Project Details	
Project Code	IIAR27Ca Pearson
Title	Defining CD200 Function and the Therapeutic Potential of Targeting the CD200 immune checkpoint in Prostate Cancer
Research Theme	Infection, Immunity & Antimicrobial Resistance
Project Type	Wet lab
Summary	Prostate cancer remains a leading cause of cancer mortality, particularly in metastatic disease where treatment options are limited. This PhD project seeks to investigate the role of CD200, an immune checkpoint protein enriched in prostate cancer stem cells, in promoting tumour growth and immune evasion. Using genetic and pharmacological approaches, the study will evaluate a novel CD200 small molecule inhibitor to determine its effects on cancer stem cell function, tumour immunity and treatment response. The project will also assess whether combining CD200 inhibition with conventional immunotherapy enhances anti-tumour immune responses, providing a potential new therapeutic strategy for advanced prostate cancer.
Description	BACKGROUND Prostate cancer: Prostate cancer (PC) is a major cause of cancer mortality worldwide, predominantly reflecting metastatic disease present at diagnosis or emerging upon androgen receptor targeted therapy (ARTT)-resistance, culminating in castration-resistant prostate cancer (mCRPC). These patients have poor prognoses (5-year survival:<30%), highlighting the urgent need for improved treatments. CD200 signalling in cancer: CD200 is a type-I transmembrane glycoprotein that functions as a novel immune checkpoint, suppressing anti-tumour immunity by inhibiting RAS/MAPK signalling and natural killer (NK) cell activity [1]. CD200 also regulates stem cell activity in multiple tissues, and is enriched in cancer stem cells (CSCs, e.g., glioblastoma and melanoma) [2]. Although CD200 mutations are rare in primary/metastatic PC (<0.3%), CD200 amplification/gain correlate with worse outcome [3], suggesting a role in PC progression and immune evasion. Thus, targeting the CD200 immune checkpoint may impair PC clonogenicity whilst overcoming tumour immune evasion and the limited efficacy of conventional immunotherapies (e.g., pembrolizumab) in PC, which exhibits low tumour mutational burden and an immunologically cold tumour micro-environment [4]. However, the role of CD200 in PC stem cell-mediated immunomodulation remains unclear. Targeting CD200-CD200R signalling: Targeting CD200-CD200R signalling has been challenging, with anti-CD200 antibodies showing limited clinical efficacy in haematological malignancies, despite good tolerability[5]. We developed a first-in-class CD200 small molecule inhibitor, p1019.7, which requires further preclinical evaluation before commencing early-phase clinical trials in solid cancers. Our previous work identified CD200+ CSCs in basal cell carcinoma (BCC) and that CD200 inhibition enhances tumour susceptibility to NK cell-mediated killing[6]. Our preliminary work in PC indicates p1019.7 treatment is non-toxic/well-tolerated, reduces PC growth in-vivo, and promotes apoptosis and immune cell infiltration.

	Moreover, CD200 is enriched in a subset human/mouse PC stem cells [2], and p1019.7 treatment suppresses mCRPC stem cell function in-vitro (unpublished data). However, it is currently unknown if CD200-positive PC stem cells evade immune surveillance directly, or create an immunosuppressive niche. Hypothesis: We hypothesise that CD200 mediates PC stem cell-mediated immune modulation and that CD200 inhibition with p1019.7 will synergise with conventional immunotherapy, providing a novel therapeutic strategy to improve outcomes in PC. RESEARCH PLAN Aim 1: Investigate the requirement for CD200 in PC stem cells 1.1 Perform colony forming, anchorage-independent and prostasphere assays in PC cells (C42B/PC-3/22Rv1/DU145/LNCaP) with stable CD200 knockdown (shCD200), overexpression or controls (SCRAM-shRNA/empty-vector). 1.2 Determine regenerative capacity (androgen-deprivation, then testosterone supplement) and self-renewal via serial passaging using PC organoids +/- Cd200 loss. 1.3 Run RNASeq analysis on PC stem cells treated with p1019.7 or vehicle, followed by functional validation (colony forming/prostasphere assays) to identify novel therapeutic targets. Aim 2: Define the immunomodulatory role of CD200 in PC. 2.1 Perform 2D/3D growth and immune cell-mediated killing assays using PC cell lines with manipulated CD200 expression (as Aim-1.1), co-cultured with immune cells (macrophages, NK-cells or CD8+ T-cells) using HoloMonitor® time-lapse imaging; assess cytokines and immune activation. 2.2 Establish which immune cells are activated in response to p1019.7 treatment using multiplex immunofluorescence to analyse the immune infiltrate in transgenic PC tumours and patient-derived PC explants. Aim 3: Determine the therapeutic benefit of combining CD200 inhibition and conventional immunotherapy in PC. 3.1 Perform 2D/3D immune cell-mediated killing assays of prostate cell lines (as Aim-1.1) co-cultured with immune cells (macrophages, NK-cells or CD8+ T-cells) in the presence of CD200i +/- pembrolizumab; measure cytokines and immune responses. 3.2 Test p1019.7 and pembrolizumab combination therapy in primary and metastatic transgenic/patient-derived explants with CD200i +/- pembrolizumab. Expected outcomes: • Define how CD200 regulates PC stem cell function and immune evasion. • Identification of novel therapeutic targets for PC. • Provide rationale for combining CD200 inhibitors with immunotherapy in PC. Student training and research input: This PhD project offers substantial opportunities for the student to shape the research direction and take ownership of key aspects of the work. While the overall aims are defined, the student will drive

	experimental design, data analysis, interpretation of results, and the development of follow-up studies arising from novel findings. In particular, the RNA sequencing studies and functional validation experiments provide scope to identify and prioritise new therapeutic targets, enabling the student to make an original scientific contribution. Throughout the project, the student will develop a broad range of highly transferable skills in cancer biology, stem cell research, immunology, and translational oncology. Technical training will include cell culture, organoid/explant ex vivo models, molecular biology techniques, immune cell killing assays, multiplex immunofluorescence, RNA sequencing analysis, and preclinical trial evaluation. The student will also gain expertise in experimental design, statistics, bioinformatics, project management, scientific writing, presentation skills, and interdisciplinary collaboration. These experiences will equip them with the independence, critical thinking, and leadership skills required for careers in academic research, biotechnology, or the pharmaceutical industry. REFERENCES [1] doi:10.3389/fonc.2023.1088038 [2] doi:10.1016/j.bbrc.2007.10.067 [3] doi:10.1158/2159-8290.CD-12-0095 [4] doi:10.1186/s12885-020-07058-y [5] doi:10.1186/s40425-019-0710-1 [6] doi:10.1172/JCI150750
Can be completed part time?	Yes
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