nurix

Leader in Targeted Protein Modulation

Targeting Degraders to the CNS for the Treatment of Cancer

Educational Session

Gwenn M. Hansen, Ph.D.

Chief Scientific Officer

AACR

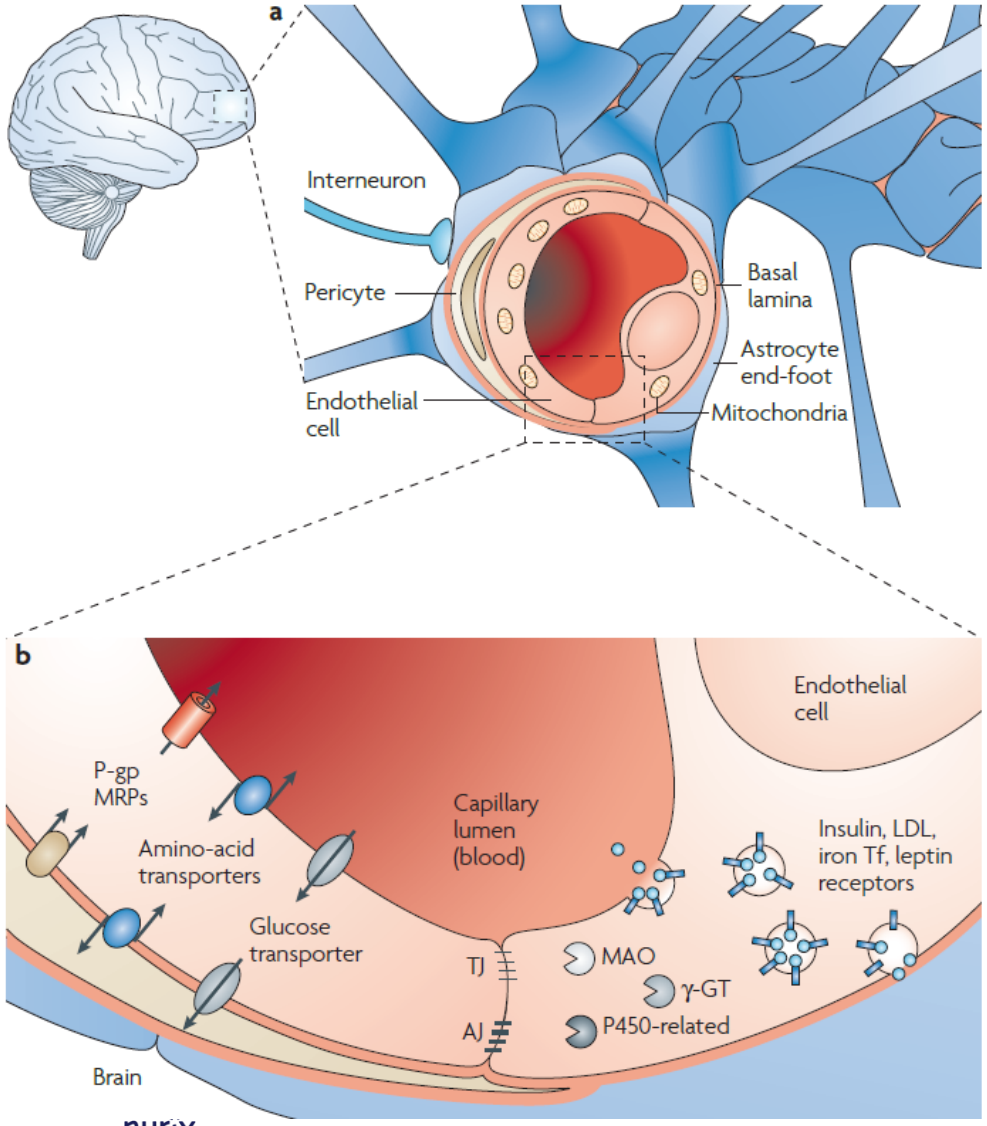
April 5th, 2024

Important notice and disclaimers

This presentation contains statements that relate to future events and expectations and as such constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. When or if used in this presentation, the words “anticipate,” “believe,” “could,” “estimate,” “expect,” “intend,” “may,” “outlook,” “plan,” “predict,” “should,” “will,” and similar expressions and their variants, as they relate to Nurix Therapeutics, Inc. (“Nurix”, the “Company,” “we,” “us” or “our”), may identify forward-looking statements. All statements that reflect Nurix’s expectations, assumptions or projections about the future, other than statements of historical fact, are forward-looking statements, including, without limitation, statements regarding our future financial or business plans; our future performance, prospects and strategies; future conditions, trends, and other financial and business matters; our current and prospective drug candidates; the planned timing and conduct of the clinical trial programs for our drug candidates; the planned timing for the provision of clinical updates and initial findings from our clinical studies; the potential benefits of our collaborations, including potential milestone and sales-related payments; the potential advantages of our DELigase™ platform and drug candidates; the extent to which our scientific approach, our DELigase™ platform, targeted protein modulation, and Degrader-Antibody Conjugates may potentially address a broad range of diseases; the extent animal model data predicts human efficacy; and the timing and success of the development and commercialization of our current and anticipated drug candidates. Forward-looking statements reflect Nurix’s current beliefs, expectations, and assumptions. Although Nurix believes the expectations and assumptions reflected in such forward-looking statements are reasonable, Nurix can give no assurance that they will prove to be correct. Forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and changes in circumstances that are difficult to predict, which could cause Nurix’s actual activities and results to differ materially from those expressed in any forward-looking statement. Such risks and uncertainties include, but are not limited to: (i) risks and uncertainties related to Nurix’s ability to advance its drug candidates, obtain regulatory approval of and ultimately commercialize its drug candidates; (ii) the timing and results of clinical trials; (iii) Nurix’s ability to fund development activities and achieve development goals; (iv) risks and uncertainties relating to the timing and receipt of payments from Nurix's collaboration partners, including milestone payments and royalties on future potential product sales; (v) the impact of macroeconomic events and conditions, including increasing financial market volatility and uncertainty, inflation, increasing interest rates, instability in the global banking system, uncertainty with respect to the federal budget and debt ceiling, the impact of war, military or regional conflicts, and global health pandemics, on Nurix’s clinical trials and operations; (vi) Nurix’s ability to protect intellectual property and (vii) other risks and uncertainties described under the heading “Risk Factors” in Nurix’s Annual Report on Form 10-K for the fiscal year ended November 30, 2023, and other SEC filings. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. The statements in this presentation speak only as of the date of this presentation, even if subsequently made available by Nurix on its website or otherwise. Nurix disclaims any intention or obligation to update publicly any forward-looking statements, whether in response to new information, future events, or otherwise, except as required by applicable law.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company’s own internal estimates and research. While the Company believes these third-party sources to be reliable as of the date of this presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal estimates and research are reliable, such estimates and research have not been verified by any independent source.

Designing Compounds With Optimal CNS Exposure:
For *small molecule* drugs, established metrics can aid in CNS-penetrant designs



(Cecchelli, et al., *Nat Rev Drug Dev*, 2007)

