



Professor Phil Quirke

## College Research Medals awarded

The research medals were instituted by the Royal College Research Committee to honour the excellence in research found in the younger members of the College and to endeavour to help their careers by providing an external view of the quality of their research. Three medals were awarded at the College during the Ceremony for New Fellows held on Wednesday 18 November 2009.

We were very pleased with the quality of applications. We found it hard to separate them when deciding the gold medal but this is to be expected when there is such a high quality of applications.

I would like to encourage all trainees who publish to submit their best paper for consideration for next year's awards. For further information please see the College website: [www.rcpath.org/index.asp?PageID=1587](http://www.rcpath.org/index.asp?PageID=1587) These medals are prestigious and will only benefit you when it comes to further applications to funders or appointment to academic or NHS posts. Good luck!

**Professor Phil Quirke**  
Chair, Research Committee

### Dr Saman Hewamana, College 2009 Gold Research Medal

My research interest is the role of Nuclear Factor Kappa B (NF- $\kappa$ B) in prognosis and treatment of leukaemia. The research described was done as part of a Leukaemia Research UK (LR-UK) sponsored Clinical Research Fellowship during the haematology registrar training programme in Cardiff.

NF- $\kappa$ B has long been considered an important factor in cancer development given its role in cell growth and proliferation and its transcriptional regulation of many anti-apoptotic genes. However, accurately and reproducibly measuring NF- $\kappa$ B has been difficult in primary tumour cells, thereby limiting study of NF- $\kappa$ B variation among chronic lymphocytic leukaemia (CLL)

patients and how this may contribute to disease progression. As a first step I was able to demonstrate that NF- $\kappa$ B was differentially expressed in CLL patients using Electrophoretic Mobility Shift Assay (EMSA) and ELISA-based assays. Also it allowed me to demonstrate that CLL cells with higher levels of the NF- $\kappa$ B subunit Rel A in the nucleus were less likely to undergo spontaneous apoptosis *ex vivo*, showing an association between the Rel A and *in vitro* survival of CLL cells. Furthermore, I showed that nuclear Rel A levels directly correlated with a shorter lymphocyte doubling time and higher white blood cell count; two important clinical parameters of disease progression. Subsequently I quantified Rel A DNA binding in nuclear extracts derived from

Dr Grainne Connolly,  
Dr Daniel Royston and  
Dr Saman Hewamana  
with Professor Peter  
Furness, President and  
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large number of unselected CLL patient samples and investigated the ability of Rel A to predict for the requirement for treatment and survival. Rel A DNA binding was strongly associated with advanced Binet stage. I was able to demonstrate that Rel A DNA binding was predictive of time to first treatment and overall survival. Finally I demonstrated that apoptosis of CLL cells could be induced by inhibition of Rel A using a Rel A inhibitory peptide and an aminoparthenolide analogue (LC-1) which is in phase 1 clinical trials in Cardiff. Furthermore there was extreme *in vitro* synergy between inhibition of NF- $\kappa$ B

and the conventional chemotherapeutic drug fludarabine in apoptosis induction in CLL.

In conclusion, my studies highlight that Rel A is an interesting prognostic marker and appears to be a valid target for treatment in CLL.

Now I have successfully completed Specialist Registrar training in Haematology and the LR-UK Fellowship, I am actively looking for an opportunity to continue research. Inspired by the research work I have done so far, my aim is to continue researching the role that NF- $\kappa$ B plays in the pathology and treatment of leukaemia.

#### **Dr Daniel Royston, College 2009 Specialty Research Medal for Histopathology**

The invasion of lymphatic vessels by tumours and subsequent spread to draining lymph nodes is a key prognostic determinant in several human cancers and guides patient management. The importance of lymph node involvement in the biology of tumour development is reflected in commonly used staging systems for cancer (e.g. TNM).

Traditionally, lymphatic metastasis was considered to be an essentially passive process in which malignant cells shed by solid tumours gain access to local pre-existing lymphatics due to their thin walls and incomplete basement membranes. However, recent advances in lymphatic biology, including the discovery of several lymphatic-specific markers, have revealed complex functional and biochemical interactions between the microvasculature of tumours and other cell types within the tumour microenvironment. Indeed, several attempts have been made to correlate the expression of various lymphangiogenic growth factors, chemokines and their cognate receptors with the metastatic potential of aggressive human tumours. Using lymphatic-specific markers such as VEGFR-3, podoplanin, PROX-1 and LYVE-1, several preliminary animal studies using xenotransplanted human tumours revealed a correlation between intra- and peritumoural lymphatic proliferation and tumour spread. However, subsequent studies in human cancers failed to identify lymphatic vessel density as a universal determinant of tumour cell metastasis and patient survival. Related studies examining the expression of potent lymphangiogenic growth factors by tumours, notably members of the vascular endothelial growth factor family (VEGF-C and VEGF-D), also failed to demonstrate a clear association with lymphatic vessel invasion, lymph node metastasis and overall patient survival.

