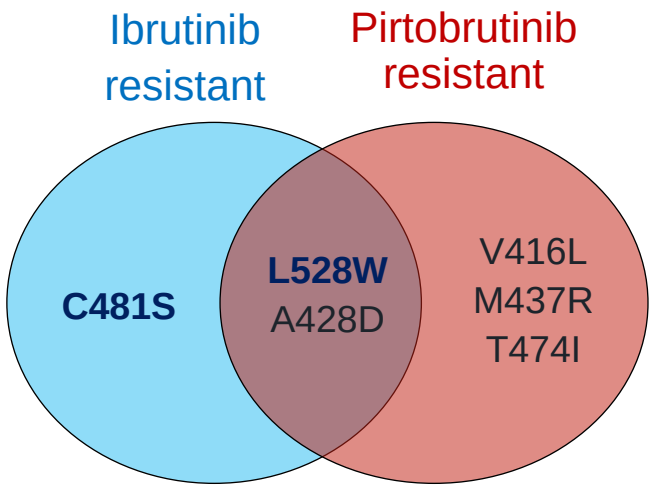
BTK DEGRADATION
& IMMUNOMODULATION

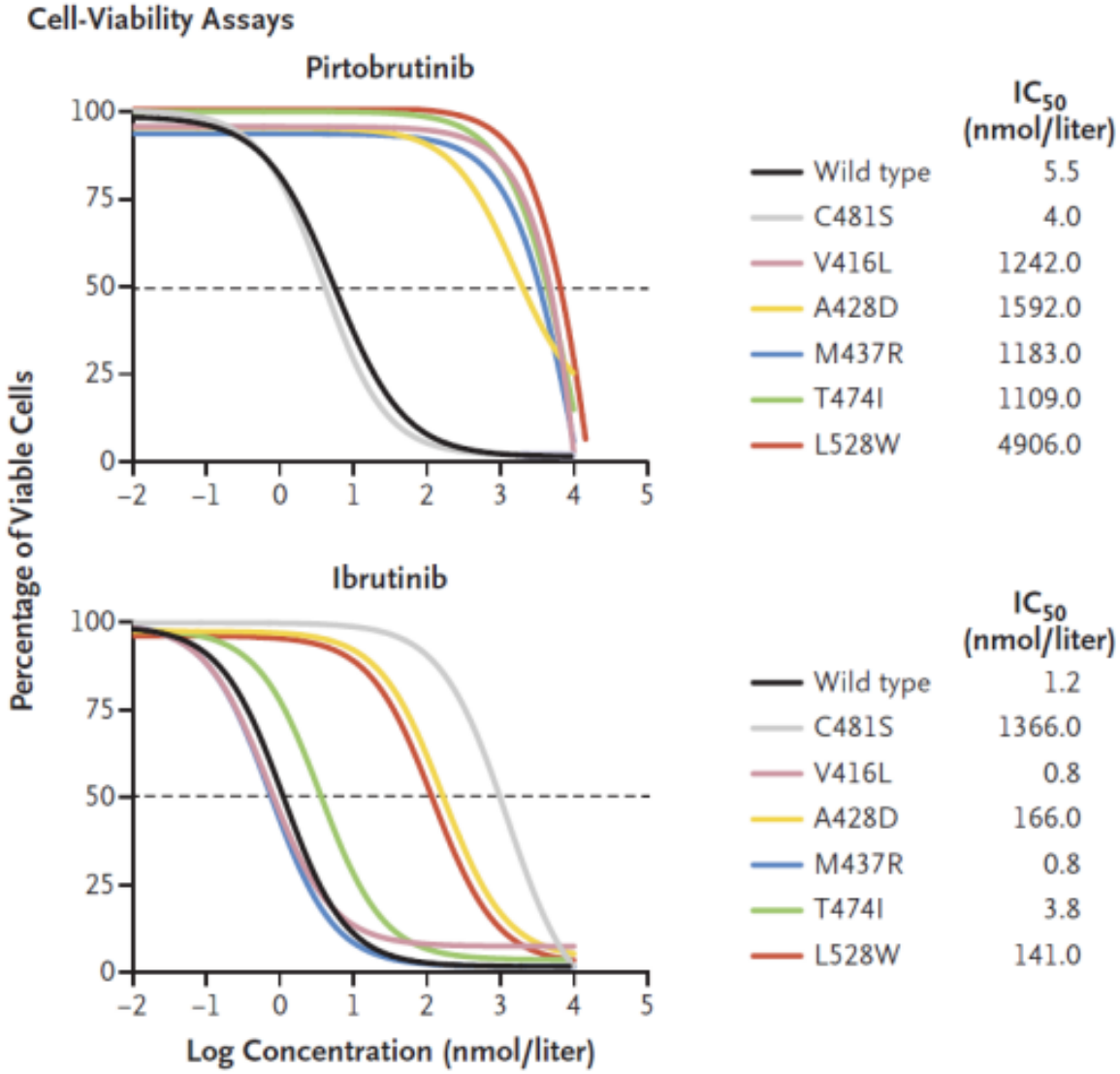
- Positive clinical activity in CLL patients, including responses in patients with BTK or BCL2 mutations
- Active in the clinic against BTK inhibitor-resistant mutations
- Complete response observed in a patient with DLBCL
- Phase 1b cohort expansion for CLL, DLBCL, and MCL patients are ongoing
- Dose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

Emerging BTK Mutations Confer Resistance to Covalent and Non-covalent BTK Inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

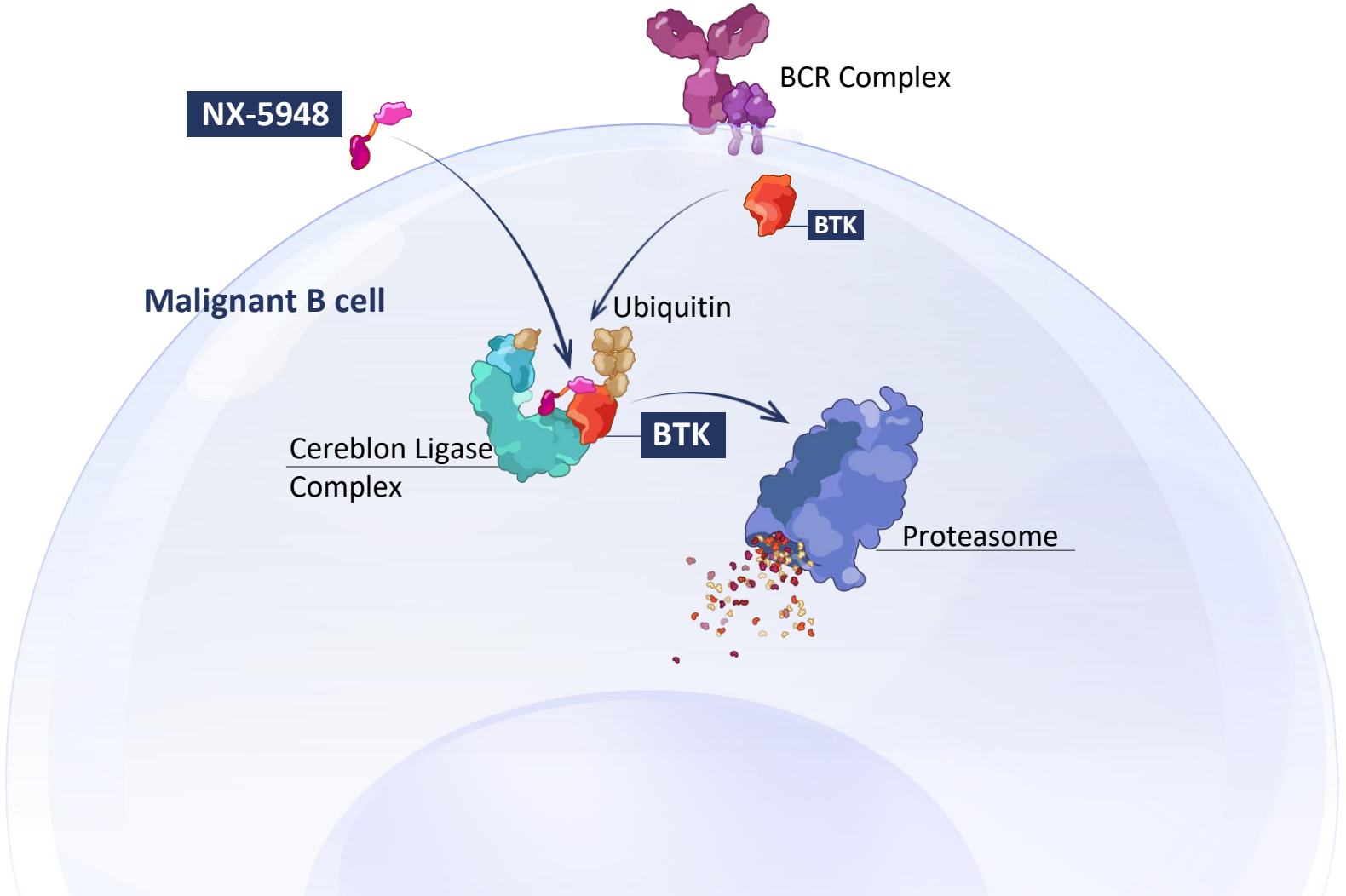
"Our data suggest potential new therapeutic approaches to overcome the newly described BTK inhibitor resistance mechanisms. For example, these data provide a rationale for therapies aimed at addressing the potential scaffold function of BTK rather than inhibiting BTK kinase activity."



