Dr Mhairi Copland and Dr Helen Wheadon
CRF PhD Application

Title: Targeting the Hedgehog self-renewal pathway to prevent survival and chemo resistance of cancer stem cells in myeloid malignancies

Summary

Acute myeloid leukaemia (AML) and chronic myeloid leukaemia (CML) arise from a genetic alteration which confers a survival and proliferative advantage to the haemopoietic stem cell. These cancer stem cells (CSCs) retain the same properties of normal stem cells; long life, multipotency, and self-renewal capacity and reside within the bone marrow niche. Emerging evidence indicates that current treatment regimes effectively target the progenitor and more mature leukaemic cells, but are unable to eliminate the more quiescent CSC population responsible for minimal residual disease, relapse and disease progression. Hedgehog (Hh) signaling, a pathway important for stem cell self-renewal and survival is deregulated in myeloid malignancies and could be a good alternative strategy to target these resistant cells. Downstream targets of Hh signaling include the anti-apoptotic factor BCL-2 and the multi-drug resistance protein-1 (MDR1) involved in drug efflux, important mechanisms for conferring survival and chemo resistance in myeloid malignancies. This study will evaluate the efficacy of targeting the Hh pathway, BCL-2, and MDR1 either alone or in combination with current treatment regimes in primary AML and CML samples and patient specific CSC models using induced pluripotent stem cells. Overall this study will determine whether targeting Hh signalling is a rational regime for eradicating the persistent CSC in myeloid malignancies.

Objectives/Aims

1. Characterisation of the Hh pathway in stromal and haemopoietic cells in normal and malignant human bone marrow (CML and AML).
2. To determine which cells in the bone marrow microenvironment are producing Hedgehog (Hh) ligands in normal haemopoiesis and in myeloid malignancies;
    a. Is the Hh ligand exerting an autocrine or paracrine effect or both?
    b. Which Hh ligands are being produced?
3. Generate and characterize induced pluripotent stem cells (iPSC) from CML and AML patient mononuclear cells (MNC).
4. To assess the efficacy of Hh, BCL-2, MDR1 pathway inhibition alone or in combination with standard treatment regimes in iPSC CSC models.
5. To validate the importance of Hh pathway inhibition alone or in combination with other treatment regimes in patient samples.

Outcome

The findings of this study will increase our understanding of how the Hh pathway is deregulated in CML and AML. It will also enable us to determine the utility of Hh pathway manipulation in myeloid disorders and whether this represents a potential therapeutic strategy in CML and AML. A positive outcome to this study is likely to lead to the development of additional early phase clinical trials of Hh inhibitors, in AML and CML and the submission of a programme grant for the further study of Hh pathway manipulation in the treatment of myeloid disorders.

Current Students

Dr Mhairi Copland:
David Irvine final year CRF PhD student currently writing Thesis
Kirstin Lund 2nd Year CRF PhD student

Dr Helen Wheadon:
Anuradha Tarafdar final year PhD student currently writing Thesis
Odette Middleton 1st Year PhD student