

ANNUAL REPORT 2011



Waikato Medical
Research Foundation



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Chairman's Report

Once again our Charitable Foundation received applications for grants much in excess of what we are able to fund. Even though our basket is small, it is good to have competition especially since we aim to be prudent funders and fund managers.

Often we support new investigators as we did in the early 1990s to Dr R. Cursons and group looking at strains of tuberculosis locally. This did not lead to a publication then, but since then all local Tb isolates have been frozen down. This is now coming to fruition in an investigation of New Zealand's largest strain which is causing a lot of disease especially among the Tangata Whenua. With collaborators in the USA, we are investigating this strain for virulence and will develop a rapid test to quickly identify the strain to assist rapid contact tracing and chemoprophylaxis to try and curb its spread.

We are very pleased that Dr Leong Leow's work on Vitamin D and Pneumonia led to such international interest and once again he is an example of a young investigator who has come back to Hamilton as a specialist physician.

We are once again indebted to Trust Waikato for their substantial help. We also thank Braemar Charitable Trust for assisting in research on cardiac surgery. We continue to explore avenues of fundraising and have decided to engage a professional fundraiser. We thank PricewaterhouseCoopers for the opportunity to work with Radio Networks for free airtime on their channels earlier this year to help raise our profile.

I am very grateful for the voluntary time given to the Foundation by the Trustees. We welcome Frank Scrimgeour (University of Waikato Management School) as a new trustee. I also regret that Mere Belzer retired as a trustee and thank her for her help.

I am proud to be part of medical research in the Waikato and witness the fruits of its endeavours to enhance patient care.

Finally without donors, there would be no Foundation – we need your help.

Dr Noel Karalus
Chairman

'I am proud to be part of medical research in the Waikato and witness the fruits of its endeavours to enhance patient care.'

Report of the Grants Committee



This year the Foundation received 11 quality applications requesting a total of \$196,023. With assistance from Trust Waikato the Foundation was able to support 10 applications. Many applications were cross institutional involving researchers from the Waikato Hospital and Clinical School, AgResearch, and the University of Auckland.

This year the applications supported work on: Vision in children who had experienced Neonatal Hypoglycaemia; the origin of microbes in mothers' milk and their effect on allergies; Investigations on oxygen, warming and negative pressure therapy on wound healing; The impact of various treatments for prostate and colon carcinoma treatment on couples' relationships; The identification of somatostatin receptor subtypes in phaeochromocytomas and paragangliomas to inform treatment options; The role of a milk derived protein, quiescin sulphhydryl oxidase, in intestinal barrier function; The utility of Botox to improve urinary flow in patients with prostate enlargement; The use of electron microscopy as a diagnostic tool to examine structural changes in mitochondria in the diagnosis of phaeochromocytomas; The structural requirements for induction of cancer-protective enzymes by isothiocyanates from the brassica plants; Whether growth hormone treatment restores normal myostatin and IGF-1 levels, with possible applications in muscle wasting and obesity therapy. Several of the grants support students.

With this support from the WMRF, many of these projects generate data for more substantial support elsewhere and are translated into useful tools, products and services used in the Waikato region and elsewhere.

I thank the grants committee: Maggie Fisher, Amanda Oakley, Roy Daniels, Michael Jameson and Noel Karalus for the reviewing and scoring of the applications. A special thank you goes to the WMRF administrator, Robyn Fenneman, for gathering, organising and meticulously presenting the applications and responses to applications.

