WAIKATO MEDICAL
RESEARCH FOUNDATION

Discovery, Innovation, Progress.

2018 ANNUAL REPORT

ALL TRUTHS ARE EASY TO UNDERSTAND ONCE THEY ARE DISCOVERED; THE POINT IS TO DISCOVER THEM - GALILEO

Board OF TRUSTEES 2017/18

Foundation Chairperson

Dr Margaret (Maggie) Fisher,
Specialist Physician, Waikato Hospital
(Ex Officio Finance and Grants Committee)

Deputy Chairperson

Professor Vic Arcus,
Professor Molecular Biology, University of Waikato

Treasurer

Ms Sharyn Bell,
Director, Staples Rodway Waikato LP

Grants Committee

Chair

Dr Adrian Molenaar,
Senior Scientist, AgResearch Grasslands, Palmerston North

Secretary

Dr Michael Jameson,
Consultant, Medical Oncology,
Regional Cancer Centre, Waikato Hospital

- Professor Vic Arcus,
  Professor Molecular Biology, University of Waikato
- Dr Deborah Harris,
  Neonatal Nurse Practitioner, Waikato Hospital
- Clinical Associate Professor Amanda Oakley,
  Dermatologist, Waikato Hospital

Finance Committee

Chair

Professor Frank Scrimgeour,
Professor of Economics, Management School,
University of Waikato

Ms Sharyn Bell,
Director, Staples Rodway Waikato LP

Mr Ian Jennings,
FIOD FNZIM

Gillian Spry,
Lawyer, Norris Ward McKinnon

Administration

Robyn Fenneman

Chairperson's REPORT

It is with pleasure I present the Annual Report on the activities of the Waikato Medical Research Foundation for 2018.

Our Grants Round was held on the 30th July with six grants approved to a total value of $73,317. A second Grants round is currently underway with outcomes to be announced in November. The second grant round is targeting Waikato researchers in the early stages of their careers.

We remain grateful for the continuing support of our colleagues involved in healthcare, our academic colleagues and our community. In particular, we value the ongoing support of Trust Waikato, Waikato/Bay of Plenty Cancer Society of New Zealand Inc, Pinnacle Health, the Respiratory Research Unit at Waikato Hospital and our DHB colleagues who support the work of the WMRF by payroll deductions.

I would like to thank the Trustees and committee members who give of their expertise and time. After 16 years as a Trustee and 12 years as Chair of the Grants Committee, Dr Adrian Molenaar has stepped down from the Foundation, having moved permanently to Palmerston North with AgResearch. We have appreciated all his efforts in overseeing our core business of funding research and his attention to maintaining standards to ensure high quality research is undertaken. Dr Molenaar was able to attend the most recent Trustee meeting and present his report in person. I repeat our expressions of thanks and high regard for his work. He carries our best wishes with him. We welcome Assoc. Prof. Polly Atatoa-Carr, University of Waikato, as a new member of the Grants Committee.

Our congratulations go to Assoc. Prof. Amanda Oakley, Trustee and member of the Grants Committee on being awarded the Companion of the New Zealand Order of Merit for services to Dermatology.

The Finance Committee, under the Chair of Prof Frank Scrimgeour, continues to grow our capital base. We welcome our new Treasurer, Sharyn Bell, who has made a seamless transition into the role. Trustee, Gillian Spry, has continued her work with the Combined Medical Research Foundations of New Zealand. This year all eight regional Medical Foundations collaborated for the first time to create a national campaign "Medical Research for Life" with a week in May targeting media coverage across all modalities.

We are indebted to our WMRF administrator, Robyn Fenneman, for the day to day running of the Foundation and in particular managing the Grants Round, the administration of the grants and communication with the Grantees.

In April, the Trustees met to develop short and long term strategic objectives for the Foundation. We have articulated our long term objectives; to promote and fund high quality medical and health research, to build research capability in our communities, build the Foundation capital and funds for research and be an effective and well recognised Foundation. From this we are establishing a marketing and communications subcommittee and welcome new Trustee, Kylie Harcourt, Hamilton business woman and company director.

We continue to support research by emergent researchers and to work on engagement with our local communities in order to promote ongoing learning to guide and measure improvement in health outcomes important to those living in the Waikato. I thank everyone for their support for the work of the Waikato Medical Research Foundation.

Dr Margaret Fisher
Foundation Chairperson

Grants CHAIRMAN'S REPORT

This year, the WMRF received 11 applications requesting a total of $201,626. Due to the funding made available by the finance committee with the assistance of the fundraising committee and with welcome sponsorship grants from Trust Waikato and Pinnacle Health, the committee recommended supporting 6 applications, and chose to use the remaining available funding to support a small grant round later in the year, targeting young investigators.

Applicants are encouraged to read the application instructions and guidelines carefully. A disappointingly large number of applicants selected referees that were too closely associated with them and consequently received reduced scores. A number of others were clearly for large capital items which, according to WMRF policy, were not supported as there are other funding sources for capital items.

Successful applications, listed in no particular order in the table below, naming just the lead investigators, are as follows:

Dr Kelly Byrne *Efficacy of Continuous Erector Spinae Block for Post-Operative Analgesia: A Triple Masked Placebo Controlled Feasibility Study*	$18,865
Dr Matthew Phillips *Low-Fat Versus Ketogenic Diet in Alzheimer's Disease: A Pilot Randomized Controlled Trial*	$24,768
Dr Carolyn Aird *Assessing the Value of Teaching Medical Students Emotional Intelligence Skills to Promote Deeper and More Meaningful Personal Reflection: A Pilot Study*	$4,824
Dr Jaimie Veale *By and For, Not On and To : An Analysis of Transgender Health Research Needs*	$15,427
Dr Odette Hart *Determination of Ongoing Physiology Abnormality in Chronic Venous Disease Post Intervention*	$12,000
Dr Marianne Elston *Investigation of Weight Gain and Appetite Following Treatment For Thyrotoxicosis: A Pilot Study*	$3,400

An application was received from Dr Myra Ruka for the Clinical Research Fellowship, to be funded by the Waikato / BOP Cancer Society, for 2018/2019. The committee are delighted to support this application and have passed their recommendations onto the CEO of the Waikato / BOP Cancer Society.

