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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• 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

The RNA-seq data (RHS) for some of the most-downregulated 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 e.g. 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