Adrian Molenaar
Chair, Grants Committee

WMRF Funded Projects Grant Round 2011	
• Vision and Visual Processing in Children who had experienced Neonatal Hypoglycaemia Dr N. Anstice (University of Auckland)	\$13,379
• Germs present in raw milk could help fight allergy risks, but where do they come from? Dr R. Bibiloni (AgResearch)	\$21,535
• Volumetric and Growth Factors Assessment of Negative Pressure Dr N. Chiang (Vascular Surgery, Waikato Hospital)	\$5,548
• Investigating the impact on Couples of a Man's Prostate or Colon Carcinoma Treatment – A Pilots Study Dr H. Conaglen (Sexual Health Research, University of Auckland)	\$18,000
• Identification of somatostatin receptor subtypes in hereditary and sporadic phaeochromocytomas and paragangliomas Dr M. Elston (Endocrinology, Waikato Hospital)	\$6,500
• Role of Quiescin Sulphydryl Oxidase in Intestinal Barrier Function Dr P. Harris (AgResearch)	\$15,000
• Defining the Optimal dose of intra-prostatic Botulinum Toxin Type A in men with refractory urinary retention who are fit for surgery Dr M. Holmes (Urology, Waikato Hospital)	\$15,000
• Assessment of Mitochondrial Morphology using Electron Microscopy for SDHB Germline Mutation Associated Phaeochromocytomas Dr W. Meyer-Rochow (Surgery, Waikato Hospital)	\$6,000
• Structural requirements for induction of cancer-protective enzymes by isothiocyanates Dr R. Munday (AgResearch)	\$22,500
• The regulation of myostatin & insulin-like growth factor-1 by growth hormone Dr R. Paul (Endocrinology, Waikato Hospital)	\$9,000



Summary of Proposals from Grant Recipients

Grant #185, Dr Rodrigo Bibiloni

Germs present in raw milk could help fight allergy risks, but where do they come from?

An allergy occurs when a person's immune system overreacts to substances in the environment. There are many different causes of allergy, and symptoms range from very mild and transient to chronic and disabling; in some patients they can be acute and potentially life threatening. Allergies are very common and affect about one in three New Zealanders at some time in their lives. Around the World, prevalence of allergy has risen over the last few decades associated primarily to a "Western" urban lifestyle as opposed to rural living.

Although the consumption of unpasteurised milk has been discouraged due to known health risks associated with pathogens, there is growing evidence that consistently suggests that consumption of unprocessed milk does decrease the risk of asthma. The mechanisms for this are not yet understood, but may be related to bacterial composition and/or the presence of milk protein or fat components that modulate the human immune system and are lost or modified during milk processing.

It has been reported that human breast milk is not completely sterile, and that bacterial components derived from the maternal intestine are transported to the lactating breast through the blood within phagocytic cells. We hypothesise that a similar mechanism of bacterial trafficking from the gut to the mammary gland may also occur in the cow, possibly contributing to the bacterial components found in raw milk. In addition, the identification of bacteria or bacterial components in unprocessed cow's milk and comparison to the breast milk may provide the foundation of new strategies on how to shape the intestinal bacterial ecosystem of the infant to aid in the prevention of allergic disorders.

Although the consumption of raw milk cannot be currently recommended as a preventive measure for allergic diseases, we believe that the proposed research initiative will contribute to unveiling the origin of bacterial components in milk and, in the long term, to deciphering the protective effects of unprocessed cow's milk on the development of asthma.

'Around the World, prevalence of allergy has risen over the last few decades associated primarily to a "Western" urban lifestyle as opposed to rural living.'



Grant #187, Dr Helen Conaglen

Investigating the Impact on Couples of a Man's Prostate or Colon Carcinoma Treatment: A Pilot Study

Prostate (PCa) and colon (CC) cancers are the two most commonly registered cancers in NZ men. However, if treatment occurs early when cancers are localised, men often survive years living with treatment side effects on their urinary, bowel and sexual functioning. These side effects impact not only the men, but also their partners.

In these cancers, treatment options for the men range from surgery through radiotherapy, androgen deprivation therapy and chemotherapy depending on the cancer. The quality of life outcomes for these various treatment options have never before been quantified in terms of the impact on a couple.

In some cancers, the involvement of partners has been identified as assisting positive outcomes for patients, but for PCa and CC, where treatment effects occur at differing stages during the man's disease, there is no clear understanding of what couples need and at what points during treatment. Recent reviews have repeated the need for more research in this area.

As clinician-researchers, the investigators have identified the need for strategies to effectively involve men's partners in recovery processes. Patients and their advocates have also identified the need for education for couples following cancer treatments. Our team has expertise in research involving couples in whom sexual function is affected by various medical conditions. By working in conjunction with the key treatment providers, we anticipate this study can provide evidence upon which to base educational assistance at appropriate times to assist couples experiencing the effects of cancer treatments.

Aims: This study aims to investigate the impact on both partners from diagnosis through various treatment options for 24 months after diagnosis. We propose an integrated examination of the health-related outcomes, sexual function and spousal experiences for each cancer type. We will examine the relative impact on couples of the various treatments, making comparison during the different stages of PCa and CC treatments. This will be undertaken using both quantitative and qualitative methodology. This application covers the pilot for the study.

