The Anticancer Effects of Supinoxin (RX-5902) in Pancreatic Carcinoma

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Abstract 238

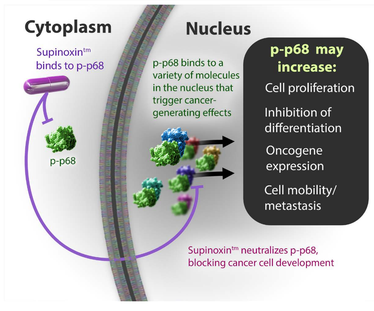
Abstract

DEAD box RNA helicase DDX5/p68, and its phosphorylated form in particular, may play several important roles in cancer by means of cell transformation, epithelial mesenchymal transition (EMT), and cell migration, deeming it a promising target for novel anti-cancer therapeutics. We have previously shown that Supinoxin (RX-5902) interacts with phosphorylated p68 on Tyr593, interfering with the phosphorylated p68-β-catenin signaling pathway. Supinoxin also inhibits motility of MDA-MB231 breast cancer cell lines and could potentially prevent metastasis in cancer. In this study, we first demonstrated anti-proliferative effects in several cell lines originated from pancreas (5 cell lines) with a high level of sensitivity to Supinoxin (IC50 of 18 nM). We also sought to examine the tumor growth inhibition (TGI) and/or tumor growth delay (TGD), and survival benefits of Supinoxin in the human pancreatic carcinoma (MiaPaCa-2) xenograft mouse model. In the MiaPaCa-2 model, at 50 and 70 mg/kg daily (oral, 5 days on/2 days off) for 3 weeks, both doses delayed tumor growth significantly (83% and 339%; P<0.001). All animals in the high dose showed complete regression (CR) and completing the study as tumor free survival (TFS; Day 65); one animal showed CR and TFS in the lower dose. Gemcitabine (120 mg/kg ip; Q3D for 4 weeks) resulted in TGD of 71% (P<0.001), with no CRs. Supinoxin did not result in a reduction in body weight gain, treatment related deaths, or clinical observations in this tumor model. These data support the potential therapeutic activity of Supinoxin in pancreatic cancer. A Phase 1 study of Supinoxin on relapse/refractory solid tumors is ongoing (NCT02003092).

Introduction

- Supinoxin (RX-5902) is an orally administered, potential first-in-class, small molecule inhibitor of phosphorylated-p68 (p-p68)
- p-p68, which is selectively overexpressed in cancer cells and is absent in normal tissue, increases the activity of multiple cancer related genes including cyclin D1, c-jun and c-myc, and plays a role in tumor progression and metastasis
- RX-5902 is currently being evaluated in a Phase I dose-escalation clinical trial in cancer patients with relapsed/refractory solid tumors (NCT02003092)

Mechanism of Action



- Platelet-derived growth factor (PDGF) stimulation leads to phosphorylation of p68 at Y593 in the cell nucleus
- The Y593-phosphorylated p68 promotes β-catenin nuclear translocation; studies to better elucidate p-p68-Wnt interaction are needed
- p-p68 facilitates β-catenin nuclear translocation by blocking phosphorylation of β-catenin by GSK-3β and displacing Axin from β-catenin
- The β-catenin nuclear translocation and subsequent interaction with transcription factors is required for the epithelial–mesenchymal transition process (initiation of metastasis for cancer progression)

Methods

In vitro

Pancreatic cancer cells were plated in 96-well plates. Twenty-four hours after plating, the cells were treated with various concentrations of RX-5902 for 96 hours. Cell growth inhibition was measured by Sulforhodamine B colorimetric (SRB) assay and IC50s were obtained.

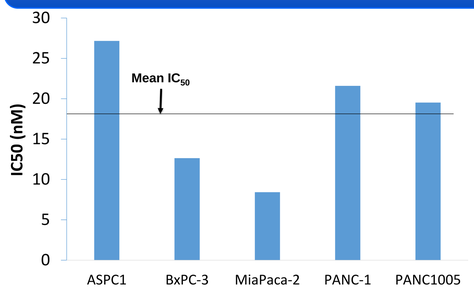
In vivo Studies:

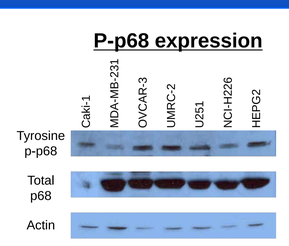
Tumor growth inhibition (TGI), tumor growth delay (TGD), and survival benefits of RX-5902 was evaluated in two human pancreatic cancer xenograft mouse models. In both models, body weight was assessed as a measure of safety and tolerability.

Model 1: Anti-tumor activity of RX-5902 was assessed in BxPC-3 human pancreatic tumor in female BALB/c nude mice after oral administration at 3, 10 and 30 mg/kg, given daily for 18 days. Starting tumor volume was ~70 mm^3.