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

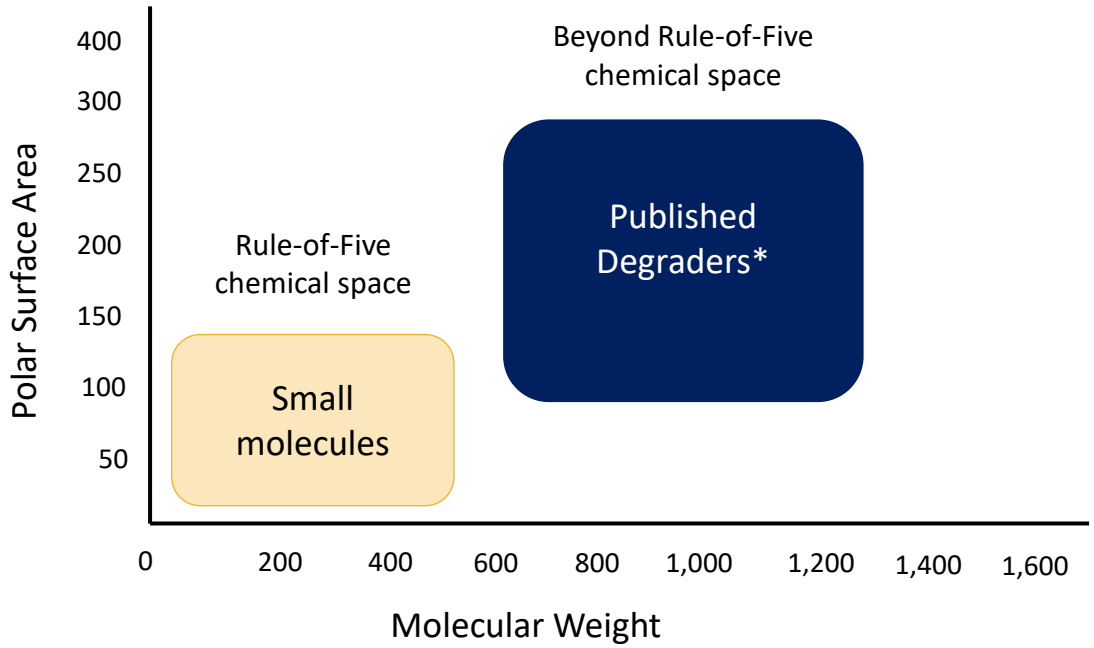
CNS MPO Properties and Parameter Ranges

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

Each property assigned a score from 0.0 to 1.0 and summed. 77% of marketed CNS drugs had an MPO score ≥ 4.0 (Wager, et al., *ACS Chem Neuro*, 2016)

Degraders Occupy Non-Traditional Chemical Space Where Historical Rules Don’t Apply

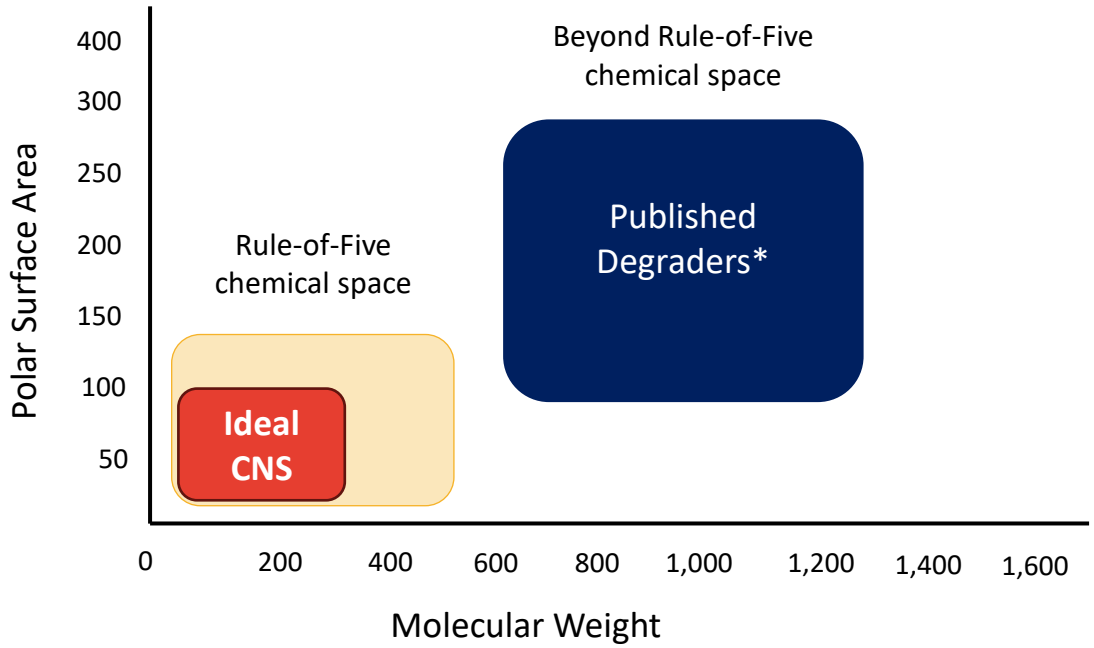
Degraders occupy space 'Beyond-the-Rule-of-Five’ where established guidelines for physicochemical properties associated with drug-likeness can't easily be applied



*3270 Degraders from PROTAC-DB 2.0. Weng et al NAR 2023 doi: 10.1093/nar/gkac946.

Degraders Occupy Non-Traditional Chemical Space Where Historical Rules Don't Apply

Designing blood-brain-barrier penetration in the bifunctional targeted protein degrader space is particularly challenging due to well-established limitations on both molecular weight and polar surface area

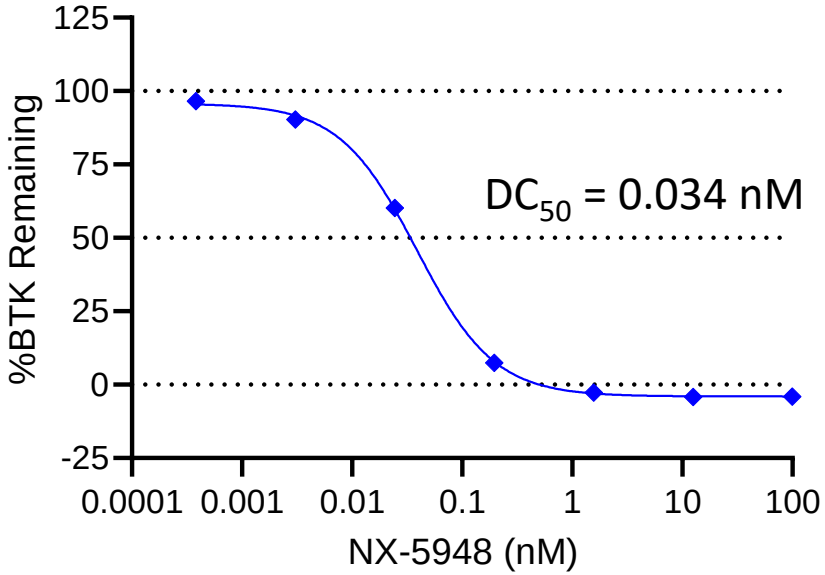


*3270 Degraders from PROTAC-DB 2.0. Weng et al NAR 2023 doi: 10.1093/nar/gkac946.

Case Study: BTK Degrader NX-5948 for the Treatment of B cell Malignancies

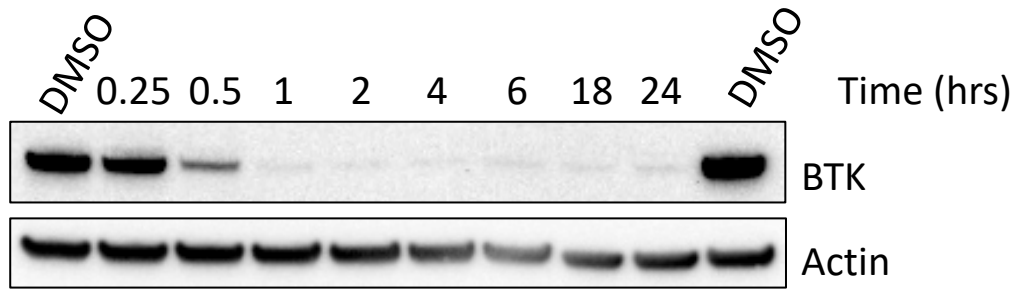
Optimized for Cellular Potency and Oral Bioavailability

Primary Human B cells



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

Ramos Cells (Human Burkitt Lymphoma)