Method: The main study will be a prospective three-year investigation following 150 couples from baseline, through therapy, with follow-ups at three and then at six-month intervals thereafter. Participants will complete questionnaires at each time-point. A sub-set of willing participants will also be interviewed at each time-point to gather further information that explains aspects of questionnaire material. The pilot will assess 20 couples and collection of their data will enable finessing of larger study and power calculations to ensure best practice.

Main outcome measures: The main outcome measures will be levels of physical, social and sexual function impairment at each time-point, for both patients and their partners. Themes from qualitative analyses will explain aspects of the quantitative comparisons. The study will inform future content of patient and partner clinical interventions at each time-point.

Relevance: This innovative study of New Zealand couples will potentially provide evidence for clinicians to use in responding to the needs of New Zealand patients being treated for these cancers. These findings will be particularly relevant given the aging of our population with increased susceptibility to these diseases, and current debate relating to PCa assessment and treatment. It will also provide significant input in an area not researched widely internationally.



Grant # 190, Dr Michael A Holmes

What is the best dose of Botox into the prostate for men in urinary retention?

“Defining the optimal dose of intra-prostatic Botulinum Toxin Type A in men with refractory urinary retention who are fit for surgery”

Men who cannot pass urine are catheterised (that is a catheter is placed through the penis into the bladder) to allow the bladder to drain. Following this men have a choice of having a permanent catheter or undergoing surgery.

This operation, called a TURP (transurethral resection of the Prostate) can have side effects and can be dangerous. Some men are too frail to have the operation. Essentially a hole is cut through the middle of the prostate while the patient is anaesthetised, a new catheter placed and the next day the catheter is removed to see if the patient can void (pee). In general, this operation is very successful; however it does not always work, involves a general anaesthetic or spinal, 1 to 2 days in hospital and can produce urinary incontinence as well as bleeding, infection and changes in blood salt levels.

The prostate is made up of muscle and glands. Botox relaxes muscle. Studies done overseas show that if we inject Botox into the prostate then most men with a catheter can pass urine without an operation. Alternatively some men will get rid of their catheter but not be quite right and can then have the surgery performed catheter free which is much safer from a sepsis point of view. These studies have suggested that the effect maybe more complex than first assumed as the prostate shrinks after injection of Botox suggesting that the benefits are from more than just smooth muscle relaxation.

The concept of using Botox in the prostate is relatively new. Doses used are based on guess work rather than any scientific basis (empirical or by observation) and no studies exist which have looked at dose variation and how this is affected by the prostate volume.

This study aims to see if the size of the prostate matters and if the amount of Botox used matters. To do this men who have a catheter in will be given an injection of Botox into the prostate under local anaesthetic, using an approach similar to taking a prostate biopsy. The dose of Botox used will vary between one of three doses. The aim is to work out

- 1) is there a best dose of Botox and
- 2) does the size of the prostate change this.
- 3) How long does this effect last
- 4) What percentage of patients undergo subsequent surgery.

It is expected that this study will lead to a better understanding of what is the correct/best dose of Botox to use for different prostate sizes, and how does such a dose affect the longevity of the effect. This in turn should be able to allow us to offer Botox to men who are catheterised with confidence that it will be effective and thereby save them a long wait on a public waiting list for surgery while living with a catheter.



Grant #192, Dr Rex Munday

Structural requirements for induction of cancer-protective enzymes by isothiocyanates

Bladder cancer is a major human health problem. In Western countries, it is the fourth commonest cancer in men and the eighth commonest in women. It has been shown that the incidence of bladder cancer is lower in individuals who consume large amounts of Brassica vegetables, such as cabbage, cauliflower, broccoli and Brussels sprouts, and consumption of such vegetables is to be encouraged. Brassica vegetables are not to everyone's taste, however, and a means to obtain the beneficial effects of Brassicas with a relatively small intake of the vegetables would be very valuable.

