Renal Research at The Sheffield Kidney Institute

The Sheffield Kidney Institute (SKI) was founded in 1990, by Professors Colin Brown and Meguid El Nahas along with their colleagues Dr Peter Moorhead and Mr Andrew Raftery, bringing together in a new, purpose-built, institution at the Northern General Hospital the renal services from the Royal Hallamshire Hospital, Northern General Renal Unit and Lodge Moor Hospital where haemodialysis has been based since the sixties. The SKI also provided provision for dedicated laboratory-based kidney research in Sheffield for the first time. This was funded by the Sheffield Area Kidney Association (SAKA) through the Helen Dearden Appeal.

Since its inception in 1990, the SKI has expanded its clinical capacity serving a population of up to 1.7 million and providing a full range of clinical services including dialysis and transplantation. The SKI is now the hub of a network of 4 satellite dialysis units providing healthcare provision for in excess of 1200 patients on renal replacement therapy.

In 1995 The SKI launched the School of Nephrology running a very successful PgD and MSc in Nephrology averaging about 15 students a year and accepting research fellows from around the globe.

Research at the SKI was built upon an established tradition started in the sixties. Dr Margaret Platts was the first Reader in Nephrology in 1965 & Mr John Williams (Cons Urologist) did the first transplant in 1968. This was followed in the seventies by Prof Colin Brown with a range of clinical research activities and innovations in the field of glomerulonephritis, renal osteodystrophy, dialysis adequacy and CAPD. The last 25 years have seen a considerable expansion of laboratory based research with emphasis on mechanisms of progressive CKD, PKD as well as studies on the role of extracellular matrix remodelling in progressive renal fibrosis.

Research at the SKI, has been supported by the setting up in 1990, by Professors Brown and El Nahas, of a charity; the Sheffield Kidney Research Foundation (SKRF). In 1993 the SKRF appointed its first Post Doctoral Scientist, Dr Tim Johnson, to join Prof El Nahas and Dr John Haylor who had already joined the Unit from the Department of Pharmacology. Albert Ong was recruited as the first clinical Senior Lecturer in 1999 to complete the current principle investigator team for laboratory based research. Other major sources of funding have included the MRC, Wellcome Trust, Kidney Research UK, Diabetes UK, PKD Foundation and numerous biotechnology and pharmaceutical companies. Research has also been considerably supported by the Sheffield Area Kidney Association (SAKA).

Today the unit has a vibrant research portfolio with the clinical research being co-ordinated by Dr Martin Wilkie and the basic lab science being headed by Prof Albert Ong at the newly formed Academic Nephrology Unit based in the Medical School at the Royal Hallamshire Hospital. From a dream in the 1980s to a small beginning in 1990 the Sheffield Kidney institute is now one of the largest kidney research centres in Europe.
Laboratory Based Research

Professor Albert Ong DM FRCP. Kidney Genetics Group

The Kidney Genetics Group is led by Professor Albert Ong. Its major research interests are in the molecular genetics, cell biology and pathogenesis of autosomal dominant polycystic kidney disease (ADPKD). In particular, the groups aim is to discover new treatments for ADPKD, to understand better how cysts form and grow in the ADPKD kidney and to improve the clinical management of ADPKD patients.

ADPKD is one of the most common monogenic human diseases known and affects around 1 in 500 people. It is caused by mutations in two genes, PKD1 and PKD2. ADPKD accounts for ~10% of patients with kidney failure in most renal units and could affect up 5 million people worldwide.

A major approach has been to address structure-function relationships of the ADPKD proteins, polycystin-1 and polycystin-2, and the role of post-translational modification in regulating protein function. Dr Ong’s group were the first to demonstrate the existence of a heterodimeric polycystin-1/polycystin-2 complex in vivo and have identified two novel domains mediating polycystin-2 homodimerisation.

Work led by Dr Andrew Streets (RCUK Fellow) has shown that phosphorylation plays a key role in regulating polycystin-2 function both in vitro and in vivo and that polycystin-1 regulates cell adhesion, both of which are critically important for the maintenance of normal tubular and glomerular morphology. A second approach has been to study the natural history of ADPKD in experimental models (mouse, zebrafish) and identify potential new therapeutic targets. Finally, the group is seeking to identify clinical risk factors for cardiovascular disease in ADPKD patients as this remains the major cause of death.

Professor Ong’s group have a number of active international collaborators. Their work is currently supported by the Wellcome Trust, the Medical Research Council, Research Councils (UK), Kidney Research UK, the Polycystic Kidney Disease Foundation (USA), the Sheffield Kidney Research Foundation (SKRF), the Sheffield Area Kidney Patients Association (SAKA) and the Polycystic Kidney Disease Charity (UK).

Key references

Dr Tim Johnson BSc PhD. Tissue Scarring & Kidney ECM processing group.

