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Identification of Selective, Orally Bioavailable Aurora A Degraders for Treatment of Pediatric and Adult Cancers

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NURIX

Disclosure Information

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Ryan Rountree

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MYCN Is a Major Oncogenic Driver of Childhood and Adult Cancers

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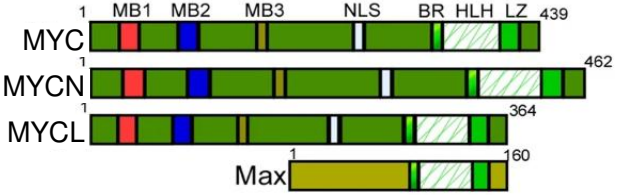
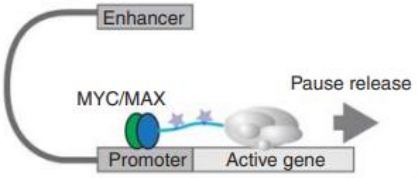
Three MYC paralogs

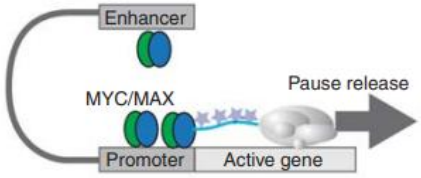


(Chen, Sig Trans & Targeted Ther, 2018)

Low MYC



High MYC



(Rahl, CSHP, 2014)

- High levels of MYC promote cell growth by transcriptional amplification of target genes
- MYCN gene is amplified in subsets of cancers and is associated with poor prognosis
- MYCN is essential for embryonic development, but not readily detectable in normal tissues

(Liu, Front Onc, 2021)

Cancer Type		*MYCN*^{amp}
Pediatric	Alveolar rhabdomyosarcoma	25%
	Neuroblastoma	18-20%
	Wilms tumor	13%
	Medulloblastoma	5-10%
Adult	NE prostate cancer	40%
	SCLC	15-20%
	BCC	17.5%
	Prostate adenocarcinoma	5%

Degradation of AURKA Eliminates Scaffolding Function to Promote MYCN Degradation

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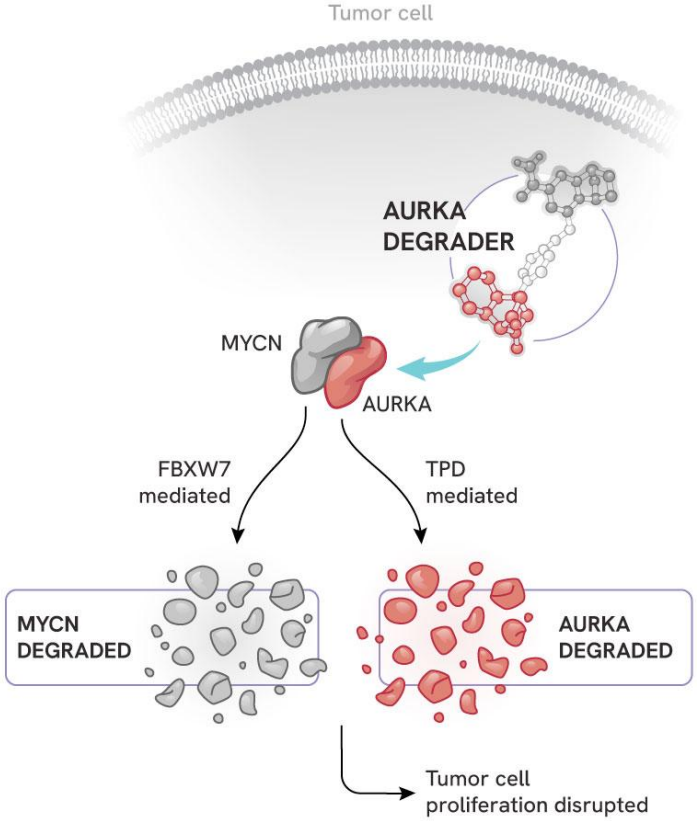

- Aurora kinase A (AURKA) functions during DNA replication, centrosome maturation, mitotic entry, and chromosome segregation
- AURKA is frequently overexpressed and associated with poor survival in adult and pediatric cancers
- Kinase-independent scaffolding activity protects MYCN from proteasome-dependent degradation via FBWX7 ubiquitylation

(Mou, Exp & Mol Med, 2021)
(Otto, Cancer Cell, 2009)

Industry Leading Platform Used to Discover Orally Active, Brain Penetrant, AURKA Degraders

