

**SCHEDULE OF MEDICAL RESEARCH  
GRANTS AND SCHOLARSHIPS  
AWARDED FOR 2010**

Kidney Health Australia's vision  
An Australia free from kidney and urinary tract disease.

*The cornerstone of any effective prevention program is a thorough understanding  
of the problem or condition you are trying to prevent.*

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## **Medical Director's Overview**

At the end of the first decade of the 21<sup>st</sup> century it seems an appropriate time to stock-take and reflect on the Australian situation with chronic kidney disease (CKD) compared to the start of the decade. Overall the picture brings little satisfaction to our organization committed to making a difference – in essence to reducing the kidney contribution to the community burden of chronic disease. The number of people on dialysis and transplant programs has increased by 169% compared to population growth of 114% over the last 10 years and we know there is substantial inequity and lack of access to the delivery of kidney care in certain regions and some States. In many regions peritoneal dialysis is “forced” on people as the first dialysis modality. There is a fourfold variation between large Units in the percentage of people on their home dialysis programs and a fivefold variation in the percentage of people (<65 years) between large Units in achieving live kidney transplantation. There is no uniformity across the country in the re-imbursment of out-of pocket expenses for home dialysis expenses and no access to carer support schemes for partners helping with home dialysis.

On the positive side CKD is now recognized by GPs to be present in 11% of all adults (the potential number from population surveys is probably ~13%) and the core preventive therapy appears to be prescribed in nearly ¾ of those in whom it is indicated. A repeat of the BEACH survey on GP activity in CKD is planned for mid-2010. Tests for CKD have been incorporated in the new National Health risk survey with biomedical markers and the recently established AIHW CKD Monitoring section is actively producing reports of much importance to the kidney sector. Of special note is the publication this year of “Overview of CKD in Australia 2009” – an excellent documentation of the current state of play. Publications appearing in the near future include an assessment of hospitalizations from CKD and one focusing on CKD in Indigenous people.

The second CKD Summit held in July resulted in a significant policy shift towards using a people based approach to Government compared to the medical model. The State based Renal Clinical Networks all presented for the first time at the Summit and this stimulated the idea that regular meetings would be advantageous to pull together the multiple activities in CKD prevention and early detection that are occurring at the State level.

### **CKD Education to Health Professionals (KCAT)**

The Kidney Check Australia Taskforce (KCAT) program has gone from strength to strength in the last 12 months. In addition to its established role in GP and practice nurse education there has been significant engagement with community pharmacists and aboriginal health workers KCAT's teaching program is now active in taking the message to Aboriginal health workers and practice nurses and KCAT is beginning to work with diabetic educators and pharmacists. KCAT is driving the clinically important reassessment of the measurement and reporting and clinical use of urine albumin and protein, the evolving role of eGFR and will be responsible for the republication of the Booklet for GPs on CKD management once there is international agreement on the new staging criteria for CKD.

### **CKD Summit**

Kidney Health Australia and the Australian and New Zealand Society of Nephrology (ANZSN) convened a national summit on July 23<sup>rd</sup> and 24<sup>th</sup> 2009 to develop a strategy and action plan to ensure the best future care of Australians with chronic kidney disease (CKD). The meeting was attended by 120 invited health professionals and stakeholders.

The definitive outcomes of the summit were agreement on the need for:

1. A coalition of stakeholders including consumers, nephrologists and nurses to go forward and engage government
2. Consensus on the aims, priorities and the narrative required to:
  - Ensure that CKD is recognised as a serious public health issue
  - Reduce the burden of CKD by early detection
  - Close the gap on best care
3. An opportunity for State Renal networks to meet and share progress bi-annually
4. A multidisciplinary national renal taskforce to develop a national renal strategy and framework, agree on a model of care, set priorities and liaise with government
5. Engagement and practice change in primary care by introducing opportunistic screening, utilising practice nurses, using a systematic follow-up and recall register and working collaboratively with other chronic diseases.

### ***SUPPORT FOR BIOMEDICAL RESEARCH***

Kidney Health Australia is the main non-government supporter of kidney and urinary tract biomedical research in Australia. There is a major focus on investigator driven research and scholarship but significant funds are also targeted to strategic projects designed to address special interest areas.

A total of sixty-three applications were received by Kidney Health Australia for funding support in the calendar year 2010. Our Medical and Scientific Advisory Committee awarded twenty-two separate grants and scholarships to the value of \$442,030 into kidney related research projects in University departments, medical research institutes and hospitals throughout Australia. Support to investigator driven research totalled \$367,030 plus an additional \$75,000 funding for strategic targeted research.

The nationally competitive Career Development Award continues in partnership with the ANZSN and the NHMRC (valued at \$500,000 over 5 years).

The Kidney Health Australia Bootle Research Fund awarded funding to one research project in 2008 valued at \$200,000.

In 2010 we allocated a second year of funds to support Renal Nurses pursuing a Masters Degree, to encourage nurses to pursue a career in renal nursing, in any of its components - clinical practice, education or research - across the continuum of chronic kidney disease, from prevention to early detection to renal replacement.

**Our total research expenditure from Board allocated funds including the Bootle Award for calendar year 2010 is \$411,000.**

The continued commitment to supporting research is evident from these figures and we anticipate the total dollars available for research from Kidney Health Australia to increase in the next few years.

In 2011 advertisements will call for a similar pattern of awards.

