Myeloma Fellowship outline

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Deciphering high-risk multiple myeloma

Background

Multiple myeloma (MM) is the most common primary cancer of the bone marrow. While survival can be extended, MM remains an incurable and fatal disease. Multiple myeloma is characterized by recurrent chromosomal translocations. In t(4;14) MM which is associated with a particularly poor prognosis, the MM SET domain (MMSET) protein is universally overexpressed and has an important tumorigenic role. MMSET is an H4K20 methyltransferase with characteristics of a transcriptional corepressor. Depletion of MMSET inhibits proliferation and induces cell cycle arrest and apoptosis of MM cells. Data are consistent with MMSET being an oncogene and that its oncogenic role is dependent on its catalytic activity. While the exact molecular targets underlying are not well understood its functional effects are mediated through reprograming of the MM epigenome through global and focal change.

Significance

Deciphering the functional basis of MMSET epigenetic reprogramming will greatly inform our understanding of the biological networks underlying development of MM. This information is clinically important in respect of current therapies for MM. Additionally the networks perturbed by MMSET may define pathways which are relevant to the development of novel therapies.

Aims of the PhD studentship

To gain insight into the epigenetic re-programing associated with chromatin remodeling in t(4;14) MM and its functional consequences.

1. The chromatin structure of MM will be determined using state of the art methods such as ChIP-Seq and ATAC-seq.

2. The chromatin looping interactions will be assayed using targeted Hi-C methodologies.

3. These data will be integrated with RNA-seq and expression data and cellular dependency of MM on aberrant gene expression assessing in in-vitro model systems.

By adopting a systems based approach to these data inform our understanding of the biological networks underlying development of t(4;14) MM.

This project is highly multi-disciplinary and our laboratory has extensive experience in all areas of the proposed research. Specifically, we shall make use a range of state of the art molecular technologies to interrogate the genome, including identification of interactions between regulatory elements. The functional consequences of deregulation of target genes will be explored using cell-based models. Our extensive in house biobanks with associated high quality clinical data will allow the relationship between epigenetic effects, somatic mutation and tumour pathology to be examined in detail.