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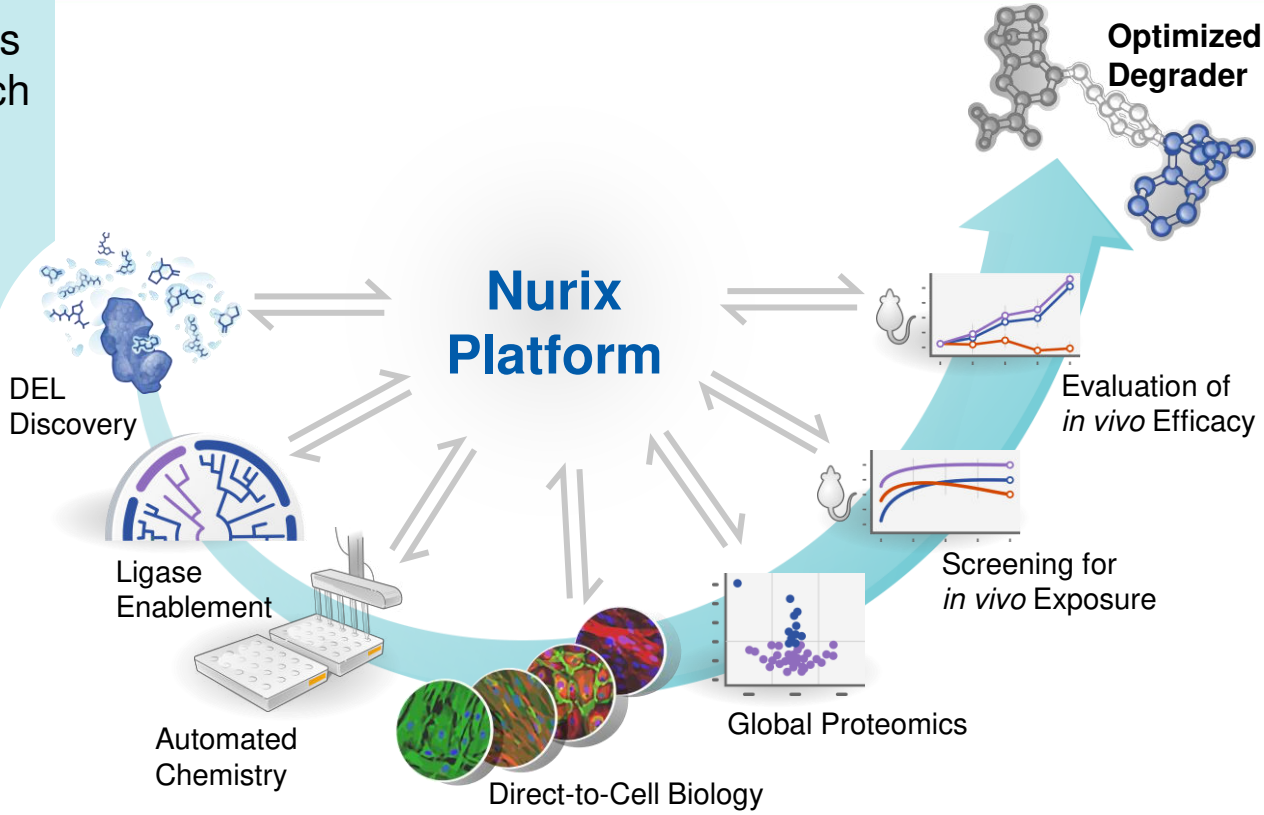
Our discovery engine leverages the combined power of data-rich DEL ligand-finding capabilities, automated chemistry, HTP cell and *in vivo* biology, and advanced machine learning to accelerate drug discovery



DEL, DNA encoded library; **HTP**, high throughput

NRX-4972 Potently Degrades AURKA and Is Proteasome-Dependent

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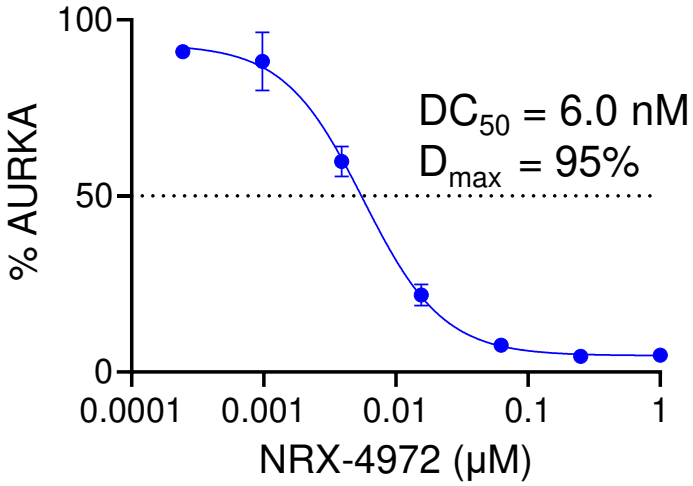
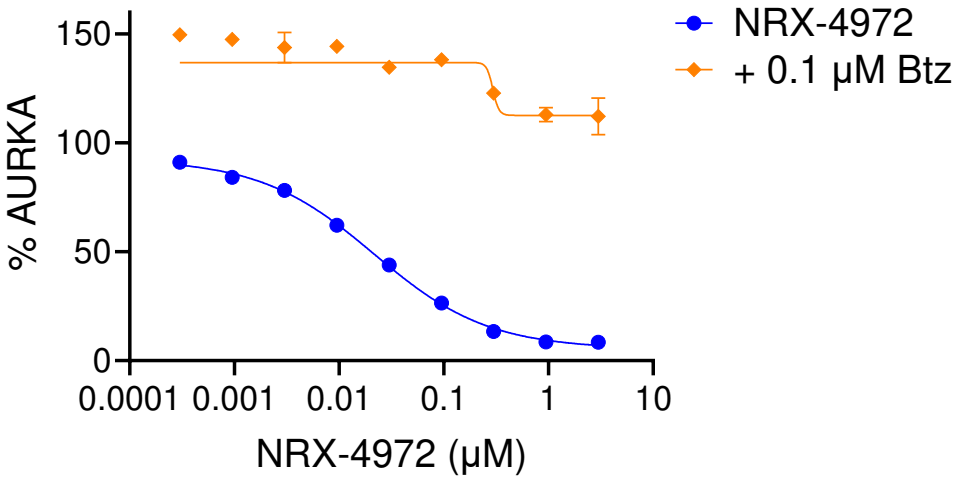
IMR32

