The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL : MRC iCASE SCHEME*

*Please note that normally to be eligible for a full award a student must have no restrictions on how long they can stay in the UK and have been ordinarily resident in the UK for at least 3 years prior to the start of the studentship. Please see the RCUK residency requirements for further information.

PROJECT DETAILS	
Project Title:	Dissecting heterogeneity in cancer-associated fibroblast (CAF):tumour interactions and personalised targeting in pancreatic ductal adenocarcinoma

SUPERVISORY TEAM	
Primary Supervisor(s):	Dr. Anguraj Sadanandam
Additional members of the supervisory team:	Prof. Rajesh Chopra, Dr. Amine Sadok and Dr. Krisha Desai
Lead contact person for the project:	Dr. Anguraj Sadanandam

DIVISIONAL AFFILIATION	
Primary Division:	Molecular Pathology
Primary Team:	Systems and Precision Medicine
Other Division (if applicable):	Cancer Therapeutics
Other Team (if applicable):	Translational Cancer Discovery

PROJECT PROPOSAL

Prognosis of pancreatic ductal adenocarcinoma (PDAC) patients remains dismal despite extensive research efforts. Response to treatment is thoroughly challenged by stromal fibrosis, a marked characteristic of PDAC; comprised mainly of cancer-associated fibroblasts (CAFs) and immune cells which offer potential therapeutic targets. Previously, in our pioneering paper we have identified cancer-specific subtypes of PDAC that showed differential responses to treatments explaining the heterogeneity within this disease (Collisson and Sadanandam, et al., 2011). These subtypes also show heterogeneity with respect to their stromal characteristics (based on our recent pre-print publication; Poudel et al., 2017). We hypothesize that the stromal heterogeneity is related to differential interactions between different types of CAFs and cancer cells.

The research interest of Sadanandam lab is to understand inter and intra-tumoural heterogeneity in gastrointestinal cancers that contribute to a variable disease course, severity and differential treatment response. Our approach involves hypothesis-driven integrated analysis of high-throughput genomics, transcriptomics and metabolomics data generated from patient tumours, transplanted and genetically engineered animal tumours and cancer cell lines. The results are then correlated with clinical information. Moreover, the predictions

generated are tested and validated at the bench using cell lines and mouse models. Our strategy follows a systems approach involving both computational biology (analysis of high-throughput data, in silico) and wet-lab (clinical samples from trials/studies and *in vitro*/*in vivo*) experiments, which go hand-in-hand to achieve the overall experimental goals.

The aim of this highly interdisciplinary and academic-industry collaborative Ph.D. project, which will be conducted in collaboration with Professor Rajesh Chopra (ICR) and Merck KGaA TIP Oncology, is to unravel the interactions between CAFs and cancer cells that are associated with inter/intra-tumoural heterogeneity and tumour progression. Our approach has significant personalised therapeutic relevance to PDAC patients such that benefits from current therapies can be maximised. Using a combination of transcriptomics/genomic profiling of more than 250 patient samples (generated in Sadanandam lab), high dimensional flow cytometry, 3D co-culture assays, *in vivo* model systems, companion diagnostic assays, and bioinformatics approaches, the Ph.D. student will understand tumour and CAF heterogeneity and their cross-talk with the cancer cells in modulating PDAC progression. Further, the student will also get hands-on experience in drug screening to validate the markers as potential therapeutic targets in collaboration with Merck KGaA.

The highly integrated nature of this project lends itself to utilization of cutting-edge wet-lab and bioinformatics tools (generated within the lab and those available publicly) to address the question in hand. Sadanandam lab pioneers in systems biology approach to classify patient tumours into clinically relevant subgroups in order to maximize treatment benefit for personalised therapy. We have published pioneering papers in the field of stratification and personalized medicine in gastrointestinal cancers specifically pancreatic cancer in high impact journals like Nature Medicine and Cancer Discovery. The lab offers a highly conducive environment and a nurturing experience to carry out doctoral thesis in interdisciplinary science. This studentship involves academic-industry collaboration and fully funded by Medical Research Council (MRC) under industrial Collaborative Awards in Science and Engineering (iCASE) scheme.

LITERATURE REFERENCES

COLLISSON, E., SADANANDAM, A., OLSON, P., GIBB, W., TRUITT, M., GU, S., COOC, J., WEINKLE, J., KIM, G., JAKKULA, L., FEILER, H., KO, A., OLSHEN, A., DANENBERG, K., TEMPERO, M., SPELLMAN, P., HANAHAN, D. AND GRAY, J. (2011). Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. *Nature Medicine*, 17(4), pp.500-503.

GUINNEY, J., DIENSTMANN, R., WANG, X., DE REYNIÈS, A., SCHLICKER, A., SONESON, C., MARISA, L., ROEPMAN, P., NYAMUNDANDA, G., ANGELINO, P., BOT, B., MORRIS, J., SIMON, I., GERSTER, S., FESSLER, E., DE SOUSA E MELO, F., MISSIAGLIA, E., RAMAY, H., BARRAS, D., HOMICSKO, K., MARU, D., MANYAM, G., BROOM, B., BOIGE, V., PEREZ-VILLAMIL, B., LADERAS, T., SALAZAR, R., GRAY, J., HANAHAN, D., TABERNERO, J., BERNARDS, R., FRIEND, S., LAURENT-PUIG, P., MEDEMA, J., SADANANDAM, A., WESSELS, L., DELORENZI, M., KOPETZ, S., VERMEULEN, L. AND TEJPAR, S. (2015). The consensus molecular subtypes of colorectal cancer. *Nature Medicine*, 21(11), pp.1350-1356.

POUDEL, P., NYAMUNDANDA, G., RAGULAN, C., LAWLOR, R., DAS, K., TAN, P., SCARPA, A. & SADANANDAM, A. 2017. Revealing unidentified heterogeneity in different epithelial cancers using heterocellular subtype classification. *bioRxiv*, doi: https://doi.org/10.1101/174847.

CANDIDATE PROFILE

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1)

Pre-requisite qualifications of applicants: e.g. BSc or equivalent in specific subject area(s)	B.Sc/M.Sc (Life Sciences, Biotechnology, Biochemistry, and related fields). Those interested in biological and computational sciences are encouraged to apply for this interdisciplinary Ph.D.
Intended learning outcomes: Please provide a bullet point list (maximum of seven) of the knowledge and skills you expect the student to have attained on completion of the project.	1. Basic/advanced molecular biology, biochemistry and bioinformatics approaches 2. Primary cell culture and cell biology assays 3. Transcriptomic/genomic profiling using different technologies including sequencing methods. 4. Multiplex immunohistochemistry and cell sorting 5. *In vivo* models