

Friends of Paul O’Gorman funded PhD Studentships

A central ethos of the principal investigators at the Paul O’Gorman Leukaemia Research Centre, and the University of Glasgow, is to invest in the development of scientists for the future. Through the hard work and loyalty of hundreds of people that have raised funds for the research effort within our Centre, we are pleased to announce the development of the Friends of Paul O’Gorman PhD studentship. This annually-awarded studentship will provide a promising science graduate the opportunity to carry out a programme of leukaemia research within our state-of-the-art facilities at the Paul O’Gorman Leukaemia Research Centre which will contribute towards their PhD. The studentship will be awarded in open competition to the most promising candidate.

This studentship has been named in recognition of Adam Renwick Martin whose generous bequest gift has made this research possible. The studentship we are offering for a start date of October 2017 is as follows:

Adam Renwick Martin PhD Studentship in Acute Myeloid Leukaemia **Epigenetic profiling of leukaemia stem cells for precision medicine**

Supervisors: Dr Xu Huang

2nd Supervisor: Dr Heather Jorgensen

Abstract: Normal development of adult tissues relies on balanced self-renewal and differentiation of tissue stem and progenitor cells, whereas the abnormal activation of self-renewal or blockage of differentiation pathways, could lead to the malignant cell proliferation and oncogenesis. Leukaemia stem cells (LSCs) as a rare cell population present in Acute Myeloid Leukaemia (AML), confer chemotherapy resistance and are responsible for maintenance and relapse of the disease. Precision medicine requires eradication of LSCs for long term remission in AML, yet the detailed mechanism driving the oncogenic dysregulation in LSC still remains elusive. Epigenetic regulators play essential roles in cooperating with transcription factors to control gene expression required for LSC maintenance. The recent development of several pharmacological inhibitors targeting these regulators, such as BRD4 and Dot1L, highlights the great potential for them as promising anti-tumour targets. We have utilised a high throughput lentivirus shRNA screen to identify the critical epigenetic regulators, knock-down of which in human AML cells promoted AML LSC terminal myeloid differentiation and/or led to the loss of their self-renewal capacity, resulting in rapid cell death while sparing normal haemopoietic stem cell function. This suggests that targeting these candidates could represent rational novel therapeutic intervention in AML. In this project, we will focus on further validating the prioritised candidates from our previous screen, in primary AML patient samples and in our established human AML xenograft mice model. We hypothesise that these identified epigenetic regulators are required to sustain specific LSC centred epigenomic profiles, through association with distinct chromatin complex(es) in human AML cells compared to normal bone marrow cells, which are responsible for selectively maintaining LSC function.

The PhD candidate will employ systems biology approaches utilising combined genomics/proteomics (such as SILAC-IP-MS, RNA-seq and ChIP-seq) and bioinformatics analysis with following aims:

- 1) to determine epigenomic profiles in AML LSCs, which are associated with the specified epigenetic regulator;
- 2) to investigate the cellular and molecular mechanisms through which the specified regulator selectively targets human AML LSCs;
- 3) to evaluate the use of the available epigenetic inhibitors in AML and provide information to facilitate and optimise the development of potent preclinical/clinical-grade drug(s).

Overall, this PhD project is expected to advance our understanding underlying the important role of epigenetic regulators in human AML LSC. The information will be used to initiate the next stage of drug discovery and propose effective combination treatments with other standard AML therapies. The knowledge acquired in this study can also be applied to research of other cancer types. Our preliminary data indicate similar roles of particular epigenetic regulators in both blood and non-small cell lung carcinoma (NSCLC). The student will also be encouraged to use NSCLC cells as an alternative model for parallel studies in this project, and broaden our view on the role of epigenetic pathways in other stem cell derived solid tumours.

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Applications: Please send a covering letter and CV, together with degree transcripts and certificates, to the respective supervisor by Friday 24th February 2017. Please include the name and contact details of two people willing to provide references.