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

PIs to complete Parts A & B and to send to your Head of Division by 1 November 2020.
Heads of Division to complete Part C and to send to hod.sec@path.cam.ac.uk

PART A: PROJECT PROPOSAL	
Division	Immunology
Supervisor	Klaus Okkenhaug
Second supervisor (If supervisor's contract ends before October 2025)	
Project title	Regulation of integrin function on Treg by PI3K
Project abstract for advert (Max 100 words)	Regulatory T cells (Treg) are a major barrier against effective immunotherapy. We have previously shown that inhibiting PI3Kdelta shifts the balance of the immune system by preferentially inhibiting Treg. It remains unknown; however, exactly why tumour-associated Treg are particularly susceptible to PI3Kdelta inhibition. The successful applicant will test the hypothesis that a major function of PI3Kdelta in Tregs is to regulate the integrin LFA-1. We will determine how kinase-dead or hyperactive mutants of PI3Kdelta affect the recruitment and migration of Tregs within tumours.
Keywords Please provide up to five	Cancer, Immunology, Treg, PI3K,
Full details (Max 250 words) **Will be published on Departmental website; please do not include confidential information**	Immunotherapy is revolutionising the treatment of cancer by engaging the immune system to eliminate tumour cells. Regulatory T cells (Treg) are a major barrier against effective immunotherapy. We have previously shown that inhibiting PI3K shifts the balance of the immune system by preferentially inhibiting Treg. It remains unknown; however, exactly why tumour-associated Treg are particularly susceptible to PI3K inhibition. The student will test the hypothesis that a major function of PI3Kdelta in Tregs is to regulate the integrin LFA-1. LFA-1 plays a key role in the recruitment of leukocytes out of circulation and into lymph nodes as well as in interactions with antigen presenting cells (APCs). They will determine how kinase-dead or hyperactive mutants of PI3Kdelta affect the recruitment and migration of Tregs within tumours. They will also monitor how mutations in PI3Kdelta

	affects Treg interactions with dendritic cells in the tumour microenvironment and draining lymph nodes. Using a CRISPR/cas9 screen of proteins that can bind PIP3 (lipid produced by PI3K), we found that Kindlin-3 is an important activator and RASA-3 a key inhibitor of LFA-1. By deleting these proteins in Tregs, we expect to suppress or increase LFA-1-dependent adhesion. Therefore, conditional knock-out models of Kindlin-3 and RASA-3 will enable analysis of the effect of both up and down-regulated LFA-1 adhesion on tumour-associated Tregs. Importantly, these models will allow us the student to assess whether deletion of RASA-3 is sufficient to restore Treg-mediated suppression of tumours in PI3K deficiency. These experiments will elucidate how PI3K-dependent LFA-1 activity controls Treg-mediated suppression of immune responses.
Three of your most important publications in support of the proposed project	Ali, Khaled, Dalya R. Soond, Roberto Pineiro, Thorsten Hagemann, Wayne Pearce, Ee Lyn Lim, Hicham Bouabe, et al. 'Inactivation of PI(3)K P110δ Breaks Regulatory T-Cell-Mediated Immune Tolerance to Cancer'. Nature 510, no. 7505 (19 2014): 407–11. https://doi.org/10.1038/nature13444. Garçon, Fabien, and Klaus Okkenhaug. 'PI3Kδ Promotes CD4(+) T-Cell Interactions with Antigen-Presenting Cells by Increasing LFA-1 Binding to ICAM-1'. Immunology and Cell Biology 94, no. 5 (2016): 486–95. https://doi.org/10.1038/icb.2016.1. Lim, Ee Lyn, Fiorella M. Cugliandolo, Dalya R. Rosner, David Gyori, Rahul Roychoudhuri, and Klaus Okkenhaug. 'Phosphoinositide 3-Kinase δ Inhibition Promotes Antitumor Responses but Antagonizes Checkpoint Inhibitors'. JCI Insight 3, no. 11 (07 2018). https://doi.org/10.1172/jci.insight.120626.