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

Division	Immunology
Supervisor	Rahul Roychoudhuri
Second supervisor (If supervisor's contract ends before October 2024)	
Project title	High-throughput discovery of mechanisms underlying tumour immunosuppression using functional genetics
Project abstract for advert (Max 100 words)	T cells have a powerful ability to recognise and kill cancer cells but their function is often suppressed within tumours limiting effective anti-tumour immunity and immunotherapy. The interstitial environment of tumours is profoundly suppressive to T cell activation. We have developed a CRISPR-based approach to enable high-throughput loss-of-function genetic screens in primary mouse tumour-reactive CD8 + T cells. This project will utilise this platform to resolve the host-encoded factors that render CD8+ T cells susceptible to suppression within the tumour microenvironment, testing the function of identified factors using mouse models of adoptive immunotherapy. Identification of novel immunosuppressive mechanisms may enable development of new immunotherapies for cancer.
Keywords Please provide up to five	Cancer, Immunity, CD8+ T cells, Immunosuppression, CRISPR
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	T cells have a powerful ability to recognise and kill cancer cells but their function is often suppressed within tumours limiting effective anti-tumour immunity and immunotherapy. In part, the interstitial environment of tumours contributes to immunosuppression. The purpose of the proposed research is to apply a genome-scale functional genetic screen to identify host-encoded factors rendering T cells susceptible to suppression by the tumour microenvironment. CRISPR/Cas9- mediated genetic perturbation screening will be performed using genome-wide libraries in pooled populations of CD8+ T cells. Mutations conferring resistance to suppression will be recovered using high-throughput sequencing. The validated data will be used to construct a global map of the complement of genetic factors involved in suppression of T cell activation by the factors present in the interstitial environment of tumours. Identified genes will be further validated using CRISPR/Cas9-mediated genetic targetting in CD8+ T cells using a mouse model of adoptive immunotherapy. Identification of novel immunosuppressive mechanisms may enable development of new immunotherapies for cancer. This project will benefit from a collaboration with the laboratory of Prof Klaus Okkenhaug at the Department of Pathology.
Three of your most important publications in support of the proposed project	Eil R, Vodnala S.K., Clever D, Klebanoff C.A., Sukumar M, Pan JH, Palmer DC, Gros A, Yamamoto TN, Patel SJ, Guittard GC, Yu Z, Carbonaro V, Okkenhaug K, Schrump DS, Linehan WM, Roychoudhuri R, Restifo NP (2016). Ionic immune suppression within the tumour microenvironment limits T cell effector function. Nature 537:539-543.

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	Roychoudhuri R, Clever D, Li P, Wakabayashi Y, Quinn KM, Klebanoff CA, Ji Y, Sukumar M, Eil RL, Yu Z, Spolski R, Palmer DC, Pan JH, Patel SJ, Macallan DC, Fabozzi G, Shih HY, Kanno Y, Muto A, Zhu J, Gattinoni L, O'Shea JJ, Okkenhaug K, Igarashi K, Leonard WJ, Restifo NP (2016). BACH2 regulates CD8+ T cell differentiation by controlling access of AP-1 factors to enhancers. Nat Immunol 17:851-60. Henning AN, Roychoudhuri R, Restifo NP (2018). Epigenetic control of CD8(+) T cell differentiation. Nat Rev Immunol. 18:340-356.