Genes responsible for severe epilepsy discovered

By Suzy Botica

Wellington-based paediatric neurologist Dr Lynette Sadleir and her international collaborators have identified genes responsible for a severe type of epilepsy that causes the death of 25 per cent of children who have it by the time they are 20 years old.

The discovery of two new genes – CHD2 and SYNGAP1 – involved in this devastating group of epilepsies (known as epileptic encephalopathy) will enable clinicians to diagnose and treat children with this condition quicker, circumventing the need for expensive and invasive investigations.

The results of this international study, the New Zealand component of which was funded by the HRC, were published online in *Nature Genetics* in May this year¹.

Epilepsy affects 0.5 per cent of the population and is the most common serious neurological illness of children and young people. Dr Sadleir, whose HRC-funded research into the genetic determinants of epilepsy is carried out at the University of Otago, Wellington, says faulty genes are an important cause of epilepsy.

“Epilepsy is a big group of disorders. We know that genetic causes account for a significant proportion of all epilepsies, but to date only 29 epilepsy genes have been identified.”

Dr Sadleir is researching all types of epilepsy, but the focus of her recent work has been on those types at the most serious end of the scale. Her collaborators include Professor Ingrid Scheffer at the Epilepsy Research Centre and Florey Institute in Melbourne, Australia, and a team of molecular geneticists at the University of Washington, in Seattle, US, led by Assistant Professor Heather Mefford.

“About two-thirds of the children I see in my Wellington epilepsy clinic have an epileptic encephalopathy. For the majority of these devastating disorders we do not know the cause. Between birth and adulthood the brain learns to develop by increasing the connections it needs,”

(Continued on page 7)
Chief Executive’s message

The HRC is right in the middle of the 2014 annual funding round, with committees meeting to consider the various types of research proposals. We recently published a summary of the different contract types that we offer, ranging from $5,000 Summer Studentships, to multimillion dollar Programmes. It may surprise you that there are 27 different contract types, which translates to 30 to 35 funding opportunities being offered each year. Most contract types (16) support people, while eight are primarily about the research idea. In terms of the funding split, the HRC expends about $75 million per annum supporting ideas and $5 million per annum supporting people.

We are acutely aware that the demand for health research support remains high. While the National Science Challenges have created an exciting new avenue, and new funding, for mission-led research – and health research is well represented in the spread of Challenges – we are not expecting any diminution in the number of proposals coming to the HRC.

Some figures provide an overview from the HRC’s perspective. In the 2006/07 year the average HRC Project grant award was $873,000. In 2012/13 it was $1.07 million (a 22.6 per cent rise), although we recognise that the rise in cost has been contained by introducing a budget cap. In both those years 36 Projects were funded. HRC income from Vote Science over that same time has shifted from $69.08 million to $82.6 million (a 19.5 per cent rise). The workforce that might potentially seek HRC funding also seems to be rising. According to PBRF data published by the Tertiary Education Commission, there has been a 35.2 per cent increase in health science academic FTEs between 2006 and 2012. From an “owners” perspective, it will be pleasing to note that research outputs have also increased. Comparing the 2006/07 and 2011/12 years, peer reviewed publications arising from HRC funding increased more than 20 per cent, and patents awarded rose from two to nine. I am struck by the apparently clear relationship – more money invested leads to more outputs, despite increasing costs.

The reality is that many applicants to the HRC will be disappointed. We know, however, that those who do receive funding carry out the highest quality health research that returns benefits to New Zealand. That keeps the team at the HRC focused on providing the best possible support to the funding process.

Dr Robin Olds
Chief Executive
Health Research Council of New Zealand
Update on the HRC 2014 annual contestable funding round

The HRC 2014 annual contestable funding round (for contracts beginning after 1 July 2014) is now well underway. The online submission system (EASY), still in its original form, has worked well with relatively few problems even during key closing times. This success is thanks to the efforts of the HRC’s Knowledge Management and Information Services group led by Vivien Lovell. The online submission system will be upgraded significantly towards the end of 2013 in time for the next HRC annual funding round.

Since early July, Expression of Interest (EOI) for Project applications have either already been through the assessing committee meeting stage or pre-scores are being collated to decide what applications to triage before a meeting. Three hundred and fifty-five EOI applications were received. After pre-scoring that number will decrease by about a third for assessing committee discussion. Applications have been allocated to discipline-based committees (five biomedical, three public health, one health delivery, one Rangahau Hauora Māori, one clinical trial). The HRC’s Project Managers are grateful that so many people in the health research community have agreed to take part in this stage of peer review. As in previous years, results for EOI and invitations to submit full applications will be available on or before 7 October 2013. The HRC expects to invite about a hundred Project applications to the full stage.

With the closing of the registration phase of all but Explorer Grants for the round, the latest potential application numbers appear similar to last year. Although some may not translate into full applications, the following registrations were received: Feasibility Study, 49 (43 last year); Emerging Researcher First Grant, 57 (56 last year); Programmes, 18 (24 last year). The closing date for full applications was on 27 September 2013, while the closing date for Programmes is 16 October 2013 (12pm).

At this time, the funding budget for the 2014 annual funding round is expected to be similar to the previous round when 5 Programme, 35 Project, 10 Emerging Researcher First Grant, 6 Feasibility Study and 3 Explorer Grant contracts worth a total of $61.5 million were approved.

About HRC News

HRC News can be viewed on the HRC website: www.hrc.govt.nz

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Advance notice – Health Innovation Partnership

The Health Innovation Partnership (HIP) between the HRC and the National Health Committee (NHC) was established to support translational research for health and disability-related technologies. Two areas of health research have been identified as important for investment by the partnership. As a result, two Request for Proposals (RFPs) will be released by the end of September/early October 2013.

These are:
- **Chronic obstructive pulmonary disease**
- **Ischaemic heart disease**

Both RFPs will offer support to teams of researchers, clinicians and key decision-makers interested in conducting applied health technology research that responds to the needs of New Zealand’s health and disability sector.

It is anticipated that the evidence generated through this research will facilitate the NHC’s role in helping the sector to spend its funding in the most effective way, and enabling it to continue to improve the health of New Zealanders within the country’s financial resources.