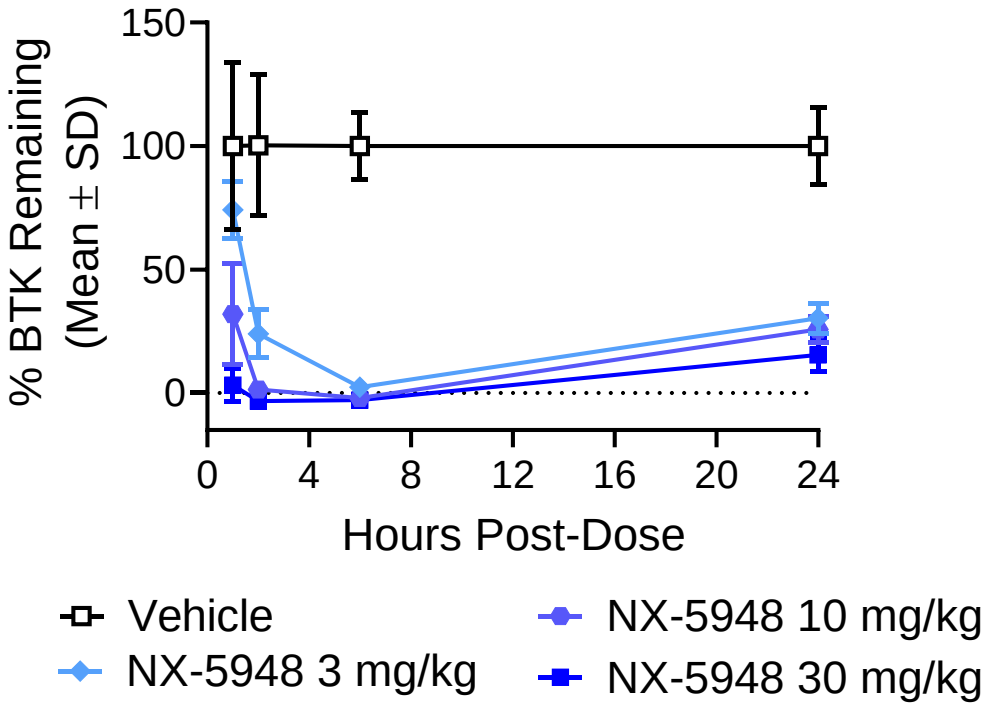
10 nM NX-5948

Case Study: BTK Degrader NX-5948 for the Treatment of B cell Malignancies

Optimized for Cellular Potency and Oral Bioavailability

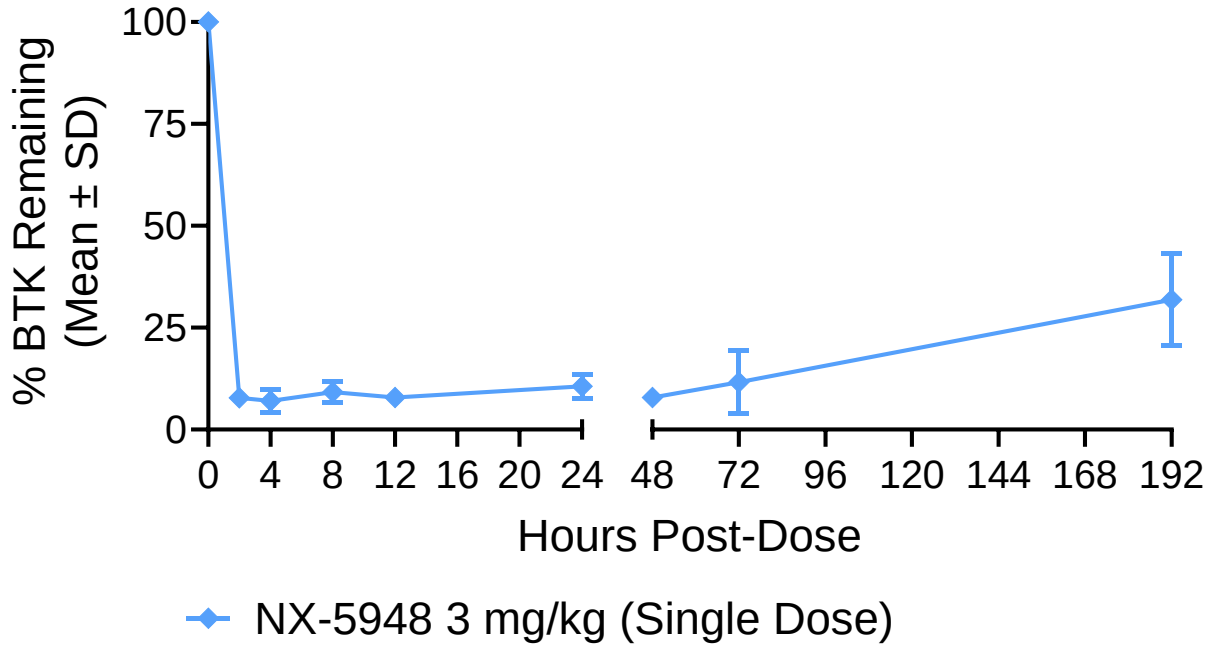
- A Single Oral Dose of NX-5948 Promotes Rapid and Compete BTK Degradation in Mouse and NHP B cells

BTK Levels in Mouse Circulating B Cells



In mice, BTK levels increased 24 hours after single dose

BTK Levels in NHP Circulating B Cells



In cynomolgus monkeys, BTK levels remained suppressed at 48 hours and return to 32% of baseline after 8 days

Case Study: BTK Degrader NX-5948 for the Treatment of B cell Malignancies

Existing metrics for predicting CNS penetration suggest NX-5948 unlikely to show CNS exposure

Six property desirability functions used to generate the CNS MPO

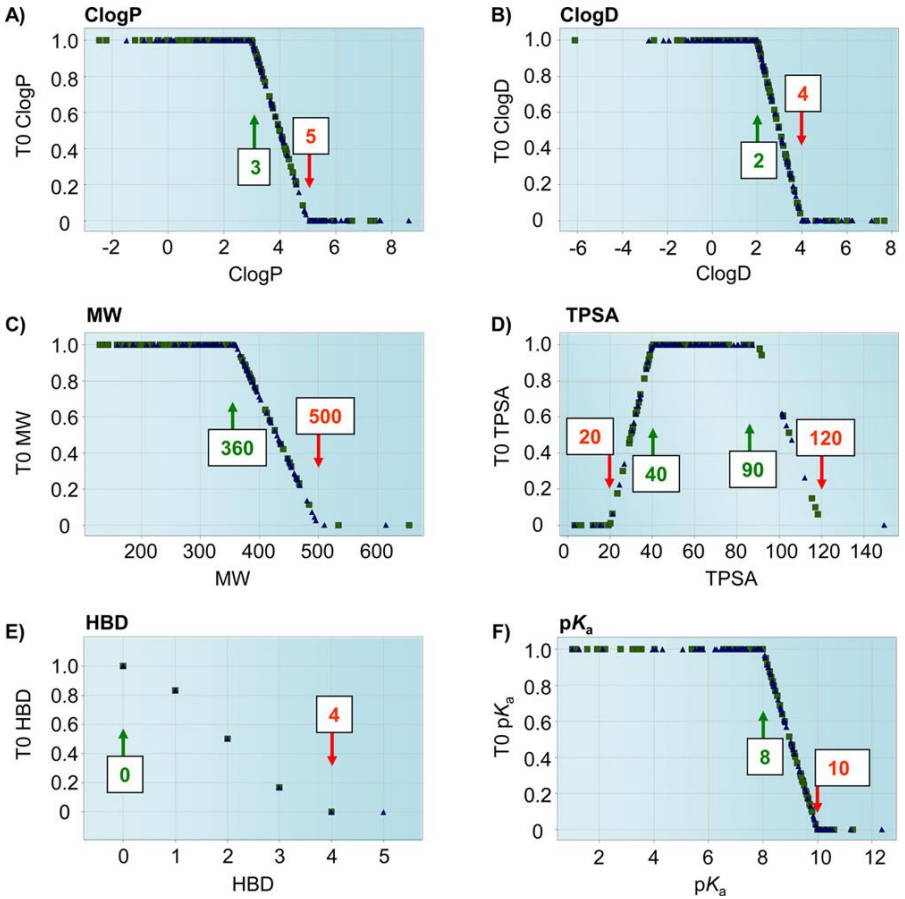
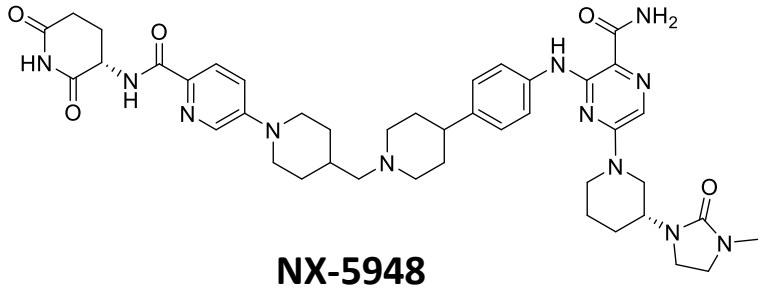