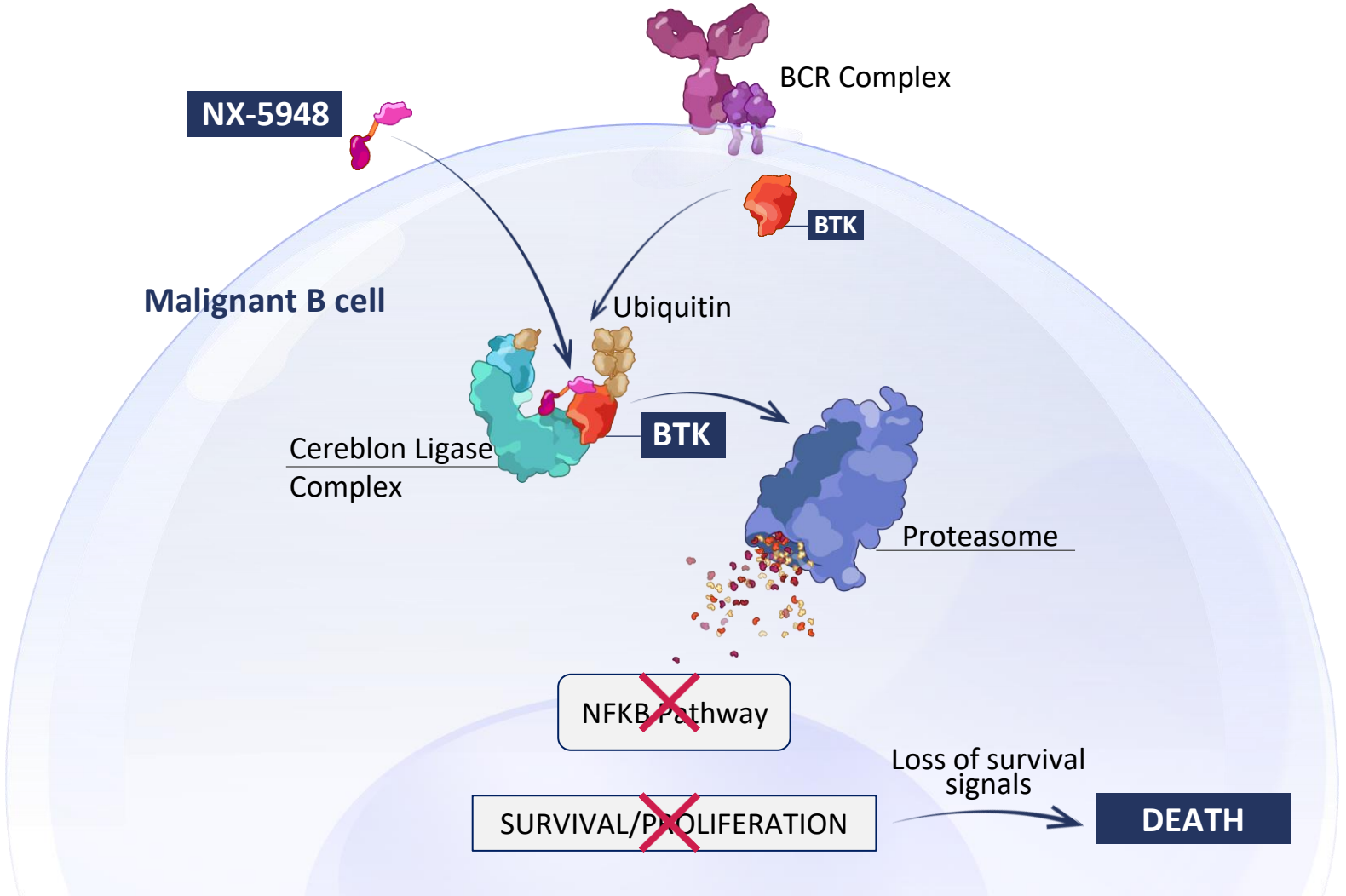


Wang et al., *N Eng. J. Med*, **2022**, 386:735-743

NX-5948 Mediates Targeted Degradation of BTK

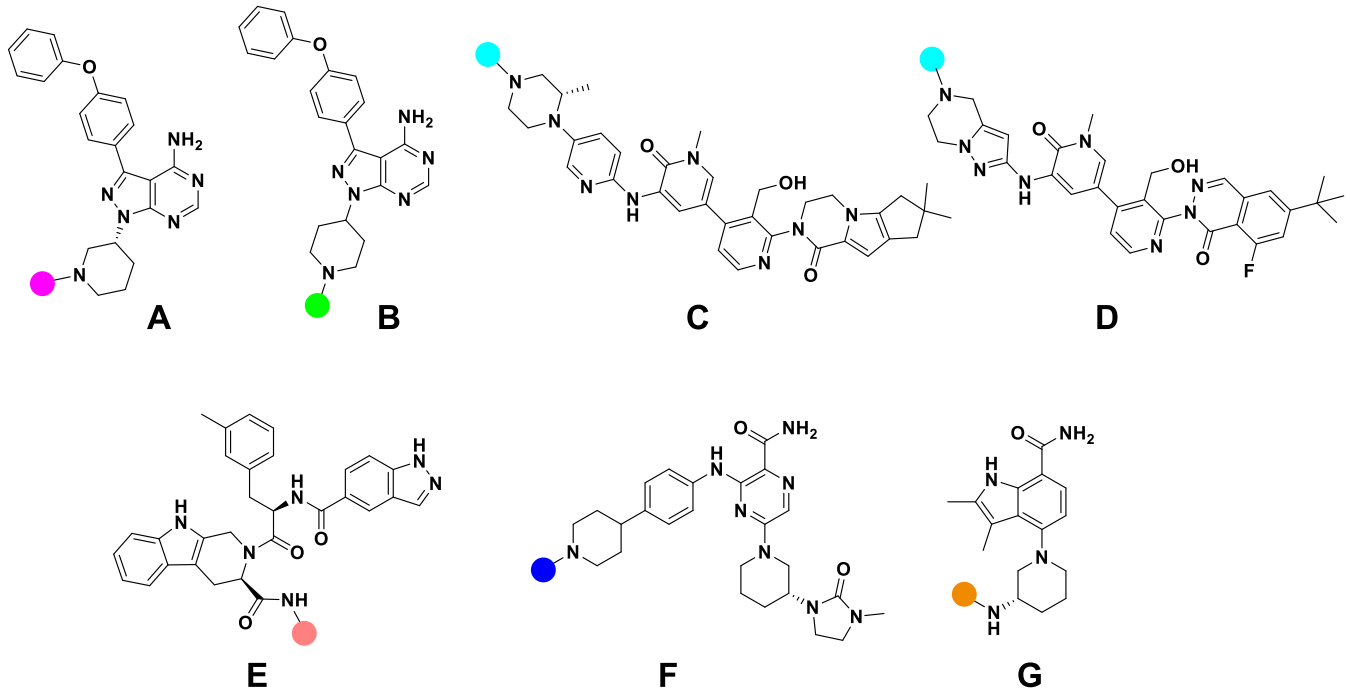


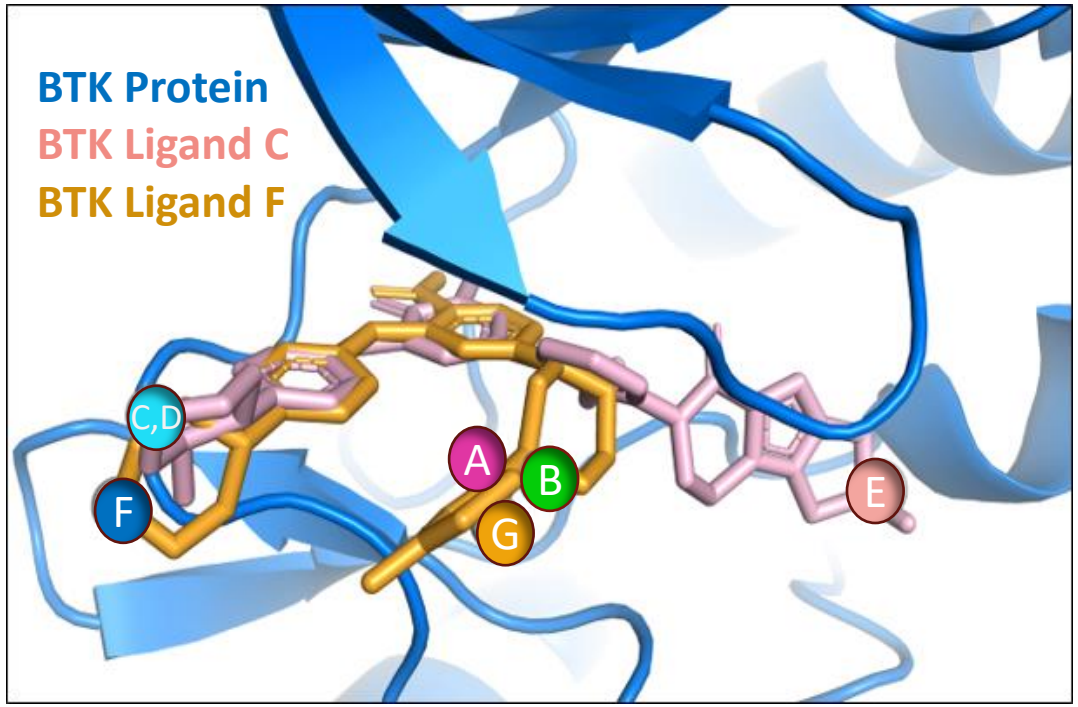
NX-5948 Mediates Targeted Degradation of BTK



BTK Ligands

Various BTK ligands were explored with unique exit vectors from BTK

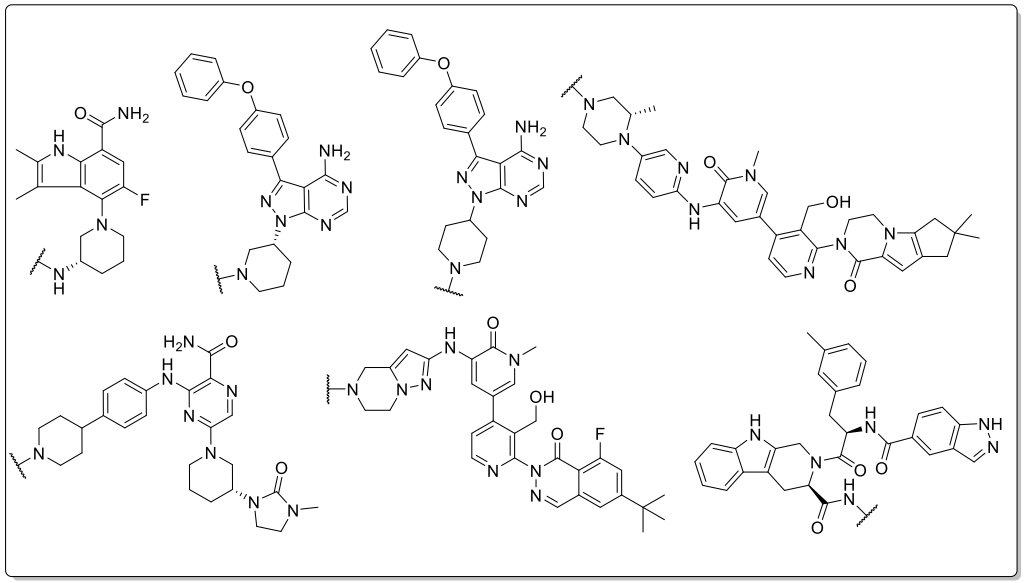




Subtle exit vector changes can have profound effects on potency, selectivity, and PK

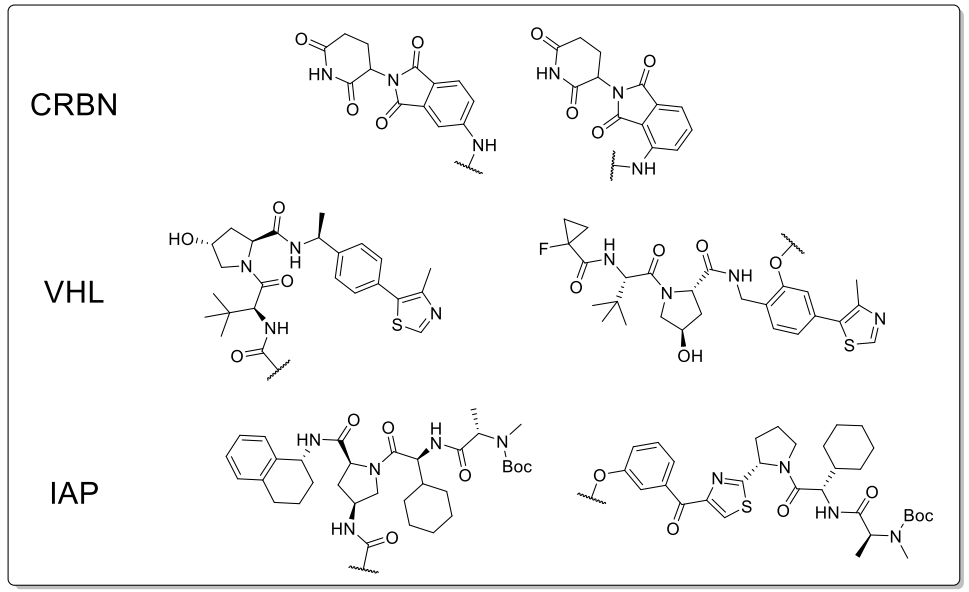
BTK Degrader Screening Approach

BTK binders combined with PEG and alkyl linkers to ligase binders for CRBN, VHL, IAP



BTK Binders

PEG & Alkyl Linkers



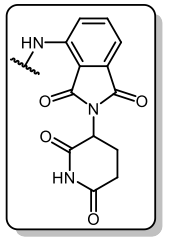
Ligase Binders

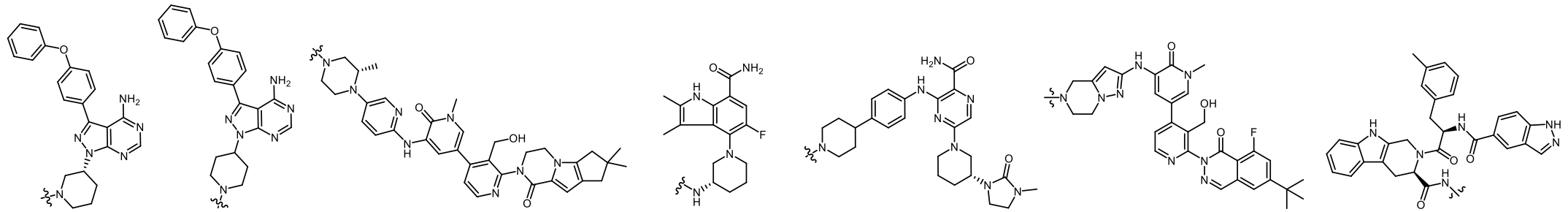
~ 200 Degraders Synthesized and Assayed

Several degraders of BTK identified, CRBN-based degraders demonstrated the best potency

