CRUK Cambridge Centre Clinical PhD project

PhD Project Title (short please)	**What limits immunotherapy as treatment for pancreatic cancer?**
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Laboratory Location	CRUK Cambridge Institute

Project Outline	**Aims and objectives** Preclinical studies have shown that combination targeting of the PD-1 immune-checkpoint, which regulates clonal CD8+ T cell responses, with diverse other treatments is efficacious. The Jodrell Lab is evaluating novel combinations for the treatment of pancreatic cancer, using pre-clinical models. The aim of these studies is to identify true synergy and selectivity of potential combinations, as a prelude to model-based combination phase I trials in patients. In the Jodrell Lab, James Thaventhiran has developed a novel and unique mouse model, named the Antigen-Receptor Signalling Reporter (AgRSR), that overcomes current limitations and can track the clonal CD8+ T cell response to 'unknown' antigens. In this system, by giving a specific chemical trigger tamoxifen, we can fluorescently mark T cells that are activated by their T cell receptor (TCR). This marking is inheritable and so all daughter cells produced by clonal expansion continue to fluoresce. The fluorescent marking is TCR dependent. Further extensions of this system suggest that T cells that have different sensitivities to the triggering antigen can be distinguished by their expression of different fluorescent colours. With this system we can track the T cell response to cancer and see how this is altered by therapy. We are already undertaking preclinical projects with previously identified PD-1 synergizing approaches (CXCR2 and CXCR4 inhibitors) and agents targeting the DNA Damage Response (DDR) pathways, evaluating agents targeting PARP (olaparib), ATR (AZD6738) and Wee1 (AZD1775). All of these agents could show greatest efficacy when optimally combined with T cell-reliant PD-1-immune checkpoint blockade.
Experimental plan	In this project the student will use the murine system to investigate how the CD8+ T cell clonal response is altered by treatment. Pilot experiments will determine the effects of therapy on T cell response in transplanted tumours. Identification of novel and significant combination treatment effects will be further validated in more naturally occurring tumour models. This is essential work to provide the scientific underpinning for the delivery of PD-1 targeted combination therapy. Combination approaches identified, may transition into clinical studies during this project, and the successful student may have the opportunity to contribute to these clinical trials.

Main Techniques	• *In vivo* animal models. • Fluorescence detection systems (flow-cytometry & confocal microscopy). • T cell functional analysis. • Next-generation sequencing.
Key References	**1.** **Steele CW, Karim SA, Leach JDG, Bailey P, Upstill-Goddard R, Rishi L*, et al.*** *CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. Cancer cell 2016, 29(6): 832-845.* **2.** **Feig C, Jones JO, Kraman M, Wells RJ, Deonarine A, Chan DS*, et al.*** T*argeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. Proceedings of the National Academy of Sciences of the United States of America 2013, 110(50): 20212-20217.* **3.** **Buchholz VR, Schumacher TN, Busch DH.** *T Cell Fate at the Single-Cell Level. Annual review of immunology 2016, 34: 65-92.*