The quadruplex-binding compound QN-302 targets the S100P gene in PDAC

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The compound **QN-302**, a tetra-substituted naphthalene diimide derivative has been previously disclosed to have single-digit nM anti-proliferative activity in a panel of human pancreatic ductal adenocarcinoma (PDAC) cell lines (Ahmed *et al*., *ACS Med Chem Lett*, 2020, **11**, 1634-1644) and significant anti-tumor activity in the MIA-PACA2 xenograft model for PDAC as well as in the KPC model. It has good bio-availability at therapeutic doses. QN-302 is currently in advanced pre-clinical development with Qualigen Therapeutics Inc

The proposed mode of action of QN-302 involves high-affinity (nM) binding to, and stabilization of G4-forming sequences, which are over-represented in cancer-related and proliferative genes

Transcriptome (RNA-seq) analyses of QN-302 in MIA-PACA2 cells has confirmed this hypothesis and has revealed a pattern of susceptible genes, involved in cancer-associated pathways and carry (G4) signals in their promoters. Expression of the S100P gene is among the most highly down-regulated as a result of drug treatment (see Table below)

RNA-seq analyses have recently been performed on tumor material from human patients, and gene changes from poorly-differentiated tumors compared with expression data from a normal pancreas. S100P is notably highly over-expressed (45-fold) in the small sample set used in this study

This agrees with data in the published 229 gene set associated with human PDAC. This set includes SPARC, CX3CL1 and S100P, which is outstanding in being over-expressed in over 2/3 of human PDAC tissues (https://www.proteinatlas.org/ENSG00000163993-S100P/pathology/pancreatic+cancer#Location). The Table below compares data for these three genes. S100P is the outstanding target candidate

The S100P gene has a G4 promoter sequence starting at -48 nu from the TSS, strongly suggestive of a stable G4 structure: 5'-TGGGTGGGGCAGTGGGGTTGGGT
Its stability, structure and interactions with QN-302 are currently being studied at UCL

Taken together, we suggest that this data supports the concept of S100P being a therapeutic target and a potential marker in future clinical studies of response to targeting by QN-302 and its effects on PDAC progression

Gene	Down-regulation by QN-302, 24 hr, MIA-PACA2 cells	P	Fold change in expression in poorly-differentiated human tumours relative to normal pancreas tissue	P	No of PG4s	Gene function	PDAC role and occurrence
SPARC	-2.252	0.61	2.685	0.07	10	Secreted protein acidic and cysteine rich	Promotes pancreatic cancer cell proliferation and migration
S100P	**-3.230**	**0.08**	**45.27**	**0.05**	**3**	Calcium binding protein involved in signal transduction	Sensitive and specific marker for the detection of PDAC, promotes PDAC growth and survival, upregulated in PDAC
CX3CL1	-2.912	0.04	2.87	0.02	5	Chemokine	Modulates the development of PDAC via JAK/STAT signalling pathway; upregulated in PDAC

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