Evaluation of Multiple BTK Binders with Flexible Linkers

A range of potency and linker lengths

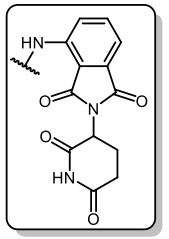


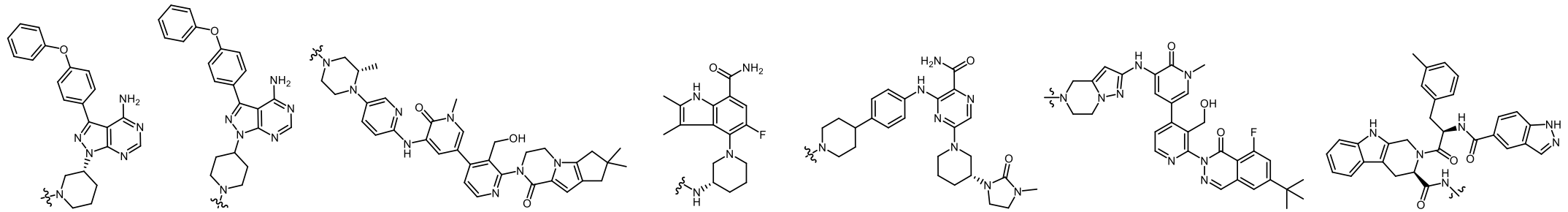


	1	2	3	4	5	6	7
Shortest linker (atoms)	23	19	7	7	7	7	24
MW (g/mol)	1005	934	965	659	850	941	1128
Dmax (%)	91	89	84	<20	86	79	50
DC_{50} (nM)	111	27	2.7	>10,000	7	25	603

Evaluation of Multiple BTK Binders with Flexible Linkers

A range of potency and linker lengths





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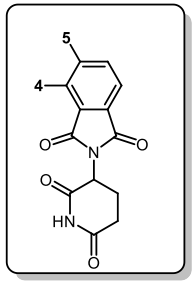
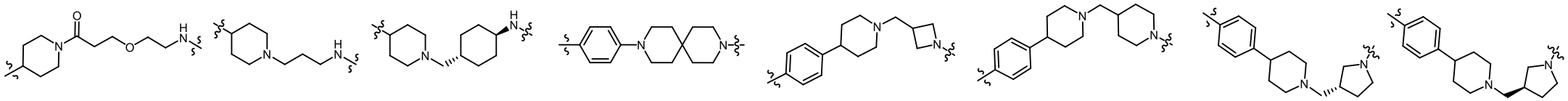
Picomolar Degradation Achieved

Moving from 4- to 5- position allows reduction in H-bond donors





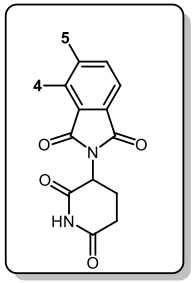
flexible hit

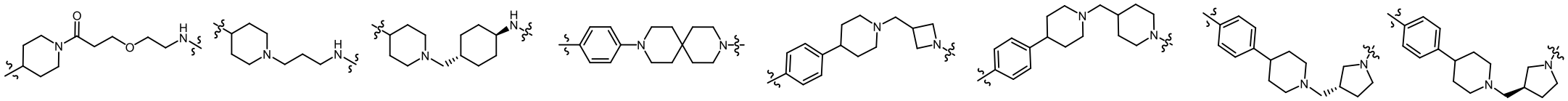
enantiomeric linkers

	1	2	3	4	5	6	7	8
Attachment	4	4	4	5	5	5	5	5
Dmax (%)	86	95	90	96	97	94	97	93
DC_{50} (nM)	7	2.3	1.8	0.9	0.9	0.7	0.4	1.3

Picomolar Degradation Achieved

Moving from 4- to 5- position allows reduction in H-bond donors



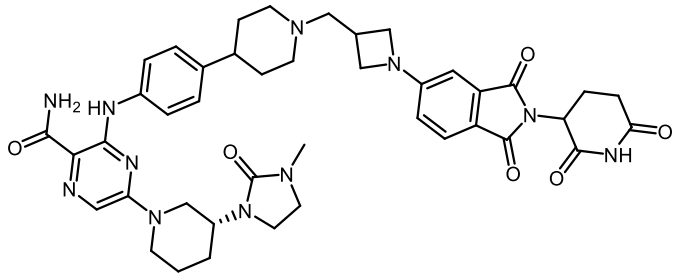


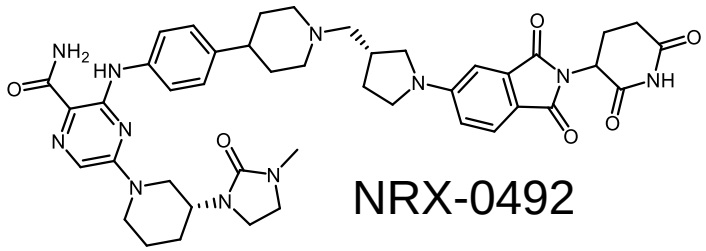
flexible hit *enantiomeric linkers*

	1	2	3	4	5	6	7	8
Attachment	4	4	4	5	5	5	5	5
Dmax (%)	86	95	90	96	97	94	97	93
DC_{50} (nM)	7	2.3	1.8	0.9	0.9	0.7	0.4	1.3

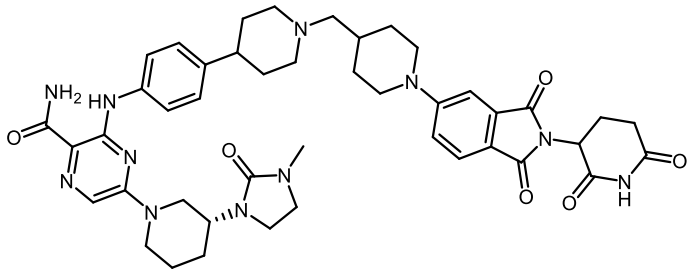
Our most potent compounds differed only in linker ring size

In vivo exposures in BALB/c mice (90 mpk single PO dose)





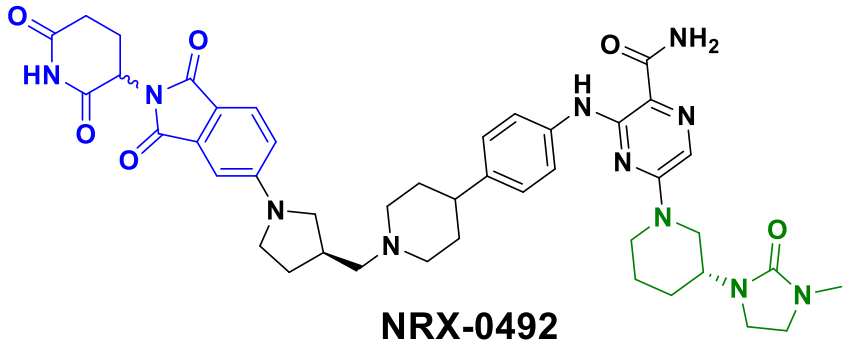
NRX-0492



Ring size	AUC last (uM*hr)	Cmax (uM)	Tmax (hr)	BTK remaining*
4	5.32	1.27	3.3	1.3%
5	8.01	2.22	5.0	4.4%
6	6.36	1.69	5.3	2.4%

Pathways to BTK Degrader Clinical Candidates

Two separate optimization strategies lead to two distinct clinical compounds

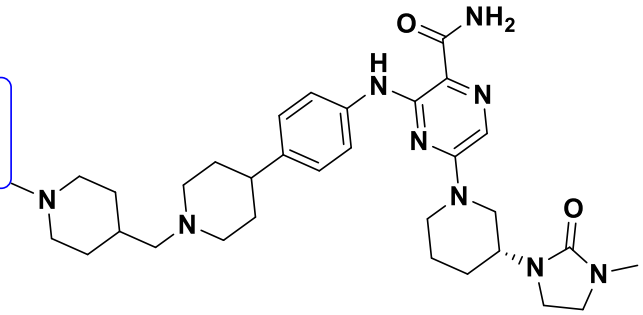


NRX-0492
High RBC : Plasma ratio
Dog =6
Cyno =11

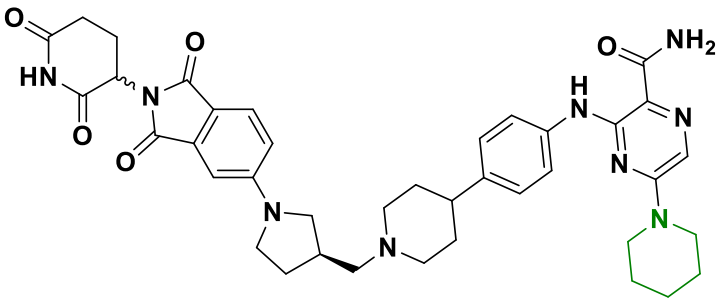
Remove IKZF1/3 degradation

Decrease molecular weight

CRBN Binder Modification



SAR of CRBN binder modifications
Exclusive degradation of BTK

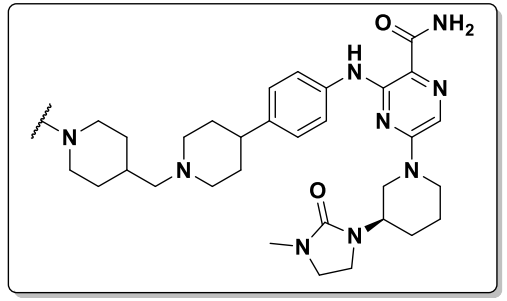


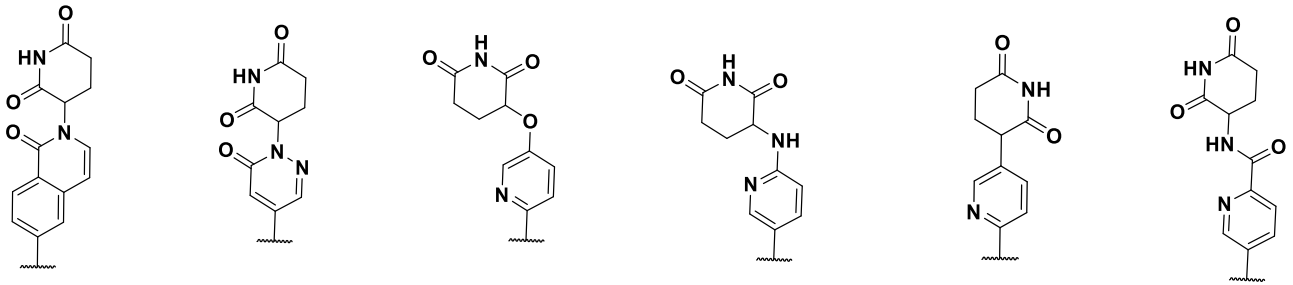
NX-2127

Nurix's First Clinical Candidate
Dual Degradation of BTK and IKZF1/3

CRBN Binder Modifications

Several modifications tolerated

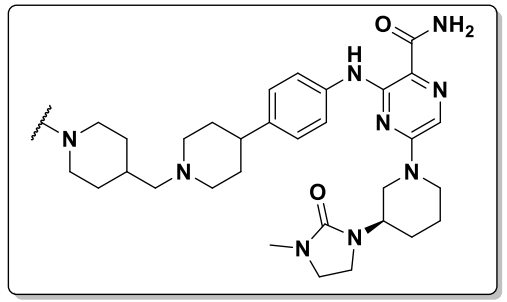


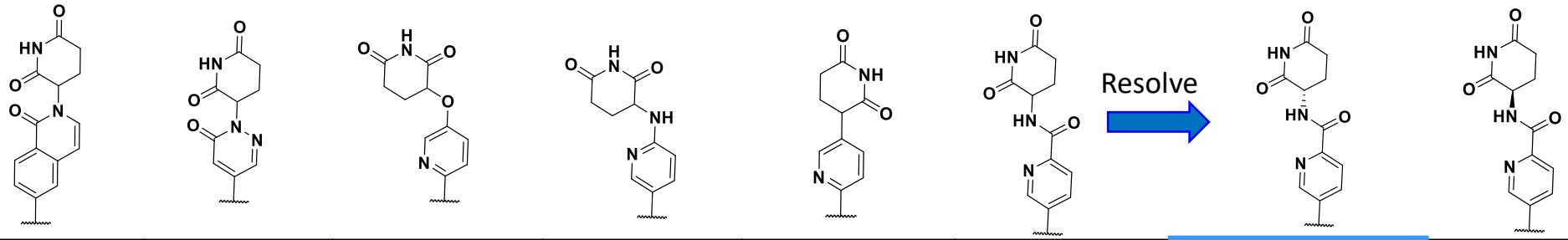


	1	2	3	4	5	6
BTK (DC_{50}, Dmax)	0.4 (98%)	0.9 (97%)	0.9 (96%)	1.1 (94%)	0.6 (99%)	0.5 (98%)
RBC:Plasma ratio Dog, Cyno	1.3, 1.8	--	--	12, 4.9	--	2.5, 1.7
% BTK Remaining 30 mpk PO	20	59	29	19	21	5

