3 Year PhD Studentship available for 2018

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

**Eligibility:** UK/EU applicants only

**Supervisors:**
- Professor Catrin Pritchard cap8@leicester.ac.uk
- Professor Dean Fennell df132@leicester.ac.uk

**Project Title:** Characterisation of macrophage phenotype and mechanisms of recruitment in mesothelioma.

**Project Description:**

**Background:**
Malignant mesothelioma is a lethal cancer that usually develops in the pleura and is increasing in incidence worldwide. Five-year survival is extremely poor and new treatments have not been developed in decades. At Leicester, in 2017, a new Mesothelioma Research Programme (MRP), directed by Prof Dean Fennell, has been initiated with investment of £2.5M from the British Lung Foundation. A key aim of the MRP is to take new therapies into clinical trials and undertake translational research to allow stratification of patients that would most benefit from the new treatments.

Mesothelioma is causally related to exposure of the mesothelial lining of the pleura to the environmental carcinogen asbestos. Histologically, mesotheliomas are grouped into three variants: epithelioid (~60%), sacromatoid (~20%) and biphasic (~20%). Exposure of mesothelial cells to asbestos initiates a number of as-yet uncharacterised events that result in inflammation and transformation, driving development of these subtypes. Apart from being involved in disease initiation. There is a growing realisation of the importance of inflammation in disease progression. Macrophages, the major cell type component of inflammation, are prevalent in advanced forms of mesothelioma, with evidence showing a link between intratumoural macrophage phenotype and prognosis of the disease. In addition, through recent transcriptomic work of primary mesothelioma samples undertaken by Dr Sara Busacca at Leicester using Cibersort, macrophages have been identified as a prevalent cell type within the tumour stroma of multiple samples.

Tumour associated macrophages (TAMs) are amongst the most frequently detected immune cells in the tumour stroma and are classified as M1 and M2 types with most TAMs being of the M2 type. TAMs represent important targets for interventional approaches. TAM centred approaches in cancer therapy include inhibition of TAM recruitment or survival or induction of TAM switching to a M1.
mode. TAMs have also been proposed to hijack PD1 antibodies, mediating resistance to anti-PD-1 immunotherapy, suggesting that TAM-targeted therapies may be used in combinatorial treatments to enhance patient outcomes.

In previous work, the Pritchard laboratory has shown that recruitment of M2-polarised macrophages to the microenvironment of lung adenocarcinomas is dependent on CC Chemokine Receptor 1 (CCR1) signalling. This has prompted a preclinical study, funded by CRUK, to test the efficacy of a CCR1 inhibitor developed by Astra Zeneca, AZD4750, in mouse lung tumour models in combination with anti-PD-1 immunotherapy. Interestingly, CCL3, the major CCR1 ligand in humans, is highly upregulated in the transcriptomic analysis on mesotheliomas, potentially suggesting that CCR1 signalling is a mediator of macrophage recruitment in the mesothelioma setting.

**Aims and experimental plan:**

For mesothelioma, there is a paucity of knowledge with regard to the role of TAMs in disease initiation, development, maintenance or response to therapy. This project aims to combine the expertise of Fennell and Busacca (mesothelioma) and Pritchard (macrophage biology) to provide a greater understanding of macrophage phenotype, the link with clinical outcomes and the mechanisms of TAM recruitment and localisation to the mesothelioma tumour microenvironment. Specifically the project will entail:

1. Immunohistochemical analysis to determine the phenotype and quantity of macrophages within the microenvironment of the three different mesothelioma subtypes and in biopsies from patients on treatment pre- and post- anti-PD1 immunotherapy. We will use digital pathology to investigate the link between macrophage phenotype/number and clinical outcomes including response and progression-free survival.
2. Analysis of the expression of key cytokines/chemokines and their receptors in the three mesothelioma subtypes and from paired biopsies using immunohistochemistry and digital pathology. We will focus on analysing CCR1 expression and its ligands (CCL3), given our previous data on CCR1 in lung adenocarcinomas and the transcriptomic data predicting high expression of CCL3 in mesotheliomas.
3. Testing the efficacy of the CCR1 inhibitor (AZD4750) in preventing the recruitment of macrophages to the tumour microenvironment in syngeneic mouse models for mesothelioma. If successful, we will examine the potential of combining AZD4750 with anti-PD-1 immunotherapy in these syngeneic mouse models.

**References:**

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”.

Project Enquiries:

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