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

Division	Immunology
Supervisor	Dr Bidesh Mahata
Second supervisor (If supervisor's contract ends before October 2024)	Prof Klaus Okkenhaug
Project title	Immune cell-mediated steroidogenesis in regulating cancer immunity
Project abstract for advert (Max 100 words)	During the past hundred years the endocrine role of steroid hormones in regulating immune cell function has been well-established. Surprisingly, we discovered that type 2 immune cells, such as T helper 2 lymphocytes, mast cell and basophils, induce de novo steroidogenesis possibly to regulate the inflammation and immunity in an intracrine, autocrine and paracrine manner. Little is known when, how and why they synthesize and secrete steroids. In this study we will analyse the mechanism of immune cell-mediated steroidogenesis and its differential regulation compared to the endocrine glands. And most importantly we will demonstrate its role in regulating anti-tumour immunity.
Keywords Please provide up to five	Immune cell-mediated de novo steroidogenesis, Steroid-producing immune cells, Tumour microenvironment, Anti-tumour immunity, Resolution of inflammation and immunity
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	Steroidogenesis is a process by which cholesterol is converted into steroid hormones in the adrenal glands, gonads and placenta. The endocrine role of systemic steroid hormones in regulating immune cell function is well-established. Surprisingly, we discovered that type 2 immune cells, such as T helper 2 lymphocytes, mast cell and basophils, induce de novo steroidogenesis possibly to regulate the inflammation and immunity in an intracrine, autocrine and paracrine manner. Little is known when, how and why these steroid-producing immune cells originate and synthesise steroids. In this study we will research on their origin, analyse the mechanism of immune cell-mediated steroidogenesis and demonstrate its differential regulation compared to the endocrine glands. Most importantly we will study its functional role in regulating anti-tumour immunity in mouse model of cancer and validate the key observations in human samples. To study immune cell-mediated steroidogenesis in vivo, we will employ our Cyp11a1-mcherry reporter and Cyp11a1 conditional knockout mice. Cyp11a1 is the first and rate-limiting enzyme of the steroidogenesis pathway. The Cyp11a1-mCherry reporter mice will be used to track the steroidogenic immune cells in vivo. Cyp11a1fl/fl mice will be used to ablate the steroidogenesis cell type specifically to determine its functional role. We will undertake multidisciplinary approaches, such as flow cytometry, gene expression analysis, ELISA, immunohistochemistry, microscopy, chromatography and mass-spectrometry, single-cell and bulk RNA-seq, and ChIP-seq. The study will provide insight of a fundamental immunoregulatory process, and show evidence that how inappropriate induction/recruitment of these regulatory cells in the tumour microenvironment promote cancer.
Three of your most important publications in support of the proposed project	1. Mahata B, Pramanik J, van der Weyden L, Kar G, Riedel A, Fonseca NA, Kundu K, Ryder E, Duddy G, Walczak I, Davidson S, Okkenhaug K, Adams DJ, Shields JD and Teichmann SA (2018) Tumors induce de novo steroid

	biosynthesis in T cells to evade immunity. Biorxiv, doi https://doi.org/10.1101/471359 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. Cell Rep 7: 1130-1142.