

Department of Pathology fully-funded PhD studentships: project proposal form

Pls to complete Parts A & B and to send to your Head of Division by 3 October 2021.
Heads of Division to complete Part C and to send to hod.sec@path.cam.ac.uk

PART A: PROJECT PROPOSAL	
Division	Immunology
Supervisor	Dr Bidesh Mahata
Second supervisor (If supervisor's contract ends before October 2025)	
Project title	Steroid-producing immune cells promote metastatic dissemination of cancer cells
Project abstract for advert (Max 100 words)	Immune cells play a dual role during cancer metastasis. They can destroy the cancer cells, as well as, can promote the metastasis. We are only beginning to understand the mechanisms of immune cell promotion of metastasis. In mice model, we observed that immune cell-mediated steroidogenesis promotes metastasis. Yet, how immune cell steroidogenesis and steroid-signalling contributes to the cancer metastasis is unknown. Therefore, we will investigate the role of steroid-producing immune cells in the promotion of cancer metastasis and how this may be exploited therapeutically. In this study we will employ genetically modified mice models, flow cytometry, RNA sequencing, mass-spectrometry and microscopy.
Keywords Please provide up to five	Cancer immunity; Metastasis; Immune cell-mediated steroidogenesis; Steroid-producing cell; Steroid-signalling
Full details (Max 250 words) Will be published on Departmental website; please do not include confidential information	Metastasis is the leading cause of death in cancer patients. To colonise distant organs, circulating tumour cells must overcome numerous obstacles such as surviving in the circulation, infiltrating and disseminating distant tissue, evading anti-tumour immunity, adapting and surviving as latent tumour-initiating seeds and eventually breaking out to replace the host tissue. Immune cells play a dual role during this process. They can destroy the cancer cells, as well as, can promote the metastasis. We are only beginning to understand the mechanisms of immune cell promotion of metastasis. We observed that immune cell-mediated steroidogenesis promotes metastasis. Yet, how immune cell steroidogenesis and steroid-signalling contributes to the cancer metastasis is unknown. Therefore, we will investigate

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	<p>the role of steroid-producing immune cells in the promotion of cancer metastasis and how this may be exploited therapeutically.</p> <p>Our first aim is to define the immune cell-mediated steroid biosynthesis during metastasis. In mice models of lung metastasis, we will characterise steroid-producing immune cells, profile and quantify the steroids. Next, we will determine the mechanisms of how steroid-producing immune cells promote metastasis. We observed that genetic or pharmacologic ablation of T cell steroidogenesis restricts lung colonisation of cancer cells. We will test whether the restriction of metastasis is because of stimulation of the anti-tumour immunity. Alternatively, we will examine whether the steroids directly promote metastatic dissemination of cancer cells to the lung. We will demonstrate the intratumoural steroid regulatory mechanisms that drive metastasis. Our ultimate aim is to exploit this knowledge to innovate therapeutic strategy for metastatic cancer.</p>
<p>Three of your most important publications in support of the proposed project</p>	<p>1. Mahata B, Pramanik J, van der Weyden L, Polanski K, Kar G, Riedel A, Fonseca NA, Kundu K, Campos LS, Ryder E, Duddy G, Walczak I, Davidson S, Okkenhaug K, Adams DJ, Shields JD and Teichmann SA (2020) Tumors induce de novo steroid biosynthesis in T cells to evade immunity. <i>Nature Communications</i> https://www.nature.com/articles/s41467-020-17339-6</p> <p>2. Mahata B, Zhang X, Kolodziejczyk AA, Proserpio V, Haim-Vilmovsky L, Taylor AE, Hebenstreit D, Dingler FA, Moignard V, Göttgens B, Arlt W, McKenzie AN, Teichmann SA. (2014) Single-cell RNA sequencing reveals T helper cells synthesizing steroids de novo to contribute to immune homeostasis. <i>Cell Reports</i> 7: 1130-1142.</p>