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LEVERAGING NQO1 BIOACTIVATABLE DRUGS FOR TUMOR-SELECTIVE USE OF POLY (ADP-RIBOSE) POLYMERASE INHIBITORS

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Therapeutic drugs that block DNA repair, including poly (ADP-ribose) polymerase (PARP) inhibitors fail because of a lack of tumor-selectivity. When PARP inhibitors and NQO1 bioactivatable drugs (ß-lapachone or isobutyldeoxynyboquinone (IB-DNQ)) 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 (NSCLC), pancreatic or breast cancers, the cell death mechanism switches from PARP1 hyperactivation-mediated programmed necrosis with NQO1 bioactivatable monotherapy to synergistic tumor-selective, caspase-dependent apoptosis with PARP inhibitors and NQO1 bioactivatable drugs. 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.

Biography

David A Boothman received his PhD from the University of Miami. He was a Postdoctoral Fellow in Dr Arthur Pardee's Lab at Harvard University and an Assistant Professor at University of Michigan. He has received tenure at University Of Wisconsin-Madison and a Full Professor at Case Western Reserve University. After 14 years at UT South-western University, he is now serving as a Professor of Biochemistry and Molecular Biology at Indiana University and the Sid and Lois Eskenazi Chair of Oncology. His research interests include: use of NQO1 bioactivatable drugs for therapy of human solid cancers alone and with ionizing radiation; use of NQO1 bioactivatable drugs to promote the tumor-selective use of DNA repair inhibitors, such as PARP inhibitors; elucidating the roles of RNA termination factors for R-loop resolution, DSB repair defects, genetic instability and cancer vulnerabilities.

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