Dimethylaminoparthenolide augments the radiation response in prostate cancer

Katherine Morel[1], Thuy Trang To[1], Steffi Tiburcius[1], Christie Orshcell[2], Pamela Sykes[3], Christopher Sweeney[1]

Affiliations: 1) South Australian immunoGENomics Cancer Institute, The University of Adelaide, Australia. 2) Department of Medicine, Indianna University, USA. 3) College of Medicine and Public Health, Flinders University, Australia

Background: Despite all research efforts, current therapies for patients with metastatic castrate resistant prostate cancer (mCRPC) can be life prolonging and palliative but are not curative. Recent advances in prostate cancer (PCa) radiotherapy using more targeted approaches than traditional external beam radiotherapy can reduce tumor burden and increase life expectancy in patients with mCRPC. Despite the benefits of a targeted approach to mCRPC therapy, normal tissue toxicity remains an obstacle. In this study, we examined the ability of dimethylaminoparthenolide (DMAPT), a naturally occurring anti-inflammatory compound, to modify tissue responses to radiation therapy.

Methods: *In vivo*, TRAMP and C57BL/6J mice were treated with oral DMAPT (100 mg/kg) and/or moderate-high-dose x-radiation. Tissues were analysed at 6hs, 24hrs, 72hrs and 8 weeks post-irradiation. *In vitro*, PCa (LNCaP, PC3 and DU-145) and non-cancer (RWPE-1 and PrEC) cell lines were examined following treatment with DMAPT and/or radiation.

Results: In mice, oral DMAPT pre-treatment provides protection from radiotherapy-induced fibrosis in penis, bladder and rectum and testicular/seminiferous tubule atrophy. In TRAMP mice, DMAPT simultaneously increases PCa cell sensitivity to radiation damage and improves tumor control. The NRF2-KEAP1 pathway is one of the main cellular defence mechanisms against oxidative stress. *In vitro* analysis indicates that DMAPT differentially affects NRF2-KEAP1 oxidative stress responses in non-cancer versus cancer cells. DMAPT increases oxidation of KEAP1 in non-cancer cells (RWPE-1 and PrEC), leading to increased NRF2 levels and significant upregulation of NRF2-dependent antioxidant enzymes (including PRDX1, MnSOD, Catalase). In PCa cells (LNCaP and PC3), DMAPT maintains KEAP1 in a reduced state and antioxidant enzymes are either downregulated or unchanged. This primes cells for a differential response to radiation.

Conclusions: We have shown that dimethylaminoparthenolide can reduce radiation-induced damage to healthy cells, while increasing PCa radio-sensitivity. Our work highlights the role that redox pathways play in this differential effect. Early-stage clinical trials have shown that orally dosed DMAPT is very well tolerated. making it an ideal candidate for use in combination with targeted radiotherapy to improve PCa patient outcomes.

Funding Acknowledgement: This work has been funded by a PCF Young Investigator Award to K. Morel (23YOUN05) and a research project grant from the Cancer Council SA's Beat Cancer Project (1120349).

Conflict of Interest Disclosure: Royalties and other intellectual property interests for C. Sweeney: Parthenolide (Indiana University); dimethylaminoparthenolide (Leuchemix). All other authors declare no conflicts of interest.