CRBN Binder Modifications

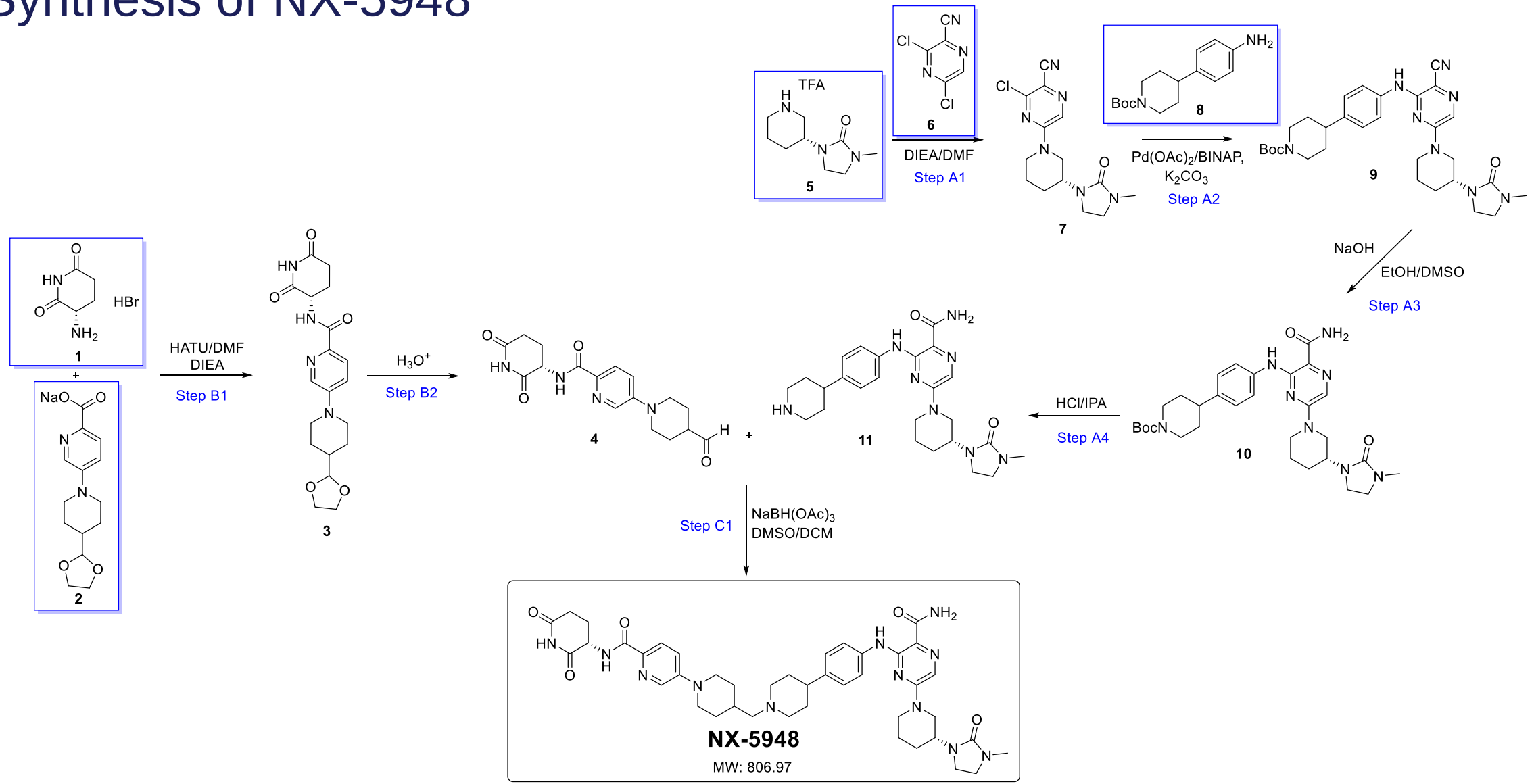
Resolution of enantiomers resulted in NX-5948





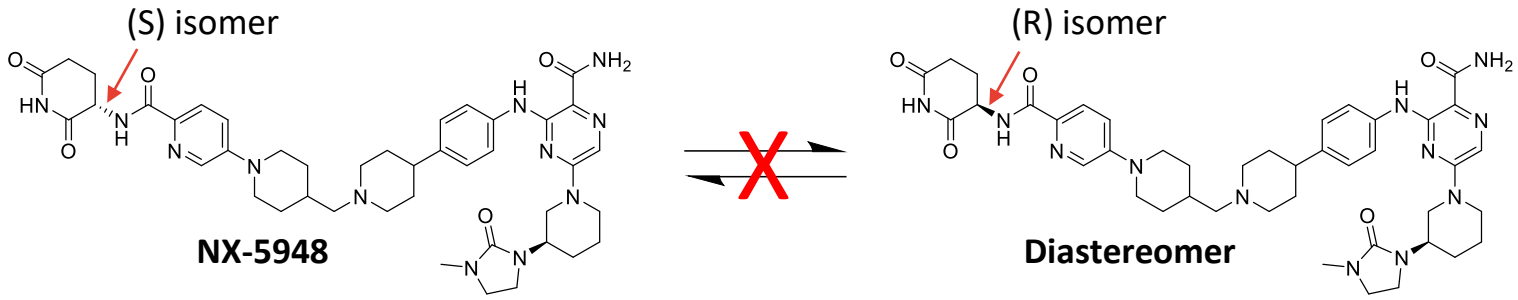
	1	2	3	4	5	6	NX-5948	8
BTK (DC_{50}, Dmax)	0.4 (98%)	0.9 (97%)	0.9 (96%)	1.1 (94%)	0.6 (99%)	0.5 (98%)	0.25 (98%)	3.1 (96%)
RBC:Plasma ratio Dog, Cyno	1.3, 1.8	--	--	12, 4.9	--	2.5, 1.7		
% BTK Remaining 30 mpk PO	20	59	29	19	21	5		

Synthesis of NX-5948



No Significant Racemization of NX-5948 was Observed

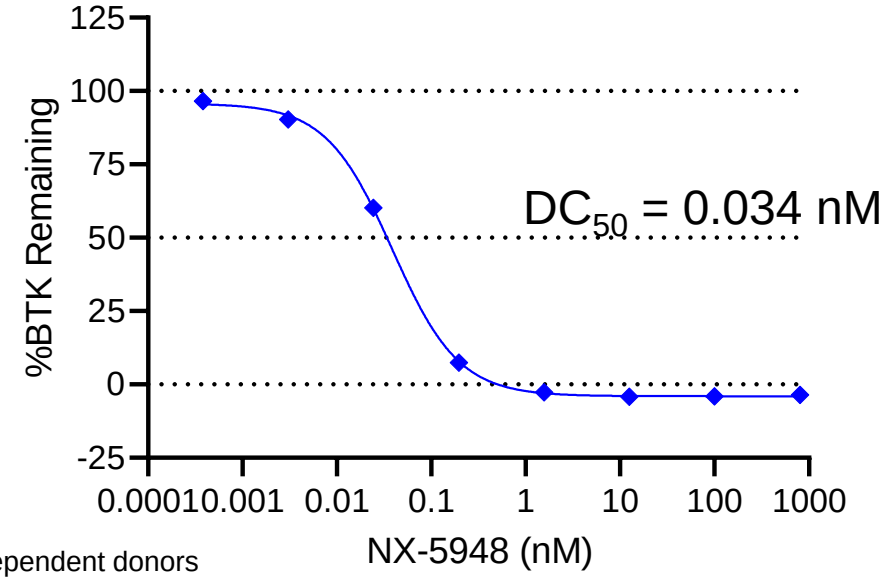
Human and cyno hepatocyte and blood incubations



- Human and cyno hepatocyte and blood incubations were carried out and analyzed using SFC to assess the possible interconversion of NX-5948 to its diastereomer.
- Relative to NX-5948, the diastereomer is < 5% formed when NX-5948 is incubated for 2 hours at 37°C in cyno and human hepatocytes.
- In cyno and human mixed gender whole blood, NX-5948's diastereomer is < 2% formed.

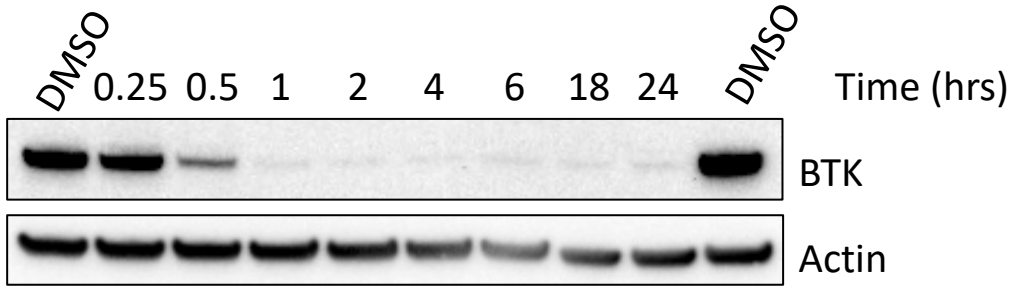
NX-5948 is a Potent and Rapid BTK Degrader

Dose Titration on Primary Human B cells



N=3 independent donors
SEM error bars are smaller than symbols

Degradation Time-Course



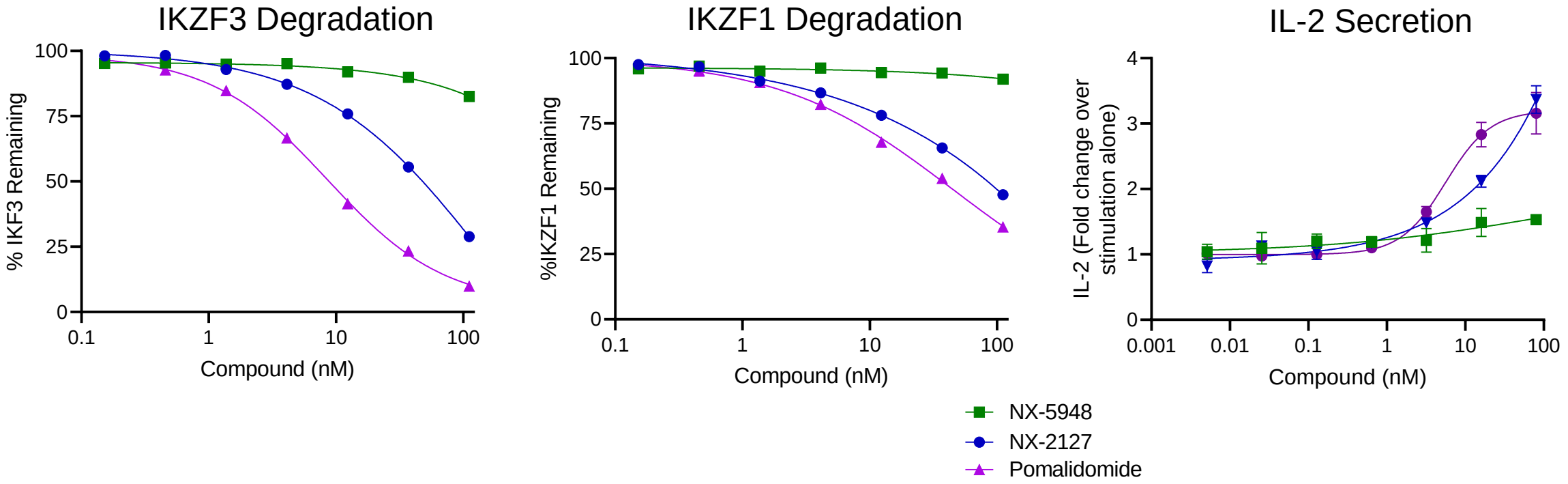
Ramos human Burkitt's lymphoma B cells incubated with 10 nM NX-5948

- Robust BTK degradation observed in primary human B cells after 4 hours of NX-5948 treatment
- BTK degradation is observed within 1 hour and is complete within 2 hours in Ramos cells

No Significant Degradation of IKZF1/3 with NX-5948 at Therapeutically Relevant Concentrations

