David A Boothman, Metabolomics 2016, 6:3(Suppl)
http://dx.doi.org/10.4172/2153-0769.C1.033

7th International Conference and Expo on

Metabolomics

November 14-16, 2016 Orlando, Florida, USA

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Leveraging an NQO1 bioactivatable drug for tumor-selective use of poly (ADP-ribose) polymerase (PARP) inhibitors

Therapeutic drugs that block DNA repair, including poly (ADP-ribose) polymerase (PARP) inhibitors, commonly fail due to a lack of tumor-selectivity. When PARP inhibitors and ß-lapachone are combined, synergistic antitumor activity results from sustained NAD(P)H levels that refuel NQO1-dependent futile redox drug recycling. Alone, β-lapachone (aka., ARQ761 in clinical form) results in dramatic loss of NAD+ specifically in NQO1+ cancer cells (non-small cell lung, pancreatic and breast cancers) that suppresses both glycolysis (at GAPDH level) and the TCA cycle. When combined with a PARP inhibitor, or in PARP1 siRNA/shRNA suppressed NQO1+ cancer cells, significant oxygen consumption rate/reactive oxygen species cause dramatic increases in DNA lesions that are not repaired due to PARP inhibition. Cell death switches from PARP1 hyperactivation-mediated programmed necrosis by β-lapachone to synergistic tumor-selective, caspase-dependent apoptosis after PARP inhibitors+β-lapachone in NQO1+ cancers, including non-small cell lung, pancreatic and breast subtypes. Enhanced antitumor efficacy and prolonged survival were noted in orthotopic human MiaPaCa2 pancreatic and A549 non-small cell lung xenograft models. This approach greatly expands the use and efficacy of PARP inhibitors for therapy of most human solid cancers.

Biography

David A Boothman has completed his PhD from University of Miami and Post-doctoral studies from Dana-Farber Cancer Institute, Harvard Medical School. He is the Director of Translational Research, Simmons Comprehensive Cancer Center, UT Southwestern Medical Center. He has published more than 150 papers in reputed journals and has been serving as an Editorial Board Member of various peer-review scientific journals.

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