## The NAE inhibitor MLN4924 inhibits the nucleotide excision repair pathway to enhance the efficacy of cisplatin treatment in both BRCA1-proficient and –deficient triple negative breast cancers

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Development of new drugs for TNBC (Triple negative breast cancer) is urgently needed due to lack of therapy. NEDD8-activation enzyme (NAE) inhibitor, MLN4924, is currently in clinical trials. We show that the TNBC cells show higher sensitivity compared to other breast cancer subtypes to MLN4924. Furthermore, MLN4924 enhances the cytotoxicity of the approved TNBC chemotherapeutics cisplatin but not doxorubicin. Importantly, both BRCA1-proficient and –deficient cells show re-replication with >4N DNA content accumulating cells in S phase leading to apoptosis and senescence. However, the BRCA1-deficient cells show less re-replication and a higher fraction of cells progressed to G1 undergoing more senescence. The re-replication is attributable due to the CDT1 accumulation via blocking its degradation which triggers DNA damage. Mechanistic investigation of increased sensitization upon MLN4924/cisplatin co-treatment revealed that neddylation substrates, nucleotide excision repair (NER) proteins, DDB2 and XPC play a key role. Neddylation of CUL4 helps DDB2 and XPC ubiquitination, which is essential for cisplatin-DNA adducts repair by NER. As expected, DDB2 accumulated and the XPC ubiquitination reduced upon MLN4924 treatment. Surprisingly, the reduced ubiquitination of XPC promotes decrease in XPC level. The alterations in the DDB2 and XPC ubiquitination and their protein levels inhibit NER by affecting the stoichiometry of repair protein assembly at the damage sites, and consequently the MLN4924/cisplatin co-treatment accumulated more cisplatin-DNA adducts. MLN4924 treatment showed activation of both ATR-Chk1 and ATM-Chk2 cell cycle checkpoint pathways, but the cells cannot repair the extensive DNA damage. Since MLN4924/cisplatin treatment shows sensitization of both BRCA1-proficient and –deficient TNBCs to cisplatin compared to PARP inhibitor, which sensitizes only BRCA1-deficient TNBC, this combination will have greater efficacy for all TNBC patients. We demonstrate a novel mechanism of MLN4924 and cisplatin sensitization and provide a strong rationale for the clinical investigation of this combination in highly drug resistant TNBC.

### Speaker Biography

Alo Ray has extensive experience in the area of DNA damage repair, cell cycle checkpoint, and DNA replication all of which play a crucial role in cancer development and progression. Her research is aimed to investigate the molecular mechanisms and biological functions of basic cellular processes required for maintaining genomic stability and integrity with a future goal of developing therapeutic interventions of cancer. She is using multidisciplinary approaches to target the DNA damage response repair and cell cycle checkpoint pathways with a goal to enhance the chemo-and radio-therapy of cancer patients. She has authored several peer-reviewed high-profile journals such as *Nature Genetics, PNAS, Molecular Cell, NAR, MCB*, and *DNA repair*. She was granted the Leukemia & Lymphoma Society Special Fellowship Award. Additionally, she was granted several grants as Principal Investigator and Co-Principal Investigator from American Cancer Society, OSU Cancer Center and NIH.

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