



Leader in Targeted Protein Modulation

Discovery of Orally Active, Brain-Penetrant, Targeted Protein Degraders

5th Annual TPD Summit

Boston, MA

October 26th, 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)

Harness ligases
to decrease
specific protein levels


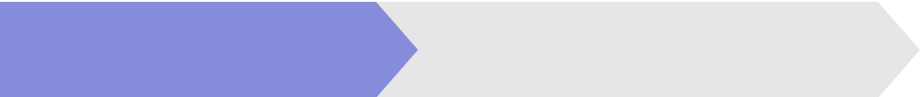



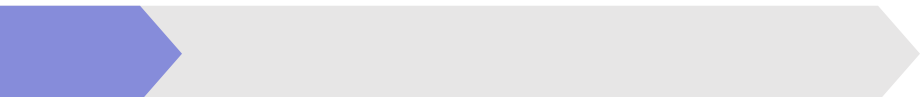



Inhibit ligases
to increase
specific protein levels

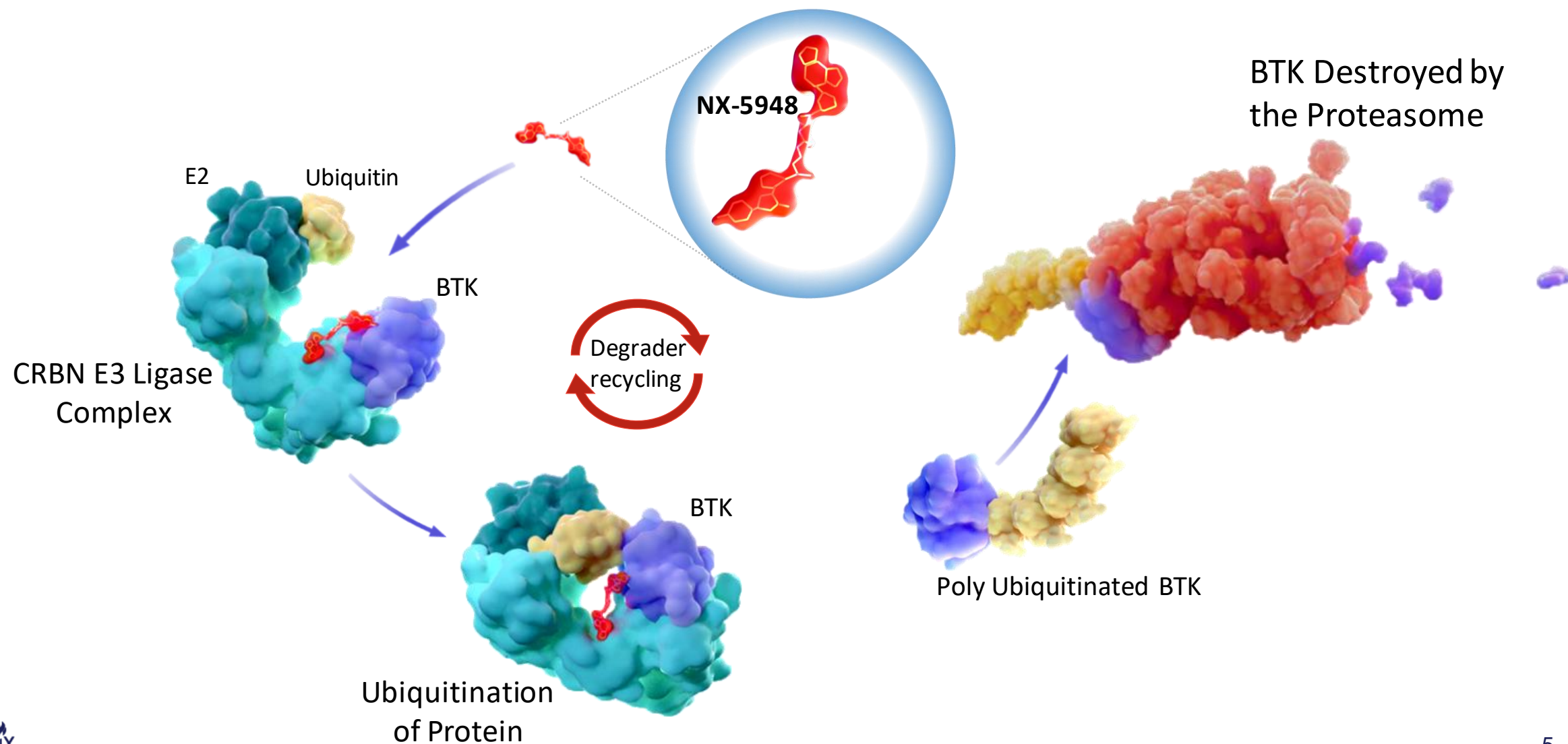
Targeted Protein
Degradation
(TPD)

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

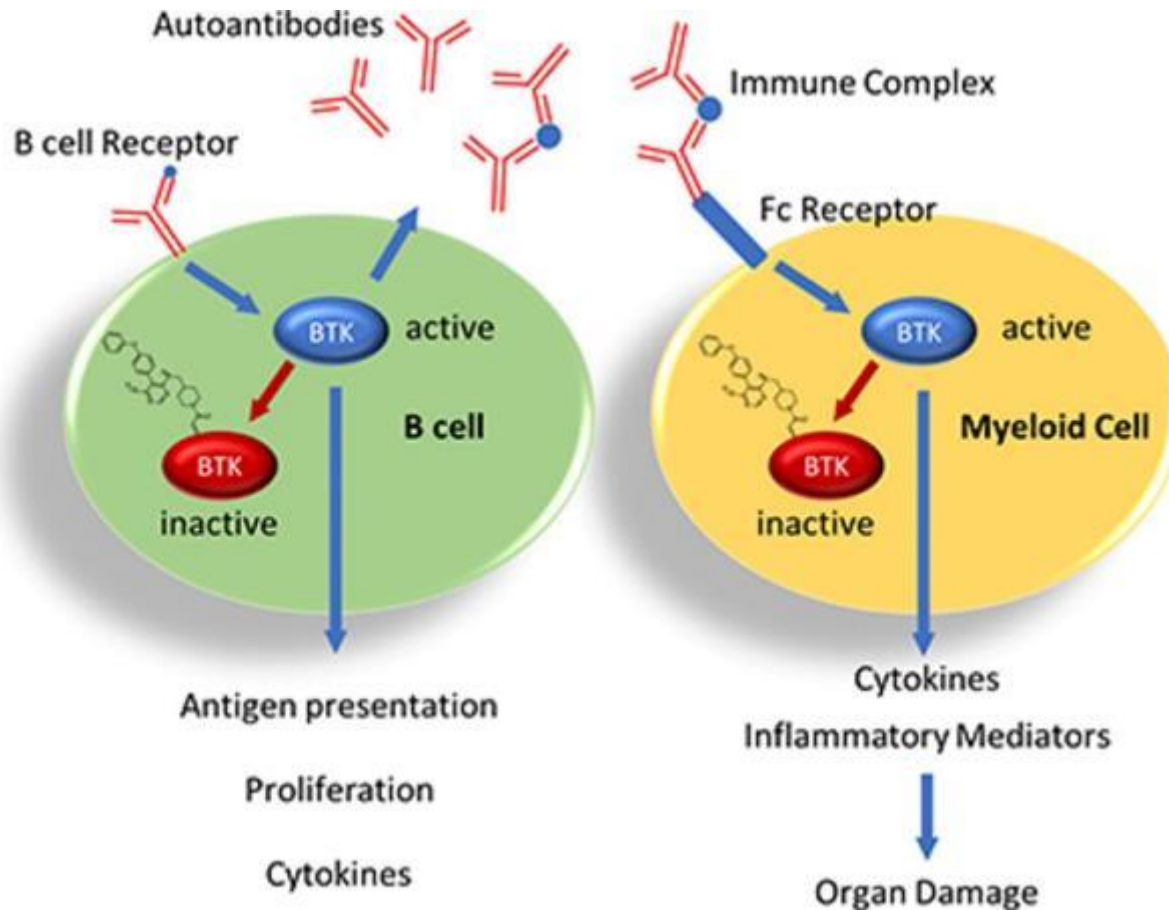
Nurix Is Advancing Four Wholly Owned Clinical Programs with a Deep Pipeline of Proprietary and Partnered Novel Targets