Unstimulated human T cells

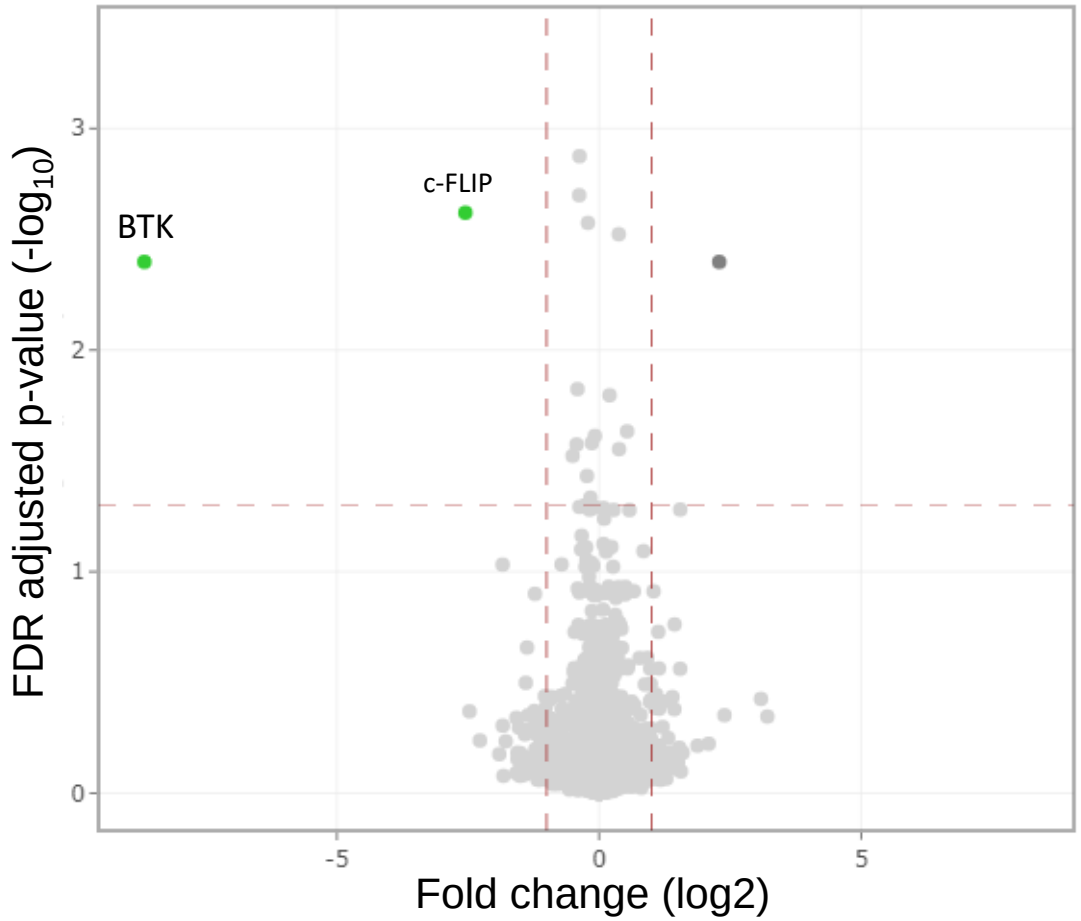
TCR stimulated human T cells



- IKZF1/3 degradation and IL-2 secretion were evaluated for both NX-2127 and NX-5948 using pomalidomide as a control
- NX-5948 showed no significant degradation of IKZF1/3 in primary human T cells and no modulation of IL-2 in TCR stimulated T cells

Proteomics Study Demonstrates NX-5948 is Selective for BTK

Human TMD8 ABC DLBCL cells incubated for 6 h with 50 nM NX-5948

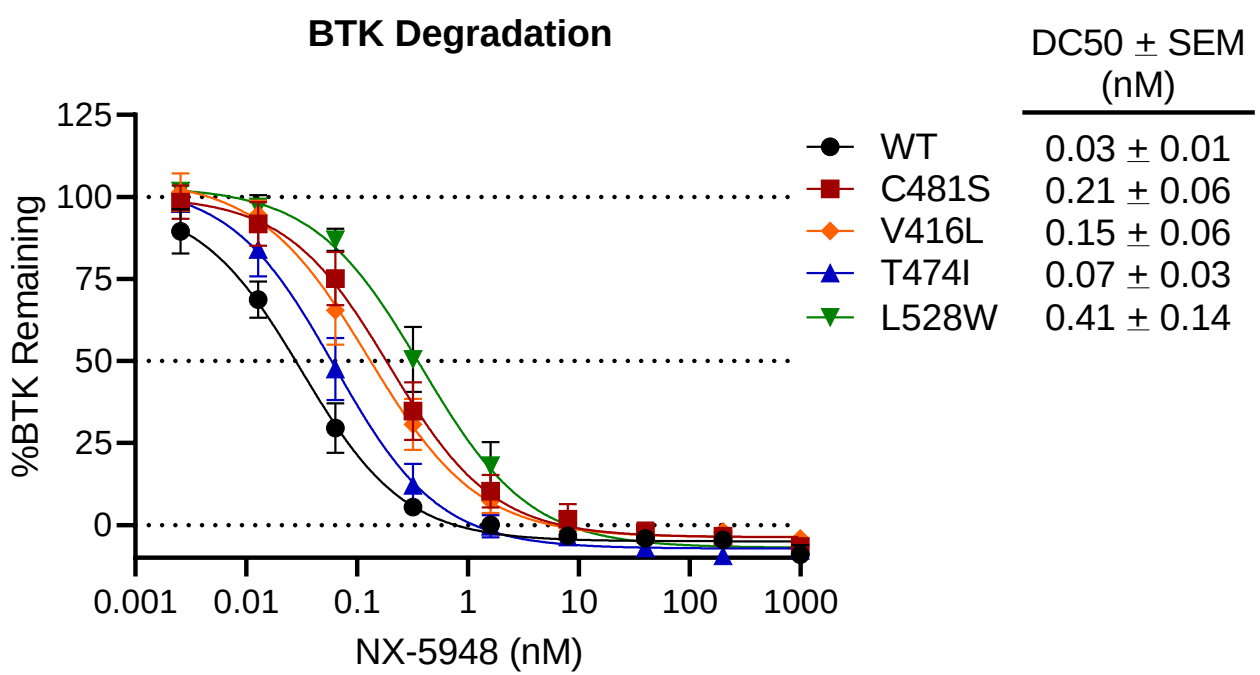


c-FLIP is an anti-apoptotic protein required to maintain survival of ABC DLBCL cells that is regulated by the BCR/NF-κB signaling axis

BTK inhibition by ibrutinib also downregulates c-FLIP in TMD8 cells (*Nurix data and Nagel; Onco Target; 2015*)

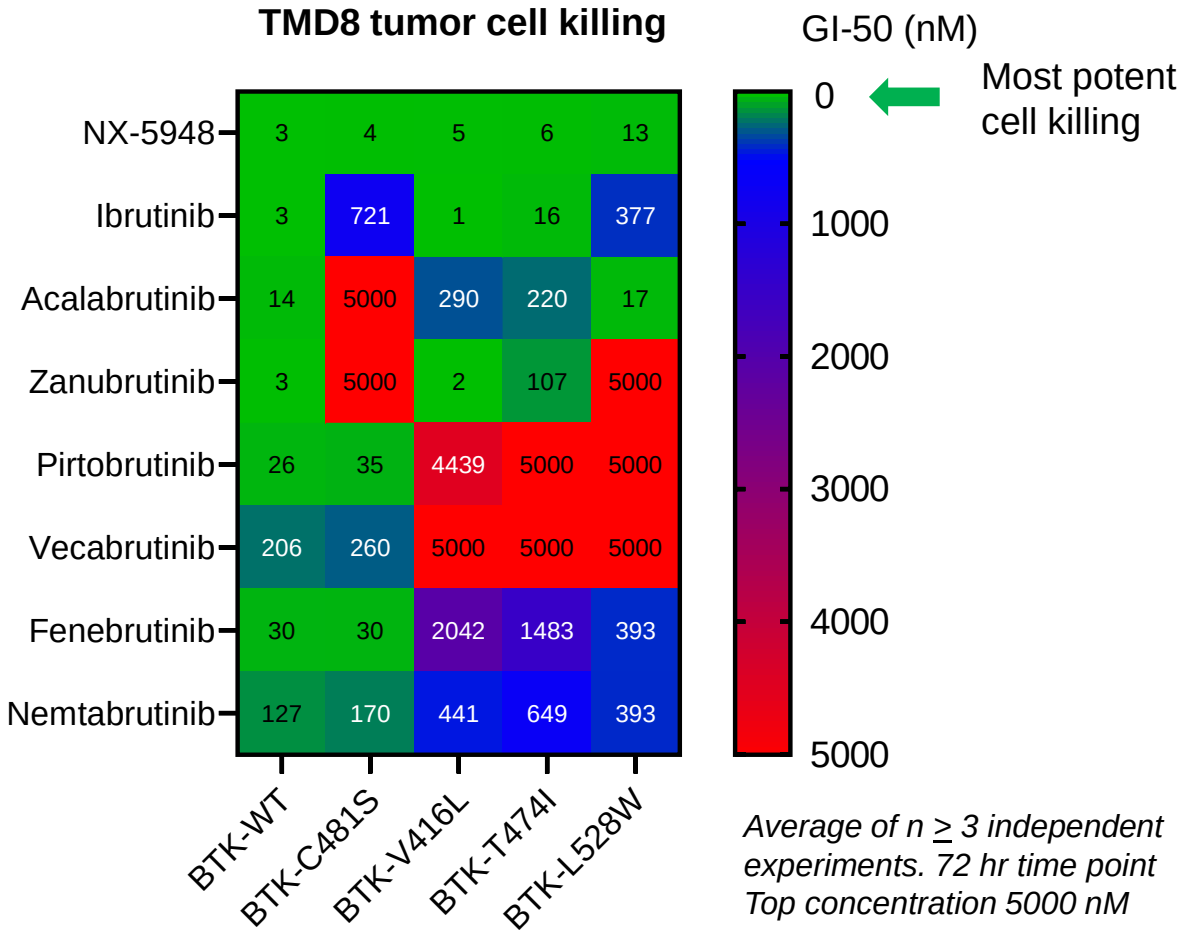
c-FLIP reduction is believed to be a secondary effect of BCR/BTK signaling loss

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



	DC50 ± SEM (nM)
WT	0.03 ± 0.01
C481S	0.21 ± 0.06
V416L	0.15 ± 0.06
T474I	0.07 ± 0.03
L528W	0.41 ± 0.14

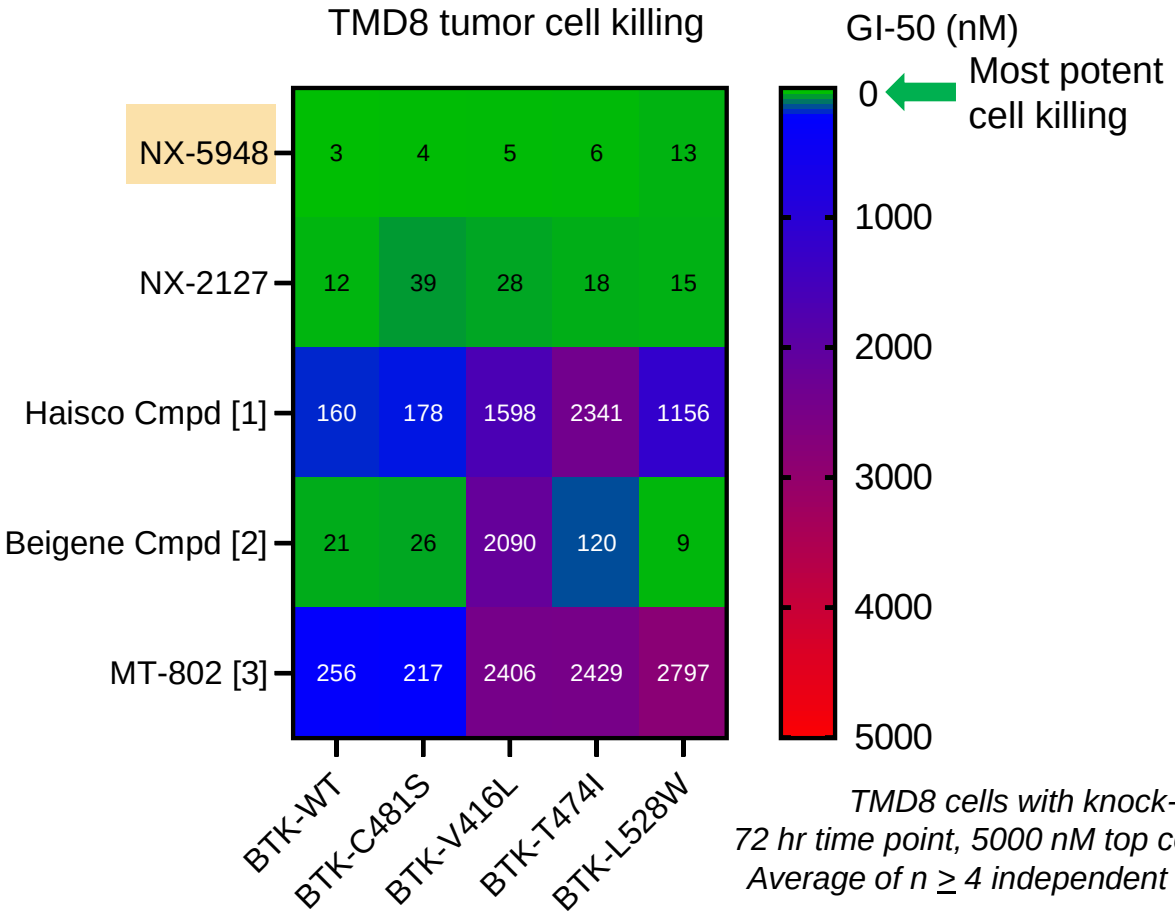
TMD8 cells with CRISPR point mutations
Flow degradation, 24 hr time point
N = 3 independent experiments



