RESEARCH PROJECT AND INNOVATION AWARDS – JUNE 2013

We received sixty-five applications in this year's research grant round (53 Research Projects and 12 Innovation).
All applications underwent normal peer review via the full Research Grants Committee (RGC) and External Referees. 40 applications (32 research projects and 8 Innovation) were short-listed for discussion at the June RGC meeting based upon scientific merit. Following discussion and scoring by the full Research Grants Committee, four Innovation and 12 Research Project applications were recommended for funding. These decisions were subsequently endorsed by our Research Strategy Committee and Board of Trustees.

Total awarded: £1,705,237

Success rate for Project grants: 22.6%
Success rate for Innovation grants: 33.3%

Dr David Long at Institute of Child Health, UCL
£153,475 over three years
Title: VEGF-C as a new therapy for polycystic kidney disease

The normal kidney structure is destroyed in polycystic kidney disease (PKD) by fluid filled cysts, leading to kidney failure. Several treatments have been tried for PKD but only one is looking hopeful and this has side-effects. We discovered changes in blood and lymphatic vessels in PKD and believe these are required for cyst growth. To test this, we treated PKD mice with a regulator of lymphatics (VEGF-C) and this reduced cyst progression. We will investigate how VEGF-C works with the aim producing a more potent inhibitor of cyst growth. This research will offer novel strategies for future management of PKD patients.

Dr Alan Salama at Royal Free Hospital, UCL
£126,745 over two years
Title: Pre-clinical studies on calprotectin as a novel biomarker and therapeutic target in ANCA-associated vasculitis and glomerulonephritis

Acute Kidney injury is common among patients with vasculitis and in many cases ends in chronic or even end stage kidney disease. Even when on dialysis or following transplantation patients may experience disease flares and we still have no robust way of predicting who will relapse, who will need more treatment and who may have their treatment minimised so as to limit side effects. We propose extending some of our previous studies by testing a new marker of disease relapse, called calprotectin, and investigating if blocking this protein actually inhibits disease.

Dr Claire Peppiatt-Wildman at University of Kent
£198,252 over three years
Title: Delineating the cellular mechanisms of cisplatin-induced nephrotoxicity

Many commonly used drugs have toxic side-effects affecting the kidney, and for many drugs the underlying mechanisms of damage are not understood, in part because of a lack of suitable technology with which to investigate them; a clearer understanding of these mechanisms should help in developing better preventive and treatment strategies. In this project we plan to use a novel imaging-based research tool in combination with slices of rodent kidney (kept alive) to study the toxic events that lead to kidney damage following treatment with CPa commonly used anti-cancer drug notorious for its toxicity by unclear mechanisms.

Dr Eugenia Papakrivopoulou at University College London
£39,775 over nine months
Title: Secreted frizzled-related protein2: a new therapeutic target for glomerular disease?

The kidney filtration unit is created from several different cell types. Damage to one of these cells, the podocyte, is a feature of glomerular diseases such as diabetic nephropathy and focal segmental glomerulosclerosis (FSGS), leading causes of end stage kidney disease requiring dialysis or transplantation. Understanding more about how podocytes are injured would help us develop new, more specific therapies to the ones currently available. We have discovered a protein that we believe may play a key role in podocyte damage and in this proposal want to test its potential as a new therapy for glomerular disease.

Dr Simon Satchell at University of Bristol
£18,061 over one year
Title: Shear-stress regulated cell-cell communication via microRNA in the renal glomerulus in diabetes

Diabetes damages the kidney filters, 'glomeruli'. These contain small blood vessels with specialised cells (endothelial cells and podocytes). In other vessels cell-cell communication is regulated by 'shear stress' generated by blood flow but this communication is disrupted in diabetes. Here we will investigate whether a similar process occurs in the glomerulus and how its disturbance in diabetes contributes to kidney damage using diabetic mice. Damage to the kidney is the most serious common complication of diabetes and this project will provide a new target for treatment by characterising a potentially key process in maintaining the healthy glomerulus