***Dr Tim Mathew***  
***Medical Director***

**INVESTIGATOR DRIVEN RESEARCH GRANTS AND SCHOLARS****CAREER DEVELOPMENT AWARD (2006-2010)**

Kidney Health Australia was pleased to have the opportunity to work in partnership with NHMRC and the Australia and New Zealand Society of Nephrology to enhance research capacity via an innovative partnership to fund a Career Development Award (approx \$500,000 over five years) in the area of nephrology. All applications were assessed by NHMRC external referees.

**Dr Greg Tesch**

Department Nephrology, Monash Medical Centre, VIC

[Mechanisms of macrophage-mediated injury as potential therapeutic targets for preventing diabetic nephropathy and insulin resistance](#)

**Progress Report**

*My research is focussed on the study of kidney inflammation, which is an important contributor to the development and progression of kidney disease. Studies of human and experimental kidney disease have allowed me to examine the mechanisms responsible for recruiting inflammatory cells into the kidney and the processes by which inflammation promotes renal injury and scarring. I have had some successes in unravelling these mysteries, but further work is needed to identify and develop new therapies. Much of what I have learned and achieved can be attributed to the opportunities made possible by societies and foundations which support kidney research.*

*This Career Development Award is allowing me to establish a research group that will identify molecules that are responsible for the inflammation which promotes diabetes and diabetic nephropathy. We will use this information to develop new strategies for preventing the damaging effects of kidney inflammation and provide patients with additional protection against the progression of chronic kidney diseases including diabetic nephropathy and glomerulonephritis.*

*In 2009, we completed studies showing that elements of the adaptive immune system (T-cells and B-cells) are not required for the progression of type 1 diabetic nephropathy. We have also examined the role of specific cell signalling pathways (MKK3-p38 and JNK) in the development of kidney inflammation and injury in type 2 diabetic nephropathy.*

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**BIOMEDICAL SCHOLARSHIPS**

These scholarships permit talented researchers to pursue full-time research for up to three years, qualifying them to obtain a doctoral degree or equivalent at the end of this period. Individual scholarships are valued at \$28,000 for scientists and \$33,000 for medical graduates, per annum. These scholarships that are tax free to the holder are an investment in the future of Australian medicine.

In 2010, two new Biomedical Scholarships were awarded, and eight were awarded continued funding. Funding allocated was valued at \$293,500.

We actively encourage students receiving KHA funding, to apply for NHMRC scholarships each year, to make the most of our research dollar.

**Sponsored Scholarships:** Kidney Health Australia encourages groups and individuals to consider supporting research in this manner. Funding biomedical scholarships is a most valued and meaningful way to ultimately promote better health outcomes in kidney patients. We are always interested in hearing from individuals wishing to donate funds for scholarships or grants. All offers are valued and presented to the Medical and Scientific Advisory Committee for consideration. If you wish to find out more, contact the Medical Director's Office and we would be delighted to discuss this with you.

**Continuing PhD scholars for 2010****Dr Abu Abraham supervised by Dr David Nikolic-Paterson and Dr William Mulley (Medical)**

Medicine and Nephrology – Monash Medical Centre, Prince Henry's Institute of Medical Research, VIC

**Inflammation in kidney disease and renal transplant rejection**

Macrophages are a subset of white blood cells which play an important role in kidney injury in glomerulonephritis and kidney transplants. Long term depletion of macrophages is not desirable. It is then important to try and identify mediators by which these cells cause injury. Metalloproteinase 12 (MMP-12) is an important mediator of injury and potentially modifiable target. This study aims to identify the role of MMP-12 in glomerulonephritis, fibrosis and renal transplants.

**Progress Report**

*Human and experimental studies have identified the macrophage pro-inflammatory response as being an important mediator of kidney injury leading to end-stage renal failure and in mediating renal allograft rejection. Long term macrophage depletion is not desirable and so it is important to identify the mediators by which macrophages cause renal injury to provide new therapeutic targets. Our studies have identified high levels of matrix metalloproteinase-12 (MMP-12, also known as macrophage elastase) production in the kidney in settings of acute macrophage-mediated renal injury. MMP12 has the potential to induce renal injury through two distinct mechanisms: (a) facilitating macrophage migration within the glomerulus and tubulointerstitium through degradation of the extracellular matrix, and (b) direct damage to the glomerular basement membrane, podocytes and tubular epithelial cells, resulting in proteinuria and histologic damage.*

*Our objective was to make a definitive study of MMP-12 in macrophage-mediated renal injury through the use of MMP-12 gene deficient mice and examining MMP-12 expression in human renal injury. Our plan involves both animal models (mouse) and human biopsy tissue study.*

**Animal Model****a) Determine the functional role of MMP-12 in renal fibrosis: Unilateral Ureteric Obstruction (UUO model):**

*UUO surgery was performed in wild type (WT) C57BL/6J and MMP-12 gene deficient mice (MMP-12<sup>-/-</sup>) by ligating the left ureter under anesthesia. UUO was induced in groups of 8 WT or MMP-12<sup>-/-</sup> mice which were killed on day 3, 7 or 14 after surgery to examine different stages of the inflammatory and fibrotic response.*

*Kidney sections have been stained for  $\alpha$ -smooth muscle actin to identify myofibroblasts and with the F4/80 antibody to detect interstitial macrophages. I am currently quantifying this staining using image analysis. The next end-points to analyse will be collagen synthesis and deposition, expression of pro-fibrotic growth factors and other matrix metalloproteinases, tubular damage and apoptosis, and the inflammatory response.*

