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Precision epigenetic targeted combination therapies for Triple Negative Breast Cancer subtypes

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Triple negative breast cancer (TNBC) is the most aggressive and heterogeneous subset of breast malignancy with worst clinical outcome. Due to lack of targetable cellular receptors for estrogen (ER), progesterone (PR) and human epithelial growth factor receptor-2 (HER2), the treatment of TNBC patients is very challenging. Clinical management for TNBC mainly relies on chemotherapeutic agents. Unfortunately, the response rate to chemotherapy is very variable in TNBC patients with high reported incidents of drug resistance. One of the urgent needs in TNBC research is to identify novel molecular targets that can work specifically and effectively to eliminate tumor cells and can also address disease heterogeneity. In this direction we developed an innovative targeted drug screen to discover combinations of molecular targets that produce synthetic-lethal effects in TNBC cells. Highly active molecular oncotargets were selected with available small molecular inhibitors and combined in dosages below one-fifth concentrations of their individual IC₅₀ values in a panel of 12 TNBC cell lines representing different molecular subtypes. The screen results identified several general and subtype specific synthetic-lethal drug combinations that were clinically relevant, among those co-inhibition of epigenetic regulator bromodomain and extra-terminal (BET) proteins showed promising effects across different subtypes. BET inhibitors OTX015 and JQ1 with proteasomes inhibitor bortezomib effectively induced iron-dependent ferroptotic cell death in most TNBC subtypes in in-vitro, in-vivo and in patient-derived 3D organoids by suppressing antioxidant GPX4 protein. Further, we found that co-inhibition of BET with Interleukin-8 receptor CXCR2 specifically induced apoptotic cell death in mesenchymal-stem like TNBC subtypes in-vitro, and in mice xenografts. These results identified novel subtype specific vulnerabilities of TNBC that can be exploited for designing promising precision medicine using epigenetic drugs.

Keywords: TNBC, synthetic-lethal, targeted therapy, BET inhibitors, ferroptosis, precision medicine

Biography:

Dr. Nandini Verma joined as a principal investigator at ACTREC, TMC, after completing her post-doctoral training at the Moross Integrated Cancer Center (MICC), Department of Cell and Molecular Biology at the Weizmann Institute of Science, Israel. Dr. Verma earned her Ph.D. from Institute of Genomics and Integrated Biology (IGIB), New-Delhi, where she mostly worked on innate immune regulatory cellular signaling. During her post-doctoral research Dr. Verma discovered important cellular regulators of EGFR signaling in TNBC cells and mechanism of drug resistance in anti-EGFR targeted therapies. Her recent research work has uncovered novel subtype specific combination therapies for TNBC treatment.