NRX-4972, a Selective, Oral, Aurora kinase A Degrader, Demonstrates Increased Efficacy in an SCLC Tumor Model, and Greater In Vitro Synergy Than an AURKA Inhibitor

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Abstract

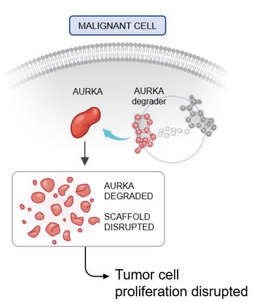
Aurora kinase A (AURKA) is frequently overexpressed in adult solid tumors, hematologic malignancies, and pediatric cancers. AURKA is a critical regulator of mitosis. Cancer cell lines particularly sensitive to AURKA loss include those derived from MYCN-amplified tumors (e.g., neuroblastoma) and from tumors with RB1 loss, such as neuroendocrine small cell cancers and CDK4/6-resistant breast cancers (Mou et al., 2021). Several AURKA inhibitors are effective in preclinical tumor models but have failed to translate into clinical efficacy. Recent studies have found that AURKA has kinase-independent scaffolding functions that are not effectively blocked through enzymatic inhibition (Otto, et al., Cancer Cell, 2009; Buchel, et al., Cell Reports, 2017).

To address the limitations of inhibitors, we developed NRX-4972, a CNS-penetrant, orally bioavailable and highly selective degrader of AURKA designed to remove both enzymatic and scaffolding functions. NRX-4972 has a superior PK/PD profile compared with an AURKA inhibitor and more effectively induces DNA damage, apoptosis, and G2/M arrest. Previously, we demonstrated that once-daily oral administration of NRX-4972 provides robust efficacy in the H82 mouse tumor model of SCLC, while an AURKA inhibitor is ineffective (Tian et al.; AACR; Cancer Res 2025;85(8_Suppl_1): Abstract 6379). Here, we demonstrate that NRX-4972 achieves superior efficacy in the same tumor model when administered twice-daily (BID). After over two months of treatment with NRX-4972, 60% of mice survived to the end of the study. In contrast, none of the mice treated BID with the AURKA inhibitors alisertib or LY3295668 survived to the end of the study.

To evaluate the benefit of AURKA degradation over inhibition in the combination setting, we performed an *in vitro* synergy screen across SCLC, NSCLC, and TNBC cancer cell lines. NRX-4972 and LY3295668 were compared in combination with a range of chemotherapeutics and targeted agents, and cell viability was evaluated for synergy using the Bliss independence model. The highest synergy scores were found in combination with NRX-4972, and more combinations with NRX-4972 resulted in synergy than with LY3295668. These data suggest that eliminating the kinase and scaffolding functions through degradation of AURKA increases the vulnerability of cancer cells to combination therapy.

Collectively, NRX-4972's superior preclinical profile highlights the potential of AURKA degraders to overcome the limitations of AURKA inhibitors and achieve meaningful therapeutic benefit.

Rationale



- 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
- AURKA has kinase-independent scaffolding functions targeted by degradation that are not effectively blocked by inhibition (e.g., MYC stabilization)

Results

Figure 1. NRX-4972 Is a Potent and Highly Selective AURKA Degrader

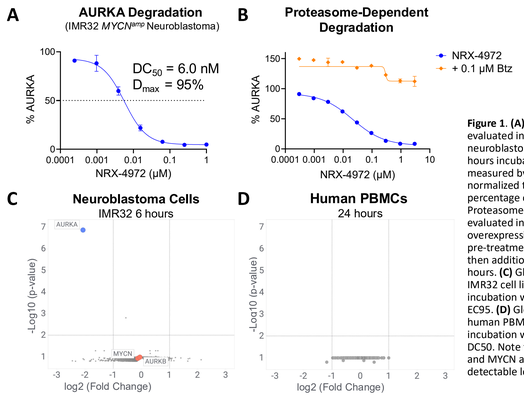


Figure 1. (A) NRX-4972 potency evaluated in human IMR32 neuroblastoma cell line after 6 hours incubation; AURKA measured by Jess Simple Western normalized to vinculin as a percentage of DMSO control. **(B)** Proteasome-dependence was evaluated in an MV4-11 AURKA-overexpression HiBiT line; 1 hour pre-treatment of bortezomib, then addition of NRX-4972 for 6 hours. **(C)** Global proteomics in IMR32 cell line after 6 hours incubation with NRX-4972 at EC95. **(D)** Global proteomics in human PBMCs after 24 hours incubation with NRX-4972 at 50x DC50. Note that AURKA, AURKB, and MYCN are not expressed at detectable levels in PBMCs.