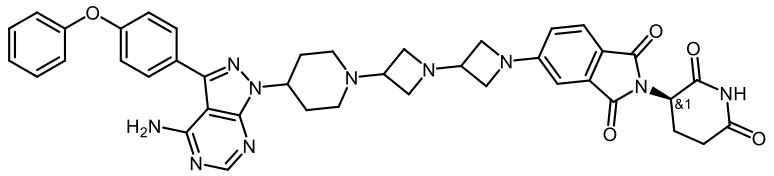
Average of n ≥ 3 independent experiments. 72 hr time point
Top concentration 5000 nM

- All inhibitors have multiple resistance mutation liabilities
- NX-5948 displays potent BTK degradation and cell killing in the context of key resistance mutations

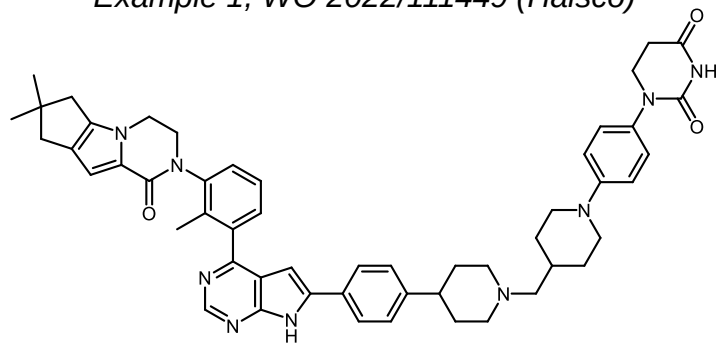
Not All BTK Degraders Are Created Equal



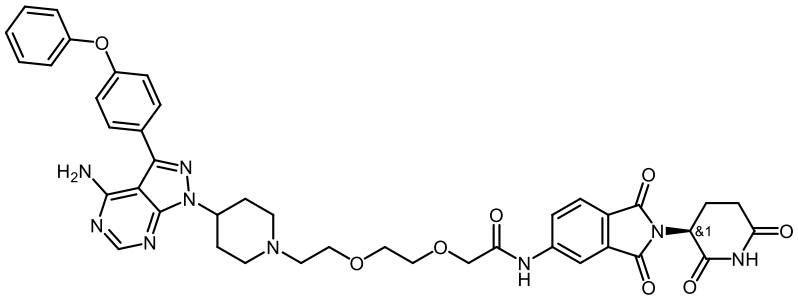
TMD8 cells with knock-in mutations
72 hr time point, 5000 nM top concentration
Average of n ≥ 4 independent experiments



Example 1, WO 2022/111449 (Haisco)



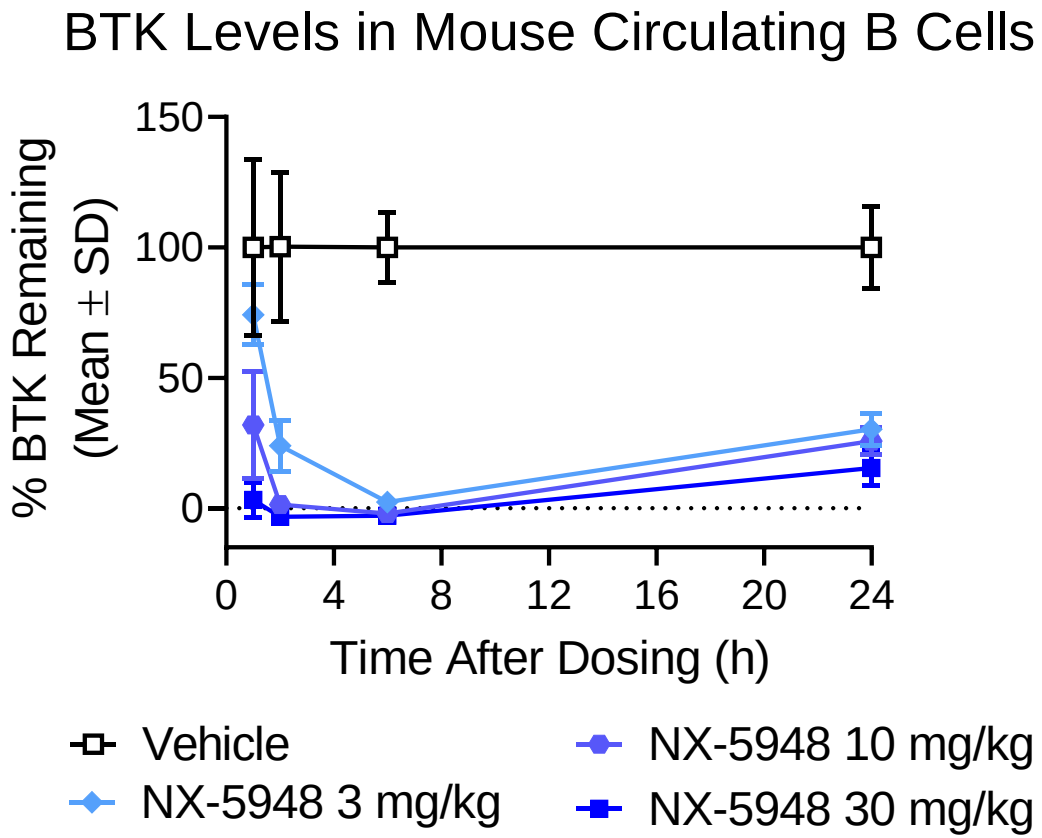
Example 10, WO 2021/219070 (BeiGene)

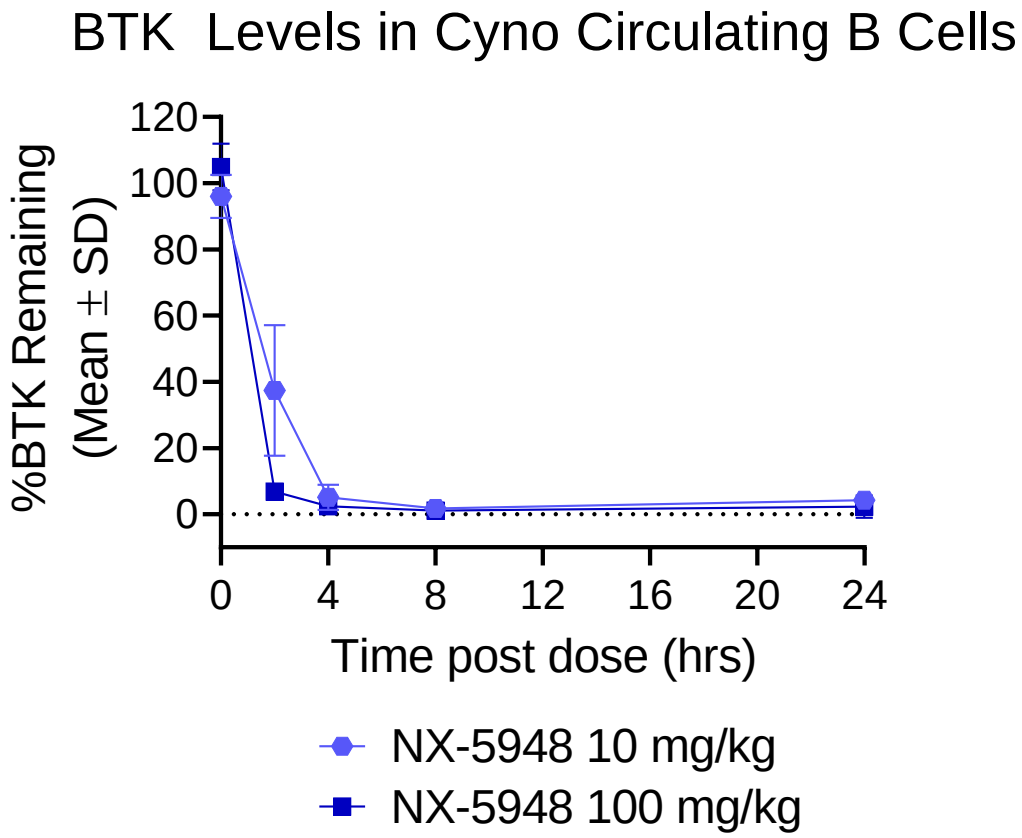


MT-802 Buhimschi et al. 2018. Biochemistry 57(26): 3564-3575.

- The ability of NX-5948 and NX-2127 to induce TMD8 tumor-cell killing was compared to other reported degraders in a 72-hour viability assay

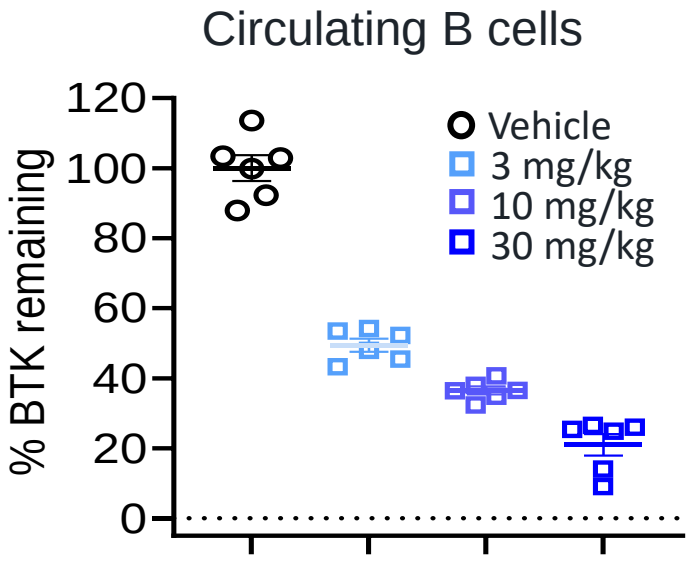
Single Dose of NX-5948 Promotes BTK Degradation in Mouse and Cyno