Individuals and organisations interested in undertaking research within the identified research themes are welcome to register their interest with the HRC by contacting **Jessica Smith**, email: jsmith@hrc.govt.nz, phone (09) 303 5227. All registered parties will receive notification of the release of the RFP. The RFP and supporting documentation will also be posted on the HRC’s website, [www.hrc.govt.nz](http://www.hrc.govt.nz) and the Government Electronic Tendering Service, [www.gets.govt.nz](http://www.gets.govt.nz).

New members appointed to the HRC’s College of Experts

The HRC’s College of Experts was established in 2012 to support the formation of the HRC’s assessing committees and contribute to the robust assessment process of grant applications. In deciding where to invest money in health research, the HRC relies heavily on the opinions of members of the College of Experts, who have been identified as having the appropriate scientific expertise and peer review experience. Members volunteer their expertise, for which the HRC is extremely grateful.

We are pleased to welcome nine new members to the College of Experts. They are:

- **Associate Professor Gabrielle Belz**, Molecular Immunology Division, Walter and Eliza Hall Institute of Medical Health, Melbourne, Australia
- **Professor Vicky Cameron**, Christchurch Heart Institute, University of Otago, Christchurch
- **Professor Richard Cannon**, Division of Health Sciences, University of Otago, Dunedin
- **Professor Tim David**, Director of the BlueFern Supercomputing Unit, University of Canterbury
- **Professor David Fergusson**, Director of the Christchurch Health and Development Study, University of Otago, Christchurch
- **Dr Seton Henderson**, Clinical Director, ICU, Christchurch Hospital
- **Dr Cathy Stinear**, Centre for Brain Research, The University of Auckland
- **Dr Martin Than**, Director, Emergency Medicine Research Foundation, Canterbury District Health Board
- **Professor Robert Walker**, Dunedin School of Medicine, University of Otago, Dunedin

![Professor Vicky Cameron](image1.png)

![Professor David Fergusson](image2.png)

![Dr Cathy Stinear](image3.png)

![Dr Martin Than](image4.png)
Natural bacteria fights off common STI

By Suzy Botica

Researchers at The University of Auckland have discovered for the first time that women have a natural defense against trichomoniasis – the world’s most common sexually transmitted infection (STI).

Lead researcher Dr Augusto Simoes-Barbosa says the results of their HRC-funded study show that a particular strain of bacteria, *Lactobacillus*, which is naturally found in the vagina, can fight off infection from the parasite that causes trichomoniasis, *Trichomonas vaginalis*. The results were recently published in the international journal on sexual health, *Sexually Transmitted Infections*.

Trichomoniasis is the most widespread non-viral STI, with about 200 million people affected worldwide. The number of New Zealand women affected by trichomoniasis isn’t known, but Dr Simoes-Barbosa says it’s likely to be close to or even higher than the more publicised STI, chlamydia.

“Although trichomoniasis can be cured, many people don’t know that they have it. More than 90 per cent of men don’t display any symptoms and act as carriers of the parasite. In contrast, about 40 per cent of women experience symptoms, including vaginal discharge and painful intercourse.”

Dr Simoes-Barbosa says that because trichomoniasis is not associated with mortality, it can get neglected. However, its potential effects are significant.

“If left untreated in women, the parasite can cause serious damage to the urogenital tract. It can also cause premature labour in pregnant women and increase the chances of contracting HIV.”

The vagina is an acidic environment that contains a range of natural probiotics, dominated by *Lactobacillus*, to protect itself from constant infection. In the vaginal fluid of a healthy, premenopausal woman, *Lactobacillus* is found at a concentration of 10 million to 100 million bacteria per ml.

However, despite indirect evidence that *T. vaginalis* and *Lactobacilli* compete against one another, this study is the first to explore the possibility that *Lactobacilli* could prevent *T. vaginalis* from sticking to the outermost cells of the cervix.

Dr Simoes-Barbosa and his colleagues developed a monolayer of vaginal cells in vitro, with a selection of nine strains of *Lactobacillus*, and tested these against three strains of *T. vaginalis*.

“Our results showed that we could virtually eliminate a very aggressive strain of parasite from binding to the host cell just using normal concentrations of *Lactobacillus* – about 1 million bacteria per ml, which is about 10 fold less than what’s commonly found in the vagina. *Lactobacillus* forces the parasite to lie dormant instead of infecting further.”

Dr Simoes-Barbosa says they don’t yet know what causes *T. vaginalis* to overpower the natural *Lactobacillus* population in some women, leading to infection. There are many factors that could come into play, including the nutrition of the women and what antibiotics they may have taken.

At the moment, the only drug used to treat trichomoniasis kills the good bacteria along with the bad, leaving the vagina – and the rest of the body – vulnerable to infection by other pathogens. Also, about five per cent of *T. vaginalis* are resistant to the pathway that activates this drug in the body.

“This study opens up the possibility of exploring natural microbes to treat an STI that affects a great deal of the population. But it could also apply to many other vaginal infections as well. A lactobacillus treatment would avoid changing the vaginal microbiota and help to restore it after treatment.”

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Accelerated pathway reduces hospital admissions for chest pain

By Mark Wright

A new fast-track cardiac diagnostic tool trialled in an HRC-funded study is already cutting down the number of unnecessary hospital admissions involving people with chest pain.

The Accelerated Diagnostic Pathway (ADP), developed by Dr Martin Than and a cross-speciality team at Christchurch Hospital, was designed to speed up the diagnostic process without compromising patient safety.

Dr Than says chest pain of suspected cardiac origin is one of the most common (5 to 10 per cent) presenting complaints in hospitals in the western world and represents up to 25 per cent of admissions. In the United States it leads to about 8 million visits per year at a cost of $20 billion annually, and it is a similar story in Europe.

“That sort of volume of patients puts a lot of strain on a health system because one of the biggest challenges in the modern era is the issue of available beds and overcrowding in the emergency department,” he says.

“When an emergency department is so overcrowded that patients are waiting for six hours compared to one hour the odds ratio for increased likelihood of harm is approximately 1.7 because staff are trying to keep so many balls in the air. The chest pain patient may be looked after well but there might be an elderly patient in the corner quietly dying of sepsis.”

Dr Than says the usual process for ruling out a heart attack is quite time consuming.

“Only about 10 to 20 per cent of patients with chest pain will have a heart attack as the cause of their pain, which means 80 per cent don’t.”

The assessment process usually involves a blood test for cardiac troponin when the patient comes in, then a later follow-up troponin test about six hours later. This later test means that patients usually have to be admitted or put in observation wards.

