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Integrated Systems Level Analysis of Myeloid Leukaemogenesis and Evaluation of The Molecular Alterations of Antigenic T-cell Receptor Repertoire Following X-irradiation

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Ionising radiation is a carcinogen and exposure can lead to an increased risk of leukaemia. Mouse models of human diseases have proven useful to develop a mechanistic understanding of disease that can inform risk assessment. More specifically, mouse models of radiation-induced acute myeloid leukaemia (rAML) have revealed the importance of genetic loss and/or mutation of genes such as Sfpi1/PU.1 and Flt3 both of which are also directly or indirectly implicated in human leukaemogenesis.

In order to build on established knowledge of the processes that drive rAML induction in the mouse and to identify the key steps in conversion of normal cells to cancer cells, transcriptomic and proteomic analyses were applied to three rAML cell lines derived from primary tumours arising in mice following x-irradiation. The analyses were also applied to the primary AMLs from which two of the lines were developed and in vivo passaged material of the remaining cell line in order to allow discrimination between biomarkers of radiation leukaemogenesis and those associated with adaptation to in vitro culture. The transcriptomic analysis of the primary rAMLs and cell lines was perfomed using lineage negative (Lin-) depleted bone marrow cells as controls. Significant similarity in the deregulated pathways was identified by transcriptomics and proteomics. The analyses suggest that primary AMLs and in vivo passaged cells are more similar to Lin- control cells than the derived in vitro passaged cell lines. Many more transcriptomic and proteomic alterations appear to be associated with adaptation to and growth under cell culture conditions. These findings strongly suggest that primary tumour materials should be used in preference to cell cultures for identification of key drivers of leukaemogenesis and furthermore use of in vitro cultured materials could be misleading.

A second project aims to evaluate radiation-induced molecular alterations of theTCR (antigenic T cell receptor) gene repertoire in peripheral blood lymphocytes in low dose irradiated mice as biomarker of exposure to,and long term effects of, low dose exposure. This is being investigated by two complementary quantitative approaches. Next generation sequencing is used to obtainin depth molecular profiling of the TCR genes expressed in control and irradiated animals and digital PCR is used to provide absolute quantification of illegitimate TCR gene recombination events.