Dr Andrew Macdonald at University of Leeds
£127,237 over two years
Title: Validation of the BK virus agnoprotein as a novel target to treat polypmavirus associated nephrology (PVAN)-a significant cause of kidney transplant rejection

PVAN is a serious, emerging complication in kidney transplant recipients, caused by the BK polyomavirus (BKV). Prevalence of PVAN afflicts up to 10% of all kidney transplant patients. There are no effective treatments for BKV, and the clinician is faced with reducing the dose of immunosuppressive drugs to allow the patient's immune system to battle the virus, risking graft rejection.
We will build on our experience of designing new therapeutics against virus proteins and find compounds that inhibit BKV. We will test these inhibitors in a cell culture model system. These studies will develop therapeutics to be used in the future to treat PVAN.

Dr Rukshnana Shroff at Great Ormond Street Hospital (GOSH)
£199,938 over three years
Title: The effects of haemodiafiltration (HDF) vs conventional haemodialysis (HD) on growth and cardiovascular markers in children. 3 H (HDF, Hearts and Height) study

Children on conventional haemodialysis (HD) die of heart disease. Also, they can be malnourished and short. Haemodiafiltration (HDF) is a newer type of dialysis that achieves better removal of toxins and excess fluid than HD. On HDF, adults have a longer survival and children show improved growth, but mechanisms are not understood.
We will follow children in the UK and Europe to compare HDF and HD. We will monitor growth, heart and blood vessel scans, blood markers and quality of life. If the 3H (HDF-Hearts-Height) study shows reduced cardiovascular morbidity and better growth, HDF may be adopted as the preferred type ofdialysis in children.

Dr Scott Wildman at University of Kent
£28,897 over two years
Title: A proof of concept, longitudinal, comparative, observational study of urinary epithelial cell infection in renal transplant patients and asymptomatic controls

Urinary tract infection (UTI) is a worrying complication of renal transplant and it can damage the new kidney. Regrettably routine tests for urinary infections are insensitive, underestimate the problem and miss some patients. We have better methods for assessing urinary infection in renal transplant recipients. These are sensitive and imply that bacteria may be hiding in the cells of the urinary tract. Using the new techniques, we wish to find out the truth about transplant patients. We are asking for funds to pump-prime this work. With the results of this work we plan to seek larger grant support for a definitive study. The ability to identify UTIs earlier in this setting would significantly improve patient care and reduce patient suffering.

Prof Steven Harper at University of Bristol
£39,612 over one year
Title: Unique vascular chambers in human glomeruli : paradigm shift for glomerular physiology in health and disease

High pressures inside kidney filters allow humans to filter ~180L of plasma into urine every day. This pressure gets even higher in kidney diseases, worsening scarring and kidney damage. All knowledge of kidney pressure is based on studies in rats, but we have found that human kidney filters are completely different from rats because they possess a large-volume chamber that could regulate blood flow. This project will discover whether this chamber regulates blood flow in unique ways, whether this chamber is damaged in diseased filters, and whether there are unrecognised and entirely new opportunities to modify these essential processes.

Assoc. Prof Nicholas Selby at Royal Derby Hospital
£84,150 over three years
Title: Can biomarker strategies identify patients at high risk of adverse outcomes following an episode of acute kidney injury?

Acute Kidney Injury (AKI) refers to an abrupt decline in kidney function and is often seen in patients who require hospitalisation. In the short-term, the development of AKI increases the complexity and duration of treatment and confers a reduced chance of patient survival. Although in many cases there is an improvement in kidney function that mirrors the patient's recovery, it is possible that episodes of AKI may have effects on patients in the longer term, leading to kidney damage over time (chronic kidney disease, CKD) or reducing long term survival. We would like to study ways in which patients at risk of worse outcomes can be identified, so they can receive intensified monitoring and treatment.