MOA	Drug Program	Target/ Delivery	Therapeutic Area	Pre-Clinical	Phase 1	Phase 2	Phase 3
TPD	NX-2127 Degradar	BTK-IKZF <i>Oral</i>	B-Cell Malignancies				
	NX-5948 Degradar	BTK <i>Oral</i>	B-Cell Malignancies				
TPE	NX-1607 Inhibitor	CBL-B <i>Oral</i>	Immuno-Oncology				
	DeTIL-0255 Cell Therapy	Adoptive Cell Therapy <i>Ex vivo CBL-B Inhibition</i>	Gynecologic Malignancies				
TPM	Wholly owned	5 targets	Multiple				
TPD	Gilead Sciences	5 targets	Multiple				
TPD	Sanofi	5 targets	Multiple				

NX-5948 Promotes Proteasomal Degradation of BTK



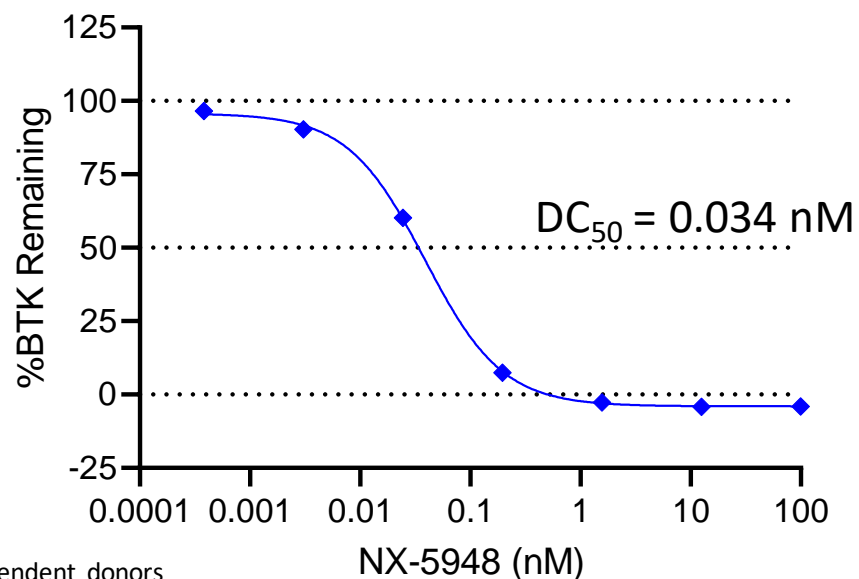
BTK Regulates Signaling Pathways that Contribute to B Cell Malignancies and Autoimmunity



- 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
- BTK degraders that cross the blood brain barrier (BBB) may have therapeutic advantage in CNS lymphoma or autoimmune diseases such as MS

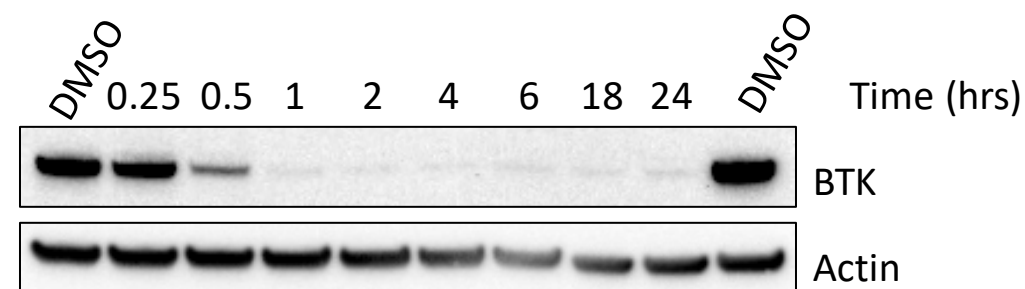
NX-5948 is a Potent and Rapid BTK Degradator

