

LABORATORY RESEARCH - GLOMERULAR CELL BIOLOGY

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The glomerulus is the elemental unit of kidney filtration, and the glomerular podocyte is a central component of this filtration barrier, disruption of which is the key feature of a multitude of kidney diseases.

One of the main focuses of the Academic Renal Unit is the study of podocyte biology, with a team of clinical paediatric and adult nephrologists at various levels of training, working side by side with basic scientists.

The resources we use are unique in the world, comprising human conditionally immortalised podocyte cell lines from normal kidneys and from patients with congenital mutations in key podocyte genes, as well as the more recent development of human conditionally immortalised endothelial cell lines, the other key cell of the filtration barrier.

Current projects fall into four basic areas:

1. The role of plasma factors in the pathogenesis of nephrotic syndromes. This utilises the resource of patients' plasma and its effect on the cell lines, concentrating on the slit diaphragm proteins, actin cytoskeleton and the signalling pathways that connect them.
2. The role of the podocyte in diabetic nephropathy. This arena of work builds on our observation that the podocyte is a novel insulin sensitive cell, and addresses the biological basis of this clinical renal disease which is by far the biggest cause of end-stage renal failure worldwide, and whose incidence is rapidly rising. This work has recently been expanded by Dr Coward, using sophisticated *in vivo* models and techniques learnt in Toronto, which are now being transferred to Bristol.
3. Influences on podocyte differentiation – we are investigating the roles of genes, cytokines, endothelial cells, matrix etc. as components of the podocyte environment that influence mature differentiation. This includes work that has revealed that mature podocytes display key features of smooth muscle cells, and will address how the podocyte changes its developmental profile in disease.
4. Co-culture of glomerular endothelial cells and podocytes, to engineer the properties of the intact filtration barrier, in order to study its specialised functions *in vitro*.

The Academic Renal Unit (ARU), based in bespoke laboratory space in Southmead Hospital, is a thriving research environment with currently 22 research staff.

This is a mix of laboratory technicians, clinical and non-clinical PhD students, MD students post-doctoral researchers and a senior non-clinical Lecturer, Dr Gavin Welsh.

Senior clinical staff consist of adult and paediatric nephrologists, and recently Professor Saleem has taken over from Professor Peter Mathieson as Head of the ARU.

Collaborations.

Our main collaborators are:

1. Susan Quaggin, Samuel Lunenfeld Institute, Toronto. Dr Quaggin has developed the world's leading laboratory in studying glomerular disease using in vivo models. Dr Coward has just completed 20 months in Toronto learning techniques and developing important new models.

2. Ania Koziell, Molecular Medicine Unit, Institute of Child Health, London. Dr Koziell is a Wellcome Senior Fellow, studying the molecular interactions of nephrin.

3. Dr Michael Lodomery, Senior Lecturer at the University of the West of England (UWE). His laboratory is interested in the biology of the WT-1 gene, and we have jointly appointed a PhD student to work on this project, who will work with the world leading proteomics and mass spectrometry technology established at UWE.

4. Professor Jeremy Tavare – Department of Biochemistry, University of Bristol. This is a valuable collaboration with a laboratory that is a world leader in glucose transport in cells.

5. Professors David Bates and Steve Harper – Microvascular Research Labs, University of Bristol. We have many links with this group, particularly in the biology of Vascular Endothelial Growth Factor (VEGF).

5. We have been approached by a number of other collaborators worldwide, particularly with respect to utilising our cell line for specific projects, and have initiated active collaborations with at least 50 of these so far, with our cell lines being distributed to over 100 laboratories worldwide.

RESEARCH GRANTS OBTAINED

2008 Medical Research Council – Programme Grant (3 years) – co-applicant –

(Principal Applicant PW Mathieson, Bristol, co-investigators, Dr S Satchell, Bristol; Dr RJ Coward, Bristol; Dr GI Welsh, Bristol)

£562,000

The cellular basis of albuminuria

2008 Medical Research Council – Strategic Project Grant (3yrs) - £350,000 – (co-applicant CM Taylor, Birmingham)

A National Study of Kidney Disease in Childhood and Adolescence

2008 Kids Kidney Research Project Grant – £100,000 (co-applicant, Dr GI Welsh, Bristol)

2008 Kidney Research UK – Project Grant - £35,000

A National Study of Kidney Disease in Childhood and Adolescence

- 2008 Kids Kidney Research – Startup Grant - £35,000
An animal model of shigatoxin associated HUS
- 2007 Kidney Research UK Phd Studentship - £58000 (3 years). (co-applicant, Dr GI Welsh, Bristol)
Identifying the causes and cellular effects of Focal segmental glomerulosclerosis (FSGS).
- 2007 Kidney Research UK project grant – £150,000 (3 years - co-applicant with S Satchell, Bristol) *Podocyte-endothelial cross-talk*
- 2006 Southmead Hospital Research Fund - £10,000 (2 years). *A proteomics analysis of FSGS plasma*
- 2006 Medical Research Council -Richard Coward was awarded a prestigious 4 year Clinician Scientist award to study the insulin response pathway in podocytes. This has funded a technician and his salary for 4 years, together with consumables for the project and amounts to approximately £725,000.

PUBLICATIONS

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CONDITIONALLY IMMORTALISED HUMAN GLOMERULAR ENDOTHELIAL CELLS EXPRESSING FENESTRATIONS IN RESPONSE TO VEGF
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American Journal of Transplantation. 6; 1666 -72 July 2006

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Redistribution of connexin43 expression in glomerular podocytes predicts poor renal prognosis in patients with type 2 diabetes and overt nephropathy
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Jeanette Eyre, Kyriakos Iannou, Blair D. Grubb, Moin A. Saleem, Peter W. Mathieson, Nigel J. Brunskill, Erik I. Christensen, Peter S. Topham

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American Journal of Physiology Renal Physiol – 2007 Feb;292(2):F674-81.

