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Leveraging NQO1 bioactivatable drugs for tumor-selective PARP inhibitor synergy for pancreas, breast and nonsmall cell lung cancers

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Therapeutic drugs that block DNA repair, including poly (ADP-ribose) polymerase (PARP) inhibitors, fail due to lack of tumor-selectivity. When PARP inhibitors and NQO1 bioactivatable drugs are combined, synergistic antitumor activity results from sustained NAD(P)H levels that refuel NQO1-dependent futile redox drug recycling. Significant oxygen consumption rate/reactive oxygen species cause dramatic (DNA) lesion increases that are not repaired due to PARP inhibition. In NQO1+ cancers, such as non-small cell lung, pancreatic and breast, the cell death mechanism switches from PARP1 hyperactivation-mediated programmed necrosis with NQO1 bioactivatable drug monotherapy to synergistic tumor-selective, caspase-dependent apoptosis with PARP inhibitors and NQO1 bioactivatable drugs. Complete metabolic profiling of cells containing or lacking NQO1 and treated with PARP inhibitor Rucaparib along with the NQO1 bioactivatable drug, ß-lapachone, demonstrated dramatic shifts from suppression of glycolytic and KREB's cycle with NQO1 bioactivatable drugs alone to apoptotic activation with PARP inhibitors along with the NQO1 bioactivatable drug. Synergistic antitumor efficacy and prolonged survival were noted in human orthotopic pancreatic and non-small cell lung xenograft models, expanding use and efficacy of PARP inhibitors for human cancer therapy. Cell death was found independent of oncogenic driver mutations or over-expressed oncogenes or loss of tumor suppressors. This work was supported by NIH/NCI R01 grants, R01 CA102792-16 and R01 CA221158-01 to DAB.

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