*These studies have involved gaining experience in animal models and learning tissue sectioning, immunostaining and methods of image analysis. I am currently learning real time RT-PCR and Western blotting to complete these studies.*

**b) Determine the functional role of MMP-12 in anti-GBM glomerulonephritis:****Mouse model of anti-glomerular basement membrane (GBM) glomerulonephritis.**

*We have just begun the animal studies in the anti-GBM model with disease being induced in groups of 6 to 8 WT and MMP-12<sup>-/-</sup> mice. Baseline urine samples have been collected and ongoing collection in the disease are underway. The major end-points will be renal histology, renal function, proteinuria, glomerular and interstitial macrophage accumulation and macrophage activation.*

**Mr Michael Krezel supervised by Dr Linda Rezmann (Science)**

Faculty of Medicine, Dentistry & Health Sciences, University of Melbourne, VIC

**A new pathway for the treatment of diabetes**

Our data suggests that during the development of diabetes, down regulation or loss of ATIP1 expression contributes to the excessive effects of growth factors on the renal glomeruli, which collectively are an important component of the long term damage induced by this disease. ATIP1 therefore offers a new approach to the understanding of the mechanisms inducing vascular damage associated with diabetes as well as increasing the understanding of the mechanism of loss of regulation of growth factors in these conditions.

**Progress Report**

*Angiotensin II (Ang II) is a circulating hormone which mediates a range of cellular responses via its receptors, the AT1-receptor and AT2-receptor. Our group has shown that a protein which interacts with the AT2-receptor, ATIP, plays a role in prostate tumour suppression through the inhibition of growth factors. Recent preliminary data suggests that ATIP may play a similar role in diabetic kidney. To further investigate this we sequenced unknown variants of rat ATIP. Armed with this information, we have been able to show that chronic hypertension causes a reduction in ATIP levels in the kidney, while blocking the Ang II receptors increases ATIP levels in the kidney. These findings suggest that ATIP may indeed play an anti-growth role in the progression of kidney diseases associated with high blood pressure and diabetes.*

**Dr Chetana Naresh supervised by A/Professor Steve Chadban and A/Professor Jonathan Craig**

*Royal Prince Alfred Hospital/University of Sydney, NSW*

[Diagnostic accuracy and predictive ability of rapid urine test for detection of proteinuria and albuminuria](#)

Leakage of albumin (albuminuria) and protein (proteinuria) in the urine is a marker of kidney disease. Detection of proteinuria in patients with CKD allows a physician to intervene appropriately and improve outcomes. Studies have shown that the degree of improvement in proteinuria in response to therapy, is a good guide to long-term cardiovascular and renal outcomes including prevention of end-stage kidney disease.

Currently the test used to quantify proteinuria involves collection of urine over a 24-hour period to estimate the amount of albumin and protein. This test is costly, cumbersome and compliance with the testing is poor. There are simple and quicker tests available that check for proteinuria and albuminuria on a 'spot' sample of urine.

The AusDiab study found an incidence of up to 6.6% of proteinuria in the general population, which equates to about 1.38 million Australians who can benefit from a 'simplified testing process'. This is an important issue which needs to be addressed clearly, given the increasing burden of CKD in our society.

**Progress Report**

**1) Diurnal Variability of Proteinuria and Albuminuria**

*This study is well advanced, having (1) ethics approval, (2) over 100 proteinuric subjects recruited to date with 67 of those successfully completed all collections required (24 h' urine, 5 spot samples and corresponding bloods), with interim analyses underway. A total of 100 subjects results will be analysed, to be completed by February 2010.*

**2) Cross-sectional study of diagnostic accuracy of spot-yrjne tests**

*Cross-sectional study to ascertain diagnostic accuracy of spot urine tests vs. 24 hour collections. This multicentre study has recruited over 200 subjects of a projected 700 across 2 centres with active recruitment ongoing.*

*All subjects will be followed longitudinally, to determine the prognostic value of spot versus 24hr urine protein and albumin excretion with respect to kidney and CYS outcomes.*

**3) Meta-analysis of Diagnostic and Prognostic accuracy of spot urine tests to determine proteinuria vs. 24 h' collections - a Cochrane based review**

*Protocol for metaanalysis completed*

*Completed Medline and EMBASE literature search of over 10870 articles*

*Inclusion / exclusion of articles for the metaanalysis completed.*

*Data extraction completed*

*Tabulation of study results completed*

*Analyses of study results underway*

**4) Epidemiology of New Onset Diabetes after Transplantation in an Australian Centre.**

*As a secondary project, I have analysed the data on 131 patients included in a study at the Royal Prince Alfred Hospital on New Onset Diabetes post Transplantation (NODAT). This was presented at the TSANZ and the ANZSN in 2008*

**Dr Niroj Obeyesekere supervised by Dr David Nikolic-Paterson (Science)**

*Department of Nephrology, Monash Medical Centre VIC*

[Mechanisms of kidney inflammation](#)

Patients who progress to end-stage renal failure require treatment by life-long dialysis or kidney transplantation. Inflammation of the kidney with infiltration by white blood cells termed macrophages is a common feature in all progressive forms of kidney disease. However, current anti-inflammatory therapy is limited to non-specific immunosuppressive drugs which have substantial, dose-limiting side effects. The aim of this project is to investigate whether a newly identified mechanism of activating the macrophage pro-inflammatory response termed TAK1 signalling plays an important role in experimental models of renal inflammation. This will be determined using a powerful genetic approach in mouse models of kidney disease. If successful, these studies will determine whether targeting TAK1 signalling is a suitable target for the development of new, specific immunosuppressive drugs.