Dose Titration on Primary Human B cells



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

Degradation Time-Course

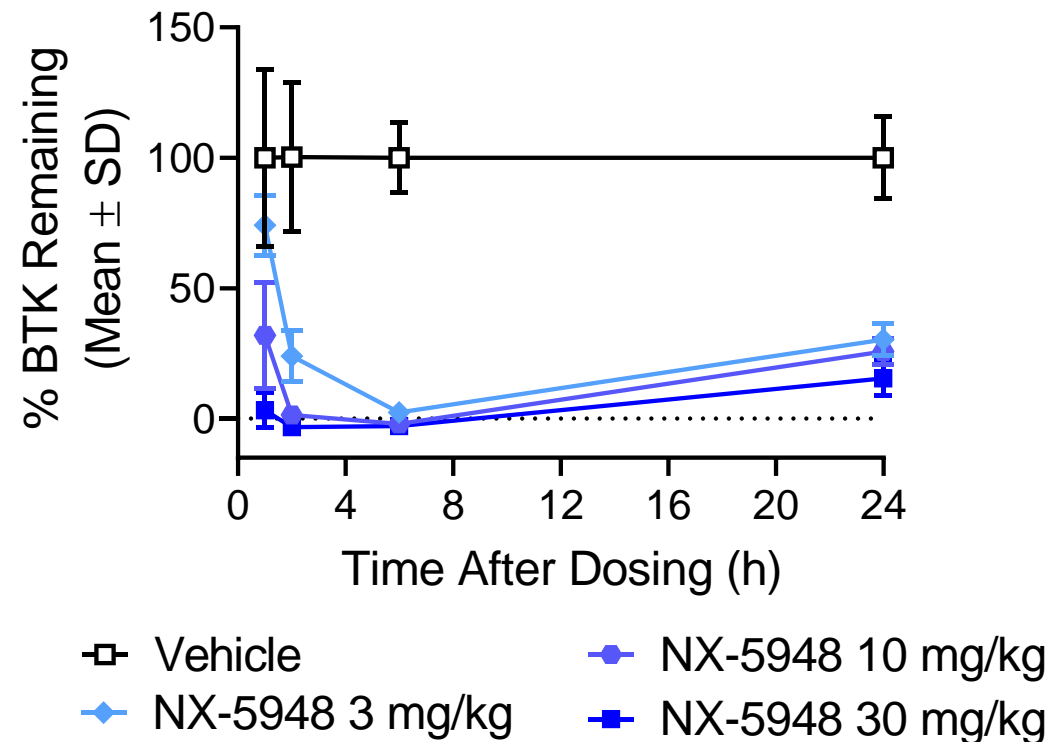


Ramos human Burkitt's lymphoma B cells
incubated with 10 nM NX-5948

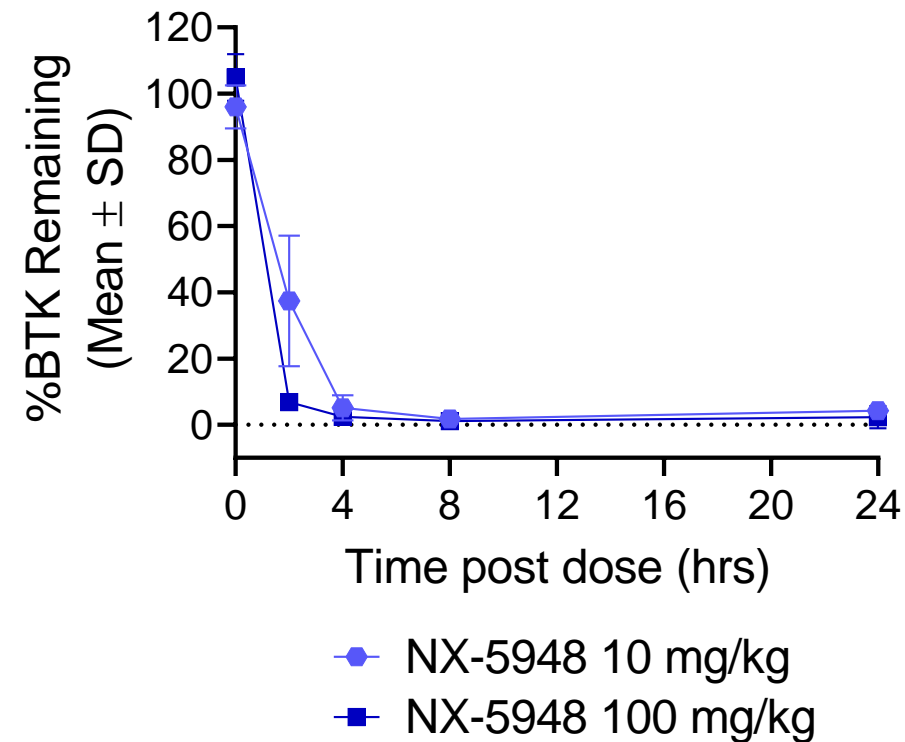
- Robust BTK degradation observed in primary human B cells after 4 hours of NX-5948 treatment
- BTK degradation is observed within 1 hour and is complete within 2 hours in Ramos cells

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

BTK Levels in Mouse Circulating B Cells

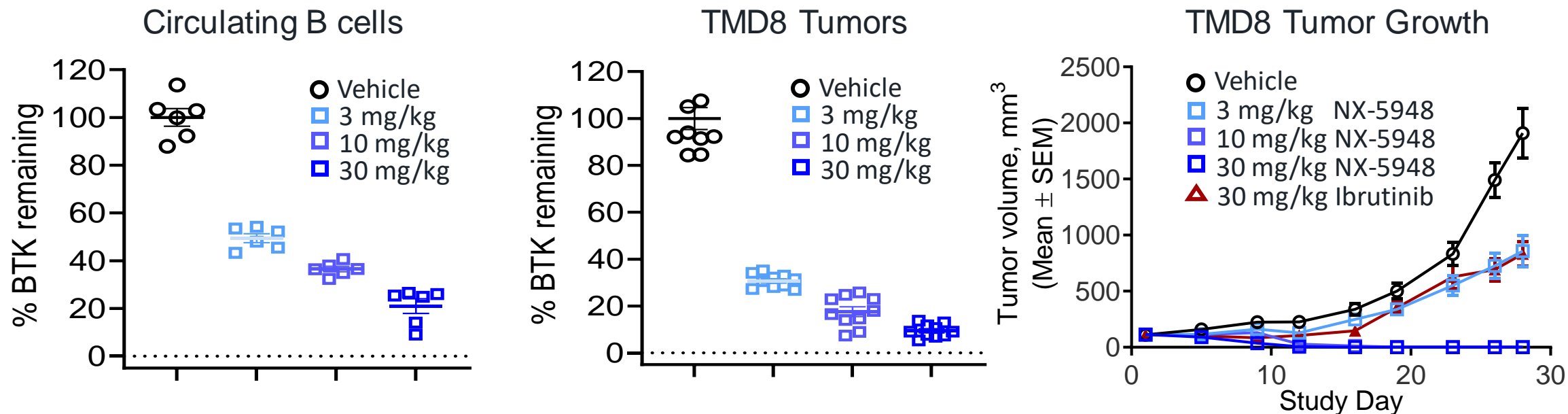


BTK Levels in Cyno Circulating B Cells



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

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



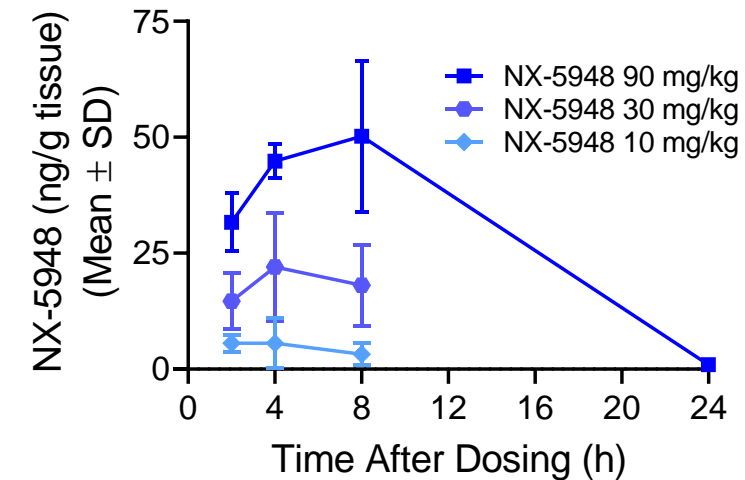
Treatment	Oral gavage dose (mg/kg)	% BTK degradation in circulating B cells	% BTK degradation in TMD8 tumor tissue	% TGI vs Vehicle (Day 26)	P value vs Vehicle
Vehicle	0	0.0±3.7	0.0±4.7	N/A	N/A
NX-5948	3	50.5±1.9	69.2±0.9	54%	0.0025
	10	63.5±1.1	82.4±2.1	100%	<0.0001
	30	79.0±3.1	90.5±0.5	100%	<0.0001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

N/A: Not applicable; TGI: tumor growth inhibition.

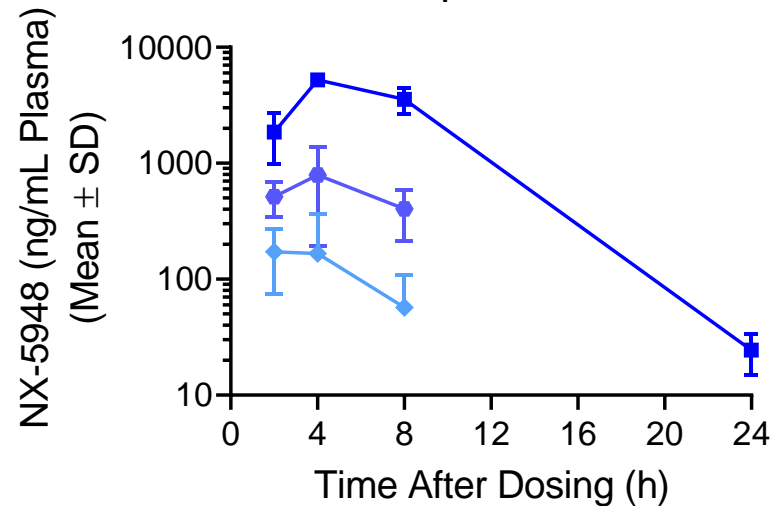
P values determined on tumor volume by mixed-effect analysis with Dunnett's multiple comparisons test