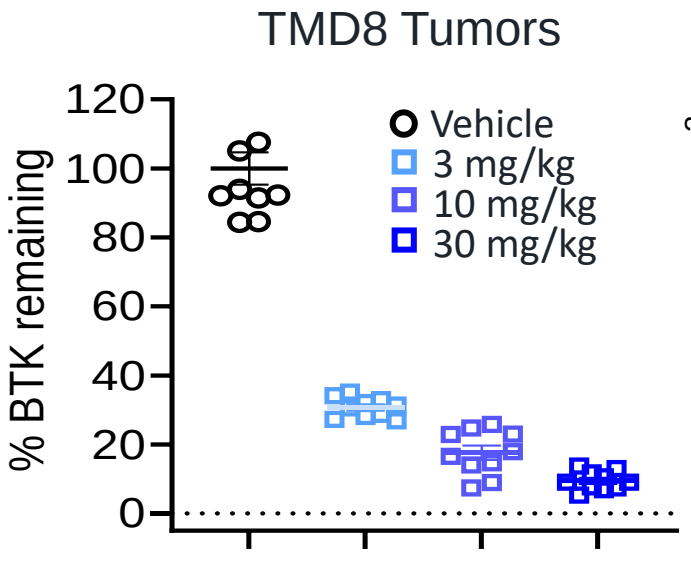


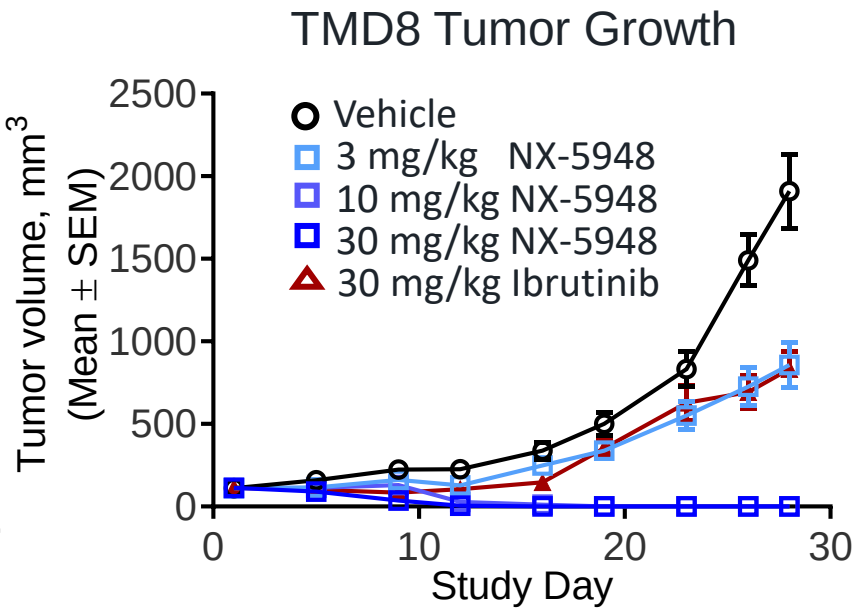


- In mice, BTK levels increased 24 hours after dosing due to BTK resynthesis
- In cynomolgus monkeys, BTK levels remained suppressed at 24 hours

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



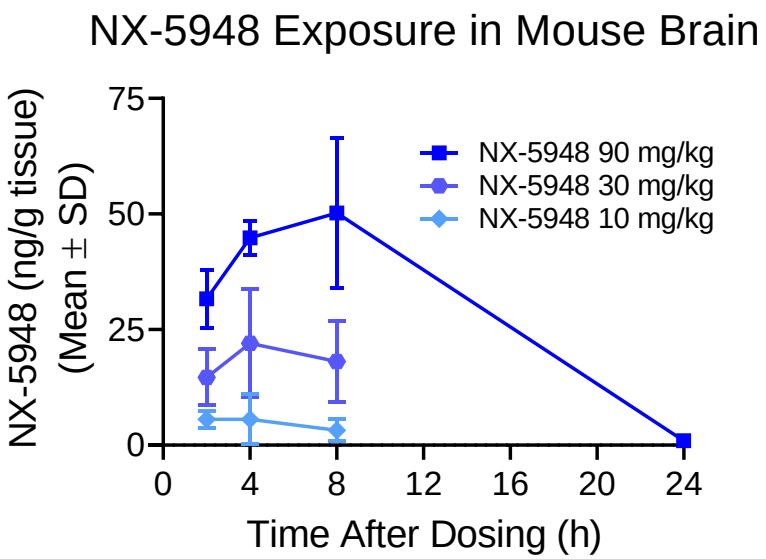


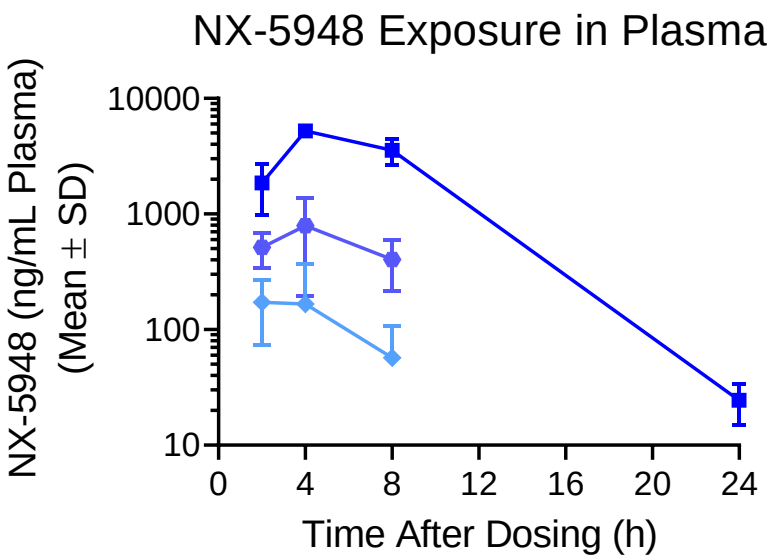


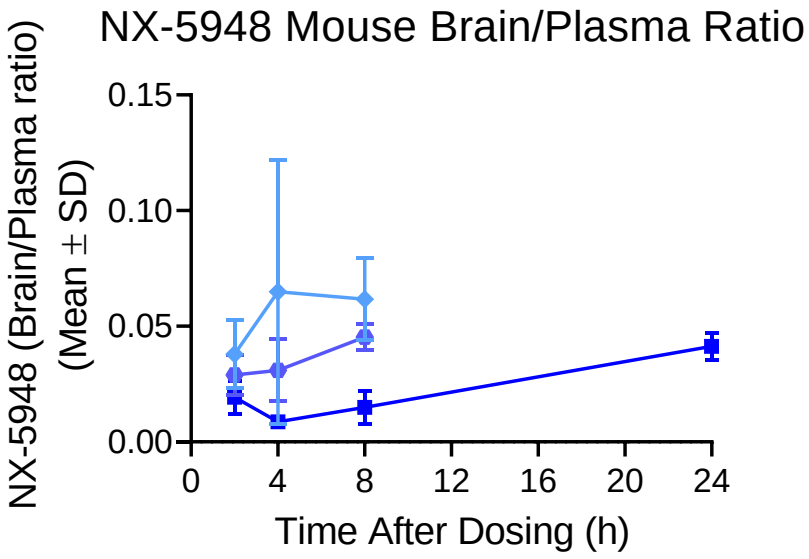
Treatment	Oral gavage dose (mg/kg)	% BTK degradation in circulating B cells	% BTK degradation in TMD8 tumor tissue	% TGI vs Vehicle (Day 26)	*P* value vs Vehicle
Vehicle	0	0.0±3.7	0.0±4.7	N/A	N/A
NX-5948	3	50.5±1.9	69.2±0.9	54%	0.0025
	10	63.5±1.1	82.4±2.1	100%	<0.0001
	30	79.0±3.1	90.5±0.5	100%	<0.0001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

NX-5948 Shows Dose-Dependent CNS Exposure by Oral Dosing

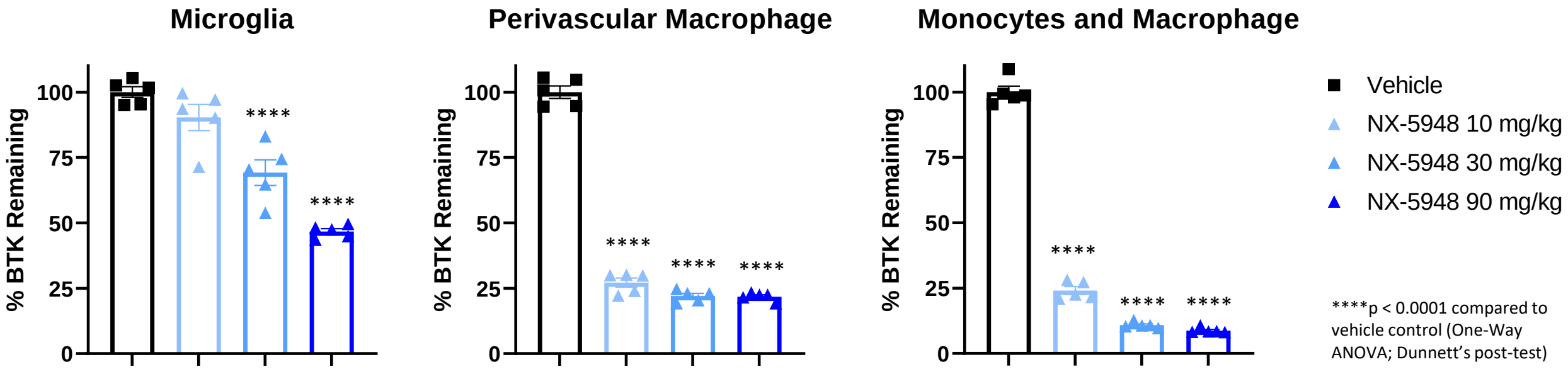






NX-5948 Degrades BTK in Brain Microglia of Naïve Mice

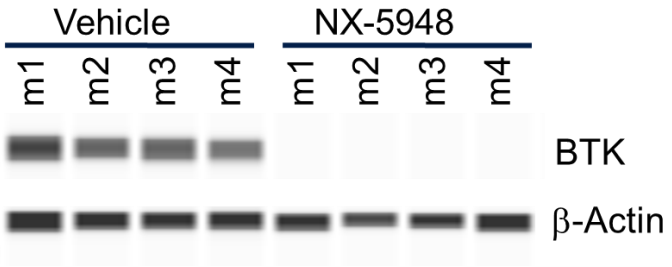
NX-5948 administered orally QD x 3 days to naïve C57BL/6J mice.
BTK levels assessed 8 h after 3rd dose by flow cytometry.