**Progress Report**

*Ligand based induction of mitogen-activated protein kinases (MAPKs) leads to cellular responses, including proliferation, differentiation and regulation of multiple transcription factors downstream. The MAPK signal transduction pathways include three types of protein kinases, MAPKKK, MAPKK and MAPK. MAPKKK phosphorylates and activates MAPKK and this turns phosphorylates and activates MAPK. TAK1 (also known as MAP3k7) is a member of the mitogen-activated protein kinase kinase (MAP3k) family of the mixed lineage kinases and is widely expressed in many cell types. This kinase integrates signals from cell surface receptors leading to activation of one or more downstream signal transduction pathways. Examples of such downstream transduction pathways include p38, JNK and NFkB. Ligands capable of activating TAK1 and the downstream pathways include TGF-β, IL-1, LPS and TNF-α. The downstream transduction pathways can lead to an inflammatory response or apoptosis depending on which pathway that is dominant e.g. the activation of NFkB is anti-apoptotic whereas the activation of p38 and JNK leads to apoptosis.*

*The major aim of my PhD is to determine the effects of TAK1 deletion in the ability of macrophages to cause renal injury. Since very little is known of TAK1 function in macrophages, I will also characterize basic functions of TAK1 in regulating pro- and anti-inflammatory responses in this cell type.*

*We are now in possession of mice LysM-Cre TAK1-flox/flox which has conditional TAK1 deleted in the macrophage lineage. We are using a CRE/lox system which is a reliable and widely used method of inactivating floxed genes (a floxed gene is a gene that has two loxed sites that can be cleaved by the CRE recombinase protein) in specific cell types. Mice have two lysozyme genes, one expressed in macrophages and granulocytes (termed LysM) and the other in Paneth cells and renal proximal tubules. By inducing CRE (which deletes the DNA between the lox P sites) under control of the LysM promoter we can conditionally delete the TAK1 gene in macrophages and granulocytes.*

**Dr Lena Succar supervised by Dr Gopala Rangan and Professor David Harris (Science)**

*Centre for Transplant and Renal Research, Westmead Millennium Institute, University of Sydney, NSW*

**[A new therapeutic approach for the treatment of crescentic glomerulonephritis](#)**

The purpose of this research project is to develop a new therapeutic strategy to prevent kidney failure in patients with crescentic glomerulonephritis. CGN is a disease which effects special cells in the filtering unit of the kidney (the glomerulus) and aggressively progresses to kidney failure. Kidney failure requiring dialysis and transplantation occurs in nearly half of affected persons. Present treatment options to prevent CGN from progressing to kidney failure are inadequate as they are associated with considerable toxic side effects and mortality, particularly in the elderly. Therefore the discovery of drugs with less toxic side effects and that address the fundamental pathobiology of CGN are urgently needed.

**Progress Report**

*Crescentic glomerulonephritis (CGN) is an important cause of kidney failure. Current treatments to prevent CGN from progressing to kidney failure involve the use of toxic immunosuppressants. The aim of this project is to investigate the role of the mammalian target of rapamycin (mTOR) pathway in mediating CGN. Our preliminary data show that mTOR inhibitors reduce disease progression in experimental CGN, and this may lead to clinical trials investigating their efficacy in humans in the future.*

**Dr Thian Kui Tan supervised by Professor David Harris (Science)**

*Centre for Transplant and Renal Research – Westmead Millennium Institute, University of Sydney, NSW*

**[The elucidation of mechanisms underlying the formation of kidney scar tissue and potential targets for treatment](#)**

Kidney fibrosis is the pathological scarring of the kidney leading to kidney failure. The mechanism underlying the formation of kidney fibrosis is unclear, however macrophages are an immune cell which have been shown to play an important roles in kidney fibrosis. The aim of this project is to investigate the role of macrophages in kidney fibrosis. Knowing the exact mechanism underlying the contribution of macrophages to kidney fibrosis could potentially lead to new treatments.

**Progress Report**

*Kidney fibrosis is the pathological scarring of the kidney which leads to kidney failure. The mechanisms underlying the formation of kidney fibrosis are unclear, however macrophages are immune cells which have been shown to play an important role in kidney fibrosis. The aim of this project supported by a KHA scholarship is to investigate the role of macrophages in kidney fibrosis. Knowing the exact mechanisms underlying the contribution of macrophages to kidney fibrosis could potentially lead to new treatments.*

**Dr Peng Wang supervised by A/Professor Steve Chadban and Dr Huiling Wu (Medical)**

*Department of Renal Medicine – Central Clinical School, University of Sydney NSW*

**[Targeting innate immunity to prevent chronic dysfunction of the transplanted kidney](#)**

End-stage kidney disease is a growing public health problem that is best managed by transplantation. The major barrier to long-term success following kidney transplantation, and consequently the premier issue in transplant research today is chronic allograft dysfunction (CAD). CAD has been used to describe the combined effect of calcineurin inhibitor nephrotoxicity chronic immunological rejection, scarring and fibrosis initiated by early post-transplant episodes of ischaemia-reperfusion injury (IFIR) and acute rejection (AR) and a host of non-specific factors including hypertension and proteinuria. Hence the pathogenesis of early post transplant events, IRI and AR, and the related late post-transplant event, chronic immunological rejection, are the focus of this research.