“Potentially there is not only a huge burden on the system, there is a lot of worry for the patient and their family for something that is not as serious as feared.”

Building on their earlier accelerated pathways studies at Christchurch Hospital, Dr Than and his colleagues made use of modern troponin assays in their two-year HRC-funded randomised control trial, which involved 544 patients.

Patients in the experimental group were given a troponin test and an ECG, as well as undergoing risk assessment using the Thrombolysis In Myocardial Infarction score (TIMI). The TIMI score was designed to predict the risk of people coming into hospital with a cardiac problem, and the risk of them coming to harm over the next 30 days.

Dr Than’s group hypothesised that if your TIMI score was zero and you had two negative troponin tests and an ECG in the first two hours then you were at less than 1 per cent risk of having a heart attack. You could therefore go home and be followed up as an outpatient, or proceed more quickly to the next in-patient investigations – also saving time.

“The results showed that we could double the number of patients that were discharged early from 10 per cent to about 20 per cent. Effectively one in five patients could be discharged within two hours.”

He says doctors in the emergency department were not forced to follow the pathway and there were a further 15 per cent of people that doctors admitted or put in observation wards.

“Potentially we could have seen 35 per cent of patients discharged early but as the pathway becomes more accepted over time those are gains that will also be picked up.”

Dr Than also points out that it was an implementation study so was run to reflect real life. The hospital did not receive extra resources and used tests...
The pathway has also been implemented at Nambour Hospital on the Sunshine Coast in Queensland without any adverse events, and the Director General of Health in Queensland wants to adopt it for the whole state.

A paper on the study will be released online on 7 October 2013 in the *Journal of the American Medical Association* (JAMA).

Dr Than and his team have also developed a new score called the Emergency Department Assessment of Chest pain Score (EDACS), which they have validated and are planning to publish on. They have secured further HRC funding to compare that score with the TIMI score.

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and pruning those that it doesn’t. However, in children with an epileptic encephalopathy, the electrical activity in the brain is so chaotic that the brain doesn't develop normally.”

For the study, Dr Sadleir recruited New Zealanders with epilepsy and their families. A detailed picture of their phenotype (physical traits as determined by their genetic makeup and environmental influences) was undertaken and subsequently genes were sequenced.

“Heather Mefford’s lab performed targeted massive parallel resequencing of 19 known and 46 novel candidate genes in 500 individuals with an epileptic encephalopathy. They found multiple individuals carrying mutations in either of the two new genes for epileptic encephalopathy: *CHD2* and *SYNGAP1*.”

Last month *Nature Genetics* announced that the same Australian, New Zealand and American collaboration, of which Dr Sadleir leads the New Zealand group, had found a cause of a specific group of the epileptic encephalopathies called Epilepsy-Aphasia Spectrum disorders. In this group of disorders previously normal children develop seizures and lose the ability to speak.

“Genes were sequenced in 519 patients with severe seizure disorders. Within this group, 44 patients had epilepsy-aphasia and nine per cent of those and their affected family members had mutations in the *GRIN2A* gene.”

To find nine per cent of patients with a genetic mutation for a particular epilepsy disorder is significant, says Dr Sadleir.

“Occasionally a gene is identified that’s responsible for 80 to 90 per cent of a particular type of epilepsy, but usually there will be multiple genes involved.”

Dr Sadleir says that epilepsy gene discovery is important because it provides a definitive diagnosis and forms the first step towards developing targeted therapies to improve the outcomes for children with epilepsy and their families.

“The genes that we find are allowing comprehensive epilepsy gene panels to be developed, which means families can find out what type of epilepsy their children have and get the correct treatment sooner. Up to 50 per cent of infants with epileptic encephalopathies will soon be able to receive quick and cost-effective diagnoses of mutations of specific genes based on this type of research.”

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Easing asthma by dealing to cold houses

By Mark Wright

Steps as simple as keeping a bedroom heated are being put to the test in an effort to reduce upper respiratory tract infections and asthma attacks.

Research by Professor Julian Crane from the University of Otago, Wellington, as part of the HRC-funded He Kainga Oranga/Community Housing and Health Intervention Research Programme will build on earlier research on whether a young child is more likely to develop asthma for the first time if they are living in a cold, damp house.

“The idea of the first study was to see if there was a relationship between the development of asthma and the conditions in which a child lived when they were young.”

They are using many of the same households to go back and do an intervention study to see if heating up the bedroom, because they found many of the bedrooms in the study were really cold, alters the frequency of upper respiratory tract infections.

“One of the biggest triggers of asthma is an upper respiratory tract infection. Children with asthma get an exaggerated response to a viral infection in the upper airway and that can trigger a severe asthma attack.”

The recently published International Study of Asthma and Allergies in Childhood (ISAAC) involving 46,000 children in 20 countries, including New Zealand, has pointed the finger at dampness as the key cause of asthma rather than allergy to moulds, Professor Crane explains.

“One of the things that has been well-established in the literature across a whole range of studies and meta-analyses is that if you live in a cold and damp environment you are more likely to have symptoms of asthma, and you are also more likely to develop colds,” he says.

“We are moving away from the idea that mould might be important, to examine whether the factor that’s responsible for the symptoms is viral rather than anything else. The theory behind that would be that if you have an environment where it’s cold and damp then maybe viruses are more likely to survive outside of the body and therefore have a higher chance of being transmitted to children.”

Professor Crane now wants to see if altering the environment by warming up the bedroom, makes any difference to the amount of virus found and the frequency of upper respiratory tract symptoms. That will involve a quantitative study of virus in the nose to see if it makes any difference.

They will study about 300 children, over this winter and the next, who will be divided into two groups. The bedrooms of the intervention group will be warmed up for the eight week trial and the temperatures of both sets of bedrooms will be monitored.

“We will take a viral sample before and then at the end to see whether there is any difference in viruses between the two groups. We may find there is no difference at all,” Professor Crane adds.

“The reason that it is of concern, particularly for New Zealand, is that we have a lot of very poor quality housing that is damp and cold. People just don’t heat their houses very much whereas in other countries they tend to do it more, and we have a lot of asthma. So the question becomes: Is there any relationship between those?”

If they do find a difference through the quantitative measurement of virus then it would be something to follow up because there would a lot of questions around how the virus is surviving outside and how is it being transmitted to the children.