A Single Oral Dose of NX-5948 to Mice Results in Dose-Dependent CNS Exposure

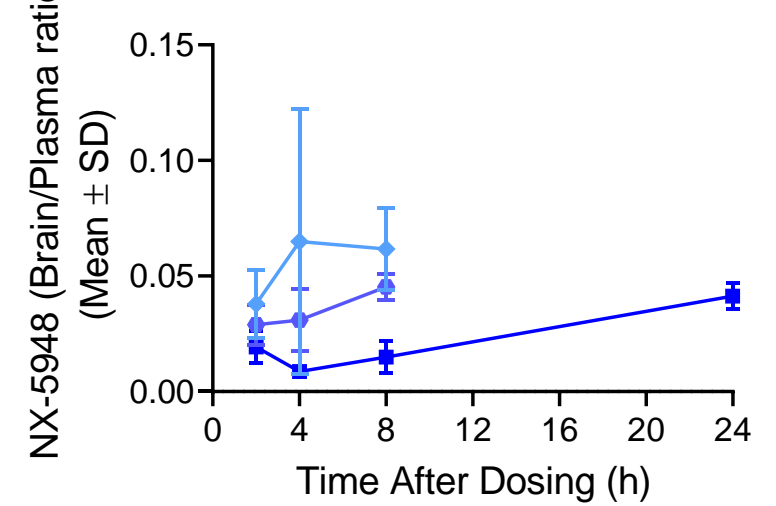
NX-5948 Exposure in Mouse Brain



NX-5948 Exposure in Plasma

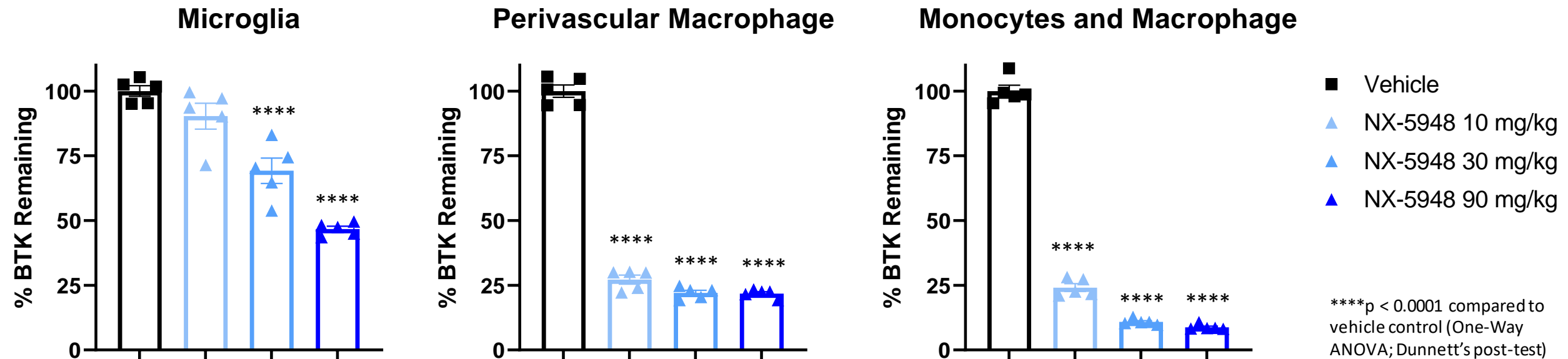


NX-5948 Mouse Brain/Plasma Ratio



NX-5948 Degrades BTK in Microglia and Macrophage in Brains 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.

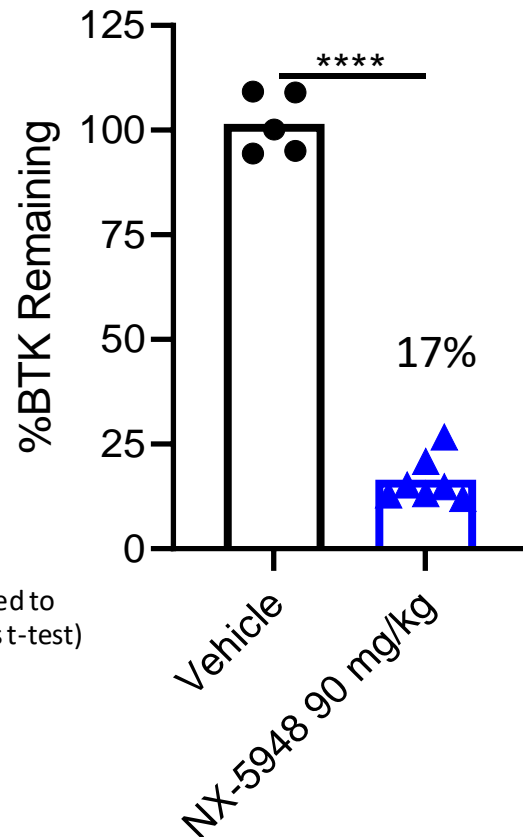


- NX-5948 drives dose-dependent BTK degradation in cells isolated from brains
- Magnitude of BTK degradation depends on dose and cell type

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

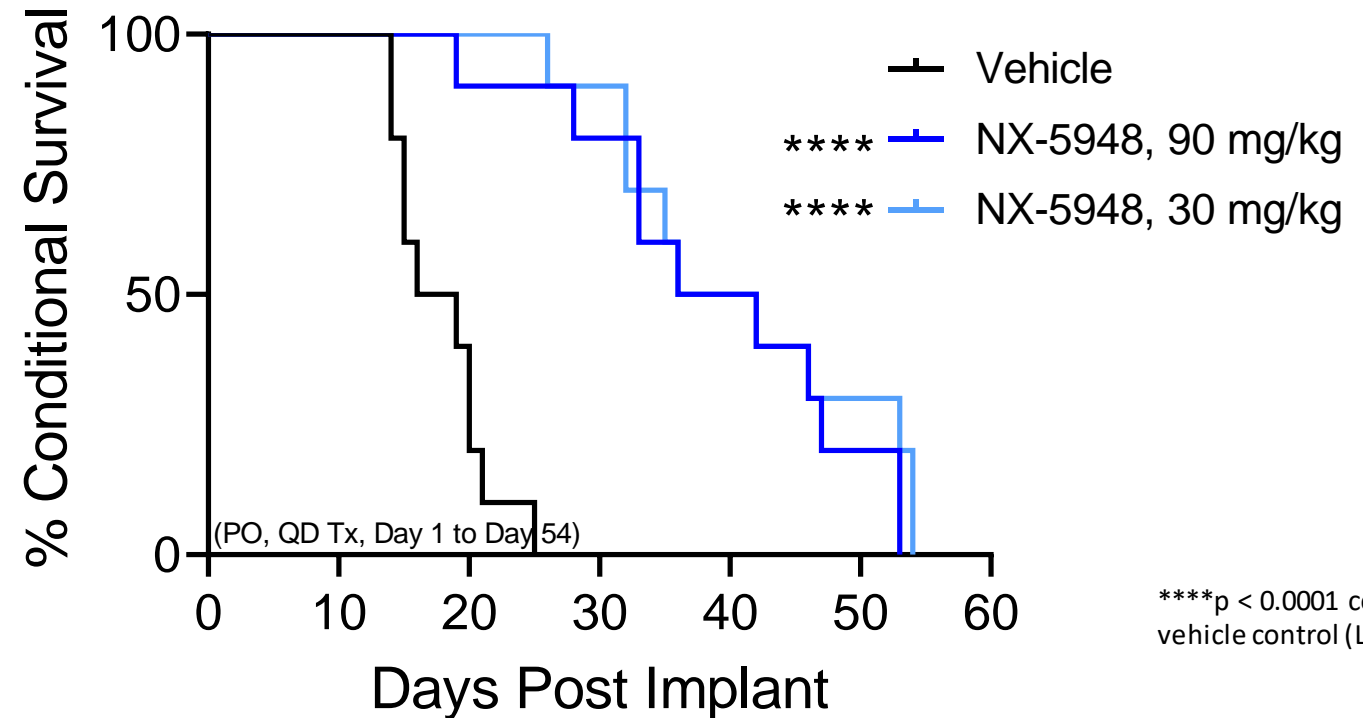
5 x 10⁵ TMD8 cells implanted by intracranial injection on Day 0
NX-5948 administered orally QD Days 1-11 (left) or Days 1-54 (right)
BTK levels assessed 24 h after the 11th dose by flow cytometry