Figure 2: NRX-4972 has High Oral Bioavailability and Superior Tissue and Brain Exposure Compared to AURKA Inhibitor LY3295668

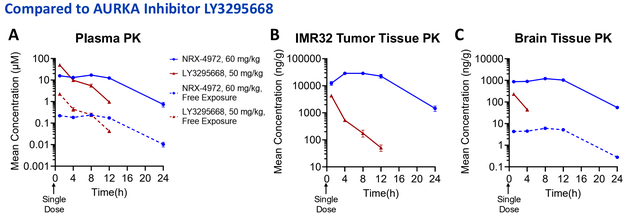


Figure 2. (A) Plasma, **(B)** tumor, and **(C)** brain exposure curves for NRX-4972 or LY3295668. Athymic nude mice implanted subcutaneously with IMR32 neuroblastoma CDX tumor cells were treated orally, single dose (QDx1), n=3. Free exposures (dotted lines) were determined for plasma but not tumor tissue. Free exposures in brain tissue were determined for NRX-4972 but not LY3295668.

Figure 3: NRX-4972 Administered Once Daily (QD) Achieves Superior Efficacy Compared to AURKA Inhibitor LY3295668

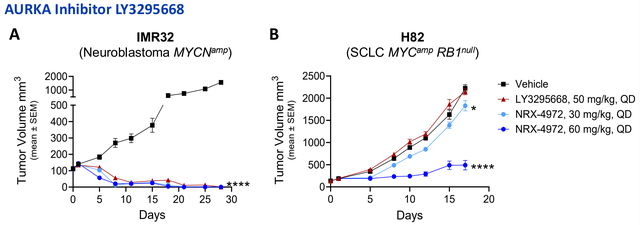


Figure 3. Athymic nude mice implanted subcutaneously with either **(A)** IMR32 neuroblastoma or **(B)** H82 SCLC CDX models were treated daily, orally, beginning on day 1, n = 10 mice per group. Statistical significance evaluated by either two-way ANOVA (IMR32) or mixed-effects analysis (H82) with Dunnett's multiple comparisons post-test. p value: * ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001, **** ≤ 0.0001

Figure 4: NRX-4972 Administered Twice Daily (BID) Further Improves Efficacy Compared To AURKA Inhibitors LY3295668 or Alisertib

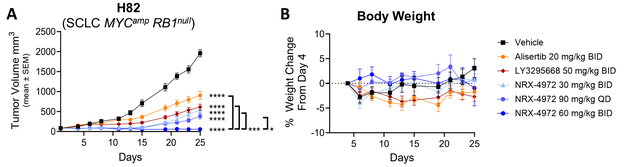


Figure 4. Athymic nude mice implanted subcutaneously with H82 SCLC CDX model were treated daily, QD or BID, beginning on day 1, n = 10 mice per group, and **(A)** tumor volume or **(B)** body weight were measured. NRX-4972 was formulated in water. Brief dosing holidays were administered to 2 mice in LY5668 group, 1 mouse in NRX-4972 60 mg/kg BID group. Statistics by mixed-effects analysis with Tukey's multiple comparisons post-test. p value: * ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001, **** ≤ 0.0001

Figure 5: NRX-4972 Administered Twice Daily (BID) Improves Survival Compared to AURKA Inhibitors LY3295668 or Alisertib

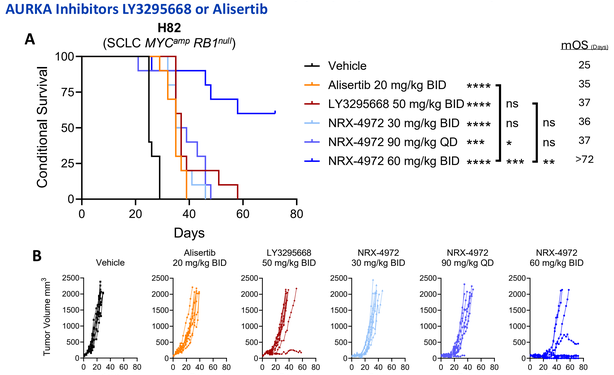


Figure 5: Animals shown in Figure 4 continued daily dose administration of treatments until end of study on day 72. **(A)** Conditional survival showing time to reaching humane endpoint with mOS (median overall survival) shown in days. **(B)** Tumor volumes of individual mice. Brief dosing holidays were administered to some mice in LY5668 or NRX-4972 treatment groups. Statistical significance of survival evaluated by Log-rank (Mantel-Cox) test, p value: * ≤ 0.05, ** ≤ 0.01, *** ≤ 0.001, **** ≤ 0.0001