(*MYCN*^{amp} Neuroblastoma)



Proteasome-Dependent Degradation



NRX-4972 potency evaluated in IMR32 cells after 6-hour incubation; AURKA measured by Jess Simple Western and normalized to vinculin as a percentage of DMSO control. Proteasome-dependence was evaluated in an MV4-11 AURKA-overexpression HiBiT line; 1-hour pre-treatment of bortezomib, then addition of NRX-4972 for 6 hours.

NRX-4972, AURKA, and CRBN Form a Ternary Complex With Strong Positive Cooperativity

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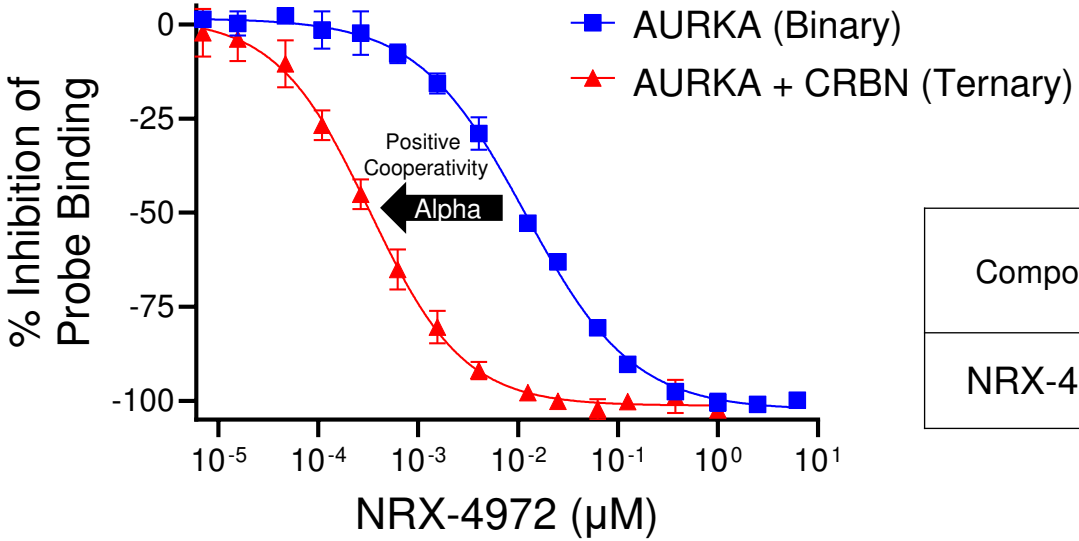

	Binary	Ternary	Cooperativity
Compound	AURKA (IC_{50} nM)	AURKA + CRBN (IC_{50} nM)	Alpha (IC_{50} ratio)
NRX-4972	11.88 ± 0.17	0.34 ± 0.05	**36 ± 6**

Alpha > 1 indicates positive cooperativity
(Alpha = Binary IC_{50}/ Ternary IC_{50})

NRX-4972 was titrated to inhibit binding of a fluorescent probe to AURKA in the presence of either AURKA protein alone or AURKA + CRBN protein (IC50 mean ± SD). Positive cooperativity (alpha > 1) indicated by NRX-4972 inhibiting probe binding more potently in the presence of AURKA + CRBN compared to AURKA alone.