Model 2: Anti-tumor activity of RX-5902 was assessed in MiaPaca-2 human pancreatic tumor in female athymic nude mice. RX-5902 was administered to 2 groups at 50 and 70 mg/kg, respectively, po, 5 on/2 off x 3 weeks. The starting tumor volume was ~120 mm^3. Gemcitabine was also administered as a control agent at 120 mg/kg by intraperitoneal injection (ip), once every third day for 4 doses (q3d x4).

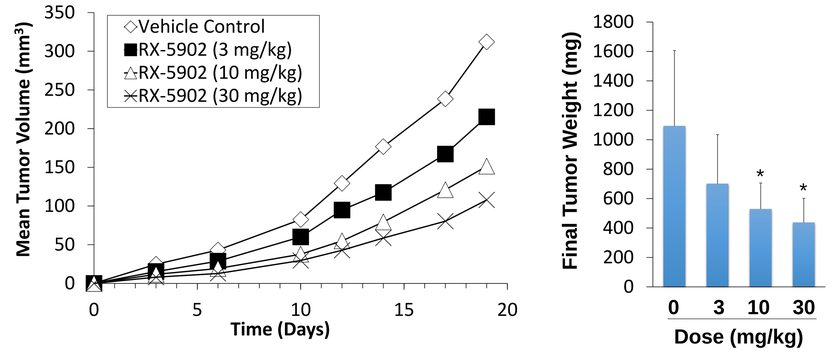
Anti-tumor Activity – In Vitro





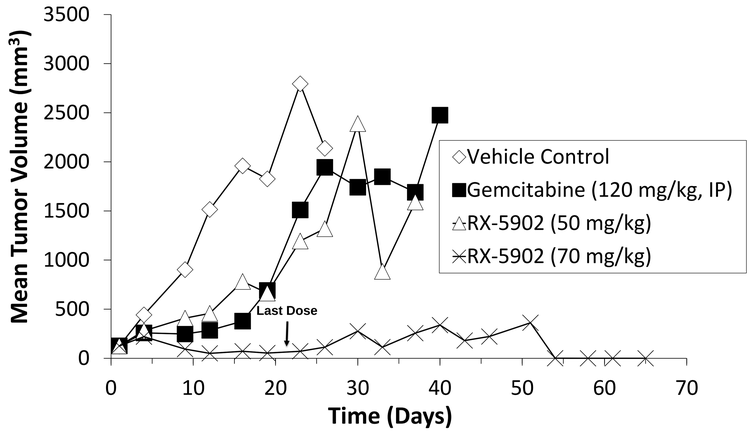
- Five pancreatic cancer cell lines were tested
- All cell lines are sensitive to RX-5902
- Overall IC_{50} ~ 18 nM across all cell lines
- High level of p-p68 expression in various cancer cell lines (Western blots)
- p-p68 may serve as a potential predictive biomarker

RX-5902 Efficacy in Mice: Model 1



Antitumor activity of RX-5902 in BxPC-3 tumor xenograft model (N=6 per group). RX-5902, at 3-10 mg/kg, when given orally once daily for 3 weeks, inhibited tumor growth and was well tolerated. *, P<0.05 vs. control (0 mg/kg dose)

Anti-tumor Activity in Mice: Model 2



	%TGD	TGI%	Tumor Regression		
			PR	CR	TFS
Gemcitabine (N=10) 120 mg/kg; IP, q3d)	71***	46	0	0	0
RX-5902 (N=10) (50 mg/kg; oral, 5on/2off)	83***	58	0	1/10	1/10
RX-5902 (N=10) (70 mg/kg; oral, 5on/2off)	339***	97	1/10	**7/10**	**7/10**

TGI on Day 23. ***, P<0.001 Compared to vehicle. PR=partial regression, CR=complete regression, TFS=tumor free survival

- Oral administration of RX-5902, when given on a 5 days ON/2 days OFF schedule for 21 days, dose-dependently inhibited tumor growth in MiaPaca-2 xenograft model
- At a higher daily oral dose of RX-5902 (70 mg/kg), 7 of 10 (70%) mice showed a complete regression and 7 of 10 (70%) mice showed tumor free survival
- Both doses were well tolerated based on body mass measurements
- Doses of 50 and 70 mg/kg in mice correspond to approximately 250 to 340 mg daily dose in human patients (assuming a 60 kg person)

Summary and Conclusions

- RX-5902 demonstrates anti-proliferative effects in various pancreatic cancer cell lines
- When given orally on a daily basis (current clinical dosing paradigm), RX-5902 inhibits tumor growth with clinically meaningful TGI% (>60%) in two xenograft models
- These data support the potential therapeutic benefits of RX-5902 in pancreatic carcinoma
- A Phase 1 study of RX-5902 on relapsed/refractory solid tumors is ongoing (NCT02003092)

Investigator Disclosures

All authors are employees of Rexahn Pharmaceuticals, Inc.

For further information about RX-5902 and Rexahn Pharmaceuticals please contact Reza Mazhari (mazharir@rexahn.com) or DJ Kim (kimdj@rexahn.com)