Figure from Wager, et al., *ACS Chem Neuro*, 2016



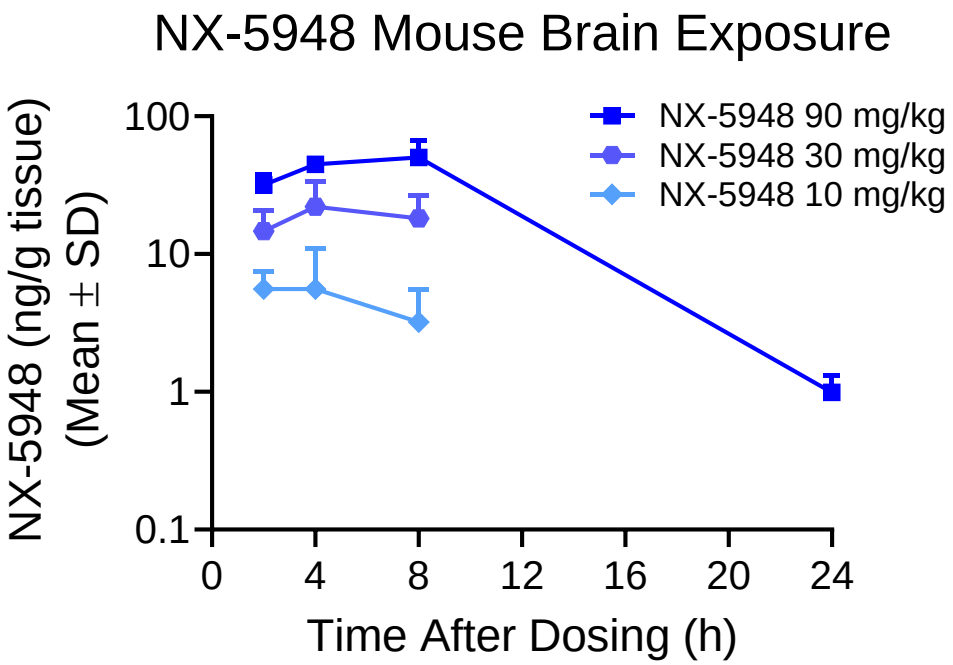
NX-5948

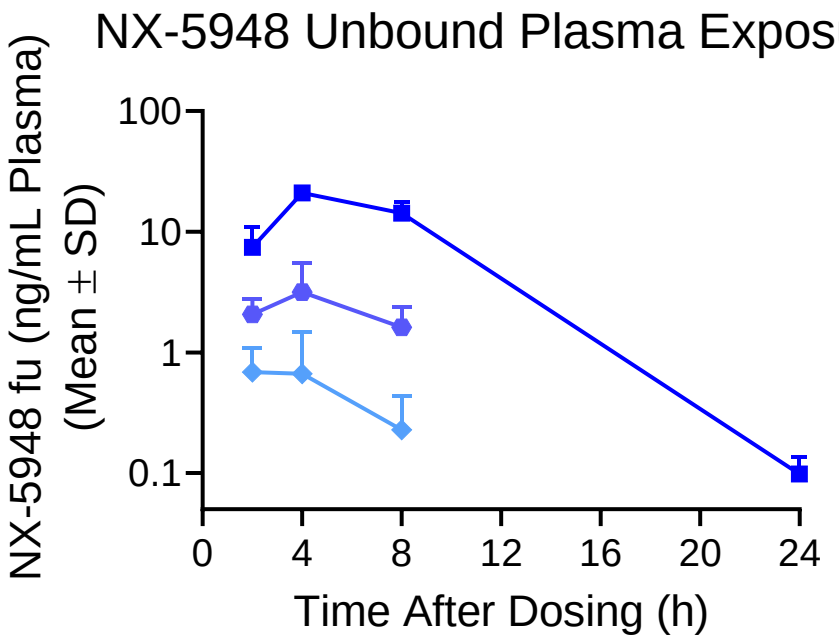
Property	More Desirable	Less Desirable	NX-5948 Property value	NX-5948 MPO score
ClogP	≤ 3	> 5	3.6	**0.7**
ClogD	≤ 2	> 4	0.9	**1.0**
MW	≤ 360	> 500	807	**0**
TPSA	40 to 90	≤ 20, > 120	202	**0**
HBD	≤ 1	> 4	5	**0**
pKa	≤ 8	> 10	9.1*	**0.45**
				Total = 2.2

*Measured pKa

MPO >4 generally required for CNS small molecules

However, a Single Oral Dose of NX-5948 in Mice Results in Dose-Dependent CNS Tissue Exposure

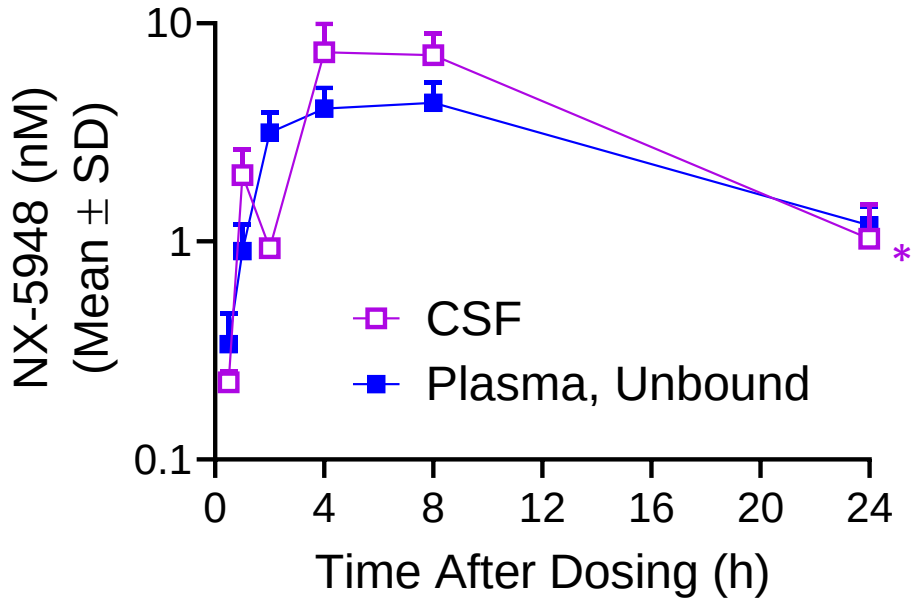




Mouse plasma protein binding = 99.6%

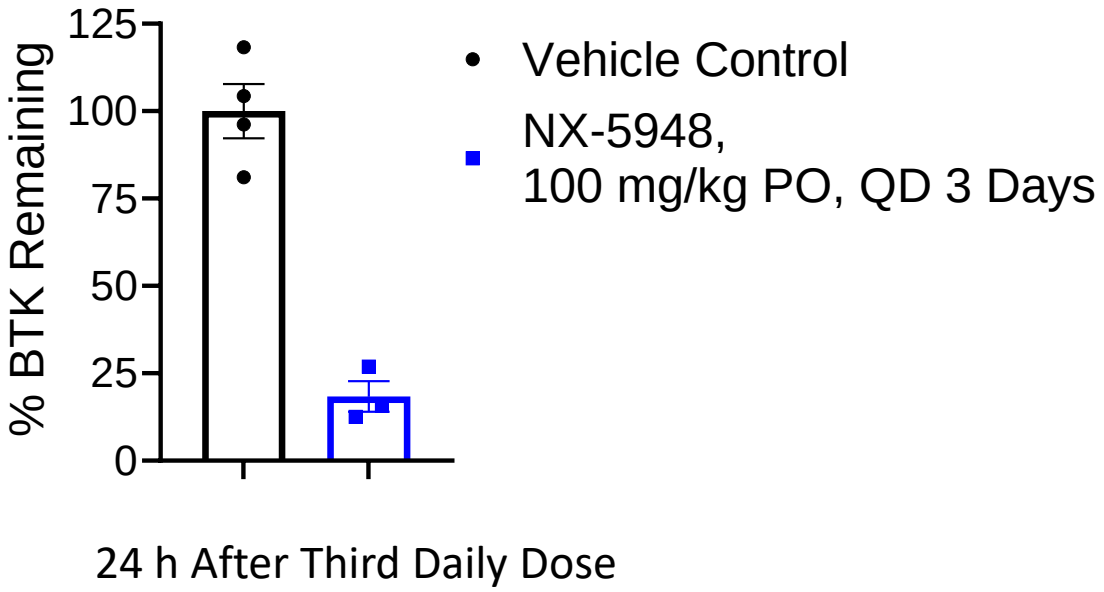
A More Detailed Study in the Rat Shows Oral Dosing of NX-5948 Results in Similar CSF and Unbound Plasma Exposures and Degrades BTK in Microglia