NRX-4972 Demonstrates Excellent Selectivity in Global Proteomic Profiling

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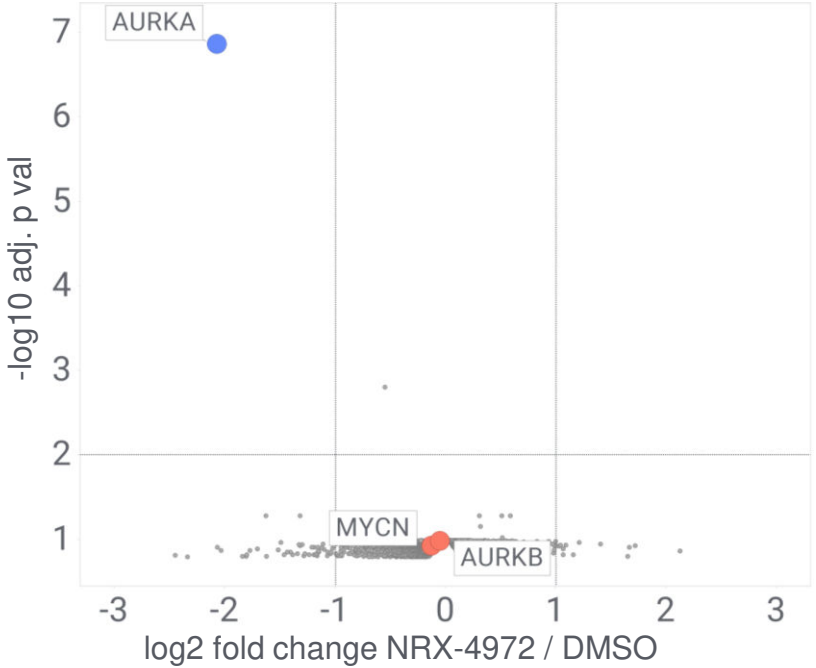
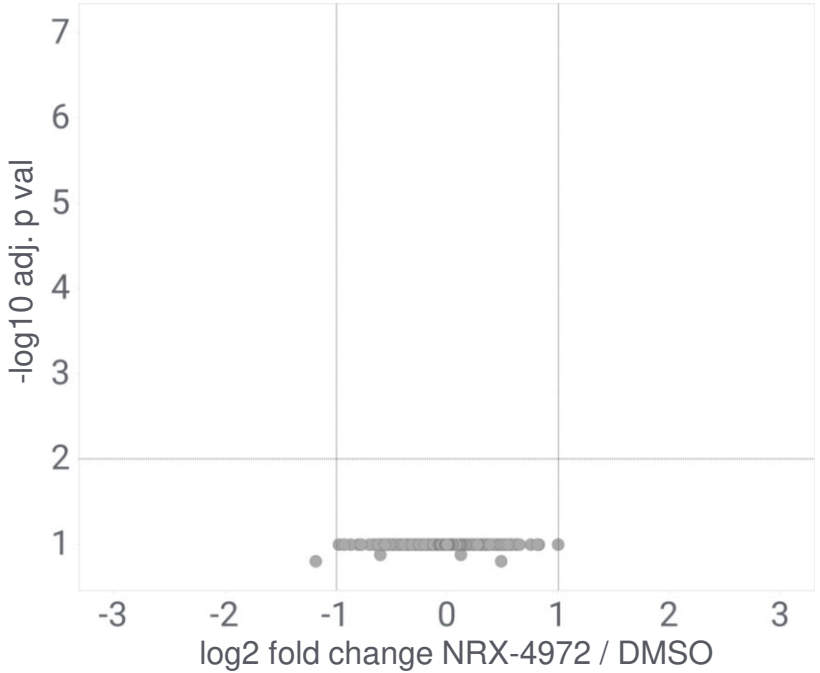
IMR32 Neuroblastoma Cells, 6 hours



NRX-4972 at EC95 = 146 nM, >9,000 proteins detected

Human PBMCs, 24 hours



NRX-4972 at 50x DC50 = 335 nM, >9,000 proteins detected

AURKA, AURKB, and MYCN are not expressed at detectable levels in human PBMCs

NRX-4972 Selectively Degrades AURKA and Partially Reduces MYCN in the SK-N-BE(2) Neuroblastoma Cell Line

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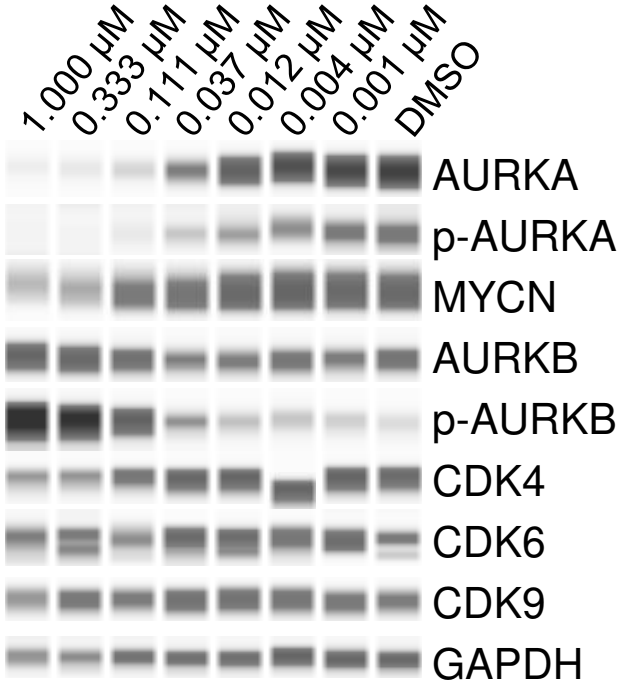
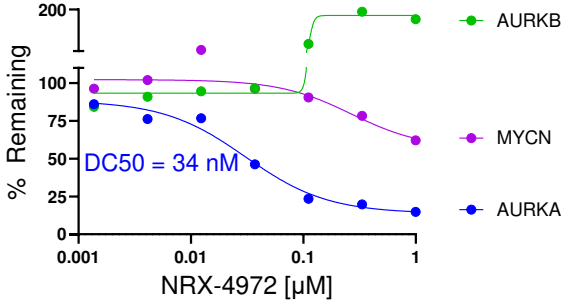
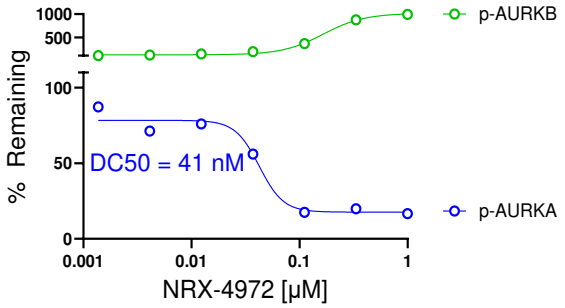
SK-N-BE(2), 24 hours



