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The potent quadruplex-binding compound QN-302 down-regulates the S100P gene in *in vitro* and *in vivo* models of pancreatic cancer: a potential therapeutic target and biomarker for PDAC

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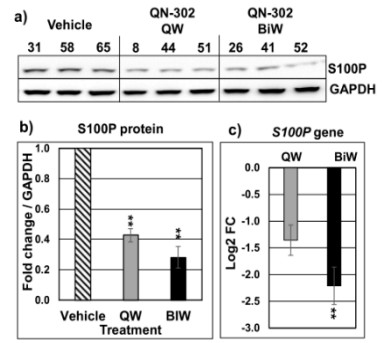
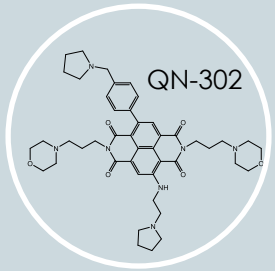
Abstract #4981



Expression data on material from MIA-PaCa2 xenograft dosing QW & BiW with QN-302 Quantitation of qPCR and Western blot data shown for the S100P gene and protein in the treated vs vehicle control animals. Statistical significances are indicated by *P < 0.05, **P < 0.01

QN-302 - a tetra-substituted naphthalene diimide derivative (Ahmed et al, 2020); high potency, targets quadruplex (G4) sequences in the promoter regions of cancer genes; 1-2 nM anti-proliferative activity in a panel of human pancreatic cancer (PDAC) cell lines; significant anti-tumor activity in xenograft, orthotopic and genetic (KPC) models of PDAC



S100P is a small Ca^{2+} calcium binding protein involved for example, in the oncogenic PI3K/AKT signaling pathway. It is over-expressed in ca 70% of human PDACs. Previous studies have suggested it as a therapeutic target and/or biomarker.

This study examines S100P levels in a small group of PDAC patients and the effect of QN-302 on PDAC cells and an *in vivo* model of PDAC. The potential of the *S100P* gene as a direct G4 target for QN-302 is also examined.

Gene	QN-302 24 h	P value	PDAC - normal	P value	No of PG4s
S100P	-3.230	0.08	45.27	0.054	60
CX3CL1	-2.912	0.040	2.87	0.017	5

Expression changes in two PDAC-expressing genes:

LHS: From RNA-seq on MIA-PaCa2 cells tumors 24 hr QN-302 exposure minus

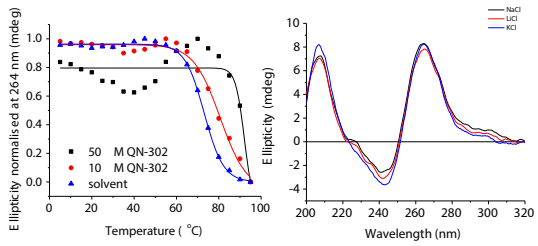
RHS: From RNA-seq on human PDAC values from normal pancreas

Bioinformatics has located ca 60 G4s in the S100P gene. This putative G4 sequence is in the S100P promoter, 48 nu upstream from the tss

5'-TGTCCCAACCCCACTGTCCCACCCTCT
3'-GGGTTGGGGTGACAGGGTGGG

Sample ID	Age	Gender	Diagnosis/tissue composition
R2971	65	Male	Poorly differentiated adenocarcinoma with invasion
R2944	65	Male	Poorly differentiated ductal adenocarcinoma with necrosis
R2824	71	Male	Moderately differentiated ductal adenocarcinoma of the head of pancreas with invasion (ductal epithelial changes of high grade
R2700	70	Male	Moderately differentiated ductal adenocarcinoma with invasion and necrosis

A list of PDAC patient samples with their diagnoses, four of which were chosen for RNA-seq. Normal pancreatic samples of three healthy male individuals with age-matching the PDAC patients were obtained commercially and used in the differential gene expression analysis



CD melting titration with 10 μM S100P G4 in 10 mM Li+ Cacodylate, pH 7.0, 100 mM KCl and QN-302

CD spectra consistent of above sequence shows a parallel G4 10 μM in 10 mM Li+ Cacodylate, pH 7.0

S100P is elevated in human PDAC, agrees with previous studies (Human Cancer Genome Project)
S100P is down-regulated by the G4 compound QN-302 in cells and *in vivo*: a potential biomarker for QN-302 therapy? The S100P gene contains a G4 in its promoter, binds QN-302. Is this G4 a major target for QN-302?

QN-302 is bio-available and well tolerated at therapeutic doses in animal models. It is being developed for clinical evaluation by Qualigen Therapeutics Inc and is currently undergoing GLP toxicity evaluation prior to IND submission. It was granted Orphan Drug status for PDAC by the FDA in January 2023.