BTK Levels In TMD8



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

Long-Term Survival

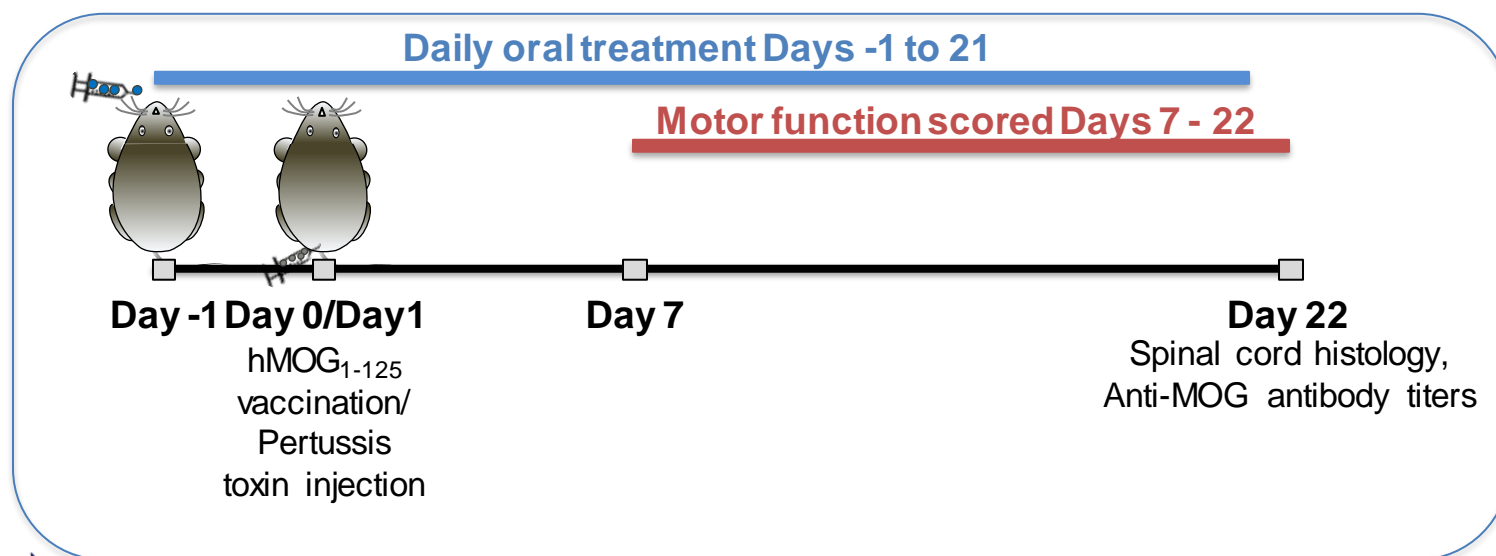


****p < 0.0001 compared to vehicle control (Log-rank test)

Comparison of NX-5948 to Ibrutinib in Antibody-Dependent EAE model

Group	N	Treatment	Dose (mpk)	Regimen
1	12	Vehicle	N/A	N/A
2	12	FTY720	3	Oral, QD, Days -1 to 22
3	12	Ibrutinib	10	
4	12	Ibrutinib	30	
5	12	NX-5948	10	
6	12	NX-5948	30	

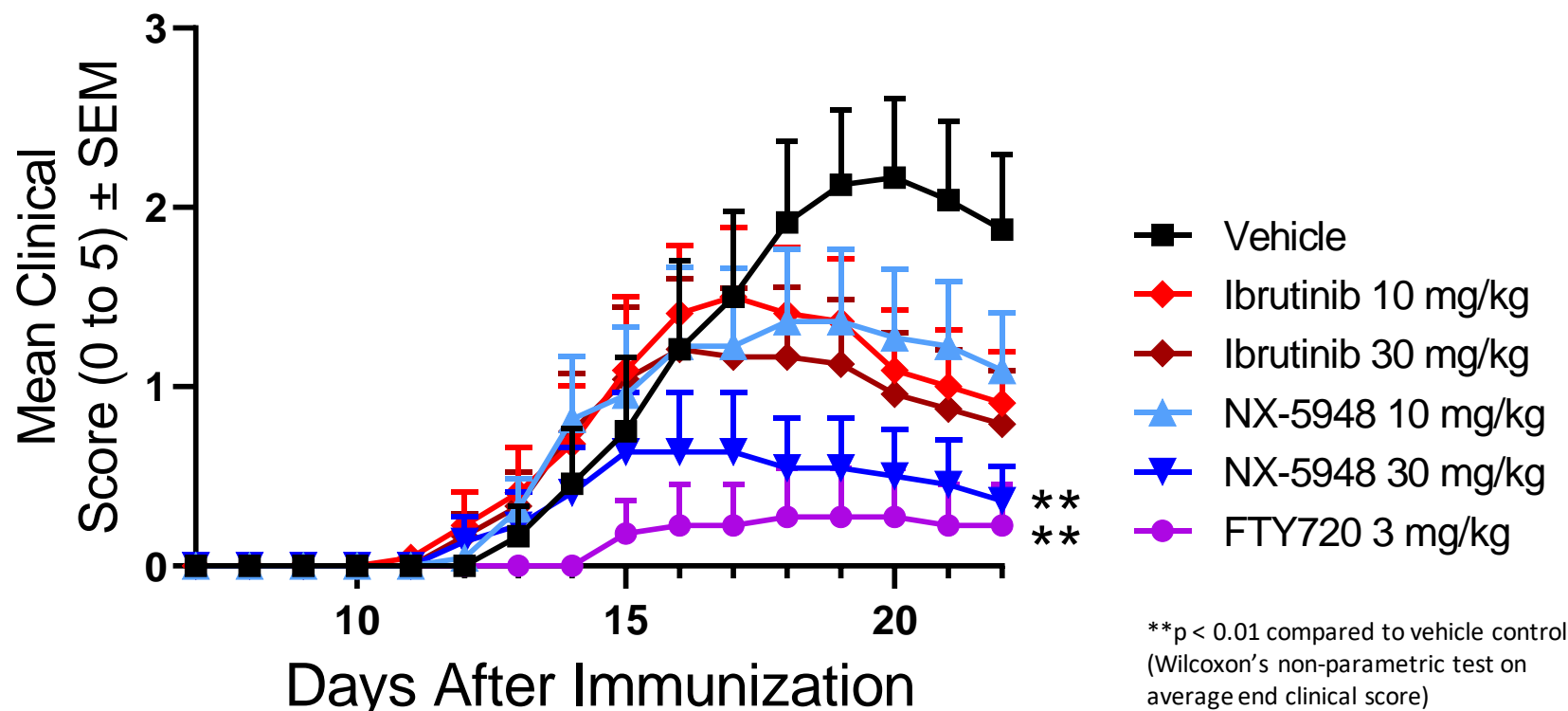
- EAE is induced by immunization with full-length human MOG (myelin oligodendrocyte glycoprotein) to initiate an autoimmune reaction similar to multiple sclerosis
- This particular EAE model is dependent upon B cells, T cells, anti-MOG Ab, and myeloid cells
- BTK functions downstream of the B cell Receptor to promote B cell activation, produce anti-MOG antibodies, and present antigen to autoreactive T cells
- BTK also functions downstream of the Fc Receptor to activate myeloid cells such as microglia against anti-MOG antibodies bound to myelin, promoting demyelination



