



SCHEDULE OF MEDICAL RESEARCH GRANTS AND SCHOLARSHIPS AWARDED FOR 2011

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.*

Medical Director's Overview

The year 2010 was marked by the release of new information suggesting that the relentless rise in new patients accepted to dialysis in Australia may be over. The trend-line for the rate of new patients starting dialysis over the last 5 years is now downwards and the absolute numbers static. The pause in the numbers accepted onto dialysis is welcomed and may represent a turning point in the battle for control of CKD though the news is tempered by the knowledge that the Australian rate is still low by International standards. Further, new information put together by the Australian Institute of Health and Welfare suggests that a number equal to those being accepted onto dialysis are dying primarily of kidney failure without dialysis. It must be noted though that the prevalence of people on dialysis continues to grow as more people enter dialysis than leave and this steadily increases the economic burden on the community from end-stage kidney failure. Our new report on this with projections of the cost to 2020 makes sobering reading. ("Economic Impact of End-Stage Kidney Disease in Australia - Projections to 2020" – downloadable from our website)

The other encouraging accomplishment in 2010 was the significant 25% increase in organ donor numbers. This has been attributed to the new initiatives in the organ donation sector. A new record of 309 deceased donors was accomplished providing 548 kidneys – up 102 kidney transplants on the previous year. This is an outstanding achievement and although coming off a low base is encouraging that the goal of reaching 20 donors per million per year might be in reach. We have continued our efforts to achieve re-imburement of expenses (reasonable and verifiable) for live donors and are building support from stakeholders for this scheme.

The early detection of CKD remains a prime goal for KHA. Another community screening program run at the end of 2010 in outer Sydney again showed that whilst 91% of the target group regularly attend their own doctor CKD is not being diagnosed. 21% of participants were newly shown to have CKD and three-quarters of these had moderate to severe CKD. Greater effort has to be made to improve CKD recognition in primary care and a collaborative approach with our partners in the National Vascular Disease Alliance is underway to address this.

SUPPORT FOR BIOMEDICAL RESEARCH

Kidney Health Australia is the main non-government supporter of kidney and urinary tract biomedical research in Australia. In 2010 the Board of Directors determined that in the future there should be a shift in the focus of our research support program towards project grants in the public health area of CKD and away from direct support of individuals and investigator driven research.

A total of forty-six applications were received by Kidney Health Australia for funding support in the calendar year 2010. Our Medical and Scientific Advisory Committee awarded twenty-one separate grants and scholarships to the value of \$425,530 into kidney related research projects in University departments, medical research institutes and hospitals throughout Australia. Support to investigator driven research totalled \$326,520, plus an additional \$75,000 funding for strategic targeted research.

The nationally competitive Career Development Award continued in partnership with the Australia and New Zealand Society of Nephrology and the National Health and Medical Research Council (valued at \$500,000 over 5 years).

The Kidney Health Australia Bootle Research Fund awarded funding to one research project in 2010 valued at \$200,000. This year's funding will complete the \$1million award which constituted our fourth major Bootle project.

Medical Grants and Scholarships For calendar year 2011

In 2010 our Nursing Scholarship program entered its third year. This program aims 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 CKD, from prevention to early detection to renal replacement.

Our total research expenditure from Board allocated funds including the Bootle Award for calendar year 2010 was \$625,530.

These scholarships permit talented researchers to pursue fulltime research for up to three years, qualifying them to obtain a doctoral degree or equivalent at the end of this period. Individual scholarships for 2010 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 \$277,000.

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

***Dr Tim Mathew
Medical Director***

Investigator Driven Research Grants and Scholars

BIOMEDICAL SCHOLARSHIPS

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In 2011, four Biomedical Scholarships were awarded continued funding. Funding allocated was valued at \$94,000.

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 2011

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. As long term macrophage depletion is not desirable and so it is important to identify the macrophage-derived mediators, such as matrix metalloproteinase-12 (MMP-12), that cause renal injury to provide new therapeutic targets. Our studies have identified high levels of MMP 12 production in the kidney in 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 extra-cellular matrix, and (b) direct damage to the glomerular basement membrane, podocytes and tubular epithelial cells, resulting in proteinuria and histologic damage.

Our studies so far show that MMP 12 does not have a significant role in non inflammatory kidney disease. However in inflammatory kidney disease MMP 12 appears to have a specific role in crescent formation (type of advanced kidney injury).