“More and more of the emphasis in early childhood asthma is on viral-associated problems. There is a focus on understanding what the virus does to cause these problems in people with an underlying genetic predisposition to develop asthma. There’s also an interaction between viruses and allergies.”

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Computer models simulate shaken baby syndrome motion

By Suzy Botica

University of Auckland PhD student Tom Lintern has built anatomical computer models of a baby’s head that can simulate the different motions generated from shaking associated with child abuse.

Mr Lintern (Ngāi Tahu) built the computer models to provide an objective way to estimate the motions that a baby experienced for a certain pattern of injury. His research is funded by an HRC Māori PhD Scholarship, and supervised by Professors Poul Nielsen and Martyn Nash, and Associate Professor Andrew Taberner at the university’s Auckland Bioengineering Institute (ABI).

The violent shaking of infants is the single most preventable cause of serious head injuries in babies under one year of age in New Zealand. Mr Lintern says the debate over the causes of brain damage during shaking has made it difficult for paediatricians to assess whether or not an infant’s injuries were the result of child abuse.

“Looking at the biomechanics of head motion during different types of shakes, I can see the importance of contact between the head and the torso. Although some people may think that shaken baby syndrome implies a non-impact motion, it’s quite clear that impact occurs between the head and other parts of the body.”

Mr Lintern says this impact produces shaking of the torso and head motion by reproducing results from a pre-existing animal model. This animal model was developed by New Zealand’s leading expert on shaken baby syndrome, Dr Patrick Kelly from Starship Children’s Hospital, and Dr Frank Bloomfield from the Liggins Institute and Starship, both of whom provided valuable clinical support during Mr Lintern’s research.

Mr Lintern used a variety of instrumentation, including wireless inertial measurement sensors, developed by ABI researcher Mark Finch, to measure linear and angular accelerations and rotations of the head and torso.

These measurements were incorporated into computer models using OpenSim software, a musculoskeletal package developed at Stanford University in the US to analyse how the skeleton moves in response to different stimuli. Mr Lintern also built an experimental dummy, replicating an infant’s geometry and other properties, as another form of model validation.

“In the literature, there’s controversy over the mechanisms of injury in shaken baby syndrome. A baby can present with bleeding on the brain or neurological issues, but what the paediatrician needs to decide is whether this was caused by an abusive incident or an accident,” says Mr Lintern.

“Much of the paediatricians’ analysis is subjective, relying on their experience. When they talk to parents and the injured child’s history doesn’t quite add up to what they’re seeing in the clinic, that’s a big red flag for them. With this computer model, I’m trying to add an objective measure to that.”

Mr Lintern began his research into the causal relationship between

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big accelerations as the head goes fast and then stops at the torso, enough to possibly produce a similar response to if a head was hit against a hard surface such as a table.

“It might not be as big an acceleration, but it’s definitely much larger than what just the shaking motion alone would produce. That means there is a whole lot more to consider when building and analysing the models.”

To link this experimental work back to the human infant, Mr Lintern used CT and MRI images from infants to build anatomical models of babies’ heads that can move around. Another ABI PhD student will use these data to predict how the baby’s brain is affected for a given head motion and then relate that to injury.

Mr Lintern, who has presented his research at a number of international conferences, is currently writing up his thesis and plans to publish the results early next year.

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Screenshots of Mr Lintern’s infant head computer model at 2 degrees flexion (left), neutral (middle), and 8 degrees flexion (right).

Mobile phone trial motivates heart patients to get moving

By Suzy Botica

Auckland heart disease patients sent personalised text messages encouraging them to exercise as part of a unique 24-week mobile health intervention have significantly increased their levels of physical activity compared to those receiving standard care only.

The HRC-funded clinical trial, led by Associate Professor Ralph Maddison from The University of Auckland’s National Institute for Health Innovation, is part of the Heart Exercise And Remote Technologies study. It is the first trial of its kind to test how effective a mobile health intervention is at improving the fitness and physical activity levels of people with ischaemic heart disease.

The trial recruited 170 people (average age 60 years) who had been admitted to either Auckland City or Middlemore Hospital with a heart condition. All the trial participants received the standard care for heart patients: they were advised to be physically active and encouraged to join a cardiac club.

In addition to this standard care, half of the trial participants were sent a personalised package of text messages five or six times a week via their mobile phones. The texts told them how much exercise they
should do, how often and at what intensity. This information was derived from a baseline fitness test that each participant underwent and recommendations from the American College of Sports Medicine. Remaining messages focused on strategies to help them exercise regularly and become more confident with exercising.

Each mobile health participant was also given a pedometer so they could record how much physical activity they did. They could log these data on a secure website to monitor their own progress. The website also provided extra information to help them keep physically active.

“At the beginning of the trial and again at the end of 24 weeks, we put all the patients on a treadmill and carried out a maximal oxygen uptake test. This measures the peak oxygen that their body can use when exercising and is the gold standard for physical fitness,” says Dr Maddison.

“Both the standard care and mobile health groups increased their VO₂, or oxygen uptake by a small amount – about 1.5 per cent. However, while there was no difference between the two groups in terms of VO₂ uptake, those participants enrolled in the mobile health programme significantly increased their levels of physical activity and walking over and above standard care.”

Dr Maddison says that this increase in physical activity probably didn't affect the participants' fitness levels because they were'n exercising at the correct intensity.

“People may think they’re exercising at a moderate intensity, but physiologically they’re not. However, an increase in physical activity among inactive people is associated with a reduction in mortality.”

To overcome this, he and his colleagues are currently undertaking a pilot study where heart patients are remotely monitored while exercising using heart rate monitors and a mobile phone app.

The results of the trial also show that the mobile health participants were more confident about being physically active than the standard care group and more motivated to get moving.

“Most people when they’ve had a cardiac event such as a heart attack don’t know where to start exercise-wise. Do I walk? How fast do I walk? What if I get chest pain again or shortness of breath? Because of this uncertainty, they don’t exercise. Our programme is about easing people into exercise, building up their confidence and providing strategies for them to overcome some of the barriers to being active.”

Exercise is the cornerstone of cardiac rehabilitation for people with heart disease. However, heart disease patients are not always referred to cardiac rehabilitation, and of those who are referred, not all of them will stick to the programme. About 50 per cent drop out halfway through.

