PROJECT SYNOPSIS, School of Life Sciences
Director of studies: Dr Nino Porakishvili

Project title: Pro-survival signalling in B chronic lymphocytic leukaemia (B-CLL) cells, mediated by the microenvironment through CD180 receptor

Background and synopsis

Introduction: B cell chronic lymphocytic leukaemia (B-CLL), the most common leukaemia in the Western world, affects individuals 50-80 years of age. It represents a high economic burden and significantly impairs quality of life of the elderly. Characteristic *in vivo* accumulation of leukaemic lymphocytes is mediated through survival signals delivered by microenvironmental stimuli through receptor/ligand interactions. B-CLL also has multiple independent prognostic markers, the most important being mutational status of *Immunoglobulin (Ig) VH* genes and expression of CD38 and ZAP70 protein kinase.
Background: Our previous studies have shown that both pattern of expression of, and ligation of CD180/RP105 – an orphan receptor of the Toll-like receptor (TLR) family – delineates three groups of B-CLL clones: CD180+responders (R); CD180+non-responders (NR) and CD180-negative. Our data are consistent with the possibility that within the microenvironment of proliferation centres in B-CLL patients, CD180 ligation (through a hypothetical endogenous ligand) provides powerful stimulatory signals to R B-CLL cells leading to their extended proliferation and survival. Our data also imply that there are different mechanisms for expansion of NR and $CD180^-$ B-CLL cells which exhibit properties of anergic cells.
Synopsis: We will use cell culture, flow cytometry and western blotting to study signalling pathways leading to activation and expansion of R B-CLL and anergy of NR B-CLL clones. Following CD180 ligation we will measure levels of resting and activated (phosphorylated) protein kinases associated with ZAP70/Syk, ERK and PI3-pathways downstream to Akt and NF-kB, and their impact on regulation of B-CLL cell survival and apoptosis. We will evaluate involvement of pro- and anti-apoptotic proteins Mcl-1,Bcl-X_L and Bax in differential responses to CD180 ligation and determine presence of apoptosis by changes in mitochondrial membrane potential. In separate experiments we will assess the impact of CD180-mediated signalling events on functions of the specific B cell receptor (BCR). Results will be analysed in conjunction with prognostic markers and course of the disease.
The outcome will be better understanding of microenvironmental stimuli that lead to survival and expansion of CLL cells and signalling pathways of CD180, to provide a basis for new immunotherapy strategies.
Technical training provided: flow cytometry, cell culture, western blot analysis, confocal microscopy.
Ethical approval has been obtained from UCLH, REC reference number 08/H0714/6 "Understanding the biology of CLL to develop new treatment opportunities".

Supervisory Team and Research Environment

Supervisor Name	Role (DoS, 2nd Supervisor, 3rd Supervisor)	No. of successful PhD/ MPhil supervisions	Current student load for 2009/10 (FTE)
Dr Nino Porakishvili	DoS	24	1
Dr John Murphy	2nd	6	0
Professor Peter Lydyard	3rd	15	1

Publications by supervisors relevant to the project:
Walton JA, Lydyard PM, Nathwani A, Emery V, Akbar A, Glennie MJ, Porakishvili N. Br J Haematol. 2010 Jan;148(2):274-84. http://www.ncbi.nlm.nih.gov/pubmed/19895614
Porakishvili *et al*., Br J Haematol, 2010. Accepted for publication.

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