Animal Model

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

UUO surgery was performed in three groups of 8 C57BL/6J and MMP-12^{-/-} mice by ligating the left ureter under anesthesia and killed on days 3, 7 or 14. MMP 12 was demonstrated to be up regulated in the obstructed kidney by Real Time PCR (RT-PCR). There was no difference in macrophage infiltration (F4/80) and myofibroblast accumulation (α -SMA), at any time point between the two groups. Extra-cellular matrix deposition quantified by collagen IV staining and the pro fibrotic gene profile (TGF- β & CTGF by RT-PCR of whole kidney sections) showed no difference between the two groups at day 7. Tubular damage judged by KIM-1 RT-PCR and apoptosis (cleaved caspase 3 immunohistochemistry) were again not different between the two groups. This data shows that macrophage infiltration, renal fibrosis and extra-cellular matrix deposition are independent of MMP 12. UUO model experiment is complete and this data is now being prepared as a manuscript for publication.

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

An initial group of 6 MMP-12 mice and 6 C57BL/6 had anti-GBM disease induced using a standard protocol. These animals were killed on day 12. A similar induction of proteinuria and a rise in serum creatinine occurred in both groups compared to normal mice. On histological analysis there was significant reduction in Bowman's capsule rupture in MMP-12^{-/-} mice. The pro-inflammatory gene profile (TNF- α & MCP-1) was reduced in MMP-12^{-/-} mice. This data suggests that MMP-12 has a specific role in crescent formation through macrophage accumulation in glomerulus, Bowman's capsule rupture and regulation of pro inflammatory molecules. Further studies are underway in this model.

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.

Lay Report

Kidney fibrosis is the pathological scarring of the kidney which leads to kidney failure. Although various factors can contribute to the development of kidney fibrosis, matrix metalloproteinase-9 (MMP-9), a scar degrading enzyme has been recognised that play an adverse rather than protective role in kidney fibrosis. The aim of this project supported by a KHA scholarship was to investigate the contribution of MMP-9 in kidney fibrosis via inhibition of MMP-9 activity. A successful outcome of this study could define a novel target for the treatment of kidney fibrosis.

Progress Report

Previously, results from our invitro studies demonstrated a primary role for MMP-9 from acrophages in the induction of tubular cell epithelial-mesenchymal transition (EMT), an important source of myofibroblasts in renal fibrosis. Moreover, we showed that MMP-9 itself is capable of inducing the entire course of tubular cell EMT and that TGF- β -induced tubular cell EMT was found to be dependent on MMP-9 activity. Preliminary timecourse results obtained from a murine model of renal fibrosis, unilateral ureteral obstruction (UUO), showed biphasic (early and late-stage) expression of MMP-9. Early and late-stage, but not mid-stage inhibition of MMP-9 activity by MMP-2/9 inhibitor or MMP-9 neutralising antibody resulted in a significant reduction in renal fibrosis.

To determine the mechanism underlying the reduction of renal fibrosis by MMP-9 inhibition in UUO, the effect of MMP-9 inhibition on osteopontin cleavage, macrophage infiltration and tubular cell EMT was analysed. Our results showed that early and late-stage, but not mid-stage inhibition of MMP-9 activity by MMP-2/9 inhibitor or MMP-9 neutralising antibody resulted in a significant reduction in MMP-9 cleaved osteopontin, macrophage infiltration, β -catenin translocation in tubular epithelial cells and the number of α -smooth muscle actin positive cells, the latter two being indicators of tubular cell EMT. So far, our results suggest that inhibition of MMP-9 activity in UUO resulted in a reduction of MMP-9 cleaved osteopontin, a potent macrophage chemoattractant, leading to a reduction in macrophage infiltration and tubular cell EMT. Currently, we have begun to confirm the role of MMP-9 cleaved osteopontin on macrophage infiltration using an in vitro migration assay and the origin of MMP-9 by in situ hybridization. It is necessary to confirm the role of MMP-9 cleaved osteopontin on macrophage infiltration as it has not previously been reported.

The findings from our in vitro studies have resulted in one first author and one co-author publication in the American Journal of Pathology (Impact factor 5.697) and results from our in vivo studies are currently under preparation for submission to the Journal of American Society of Nephrology (Impact factor 7.689). Results from in vivo studies were presented at 2010's Australian and New Zealand Society of Nephrology annual scientific meeting and has also been accepted for a poster presentation at the American Society of Nephrology annual scientific meeting.

