

College PhD Studentship in Cancer Research

Studentship Number: MBSP/10/02

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Project description:

Exploring the therapeutic potential of the P53 pathway in chronic lymphocytic leukaemia

The development of chronic lymphocytic leukaemia (CLL) is influenced by the onset of genomic instability in B-cells and their incapacity to mount a normal response to DNA damage. p53, which is mutated in numerous cancers, regulates the reaction to genotoxic stress and promotes DNA stability. However, wild-type (wt)p53 is often expressed at high levels in malignant B-cells without triggering cell cycle arrest and/or apoptosis.

Our **hypothesis** is that loss of wtp53 function in CLL is due to alterations in other members of the p53 pathway that, if restored, could lead to a p53-mediated destruction of malignant cells. A collaboration between the Macip and Dyer labs has been established to exploit our expertise in p53 (SM) and B-cell malignancies (MJS) with the **goal** of harnessing the power of p53 as a therapy for CLL.

Our **preliminary data** show that a phosphorylated species of wtp53 is upregulated after stimulation of CLL cells using conditions that mimic those found in lymph nodes, but it is incapable of inducing cell arrest/death. Surprisingly, p53 transcriptional activity is progressively lost and the protein accumulates in the cytosol in association with mitochondria. Our **research plan** will use CLL cells obtained from patients to:

- Characterize p53 activation of downstream target genes and miRNA, as well as transcription-independent pro-apoptotic pathways.
- Elucidate the determinants of p53 subcellular localization in CLL cells.
- Identify the p53 effects on mitochondrial function.
- Study DNA damage-induced arrest/apoptosis and the role of mitochondria in these processes.
- Investigate the status of p53 activators (such as ATM and ATR) and the post-translational modifications induced in the presence or absence of genotoxic stress.
- Explore the role of classic and new p53 modulators that we have recently identified (such as retinoic acid and interferon pathways) in re-establishing p53 activity.
- Correlate the expression profiles of p53 pathway members with the clinical information associated with the samples, in order to uncover putative prognostic biomarkers.

The **expected outcome** of our experiments is to determine how and when p53 functions are lost in CLL and what interventions could reinstate them. This multidisciplinary approach to a clinical problem has the potential to improve treatments of CLL, the commonest form of leukaemia and presently incurable.