The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL

PROJECT DETAILS	
Project Title:	Characterising subtype-specific signalling, drug response and personalised therapy in anti-EGFR resistant colorectal cancer
Primary Supervisor(s):	Anguraj Sadanandam
Associate Supervisor(s):	Krisha Desai
Backup Supervisor: (must have IRS status)	Udai Banerji
Lead contact person for the project:	Anguraj Sadanandam
DIVISIONAL AFFILIATION	
Primary Division:	Molecular Pathology
Primary Team:	Systems and Precision Cancer Medicine

PROJECT PROPOSAL

Overall survival from metastatic colorectal cancer (mCRC) remains poor. Despite the successful introduction of targeted therapies for mCRC, including anti-EGFR monoclonal antibodies and anti-angiogenic agents, initial good clinical responses are often confounded by acquired resistance in subsets of patients. *New targeted therapies and predictive biomarkers that spare patients from unnecessary treatment-related toxicity and ultimately increase the overall therapeutic ratio are urgently required.* Here we address this need by building on: a) our pioneering finding that CRCs can be stratified into at least four/five distinct subtypes based on gene expression profiles; and b) compelling preliminary evidence that certain gene biomarkers predict responses to certain tyrosine kinase inhibitors in certain cetuximab-resistant CRCs.

Sadanandam lab (*Nature Medicine 2013; JCO PO 2020; Cancer Cell 2020*) previously defined five gene expression CRC subtypes (CRCassigner-786) - goblet-like. Enterocyte, stem-like, inflammatory, and transit-amplifying (TA). Later, we published four CRC consensus molecular subtypes (CMSs; *Nature Medicine* 2015). Notably, the CRCassigner and CMSs were equivalent, except that the TA and enterocyte subtypes were combined into the CMS2 subtype. Furthermore, we have extensively developed and validated clinical assays for both CRCAssigner and CMS subtypes using NanoString assay (Ragulan et al., 2019).

These molecular subtypes also had distinct prognoses and clinical responses to treatment. Based on the response to anti-EGFR therapy response, we subclassified TA CRCs into two distinct sub-subtypes: cetuximab-sensitive TAs (CS-TAs) and cetuximab-resistant TAs (CR-TAs). CS-TAs overexpress known positive predictors of cetuximab response and EGFR ligands (epiregulin and amphiregulin). In contrast, CR-TA tumours appears to respond to certain other tyrosine kinase inhibitors *in vitro*. Understanding these kinase signaling associated with anti-EGFR therapy resistance and validating subtype-specific pharmacological inhibition of existing drugs using specific biomarkers are required; this is the main focus of this proposal.

This project will involve cutting-edge technologies such as single cell sequencing, proteomic analysis of signalling, three-dimensional organoids and *in vivo* models. Along with these technologies, machine-learning and bioinformatics-based genomics analysis will be employed. The student will have an opportunity to learn

multidisciplinary science of cancer.	
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)	BSc or MSc
Intended learning outcomes:	The learning outcomes for the student are: a) understanding the basics of cancer, stromal biology, machine learning and personalized medicine, b) get trained in interdisciplinary field of computational genomics to learn bioinformatics, statistics and mathematics and how to apply to above cancer project and c) learn single cell sequencing and animal experiments and handling of high-dimensional data (RNAseq/exome) from cancer field.
ADVERTISING DETAILS	
Project suitable for a student with a background in:	☒ Biological Sciences ☐ Physics or Engineering ☐ Chemistry ☐ Maths, Statistics or Epidemiology ☐ Computer Science ☐ Other (provide details)
Keywords:	**1. colorectal cancer**
	2. subtypes
	3. tyrosine kinase
	4. patient derived models
	5. single cell sequencing
	6. Personalised therapy