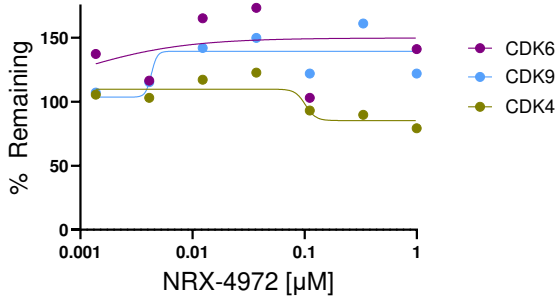
Total Protein Levels



Phosphoprotein Levels



CDK Family



%Remaining calculated as protein level normalized to GAPDH as a percentage of amount in DMSO control lane

NRX-4972 Has High Oral Bioavailability and Is More Tissue and Brain Penetrant Than AURKA Inhibitor LY3295668

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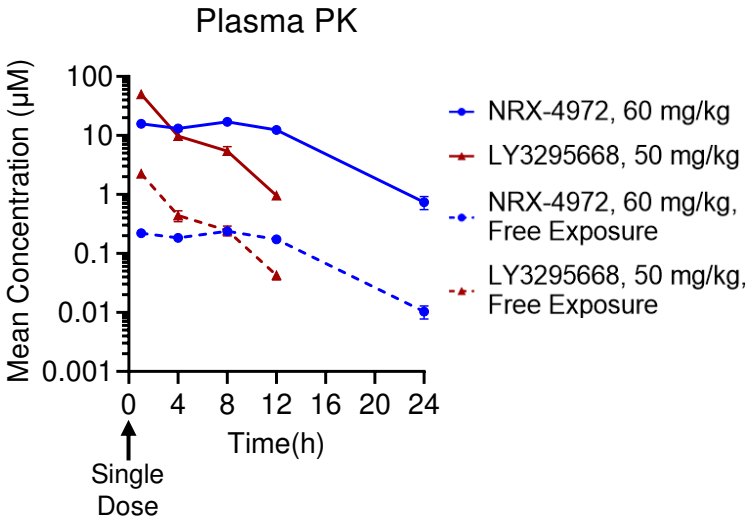
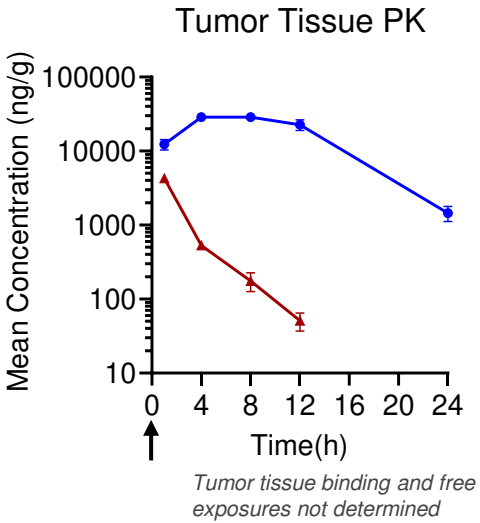
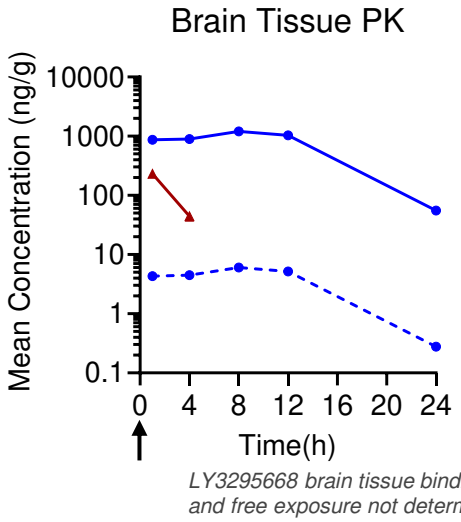




Tumor tissue binding and free exposures not determined



LY3295668 brain tissue binding and free exposure not determined

- NRX-4972 exhibited higher plasma, tumor, and brain exposures compared to AURKA inhibitor LY3295668
- NRX-4972 has 58% oral bioavailability in mice and moderate clearance (17.5 mL/min/kg)

Plasma, tumor, brain exposure curves: athymic nude mice implanted subcutaneously (SC) with IMR32 neuroblastoma CDX model were treated orally, single dose (QDx1), n=3 per timepoint
Bioavailability and clearance: C57BL/6 mice were treated with a single dose either intravenously (IV) at 1 mg/kg or orally (PO) at 10 mg/kg

After a Single Oral Dose, NRX-4972 Rapidly Degrades AURKA Kinase in the IMR32 Neuroblastoma Tumor Model