Dr Patrick Mark, University of Glasgow
£39,850 over two years
Title: Detection of uraemic myocardial fibrosis with non-contrast cardiac magnetic resonance imaging

Patients with kidney failure requiring dialysis treatment have a very high risk of heart disease. One factor, which is associated with this increased risk, is enlargement of the muscle of left ventricle, the main chamber of the heart. This puts patients at risk of abnormal heart rhythms (arrhythmia) which can be life threatening. We will study a new method of MRI scanning to detect scar tissue within the left ventricle, which puts patients at higher risk of arrhythmia. We hope this MRI method will also us to identify high-risk patients, to ensure that we can target better treatment in future.

Dr Jill Norman at Royal Free Hospital, UCL
£191,598 over three years
Title: Targeting the Platelet-derived Growth factor (PDGF) receptor-ligand pathway in progression of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is a common kidney disease leading to renal failure. Kidneys progressively enlarge due to expansion of cysts surrounded by variable amounts of scar tissue (fibrosis) produced by fibroblasts. Fibrosis is thought to accelerate decline in kidney function but how this happens in ADPKD is unknown. A family of factors called PDGFs are thought to be important in fibrosis. These factors bind to receptors on the surface of fibroblasts and induce cells to produce scar tissue. The proposed studies will define how PDGFs and their receptors are involved in ADPKD and may lead to new therapies to delay kidney failure.

Dr Andrew Salmon at University of Bristol
£128,859 over two years
Title: Endothelial glycocalyx restoration as novel therapy in proteinuria

Diseases in which kidney filters leak protein (proteinuria) are the most common causes of endstage renal disease (ESRD). Current treatments (e.g. ACE inhibitors) partially reduce proteinuria and slow ESRD development, but the effects are incomplete and new treatments are required.
We have found that the innermost lining ("endothelial glycocalyx") of kidney filters is damaged in animals with proteinuria, and that this endothelial glycocalyx can be regenerated. This project will reveal exactly how the glycocalyx is damaged in proteinuria, whether the same phenomena occur in human disease, and test whether factors that restore endothelial glycocalyx can improve kidney function in proteinuria.

Dr Jacques Behmoaras at Imperial College London
£178,703 over 2 ½ years
Title: Identification of new drug targets in macrophage-dependent crescentic glomerulonephritis by targeted gene deletion in the rat

Glomerulonephritis (GN) means the inflammation of the filtering unit of the kidney, the glomerulus. In crescentic GN, immune cells such as macrophages infiltrate the glomerulus promoting inflammation and leading to its destruction. We have beenusing a model of crescentic GN in a rat strain called the Wistar Kyoto (WKY). Induction of crescentic GN in this strain mimics the human condition. This model enabled us to identify genes that cause crescentic GN. In this proposal we will use WKY rats where three genes that are expressed by macrophages are inactivated. This will allow us to understand the mechanisms of GN.

Dr Aine Burns at Royal Free Hospital, UCL
£15,617 over six months
Title: Validation of the distress thermometer in a UK renal population

Older patients with advanced kidney disease experience distress probably related to symptoms, co-existing disease, transport problems, and depression amongst other things. We routinely measure distress levels, reported by patients in clinic, using a simple distress thermometer. We will compare distress thermometer scores with score for measures of symptoms, depression, and quality of life in renal patients. This will allow us to say with more certainty what a high DT score means for the patient in real terms.

Prof Andrew Fry at University of Leicester
£134,468 over two years
Title: The role of Nek8 and inversin cystic kidney disease proteins in coordinating ciliary function with cell cycle progression

Cystic kidney diseases represent a major health burden for which there are few effective treatments. Yet we are far from understanding the cell biology behind these diseases. Here, we propose to study the regulation and function of two proteins, Nek8 and inversin, mutated in an inherited childhood cystic kidney disease. These proteins coordinate signals received by developing kidney cells at antenna-like structures on the cell surface, called primary cilia. Defective signalling leads to loss of cell division control and cyst formation. Our aim is to provide new insights into cystic kidney disease mechanisms that will ultimately lead to new therapies.