The protection against bladder cancer afforded by Brassica vegetables is attributable to their ability to form compounds called isothiocyanates when cut or chewed. These substances are powerful inducers of Phase 2 enzymes in the urinary bladder. These enzymes are our most important defence against cancer. They convert cancer-causing chemicals into harmless substances that can easily be eliminated from the body, and thus protect against tumour formation. More than 120 isothiocyanates have been identified in plants, and each species contains a characteristic suite of such substances. The various isothiocyanates differ greatly in their ability to increase tissue levels of the protective enzymes. Ideally, for an acceptable means of protection against bladder cancer in humans, one would select plants that contain those isothiocyanates that are the most potent inducers of the beneficial enzymes in the bladder. With the innumerable plants in the Brassica family, and the large number of isothiocyanates that they may contain, individual assessment is not feasible. What is needed is an understanding of the structural characteristics of isothiocyanates that control their ability to induce the beneficial enzymes.

In previous studies, we have shown that a methyl group adjacent to the isothiocyanate moiety increases inductive activity in the bladder. Furthermore, the way in which substituents are arranged around the isothiocyanate group has a major influence on inductive ability. In the present study, we propose to further investigate the structural requirements for high inductive activity. Identification of such requirements will permit the selection of Brassica vegetables with a high potential for protecting against bladder cancer. Furthermore, such knowledge will help in understanding the mechanism by which these substances interact with tissue signalling systems to increase tissue enzyme activities, and possibly lead to the development of substances with particularly high activity, which would be of great value in cancer chemoprevention.

Completed Reports from Past Grant Recipients 2008 - 2010

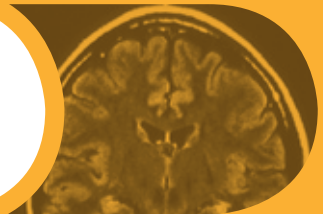
DR LEONG LEOW

// A Study of Vitamin D, Innate Immunity and Severity of Community Acquired Pneumonia and Exacerbations of COPD in Adults



DR G JACOBSON

// Development of Mimetic Peptides for Targeted Modulation of Gap Junctions in the Cerebral Cortex – Potential for Control of Seizures



DR TOM WHEELER

**// Immune Defence Proteins in Human Milk:
Differences Between Preterm and Term Deliveries**





Grant # 137, Dr Leong Leow

A study of Vitamin D, Innate Immunity and Severity of Community Acquired Pneumonia and Exacerbations of COPD in Adults

Background and objective: Vitamin D regulates the production of the antimicrobial peptides cathelicidin and beta-defensin-2, which play an important role in the innate immune response to infection. We hypothesized that vitamin D deficiency would be associated with lower levels of these peptides and worse outcomes in patients admitted to hospital with community acquired pneumonia.

Methods: Associations between mortality and serum levels of 25-hydroxyvitamin D, cathelicidin and beta-defensin-2 were investigated in a prospective cohort of 112 patients admitted with community acquired pneumonia during winter.

Results: Severe 25-hydroxyvitamin D deficiency (<30 nmol/L) was common in this population (15%) and was associated with a higher 30-day mortality compared with patients with sufficient 25-hydroxyvitamin D (>50 nmol/L) (odds ratio 12.7, 95% confidence interval: 2.2–73.3, $P = 0.004$). These associations were not explained by differences in age, comorbidities, or the severity of the acute illness. Neither cathelicidin nor beta-defensin-2 levels predicted mortality, although there was a trend towards increased mortality with lower cathelicidin ($P = 0.053$). Neither cathelicidin nor beta-defensin-2 levels correlated with 25-hydroxyvitamin D.

Conclusions: 25-hydroxyvitamin D deficiency is associated with increased mortality in patients admitted to hospital with community acquired pneumonia during winter. Contrary to our hypothesis, 25-hydroxyvitamin D levels were not associated with levels of cathelicidin or beta-defensin-2.



Grant # 173, Dr G Jacobson

Development of Mimetic Peptides for targeted modulation of gap junctions in the cerebral cortex – potential for control of seizures

Epilepsy is a major cause of disability in New Zealand. Although it is difficult to be sure of the exact numbers, approximately 1% of individuals worldwide have the disease, suggesting that there are around 40,000 people with epilepsy in this country.

Drugs that are currently used to treat epilepsy are often ineffective and have many side-effects. For these reasons, there is a need for better treatment options. One area that is of interest is the role of cell-to-cell pores (called gap junctions), which link brain cells together. These cell pores may make seizures worse or better, depending on the types of cells you are looking at.

