A comparison of the activity of the quadruplex-targeting experimental drugs QN-302 and CX-5461 (Pidnarulex) in wild-type and gemcitabine-resistant pancreatic cancer cells

Abstract # 390

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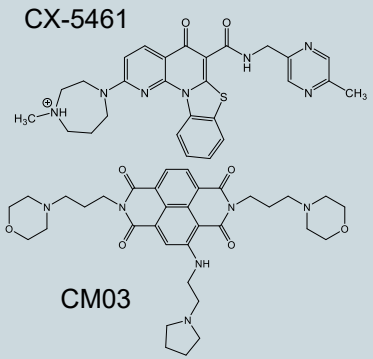
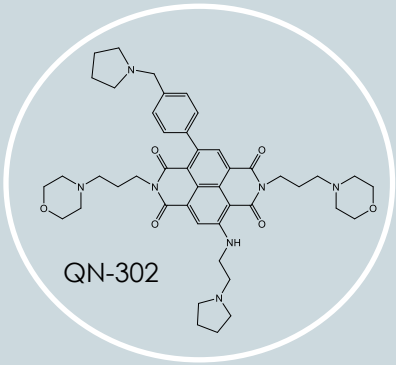


- QN-302: a tetra-substituted naphthalene diimide derivative (Ahmed et al, ACS Med Chem Lett, 2020)
- Designed as a potent compound for targeting quadruplex (G4) sequences in the promoter regions of cancer genes
- Has 1-2 nM anti-proliferative activity in a panel of human pancreatic cancer (PDAC) cell lines
- Has significant anti-tumor activity in xenograft, orthotopic and genetic (KPC) models of PDAC
- The structurally unrelated compound CX-5461 is also a G4-binding agent, with activity in BRCA1/2 deficient cells and tumors in early-stage clinical trials in solid DNA repair defective cancers
- We have previously reported that CM03, a precursor to QN-302, is highly active in both wild-type and gemcitabine-resistant PDAC cell lines
- Whole-genome transcriptome analysis showed that CM03-sensitive genes are largely unaffected in the resistant lines.



The tables below show that QN-302 (10-fold more potent than CM03), retains potency in the two gemcitabine resistant cell lines. CX-5461 also does this although it is 50-100 times less potent. **Up-regulated G4 genes in the resistant line are down-regulated by QN-302** The retention of QN-302 activity in chemo-resistant PDAC cell lines suggests that it will offer significant advantage in the clinic over gemcitabine-based therapies. Gemcitabine either alone or in combination is still a mainstay of current PDAC treatment. Resistance to gemcitabine is common and is a major contributor to the poor outcomes for most PDAC patients.

Cell growth inhibition IC_{50} values for the parental (GS) and gemcitabine-resistant (GR) cell lines. IC_{50} values are from SRB 96-hr assays. GemResist lines were obtained by repeated passage

Compound	MIA-PaCa2 Parental (S)	MIA-PaCa2 GemResist	PANC-1 Parental	PANC-1 GemResist
Gemcitabine	6.5 ± 0.7	11055.7 ± 540.0	23.3 ± 8.4	28750.9 ± 6121.3
CM03	13.0 ± 8.4	14.9 ± 8.3	10.4 ± 1.2	15.5 ± 1.8
CX-5461	90.3 ± 30.7	88.7 ± 22.0	32.9 ± 7.6	58.8 ± 13.8
QN-302	**2.6 ± 1.0**	**3.8 ± 1.2**	**2.3 ± 0.4**	**3.3 ± 0.7**

Expression changes in QN-302 G4 genes, from RNA-seq on parental and GemResist MIA-PaCa2 cells, 24 hr QN-302 exposure. **Down regulation of these genes observed in both S and R lines**

Gene id	log_2FC [GR vs GS]	log_2FC [GS & QN-302]	log_2FC [GR & QN-302]
GLI1	3.60	-1.84	-0.67
MAPK11	0.00	-1.72	-3.21
hTERT	-0.29	-1.03	-4.01
BCL2	0.44	-0.48	-1.75

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.