NX-5948 Exposure in Rat (100 mg/kg PO, QD 1 Day)



Rat plasma protein binding = 98.4%

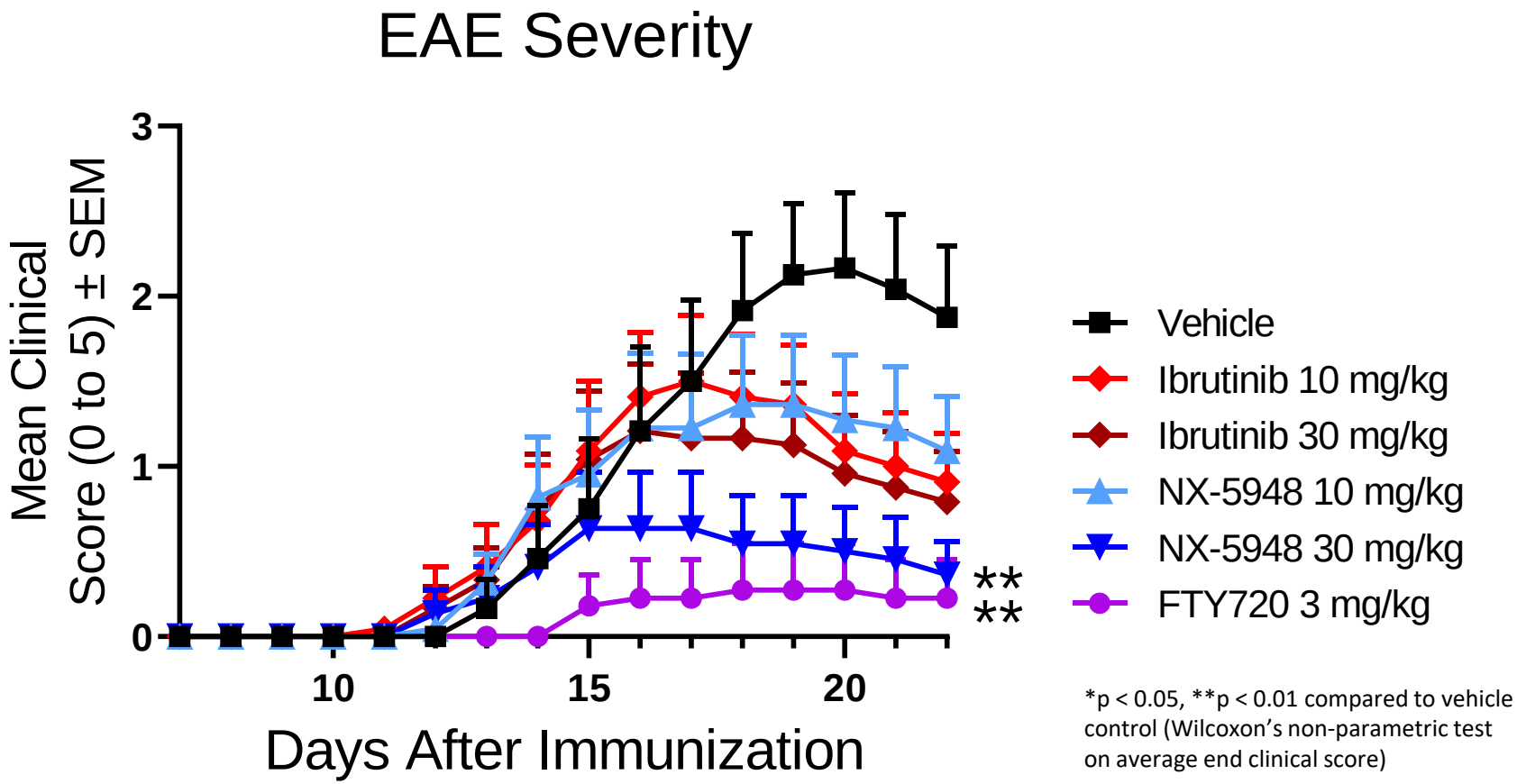
BTK Quantification in Microglia



*One of three CSF samples collected at 24 h was excluded as an outlier based on criteria defined by Motulsky et al., Detecting outliers when fitting data with nonlinear regression – a new method based on robust nonlinear regression and the false discovery rate. BMC Bioinformatics 7, 123 (2006).

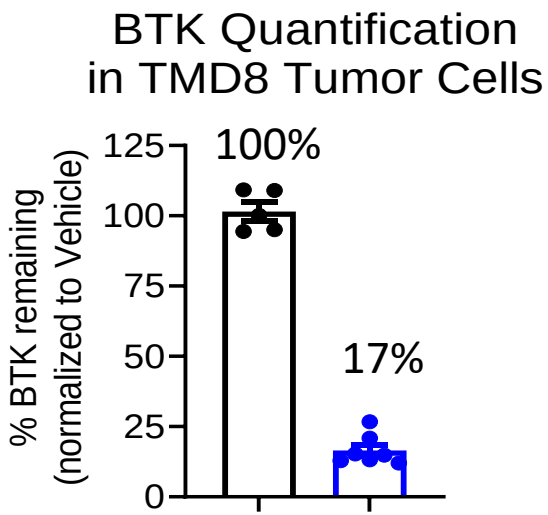
NX-5948 Superior to Ibrutinib in Preclinical Model of CNS Disease

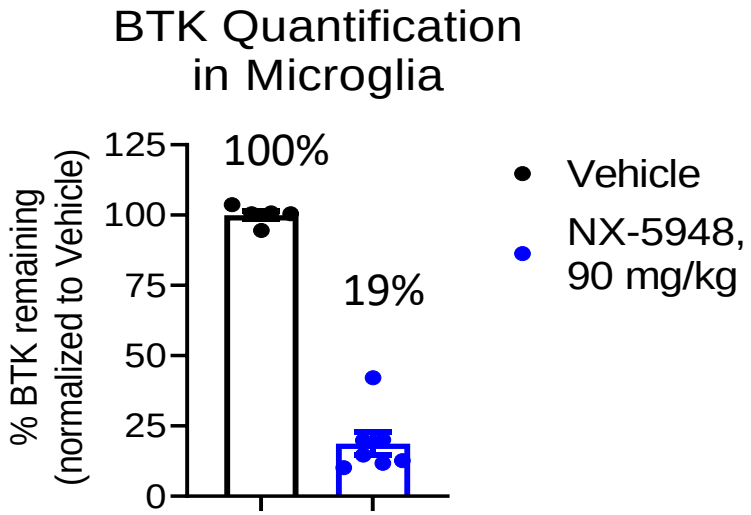
Experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis

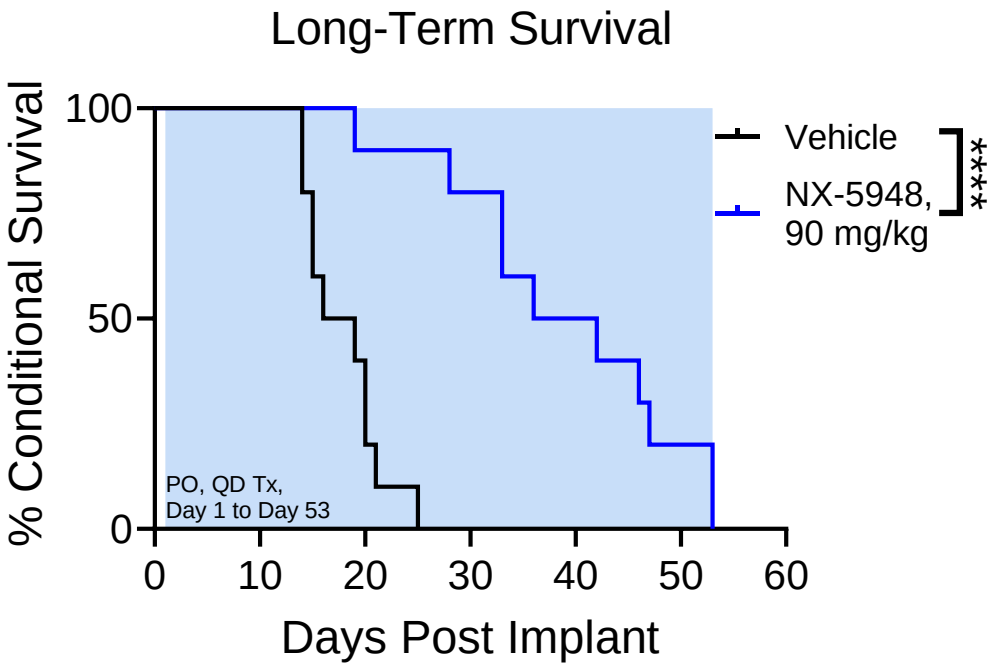


*p < 0.05, **p < 0.01 compared to vehicle control (Wilcoxon's non-parametric test on average end clinical score)

Daily Oral Administration of NX-5948 to Mice With Intracranial TMD8 DLBCL Tumors Degrades BTK in Brain-Resident Cells and Prolongs Survival



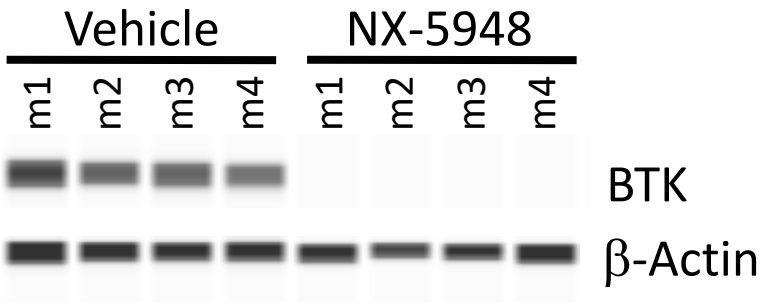


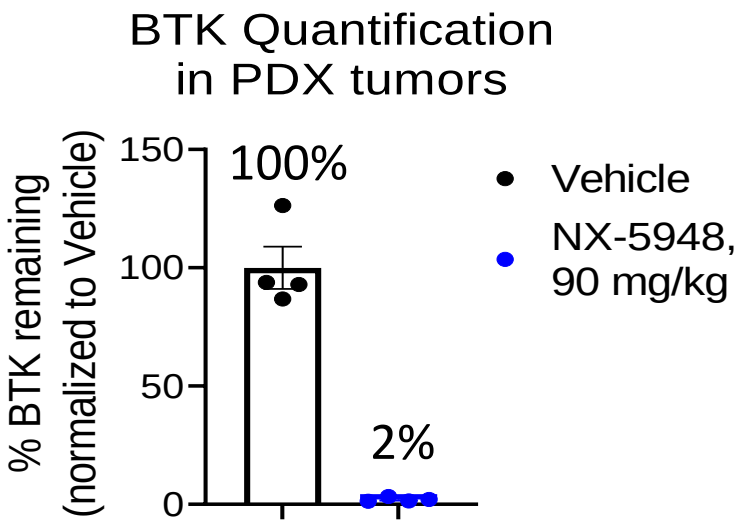


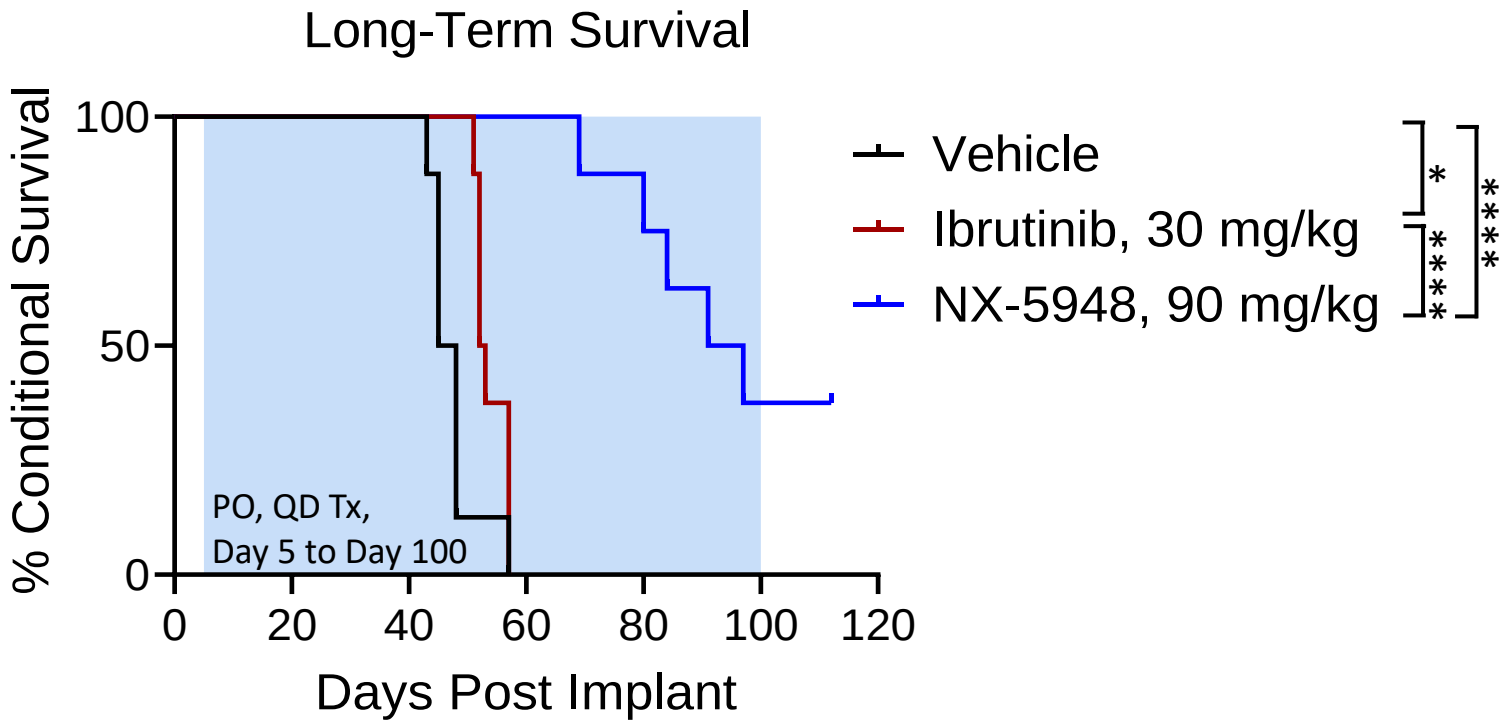
5 x 10^5 TMD8 cells implanted by intracranial injection on Day 0
NX-5948 administered orally QD Days 1-11 (left) or Days 1-53 (right)
BTK levels assessed 24 h after the 11^{th} dose by flow cytometry