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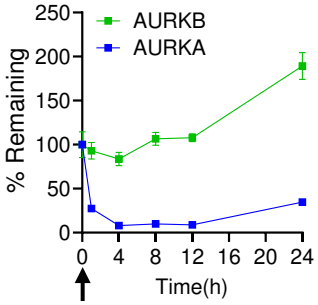
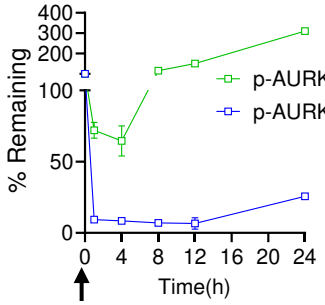
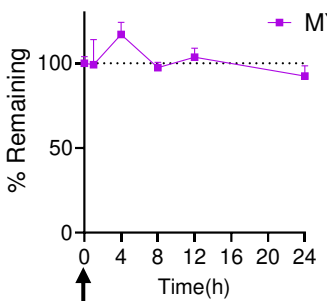
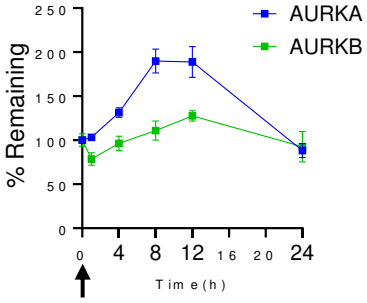
NRX-4972 AURKA degrader, single oral dose, 60 mg/kg

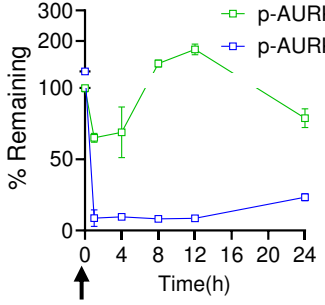


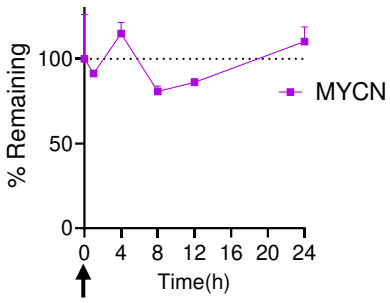




LY3295668 AURKA inhibitor, single oral dose, 50 mg/kg







Athymic nude mice implanted subcutaneously with IMR32 neuroblastoma CDX model were treated orally, single dose (QDx1)
IMR32 tumor protein levels measured by Jess Western, normalized to human GAPDH. % remaining calculated relative to vehicle control, n = 2 or 3 per timepoint

Following Three Days of Administration, NRX-4972 Leads to Prolonged Suppression of p-AURKA Kinase and Reduced Levels of MYCN

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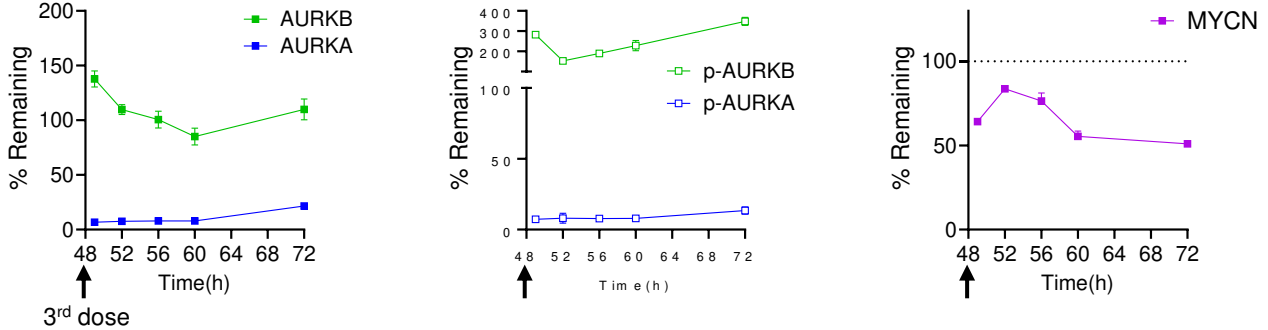
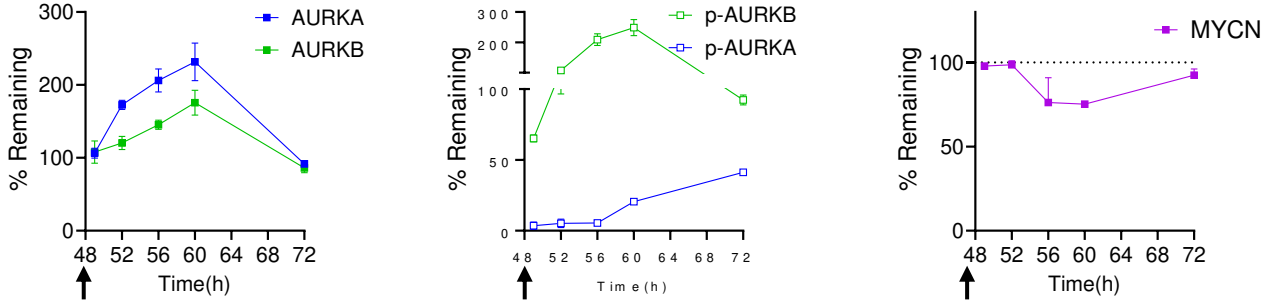
NRX-4972 AURKA degrader, 3 daily oral doses, 60 mg/kg



LY3295668 AURKA inhibitor, 3 daily oral doses, 50 mg/kg



Athymic nude mice implanted subcutaneously with IMR32 neuroblastoma CDX model were treated daily, orally, for 3 days (QDx3)
IMR32 tumor protein levels measured by Jess Western, normalized to human GAPDH. % remaining calculated relative to vehicle control, n = 2 or 3 per timepoint

