Inhibition of HSF1 Demonstrates Therapeutic Efficacy in Preclinical PDX Models of Human Cholangiocarcinoma

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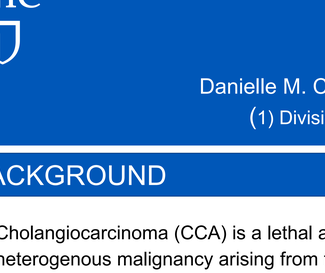
BACKGROUND

- Cholangiocarcinoma (CCA) is a lethal and heterogenous malignancy arising from the biliary tree
- Treatment success has been hindered by primary or acquired resistance despite the development of targeted therapies
- *ARID1A* mutations are observed in up to 14% of CCA tumors
- NXP800 is a heat shock factor 1 (HSF1) inhibitor with activity previously noted in ovarian cancer with *ARID1A* mutations

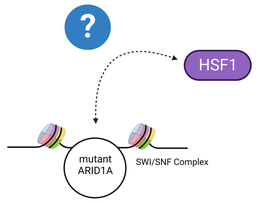
OBJECTIVES

- Evaluate therapeutic efficacy of NXP800 and HSF1 inhibition in cholangiocarcinoma



Schematic of HSF1 biological role in cancer cell survival and NXP800 mechanism

- Determine the CCA epigenetic regulation and disruption of the ARID1A complex



Schematic of HSF1 interaction with ARID1A

METHODS

- NXP800 was utilized to treat and generate dose response curves in both human and murine CCA cell lines
- Whole Exome Sequencing was done on two patient derived xenograft (PDX) models to characterize *ARID1A* mutation presence and activity in CCA
- Nod scid mice were implanted with either an *ARID1A* frameshift mutant PDX model or an *ARID1A* wildtype PDX model of cholangiocarcinoma
- HSF1 inhibition using NXP800 was tested as a therapeutic strategy in the two chosen PDX models

RESULTS

FIGURE 1

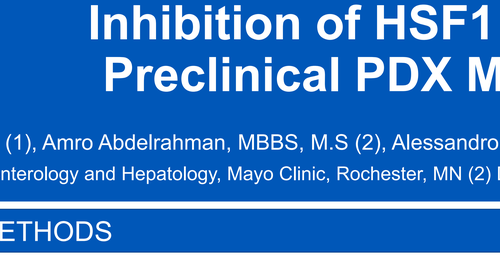


Figure 1: Dose response curve in one murine and two human CCA cell lines to NXP800

FIGURE 2

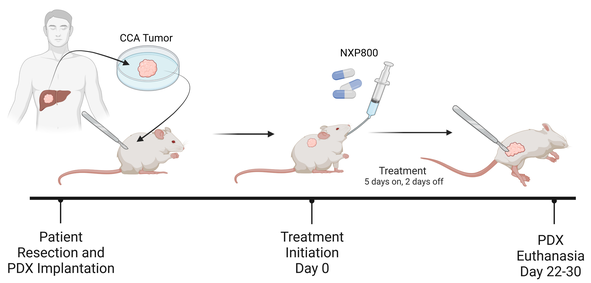
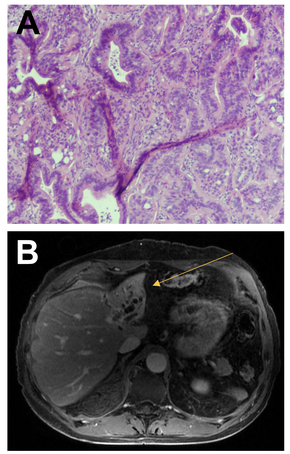
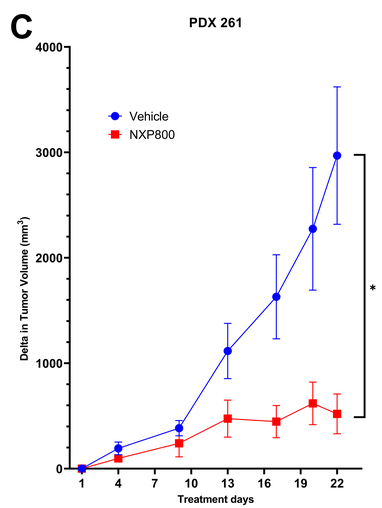


Figure 2: *In vivo* NXP800 treatment study in PDX CCA models.

FIGURE 3

PDX 261 65 yo male, intrahepatic cholangiocarcinoma, *ARID1A* frameshift mutation





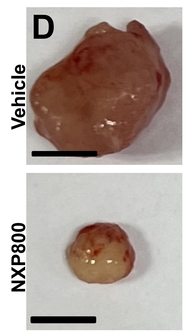
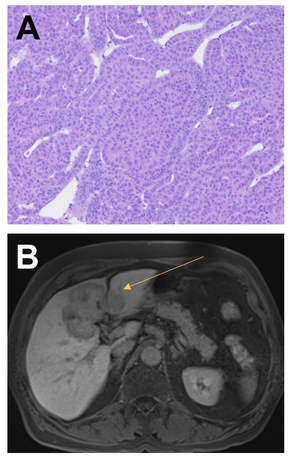
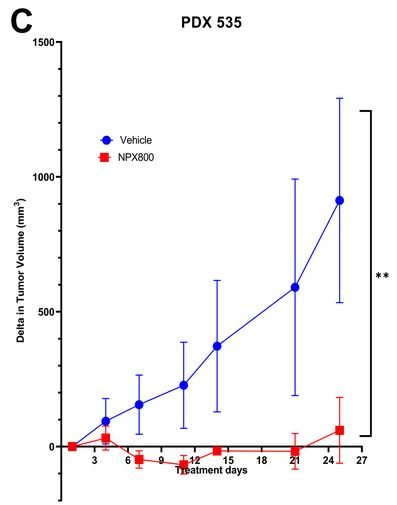


Figure 3: **(A)** Histology characterization of PDX 261 tumor. **(B)** Gross image of patient before resection. **(C)** Tumor volume following NXP800 treatment in nod scid flank **(D)** Gross images of mouse tumor following NXP800 treatment, bar 1 cm.

FIGURE 4

PDX 535 78 yo male, intrahepatic cholangiocarcinoma, *ARID1A* wild type, FGFR1 and 2 overexpression





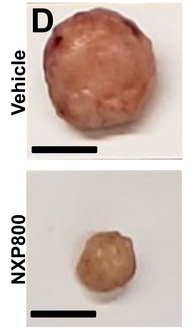


Figure 3: **(A)** Histology characterization of PDX 535 tumor. **(B)** Gross image of patient before resection. **(C)** Tumor volume following NXP800 treatment in nod scid flank **(D)** Gross images of mouse tumor following NXP800 treatment, bar 1 cm.

CONCLUSIONS

- NXP800 has picomolar efficacy in both human and murine CCA cell lines *in vitro*
- HSF1 inhibitor, NXP800, demonstrated significant therapeutic response in *ARID1A* mutant and wildtype CCA PDX tumors

FUTURE DIRECTIONS

- Continuation of treatment of both murine and human CCA cell lines with NXP800
- Use of heat shock factor 1 inhibition to treat PDX models with previous characterized HSF1 mutations
- Use of NXP800 as a therapeutic strategy to treat multiple syngenic murine models of CCA

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FUNDING SOURCES

1. Mayo Clinic Department of Surgery
2. Mayo Clinic Center for Individualized Medicine

Abbreviations: ∗ p-value ≤ 0.05; ∗∗ p-value ≤ 0.01