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

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





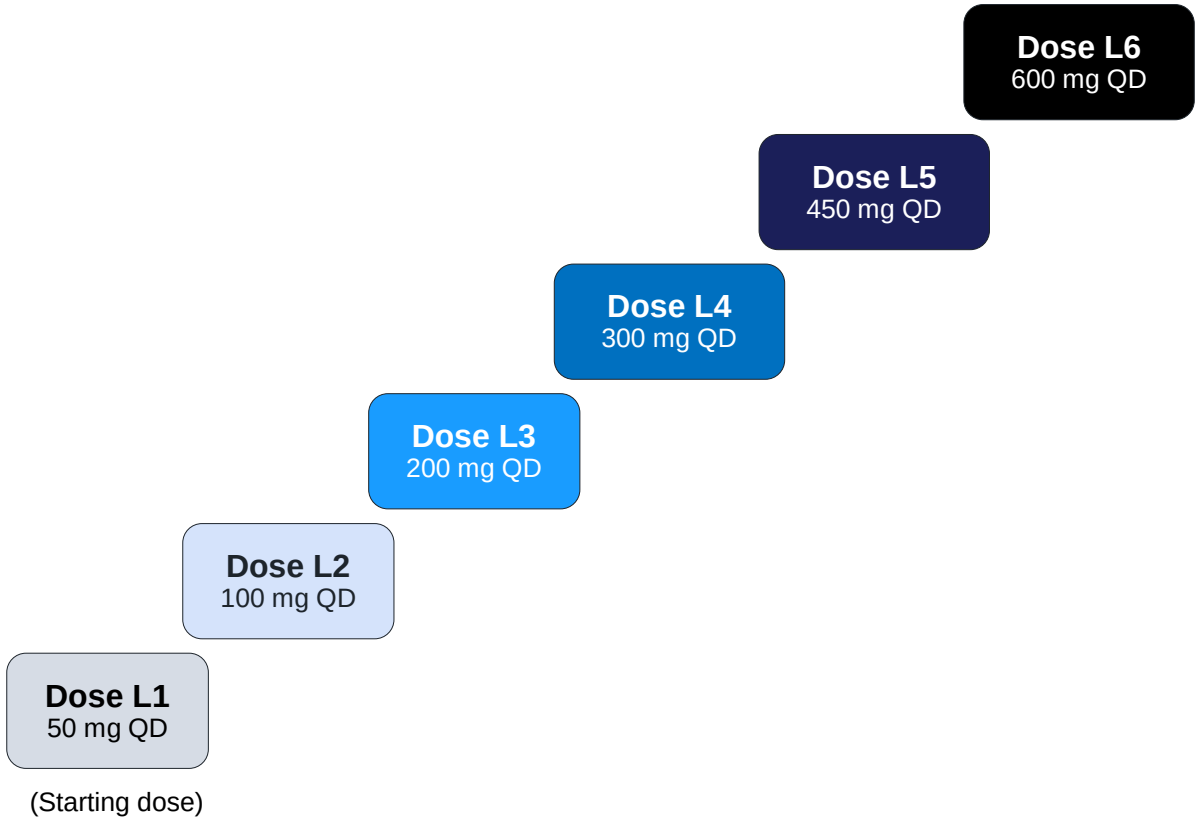


SC1 cells are derived from a patient with highly refractory CD79b and EVT6-mutant large B-cell secondary CNS lymphoma, resistant to R-CHOP, high-dose methotrexate/rituximab, etoposide, Ara-C and irradiation.

Phase 1 Trial of NX-5948 in Adults With Advanced B-cell Malignancies

Only BTK Degrader trial to permit patients with CNS involvement at baseline

Phase 1a dose escalation
B-cell malignancies (N = up to 66 CLL and up to 66 NHL/WM)



Potential Phase 1b dose expansion
(N = up to 160 patients)

CLL/SLL dose level A
Prior BTKi and BCL-2i

CLL/SLL dose level B
Prior BTKi and BCL-2i

MCL[a]
Prior BTKi and anti-CD20 CIT

MZL[a]
Prior anti-CD20 CIT and ≥2 prior LoT

WM[a]
Prior BTKi and ≥2 prior LoT

DLBCL[a,b]
Prior anthracycline, anti-CD20 CIT + 1 LoT[c]

FL
Prior anti-CD20 CIT + 1 LoT[c]

PCNSL/SCNSL
Who have progressed or had no response to ≥1 prior LoT

[a]Includes patients with secondary CNS involvement; [b]Subtypes include: transformed indolent lymphoma (e.g., grade 3b/transformed FL), Richter-transformed DLBCL, high-grade B-cell lymphoma with MYC and BCL-2 and/or BCL-6 rearrangements, high-grade B-cell lymphomas NOS; [c]Additional lines of therapy include anthracycline for non-GCB DLBCL and BTKi for MCL

Can We Identify Additional CNS-Penetrant Degraders?

>12,000 Nurix degraders designed between 2022-2023 plotted by MW vs PSA

Compounds represent 34 programs, colored by target

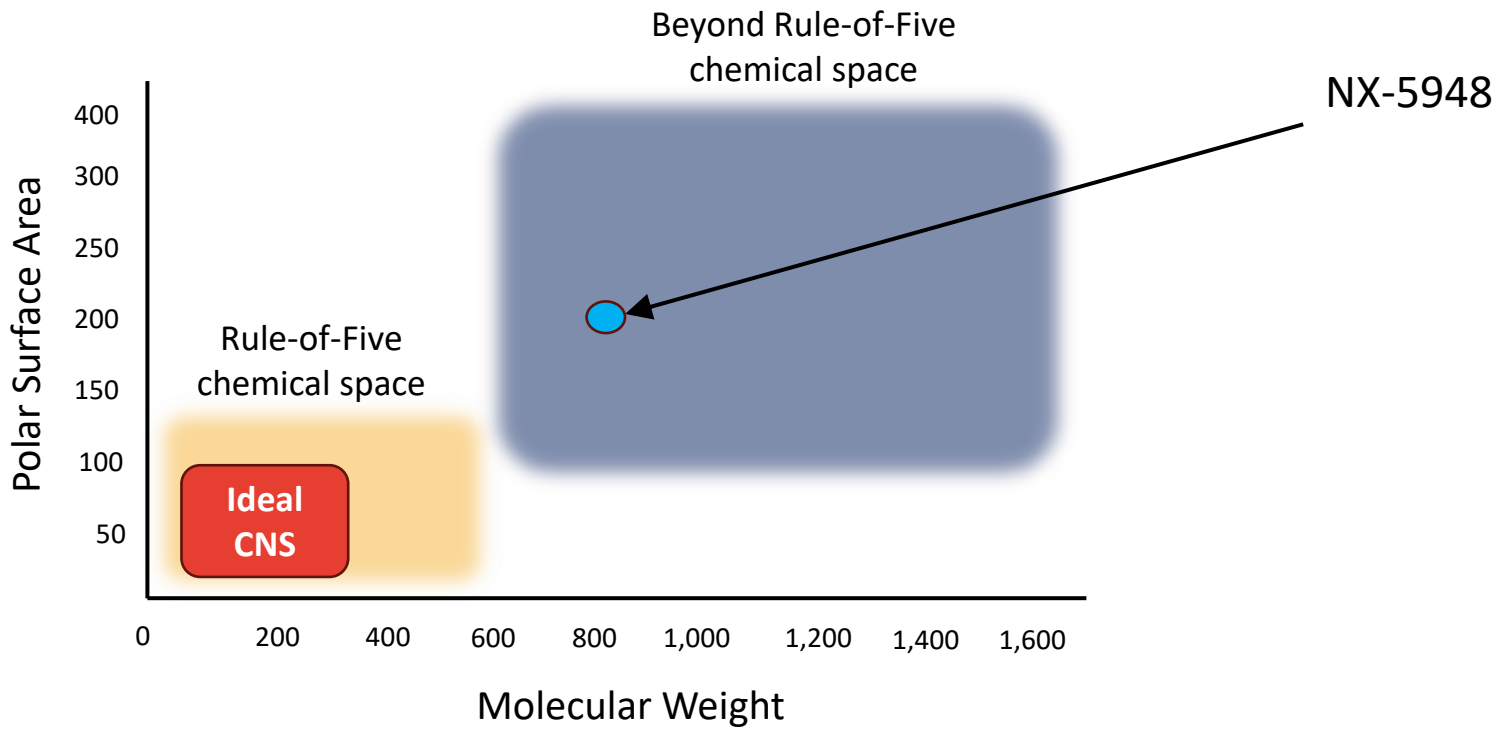
Broad property space anchored by profile of POI binder

Represents a larger property range vs public database

When You Lack a Rulebook, You Screen

CNS-penetrant drugs occupy a small quadrant of the traditional small molecule chemical space

What Parameters Define CNS-Penetrant Degraders?



