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Title: Immune oncology therapy for breast cancer: CCR5 inhibitors enhance breast cancer cell killing and reduce doxorubicin-induced cardio-toxicity

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We previously showed that the G-protein coupled receptor CCR5 is expressed on both immune and epithelial cells of ~50% of human Breast Cancers (BCa), thereby inducing cancer "stemness", cell survival and DNA repair and a pro-metastatic phenotype. CCR5 inhibition by small molecules (Maraviroc) or a humanized monoclonal antibody (Leronlimab) reduced the breast cancer metastatic burden in murine models, with distinct impact on secretomes and promising results in a Phase 1B/2 study. With cancer survivors estimated at 19 million in the USA by 2025, DOX-induced cardio-toxicity is considered part of the "cardio-oncology epidemic".

Herein, we show that:

i. CCR5 inhibitors (CCR5i) enhanced DOX-induced cell death of breast cancer cells.

ii. CCR5 and its ligand CCl5 were induced by DOX in cardiac myocytes in both the hearts of patients undergoing cardiac transplantation for DOX-induced cardiomyopathy and in a murine model of DOX-cardiac toxicity.

iii. CCR5i protected human iPSC-derived cardiomyocytes and isolated canine cardiomyocytes from DOX- induced cell death.

iv. CCR5i substantially reduced (>90%) DOX-induced cardiac dysfunction in mice.

We conclude that CCR5 inhibitors (CCR5i) are "dual function" compounds that provide both cardiac protection and enhanced breast cancer cell killing in the presence of DNA damaging chemotherapy agents. Our studies may have a broad impact by identifying a novel approach to both enhancing therapeutic efficacy and providing cardio-protection from DNA damaging agents that are widely used in cancer treatment.

Keywords: Breast cancer, Metastasis, CCR5, Cardio-toxicity, Prevention.

Biography

Richard Pestell, AO, MD, PhD, MB, BS, MBA, FRACP, FACP is President Pennsylvania Cancer and Regenerative Medicine Center, Philadelphia, USA. He is a clinician scientist who was appointed Officer of the Order of Australia in the 2019 Queen's Birthday Honors for distinguished service to medicine, in the fields of endocrinology and oncology. He has >700 published works (>89,000 citations, H index 153) and holds patents in cancer diagnostics and treatment. He was previously Executive Vice President Thomas Jefferson University, Philadelphia, USA. He received MD and PhD degrees from Melbourne University, his MBA from NYU and was the Winthrop Fellow at Harvard Medical School and was Clinical Fellow at Massachusetts General Hospital. He identified key genetic target for cancer stem cells governing the onset and progression of cancer, with issued patents that have led to a current clinical trial.