

RENAL SCIENTIST'S NEWSLETTER

Renal Research in Aberdeen

Aberdeen has a long history of active renal research spanning both clinical and laboratory based programmes. This successful translational approach continues to expand. Our research is carried out in new, purpose built buildings in the research-laboratories of the Institute of Medical Sciences and in the clinical research setting of the Health Sciences Building, both located on the Foresterhill site in Aberdeen. These incorporate state of the art facilities, located on the same site as, and in close proximity to, the major teaching hospital serving the North East of Scotland. This environment enables scientists and clinicians to interact and has facilitated the development of high quality translational research programmes within the Schools of Medicine and Dentistry and Medical Sciences to foster a real “blue skies to bedside” approach to renal medicine.



Institute of Medical Sciences and Health Sciences Building, University of Aberdeen

Laboratory based renal research within the Division of Applied Medicine in Aberdeen is centred on the immunological basis of glomerular injury as a target for therapy (Renal Immunology Group – Lead Investigators Dr. Heather Wilson, Dr. Lars Erwig and Prof Rob Barker). Other important areas of research in Aberdeen include the assessment and prediction of drug-induced nephrotoxicity (Clinical Pharmacology Group) and an integrated programme of research into renal failure, particularly end stage renal disease and acute renal failure, including economic evaluation, epidemiology and provision of an evidence base for clinical practice through systematic literature review. Translational and clinical research interests focus on ANCA associated vasculitides, systemic lupus erythematosus and other macrophage-mediated vascular diseases including atherosclerosis and anti-phospholipid syndrome.

The ultimate aim of the laboratory based Renal Immunology Group is to use improved understanding of the pathogenesis of immune-mediated diseases that

cause kidney failure to develop novel and more effective treatments. Macrophage and T cell infiltration is a consistent feature of inflammation and is observed in all types of severe and progressive renal disease. Importantly, this is true not only for primary inflammatory or immune-based diseases, such as glomerulonephritis and renal transplant rejection, but also for conditions that do not have a primary immune basis, such as ureteric obstruction and diabetes. In all these diseases, the function of infiltrating macrophages and type of T cell subsets correlates with the severity of disease, supporting their role in the pathogenesis, and the group uses both *in vitro* and *in vivo* studies to dissect the underlying mechanisms responsible.

Dr Heather Wilson's work is centred on the role of infiltrating macrophages as a target for treatment of renal disease, not only because they have been shown to be pathogenic, but also because of their potential to facilitate resolution of injury and to promote tissue repair. This makes macrophages potential therapeutic targets. Her research interests are primarily focussed on the factors that control macrophage activation, and the ways in which differential macrophage activation regulates tissue injury and repair, especially in rodent models of nephritis. Her current research aims to elucidate the integrated signalling pathways that direct macrophage function, and how these pathways can be manipulated to divert activation to inhibit the destructive properties but exploit macrophage reparative attributes to restore regulation to the inflammatory response. She has demonstrated proof of this principal by inhibiting the pro-inflammatory transcription factor, NF κ B to create an anti-inflammatory therapeutic macrophage that down regulates renal inflammation in experimental models. She is now focussing on more practical methods of developing macrophages to become therapeutic cells and for this purpose is investigating the role of Suppressors of Cytokine Signalling (SOCS) proteins of which two (SOCS1 and SOCS3) have an important regulatory role in macrophages. She has shown using siRNA knockdown technology and adenoviral based gene over-expression systems that SOCS3 controls the pro-inflammatory potential of macrophages and in its absence macrophages become actively anti-inflammatory. Furthermore, loss of SOCS3 expressing macrophages in inflamed glomeruli is associated with a reduction in inflammation in experimental models of nephritis confirming the functional importance of these cells.

She is also exploring whether SOCS1 and 3 can act as potential biomarkers for macrophage activity in nephritis as well as in other macrophage-associated inflammatory diseases, including atherosclerosis. Her collaborative research focuses on the molecular imaging of macrophages as a non-invasive method of identifying vulnerable atherosclerotic plaques and the subtypes of macrophages within plaques isolated from different anatomical localisations in patients with

cerebrovascular atherosclerosis and peripheral arterial disease (with Dr J Brittenden); the role of differentially activated macrophages and dendritic cells in inducing Th17 inflammatory T cells under specific disease conditions (with Prof RN Barker); and the effect of maternal iron deficiency on kidney development and blood pressure regulation in the offspring (with Prof H McArdle/Dr Lorraine Gambling).