Kidney transplantation is the optimal treatment for patients suffering from end-stage kidney disease. Chronic transplant dysfunction is the major barrier to long-term health after transplantation, and is the subject of this application. Our studies suggest a signalling system activates immunity and leads to chronic transplant dysfunction. We aim to block this signalling system in mouse models to identify clinically applicable treatments to prevent kidney transplant failure.

**Progress Report**

**Project 1.** *To optimise adriamycin dose in a mouse model of adriamycin nephropathy (AN) by using wild type and toll like receptor (TLR) knockout mice.*

**Results:** *Our results suggested that 10-10.5mg/Kg is the optimal dose of adriamycin in this model. The results from WT and TLR knockout mice with three different doses of adriamycin showed a similar pattern: TLR2<sup>-/-</sup> mice with adriamycin incurred worse injury in the kidney.*

**Project 2.** *To determine whether Toll-like receptor 2 (TLR2) or TLR4 is required for the development of AN. Majority of this work has been completed.*

**Results:** mRNA expression of TLR4 & TLR2 and their endogenous ligands was significantly upregulated in AN kidney in WT mice. Compared with WT, TLR2<sup>-/-</sup> and MyD88<sup>-/-</sup> mice with AN incurred worse injury, with significant increases in proteinuria ( $p < 0.05$  &  $0.01$ ) and glomerulosclerosis ( $p < 0.05$  &  $0.01$ ). However, TLR4<sup>-/-</sup> mice show no significant difference in proteinuria and glomerulosclerosis compared with wild type mice.

**Project 3.** To determine whether TLR signalling in AN is through the MyD88 pathway. Majority of this work has been completed.

**Results:** Proteinuria and glomerulosclerosis were significantly worse in MyD88<sup>-/-</sup> mice with AN than TLR2<sup>-/-</sup> mice with AN ( $p < 0.05$ ). MCP-1 expression ( $p < 0.05$ ), tubular apoptosis ( $P < 0.01$ ), interstitial accumulation macrophages ( $p < 0.05$ ) and CD8 T cells ( $p < 0.01$ ) were significantly elevated compared with WT with AN.

**Presentation**

Wang P et al. TLR2 deficiency exacerbates injury in Adriamycin Nephropathy. Oral presentation at ANZSN, Hobart 2009.

**Publication**

1. Wu H, Craft ML, **Wang P**, Wyburn KR, Chen G, Ma J, Hambly B, Chadban SJ IL-18 Contributes to Renal Damage after Ischemia-Reperfusion. *J Am Soc Nephrol*. 2008 Sep 24

**Future research plan:**

(1). confirmation of this result using blocking antibodies

(2) Mechanistic analysis of why injury is exacerbated in TLR2 deficient mice, including and dissection of inflammatory and fibrotic phases of injury and examination of the role of hyaluronan.

**ROCHE BIOMEDICAL SCHOLAR**

Roche Products Pty Ltd is now generously supporting one Kidney Health Australia Biomedical Scholarship annually, targeted at a clinically trained individuals (doctor, nurse or pharmacist) undertaking full time research related to CKD. Funding biomedical scholarships is a most valued and meaningful way to ultimately promote better health outcomes in the kidney community.

*The awardee selected is:*

**Dr Siddharth Rajakumar supervised by Dr Karen Dwyer and A/Professor Peter Cowan (Medical)**

Department of Medicine – St Vincent's Health, Immunology Research Centre, University of Melbourne, VIC

**CD39 Protects in Renal Ischaemia Reperfusion Injury**

The interruption of blood flow causes organ damage. Restoration of blood flow is essential but causes further injury – 'ischaemia reperfusion injury' (IRI). Conditions such as heart attack, stroke, kidney failure and organ transplants involve IRI. CD39 is a molecule that has been shown to protect organs from IRI. This research will explore the mechanisms behind this protective effect in a mouse kidney model to aid the development of therapeutic agents to minimise the impact of IRI.

**Progress Report**

*The disruption of blood flow to an organ will eventually lead to tissue death. The restoration of blood flow is essential but, paradoxically, leads to further injury (a complex process termed ischaemia-reperfusion-injury, IRI). IRI is important in many clinical settings including acute kidney injury, organ transplantation, stroke and heart attacks. Thus the ability to attenuate IRI has potentially wide-ranging applicability. We are studying the role of a particular biochemical pathway that culminates in the generation of the molecule adenosine in a mouse model of kidney IRI in order to better understand the underlying pathological processes and identify potential therapeutic targets. In the renal IRI model we modulate the pathway using pharmacological agents and genetically-modified mice. We have shown that mice are protected from IRI by increased activity of the enzyme CD39 and that this is dependent on a particular (2B) adenosine receptor. We have also demonstrated that a deficiency in, or blocking the action of, the enzyme CD73 leads to reversible protection from IRI.*

*Furthermore this is also dependent on the A2B adenosine receptor. Ongoing work focuses on the underlying cellular and biochemical mechanisms leading to the demonstrated protective effects and the identification of potential therapeutic targets. Preliminary findings have been published in the journal Transplantation, presented at the meetings of the Australian and New Zealand Society of Nephrology and the Transplantation Society of Australia and New Zealand, and will be presented at the 2009 meetings of the International Xenotransplantation Association and the American Society of Nephrology.*