Figure 6: Twice Daily (BID) Regimen Improves NRX-4972 Target Coverage Compared to AURKA Inhibitors and Increases Tumor DNA Damage and Apoptosis

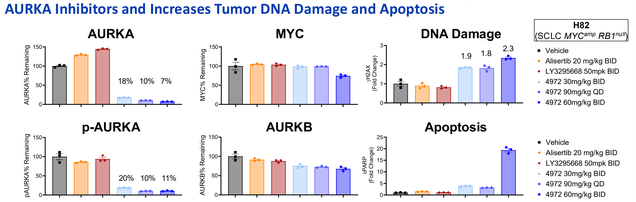


Figure 6: Athymic nude mice implanted subcutaneously with H82 SCLC CDX model were treated orally either QD or BID for 3 days. Tumor tissue was isolated either 24 hours (QD) or 12 hours (BID) after the final dose administration. Protein levels were measured by Jess Western, normalized to human GAPDH, and % remaining or fold change was calculated relative to vehicle control, n = 3 per timepoint. DNA damage marker: phospho-H2A.X (Ser139), p-AURKA: phospho-AURKA (Thr288), apoptosis marker: cleaved PARP.

Figure 7: NRX-4972 Degrader Achieves Higher In Vitro Bliss Synergy Scores Than AURKA Inhibitor Across Cancer Cell Lines In Combination With Chemotherapy or Targeted Agents

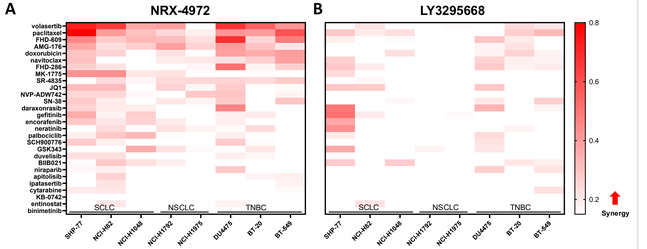


Figure 7. (A) NRX-4972 or **(B)** LY3295668 were tested for potential synergies in combination with 28 anti-cancer agents on 8 cancer cell lines for a total of 448 unique combination matrices. Single and combination agents were plated in a 6x6 dilution matrix with control wells and incubated for 5 days. Viability was determined by measuring intracellular ATP content with ATP Lite™, and effect-base synergy was determined by calculation of Bliss scores. The highest excess over Bliss score is shown as a heat map with red color of increasing intensity from 0.15 to 0.8.

Figure 8: NRX-4972 Combined With Paclitaxel Achieves Higher Bliss Synergy Scores Than AURKA Inhibitor Across Multiple Cell Lines

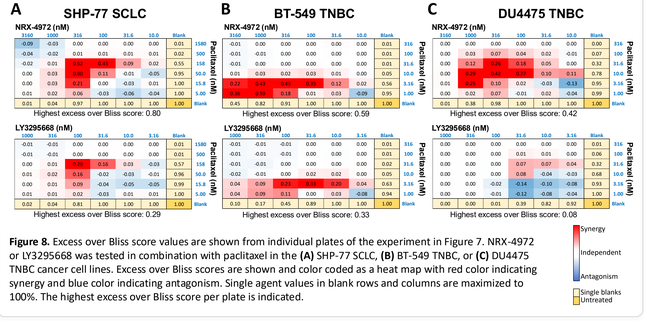


Figure 8. Excess over Bliss score values are shown from individual plates of the experiment in Figure 7. NRX-4972 or LY3295668 was tested in combination with paclitaxel in the **(A)** SHP-77 SCLC, **(B)** BT-549 TNBC, or **(C)** DU4475 TNBC cancer cell lines. Excess over Bliss scores are shown and color coded as a heat map with red color indicating synergy and blue color indicating antagonism. Single agent values in blank rows and columns are maximized to 100%. The highest excess over Bliss score per plate is indicated.

Conclusions

- NRX-4972 is a potent and highly selective AURKA degrader
- NRX-4972 is CNS-penetrant and has a superior PK/PD profile compared to an AURKA inhibitor
- NRX-4972 has superior efficacy to inhibitors in SCLC tumor models, especially when administered with a twice daily (BID) regimen
- NRX-4972 administration downregulated MYC and induced DNA damage, apoptosis, and G2/M arrest more effectively than AURKA inhibitors
- NRX-4972 synergized more strongly and with more combination agents than an AURKA inhibitor to kill TNBC, SCLC, and NSCLC cell lines

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