I collectively thank the Grants Committee (Maggie Fisher, Michael Jameson, Amanda Oakley, Vic Arcus and Deborah Harris, and one new member: Polly Atatoa-Carr) and Ian Jennings, representing the Finance Committee, for doing an excellent job in reviewing, discussing and scoring the applications.

A special thank you goes to the WMRF administrator, Robyn Fenneman, for gathering, organising and meticulously presenting the applications to the committee and responding to applicants.

This is my last report as due to a WMRF policy change, all Board and Committee Members are required to be residents of the Waikato. It has been an honour and a pleasure to serve as a Board and Grant Committee Member since 2003 and Grants Chair from 2007 to the present.

Dr Adrian Molenaar
Chair, Grants Committee
(2007 – 6 August 2018)

Summary OF FUNDED PROJECTS
2018 GRANT ROUND ABSTRACTS

GRANT #292 // CAROLYN AIRD, CLINICAL RESEARCH AND TEACHING FELLOW, UNIVERSITY OF AUCKLAND / WAIKATO CLINICAL CAMPUS, WAIKATO HOSPITAL

Assessing the value of teaching medical students emotional intelligence skills to promote deeper and more meaningful personal reflection: A pilot study

Background: Reflection is a deliberate process used to enable a greater understanding of one's self and/or a situation which informs future actions.1,2 Within medicine, reflection has been shown to encourage effective, lifelong learning and diagnostic accuracy in decision making, and has also been shown to increase empathy.3,4 The role of reflection in medical education and medical practice is increasing, as both a means of promoting effective learning and as part of ongoing licensing and revalidation.

Balanced reflective practice requires students and doctors to recognise the role of emotional experience within their work. To perform this effectively and safely, doctors need to be equipped with basic emotional intelligence (EI) skills. EI can be defined as an individual's ability to recognise emotions in themselves and others, and use this understanding to modify their thinking and behavior.

The University of Auckland has introduced a whole domain of learning across their programme called the "Personal and Professional Skills" (PPS) domain and one of the themes of the domain includes reflective practice.5. There is, however, a paucity of evidence in the literature regarding appropriate methods to teach the skills needed to enable doctors and medical students to perform personal reflection.

Aim: To develop and assess the utility, feasibility and acceptability of an intervention to increase the personal reflection skills of medical students undertaking their 5th year Paediatric attachment.

Design: Prospective pilot cohort study.

Methods: From the start of the 2019 academic year, 5th year medical students from the University of Auckland undertaking their paediatric attachment at Waikato Hospital will either be assigned to participate in a programme specifically designed to teach EI and reflective practice skills alongside the usual Paediatric teaching programme (the intervention group), or to undertake the usual Paediatric teaching programme only (the non-intervention group). Six groups of 4-5 students will take part, with intervention groups alternating with non-intervention groups over the course of the year. The study intervention has been designed, and will be delivered by clinical psychologists who are members of our research team. The personal reflective ability of all students will be measured using standardised tools at baseline, and over the course of the students' Paediatric attachment, with comparisons made within and between groups in order to evaluate the effect of the intervention. Students in the intervention group will also complete a survey to assess their enjoyment of, and perceived benefit from the intervention.

Expected benefits: This pilot study will provide the opportunity to assess the feasibility of undertaking the proposed intervention with 5th year medical students during the course of their clinical Paediatric attachment, and whether the intervention helps students to develop and refine their personal reflection skills. The findings of this pilot study have the potential to influence the teaching curriculum for University of Auckland medical students, improving the ability of future graduates to engage in effective, life-long learning, and thus deliver better patient care.

GRANT # 294 // KELLY BYRNE, CONSULTANT ANAESTHETIST, WAIKATO HOSPITAL

Efficacy of continuous erector spinae block for post-operative analgesia: A triple masked placebo controlled feasibility study

This study aims to test a new regional anaesthetic technique for pain control following surgery. This technique has been described in case reports and case series in the literature but a robust, placebo controlled trial has not previously been carried out.

The erector spinae block(ESB) is a regional anaesthetic technique that aims to provide pain relief to the anterior chest wall. It is less invasive and more easily undertaken than an epidural or paravertebral block which are at the moment the alternative pain relief techniques for these types of surgeries.

The ESB is undertaken by placing a needle under the strap muscles of the back and injecting local anaesthetic. In this potential space, the nerves that supply the chest wall run, on their way from the spinal cord to the chest wall. The needle placement for this block is further from the spinal cord and lung, than an epidural or paravertebral block. Therefore is easier and safer to perform.

This study will take people having surgery to the chest wall or lung (primarily mastectomy or lung resection surgery) and test whether the ESB works as pain relief for these types of surgery. All patients will have a peripheral nerve catheter placed under the erector spinae muscles, and half will receive local anaesthetic and half will receive a placebo(normal saline). They will then receive a general anaesthetic and routine cares for their surgery and hospital stay. In addition to the initial block, they will receive an infusion of either local anaesthetic or placebo for the 48 hours following surgery.

The primary outcome measures for this study are pain scores at 24 and 48 hours following surgery. Secondary outcomes include patient centred outcomes such as quality of recovery and patient satisfaction, pain medication usage for the first 48 hours following surgery, and assessment of the degree of numbness in the area that the ESB should be working.

The expected benefits of this study are providing evidence as to whether this new regional anaesthesia technique works for providing pain relief, and whether provision of this regional anaesthetic technique improves the quality of recovery for the patient. This is an important study for us to do, as it will provide information about whether this easier and safer regional anaesthetic technique provides the expected benefits, or whether the added expense and inconvenience to the patient of placing this block does not improve the pain relief or quality of recovery following surgery.