The Tissue Scarring and Kidney ECM processing group led by Dr Tim Johnson is currently the largest research group at SKI. Its aim is to understand the pathobiology of the scarring process and develop novel interventional strategies to slow or regress the development of chronic kidney disease.

The group has a wide range of interests, but its core research goal is the role of Transglutaminase type 2 (TG2) in progressive kidney scarring. Dr Johnson initiated studies on TG2 in kidney fibrosis in 1995 and in the following years has demonstrated its expression in a range of kidney diseases, its mode of action, its importance in the scarring process using TG2 knock out studies and recently published 2 interventional studies using experimental TG inhibitors. Current studies are looking at the cell trafficking mechanism of TG2 with the aim of developing a novel and specific intervention strategy (Dr Che yi Chou), development of TG2 therapeutic antibodies in collaboration with MRC-T (Dr Phil Watson, Dr Bouka Mammra, Dr Osama Ben Ayad, Dr Basma); Syndecan 4 as a TG2 co receptor for localisation and cell export in CKD (Wellcome Trust. Dr Linghong Huang & In collaboration with Dr Eli Verderio Edwards & Alessandra Scarpellini at Nottingham Trent University), Role of TG2 in epithelial mesenchymal transdifferentiation (Prof El Nahas, Dr Sanna Dawish), isolation of natural TG2 modulating compounds (Zoe Hau) in collaboration with the biotechnology industry and using TG2 and its products as urine markers of kidney fibrosis in collaboration with Pfizer Pharmaceutical (Dr Michelle Da Silva).

Away from TG2 the group has several other interests. These include a BBSRC CASE studentship with Pfizer investigating if inhibitors of Thrombin activated fibrinolysis inhibitor (TAFI) can elevate Plasmin activity in CKD and if this reduces kidney fibrosis (John Atkinson). In addition a multi centre award from Baxter (Manchester, Stoke, Cardiff & Sheffield) to look at Encapsulating Peritoneal Sclerosis (EPS) (a potentially fatal complication of peritoneal dialysis) has seen a local collaboration with Dr Martin Wilkie to perform Proteomic analysis of effluent dialysis fluid (Tony Buxton) to look for early biomarkers of EPS as well as understand its pathobiology and triggers. An off shoot of this are 2 PhD studentships looking at EPS using a more classical approach with investigations of changes in Matrix metalloproteinases, TIMPS, and TG2 biochemistry (Dr Samir Osta) as well as the Fibrinolytic System (Dr Osama Maskhut). The group continues to work closely with Professor El Nahas on several projects, most notably looking at urine biomarkers of CKD in patient population based on early proteomic studies and a particularly interesting cytology approach (Dr Naji Eltemtam). Also in EMT protects with a interest in looking at how albumin induces EMT in epithelial cells and the underlying mechanism of this (Dr Juma Ibrini &Dr Sanna Dawish)

Key references

Professor Meguid El Nahas, PhD, FRCP. CKD Epidemiology Research group

Professor El Nahas was appointed consultant renal physician at the SKI in 1986 and established the units laboratory based program soon after. He has held the inaugural Chair of Nephrology in Sheffield since 1996. He has withdrawn slightly from laboratory based research in recent years but still maintains his long term interest in CKD being still heavily involved in urine proteomic studies in a collaborative role with Dr John Haylor determining changes in urine profiles both in models of CKD (Melissa Vickers) and in various patient populations (Dr Ali El Fatori). He is currently co-chairing the EU Cooperation for Science and Technology EUROKUP initiative for the study of proteomics in kidney disease. He also maintains the lead role in EMT studies working collaboratively with Dr Tim Johnson’s group in the investigation of BSA induced EMT. His predominant interest in recent years has been both the mechanisms and epidemiology of CKD with a particular interest in both the incidence and early detection of CKD. The KEAPS (Kidney Evaluation and Awareness Programme in Sheffield) and KEOPS (Kidney Evaluation of Obese Population in Sheffield) have been key studies highlighting a strong link between social depravation and CKD.

Dr. John Haylor, Experimental Modelling Group

As a pharmacologist working in vivo, Dr Haylor shares the Institute’s interest in drug development to slow the progression of chronic kidney disease. The group uses a number of rodent models including, sub-total nephrectomy, ureteral obstruction, ischaemic injury, polycystic kidney disease and transplantation in collaboration with other members of the Institute.

Projects with Dr Tim Johnson, have demonstrated exciting properties of Transglutaminase inhibitors, reducing matrix deposition and the development of renal fibrosis in rat models of sub-total nephrectomy and diabetes. Projects with Dr Arif Khwaja involve the use of cyclin-dependent kinase inhibitors and MEK inhibitors to reduce myofibroblast proliferation, while a joint project with Mr Badri Shrestha, Director of Kidney Transplantation, has established a rat kidney transplant model of chronic allograft nephropathy (CAN). This model is now being used to examine the effects of drugs to slow the development of CAN through inhibiting cell proliferation or matrix deposition. An ongoing collaboration with Prof Albert Ong has identified ischaemic injury as a potent modifying factor for disease progression in experimental ADPKD.

