

ATM inhibition sensitises prostate cancer cells to PARP inhibitors

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Background: Selective killing of homologous recombination (HR) deficient cancer cells by PARP inhibitors, via a mechanism coined synthetic lethality, has been well supported by clinical trial data. However, somatic deficiency in the sensing and signalling of DNA double strand breaks (DSBs) and in HR pathways represents only a small fraction of prostate tumours, including ATM mutations in ~5% of prostate tumours. An alternative strategy to induce synthetic lethality is dual inhibition of PARP and DSB signalling pathways, although the specificity of this approach remains untested.

Methods: Using a number of in vitro, in vivo and biochemical and molecular biology based assays, herein, we describe ATM inhibition as a chemosensitiser to PARP inhibition in HR-proficient prostate cancer cells.

Results: We find the combined effect of PARP and ATM inhibitor therapy to be effective in prostate cancer models but not in benign immortalised cell lines. We also observe up-regulation of DNA damage response pathways in the transcriptional profiles of malignant but not benign prostate samples, and suggest that the increased dependence of prostate cancer cells on these pathways renders them particularly sensitive to a lethal burden of DSBs.

Conclusion: We demonstrate pre-clinical efficacy of ATM/PARP dual inhibition on prostate cancer cells using ex vivo patient-derived tissue and in vivo xenograft models, with minimal systemic toxicity, supporting further evaluation of this treatment strategy in clinical trials.

Conflict of Interest: SPJ is a founder, shareholder and Director of Mission Therapeutics Ltd. and Adrestia Therapeutics Ltd.; is a Science Partner of Ahren Innovation Capital LLP; receives laboratory research funding from AstraZeneca; and is a named inventor on patents describing the use of PARP inhibitors in cancer therapy. The other authors have no other relevant conflicts to declare.

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