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](#)

Lay Report

Our study into the 'what', the 'how' and the 'why' blood-pressure behaves the way it does on haemodialysis is now well and truly underway at Melbourne Health. The project has successfully navigated all the usual preclinical hurdles in terms

Medical Grants and Scholarships For calendar year 2011

of ethical approval, equipment purchase and project setup and has been steadily recruiting new patients for the past few months. A separate preliminary study has been successfully completed validating the use of all new equipment in our local population and several education sessions have been run with dialysis and medical staff to raise awareness of our research. Patient feedback so far has been extremely positive. At present we have enrolled approximately 10% of our overall target number of patients and look to be on-track to achieve our target recruitment by the end of 2011.

Progress Report

We are pleased to report that following Melbourne University enrolment and formal project commencement in early 2010 our research is proceeding in line with initial projections. Significant milestones achieved so far include;

- Final approval sign-off from local Human Research/Ethics Committee,
- Preliminary assessment of the relevant medical and physiological literature (remains ongoing and dynamic to new papers and presentations – of which there have been several highly relevant publications since project commencement, highlighting the acuity and relevance of our research),
- Sourced external funding for purchase of necessary technological equipment with integration into our new fleet of haemodialysis machines across the NWDS service (commissioned and completed June 2010),
- Preliminary testing of the measurement devices and feasibility trials on local patient cohort (five patients),
- The formal recruitment of the first fifteen (15) patients into the study (a mix of newly commenced, and established dialysis patients) – all have completed initial phenotypic study and have consented to further (repeat) assessments. Several patients have undergone second/third assessments as part of the “reproducibility” sub-study. These patients phenotypes are currently the subject of interim analysis that will be presented together with biochemical data at an invitational meeting in Oxford (UK) in November 2010. Our initial impressions are that despite incorporating a fairly heterogeneous group, some common patterns of behaviour are beginning to appear at various intradialytic timepoints.
- Genotype samples for each patient have been collected and remain in storage awaiting batch processing.
- Initial biochemical protocol has been revised to include analysis of stored serum at pre, intra and post-dialytic time points, for potentially vasocative peptides/cytokines either removed, or added, by the dialysis treatment.

Completion of our interim analysis is imminent, and looks likely to lead to a refinement of our biochemical testing protocol. Recruitment continues with the primary target of 150 patient assessments, though at times has been limited by the relative high acuity service our centre provides to a fluctuant group of medically unstable inpatients (who fall outside our target study populations). That usual expected, and unexpected, teething issues associated with a new clinical project have arisen and been dealt generated, currently represents the most significant challenge going forward. We remain confident that the project is proceeding according to expected timelines and remains on-track from completion without the need to significant alteration or application for extension.

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 2011.

Mr Zivai Maburuse - Master of Nursing - Edith Cowan University, WA / Flinders University, SA

Miss Marie McIntosh - Master of Nursing - Nurse Practitioner - University of Newcastle, NSW

Mrs Jacqueline Moustakas - Master of Nursing (Research) - Flinders University, SA

Mrs Jane Van Der Jeugd - Master of Nursing - Nurse Practitioner - Flinders University, SA

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.

Mr Andrew Blandford supervised by A/Prof Glenda Gobe*Centre for Kidney Disease Research, Princess Alexandra Hospital, QLD*[A novel biomarker for Chronic Kidney Disease](#)

Ageing is the strongest risk factor for increased incidence of chronic kidney disease (CKD). Oxidative stress is a feature of ageing. CKD and cardiovascular disease. We have recently identified significantly elevated levels of an oxidant handling protein, p66Shc, in models of CKD associated with oxidative stress (Percy et al, 2009). Loss of p66Shc is known to lead to increased healthy life span and decreased incidence of some diseases (Menini et al, 2006), but its role in the pathogenesis of clinical CKD is not known.

Staging of CKD is often determined via estimated glomerular filtration rate (eGFR), but there are some criticisms for this method, and at present biomarkers for CKD progression are needed. From our current results, and publications by others in the literature, the following hypothesis has been developed: In stage 2-4 CKD patients, increasing levels of p66Shc will reflect the increasing progression of CKD. The aim is to measure levels of p66Shc (endogenous and activated/phosphorylated) in the blood and urine of patients with stage 2-4 CKD and to compare these results with various parameters of CKD (cause and outcome) already recorded for the same patients at the Princess Alexandra Hospital Department of Nephrology. The significance of the project is that by establishing a link between p66Shc and increasing progression of CKD, these results may provide a predictive biomarker for CKD progression.

Mr Danny Kiet Hua – supervised by Dr Germaine Wong*Centre for Kidney Research - Children's Hospital of Westmead SA*[How cost-effective is Cidofovir in BK virus infection in kidney disease](#)

Using a modelled economic evaluation, the study aims to: 1) estimate the healthcare costs and outcomes of using Cidofovir for the treatment of BK nephropathy (BKVAN) in renal transplant recipients and 2) to identify the influential and uncertain variables of Cidofovir treatment in transplant recipients, which will translate into future topics of research priorities.