GRANT #296 // MARIANNE ELSTON, CONSULTANT ENDOCRINOLOGIST, WAIKATO HOSPITAL

Investigation of weight gain and appetite following treatment for thyrotoxicosis: A pilot study

Thyrotoxicosis (overactive thyroid) is a common endocrine disorder. Weight loss is common in untreated thyrotoxicosis, despite an increase in appetite, in addition to symptoms of an increased metabolic rate such as heat intolerance, sweating, palpitations and tremor. With restoration of normal thyroid levels, most patients not only regain the weight they had previously lost, but appear to continue to gain additional weight over the subsequent several months. This has significant implications for adherence with medical therapy, particularly if the person perceives the extra weight gain to be a result of treatment. Whilst there have been some preliminary studies investigating the controls of appetite and body weight in thyrotoxicosis, the mechanism for weight gain following restoration of a normal thyroid state remains poorly understood.

In a pilot study we have investigated changes in body weight along with measurements of appetite and food intake in a group of thyrotoxic patients at baseline, then 6 weeks, 6 and 12 months following treatment, and compared this to a control group of euthyroid patients. Funding for measurement of ghrelin, a hormone affecting appetite, has the potential to add valuable information to this study.

The results will be used to develop a larger prospective trial in this area to help minimise weight regain in patients during treatment of thyrotoxicosis and further projects to improve our understanding of the mechanisms of thyroid related regulation of appetite and satiety.

GRANT #301 // JAIMIE VEALE, SENIOR LECTURER, SCHOOL OF PSYCHOLOGY, UNIVERSITY OF WAIKATO

By and For, not On and To: An Analysis of Transgender Health Research Needs

Transgender people are one of society's most disadvantaged groups, with serious health inequities especially in the areas of mental health and sexual health. Traditionally, research has been conducted on the transgender community rather than with the transgender community, meaning that transgender people have had little input into research topics nor the interpretation of the results. As a result, transgender-specific health issues are in serious need of research to address the health inequities faced by transgender people. These issues include barriers to healthcare access, challenges with accessing bathrooms and other gender-segregated spaces, inability to be able to access appropriate legal documentation, informed access to and gender-affirming hormones and surgeries, fertility and pregnancy experiences, sexuality, and chest binding.

The goal of this project is to conduct a systematic investigation into the specific gaps that exist in transgender health research as a result of the research being led largely by non-transgender people. Feedback will be sought from an online community forum and through interviews of key transgender health advocates and researchers. These findings will undergo thematic analysis and result in a publication and the development of a longitudinal survey to use in a future phase of the project.

This project will be the first step in a larger project to follow a large cohort of transgender people over many years. The key benefit of the project is that it will ultimately enable the gathering of information vital for transgender people to make informed decisions about crucial components of their health and wellbeing. It will also provide the foundations for developing policies and initiatives to support transgender people, community organisations, and healthcare providers, and to overcome the serious health inequities and barriers that we face.

GRANT #297 // ODETTE HART, VASCULAR REGISTRAR, WAIKATO HOSPITAL

Determination of ongoing physiology abnormality in chronic venous disease post intervention

Chronic venous disease (CVD) is a common condition affecting a significant number of patients presenting to vascular clinics. Large scale research has found that in the general population the prevalence CVD was 9.4% in men and 6.6% in women. Varicose veins (mild to severe) occur in around 40% of men and 30% of women. In addition ankle swelling occurs in 7% of men and 16% of women in the general population. Thus the treatment of CVD accounts for a significant economic impact on resources. Notably, in countries with developed health care systems, CVD incurs costs attributable to 1-3% of the total health care budget, or $3 billion annually in the United States. Over recent decades, there has been significant improvement in the diagnosis, evaluation and treatment of CVD attributable to increased research focus and the development of new technologies. However, there remains no established algorithm to predict which patients with early disease will eventually develop skin changes or ulceration. In addition, there is a lack of evidence comparing the development of skin changes or ulcers in patients with superficial venous insufficiency, deep venous insufficiency, or a combination of both superficial and deep insufficiency.

This pilot study aims to determine the severity and type (superficial/deep/mixed) of CVD in patients presenting to vascular clinic. Also to determine a correlation between the severity of CVD and tissue oxygenation in the lower leg; and measure the change in tissue oxygenation in the lower leg before and after treatment (improved, un-changed, deteriorated)..

This pilot study is a prospective study, where participants which meet inclusion and exclusion criteria will undergo initial examination with clinical examination, duplex ultrasound and air plethysmography to determine the severity and type of CVD. In addition, HyperView measurement will be used to determine tissue oxygenation at initial consultation. Participants will be separated in three categories being compression therapy, open surgical management or endovenous management based on their severity and type of CVD (as per clinical examination, ultrasound and air plethysmography). Participants will be followed up at 28 days and 3 months with repeat clinical examination, air plethysmography and HyperView measurement to determine physiological changes in disease states.

There is major potential for the reduction in patient suffering and a reduction in the economic burden from prevention of skin changes and ulceration in CVD. This prospective pilot study will provide new knowledge on tissue oxygenation in the lower limbs of patients suffering from CVD prior to and after venous disease treatment. This will be used in further research to establish an algorithm to predict which patients with early disease will eventually develop skin changes or ulceration. It will also allow better matching of patient presentation, pathology and treatment.

GRANT #300 // MATTHEW PHILLIPS, CONSULTANT NEUROLOGIST, WAIKATO HOSPITAL

Low-Fat Versus Ketogenic Diet In Alzheimer's Disease: A Pilot Randomized Controlled Trial

Alzheimer's disease (AD) is a common, age-associated, progressive neurodegenerative condition that affects 6% of the population aged over 65 years. AD is typically characterized by impaired cognition and function, resulting in significantly impaired quality of life for patients and family members. Current treatments consist of a handful of minimally effective medications; new treatments that will prevent, delay, or treat the symptoms of AD are urgently needed.

Brain energy metabolism is impaired in AD. Specifically, it is characterized by a pathological, region-specific decrease in the brain's ability to use glucose, with cerebral glucose metabolism reduced by 20 to 40% in large regions of brain, particularly the temporal, parietal, prefrontal, and posterior cingulate regions. Moreover, impaired glucose metabolism occurs in pre-symptomatic, at-risk young adults (such as APO-E4 carriers), years before AD-associated neuron loss occurs.