Empirical Testing Funnel for Identifying Degraders that Cross the BBB

Cellular Degradation Screen
- Primary target degradation assay (e.g. HiBiT)
- Selectivity assessment on counter-target(s)

Tier 1 ADME Profiling
- Ksol, LogD, PPB, liver & plasma stability

Scale Up of Cellular Hits
- DC_{50} < 100 nM; D_{max} > 70%; selective for target
- $T_{1/2}$ > 60 min in plasma, microsomes, hepatocytes

Primary PK Screen
- 1 mg/kg IV, 10 mg/kg PO for mouse PK
- Establish %F, CL

Primary PK/PD Screen
- 90 mg/kg PO
- Plasma and tissue PK
- Tissue PD (e.g. blood, spleen, brain, flank tumor)

Screening conditions refined as activity increases
- Lower dose, higher Dmax

Scale Up of In Vivo Hits
- Dmax > 50% 24 h after single oral dose

Multi-Day PK/PD Profiling
- Acute and steady state PK/PD in mice
- Target degradation and resynthesis kinetics
- Brain and CSF PK/PD in mice or rats

Tier 2 ADME profiling
- Cyp inhibition & induction, Caco2, TDI, MetID
- Selectivity profiling

Late-Stage Assessment
- Degraders with range of ability to cross BBB
- Disease models of interest
- Cross-species PK/PD profiling

<u>Primary PK/PD Screening</u>

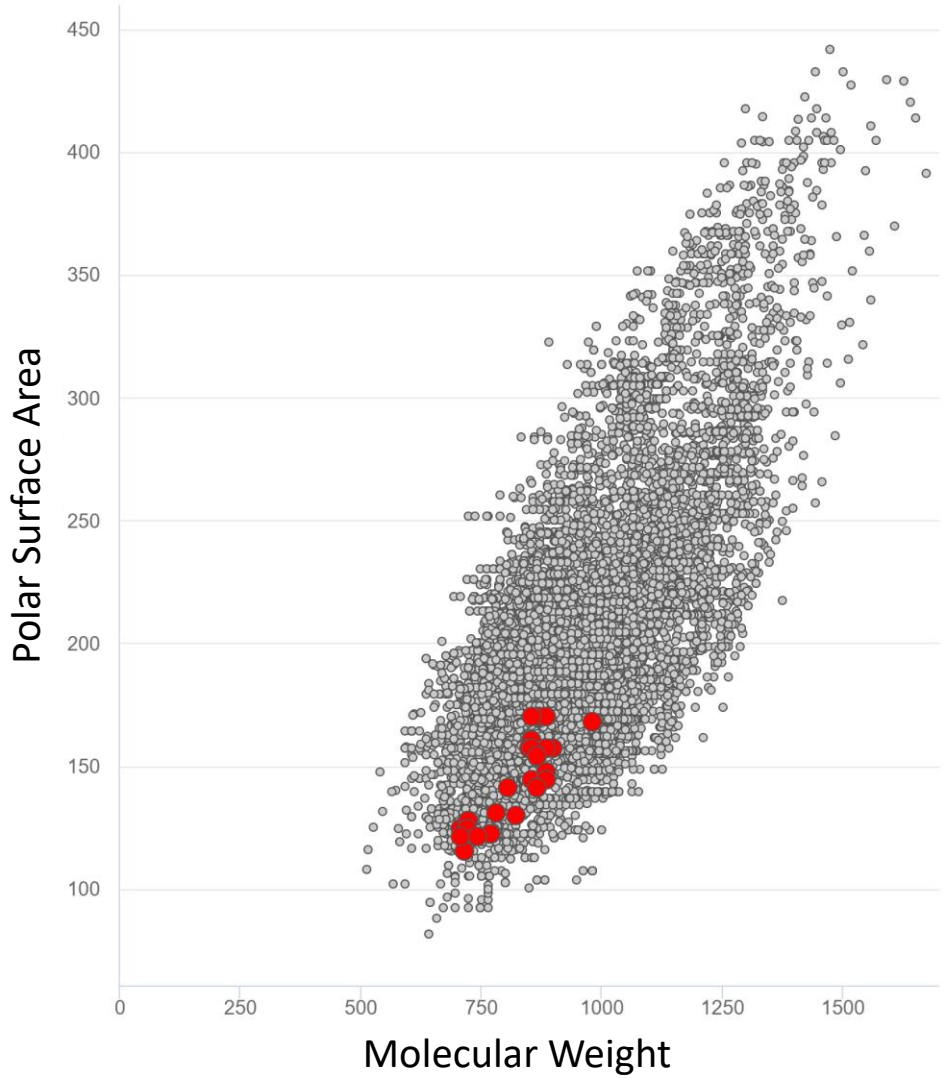
- If target is expressed outside of the brain, PK/PD is initially prioritized in peripheral blood or tissues
- If target is only expressed in brain, plasma PK is initially prioritized

➢ Brain PK/PD performed on compounds with high %F, low CL

➢ In-depth brain and CSF PK/PD assessed on leads

All programs screened to date have achieved significant BBB penetration

CNS-Penetrant Degraders Cluster in Small Quadrant of Degrader Design Space



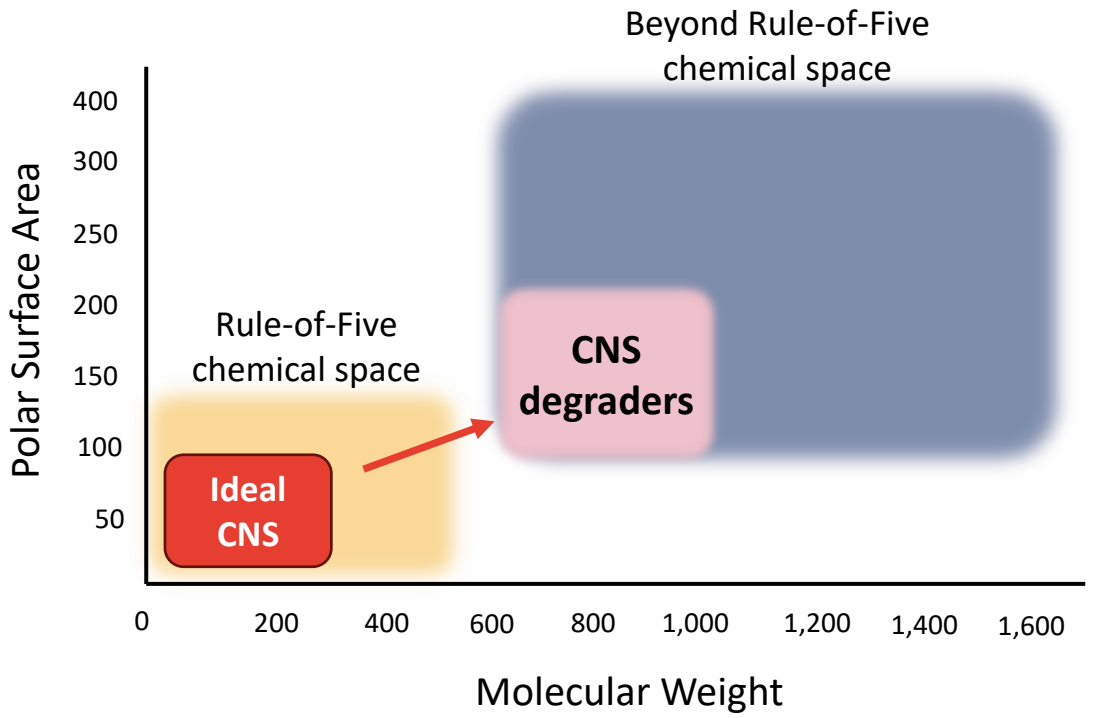
- CNS Exposure
- No CNS Exposure, or Not Selected For PK/PD Screening

Empirical Screening for CNS-Penetrant Degraders is a Viable Discovery Strategy

>50% of Degraders emerging from dedicated in vivo testing funnel show CNS penetration

CNS-penetrant degraders are much more prevalent than expected

Molecular weight range limitation of small molecule design space for CNS is not relevant for degraders



Thank you

nurix