**Newly awarded PhD scholars****Dr Erika Camara supervised by A/Prof Markus Schlaich (Science)**

*Department of Physiology – Monash University, Baker IDI Heart & Diabetes Institute VIC*

[The effects of renal denervation on sympathetic, metabolic and psychometric parameters in patients with resistant hypertension](#)

Cardiovascular disease represents all conditions and diseases of the heart and blood vessels including coronary heart disease, stroke, peripheral cardiovascular disease, heart failure and kidney failure. Cardiovascular disease will remain the single leading cause of death worldwide with an estimated 20 million people dying mainly from heart disease and stroke by 2015. One of the major risk factors for this alarming figure is elevated blood pressure (hypertension). It is evident that alternative options are required to supplement the current therapeutic treatment regimes to reduce this burden. It has been demonstrated that hyperactivity of renal nerves is a major contributor to the progression of hypertension. The current research project aims to investigate the effects of a novel catheter based procedure that “silences” these nerves on blood pressure regulation and a variety of other aspects that are crucial for cardiovascular health in patients with medication-resistant hypertension. The overall aim of this research study is to demonstrate that his novel procedure not only has the potential to reduce blood pressure levels but also beneficially affects similarly important aspects such as glucose control, inflammatory markers and other aspects in patients with substantially elevated blood pressure levels who are at a substantially greater risk of developing cardiovascular disease or even death.

**Dr Scott Wilson supervised by Prof Stephen Harrap (Medical)**

*Department of Nephrology – University of Melbourne, Royal Melbourne Hospital VIC*

[Comprehensive phenotypic analysis of blood pressure changes on dialysis and the mechanisms that lead to these in patients with chronic renal failure with stratification by ENaC sub-unit genotype](#)

Kidney disease is increasing worldwide and placing increasing demands on health resources. Much of this demand relates to the accompanying cardiovascular disease that is the major causes of sickness and death in kidney patients. As a major contributor to heart attack and stroke, blood pressure is a very difficult problem in kidney disease. People having artificial kidney treatment with dialysis often have high blood pressure most of the time, but during treatment, blood pressure can drop precipitously and be equally as dangerous. Surprisingly, very little is known about these swings in blood pressure. Important questions have not been answered such as: What pattern do these changes take? Why do they occur? How can they be predicted and best avoided? The goal of this research is for the first time ever to measure blood pressure continuously in a large group of kidney patients on artificial kidney treatment. These measures will be carefully analysed to determine ways, including genetic testing, in which dangerous patterns of blood pressure can be predicted and averted. The result of this research will continue to be better health of patients with kidney disease.

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**SEEDING GRANTS**

These Seeding Grants, valued up to \$15,000 are designed to allow investigators to begin a new project and develop it to a point where they are ready to attract a more substantial grant, which has led to the establishment of several large projects. In 2010 Kidney Health Australia is funding three Seeding Grants - total value \$33,520.

**Continuing PhD scholars for 2010****Dr Kym Rae assisted by Professor Eugenie Lumbers and Roger Smith**

*Department of Rural Health – Rural Clinical School, University of Newcastle NSW*

[Stress During Pregnancy and the Developmental Origins of Renal Disease in Aboriginal Australians](#)

It is well established that Indigenous Australians are more likely to suffer diabetes and end stage renal disease than Non- Indigenous Australians. A healthy kidney is paramount in prevention of these diseases. This grant focuses on developing an understanding of the role that stress can play on the development of the kidney in pregnancy. That is, that increased exposure to stressors including maternal renal disease, chronic infections, cigarette smoking, sociological stress through racial discrimination and the stress of major life events, activates the production of hormones through the hypothalamic-pituitary-adrenal axis (HPA). The hormones of interest are cortisol and increasing placental production of corticotrophin releasing hormone. This pathophysiological stress response leads to preterm birth of small babies. In addition, preterm birth, intrauterine growth retardation as well as high fetal cortisol levels consequent upon maternal stress and impaired maternal renal function, impair fetal renal development.

We hope that with an understanding of the impacts of these processes in pregnancy we can potentially diagnose those at risk of kidney disease early in life. This may help with future diagnostics, planning additional appropriate care for Indigenous women in pregnancy and improving the long term health outcomes for Indigenous women and their infants.

As part of this program of research, we are committed to working in partnership with, and increasing the research capacity building of, our local Indigenous community. As part of this commitment, this project has seen the employment of a local Aboriginal woman who has completed training and education to ensure that she has skills to enable her to develop her research capacity. In the future it is hoped that she will design and develop her own research programs to assist in improving Indigenous health.



**Progress Report**

The award from Kidney Health Australia has allowed for our organization to employ Ms Loretta Weatherall, a Kamilaroi woman who is based in Tamworth. Loretta has spent 2009 completing her Indigenous Research Capacity Building Cert IV to develop her research assistant skills. She will graduate from this Cert IV course in early 2010. In addition, she has completed her Pathology Specimen Collection Certificate through TAFE to ensure that she can collect all pathology samples as required for the study.

Loretta has worked tirelessly in ongoing Community consultation for this program and assisted in writing of Ethics documentation. In addition, Loretta has worked specifically on developing appropriate survey techniques for this study. The final decision on this meant that participants can complete all surveys using a handheld computer that data can be stored on, and ensuring their privacy whilst doing so.

