The quadruplex-binding compound QN-302 in the MIA-PaCa2 pancreatic adenocarcinoma model shows no cardiac or neurological liabilities at therapeutic doses

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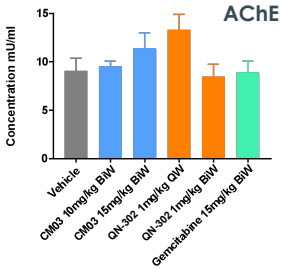
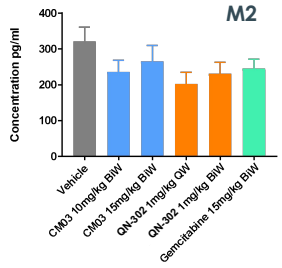
The compound QN-302, a tetra-substituted naphthalene diimide derivative has single-digit nM anti-proliferative activity in a panel of human pancreatic ductal adenocarcinoma (PDAC) cell lines (Ahmed *et al*., *ACS Med Chem Lett*, 2020, **11**, 1634-1644) and significant anti-tumor activity in the MIA-PACA2 xenograft model for PDAC as well as in the KPC model. It demonstrated favorable bioavailability at therapeutic doses. QN-302 is currently in advanced pre-clinical development with Qualigen Therapeutics Inc. Here we present preliminary toxicological data ahead of the regulatory toxicology study required for clearance into clinical trials in the US and Europe. This data provides evidence that QN-302 does not produce adverse toxicological reactions in mouse models at therapeutic doses.

A. Studies against a standard industry (CEREP) receptor panel

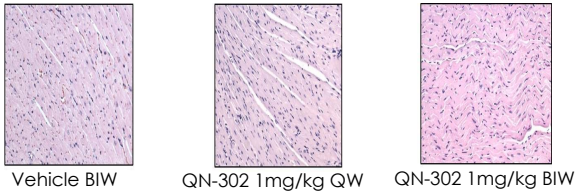
- In vitro at 1 μM QN-302 inhibits acetylcholinesterase (AChE) by 53%, muscarinic receptor (M2) by 79%. Both these receptors are involved in cardiac function.
- At 10 μM QN-302 inhibits hERG receptor by 5%. hERG is a key cardiac receptor and its inhibition would indicate major challenges for a therapeutic project
- But IC_{50} for QN-302 in MIA-PACA2 PDAC cells is ca 1 nM, ie a 1000-fold lower level
- Conclusion: no receptor binding liabilities are likely at therapeutic doses in mice
- In vivo ELISAS on plasma samples from MIA-PACA2 xenografts treated with QN-302, gemcitabine and CM03
- No significant changes in AChE and M2 levels were observed for any treatment group compared to controls





B. Histology on kidney, heart and brain from MIA-PACA2 xenografts treated with QN-302 or gemcitabine

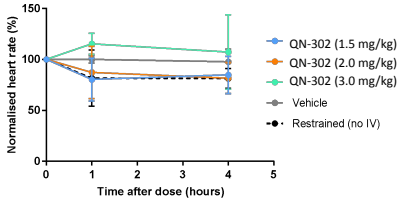
- No damage to heart tissue observed in QN-302-treated animals
- No kidney damage - the small effects on electrolytes seen in blood chemistry analyses are not due to any damage: are largely reversible.
- Small effects in brain tissue suggest that a small % of compounds do cross the blood brain barrier. These effects are reversible as the images from after the out-growth period had fewer abnormalities
- No abnormal behavioural effects were observed during the xenograft studies

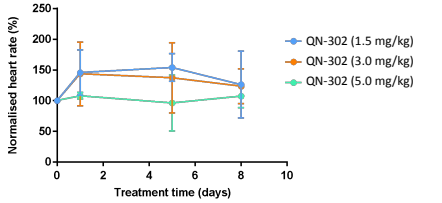


Images of cardiac muscle. Histological analysis of vehicle treated animals shows the normal morphology of the myocardium with normal distribution of cardiomyocytes

C. Effects of QN-302 on murine heart rate in vivo

Measured in real time using a MouseSTAT® heart rate monitor, recorded pre-dose to obtain a baseline, then 1-hour post compound administration after the 1st, 2nd and 3rd dose





No significant adverse effects were observed on heart rate even at dosage levels > than that used in the therapy exps (1 mg/kg)

The lack of effects on ACE and M2 receptors in vivo, the absence of effects on heart, liver and brain tissue from treated animals, and the normality of heart rate during treatment indicate that treatment of MIA-Paca2 tumor-bearing mice with QN-302 does not have a cardio-, nephro- or neurotoxic burden at therapeutic doses

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