Although brain glucose utilization is impaired in AD, ketone utilization is not. Ketones are a fat-derived alternative fuel source, produced by the liver, that are readily usable by brain tissue when glucose is in short supply. In AD, those same regions that exhibit reduced glucose metabolism maintain a normal ability to uptake and utilize ketones, implying that a high-fat, low-carbohydrate "ketogenic" diet might improve brain energy metabolism and alleviate AD symptoms.

To date, four preliminary studies have examined the effects of ketosis in patients with mild cognitive impairment (MCI) or AD. While all four studies reported positive findings, they were of limited design and extrapolation. Two studies did not examine the effects of a true ketogenic diet, only a ketone supplement, and it is likely that an all-encompassing diet approach would confer additional beneficial effects (for example, by additionally stimulating neuron mitochondrial biogenesis) beyond ketosis alone. One study only involved small numbers of patients with MCI, and another study was a single-arm design, with no control group, thus a placebo effect may have interfered with the results. Furthermore, all four studies were hampered by (1) their emphasis on cognitive outcomes, rather than also emphasizing function and quality of life outcomes which are increasingly recognized as essential in AD, and (2) very modest levels of sustained ketosis, raising a question as to whether the level of ketosis was "high enough" to achieve maximal benefit.

Given this background, our objective is to perform a pilot randomized trial on a population of 60 to 80 AD patients to examine the plausibility and safety of maintaining a low-fat versus a ketogenic diet for 12 weeks, whether either diet group significantly improves in cognition, function, and quality of life, and whether one group shows greater improvements compared to the other.

We believe that the interaction, education, and possible therapeutic effects conferred by this study will significantly benefit the participating patients and family members. On a greater level, if this randomized trial shows that a patient-empowering dietary approach can significantly improve AD, it may open up a desperately needed additional therapeutic avenue for patients everywhere suffering from this devastating condition.

Past GRANT RECIPIENTS FINAL REPORTS AND FINDINGS

GRANT # 278 // MARIZA GOMES REIS
FOOD AND BIO-BASED PRODUCTS GROUP, AGRESEARCH LTD

Does bacterial transformation of milk lipids occur in the infant bowel?

Fats are important components of infant nutrition, supplying 50 to 55% energy and helping the growth and development of the infant. Human milk and infant formula contain, saturated, monounsaturated and polyunsaturated fats that are important for regulating growth, inflammatory responses, immune function, vision, cognitive development and motor development systems in newborns. Human milk contains a wide variety of lipid components, present as milk fat globules (MFG) with a core containing triglycerides (more than 98% of total lipids), surrounded by a MFG membrane (MFGM) with phospholipids, and esterified cholesterol and glycosylated lipids. Lipid composition of breast milk varies according to lactation stage, during the day and is strongly influenced by the mother's diet. In most infant formulas currently marketed, fat source used is a blend of vegetable oils, with a simpler composition than the lipid composition of breast milk, although the major fatty acids are similar in human milk and infant formula.

Recent studies have shown that bowel bacteria can metabolize polyunsaturated fatty acids, specifically linoleic acid, to generate several metabolites such as conjugated linoleic acid (CLA), hydroxyl fatty acids and oxo fatty acids that may affect host heath (Kishino et al 2013, Bergamo et al, 2014, Miamoto et al, 2015, Kaikiri, et al, 2017).

Microbial colonisation of infant intestine is an intricate process which is influenced by many factors, including child's nutrition (breast milk or infant formula). Within the first year of life, the enteric microbiota is highly dynamic, and after the initial year, the microbial population stabilizes and resembles that of the adult. Different environmental factors during this critical period may influence the gut microbial composition, potentially impacting upon later life such as allergies and metabolic disorders (Chong et al, 2018, Koenig et al, 2011).

We observed that particular bacterial species isolated from infant faeces chemically transform linoleic acid (LA) and docohexadecanoic acid (DHA) under controlled laboratory conditions. However, in real life the polyunsaturated fatty acids (FA) in milk may not reach the large bowel in significant amounts, or the bacterial species may be inactive with respect to fatty acid metabolism due to habitat restrictions. Confirmation of FA metabolites in infant faeces would support further studies to better understand the importance of dietary milk fats in infant nutrition and its relationship with bowel microbiota, leading to development of improved formulations for infant nutrition. Therefore, the aim of this study was to determine if the microbiota in the infant bowel has the capability to metabolize polyunsaturated FAs. We collected faecal samples from breast milk fed infants, formula-fed infants and mixed breast milk and formula fed infants and measured the levels of specific polyunsaturated FA metabolites in these faecal samples. Samples were collected from 44 babies across the three feeding regimes. To provide a measure of temporal consistency of variability within an individual, two samples were collected from 29 babies approximately 2-4 days apart, distributed across the three different groups. A total of 78 faecal samples were collected and analysed.

The mainfindings were:

1. This study shows for the first time that microbial transformation of milk polyunsaturated fatty acids occurs in the infant bowel (Figure 1).
2. Variability in the faecal concentration of the metabolites was observed among individuals in the same group and also at different collection times for the same infant (Figure 2).
3. Milk diet does not appear to affect the faecal concentration of individual polyunsaturated fatty acids metabolites.
4. The presence of both CLA isomers was observed in all samples.
5. HYA was found in most of the samples. For samples collected from the same infant at two time points, HYA was not detected in one sample from the breast milk fed group, seven samples from the infant formula fed group and one sample from the mixed fed group.
6. OxoA was detected in samples but at levels below quantification limit.

Figure 1. Faecal concentration of c9,t11-CLA (A), t9,t11-CLA (B) and HYA (C), according to the feeding status at fecal sample collection (BF – breast milk fed; IF – Infant formula fed; M – combination of breast milk fed and infant formula fed). Statistical significant differences were not observed among concentration of metabolites and feeding regime based on ANOVA and Tukey's honest significance test at 5% level of significance.