“This mobile phone intervention wasn’t designed to replace current cardiac rehabilitation programmes, but rather to provide other options for those people who can’t attend these programmes for whatever reason, such as work or family commitments, or cost.”

Dr Maddison and his colleagues are now planning to extend this study to all aspects of cardiac rehabilitation – nutrition, exercise, smoking cessation, medication adherence, psychological support and general heart messages.

“Our findings suggest that a relatively cheap and easy to implement intervention can have a sustained, positive effect on physical activity levels in people with cardiovascular disease. I think we’ve only just scratched the surface in terms of what we can do.”

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Study reveals New Zealand workers’ exposure to carcinogens

By Suzy Botica

A comprehensive study of New Zealand’s major industries has found that there are very few with no known or suspected exposure to carcinogens.

The study’s lead researcher, Dr Andrea ‘t Mannetje from Massey University’s Centre for Public Health Research in Wellington, says most industries had a potential for exposure to several known human carcinogens. Agriculture, construction, health services, and machinery and equipment, metal products, and wood and paper manufacturing were repeatedly associated with an increased risk of occupational cancer.

“These industries have a high number of workers potentially exposed to carcinogens due to the large size of the industry and the high exposure prevalence within the industry,” says Dr ‘t Mannetje.

“There are more than 50 known human carcinogens present in New Zealand workplaces, including asbestos, benzene, involuntary smoking and wood dust, and more than an additional 100 possible or probable ones.”

The study identified sun exposure and diesel engine exhaust fumes as two of the main carcinogens in the agriculture industry, while sun exposure, wood dust, silica and compounds found in paint (e.g. chromium, lead) were common in the building industry.

In the health services industry, shift work was identified as a potential carcinogen, with an increased risk of breast cancer. Health services workers could also be exposed to potential carcinogens such as radiation and drugs used to fight cancer, but which can themselves be carcinogenic.

The study was funded by the Department of Labour (now the Ministry of Business, Innovation & Employment) and the HRC as part of the HRC’s Partnership Programme. It involved researchers from the Centre for Public Health Research, US National Cancer Institute, University of Utrecht (Holland) and the International Agency for Research on Cancer (IARC).

The National Occupational Health and Safety Committee estimates that between 237 and 425 people die each year from occupational cancer in New Zealand. This data is largely based on overseas epidemiology studies, but Dr ‘t Mannetje says there is no reason to believe that the situation in New Zealand is any different, “in fact the figures are probably an underestimate”.

“This study provides national data on the extent and industrial distribution of occupational exposure to carcinogens, which will help to develop and implement successful strategies to prevent exposure,” she says.

The researchers have developed a New Zealand-specific information system on occupational exposure to carcinogens (NZ-CAREX – Carcinogen Exposure New Zealand). NZ-CAREX provides a list of carcinogens that can occur in each industry and the number of potential people exposed to them within that industry. The list is based on the international CAREX evaluations and local expert assessments.

“The NZ-CAREX database will be available to use for a wide range of carcinogens and industries, and we will continue to update it for other carcinogens not yet included,” says Dr ‘t Mannetje.

In addition to NZ-CAREX, the study team has also developed a system specifically for estimating New Zealand farm workers’ exposure to agricultural chemicals called NZ-ACEM (Agricultural Chemicals Exposure Matrix). Dr ‘t Mannetje hopes this system will provide much-needed information about the use of pesticides that will aid epidemiological studies into the association between specific pesticides and cancer.

“Farmers have an increased risk of certain cancers but which exposures are responsible isn’t known. Over a working life the average farmer would have been exposed to such a wide range of pesticides that it’s hard to link an increased risk to a particular exposure.”

“There are no known carcinogens currently being used in New Zealand’s agriculture industry, but there are
Evidence base needed for paediatric emergency care

With 250,000 New Zealand children presenting to emergency departments for acute emergency care, Starship Paediatrician Dr Stuart Dalziel, a specialist in the field, says the evidence base for paediatric emergency medicine (PEM) should be more extensive.

Dr Dalziel has been awarded an HRC practitioner research fellowship in paediatric emergency research which he will use to consolidate the country’s PEM evidence base through a range of research projects.

“The figure of 250,000 emergency department visits per year averages out to one visit every three years per child for the duration of their childhood. Thus it is exceptionally common for children to be seen in emergency departments – and outside of general practice this represents the biggest interaction that children have with the health care system,” he says.

“Despite the frequency of these presentations, the evidence base for paediatric emergency medicine is probably not as extensive as it should be.”

Dr Dalziel says he will address that shortfall through three projects. The first is a randomised controlled trial of two treatment strategies for children in convulsive status epilepticus, comparing the current first line treatment phenytoin with a newer agent levertiracetam. This project is the first randomised controlled trial in the field that’s ever been undertaken.

“Convulsive status epilepticus is the most common severe neurological emergency for children. About a quarter of children who present end up requiring intubation and admission into intensive care.”

That study will take place through the PREDICT (Paediatric Research in Emergency Departments International Collaborative) research network, involving emergency departments associated with all the children’s hospitals in Australia and New Zealand, as well as a number of larger mixed emergency departments.

Dr Dalziel says a second randomised controlled trial will look at the use of prednisolone in pre-schoolers who present to emergency departments with wheeze – the most common reason to present to emergency departments for pre-schoolers.

“There is some international evidence suggesting that prednisolone may not be useful in these children, but currently our practice is to still use it,” he says. “This project will provide local knowledge confirming the benefits, or lack of benefit, of this treatment which is regularly used.

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both in emergency departments and primary care.”

The third study will examine knowledge translation and whether clinicians are assimilating the latest information in PEM and applying it the clinical situation.

Dr Dalziel says they will bring in evidence from the most recent study conducted in the PREDICT research network, which looked at the management of bronchiolitis in children under the age of one.

“Bronchiolitis is another viral respiratory illness and the most common reason for children less than one to be admitted into hospital,” he explains.

“We will look at 18 hospitals around Australia and New Zealand and examine different ways we can support clinicians to work out what’s the appropriate way to get the vast majority of them doing the most appropriate evidence based management for the children they are treating. We’re looking more at the system delivery than necessarily the evidence base.”

There’s a wide variety of reasons why clinicians make the decisions they do, says Dr Dalziel.