Final ethics approval has been given by the Hunter New England Human Research Ethics Committee and the Aboriginal Health and Medical Research Ethics Committee in September 2009. This process has taken much longer than anticipated due to the sensitive nature of research in Indigenous communities.

Ongoing funding would continue to support Loretta's role in participant recruitment, data analysis and presentation of findings.

**Newly awarded PhD scholars****Dr Wai Lim**

Department of Endocrinology and Diabetes - Sir Charles Gairdner Hospital, University of Western Australia, WA

[Epidemiology of decreasing renal function and its association with morbidity and mortality in elderly Australian women](#)

Declining renal function is a major cause of morbidity and mortality in affluent populations, with major health cost implications. The causes of this decline are associated with genetic, dietary and lifestyle habits. The aim of this research is to determine the prevalence of early chronic kidney disease and its decline with age in elderly women in Western Australia. In addition the dietary and lifestyle habits and selected biochemical markers that may predict declining renal function will be assessed. This will be achieved by assessing renal function using at baseline (1998) and a 5 and 10 years in 1500 women recruited from the community to identify predictors of declining renal function in these women in relation to cardiovascular and skeletal disease using already completed ascertainment of hospitalisation to any private or public hospital in Western Australia and complete ascertainment of the cause of death using the Hospital Morbidity Data System supplied by the Western Australian data linkage unit from 1998 to 2008.

**Dr Germaine Wong**

Centre for Kidney Research - The Children's Hospital at Westmead, NSW

[Monitoring for chronic kidney disease \(CKD\)](#)

We proposed two specific, but overlapping projects, designed to optimise the management of CDK and to evaluate the impact of monitoring in people with CKD. This program of research aims to 1) identify the optimal strategies for monitoring kidney and associated disease, including which tests and the frequency of testing, the costs and benefits of routine monitoring of people with kidney disease; 2) evaluate the effectiveness of a diagnostic support tool developed previously (based upon changes in serum creatinine levels) to identify potential adverse events post kidney transplants. We will evaluate data from population-based cohort studies, such as the 45-Up study to determine the major risk factors and predictability of these risk factors for the progression to end-stage kidney disease (ESKD). Using individual patient datasets from randomized controlled trials (e.g. SHARP, that included people with early, moderate and advanced-stage CKD), the impact of monitoring in people with CDK using biochemical markers such as serum creatinine will be evaluated. A randomised controlled trial will be conducted to determine the clinical effectiveness and costs of using the proposed decision support tool (compare to standard care) for the detection of adverse clinical events post transplants.

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**SCHOLARSHIPS FOR NURSES PURSUING MASTERS DEGREE**

Kidney Health Australia provides grants for Registered Nurses wishing to study for a Masters Degree in Nursing or Public Health. The aim of the program is to encourage nurses to pursue a career in renal nursing in any of its components - clinical practice, education or research - across the continuum of chronic kidney disease from prevention to early detection to renal replacement.

Four renal nurses were awarded scholarships valued at \$3,000 each, for a maximum of three years –total of \$12,000 for calendar year 2010.

**Mr Brenton Shanahan** - Master of Advanced Practice - Health Professional Education - Griffith University, QLD *(continued)*

**Mr Peter Sinclair** - Master of Nursing (Research) - University of Newcastle, NSW *(continued)*

**Ms Anna Lee** - Master of Nursing (Nurse Practitioner) - University of Technology Sydney (UTS), NSW

**Ms Annette Bezzant** - Master of Nursing (Nurse Practitioner) - Deakin University, VIC

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## SUMMER VACATION SCHOLARSHIPS

These scholarships are now valued at \$2,000 each, and are designed to provide assistance to undergraduates undertaking summer vacation research in the area of kidney and urinary tract.

### **Ms Ainslie Camerons supervised by Dr David McMillan**

*Bacterial Pathogenesis Laboratory, Royal Brisbane Hospital, Queensland University of Technology, QLD*

[Functional genomic analysis of group G streptococcus, a bacterium that causes kidney disease.](#)

Group G streptococcus (GGS) and Group A streptococcus GAS are closely related bacteria that causes a number of disease including the kidney disease post-streptococcal glomerulonephritis (PSGN). While the incidence of this disease is relatively minor in the Australian Caucasian population, rural indigenous communities suffer from severe outbreaks of APSGN every few years. GAS is considered the most pathogenic of the two bacterial species. As a consequence, much research has focused on this organism. The current proposal seeks to address a lack of fundamental knowledge about how GGS. The aim of the project is to identify genes that contribute to fundamental pathogenic processes of GGS. Through the identification for these genes, and comparison with similar genes in GAS, novel strategies for prevention of streptococcal infection, and subsequent disease, may be developed.

### **Mr Christopher Wong – supervised by Prof Prashanthan Sanders**

*Department of Cardiology - Royal Adelaide Hospital, University of Adelaide SA*

[Renovascular hypertension and cardiac remodelling: local expression and activity of angiotensin-II and angiotensin-converting enzymes in the ovine atria](#)

Patients with renal disease, such as that due to renovascular hypertension, are at high risk of cardiac death. Angiotensin-11 and angiotensin converting enzymes are important proteins that have been shown in numerous studies to play an important role in cardiac function. Limited information exists on their role during disease states, however, and how they may adversely affect cardiac structure and function remains unclear. Our study aims to explore the effect of renovascular hypertension on the local expression and function of these important proteins in the heart. This will allow insights into the mechanism of cardiac disease during renovascular hypertension, which may lead to new therapeutic pathways.