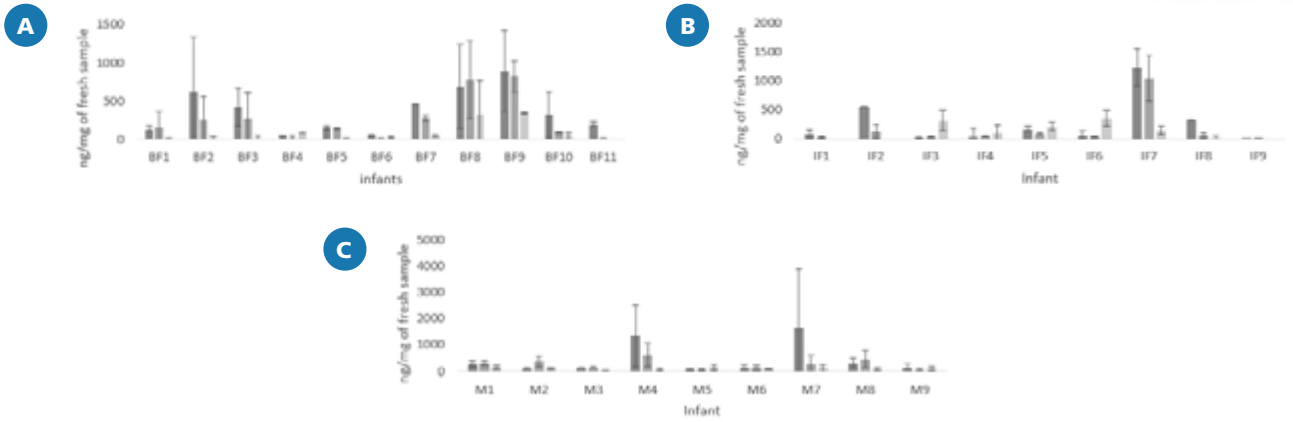
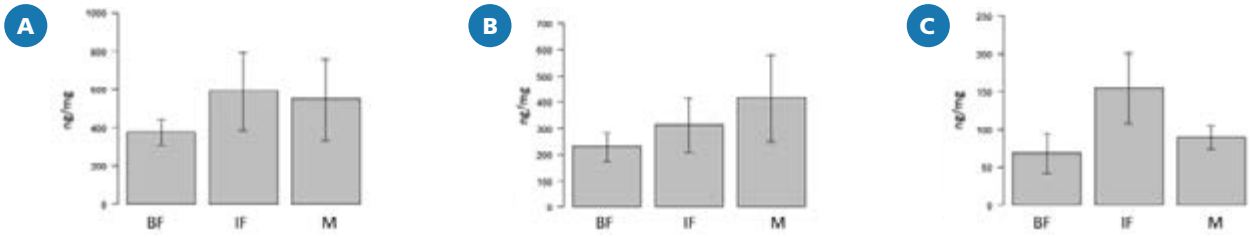


Figure 2. Concentration of c9,t11-CLA, t10,c12-CLA and HYA (10-hydroxy-C18:1) of 29 infants, according to the feeding status at fecal sample collection (A – breastfed; B – Infant formula fed; C – combination of breastfed and infant formula fed). The bars represent the standard deviation of the two samples of the same infant collected 1 to 4 days apart for the different infants



Recommendations: Variability in the faecal concentration of these metabolites is worth further investigation as it might be linked to absorption rates among individuals and heath attributes.

In future studies we would recommend additional information is obtained, such as: composition of the mother diet and infant formula, as well health characteristics of the babies and mothers, including allergies information.

References:

Bergamo, P., Luongo, D., Miyamoto, J., Cocca, E., et al. (2014). J. Funct. Foods. 11:192.
Chong, C.Y.L, Bloomfield, F.H., O'Sullivan, J.M. (2018). Nutrients, 10:274.
Kaikiri, H., Miyamoto, J., Kawakami, T., et al. (2017). Int. J. Food Sci. Nutr. 68:941.
Kishino, S., Takeuchi, S.B., Park, S.B., et al. (2013). Proc. Natl. Acad. Sci. USA. 110:17808.
Koenig, J.E., Spor, A., Scalfone, N., et al. (2011). Proc. Natl. Acad. Sci. USA. 108:4578.
Miyamoto, J., Mizukure, T., Park, S.B., Kishino, S., et al. (2015). J. Biol. Chem. 290:2902

GRANT #258 // DR JOANNA HICKS
RESEARCH ASSOCIATE, PROTEINS AND MICROBES LAB/FACULTY OF SCIENCE AND ENGINEERING, UNIVERSITY OF WAIKATO

The Role of the FitAB Toxin-Antitoxin System in the Maintenance of the Carrier Population of Neisseria gonorrhoeae

Summary: The FitAB toxin-antitoxin system belongs to the VapBC TA family. Members of the VapBC family are hypothesised to play role in the persistence of Mycobacterium tuberculosis and other bacterial pathogens. The antitoxin (VapB) consists of a DNA binding domain that binds to its own promoter to regulate expression and binds to VapC inhibiting its activity. VapC, belongs to the PIN-domain family of proteins, which cause growth arrest by virtue of their ribonuclease activity.

The aim of this research project was to characterise the role of the FitAB toxin-antitoxin system (that belongs to the VapBC family) in intracellular replication and cellular trafficking of the gonococcus (GC) Neisseria gonorrhoeae. Trafficking and intracellular replication are incredibly important for establishment of infection and intracellular replication is hypothesised to play a role in the maintenance of an asymptomatic carrier population.

