CRUK Cambridge Centre MRes rotation project

Rotation Project Title (short please)	**Modelling pancreatic cancer with organoids: a translational study**
Head of Laboratory (PI) Name	Dr Christine Farr (Lecturer)
Second supervisor if applicable	
Programme	Cellular & Molecular Biology
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Project Outline	**Aims and Objectives:** Pancreatic ductal adenocarcinoma (PDAC) has the poorest prognoses of all solid tumours. This likely reflects multiple factors, including desmoplasia, a hyper-proliferation of surrounding stromal cells which inhibits delivery of chemotherapy. Current efforts are been directed towards stromal-targeted therapies, with a focus on stellate cells (PSCs) responsible for desmoplasia. Vitamin D receptor agonists induce PSC differentiation and increase response to chemotherapy in animal models. Inecalcitol is a novel VDR with reduced hypercalcaemic properties. Our study makes use of biopsies from patients with advanced PDAC within a Phase IIb clinical trial testing **inecalcitol** (Cancer Trials Ireland 16-06, Lead: Prof Bryan Hennessy, RCSI, Dublin). Trial starts enrolling September 2018. **Hypotheses tested in our research will include whether:** (i) Specific molecular subtypes of PDAC and/or PSCs demonstrate preferential sensitivities to inecalcitol; (ii) Adipocytes support PDAC cell survival and activate PSCs through reciprocal signalling; (iii) Therapeutic responses with inecalcitol can be replicated in *in vitro* models, and (iv) Responses *in vitro* correlate with changes in gene expression. **The MRes project will analyse unique clinical samples by:** (i) developing new methods for organoid/ stromal cell co-culture, and using (ii) RNA Seq to study gene expression in patient biopsies and organoid co-cultures. Newly described methods will be used for data analysis. The hope is that a better understanding of stellate cells will provide new therapeutic avenues for patients with pancreatic cancer.
Experimental plan	This MRes project will focus on: 1. Establishment of PDAC organoid co-cultures with pancreatic stellate cells (PSCs) using recently developed protocols; 2. Developing novel methods for organoid/ adipocyte co-cultures. 3. Effects of inecalcitol within these organoid co-culture models and 4. Studying gene expression in organoid co-cultures. In the longer term, functional assays and gene expression analysis will be useful to examine reciprocal signalling pathways between PDAC subtypes and stromal cells. Taken together, new gene expression-based classification of PDAC and organoid co-cultures will provide a framework for interpreting the effects of stromal targeted therapy in the ongoing clinical trial.

Main Techniques	Organoid preparation and culture (in consultation with Dr Meritxell Huch, Wellcome Trust/CRUK Gurdon Institute and colleagues within the Glover and Martinez-Arias groups in the Dept of Genetics). RNA-seq (in consultation with Dr Darran O'Connor, RCSI, Dublin and colleagues within the Genetics Dept).
Key References	1. Sherman MH, Yu RT, Engle DD, Ding N, Atkins AR, Tiriac H, Collisson EA, Connor F, Van Dyke T, Kozlov S, Martin P, Tseng TW, Dawson DW, Donahue TR, *et al,* Vitamin D receptor-mediated stromal reprogramming suppresses pancreatitis and enhances pancreatic cancer therapy, Cell 159(1), 80-93 (2014). 2. Broutier L, Andersson-Rolf A, Hindley CJ, Boj SF, Clevers H, Koo BK, Huch M, Culture and establishment of self-renewing human and mouse adult liver and pancreas 3D organoids and their genetic manipulation, Nat Protoc., 9, 1724-1743 (2016). 3. Öhlund D, Handly-Santana A, Biffi G, Elyada E, Almeida AS, Ponz-Sarvise M, Corbo V, Oni TE, Hearn SA, Lee EJ *et al*, Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer, J Exp Med, 214,579-596 (2017).