In this study we have developed techniques for testing a particular type of chemical called mimetic peptides (small proteins), which are designed to block these pores. We have established that under the right conditions, slices of mouse brain tissue made to show seizure activity can be kept alive for sufficiently long (10-15 hours) to test the effectiveness of mimetic peptides. We have designed a unique range of these chemicals that will allow testing of blockade of pores between different cell types.

Further ongoing experiments will test the effectiveness of these compounds at reducing seizure activity in the mouse brain slices. Compounds that are found to be effective will be further explored for their possible development into new treatments for epilepsy. This study will also help us to better understand the mechanism of how seizures begin.



Grant #182, Dr Tom Wheeler

Immune Defence Proteins in Human Milk : Differences between preterm and term deliveries

Lay summary

Milk has multiple functions. Besides providing a source of nutrients to the newborn, it also contains a number of proteins that contribute to the defence against infections. The levels of these proteins may have a big influence on a baby's health and wellbeing. For many of these proteins, it is not known how their abundance in milk varies in a typical human population, or indeed within an individual over time. Nor is it known whether this abundance is altered when a mother gives birth prematurely. These premature infants are particularly vulnerable to infection and the levels of these proteins in the milk from such mothers may not be the same as for full term gestation, since like the infant, the mammary gland itself follows a co-ordinated development leading to milk production, which is timed to coincide with a normal length gestation.

This project aimed to assess the abundance of five such defence-associated proteins in milk from 30 mothers, 10 from each of three groups – full term deliveries, premature deliveries (32-38 weeks) and very premature (less than 32 weeks). Each volunteer provided milk samples at two different times. The range and variability of the abundance of these proteins was assessed within each study group, between the three groups, and between the two samples from each volunteer.

In total, 29 out of the anticipated 30 volunteers were recruited to provide milk at two time points; 2 weeks and 5 weeks after giving birth. Analysis on them is almost complete, and a preliminary statistical analysis has been done. From the preliminary data to date, it was found that the variability within each group is quite high compared to the major milk proteins, and that this variability is independent of the length of gestation. There is also some variation between the two samples taken at two different times from each mother, but this appears to be less than that between mothers. Further work will solidify these preliminary findings. The final data will be prepared for publication in a science journal.

'premature infants are particularly vulnerable to infection and the levels of these proteins in the milk from such mothers may not be the same as for full term gestation.'

2011 Financial Highlights

Waikato Medical Research Foundation (Inc)

These financial highlights have been extracted from the audited financial statements of the Waikato Medical Research Foundation (Inc). A full copy of the audited financial report for the year ended 31 May 2011 is available from the Foundation's office, Peter Rothwell Academic Centre, Waikato Hospital, or on the website www.wmrf.org.nz

Statement of Financial Position as at 31 May 2011	2011	2010
Accumulated Funds	\$1,329,432	\$1,261,614
<i>Represented by:</i>		
Current Assets		
Westpac	197,952	143,125
ASB	6,954	140,607
Staples Rodway Trust Account	-	13,092
	204,906	296,824
Investments		
Cash and Equivalents	262,145	79,708
NZ Fixed Interest	803,996	886,469
NZ Listed Property	83,067	71,607
Australian Investments	148,913	54,159
American Investments	8,186	8,103
British Investments	1,348	1,527
	1,307,655	1,101,573
Total Assets	1,512,561	1,398,397
Current Liabilities		
Accounts Payable	183,129	136,783
Net Assets	\$1,329,432	\$1,261,614

Statement of Financial Performance for the year ended 31 May 2011

Income	2011	2010
Dividends	10,506	12,797
Donations	13,700	9,560
Grants refunded	47,968	-
Grant - Trust Waikato	65,000	65,000
Interest	76,016	65,930
Unrealised gain on investments	30,891	28,731
	244,081	182,018
Expenditure		
Administration expenses including website	11,838	12,158
Advertising and promotion expenses	4,555	3,069
Audit fee	2,449	4,500
Fees paid to auditor for other services	5,543	5,465
Foreign exchange loss	1,622	729
Grants	139,962	141,846
Loss on realisation of investments	4,886	4,010
Portfolio management fees	5,408	5,293
	176,263	177,070
Net surplus	\$67,818	\$4,948

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