NRX-4972 Induces DNA Damage Response, Apoptosis, and G2/M Arrest More Effectively Than an Inhibitor in the IMR32 Tumor Model

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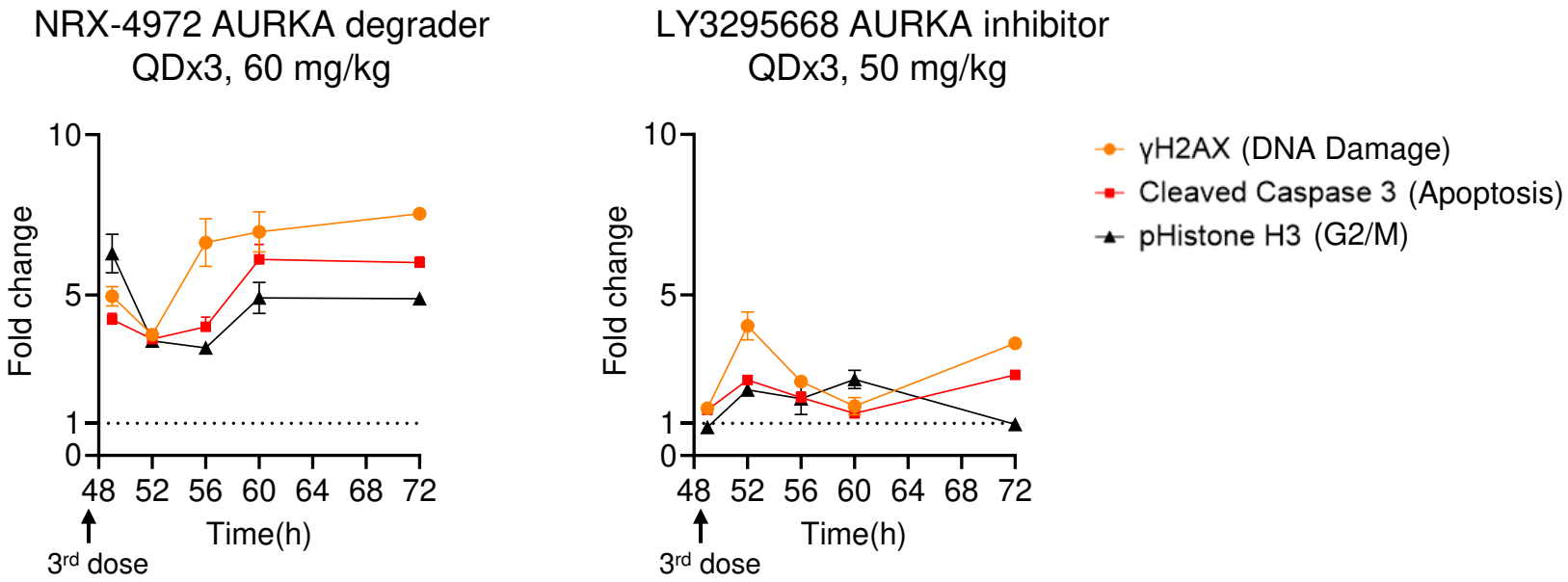

Athymic nude mice implanted subcutaneously with IMR32 neuroblastoma CDX model were treated daily, orally, for 3 days (QDx3)
IMR32 tumor protein levels measured by Jess Western, normalized to human GAPDH. % remaining calculated relative to vehicle control, n = 2 per timepoint

Pilot Studies with Prior Leads Caused Regression of IMR32 Tumors, While Inhibitors Only Achieved Stasis

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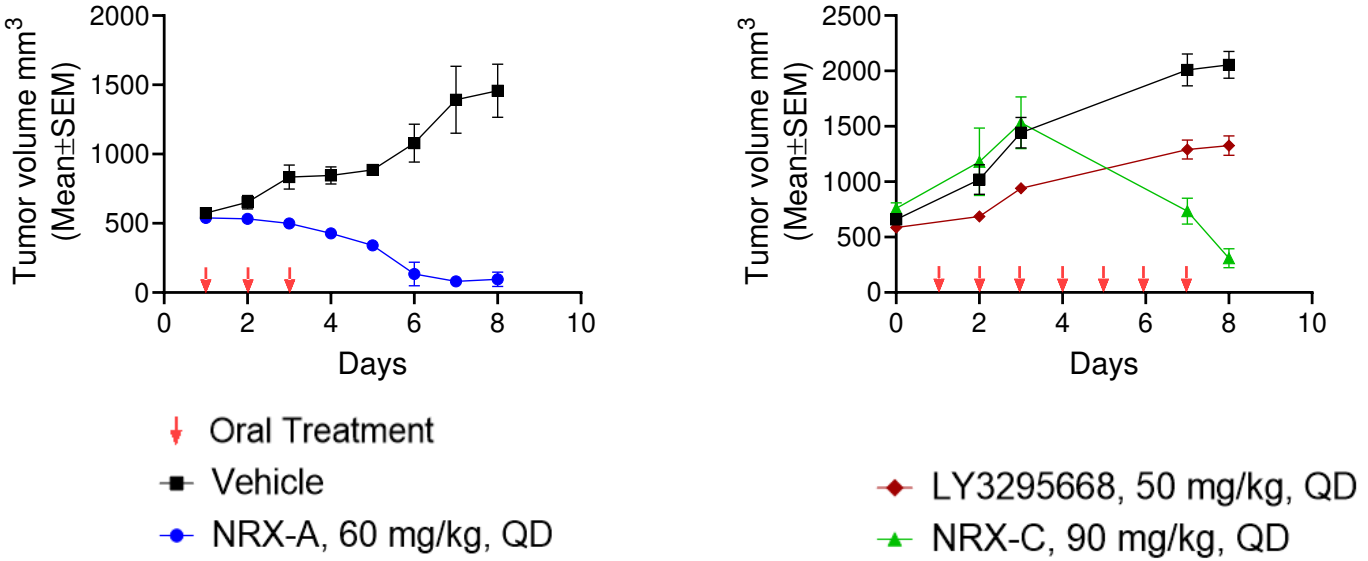