Results: We have characterised the biochemical activity of the FitB protein, and have determined it cuts RNA in a magnesium-dependent, sequence-specific manner. The length of RNA FitB cuts is different to previously characterised VapC enzymes, leading to development of a new method to determine sequence specificity. Using intracellular replication assays with epithelial cells and fitAB gene deletion strains we see a marked difference between wild-type and gene deletion strains, which confirms the FitAB TA system plays a role in intracellular replication. We show that 24 hours post invasion of epithelial cells the wild-type strains are continuing to replicate whereas replication of gene deletion strains drastically decreases. We have taken RNA samples from various time points during this experiment and are awaiting the transcriptomes for these from the Beijing Genomics Institute (BGI). We hypothesise that metabolism is affected or 'uncoupled' in the gene deletion strain compared to the wild-type leading to faster intracellular replication. In support of this hypothesis during extracellular growth we see a marked difference in the pH of the culture of the wild-type strain compared to the gene deletion strain with the gene deletion strain resulting in a much more acidic culture pH, suggestive of a mis-regulation or 'uncoupling' of metabolism leading to acidic intermediates accumulating.

Conclusions: We have determined that the FitAB toxin-antitoxin system plays an important role in intracellular replication of N. gonorrhoeae. We have optimised our RNA extraction protocol from intracellular replication assays and are awaiting our transcriptome data for eight and 10-hour time points. We also show that FitB has sequence-specific ribonuclease activity that is magnesium- dependent, and have developed a new method to identify its sequence specificity. We are in the process of determining the exact sequence it targets. Upon analysis and confirmation of our transcriptome data, we will submit the results of this study to a peer-reviewed journal. Reconciliation of transcriptomic data with the sequence-specificity of FitB will determine the role of FitAB in intracellular replication, and in doing so provide hints as to the mechanism of persistence of N. gonorrhoeae. A detailed understanding of persistence and the asymptomatic carrier state of N. gonorrhoeae will provide vital information for the treatment of this disease in the future.

GRANT 230 // MR GRANT CHRISTEY
CLINICAL DIRECTOR OF TRAUMA SERVICES, WAIKATO HOSPITAL

Rural, Semirural, and Urban Trauma in the Midland Region of New Zealand

Aim: The aim of the study is to determine the detailed nature and volume of injury associated with urban, semirural, and rural communities in the Midland Region of New Zealand.

Methods: A retrospective review of anonymised, prospectively-collected MTS registry data for the period 1 January 2012 to 31 December 2017 was conducted. Inclusion criteria for the study were: patients admitted to a Midland base hospital as a result of, and within 7 days of injury occurring within the Midland region excluding Tairawhiti DHB which was a more recent addition to the registry. Consistent with trauma registries internationally, patients were excluded if they sustained insufficiency or periprosthetic fractures, exertional injuries, hanging/ drowning/asphyxiation without evidence of external force, poisoning, ingested foreign body, injury as a direct result of pre-existing medical conditions or late effects of injury, or the injury occurred more than 7 days prior to admission. Variables examined included: patient demographic characteristics, injury event information, in-hospital management, type and severity of injuries, length of stay and discharge destination. These variables have been analysed in relation to patient domicile according to three principle rurality groups: urban, semirural, and rural, to identify similarities and variations between the groups.

Results: The study has shown significant variations in the patterns and incidence of trauma between the three domicile rurality groups:

1. Males aged 15-34 years living in rural and semirural areas are at extreme risk of injury. Compared to females of the same age, urban males are at 3 times higher risk of hospitalisation due to trauma, while males residing in rural and semirural areas are at almost 4 times higher risk. (Fig.1)

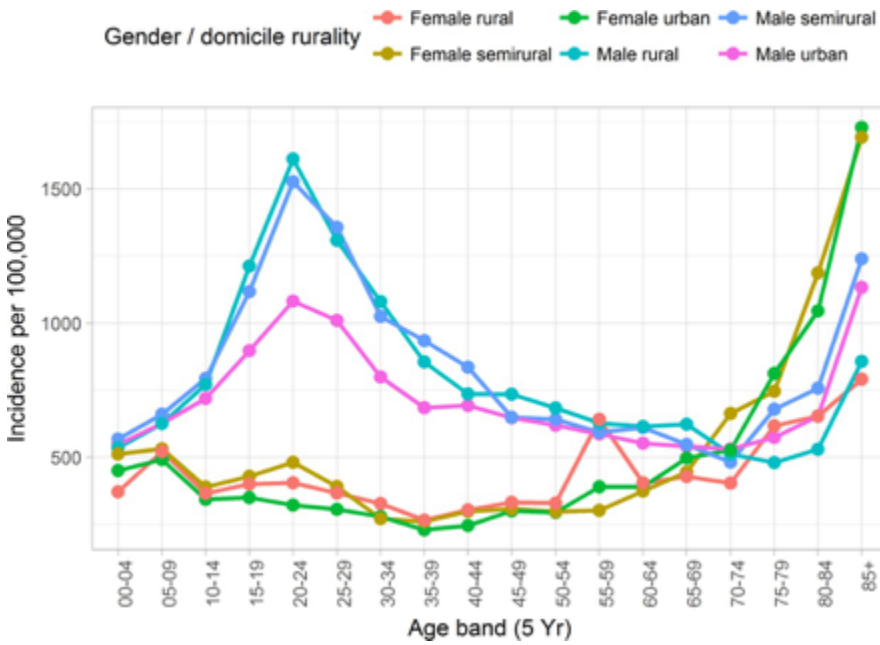


Figure 1. Annualised incidence of trauma per 100,000 population/Yr in Midland Region domiciled patients, 2012-2017, by age, gender, and rurality of patient domicile.

2. Road traffic and motorcycle crashes are common causes of injury among young males (15- 34 years) living rurally. Machinery and quad bike related injuries are also more common among this group. Injuries among those living in urban areas are dominated by falls, particularly among older adults aged 70 years and over.

3. Semirural populations exhibit a complex combination of both rural and urban trauma. They include both the same peak in trauma seen among young rural males 15-34 years and same the high incidence of trauma seen among urban dwelling older females.