Targeted or Strategic Research

This year \$100,000 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 annually towards its general operating costs. Learn more at www.anzdata.org.au

PROJECT GRANTS

Thirteen applications were received with four awarded funding by the Medical and Scientific Advisory Committee with a total funding of \$199,344.

Dr Katrina Campbell*Nutrition & Dietetics - Princess Alexandra Hospital QLD*[Salt intake and risk of heart disease in chronic kidney disease](#)

Kidney disease is a major cause of death and illness in Australia, and is responsible for significant health care costs. Cardiovascular disease is the leading cause of death in those with kidney disease, and is related to worsening kidney function. Many risk factors for both cardiovascular disease and kidney disease progression – including high blood pressure, vascular stiffness, fluid overload, urinary protein and inflammation – are linked to high dietary salt intake. However, studies of the effect of high versus low sodium in humans with kidney disease are lacking; most evidence comes from studies in animals or humans with healthy kidneys. Yet salt may be handled differently by the damaged kidney and may be more harmful to those

with kidney disease. Quality studies on the effect of high salt intake in those with kidney disease are needed. This project will investigate the effect of a high versus a low sodium diet in participants with moderate kidney disease. We will measure blood pressure, vascular stiffness, urinary protein and fluid volume during a high sodium intake and then a low sodium intake to determine whether cardiovascular risk factors and risk factors for kidney function decline are increased with a high sodium intake.

Prof Zoltan Endre

Department of Nephrology - Prince of Wales Hospital NSW

[Investigating fragments of kidney cells in the urine for markers of kidney disease](#)

Animal models of kidney injury can be successfully reversed provided that appropriate treatment is instituted before or soon after injury, but the currently used marker of kidney function in man, urinary creatinine, does not provide early warning of kidney injury. Therefore, there has been much recent research aimed at discovering biomarkers from the urine better able to detect early kidney injury in man. However, there is no consensus as to which biomarker is most useful, and so far all such biomarkers cannot reliably detect kidney injury in mixed populations where the time of injury is unclear. This project aims to compare biomarkers of kidney injury in whole urine with those in urinary exosomes, small membrane-bounded structures derived from kidney cells which contain samples of the proteins and mRNA from inside these cells. The constituents of these exosomes are different from those present in whole urine: the latter are often degraded, and contain proteins from many sources other than the kidney. We believe that a study of exosome proteins and mRNA will provide candidate biomarkers of kidney injury than do biomarkers in whole urine.

Prof Carmel Hawley

Department of Nephrology - Princess Alexander Hospital QLD

[A Study Investigating the Role of Cardiac Hormones in Managing Patients With Chronic Kidney Disease](#)

Compared with the general populations, dialysis patients have a *100-fold* increased risk of dying from heart disease which has remained unchanged over the last decade. The main factor which predicts this risk in dialysis patients is abnormal heart muscle structure and function. Excess body fluid and high blood pressure are critical risk factors leading to these heart abnormalities. Current tests to identify dialysis patients at high risk are quite inaccurate and optimum blood pressure/fluid targets remain undefined. There is an urgent need for a blood test that accurately detects the early stages of heart injury to enable effective treatments. NT-proBNP is a heart hormone released during heart stress and early studies suggest it can predict which dialysis patients do poorly. The aim of our research is to develop a monitoring guideline based on regular testing on NT-proBNP to identify high-risk dialysis patients early. This would enable treatment *before* a serious medical complication occurs, potentially improving patient outcomes on dialysis. We will achieve this by testing NT-proBNP monthly in a group of 150 dialysis patients for 2-years, and correlating changes in the hormone levels with changes in patient symptoms, their health, body fluid state, and heart structure and function.

Dr Wai Lim

School of Medicine and Pharmacology - Sir Charles Gairdner Hospital WA

[Renal function, vascular calcification and atherosclerotic vascular disease](#)

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. This project will measure 10 years of data on the progression of aortic calcification in the CAIFOS cohort, sampling the 10 year serum creatinine levels adding to the 5 years of data we have already collected. Cystatin C will also be measured at cardiovascular, renal and skeletal disease. In addition to this, the dietary and lifestyle habits and selected biochemical markers that may predict declining renal function will also be assessed. This will be achieved by assessing renal function at baseline (1998) and at 5 and 10 years in the 1500 women recruited from the community to identify predictors of declining renal function in these women in relation to cardiovascular and skeletal disease using an already completed database of complete ascertainment of hospitalization 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.