- Studies performed with increased tumor burden to assess activity of early leads and evaluate the potential benefit of degradation over inhibition

Athymic nude mice implanted subcutaneously with IMR32 neuroblastoma CDX model were treated daily, orally, for 3 or 7 days (QDx3 or QDx7); n = 2 to 5 mice per group

NRX-4972 Is Efficacious in Both IMR32 Neuroblastoma and H82 SCLC Tumor Models

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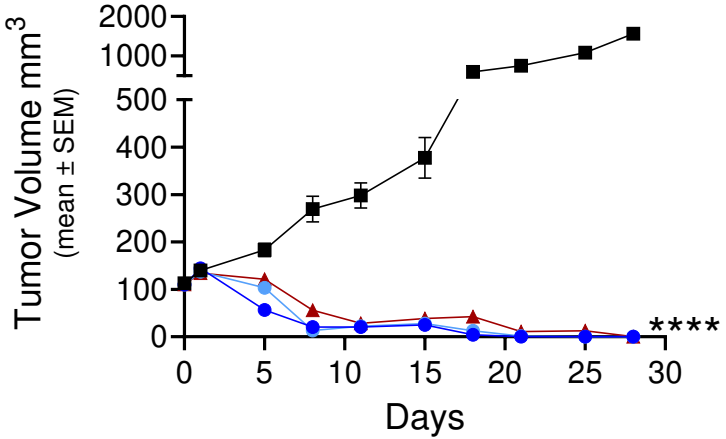
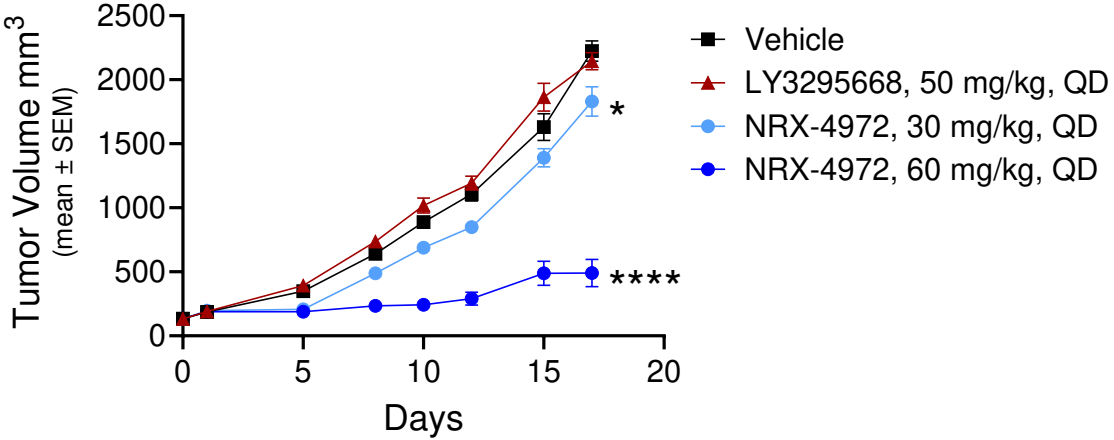
IMR32
(Neuroblastoma *MYCN*^{amp})



H82
(SCLC *RB1*^{null})



- Degradation maximizes target coverage and provides superior efficacy compared to an inhibitor

Athymic nude mice implanted subcutaneously with either IMR32 neuroblastoma or H82 SCLC CDX models were treated daily, orally, beginning on day 1, n = 10 mice per group. Statistical significance evaluated by either two-way ANOVA (IMR32) or mixed-effects analysis (H82) with Dunnett's multiple comparisons post-test.
*p value: * ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001, **** ≤ 0.0001*

Summary

- NRX-4972 is a potent and highly selective AURKA degrader
- NRX-4972 penetrates the CNS and has a superior PK/PD profile compared to an AURKA inhibitor
- Three days of daily oral NRX-4972 administration downregulated MYCN and induced DNA damage, apoptosis, and G2/M arrest more effectively than an AURKA inhibitor in IMR32 xenograft tumors
- NRX-4972 is efficacious in both the IMR32 neuroblastoma and the H82 SCLC tumor models
- NRX-4972 warrants further preclinical assessment of cancer types and therapeutic opportunities

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