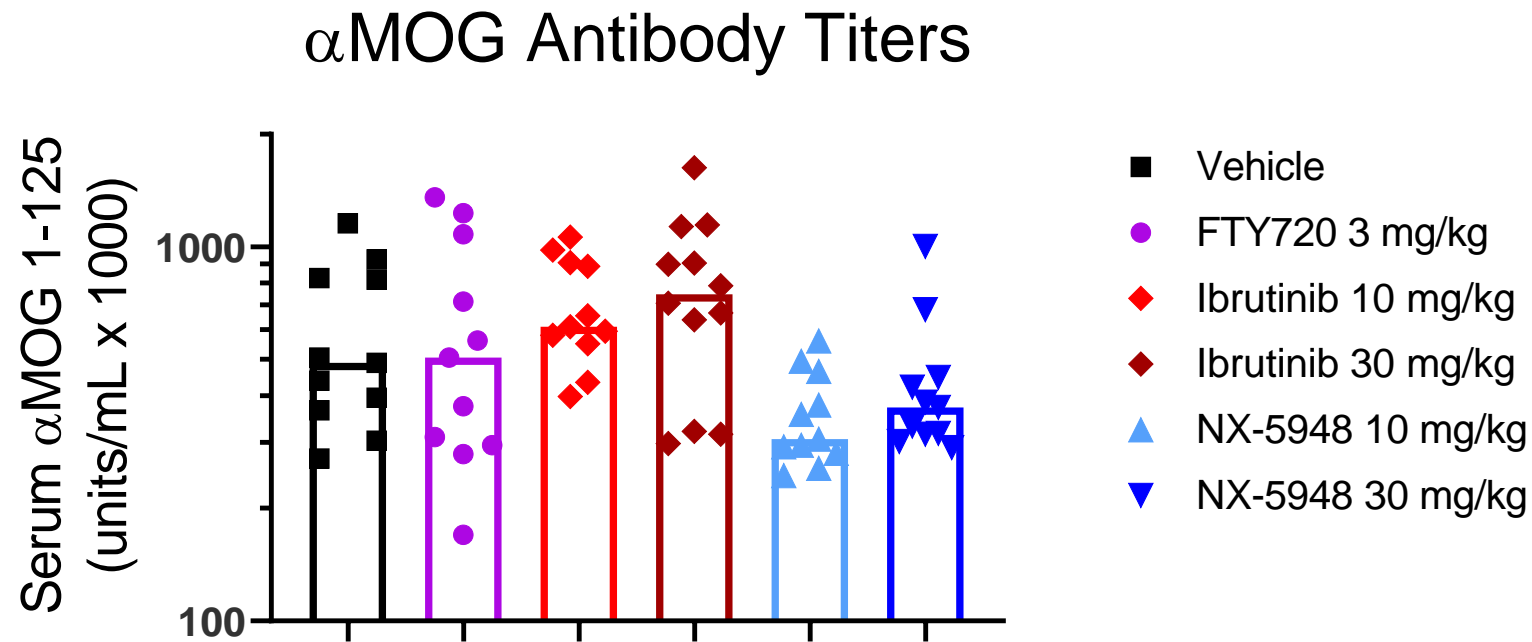
NX-5948 Improves EAE Clinical Scores and Provides Greater Benefit than Ibrutinib

Disease initiated on Day 0 with full-length human MOG₁₋₁₂₅ and pertussis toxin
Daily oral administration of NX-5948 or Ibrutinib Days -1 to 22