Clinical projects with Prof El Nahas include urinary biomarker studies utilising proteomic techniques and the use of insulin-like growth factor I to improve the GFR in patients with stage 5 CKD. The clinical problem of nephrogenic systemic fibrosis (NSF) induced by gadolinium containing MRI contrast agents is being investigated and an animal model has been established. Current evidence supports the lack of effect of macrocyclic chelates such as Dotarem™ compared to the potential concerns regarding the properties of linear chelates such as Omniscan™.

Selected Publications

Clinical Based Research

Martin Wilkie - Clinical Research at the Sheffield Kidney Institute

There has been a strong tradition of clinical renal research at Sheffield over the last 25 years with major interests being in the areas of chronic kidney disease, cystic kidney disease, glomerulonephritis, dialysis research, mineral bone disorder and transplantation.

Professor Colin Brown had a broad clinical research interest including studies into glomerulonephritis through to a fruitful collaboration with Professor Goumenos from Patras University, Greece and studies into bone pathology in collaboration with Professor Kanis in Sheffield. This group explored the use of active vitamin D in patients with chronic kidney disease, low calcium dialysate in peritoneal dialysis, and exploratory studies of bisphosphonates in renal bone disease.

In the early 1990s Prof Brown became interested in icodextrin for peritoneal dialysis, participating in the MIDAS study, collaborating with Professor Raymond Kredit from Amsterdam University to study solute clearance using icodextrin and publishing with Martin Wilkie a single centre experience its use for PD patients with ultrafiltration failure. Prof Brown subsequently published studies on the use of 4% icodextrin to reduce adhesion formation following gynaecological surgery. The interest in icodextrin continued in Sheffield through the evaluation of a combination dialysate (icodextrin 7.5% / glucose 1.36%) with a detailed single exchange study conducted by Sarah Jenkins and a pilot 4 week study conducted by Fiona Dallas

Sheffield has participated in many collaborative clinical studies involving dialysis patients – including studies of erythropoietin stimulating agents, immunosuppressants, phosphate binders, calcimimetics as well as studies of dialysis solutions for peritoneal dialysis, solute clearance on HD and quality of life in renal patients. Current research interests include the role of parathyroidectomy in renal patients, transplant glomerulopathy and studies of encapsulating peritoneal sclerosis in PD, with Sheffield as one of the founder centres of the UK EPS study. An investigation using proteomics to explore EPS is currently under way.

Sheffield has been a DOPPS site since the study was initiated, and was a founder site for the UK Renal Registry. Haemodialysis prescription was also adopted early in Sheffield (after a visit by Colin Brown to Frank Gotch in the early 1990s) and Sheffield continues to have a strong reputation for high quality dialysis (UK Renal Registry data).

A key objective in Sheffield is to access the benefits of new innovations for our patients through engagement in clinical research. The advent of the clinical research networks (CLRN) provides the opportunity for collaboration in important projects through engagement in NIHR portfolio adopted studies and we intend to increase our involvement in such work throughout the coming years.

Key references

- Jenkins SB, Wilkie ME: An exploratory study of a novel peritoneal combination dialysate (1.36% glucose/7.5% icodextrin), demonstrating improved ultrafiltration compared to either component studied alone. Perit Dial Int 23:475-480, 2000
Professor Brown can be considered the father of the Sheffield Kidney Institute. He was appointed to The Royal Hallamshire Hospital in 1979 after being trained at Guy's Hospital with Prof Stewart Cameron. Having officially retired in 2008 he still continues a keen interest in research at the Sheffield Kidney Institute especially in glomerulonephritis and its treatment with immunosuppressive drugs.

Glomerulonephritis. In the 1980s he worked with Dr. John Shortland (Cons Pathologist) to develop a major interest in GN in Sheffield. Over the next 2 decades a number of papers in this area were published which saw Professor Brown being involved in some of the MRC national RCT clinical trials in this area and become a member of the MRC glomerulonephritis Committee.

Renal osteodystrophy. In collaboration with Dr. John Kanis (Dept. was a WHO unit for bone disease) Professor Brown worked on a number of RCT clinical trials on the management of renal osteodystrophy involving detailed studies on bone morphology.

Dialysis. Working with several other interested Renal units Prof Brown was part of a team that developed a new dialysis solutions in CAPD called Extraneal (icodextrin) which was the subject of a successful a national clinical trial. Further he introduced new techniques of high flux haemodialysis and more economically effective methods of managing a haemodialysis unit.

Abdominal Adhesions. Prof Brown developed the use of icodextrin in the prevention and diminution of intra-abdominal adhesions after abdominal surgery with a large national clinical trial unique to this area. This trial led to the provision of both FDA and European Approval for clinical use and he continues to hold the patent of this inventive use of icodextrin.

### Key References