



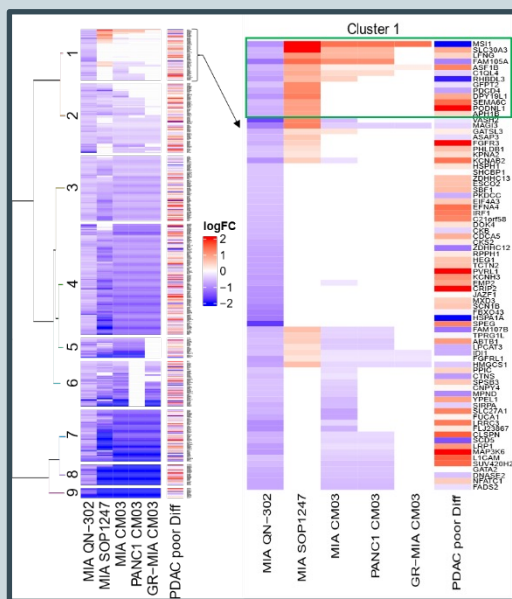
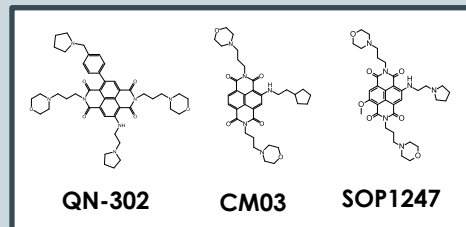
Target genes in pancreatic cancer cells of the Pan G-Quadruplex clinical candidate compound QN-302 revealed by comparative transcriptome profiling

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Abstract #
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- QN-302 is a pan-quadruplex (G4) compound that targets G4s in promoter regions and down-regulates the expression of many cancer genes and pathways
- Orphan Drug status for PDAC was granted by FDA in January 2023
- Qualigen Therapeutics Inc was granted IND clearance for QN-302 by FDA in July 2023
- Patient recruitment for US multi-center Phase I trial starting in 4Q23



QN-302 is 10-fold more potent than two related analogs, CM03 and SOP1247 in MIA-PACA2 cells (SRB 96 h and G4 stability shown in Table below)
Data also for CM03 in a GEM-resistant line and in PANC-1 cells
RNA-seq and cluster analysis used to examine possible differences and the basis of the superior potency of QN-302

	QN-302	CM03	SOP1247
IC₅₀ 96 hr (nM)			
MIA-PACA2	1.3	9.0	13.8
PANC-1	1.4	15.6	15.7
CAPAN-1	5.9	26.5	38.8
Bx-PC3	2.6	15.5	20.5
MIA-PACA2-GemR	3.8	14.9	N/A
ΔT_m (°)	23.1	17.6	18.4

Genes with log₂FC < -0.5 and a false discovery rate < 0.05 to eliminate those unlikely to be statistically significant were retained for cluster and subsequent analyses of the RNA-seq data. Putative G4 sequences (PQs) in an individual gene were estimated from the occurrence of the canonical G4 motif (G₂₃N1-7G₂₃N1-7G₂₃N1-7G₂₃). Hierarchical cluster analysis (LHS) was used to identify 9 distinct clusters of genes from their expression patterns.

The RNA-seq data (RHS) for some of the most down-regulated genes show changes in G4-rich genes in hedgehog, WNT, axon guidance, signal transduction and hippo pathways as well as in some transcriptional, chemokine and transporter genes. Responses to CM03 and SOP1247 are similar, reflecting their close structural similarity and their similar G4 binding. QN-302 affects far fewer genes (data not shown), but also several genes that are mostly unaffected by the other compounds, coding for eg NTN4 in the WNT/β-catenin pathway; GLI1 in the hedgehog pathway; CX3CL1, a chemokine; S100P, a Ca²⁺ protein; CLIC3, ion channel.

We conclude that QN-302 in PDAC cells produces significant changes in the pattern of down-regulated G4 genes compared to the two related but less potent compounds. This may be a consequence of differences in G4 affinity at the promoter level, which have yet to be established. It is notable that the G4-rich genes NTN4, GLI1, CX3CL1, S100P, CLIC3 down-regulated by QN-302, are up-regulated in human PDAC (www.proteinatlas.org) and correlate with disease progression, supporting the hypothesis that these genes are involved in the therapeutic response to QN-302

Functional relevance, gene name	SOP1247 in MIA-PaCa2	CM03 in MIA-PaCa2	CM03 in MIA-PaCa2R	CM03 in PANC-1	QN302 in MIA-PaCa2	PQS
Hedgehog pathway						
GLI1	-0.13	0.03	-0.57	-0.57	-1.84	15
GLI2	-0.74	-1.24	0.00	0.38	-0.15	71
GLI3	2.63	-0.58	0.00	0.28	-0.47	13
GLI4	-2.67	-1.26	-2.76	-1.71	-0.90	11
WNT pathway						
WNT5B	-0.66	-0.97	0.34	-0.01	-0.58	8
DVL1	-1.87	-1.35	-2.68	-1.56	-0.77	30
AXIN1	-0.92	-0.72	-1.35	-0.74	-0.39	18
APC2	-3.20	-1.61	-3.17	-1.62	-1.06	4
Axon guidance						
PAK1	-1.39	-1.13	-1.74	-1.11	-0.22	14
ROBO3	0.08	-0.53	-1.09	-0.85	-0.23	19
PLXNA1	-1.82	-1.96	-2.55	-1.50	-0.92	54
NTN4	3.47	4.04	N/A	0.95	-2.46	13
Hippo pathway						
TAZ	-0.88	-1.10	-1.49	-0.74	-0.56	8
TEAD2	-0.52	-0.91	-0.37	0.21	-0.61	19
TEAD3	-0.14	-0.66	-0.33	0.07	-0.43	29
TEAD4	-0.50	-0.31	-0.77	-0.04	-0.13	34
SHANK2	-2.4	-1.96	N/A	-0.44	-0.37	203
SHANK3	-1.34	-0.85	-0.95	-1.12	-0.11	42
Transcriptional genes						
PRDM16	-3.88	-3.39	-3.48	-3.14	-1.91	260
TP73	-1.49	-1.19	-2.37	-0.99	-0.61	91
CBFA2T3	-2.90	-2.86	-3.32	-2.24	-1.50	96
MYC	-0.02	0.34	0.71	0.71	-0.07	4
Chemokines						
CX3CL1	-1.08	-1.82	N/A	0.62	-2.91	5
CXCL1	-2.90	-1.38	-1.38	-1.69	-1.37	1
Signal transduction pathways						
KRAS	0.22	-0.15	-0.17	0.05	-0.10	4
MAPK11	-2.12	-2.56	-3.03	-1.59	-1.72	18
MAPK12	-1.11	-1.23	-0.68	-1.44	-0.70	18
AKT1	-1.20	-0.98	-1.55	-1.04	-0.37	44
ARF6	-0.99	-0.54	-0.99	-0.69	-0.22	7
IGSECT	-0.79	-0.53	-0.80	-0.50	-0.20	82
Transporter related						
SLC19A1	-4.70	-3.94	-5.25	-2.05	-2.27	38
SLC29A1	-0.49	-0.16	-0.80	-0.15	-0.17	25
CLIC3	1.05	0.82	N/A	-0.29	-2.77	6
Misc function						
BCL2	-1.76	-1.24	-1.82	N/A	-0.48	21
NTERT	-3.32	-2.47	-4.21	-0.98	-1.03	15
S100P	-0.53	N/A	1.47	N/A	-3.23	60