A number of alternative mechanisms have been invoked to explain the process of tumour cell infiltration and spread via the lymphatic vasculature. Recently, tumoural blood vessels with an altered gene expression profile have been identified, with several tumour endothelial markers (TEM) being directly implicated in tumour metastasis. This raised the question of corresponding changes being identified in the gene expression profile of tumoural lymphatics. We addressed this issue by comparing the RNA profiles of primary lymphatic endothelial cells isolated from normal tissues and from the vasculature of a highly metastatic murine fibrosarcoma (T241/VEGF-C). We revealed significant differences in the expression of several genes including those involved in the formation of endothelial cell junctions, subendothelial matrix and vessel growth/patterning. Furthermore, we showed that at least one of these molecules, endothelial specific adhesion molecule (ESAM), is significantly up-regulated on the lymphatics of several human cancers, including colorectal cancer and human head & neck squamous cell carcinoma. Moreover, the expression of ESAM by tumoural lymphatics dramatically correlated with the incidence of lymph node metastasis. These findings raise the prospect of identifying future biomarkers of lymphatic metastasis.

Recent, unpublished work in our laboratory using a murine model of lymph node metastasis has also revealed exciting evidence that a lymphatic-specific monoclonal antibody can modulate the invasion and spread of tumour cells to draining lymph nodes. This antibody appears to directly mediate tumour cell/lymphatic endothelial cell interactions *in vitro*. These preliminary results help shed light on the detailed interactions between tumour cells and lymphatic vessels, and may help inform the search for new generation anti-tumour therapies.

**Dr Grainne Connolly, College 2009 Specialty Research Medal for Clinical Biochemistry**

Cardiovascular disease is the leading cause of premature death in patients with end-stage renal disease. Although renal transplantation remains the gold standard for renal replacement therapy in end-stage renal disease, the cardiovascular death rate remains much higher than in the general population. Even a minor decline in renal function is associated with increased cardiovascular risk and poorer outcome following a cardiovascular event.

Patients on dialysis and with renal transplants do not come with a blank cardiovascular risk profile. Many have been exposed to a number of conventional cardiovascular risk factors and uraemic abnormalities long before the start of renal replacement therapy. Renal transplant recipients can have their higher cardiovascular risk compounded by the use of immunosuppression which contributes to the development of dyslipidaemia, obesity and post-transplant diabetes.

Renal transplant recipients therefore continue to represent a special group of individuals with chronic kidney disease, who are both immunosuppressed and at heightened cardiovascular risk.

As traditional cardiovascular risk factors do not fully explain the burden of vascular disease in this population, interest has focused on the role of non-conventional and 'uraemia-related' cardiovascular risk factors. Improved understanding of the pathogenesis of cardiovascular disease and identification of biochemical markers contributing to this proc-

ess or highlighting those transplant recipients who will benefit most from aggressive treatment and intervention is crucial to improve the longevity of this population.

My research, supported by a Fellowship from the Northern Ireland Kidney Research Fund, assessed the predictive value of established and novel cardiovascular risk factors in relation to all-cause mortality and the occurrence of cardiovascular events in a prospective cohort study of renal transplant recipients.

This research has yielded several interesting and clinically significant results. It is the first study to show that in renal transplant recipients, a higher serum phosphate is a predictor of mortality, and to suggest that phosphate provides additional, independent, prognostic information to that provided by traditional risk factors in the risk assessment of patients with a renal transplant. In addition, elevated troponin T, elevated homocysteine concentration and lower retinol concentration have been identified as significant independent predictors of mortality in patients with a renal transplant.

This study therefore confirms the significance of non-conventional biochemical markers in the pathogenesis of cardiovascular disease in patients with a renal transplant. As these markers are readily available in clinical practice, they could be used to identify patients at highest risk of death, while continued follow-up of this study population should enable the development of a cardiovascular risk algorithm for renal transplant recipients.