“It might be tradition – people often do things because it is the standard way everyone does it in their institution, despite a lack of evidence. Or they may undertake an intervention or treatment because people feel more comfortable doing something active even when the evidence supports observation and supportive care only.”

He says the project will help identify the best strategy for bringing about changes in practice within emergency departments in Australia and New Zealand.

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Vital predictors of severe H1N1 infection in children identified

A global research project involving 79 emergency departments from twelve countries has identified six factors associated with severe outcomes for children presenting with influenza-like illness.

The research, led by Dr Stuart Dalziel, was published recently in the British Medical Journal (BMJ)1.

He says the research project was driven by the 2009 global pandemic when emergency departments around the world, particularly paediatric emergency departments, were swamped with the number of children presenting with influenza-like illness.

“At that time there was no clear knowledge to say what are the exact risk factors at presentation to emergency departments for predicting who would go on and get severe disease.”

The retrospective case control study included 265 children with H1N1 infection in Europe, the Middle East, North America and Australasia who were admitted to intensive care units for active treatment, and/or who died.

The children were compared to a control group of other children who just presented with influenza-like illness but only ended up in the wards for a few days or were sent home from the emergency department.

“What we were trying to establish were the key independent risk factors for that severe outcome of death or intensive care admission, at the time they were seen at the original presentation to the emergency department,” says Dr Dalziel.

The study authors identified six factors associated with severe outcome in children presenting with influenza-like illness. They were: a history of chronic lung disease; a history of cerebral palsy/developmental delay; signs of chest retractions (laboured breathing); signs of dehydration; requirement for oxygen; and a fast heart rate relative to age.

Dr Dalziel says identifying those key risk factors means clinicians can be alerted to children who are at risk of severe outcomes during future pandemics.

“That’s important not only from the point-of-view of planning resource allocation during future pandemics but it also helps clinicians when they’ve got an individual patient in front of them with presumed influenza.”

H1N1 remains one of three main influenza viruses present in the community in the current flu season.

Dr Dalziel says the study shows the benefit of international collaboration and cooperation in research to produce findings capable of being reproduced around the world.

“In order to robustly answer a large number of the scientific questions that we have in paediatric emergency medicine, and medicine in general, we require appropriately powered studies with clinically meaningful end-points. This is better achieved through multi-centered studies, rather than studies in single institutions. One of the benefits of such an approach is that the evidence generated is highly generalisable. For the H1N1 study we had countries in four of the WHO’s six regions. That gives us a pretty good idea that this doesn’t just work in Auckland New Zealand – it works in North America, it works in Europe, and it works in Asia.”

1 BMJ/2013;347:f4836 doi:10.1136/bmj.f4836 (Published 12 August 2013)
Exciting prospects for cancer research

By Suzy Botica

Cancer is the leading cause of death for both males and females in New Zealand, accounting for nearly a third of all deaths in 2010. Despite this sobering statistic, there is good reason for hope. Here we look at three cancer-related studies to receive funding in the HRC’s 2013 funding round, all of which look set to have a significant influence on future cancer treatments.

First named investigator: Professor William Denny
HRC Programme: Rational design of kinase inhibitors to target cancer
Funding allocated: $4,923,458

Professor William Denny and his team at The University of Auckland have an excellent track record in developing drugs to block the pathways that drive the development of many cancers. Their main target is the phosphoinositide-3 kinase (PI3K) signalling pathway, which is probably one of the most important pathways in cancer metabolism and growth.

“Genetic mutations in genes called oncogenes are major drivers in the development and progression of cancer. More than 30 per cent of tumours contain mutations in genes that result in the activation of the PI3K signalling pathway in cells,” says Professor Denny.

With the help of funds from a previous HRC-funded grant, Professor Denny and his team have already developed a potential anti-cancer drug (PWT33597) targeting the PI3K pathway that has now completed phase 1 clinical trials. Professor Denny’s 2013 HRC Programme grant will expand on this work to answer major unresolved questions about PI3K drug discovery, including how selective for PI3K should the drugs be? And how do you overcome drug resistance?

“Answering these questions will help us to guide the development of more effective ‘second generation’ inhibitors of PI3K for treating cancer,” says Professor Denny.

First named investigator: Associate Professor Peter Sykes
HRC Project: The conservative management of young women with CIN2
Funding allocated: $1,196,179

The risk of women getting cervical cancer can be greatly reduced if precancerous lesions are identified and treated. However, there is evidence that these treatments can, in addition to immediate complications, have an adverse effect on pregnancy outcomes.

University of Otago, Christchurch, Associate Professor Peter Sykes is using his 2013 HRC Project grant to determine if women with moderate abnormalities of the cervix (CIN2) would benefit from observational management rather than invasive cervical treatments. The study aims to recruit 600 women under the age of 25 with CIN2.

“Precancerous changes are graded as CIN 1, 2 and 3. CIN1 lesions normally regress and aren’t usually actively treated, whereas CIN3 lesions have a significant chance of becoming cancerous and are always treated. The situation is less clear for women with CIN2,” says Dr Sykes.

“The literature suggests that 40 to 75 per cent of CIN2 lesions will regress, particularly in younger women [under 25]. This large, multi-centre study will determine if observational management is a valid option for young women with CIN2.”

The results from this study will help inform the next review of the National Cervical Screening Programme guidelines for managing abnormal cervical smears.

First named investigator: Dr Jeffrey Smaill
HRC Project: Novel small molecule therapeutics for treatment of smoking-related lung cancer
Funding allocated: $1,180,810

Some smoking-related lung cancers contain high levels of FGFR1 (Fibroblast Growth Factor Receptor 1). This receptor drives tumour growth and is also a major cause of resistance to chemotherapy.

New drugs designed to block FGFR1-4 have been developed, but they can produce severe side-effects, including

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tissue calcification and anorexia, which may ultimately limit their clinical use.

Dr Smaill and his collaborators at The University of Auckland have invented a ‘stealth’ drug technology that can substantially increase the delivery of active drugs to the tumour, while sparing healthy tissues. Their first such drug, PR610, targeted a similar receptor to FGFR1 and entered human clinical trials in New Zealand and the United States in 2012. Now they will use their 2013 HRC grant to target FGFR1-4.

“We’ll follow a similar path to that used for the successful development of PR610 to make new FGFR drugs that promise to be less toxic and more effective at treating smoking-related lung cancer. It’s a unique approach with a uniquely New Zealand technology,” says Dr Smaill.