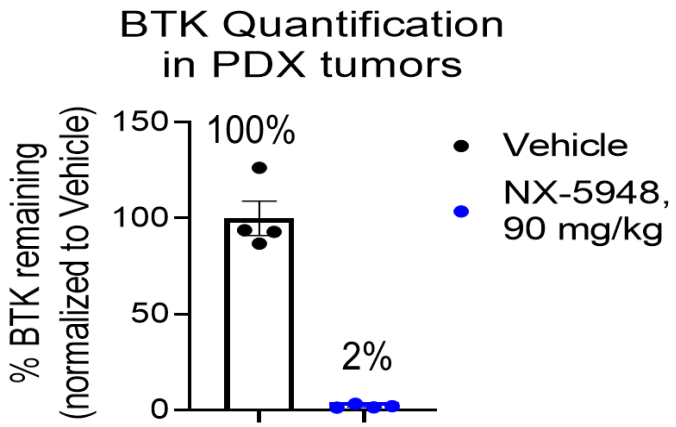


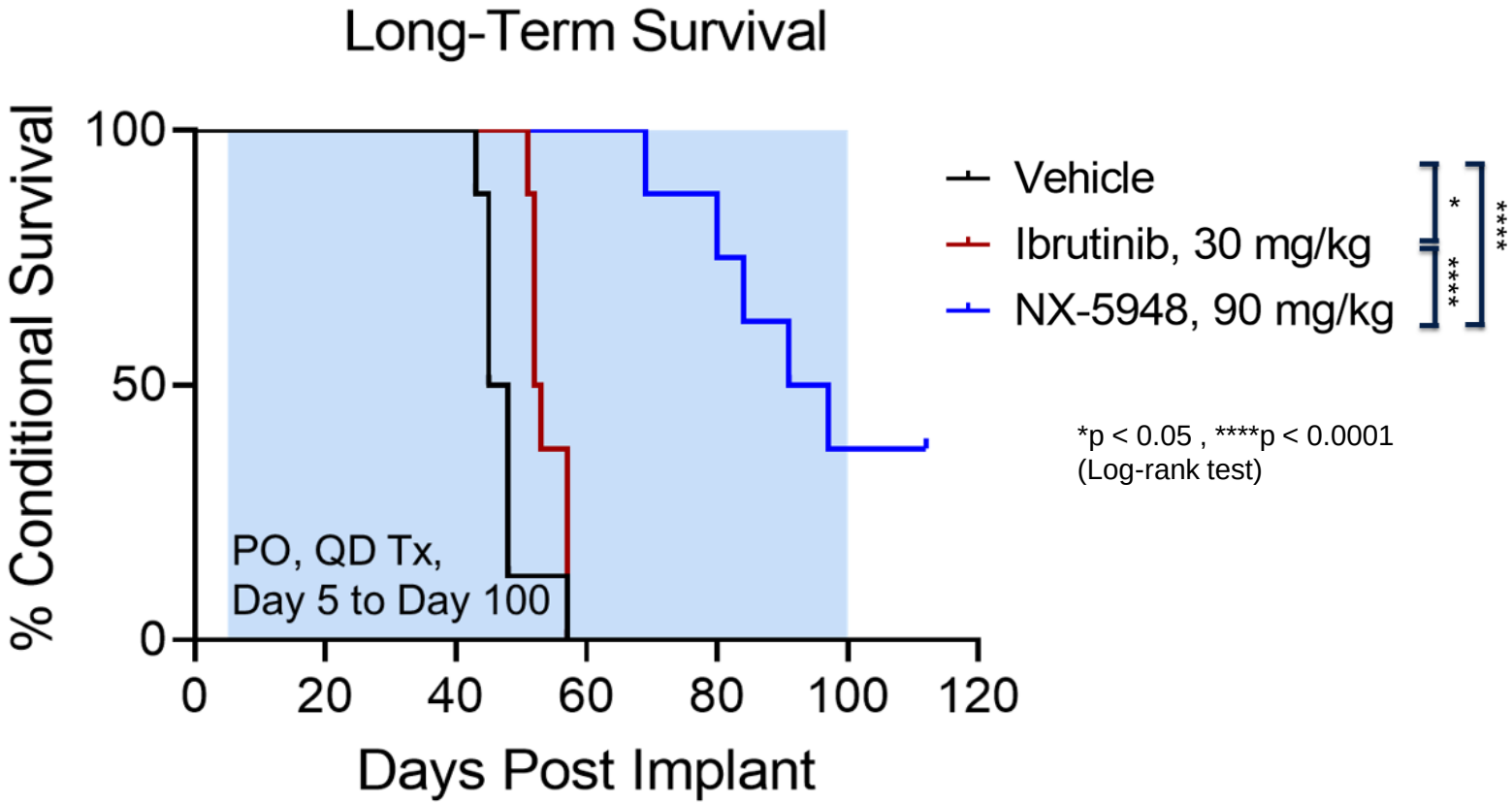
- NX-5948 drives dose-dependent BTK degradation in cells isolated from brains
- Magnitude of BTK degradation depends on dose and cell type

Daily Oral Administration of NX-5948 to Mice Implanted with SC1 DLBCL PDX Cells in Parenchyma Drives Potent BTK Degradation and Prolongs Survival

SC1 DLBCL cells implanted by intracranial injection
90 mg/kg NX-5948 administered orally QD from days 5-100 (right)
BTK levels assessed 6 h after 3 days of daily dosing by western blot (left)



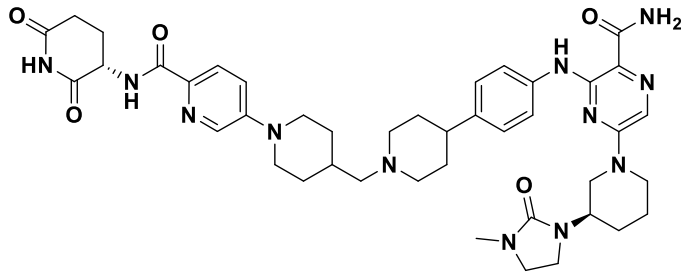




*p < 0.05 , ****p < 0.0001
(Log-rank test)

In collaboration with Rubenstein lab, UCSF

NX-5948 Cellular Potency and Cross-species PK



	Degradation Results
BTK DC_{50} (Dmax): WT/C481S TMD8 cells @4h	0.32 nM (97%) / 0.21 nM (97%)
BTK DC_{50} Primary human B Cells	0.034 nM (98%)

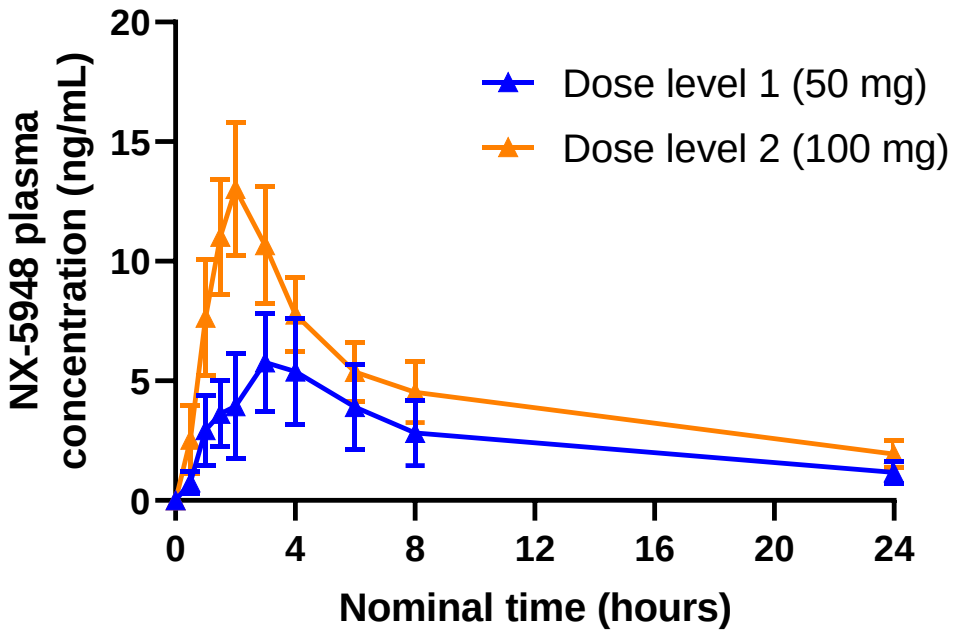
	Mouse	Rat	Dog	Cynomolgus Monkey
Cl_{obs} (mL/min/kg), 1 mpk IV bolus	6	31	68	39
AUC (hr*µM), 10 mpk PO	4.6	1.3	0.3*	0.18
C_{max} (µM), 10 mpk PO	0.891	0.098	0.014*	0.014
$V_{ss,obs}$ (L/kg), 1 mpk IV	1.18	8.0	44.3	19.2
F (%)	7-25	16	9	2
In Vitro Plasma Protein Binding (%)	99.6	98.4	97.6	92 (97.1 humans)

* normalized from 5 mg/kg PO dose

- No issues with *in vitro* ADME, *in vitro* tox assays were clean
- DRF and 28-day in rats/NHP supported advancement to clinic

Preliminary Data Suggest that NX-5948 Exhibits Dose Proportional Pharmacokinetics

Mean (± SEM) Cycle 1 Day 1 pharmacokinetic profile of patients treated with NX-5948



Data cutoff: December 1, 2022

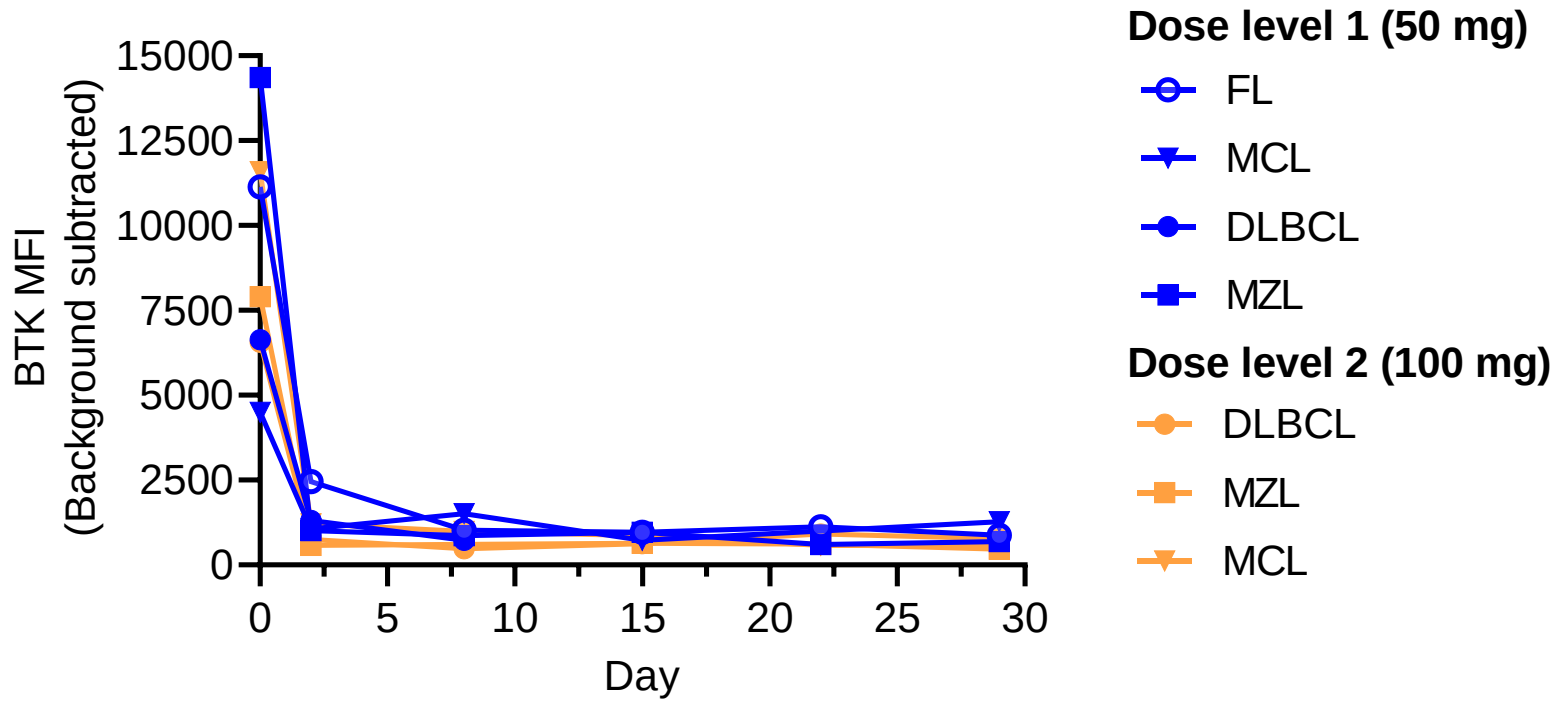
	Cycle 1, Day 1			
Dose	C_{max} (ng/mL)	$AUC_{0–last}$ (h*ng/mL)	T_{max} (hours)	$t_{1/2}$ * (hours)
50 mg n=4	4.52 (102)	42.1 (152)	3.0	12.8 (19.9)
100 mg n=3	12.3 (45.3)	99.6 (50.2)	2.0	12.4 (9.39)

C_{max} and $AUC_{0\text{-last}}$ are presented as geometric mean (geometric %CV); T_{max} is presented as median; $t_{1/2}$ is presented as mean (%CV); *AUC extrapolation >20%

- The half life of ~12.6 hours supports once daily dosing.
- The T_{max} of 2–3 hours suggests fast absorption.
- Exposures (both AUC and C_{max}) increase linearly with dose.

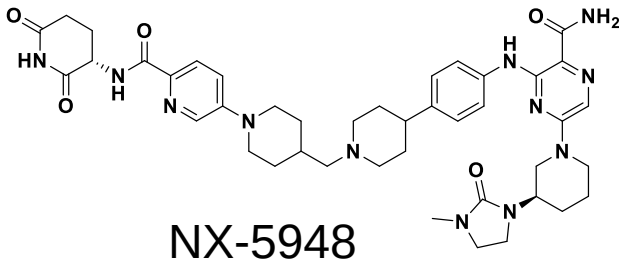
NX-5948 Resulted in Rapid, Robust and Sustained BTK Degradation in all Patients Dosed

- NX-5948 induced sustained BTK degradation of 89±4% at Cycle 2 Day 1 across dose levels



FL (follicular lymphoma), DLBCL (diffuse large B cell lymphoma), MCL (mantle cell lymphoma), MZL (marginal zone lymphoma)

Summary



NX-5948

- NX-5948 is a highly potent, CNS penetrant, targeted protein degrader of BTK in Phase 1 clinical development for B cell malignancies
- NX-5948 displayed potent BTK degradation and cell killing in the context of clinically relevant resistance mutations and was superior to other BTK inhibitors and degraders tested
- Oral administration of NX-5948 demonstrated superior tumor growth inhibition and prolonged survival in mouse models of CNS lymphoma
- NX-5948 exhibits predictable human PK and leads to rapid, robust and sustained BTK degradation when dosed once daily
- NX-5948 preclinical data supports further exploration of NX-5948 to treat B cell malignancies

Thank you!