EAE Severity

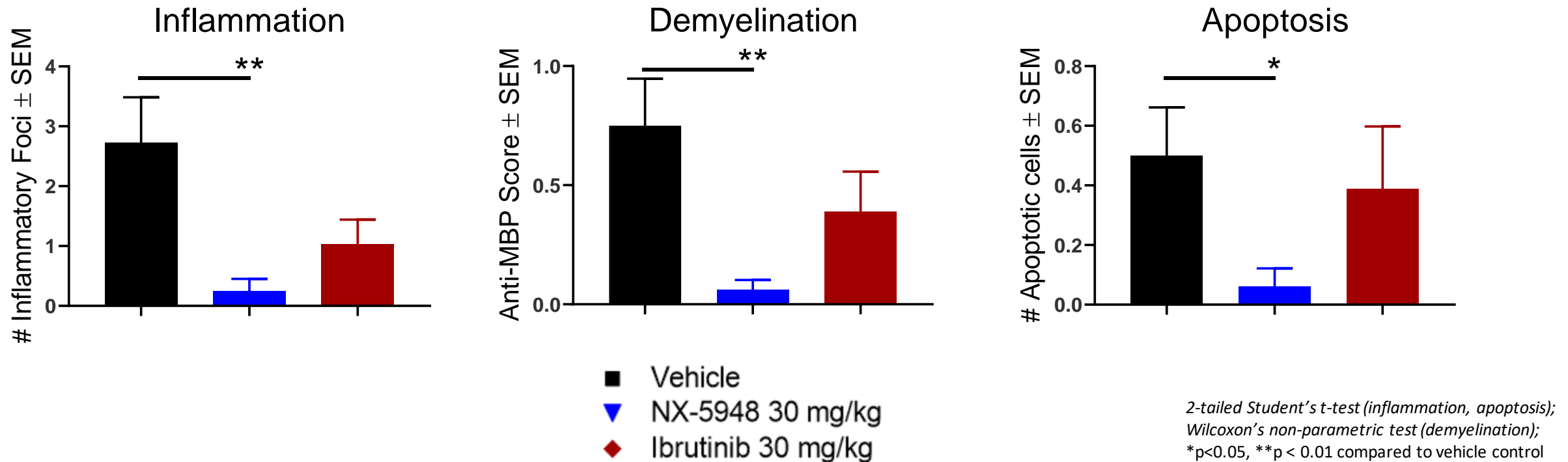


NX-5948 Treated Groups Have Trends of Lower α MOG Antibody Titers



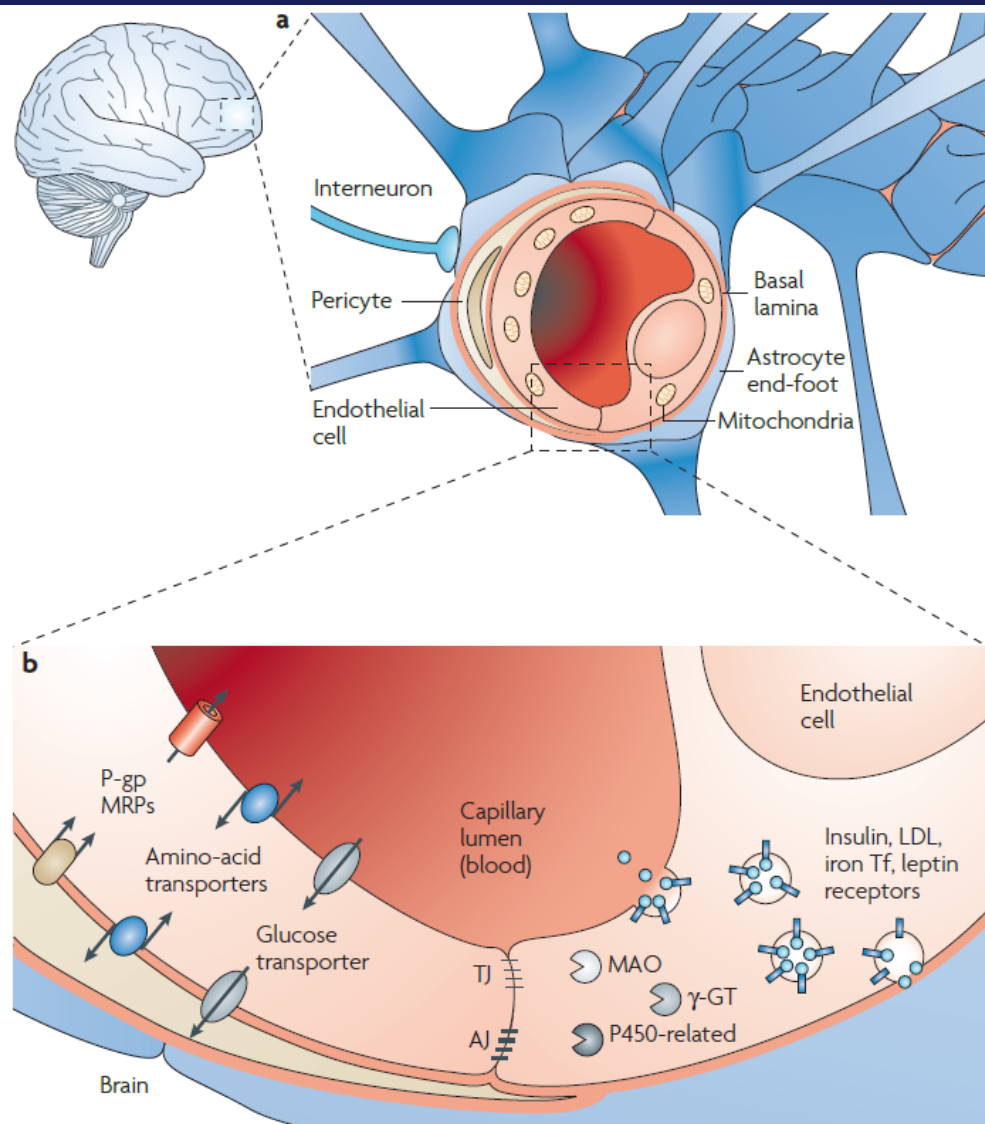
Statistical comparison vs. vehicle by One-Way ANOVA with Dunnett's multiple comparison test (significance not reached)

NX-5948 Improved Histological Findings Associated with EAE More Strongly Than Ibrutinib



- NX-5948 dramatically reduced inflammation, demyelination, and apoptosis in the spinal cords of treated mice
- Degradation of BTK in brain-resident myeloid cells may contribute to the superior activity of NX-5948 over ibrutinib

How Do We Design Degraders that Cross the Blood Brain Barrier?



- The BBB is a selective barrier that protects the brain from harmful compounds and precisely regulates its microenvironment
- The CNS multiparameter optimization score (MPO score) defines chemical properties that are optimal for CNS therapeutic agents

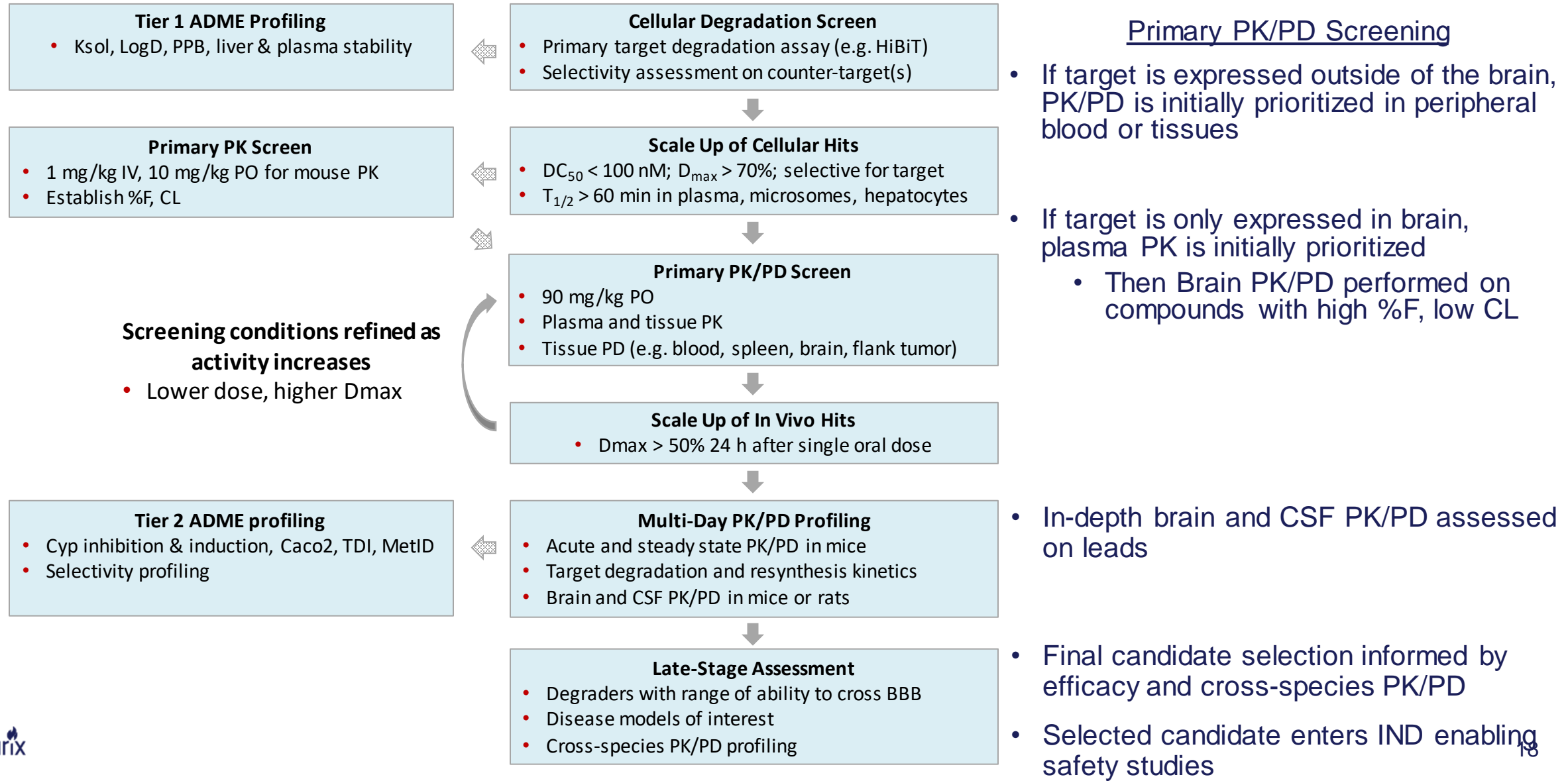
CNS MPO Properties and Parameter Ranges

Property	More Desirable	Less Desirable
ClogP	≤ 3	> 5
ClogD	≤ 2	> 4
MW	≤ 360	> 500
TPSA	40 to 90	$\leq 20, > 120$
HBD	≤ 1	> 3
pKa	≤ 8	> 10

Each property assigned a score from 0.0 to 1.0 and summed. 74% of marketed CNS drugs had an MPO score ≥ 4.0 (Wager, et al., *ACS Chem Neuro*, 2010)

- Determining the parameters and characteristics that predict CNS exposure of degraders are of high interest

Nurix Has Established a Testing Funnel for Identifying Degraders that Cross the Blood Brain Barrier



Potent Orally-Active Degraders of an Undisclosed Target Were Identified and Selected for CNS Evaluation

