

## **Time-Dependent PARP7 Inhibition Allows for Enhanced Nucleic-Acid Sensing within Breast Cancer**

**Abstract:** Radiotherapy (RT) is a precision tool used in the clinic to induce DNA damage in tumors. While healthy cells can quickly resolve nucleic acids (NAs) in the cytosol and stimulate the Type I Interferon response through cGAS/STING, literature and preliminary data from our lab have shown that overexpression of PARP7 can be exploited by cancer cells to evade NA sensing, and ultimately, evade cell death. It is understood that PARP7 inhibition enhances NA sensing, but it remains unclear the duration of this effect following perturbation of NAs in the cytosol. The purpose of this study was to characterize inflammatory signaling following transfection of an immunostimulatory dsDNA molecule (ISD90), as a proxy for NAs released by RT, with inhibition of PARP7 over time. The ISG production in the absence of aberrant PARP7 signaling could be a powerful therapeutic for cancer patients in combination with RT where frontline therapies fail. Gene expression data suggests that cytokine production increases with time following transfection. Future directions include looking at cell death pathways that are activated from this combination treatment.