4. Maori residing in each of the rurality groups are at approximately 50% greater risk of hospitalisation due to trauma than non-Maori. Assault, struck (unintentional), and road traffic crash injuries are common causes of injury in each of the domicile rurality groups. (Table.1)

Domicile rurality / Ethnicity	Incidence per 100,000/Yr.	RR (CI)	P
Urban Non-Maori	506	Reference	
Semirural Non-Maori	545	1.08 (0.95-1.22)	ns
Rural Non-Maori	537	1.06 (0.94-1.19)	ns
Urban Maori	797	1.57 (1.41-1.76)	0.001
Semirural Maori	785	1.55 (1.39-1.74)	0.001
Rural Maori	774	1.53 (1.37-1.71)	0.001

Table 1. Maori and Non- Maori/domicile-rurality gradients in ethnicity adjusted incidence of trauma among Midland Region resident patients (Excluding Tairawhiti DHB), 2012-2017, and relative risk (RR) derived from Poisson regression.

5. Across the Midland region, rural dwelling patients had almost three times higher rates of transfer from first arrival facility onwards to a second acute care facility. However, subsequent transfers to a third or more facility were significantly lower among rural resident patients than for urban resident patients. This may be a positive sign that most decisions surrounding first inter-hospital transfers for rural patients are appropriate.

6. Outcomes were similar between the three rurality groups. The demographic differences identified in this study may help to explain this. For example, the slightly longer average length of stay (LOS), and marginally higher case fatality rates, observed among urban residents may be linked to the high incidence of trauma among older persons (70+ Years), especially older females living in urban and semirural areas. Longer LOS and higher case fatality rates have previously been observed among older persons, even for those with non-major injuries. Further study will be required to examine this in greater detail.

Conclusions: Within the Midland region there are differences in rates of trauma according to the rurality of where patients live. These disparities are strongest among young males who live rurally, and among older persons who live in urban and semirural areas, as well as overall higher rates among Maori versus non- Maori. Distinct causes and circumstances of injury underlie each of these at-risk groups. Semirural populations reveal an interesting pattern of injury incidence. They appear to align with urban or rural risk profiles dependent on age and cause that may reflect an urban migration of older persons from rural to urban settings. Conversely, risk profiles in 15-35 year olds appear to be similar. Rates for Maori are high across all rurality groups and appear to be less influenced by rurality than previously thought: this requires further analysis. We have shown that it is inadequate to rely on rurality to explain the variability in risk profiles and outcomes, but that there are complex interplays between social, ethnic and age groups, and their related activities that are influencing incidence rates. It is clear that deeper knowledge concerning population groups at risk that have been identified is required in order to accurately direct care planning and design of prevention campaigns into these communities.

GRANT #242 // DR STEPHEN EVANS, CANCER CLINICAL TRIALS, ONCOLOGY DEPARTMENT, WAIKATO HOSPITAL

Title Phase 1b pharmacokinetic (PK) and pharmacodynamic (PD) trial to identify the optimal selenium (Se) compound for use with cancer therapies

Human studies of Selenium supplementation during cancer therapy have reported significant reduction in toxicity with number of commonly used cytotoxic drugs. Dr Evans and co-workers ongoing research into establishing the optimal form and dose of selenium for use in this patient group is summarised in this recent publication.

Publication: Comparative Safety and Pharmacokinetic Evaluation of Three Oral Selenium Compounds in Cancer Patients

Stephen O. Evans, et al. Biological Trace Element Research

See Link: https://doi.org/10.1007/s12011-018-1501-0

GRANT #273 // DR MIINA KARALUS, POPULATION HEALTH, WAIKATO HOSPITAL

Virtual health care trial to prevent recurrent Rheumatic Heart Disease amongst Waikato young people with Rheumatic Fever

The primary objective of this study was to determine whether an incentive programme, consisting of a mobile phone and monthly "top-up" (for data/calls), would increase secondary prophylaxis injections over a one-year period compared to a baseline period prior to the intervention. Results showed this strategy appears to have a strong impact for partially adherent patients, particularly during the early periods following the initiation of the intervention. Enhancing communication with patients who returned to care may result in more sustainable adherence.

Publication: Efficacy of an incentive intervention on secondary prophylaxis for young people with rheumatic fever: a multiple baseline study. *John G. Oetzel1* , Chunhuan Lao1, Michelle Morley2, Kathy Penman3, Maree Child3, Nina Scott3 and Miina Karalus3*

Oetzel et al. BMC Public Health (2019) 19:385

See Link: https://doi.org/10.1186/s12889-019-6695-3

GRANT #281 // DR TIMOTHY EDWARDS SENIOR LECTURER, SCHOOL OF PSYCHOLOGY, FACULTY OF ARTS & SOCIAL SCIENCES, UNIVERSITY OF WAIKATO

Using Dogs for Lung Cancer Screening

Progress Report: After receiving funding for this research project from the WMRF, we received significant support for the project from the HRC and the University of Waikato. The support that we received from the WMRF helped to get this project started and made this additional funding possible. The HRC funding will enable us to go beyond the training phase into blind testing phases and will also allow us to simultaneously conduct chemical analyses of the samples and work toward development or improvement of existing machine-based technology for lung cancer diagnosis.

We have successfully recruited nearly 300 patients for this study from the Waikato DHB. Each patient has provided both breath and saliva samples, which will allow us to evaluate the accuracy of the dogs with both sample types. We are also working to establish partnerships with additional clinics in New Zealand where we can recruit patients. This would allow us to increase our recruitment rate and also help to test the feasibility of a central screening system involving bio-detectors, such as dogs, or machine-based alternatives.

Seven dogs have been recruited and trained to operate the automated apparatus that we use for scent-detection research. The dogs are currently in the process of transitioning to the medical samples, as they were initially trained using a standard chemical. We anticipate that we will be able to complete the training phase of the project over the next several months, at which point we can transition into the all-important blind testing phase.