Some members of the Renal Immunology Group in Aberdeen

Dr. Lars Erwig has a longstanding interest in the role of macrophages in the progression and healing of inflammation. His initial work has focussed on the signals that activate macrophages *in vitro* and in glomerulonephritis and he has developed the concept of macrophage programming to explain how macrophages function within inflamed or otherwise damaged tissue where they are exposed to complex environments. Dr. Erwig has expanded on his original work during a recent Wellcome Fellowship by examining the consequences of apoptotic and opsonised cell uptake for macrophage function. He has identified profound differences in how macrophages and dendritic cells digest ingested cells. These findings have direct implications for the reparative properties of macrophages in renal or other organ specific inflammatory conditions. Understanding the molecular mechanism underlying clearance of dying cells and pathogens by macrophages, in particular the role of small GTPases in macrophage phagosome maturation has now become the focus of his laboratory based research and is at the centre of his recently awarded Scottish Senior Clinical Fellowship. His clinical research interest cover a wide spectrum of autoimmune disease and include numerous clinical trials and translational studies in ANCA associated vasculitides (with the European Vasculitis Study Group), SLE (familial genetics with Prof T. Vyse and the therapeutic potential of soluble CTLA with Prof R. Barker and Dr F. Ward) and anti-phospholipid syndrome (with Prof M. Greaves).

Professor Rob Barker's work concentrates on elucidating the pathogenesis of renal diseases caused by autoimmune attack on the renal glomerulus, with a particular focus on the balance between effector and regulatory helper T cell

subsets. The aim is to design new approaches to treatment by understanding the mechanisms by which immune tolerance to renal autoantigens is maintained in health and lost in disease. Goodpasture's disease provides the prototypical example of glomerulonephritis for the work, building on previous studies in Aberdeen and with collaborators elsewhere to characterise the target autoantigen and the helper T cells that recognise it. Largely as a result of this work, the autoreactive helper response in Goodpasture's disease is now one of the best characterised in any human autoimmune disease, providing opportunities for specific clinical intervention. Professor Barker's current studies aim to exploit regulatory T cell subsets to protect the Goodpasture antigen in the glomerular basement membrane, the NC1 domain of the $\alpha 3$ chain of type IV collagen, from autoaggression. In particular, the potential therapeutic roles of regulatory T cells that secrete the suppressive cytokine interleukin 10 and those that cross-react with the co-localised and highly homologous $\alpha 5$ chain of type IV collagen are being explored. Work in Aberdeen has revealed that the $\alpha 5$ chain is securely protected from autoaggression by regulatory T cells, and that these cells can be manipulated to also re-instate tolerance to the $\alpha 3$ chain and other glomerular autoantigens.

The pharmacological aspect of renal research in Aberdeen is centred on the prediction of nephrotoxicity (Professor Gabrielle Hawksworth). The morphological, biochemical and functional heterogeneity of the kidney necessitates the use of pure cultures of renal cells for mechanistic toxicological studies. Professor Hawksworth's group are focussing on the proximal tubule, since this is the main target of drug-induced nephrotoxicity and have demonstrated that primary cultures of human proximal cells can be used to predict drug- and chemical-induced nephrotoxicity *in vivo*. Decrease of transepithelial resistance (TER) *in vitro* is another predictor of chemical-induced nephrotoxicity *in vivo* and she is also investigating the signalling systems resulting in altered localisation of junctional proteins, responsible for decreased resistance and increased permeability, as part of a programme to protect against drug-induced nephrotoxicity. Renal proximal tubular transporters are frequently implicated in drug-induced nephrotoxicity therefore her third line of investigation is the regulation and substrate specificity of human renal organic anion (OAT) and cation (OCT) transporters and the multidrug resistance-associated proteins as efflux transporters.

Together, the different complementary aspects of basic and clinical renal research in Aberdeen combine to provide the critical mass necessary to deliver real improvements in patient care.

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