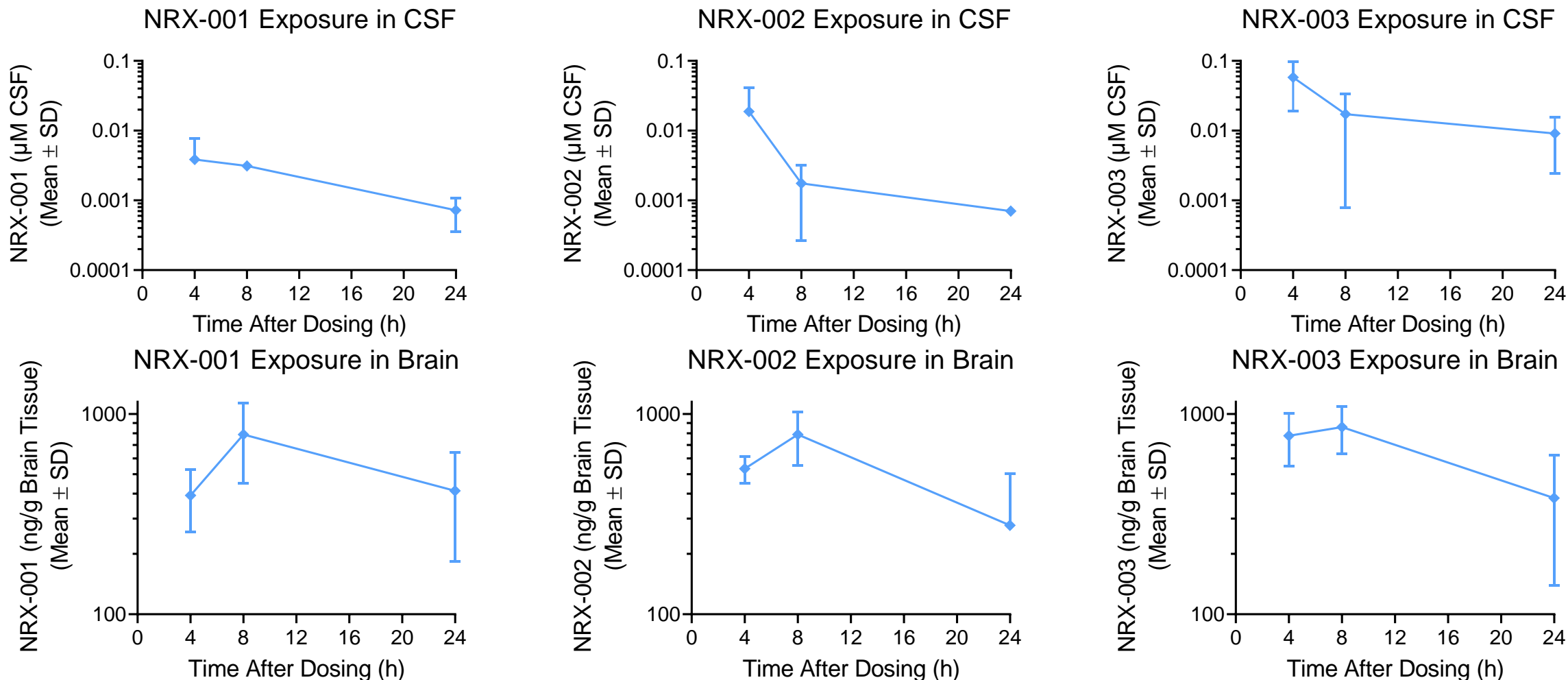
Goal: Develop degraders that suppress T cell function for treatment of autoimmune and inflammatory diseases

- Target Expressed in T cells and other immune cells

	NRX-001	NRX-002	NRX-003
Cellular Degradation (HiBiT)	DC ₅₀ : < 0.01 nM D _{max} : 88%	DC ₅₀ : 0.62 nM D _{max} : 84%	DC ₅₀ : < 0.01 nM D _{max} : 88%
In Vitro Plasma Protein Binding (Mouse, %)	95%	97%	96%
In Vivo Clearance (Mouse, mL/min/kg)	2.7	14.2	20.7
Oral bioavailability (Mouse, % F at 10 mg/kg)	26%	43%	32%
In Vivo PD Mouse, PO, 30 mg/kg, 24 h (% Degradation in Splenocytes)	88%	74%	92%
CNS MPO Score (Range 0 – 6, ≥ 4 is desirable range)	1.2	1.5	2.4

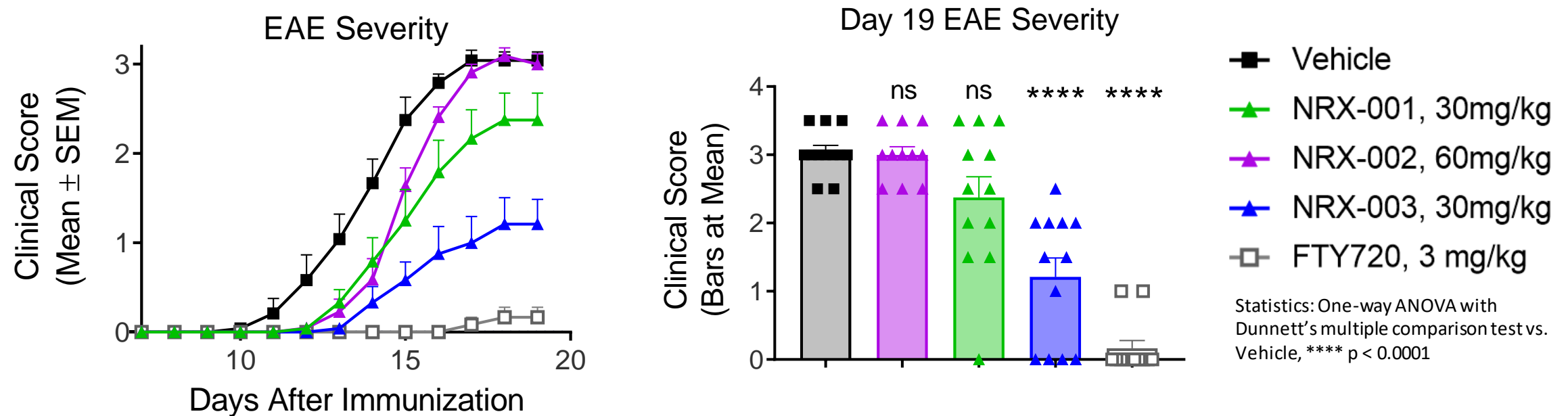
Degraders had a range of CNS exposure, despite low CNS MPO scores

Single oral dose administered to mice at 150 mg/kg



Lead Compound was Selected Based on Performance in a T Cell Dependent EAE Model

Disease initiated on Day 0 with human MOG₃₅₋₅₅ peptide and pertussis toxin
Daily oral administration of compounds beginning Day -1



- Ongoing characterization of the PK/PD relationship will include analysis of brain exposure, target degradation, and phenotype of immune cells that infiltrate the brain during the course of disease

Summary

- Discovery of oral, CNS-penetrant, targeted protein degraders is enabled by a testing funnel that evaluates ADME, potency, exposures, and efficacy in a step-wise process
- NX-5948 is an oral CNS-penetrant, targeted protein degrader of BTK
 - Degrades BTK in primary human B cells ($DC_{50} = 0.034$ nM), cancer cell lines, and tumor xenografts
 - Promotes BTK degradation in microglia and periventricular macrophage of naïve mice
- NX-5948 significantly degrades BTK in brain-resident tumor cells and extends survival in a mouse model of CNS lymphoma
- NX-5948 provides superior activity to ibrutinib in an antibody dependent model of EAE
- Using the established testing funnel, a targeted protein degrader with CNS exposure was identified that has superior efficacy in a T-cell driven model of EAE
 - Additional characteristics beyond CNS MPO scores may be needed to predict CNS exposure for degraders



Thank you
Nurix Therapeutics