See Link: https://theconversation.com/dogs-sensitive-noses-may-be-the-key-to-early-detection-of-lung-cancer-99575

Financial Statements
FOR THE YEAR ENDED 31 MAY 2018

STATEMENT OF FINANCIAL POSITION

As at 31 May 2018	2018	2017
	$	$
Current Assets		
Cash & Bank Balances	483,546	1,464,881
Prepayments	6,708	6,708
Term Deposits	1,708,776	777,292
Total Current Assets	2,199,030	2,248,881
Non-Current Assets		
Term Investments	1,170,347	884,155
Total Assets	3,369,377	3,133,036
Current Liabilities		
Accounts Payable	25,358	3,669
Related Party Payables	-	385
Total Liabilities	25,358	4,054
Net Assets	3,344,019	3,128,982
Accumulated Funds		
Capital	3,344,019	3,128,982
Total Accumulated Funds	3,344,019	3,128,982

STATEMENT OF FINANCIAL PERFORMANCE

As at 31 May 2018	Actual 2018	Actual 2017
	$	$
Revenue		
Donations, fund raising and other similar revenue	266,150	226,119
Interest, dividends and other investment revenue	141,131	106,370
Total Revenue	407,281	332,489
Less Expenses		
Grants and donations	144,155	202,780
Other expenses	48,090	53,264
Total Expenses	192,244	256,044
Surplus	215,037	76,446

Financial Statements prepared by Staples Rodway Chartered Accountants, Hamilton
Financial Statements audited by Campbell & Campbell Accounting Associates Ltd, Hamilton

WAIKATO MEDICAL RESEARCH FOUNDATION
Best Paper Award

The Waikato Clinical Campus and Waikato Medical Research Foundation have invited PhD and MD candidates to submit their publications for consideration for this award.

Papers are judged by senior academics from across the Faculty of Medical and Health Sciences and the Waikato Medical Research Foundation.

2017 Award was presented to Stephen Evans

Development of a qPCR Method to Measure Mitochondrial and Genomic DNA Damage with Application to Chemotherapy Induced DNA Damage and Cryopreserved Cells

2016 Award was presented to Zuzana Obertova

Survival disparities between Maori and non-Maori men with prostate cancer in New Zealand.

2015 Award was presented to Darren Hight

Emergence from general anaesthesia and the sleep-manifold. Frontiers in Systems Neuroscience.

2014 Award was presented to Deborah Harris

Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial

Thank you TO OUR DONORS

The Trustees of the Foundation wish to thank all who have generously donated since our inception in 1986. From 1986 to 2018, the Foundation has supported researchers in the following institutions:

Waikato District Health Board	$1,340,366.76
University Of Waikato	$755,827.90
Faculty Of Medical Health Sciences, University Of Auckland –	
Waikato Clinical Campus	$371,133.00
AgResearch	$624,788.00
WINTEC	$64,184.00
Private Researchers	$207,019.00
Total Research Supported Since 1986	$3,363,428.66

A detailed listing of donors is available via our website: **www.wmrf.org.nz**

Donation FORM

This form can be downloaded from our website: **www.wmrf.org.nz**

I wish to make a donation to the Waikato Medical Research Foundation

Please tick one :

O $50 O $100 O $200

O $500 O $1000 O $2000 Other (Amount $_____)

O I enclose a cheque made out to: Waikato Medical Research Foundation

O I have made a direct payment to WMRF Bank Account: Westpac 030 306 0208170 01
(Please include your name as reference for the payment)

O Please send me a receipt

As we are registered with the Charities Commission (Charities Commission No: CC20443), all donations to Waikato Medical Research Foundation over $5.00 are tax deductible.
Please complete your details and post / fax for a receipt.

Name of donor: _____

Address: _____

Daytime telephone: _____

For future contact, we would like to email interested parties, and if you wish to receive information from us, please complete below:

Email address: _____

WAIKATO MEDICAL RESEARCH FOUNDATION
Discovery, Innovation, Progress.

Post to: Private Bag 3200, Waikato Mail Centre Hamilton 3240
Phone: (07) 839 8750 **Fax:** (07) 839 8712
Email: wmrf@waikatodhb.health.nz
Web: www.wmrf.org.nz

History
OF WAIKATO MEDICAL RESEARCH FOUNDATION

In 1986 the Waikato Medical Research Foundation (Inc) was established and incorporated to promote, encourage and sustain medical research in the Waikato Region. At the time, Professor Michael Selby explains:

The aim was to undertake research that would be of benefit to the Waikato. Obviously we were hoping that the research would have wider applications than the Waikato. Inevitably, if you make any advances, the very nature of scientific work is that it gets published, and therefore you hope that the benefit will be widespread and therefore the people of the Waikato would benefit along with everybody else – that was the aim. So, we did put emphasis on publication, and therefore, of course quality – so that was part of the initial requirement.

The Waikato Medical Research Foundation has been established to enable ethical medical research to take place within the region. Medical Research will benefit everybody, and it warrants the support of all citizens.

In forming the Foundation, and going to the general public in the early years of fundraising, it stressed the importance that this is a local body. When initially formed, The foundation stressed to members of the general community in Hamilton and outlying areas that there were medical or health problems specific to the Waikato area, and that it was important to have a locally administered fund – and now 25 years on, the purposes of this Foundation are still as it was when initially formed.

The Trust was founded in 1986 with a capital pool of $1m.

Board of Trustees (1996)

Standing (left to right) Denis Jury, Andrea Donnison, Don Llewellyn, Ross McRobie. Sitting (left to right) Ken Mackay, John Gillies, Michael Selby, Brian Smith, James Grace

THOSE WHO SIGNED THE TRUST DEED IN 1986 WERE:

Charles Beresford, Physician, Waikato Hospital,

John Gillies, Paediatrician, Waikato Hospital,

Jack Havill, Anaesthetist, Waikato Hospital,

Jim Grace, Solicitor,

Dryden Spring, a company director,

Michael Selby, Professor at the University of Waikato,

Jack Wilson, Head of TECH,

David Braithwaite, a company director,

Brian Smith, a chartered accountant

and

Valerie O'Sullivan of Matamata.

WAIKATO MEDICAL RESEARCH FOUNDATION

Discovery, Innovation, Progress.

Private Bag 3200, Waikato Mail Centre Hamilton 3240
Phone: 07 839 8750 **Fax:** 07 839 8712
Email: wmrf@waikatodhb.health.nz
Web: www.wmrf.org.nz