Reddy GR, Pushpanathan MJ, Ransom RF, Holzman LB, Brosius FC 3rd, Diakonova M, Mathieson P, Saleem MA, List EO, Kopchick JJ, Frank SJ, Menon RK.

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A novel renal perspective of preeclampsia: a look from the podocyte.
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Richard JM Coward, Gavin I Welsh, Ania Koziell, Jeremy Tavaré, Peter W Mathieson, and Moin A Saleem

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KIBRA interacts with PATJ and synaptopodin and modulates directional migration of podocytes
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Am J Physiol Renal Physiol. 2009 Jun;296(6):F1279-90.

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Inhibition of p66ShcA longevity gene rescues podocytes from HIV-1-induced oxidative stress and apoptosis.
J Biol Chem. 2009 Jun 12;284(24):16648-58. Epub 2009 Apr 21.

Popular Journal Papers

1. Recent advances in understanding nephrotic syndrome – light at the end of the tunnel. *Silver Lining Magazine* – 2006
2. Cystic Kidney Diseases - *Silver Lining Magazine* – 2008

Reviews

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The bioactivity of plasma factors in focal segmental glomerulosclerosis
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New insights into the function of the Wilms tumour suppressor gene *WT1* in podocytes

Avril Morrison, Rebecca Viney, Moin Saleem and Michael Lodomery
Nephrology, Dialysis and Transplantation – Epub 2008 Apr 2

Henao DE, Saleem MA, Cadavid AP.

Glomerular Disturbances in Preeclampsia: Disruption Between Glomerular Endothelium and Podocyte Symbiosis.

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A Fair reason for failing to thrive. April 2008 Arch disease childhood educational supp 93(2):50-7

Nephrin – signature molecule of the glomerular podocyte?

Welsh GI and Saleem-MA

Journal of Pathology – 2009

Book Chapters

1. Forfar and Arneil – Textbook of Paediatrics (reference textbook)
Nephrology chapter (55 pages) for current edition –published 2008

2. Oxford Handbook of Nephrology – Chapter Author, Cystic kidney Disease
published 2009

CLINICAL RESEARCH

National Study of Rare Diseases in Renal Medicine

(RaDaR)

A major initiative to set up and run a national infrastructure for renal rare disease cohort data collection and follow up, run in partnership with the UK Renal Registry, BAPN and Renal Association.

Funding is from the Medical Research Council, Kidney Research UK and North Bristol NHS Trust.

Other areas of research in the department include:

- Randomised prospective, double blind placebo controlled study to determine whether the use of steroids reduces the incidence and severity of nephritis in HSP. (Lead investigators J Dudley, G Smith, EJTizard)

The data collection is now complete and we are currently analysis the results. Three hundred and fifty three patients entered into the randomised part of the study and a further 108 were recruited for information only. This is the largest randomised controlled study of steroids in HSP and we hope to be presenting the final results in the near future. Anne Morais, the research nurse who is co-ordinating this should be congratulated again on her continuing hard work. The co-operation of all the participating centres has been greatly appreciated.

- EBV vaccine pilot study. (Local investigator EJ Tizard)

This is a study organised by the Cancer Research UK (CRUK). Currently Bristol and Great Ormond Street are the centres involved in the pilot study. This is a Phase 1 dose and safety trial in patients awaiting renal transplantation. It is hoped that this vaccine will help in preventing EBV infection post transplant and reduce the risks of post transplant lymphoproliferative disease. This study is now completed. The vaccine appeared safe and 80% achieved adequate antibody levels after 3 doses. It appeared that a booster dose may be necessary are we are currently looking into a further study to establish whether this would be beneficial.

- Pneumococcal study (Lead investigators R Coward, A Finn)
Pneumococcal vaccines in high risk patients. In collaboration with Professor Adam Finn (Bristol University) we are studying if the 7 valent pneumococcal vaccine is efficient in giving immunosuppressed renal patients protection against pneumococcus.
 - Renal disease in children in the African subcontinent. R Coward
The type of proteinuric disease in Africa is different to that observed in the West and through a link Bristol University has with Mbarara University of Science and Technology Dr Coward has been involved in studying renal disease in Uganda and also delivering post graduate teaching to local doctors.
 - A sibling-pair study to identify the genes for vesicoureteric reflux and associated kidney disorders. Local investigator: Dr Jan Dudley. Principal researchers: T. Goodship, Newcastle and A. Wolf, Great Ormond Street. Twenty seven sibling-pairs from the Bristol unit have been referred to the study co-ordinator, Ambrose Gullett
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Multicentre trials

In addition to these local studies the department participates in a number of multi-centre projects including:

- ◇ Randomised study of tacrolimus, azathiaprine and steroids with or without additional simulect in renal transplantation-follow up of these patients continues
- ◇ Long-term follow up of children with cystinosis via the cystinosis registry
- ◇ Long-term follow up of children with oxalosis via the oxalosis registry
- ◇ C2 Nephrotic Study and C2 Transplant Study-completed currently being analysed
- ◇ The HUS European Registry Study. Local Researcher : Dr Carol Inward. Principal Researcher: Dr Mark Taylor.
- ◇ Nephrotic syndrome-long or short course of steroids at initial presentation

CHARITY

The charity NeST (Nephrotic Syndrome Trust), launched at Twickenham Rugby Ground in June 2005 by the New Zealand rugby legend Jonah Lomu, who is our ambassador. The proceeds all go towards the ongoing research in Bristol, and details can be found on www.nstrust.co.uk
