Caged Rucaparib: Cancer Directed Delivery of PARPi

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Topic: Ovarian

Objectives
Poly (ADP-ribose) polymerase inhibitors (PARPi) have revolutionized the treatment of ovarian cancer, improving progression free survival in the upfront and recurrent setting. Unfortunately, due to side effects patients often require dose reductions or altogether discontinue PARPi therapy. Additionally, due to bone marrow toxicity, PARPi cannot be effectively combined with chemotherapy. Recently, it was demonstrated that a ferrous iron-activated MEK inhibitor can circumvent MEKi related toxicity in non-tumorigenic tissues. Therefore, we developed a ferrous iron-activated form of rucaparib to target cancer cells while mitigating PARPi toxicity.

Methods
Normal cells maintain a lower concentration of intracellular labile ferrous iron (Fe(II)) as compared with cancer cells. We introduced an Fe(II)-sensitive 1,2,4-trioxolane moiety at a reactive amine in rucaparib, creating a Fe(II)-activatable form of rucaparib (TRX-Ruc). A negative control, Di-Ruc, that cannot be activated by Fe(II), was also synthesized. Both compounds were then tested for their ability to inhibit PARP using a cell-free PARP1 assay. Cellular antiproliferative activity was tested in UWB -/- (BRCA1-deficient ovarian cancer cells) using the CellTiterGlo viability assay, and intracellular inhibition of PARP was evaluated with a parylation Western blot.

Results
In the cell free PARP1 inhibitor assay, the IC50 of rucaparib was 2.9 nM while TRX-Ruc had significantly decreased potency, with an IC50 of 92.3 nM. Di-Ruc had no inhibitory effect as expected. UWB -/- viability was decreased by rucaparib and TRX-Ruc with an equivalent IC50 of approximately 300 nM while Di-Ruc only had an effect at very high concentrations. To ensure the mechanism of TRX-Ruc on cell viability was due to PARP inhibition, a parylation western was performed. Both rucaparib and TRX-Ruc inhibited parylation while the negative control, Di-Ruc had only minimal effects.

Conclusions
The addition of an Fe(II)-sensitive “TRX” moiety on rucaparib significantly reduces the biochemical activity of rucaparib in the absence of Fe(II). However, in an ovarian cancer cell line, the activity of TRX-ruc is restored leading to decreased cell viability, which we demonstrated was realized through the inhibition of PARP. This new Fe(II)-sensitive compound is an exciting and novel approach to deliver PARPi specifically to cancer cells, potentially reducing toxicity and allowing effective combinations of PARPi with other cytotoxic therapies.