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## TARGETED OR STRATEGIC RESEARCH

This year \$75,000 was awarded by the Medical and Scientific Advisory Committee to targeted areas deserving support and assisting Kidney Health Australia in its mission to free Australia of kidney disease.

## ANZDATA REGISTRY

The internationally acclaimed ANZDATA Registry has been funded substantially by Kidney Health Australia since its formation. It is one of the major accomplishments of the Australian and New Zealand nephrology community and has contributed importantly to knowledge, planning and best practice in clinical care over many years. For calendar year 2007, MSAC awarded ANZDATA Registry \$75,000 towards its general operating costs. Learn more at [www.anzdata.org.au](http://www.anzdata.org.au)

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## THE BOOTLE AWARD PROJECTS

The Bootle Bequest has allowed the funding of four major strategic areas of research since awarded first in January 2003. All projects groups were required to guarantee the contribution of matching funding for these research projects, which has had the effect of doubling the initial value of the \$2 million plus bequest.

## BACKGROUND TO THE BOOTLE AWARD

Kidney Health Australia established a major research program grant arising from an initial bequest of over \$2 million dollars from the estate of Miss Elizabeth Bootle, dedicated to research in nephrology and urology. The Kidney Health Australia Board decided to allocate the capital and interest of these funds to projects commencing in the near future, rather than to invest the bequest funds for use in the longer term.

The Medical and Scientific Advisory Committee of Kidney Health Australia recommended to the Board that the Bootle Bequest be used primarily for developing and securing the academic career of Australian scientists or medical graduates in the area of nephrology. It was recommended that this be accomplished by the award of major grants (up to \$200,000/year for 5 years) with the proviso that the recipient institution **would match those funds from other sources**. The residuum of the bequest was recommended to be used for projects deemed to be in the national nephrology interest.

The first research project began in 2003, and the second project funded started in 2006, **injecting more than \$5 million dollars into kidney research** that will benefit Australians and populations worldwide at risk from kidney disease.

### ***NOVEL DIABETES RESEARCH (2006 - 2010)***

#### **A/Professor Merlin Thomas**

*Baker Heart Research Institute - VIC*

[Explore a novel link between insulin and the complications it causes](#)

The fourth and final Bootle Award - \$1 million dollars over 5 years from the Bootle Bequest was awarded to A/Professor Merlin Thomas, and then matched by Baker Heart Research Institute, injecting a total of \$2 million dollars in this research area in Australia.

A/Professor Thomas will soon commence clinical trials to explore a novel link between sugar and the complications it causes. To use an analogy, high blood sugar is like adding petrol to fire. High blood sugar fuels the creation of destructive modified protein. This important research will look at ways to contain the fire no matter what is added to it, thus negating the effect of high sugar levels. A/Professor Thomas is developing a test that medical practitioners will be able to use on people with diabetes to see how much of the modified protein is in their system. Doctors will then be able to easily and quickly ascertain the level or risk of kidney damage in their patients and could also use this test on patients who are at risk of contracting diabetes to ensure that their organs do not start to deteriorate as a result of the disease.

Diabetes is the single most common cause of kidney disease in the Australia. Over the past 10 years the incidence of diabetes in dialysis and transplant programs has more than doubled. This has occurred despite the presence of clear guidelines for the management of kidney disease and established methods to slow its progression. Thus, there remains an urgent need for new targets and new interventions to stem the inexorable tide of diabetic kidney disease. Although a number of factors operate in diabetes, one pivotal pathway appears to be the formation and accumulation of advanced glycation end products (AGEs). AGEs are formed when sugars bind to protein, making it sticky, sweet and brown. In food like chocolate and caramel, this reaction is appetizing. But when sugar accumulates in diabetes, this same process contributes to blindness, heart disease and kidney failure. This reaction leads to changes in the shape and function of AGE-modified proteins, which gradually build up in tissues, making them in turn more stiff; literally 'hardening' the arteries'. AGEs also activate specific receptors in the body to trigger inflammation and injury. Our work specifically examines the damage caused by AGEs and ways of measuring their impact and accumulation. In addition, with the support of KHA we are developing new methods to reduce the damaging effects of AGEs on the kidney, and testing them in both experimental systems and for the first time in clinical trials.

The growing epidemic of diabetes already affects over one million Australians and twice that number again is at risk of developing diabetes in the next five to ten years. For the millions of people with diabetes who struggle to try to control their sugars every day, an understanding of this pathway will provide an important advance to their care.

Millions of Australians are living with diabetes, the lead cause of kidney failure. Despite the clear and present danger of diabetes, the role of high sugars in causing kidney failure blindness and heart disease is poorly understood. Diabetes has been identified as triggering 30% of kidney disease. The results of this research will provide the foundation for early detection and prevention of kidney disease from which one in three Australians is at risk. The overall cost of kidney disease in the community is substantial with the disease being the seventh most common cause of death in Australia. The contribution of kidney failure to mortality in Australia has been seriously underestimated with a conservative estimate indicating that kidney failure causes or contributes to at least 9.5% of all deaths in Australia.

#### ***Progress Report:***

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