NXP900, a novel YES1/SRC kinase inhibitor currently in clinical development, potently inhibits tumor growth in FAT1 mutated xenograft models

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Introduction

NXP900, a highly-potent SRC family kinase (SFK) inhibitor (IC_{50} of 0.47 nM against YES1) has previously demonstrated high SFK selectivity and the capability to lock the protein at its native "closed" conformation (type 1.5 inhibitor), resulting in inhibition of both enzymatic and scaffolding activities[1]. Conversely, multi-kinase inhibitors dasatinib and bosutinib target the "open" conformation (type 1 inhibitors), thus promoting SFK association with signalling partners and, as a consequence, inducing a paradoxical enhancement of SFK activity when the inhibitor dissociates from the ATP site[2].

FAT atypical cadherin 1 (FAT1), a tumor suppressor gene encoding protocadherin, is among the most frequently mutated genes in human cancers. Loss of FAT1 in various tumor cells, including squamous cancer cells, results in increased protein levels and activity of the hippo pathway transcriptional regulator YAP1. In turn, this increase leads to nuclear localization and elevated expression of YAP1/TAZ pro-oncogenic target genes, resulting in increased tumor cell proliferation[3]. Furthermore, FAT1 loss contributes to whole-genome doubling through the dysregulation of YAP1[4]. Nuclear localization of YAP1 is regulated by direct phosphorylation by YES1 and SRC kinases[5,6], hence we hypothesized that FAT1 mutated models would be sensitive to NXP900.

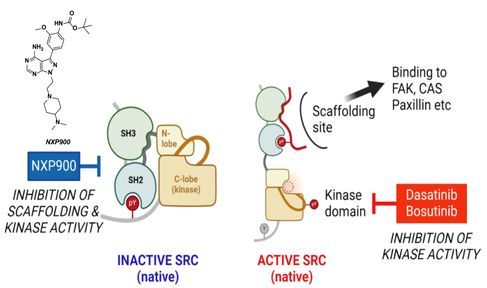
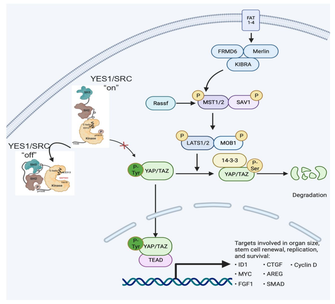


Figure 1. Mechanism of SRC inhibition. NXP900 locks SRC in its native inactive conformation inhibiting both catalytic and scaffolding functions (made with Biorender).

FAT1 mutations contribute to YAP1 dysregulation



- Inactivating genomic alterations in key Hippo genes including **FAT1**, NF2 and LATS1 lead to reduced YAP1 degradation.
- SRC and YES1 phosphorylate YAP1 Y357 promoting nuclear accumulation.
- Nuclear YAP1 regulates gene expression impacting cell proliferation, migration, EMT, differentiation, and drug resistance.

Figure 2. Hippo pathway inactivating mutations lead to YES1/SRC-dependent YAP1 nuclear accumulation (made with Biorender).

Squamous cancer patients present genetic alterations in *YES1*, *YAP1* and *FAT1*

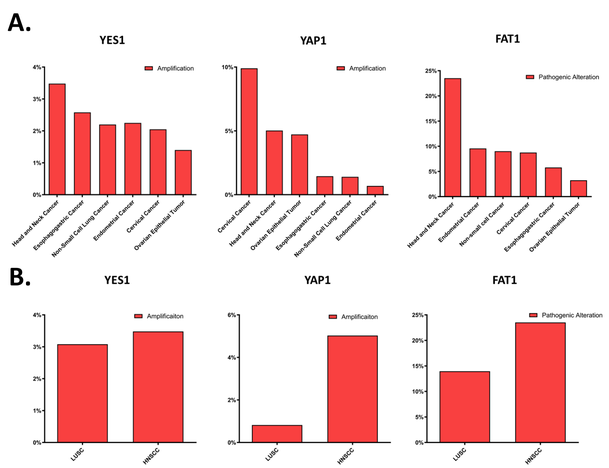


Figure 3. Study of genetic alterations of *YES1*, *YAP1* and *FAT1* in different cancer patient populations. Levels of gene amplification (at least 4 copies per GISTIC) of *YES1*, *YAP1* or *FAT1* pathogenic alterations (inclusive of mutation and deep deletions) in **A.** cervical, ovarian, endometrial, esophagogastric, head and neck, and NSCLC cohorts. **B.** Lung squamous (LUSC) and head and neck squamous cell carcinoma (HNSCC). Data Source: The cBio Cancer Genomics Portal[7].

