Characterisation of disordered metabolism in the stem cell niche during leukaemia evolution

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This PhD position in the Haematological Malignancies Programme provides a unique opportunity for a highly motivated individual to conduct research within a multi-disciplinary group of basic researchers and clinician haematologists, using cutting edge technology. In a broad sense, the student will learn the scientific process and how to become an independent productive scientist. More specifically, this PhD studentship provides a unique opportunity to study two poorly understood but critical and interrelated areas of cancer biology: the contribution of altered cell metabolism to cancer induction and maintenance and the role of the microenvironment in modulating this during cancer evolution.

Project Description

Introduction
It has long been known that the majority of cancers develop over time due to the stepwise acquisitions of mutations rather than through a single catastrophic event. Moreover, it is now appreciated that tumours are an ecosystem, with malignant cells and their microenvironment as constituent parts and a continuous cross-talk between these elements driving cancer progression. In addition, although documented for decades, the unique metabolic requirements of cancer cells have recently been highlighted as causal and not just a consequence of the transformed state. Importantly, the likelihood that this metabolic reprogramming confers therapeutic vulnerabilities upon malignant cells has sparked interest in the mechanisms and consequences of this process and the main players that mediate it. Cells of the microenvironment, such as bone marrow mesenchymal stromal cells (BMSCs) and endothelial cells, contribute to the metabolic reprogramming of leukaemic cells by fuelling these cells with metabolites, supporting aerobic glycolysis, decreasing the mitochondrial potential and ROS levels and increasing the threshold to undergo apoptosis. Of note,
The knowledge available linking metabolic reprogramming to cell non-autonomous cues in leukaemia mainly derives from studies on myeloid reprogramming to cell non-autonomous cues in leukaemia, which are an important focus of the Huntly and Mendez-Ferrer laboratories. However, this field is in its early infancy. Using our expertise in the cell autonomous development of leukaemia (Huntly) and malignant niche (Mendez-Ferrer), the student will be able to take a multidisciplinary approach and use cutting edge technology to address both cell autonomous mechanisms within mutated cells and non-cell-autonomous signals from the aberrant microenvironment which likely conspire to alter local metabolism and drive leukaemogenesis.

**Background**

Research in the Huntly laboratory is focused on the mechanisms whereby blood stem cells are subverted during the genesis of malignancies. Leukaemias have recently been demonstrated to be wholly dependent upon a small population of so-called cancer stem cells. These cells represent the critical targets for treatment and a greater understanding of their biology and its interface with normal stem cell function is fundamental to improving treatment outcomes. The focus of the Huntly laboratory is on this interface. The Huntly lab is examining the role of mutations that occur in and alter the role of haematopoietic stem and progenitors as early events before leading to the subsequent development of leukaemias and lymphomas (pre-leukaemic stem cells). Many of these mutations alter epigenetic regulation, enhancer function and transcriptional programmes (1) and these are all ongoing areas of investigation within the lab. Therapeutically, a recent example of this work is the identification of the Bromodomain and extra terminal (BET) proteins as critical mediators of leukaemia stem cells in AML and the development of an inhibitor of these proteins (2) that has already entered early phase clinical trials in relapsed blood cancers.

The Méndez-Ferrer laboratory research is focused on the regulation of the haematopoietic stem-cell niche in health and disease. Blood stem cells reside in specialised niches that allow them to self-renew, proliferate, differentiate and migrate according to the organism’s requirements. His group studies multisystem regulatory mechanisms by which the haematopoietic stem cell niche fulfils these complex functions and how the deregulation of these mechanisms contributes to haematological disorders. The group has demonstrated that the brain regulates a peripheral stem cell niche in the bone marrow partly through sympathetic innervation of nestin+ niche cells (3). Damage to this regulatory network, whose constituents might share a related ancestry, is required for the manifestation of myeloproliferative neoplasms (4). Neuroendocrine regulation of bone marrow stem cells by adrenergic signals or by sex hormones could potentially offer novel therapeutic approaches currently being tested in two Phase-II multicentre clinical studies.

**Central questions**

The purpose of this studentship is to understand both intrinsic and extrinsic changes in leukaemic stem cell (LSC) metabolism that critically promote LSC survival and/or resistance to chemotherapy. This project builds on preliminary data suggesting that 1) AML cells transform their microenvironment to promote their own survival and resistance, dependent on specific metabolites and BMSC-mediated protection from ROS (Mendez-Ferrer); 2) specific metabolites can reshape the epigenetic landscape in ways that promote tissue invasiveness (5) and leukaemogenesis (Huntly). Also, recent work from the Amit lab has shown that the epigenetic regulation of some haematopoietic cells (such as macrophages) is imprinted and can be reshaped by signals from the tissue environment. In collaboration with Christian Frezza (MRC Cancer Unit) and Jules Griffin (Department of Biochemistry), we propose to use cutting edge technology (MS and Maldi-MS) to measure metabolites in samples from mouse models available in our labs and mimicking different
stages of human leukaemogenesis, in relationship with niche cells and response to therapy. Functional studies will be performed first in vitro (optimised cultures and co-cultures available) and followed by in vivo validation of the key candidates. Samples from human cells and bone marrow biopsies (trephines) from AML patients are available to establish the clinical relevance of these findings and support any pre-clinical therapeutic data.

**Relevance to cancer**
If awarded, this studentship could increase our understanding of the biological processes underlying the development, survival and resistance of AML and might lead to the design of more effective and urgently needed therapies for this aggressive malignancy.

**Experience gained**
The student will receive broad training in stem cell biology and oncogenesis, covering both theoretical and practical milestones in this research field. The training will be truly multidisciplinary thanks to combined supervision by clinician scientists and basic researchers with expertise in myeloid malignancies (Huntly) and their microenvironment (Mendez-Ferrer), and interactions with experts in the metabolic reprogramming of cancer cells (Christian Frezza, MRC Cancer Unit), and lipid metabolism, inflammation and cancer (Jules Griffin, Department of Biochemistry). Further and regular interactions with other groups in the Cancer Centre and the Stem Cell Institute will provide a unique training opportunity that will be further strengthened with the participation in seminars, international conferences and meetings covering both fundamental science and its application in patients. The project will provide broad training in cell and molecular biology, tissue culture, work with mouse models and primary human samples. More broadly, we will stimulate motivation for creative and rigorous research generated through independent thinking but we will also encourage team work and interdisciplinary collaborations.

**References**
Applications

To apply for this studentship please see http://www.cambridgecancercentre.org.uk/studentships

For general enquiries please contact Tina Thorn tina.thorn@cruk.cam.ac.uk

For further information or questions relating to this project please contact:

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