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New chemistry transforms vaccine manufacture

Article and photo supplied courtesy of the Maurice Wilkins Centre at The University of Auckland

Honours student Tom Wright, from The University of Auckland, has created a new kind of chemistry to dramatically simplify the manufacture of drugs targeting the immune system, and the technology has been patented.

Tom Wright

This research came out of a HRC Project grant to Maurice Wilkins Centre principal investigator Professor Margaret Brimble (Tom’s supervisor) and Director Professor Rod Dunbar, to arm peptides (segments of protein) to better target the immune system.

Tom’s discovery will be used to develop new peptide-based immunotherapies such as cancer vaccines, and the work may not be far from the clinic, as the new chemistry can be used in a manufacturing facility at The University of Auckland that was recently licensed by MedSafe to produce medicines for clinical trial.

Tom has developed a simple and elegant new method of joining an antigen (a signal for the immune system to attack a specific target) with an adjuvant (a general danger signal which helps the immune system recognise antigens as a threat it should respond to).

It allows the two to be connected in a single reaction, as opposed to the more complex multi-step process required by conventional chemistry. Essentially, it is a modular click-together system that allows many antigens and adjuvants to be joined quickly and easily, and the resulting compounds screened for useful biological activity.

The work has already appeared in Synlett and is soon to be published in Angewandte Chemie, one of the most prestigious journals in the field.

The antigens that have been tested to date are relatively short peptides. The next step for the research group will be to trial the method on longer peptides that can be potentially used to treat a wide range of cancer patients. As for Tom, though, he’ll soon be off to Oxford after winning a Rutherford Foundation scholarship for his doctoral studies there.

The work has also led to the creation, with Dr Anna Brooks in Professor Dunbar’s laboratory, of a new means of testing compounds like these using human blood samples. Because blood contains the mix of immune cells and chemicals found in the body it provides an immediate indication of the human immune response to these molecules.
Kidney expert targets protein ‘switches’ in two new grants

By Suzy Botica

This year, in his first attempt at applying for HRC funding, Associate Professor Alan Davidson was awarded two Project grants to undertake world-leading research into kidney injury and disease. Here we profile Dr Davidson’s research, which aims to provide the groundwork for developing new regenerative treatments for kidney patients.

“Many regenerative pathways that happen in fish – and in our bodies – are similar to the pathways that are involved in making organs during embryo development. We’re interested in how we can use that information to develop new therapies for kidney disease.”

On the first grant, Dr Davidson is focusing on key cells in the kidneys called podocytes. These strange-looking cells wrap around the capillaries of the kidney’s blood filters “like an octopus” and are the main part of the filters damaged in chronic kidney disease.

“When you lose these podocytes, the other cells have to compensate for that loss. They can do that to a certain extent, but they reach a point where they can’t function properly and start leaking protein into your urine, a condition called proteinuria. This in turn damages the rest of the kidney.”

Dr Davidson’s lab is examining the function of two proteins – WT1 and WTX – that bind together and ‘switch on’ genes which help to keep podocytes healthy. He’s collaborating with Professor Stephen Robertson from the University of Otago, a clinical geneticist whose laboratory was the first in the world to identify human patients with mutations in WTX2.

“When podocytes get injured they tend to switch off WT1. This is a big problem because WT1 is the particularly affected by this because of our high rate of kidney failure among Māori and Pacific peoples. One in 10 New Zealanders is now estimated to have chronic kidney disease,” says Dr Davidson.

With his two HRC grants, Dr Davidson is researching several transcription factors – proteins that ‘switch’ genes in the cell either on or off – which he and his team have already shown play a major role in maintaining kidney health1. To begin with, Dr Davidson, an expert in zebrafish kidney development, is using zebrafish as a model of human kidney disease.

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master regulator of the genes that the podocytes need to function properly.”

Dr Davidson is interested in WT1 and the other proteins it interacts with – WTX and Nrf1 – both of which have been linked to the podocyte’s ability to protect itself.

In the second HRC grant, the focus is on the transcription factor Hnf1b, which Dr Davidson’s team has shown for the first time to be essential to the kidney’s million or so nephrons.

“When you think of the kidney in its most basic form, there’s a blood filter attached to a tube: that structure’s called a nephron. The blood is filtered into the nephron and the tube re-extracts all the important stuff that your body needs, such as glucose. In the process, it balances salt and water levels in our body.”

“If you remove Hnf1b, the tube will form, but it doesn’t have any of the transporters that you need to extract the ‘goodies’ from the urine. Hnf1b actually turns the tube into something functional in the kidney.”

“If we can identify the genes that Hnf1b switches on, we’ll be able to develop new regenerative treatments that speed up kidney repair following acute kidney injury.”

Dr Davidson says fresh ideas for new kidney treatment options are urgently needed, especially given that New Zealand has one of the lowest rates of organ transplants in the western world.

“Once you go into kidney failure there’s not a whole lot that can be done. Most patients eventually end up on haemodialysis, which puts a huge strain on their bodies and leads to a gradual decline in health. That’s what drives our research.”


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**Upcoming closing dates**

For an up-to-date list of all application registration, opening and closing dates please go to the HRC website: [www.hrc.govt.nz](http://www.hrc.govt.nz).

**Ngā Kanohi Kitea Development Grant**
Applications close on 15 October 2013 (12pm)
Hard copies of full applications are due at the HRC by 18 October 2013 (5pm)

**Emerging Researcher First Grants Feasibility Study**
Hard copies of full applications are due at the HRC by 1 October 2013 (5pm)

**Explorer Grants**
Full application registration opens on 11 October 2013 (8am)
Full application registration closes on 1 November 2013 (12pm)

**Programmes – Full applications**
Online submission system closes on 16 October 2013 (12pm)
Hard copies of full applications are due at the HRC by 18 October 2013 (5pm)

**Projects – Full application – Invitation only**
Online submission system opens on 7 October 2013 (8am)
Online submission system closes on 20 November 2013 (12pm)
Hard copies of full applications are due at the HRC by 22 November 2013 (5pm)

**Ngā Kanohi Kitea Full Project Grant**
Online registration opens on 3 December 2013 (8am)
Online registration closes on 17 December 2013 (12pm)
Applications close on 11 March 2014 (12pm)
Hard copies of full project applications are due at the HRC by 14 March 2014 (5pm)
‘Fire together, wire together’ project shows promise for stroke patients

By Mark Wright

A technique known as paired muscle stimulation is showing promise as a way of promoting plasticity in the nervous system so that undamaged parts of the brain can compensate for functions lost after stroke.

