3 Year PhD Studentship available for September 2019

**Department:** Genetics & Genome Biology - Leicester Cancer Research Centre

**Supervisors:**
- Dr Cristina Tufarelli
- Dr Richard Badge
- Dr Alessandro Rufini
- Jon Lund (School of Medicine, Nottingham)

**Eligibility:** UK/EU applicants only

**Project Title:** Relationship between repetitive DNA and clinical radiosensitivity in rectal cancer

**Project Description:**

Radiotherapy is used in a large proportion of patients before surgery for rectal cancer to shrink the tumour and improve the chances of complete removal at operation. A UK study found a complete response to radiotherapy in only 10% of patients, with a considerable variation in response. Work on cells in the laboratory supports the hypothesis that radioresistance and genomic instability in cancer may be attributed to changes in activity of DNA methyltransferases (DNMTs). It has been proposed that the role of DNMTs is to prevent activation of repetitive elements such as LINE-1s, whose activity is a common feature of colorectal cancer (CRC). Our group has found that many LINE-1 promoters are active in CRC, driving aberrant expression of coding and non-coding transcripts. This project will explore the potential of these proteins as predictive biomarkers for radiation response and to identify the molecular mechanisms underlying their expression. Understanding why there are different responses between patients to radiotherapy may allow us to select who will benefit and those who can avoid unnecessary treatment. This work will improve the understanding of why responses to radiotherapy vary so much and may eventually lead to a method of sensitising tumours to radiotherapy.

**Background**

Radiotherapy is used in a large proportion of patients before surgery for rectal cancer but there is a considerable variation in response to it. Work on cells in the laboratory supports the hypothesis that radioresistance and genomic instability in cancer may be attributed to changes in activity of DNA methyltransferases (DNMTs). It has been proposed that the role of DNMTs is to prevent activation of repetitive elements such as LINE-1s, whose activity is a common feature of colorectal cancer (CRC). Our group has found that many LINE-1 promoters are active in CRC, driving aberrant expression of coding and non-coding transcripts. This project will explore the potential of DNA methyltransferase induced changes in protein expression as predictive biomarkers for radiation response.

**Hypothesis**

Radiosensitivity of tumours can be predicted through identification of aberrantly expressed proteins linked to changes in DNA methyltransferases and LINE-1 promoter activity.
Experimental Methods and Research Plan

1. Identify LINE-1 promoters aberrantly active in rectal cancer and the protein coding transcript they drive. Through the exploitation of the large datasets made available through the cancer genome project, including genomic, transcriptomic and epigenomic as well as clinical details for more than 400 colorectal cancer patients. These will be analysed to create lists of LINE-1 driven transcripts from these transcripts from the transcriptomic datasets and then select the transcripts with higher potential as biomarkers.

2. Use archival rectal tumour samples to investigate the relationship between their expression of and tumour radiosensitivity. This pilot study aims to gain an insight into whether levels of LINE-1 driven proteins in rectal cancers correlate with the different levels of radio-sensitivity that are frequently observed in the same histological cancers (rectal adenocarcinoma) treated by the same dose of radiotherapy. GNGT1, cMET, RAB3IP and CHRM3 that are known to become expressed in CRC due to LINE-1 promoter activity will be used in the initial experiments; high scoring transcripts identified in aim 1 can be included for validation at later stages. The experiments will be initially performed on 15 matched normal and tumour samples each from radiosensitive, radioresistant and intermediate sensitivity tumours looking at GNGT1, cMET, RAB3IP and CHRM3 amarkers that are known to become expressed in CRC due to LINE-1. Next, immunostaining will be performed using commercially available antibodies and protein expression will be compared in normal versus tumour tissue sections and in radiosensitive versus radioresistant tumours.

3. Determine if these proteins can be detected in liquid biopsies from CRC patients using ELISA based techniques and Luminex platforms to test whether these proteins can be detected in sera and FIT samples. Samples from 40 patients and 40 age matched healthy volunteers will be used for the study in sera. For the studies in FIT samples, 40 samples collected using FIT tubes before testing and 40 samples recovered from the screening platform at the end of the procedure will be analysed.

Funding details:

This project is in competition for a College of Life Sciences (CLS) PhD Studentship. The Studentships are for three years, starting September 2019, and offer tuition fees at UK/EU rates and a Stipend at UK Research Council rates. *

*Please note, this College of Life Sciences (CLS) PhD Studentship is joint funded by Leicester Precision Medicine Institute and local charity Hope Against Cancer.

Entry requirements:

Applicants are required to hold/or expect to obtain a UK Bachelor Degree 2:1 or better in a relevant subject.

The University of Leicester English language requirements apply where applicable.

How to apply:

You should submit your application using our online application system.

Apply for a PhD in Cancer Research /September 2019
In the funding section of the application please indicate you wish to be considered for a **CLS Cancer research Studentship**

In the proposal section please provide the name of the supervisor and project you want to be considered for. You do not need to include a proposal but please include a personal statement giving details of why you want to be considered for this project.

**Project / Funding Enquiries:** Dr Cristina Tufarelli  cristina.tufarelli@leicester.ac.uk  
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**Application enquiries to** [pgradmissions@le.ac.uk](mailto:pgradmissions@le.ac.uk)

**Closing date for applications**  25\(^{th}\)  February 2019