3 Year PhD Studentship available for 2018

Department: Genetics & Genome Biology - Leicester Cancer Research Centre

Eligibility: UK/EU applicants only

Supervisors: Dr David Guttery dsg6@leicester.ac.uk

Project Title: A personalised approach to detect and treat endometrial cancer recurrence through mutation tracking in circulating tumour DNA and \textit{in vitro} drug combination studies.

Project Description:

Background

Endometrial cancer (EC) is the most common gynaecological cancer in the UK (nearly 10,000 new cases/year) \cite{1}. Long-term outcome for most patients with early stage, hormone sensitive subtypes (low-risk) disease is excellent but this is not the case for the 60\% of cases who are diagnosed with an aggressive subtype (high-risk) or with advanced disease. In 75\% of cases when EC recurs it has spread outside of the pelvis to several distant sites and so the long-term survival is poor, around a year \cite{2}. The treatment options for recurrent EC are limited, usually chemotherapy or hormone therapy, and surgery is rarely an option due to the extent of cancer spread. New targeted therapies are on the horizon for EC, which will hopefully improve long-term outcome in advanced/recurrent cases; however, in-depth genetic analysis of each patient tumour will be needed to guide and monitor treatment.

There is no EC tumour marker that can predict or detect recurrence in high-risk patients and follow-up examination is often very difficult due to the high levels of obesity in EC patients. Furthermore, as most sites of metastatic EC are outside the pelvis, clinical examination often reveals very little useful information. If cancer recurrence is suspected, a scan is performed to look for tumour deposits, which are subsequently biopsied, often a major invasive procedure that carries risk, for example lung biopsy.

Circulating tumour DNA (ctDNA), the tumour-derived fraction of cell-free DNA (cfDNA) has emerged as an attractive, cheap and sensitive method for monitoring cancer burden and detecting cancer recurrence significantly earlier than scans. We and others have utilised next-generation sequencing (NGS) and digital droplet PCR (ddPCR) for analysis of ctDNA \cite{3,4}. However, to date no study has utilised the potential of tumour profiling and ctDNA mutation tracking to predict and detect relapse in high-risk and recurrent EC patients and to guide \textit{in vitro} drug studies that could define patient stratification and improved therapeutic strategies.

Aims and objectives

The aim of this studentship is to determine whether tumour profiling and mutation tracking in ctDNA can predict and detect relapse in high-risk and recurrent EC patients and, with this
information, perform *in vitro* drug studies to develop a personalised medicine approach for treating patients based on their molecular profile. The specific objectives will be:

1) To perform next-generation sequencing on tumours from patients on follow-up with high-risk and recurrent EC to determine whether tumour profiling can highlight mutations that can be tracked in ctDNA. Can we personalise the patients therapy based on their somatic mutational profile?

2) To use ctDNA from high-risk and recurrent EC patients to monitor response to adjuvant chemotherapy/radiotherapy and detect those who are likely to relapse. Can ctDNA accurately predict and detect relapse early?

3) Based on known driver mutations and mutations discovered by tumour profiling, to perform *in vitro* targeted studies in EC cell lines, using CRISPR-Cas9 to mimic the mutations of interest, in order to investigate sensitivity to targeted drugs, alone or in combination. Can tumour profiling and *in vitro* studies guide therapy?

**Experimental approach**

*Objective 1* – To detect key mutations for mutation tracking and *in vitro* drug studies, a bespoke targeted NGS panel for Ion Torrent sequencing of core biopsies incorporating key EC mutations associated with relapse will be developed. FFPE tissue from 10 – 15 high-risk and recurrent EC patients currently on follow-up will be analysed to determine the mutational profile of the tumour and whether targetable mutations are present, which will provide novel targets for *in vitro* drug studies.

*Objective 2* – To track mutations in ctDNA, the student will produce a shortlist based on molecular profiling in each patients primary tumour and use ddPCR to track at least 1 mutation in matched cfDNA from 3-monthly follow up blood samples to determine whether ctDNA can be a useful tool for early detection and prediction of relapse. We already have pilot data showing that ctDNA can be detected in plasma of advanced stage ECs, and this presents an exquisitely sensitive method for tracking mutations for early detection of relapse.

*Objective 3* – A subset of known EC mutations and mutations identified as part of Objectives 1 and 2 will be investigated for drug responses in EC cell lines, which Dr Macip’s group has extensive experience in (5). Using CRISPR-Cas9 gene editing, we will incorporate the key mutations in these cell lines, in order to determine how this affects drug sensitivity. The student will assess the impact on cell survival of a panel of targeted drugs as well as new drug combinations, including novel therapies in EC such as CUDC-907. The results of this will be used to develop early phase trials of new agents in advanced/relapsed EC.

**References:**

1. NCIN (2013)


**Funding details:**

This project is in competition for a College of Life Sciences (CLS) PhD Studentship. The Studentships are for three years, starting September 2018, and offer tuition fees at UK/EU rates and a Stipend at UK Research Council rates.

**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:**

Apply online using our online application system

Studentship-specific guidance for completing the online application form: Under Area of Study, select “Cancer Studies Research”; under intake date, “September 2018”.

In the Funding section, select “Studentship” and then, in the drop-down menu, select “College of Life Sciences Funded Studentship”.

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