Dr Jonathan Shemmell

The 32 month HRC-funded project, headed by Dr Jonathan Shemmell from the University of Otago, Dunedin’s Brain Health Research Centre, is particularly focused on improving movement function.

“We believe that the adaptability of the nervous system is great enough that if we can find ways of encouraging the nervous system to become more plastic than it already is, and plastic in different ways, then we can help people regain functions that they might have lost.”

Dr Shemmell says experiments in what is called synchronous sensory input go back several decades. In these experiments two digits on an animal received the same sensory input at the same time. This seemed to produce a remapping of the sensory areas of the brain so that the representations of the two muscles’ movements were effectively fused in the brain.

“Essentially we're trying to achieve the same thing using paired muscle stimulation with the end result being an improvement in movement function. We are particularly interested in hand function because it often suffers the greatest impairments after stroke. This is probably because fine movements of the hand require a large amount of neural resources in the brain in the first place,” he says.

“If we can give people some hand function back we could restore some of their ability to undertake independent activities and look after themselves on a daily basis.”

Dr Shemmell and his colleagues wanted to see if by stimulating two muscles repeatedly over a period of time you get this fusion of the representation of those muscles, both in the sensory cortex and the motor cortex, which results in improved functionality.

“We also wanted to see whether this was possible between muscles separated by some distance anatomically,” he explains.

“Our end goal is to see whether we can stimulate a hand muscle at the same time as a muscle of say the upper arm or the shoulder area and see if we can get the representations of two quite anatomically disparate muscles to fuse in the brain.”

The hope is that some of the neurons that have survived and are still capable of controlling the upper arm and shoulder region could be stimulated to provide control to the hand and restore functionality.

They hypothesised that the synchronous stimulation of the muscles would be important so they set up an experimental method where they compared synchronous stimulation to stimulation 5 milliseconds (ms), 10ms and 75ms apart.

What they found though was that the synchronous stimulation and 5ms stimulation results were indistinguishable, despite their expectation that synchronous stimulation would be demonstrably more successful.

Dr Shemmell says that rather than needing synchronous input, perhaps there is a time window of peripheral input that can still allow this technique to be successful.

“The key may be the length of time the stimulation takes or is repeated rather than the timing between muscle stimuli. That’s the major thing to come out of the study. Our next move will be to try longer stimulation protocols because this study has convinced us that we will need significantly longer to produce robust changes in cortical function.”

“The study has improved our understanding of what I think we require in terms of the strength of changes that we are looking for to be able to help people with stroke.”

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Clinicians and researchers partner to tackle major health challenges

The HRC has offered more than $750,000 in funding for four research partnership projects that will help improve New Zealand’s health care services in the short term.

The projects are funded through the HRC’s Research Partnerships for New Zealand Health Delivery (RPNZHD) initiative, which requires health researchers to work in collaboration with health delivery organisations.

“We’re pleased to be able to support research opportunities for more frontline clinicians. These high quality research partnerships will provide innovative and workable solutions to some of the major health challenges facing New Zealand – and in quick time,” says HRC Chief Executive Dr Robin Olds.

Professor Barry Taylor from the University of Otago, Dunedin, will lead a project to investigate whether placing infants in a pēpi-pod (a plastic container with a fitted mattress) for overnight sleep in their homes is a safe way of decreasing New Zealand’s high rate of Sudden Unexpected Death in Infancy (SUDI). The research will use infra-red video and measure the infants’ heart rate, blood oxygen levels and body temperature.

“The results will provide urgently needed evidence to support (or otherwise) the current plans that are being implemented in many district health boards,” says Professor Taylor.

Professor Doug Sellman from the University of Otago, Christchurch, will examine a ‘food addiction’ approach to obesity involving an obesity recovery network called Kia Akina. The project will test the feasibility, short-term effectiveness and participant satisfaction of Kia Akina within the primary health care setting.

“There is a serious need to develop new non-surgical ways of treating obesity because obesity-related diseases are expensive for New Zealand, traditional non-surgical methods are not working, and surgery is very costly,” says Professor Sellman.

If shown to be effective, Kia Akina will be developed as a non-commercial, low cost network for obesity recovery throughout New Zealand.

Dr William Abbott from the Auckland District Health Board will design a diagnostic test to detect chronic hepatitis B virus (HBV) patients with early-stage liver inflammation. Detection and treatment of early-stage liver inflammation substantially lowers the risk of liver cancer. This test will potentially enable physicians to start early treatment for chronic hepatitis B, helping to improve patient outcomes and reduce the costs associated with screening for and treating liver cancer.

More than a million litres of 0.9 per cent saline are administered to acutely ill patients around the world daily. However, recent data suggests that the use of 0.9 per cent saline for intravenous fluid therapy may increase the risk of developing acute kidney injury. Dr Paul Young from the Medical Research Institute of New Zealand will compare the routine use of 0.9 per cent saline for fluid therapy in Intensive Care Unit (ICU) patients with intravenous fluids that have lower chloride concentrations such as Plasma Lyte® 148. This research partnership will engage frontline clinicians with world-leading ICU clinical researchers.

2013 Research Partnerships for New Zealand Health Delivery – Projects offered funding

Dr William Abbott
Auckland District Health Board
Prediction of serious liver inflammation in chronic hepatitis B virus infection
18 months, $174,386

Professor Douglas Sellman
University of Otago, in partnership with Christchurch PHO, Papanui Medical Centre, Christchurch South Medical Centre
Recovery from obesity – Kia Akina: A community-based food addiction programme
18 months, $176,310

Professor Barry Taylor
University of Otago, in partnership with Hawkes Bay DHB
Pēpi-pods for a safe infant sleep? A video, physiological and thermal evaluation
18 months, $200,000

Dr Paul Young
Medical Research Institute of New Zealand, in partnership with Capital and Coast DHB, Canterbury DHB, Auckland DHB, Baxter Pty and Australian and New Zealand Intensive Care Research Centre
0.9 per cent saline vs. Plasma-Lyte® for fluid therapy in the ICU
18 months, $200,000.