FORM E – PROJECT SYNOPSIS, School of Life Sciences

Project title: Functional studies on the role of the ZFP36 protein family in normal and malignant B cell populations

Cross School Project? **No**

If so, name of other School/s:

The proposal falls into the following priority area(s), Please underline: East Medicine, Ageing Research, informing policy and practice, New technologies for Biosciences

Background to research and synopsis (for those projects which have ethical considerations or issues of confidentiality: please address explicitly in an attachment to this form)

Gene expression can be controlled by transcriptional and post-transcriptional mechanisms. There is good evidence that post-transcriptional mRNA regulation is involved in regulating lymphocyte growth, differentiation and tumorigenesis [1]. ZFP36L1 is a member of the ZFP36 protein family which comprises three human proteins; ZFP36, ZFP36L1, ZFP36L2. These proteins mediate post-transcriptional mRNA regulation by binding to adenine uridine rich elements (AREs) in the 3' untranslated (3'UTR) of certain mRNAs including, growth regulatory genes (cytokines, transcriptional factors) and mediating mRNA degradation. The focus of the research project will be to identify functional roles of ZFP36 proteins in normal and malignant B cell populations and to explore the possibilities of utilising ZPF36 proteins as diagnostic/therapeutic target for B cell malignancies.

The present proposal will focus on two main areas:

1. Identification of ZFP36L1/L2 targets in lymphoid cell lines lymphocytes using RNA binding protein immunoprecipitation (RIP). RIP methods will be used to identify ZFP36L1 mRNA targets in B cell lines where these proteins are expressed. Cell lysates will be prepared and lysates will be precleared and then incubated with specific antibodies to ZFP36L1. Immunoprecipitation will be carried out using protein A/G beads. RNA will be isolated from all RIP material. RNA-Seq will be used to identify mRNA targets present in immunoprecipitated material.
2. Testing biological roles of ZFP36L1 mRNA targets in B cells using siRNA and overexpression strategies to recapitulate ZFP36L1/L2 effects on cell functions. In order to investigate the biological roles of candidate ZFP36L1/L2, our basic strategy will be to re-capitulate ZFP36L1 effects in cells by viral-mediated expression or knockdown of individual ZFP36L1/L2 target mRNAs. Effects of this on B cell functions of cell growth survival and apoptosis will be then investigated using a number of functional assays similar to that previously described [2,3].

The student will gain experience in modern cellular and molecular biological approaches to investigating gene functions in mammalian cells.

Supervisory Team and Research Environment

Supervisor Name	Role (DoS, 2nd Supervisor, 3rd Supervisor)	No. of successful PhD/ MPhil supervisions	Current student load for 2012/13 (FTE)	School (for cross School projects)
Dr John Murphy	DoS	7	1	
Dr Nino Porakishvili	2nd	>10	2	

Please list recent publications by supervisors relevant to the project:

1. **Baou M, Norton JD and Murphy JJ (2011). AU-rich RNA binding proteins in hematopoiesis and leukemogenesis. Blood 118, 5732-5740.**
2. **Baou M, Jewell A, Muthurania A, Wickremasinghe RG, Yong KL, Carr R, Marsh P and Murphy JJ. (2009). Involvement of Tis11b, an AU Rich Binding protein, in induction of apoptosis by Rituximab in B-CLL cells. Leukemia 23, 986–989.**
3. **Nasir A, Norton JD, Baou M, Zekavati A, Bijlmakers M, Thompson S, Murphy JJ (2012). ZFP36L1 negatively regulates plasmacytoid differentiation of BCL1 cells by targeting BLIMP1 mRNA. PLOS One 7(12): e52187. doi:10.1371/journal.pone.0052187**

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