NXP900 inhibits squamous cancer cells proliferation and YAP1 nuclear localization

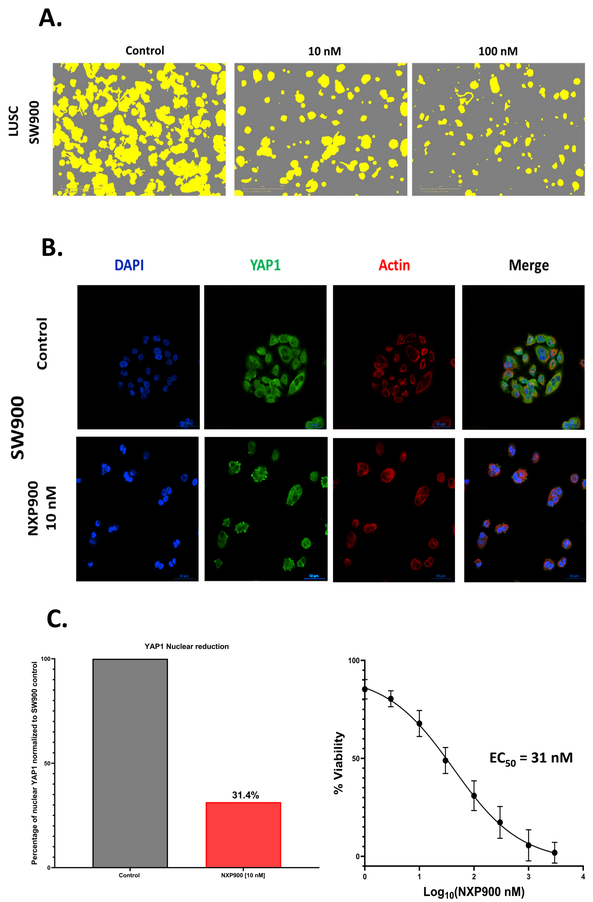


Figure 4. Study of LUSC proliferation and YAP1 localization after treatment with NXP900. A. IncuCyte images of SW900 LUSC cells (masked in yellow) after treatment with DMSO (control) or NXP900 at different concentrations. **B.** Immunofluorescent confocal imaging study of YAP1 localization in SW900 cells, NXP900 at 10 nM for 24-hours (x60). **C. Left:** Quantification of nuclear YAP1 in SW900 cells after treatment with NXP900. **Right:** Dose-dependent curve of SW900 cells treated with NXP900 for 72-hours (n=3).

NXP900 demonstrates potent *in vivo* tumor growth inhibition in *FAT1*-mutated squamous carcinoma models

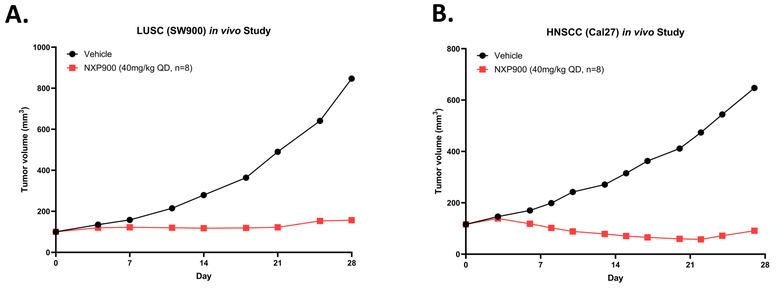


Figure 5. *In vivo* efficacy study in *FAT1*-gene across mutated lung, and head and neck squamous cell carcinoma models: vehicle versus NXP900.
Model: NSCLC *FAT1*^{MUT} – SW900 and HNSCC *FAT1*^{MUT} - Cal27 mouse models (no other known drivers). **A.** Analysis of LUSC tumor volume across 28 days (SW900: SNV causing LOF and protein change p.E2705Ter). **B.** Analysis of HNSCC tumor volume across 27 days (Cal27: heterozygous FAT1 copy loss).

Conclusions

- NXP900 inhibits YAP1 nuclear localization and cell proliferation at low nM concentration in *FAT1*-mutated squamous carcinoma cells.
- NXP900 potently inhibits tumor growth *in vivo* in *FAT1*-mutated squamous xenograft models.
- Our data suggests that NXP900 has therapeutic potential as single agent in *FAT1*-mutated cancers.
- A Phase 1b study in patients with *FAT1, YES1* and other genomic alterations in solid tumors is actively recruiting (NCT05873686).

Acknowledgements and Contacts

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