ABSTRACTS

Queenstown Research Week:
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MD1: Modulation of microRNAs - a mechanistic approach for the treatment of diabetic heart disease.

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Diabetic heart disease (DHD) is the presence of heart disease, specifically in diabetic patients. DHD is the major cause of mortality in diabetic individuals. We, along with others, have demonstrated that dysregulation of cardiomyocyte-specific microRNAs (miRNAs) is correlated with impaired cardiac function and cell survival. Our preliminary searches revealed three miRNAs that play a crucial role in the development of microangiopathy (miR-126), stem cells dysfunction (miR-30c) and apoptosis (miR-320a), the hallmarks of DHD. As a next step we aimed to determine if *in vivo* therapeutic modulation of these miRNAs can be beneficial in prevention/treatment of DHD.

We used a mouse model of type 2 diabetes (db/db mouse) to test our hypothesis. MiRNAs were modulated either by an injection of miRNA mimics to overexpress miR-126 and miR-30c and anti-miR to inhibit the activity of miR-320a. Further, we also trained these mice to daily exercise regime to determine if exercise is able to prevent the activation of miRNAs associated with DHD. Serial echocardiography analysis following different forms of treatment showed that therapeutic modulation of miRNAs preserved cardiac function. Molecular and histological analysis at the end of the treatment period showed marked improvement in the angiogenesis and reduced apoptosis and fibrosis. Interestingly exercise training exhibited similar improvement in these mice.

These novel findings, therefore, demonstrate that *in vivo* therapeutic modulation of miRNAs in type diabetic mice is safe and beneficial, suggesting its potential to be translated to the clinic.

MD2: Linking epicardial fat to cardio-metabolic disease: evidence from basic research.

Aitken-Buck, H.M.[1], Waddell, H.M.M.[1], Babakr, A.A.[1], Moore, M.K.[2], Berkahn, E.F.[1], van Hout, I.[1], Fomison-Nurse, I.C.[1], Moharram, M.M.[2], Stiles, M.K.[3], Tse, R.D.[4], Coffey, S.[2], Jones, P.P.[1], Lamberts, R.R.[1]

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Clinical research has established a strong link between epicardial adipose tissue (EAT) deposition and cardio-metabolic disease. In contrast, due to a paucity of pre-clinical investigation, there is a poor understanding of how EAT morphology changes in cardio-metabolic disease and how EAT affects heart function. This talk will highlight the avenues our group have taken to address these gaps in the understanding.

Using EAT procured from post-mortem and patient cohorts, we found that EAT adipocyte size is not robustly associated with classical predictors, including age, body mass index (BMI), or overall adipose deposition around the heart. Stratification by BMI category found that EAT from individuals with obesity contains more small adipocytes, suggesting adipocyte hyperplasia might drive EAT expansion in obesity. Further stratification by sex found the utility of age, BMI, and overall EAT volume as predictors of EAT adipocyte size and lipid droplet morphology is sex-specific. The role of EAT in cardiac pathophysiology was examined by exposing human myocardium to the secretory products of human EAT. Exposure to the EAT secretome increased the propensity for pro-arrhythmic myocardial contractions while also inducing a positive inotropic effect. Separate muscles were then treated with the EAT-derived adipocytokine, resistin, to determine the specific role of resistin in the arrhythmogenic and inotropic effects of the EAT secretome. Like the general EAT secretome, resistin increased cardiac contractility. However, this was not paralleled by an effect on arrhythmia propensity, suggesting factor-specific effects of EAT secretory products.

Our research indicates that EAT adipocyte morphology is influenced by biological sex and not significantly by adiposity, as is typical for other adipose depots. Additionally, we show that the EAT secretome can alter cardiac function, suggesting that signalling from EAT might directly affect heart health. This pre-clinical work begins to clarify important morphological and functional roles of EAT in cardio-metabolic disease development.

MD3: The CALCRL receptor: A potential new genetic determinant of diabetic kidney disease in NZ.

Chang, H.H.G.[1], Leask, M.P.[2,3], Kallingappa, P.K.[4], Merry, T.L.[5], Hotu, C.[6], de Zoysa, J.[7,8], Walker, C.[9], Tutone, V.[10], Fronius, M.[11], Shepherd, P.R.[1], Hay, D.L.[12], Merriman, T.R.[2,3], Davidson, A.J.[1]

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Type 2 diabetes is a huge problem in Aotearoa, affecting approximately 6% of the population. Māori are disproportionally affected by diabetes, with incidence rates 2-3 times higher than other ethnicities. Diabetes is the leading cause of end-stage renal disease due to vascular injury and altered blood filtration dynamics. The burden of kidney disease is also greater for Māori with incidence rates 3-7 times higher than non-Māori in those of working age. While the underlying causes of these health disparities in Māori are presumed multifactorial, a genetic contribution is one likely component.

Through a consortium effort, we have identified a coding variant in the hormone receptor gene *CALCRL* that is common in people with Māori and Pacific ancestry but virtually absent in other ethnicities. We have shown that the *CALCRL* variant correlates with poor kidney function and inferior glucose metabolism in a large human cohort. Functional analyses revealed that the variant causes hyperactivation of adrenomedullin-CALCRL signalling (an axis that regulates pancreatic function and blood pressure). Our data suggest that the *CALCRL* variant may predispose carriers to insulin insufficiency and poor blood pressure control, thus accentuating the progression of diabetic nephropathy.

MD4: The paradoxical role of IL-6 in cardiometabolic health.

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IL-6 is a pleiotropic cytokine that is primarily secreted from immune cells in response to infection/inflammation, and from skeletal muscle in response to exercise. Genetic association studies have consistently shown that variants that increase IL-6 signalling associate with an increased risk of a host of cardiometabolic and inflammatory diseases. Paradoxically, exercise increases circulating IL-6 up to 100-fold and recent evidence suggests that this increase is involved in coordinating exercise training-induced cardiometabolic benefits. To investigate the contrasting dynamics of IL-6 on cardiometabolic health in a physiological context we generated a mouse model of a common human IL-6 promoter genetic variant, rs1800795 (IL-6 -174G>C). Consistent with human reports, knockin of the C allele in mice resulted in a 2-fold greater increase in IL-6 response to exercise and lipopolysaccharides. Preliminary data suggests while rs1800795 genotype does not greatly effect metabolic homeostasis in young healthy mice, but when fed a high fat diet the C allele has a sexually-dimorphic impact on weight gain and glucose homeostasis, and aspects of this phenotype can be rescued by running wheel access. Further studies are aimed at testing the hypothesis that under conditions of metabolic stress the rs1800795-C allele will impair cardiometabolic function as a result of chronically elevated IL-6 concentrations, and this will be reversed by exercise training, indicating that the greater acute exercise-induced increase in IL-6 in mice with a C allele results in greater cardiometabolic benefits from exercise training.

MD5: Unravelling novel gut-brain axis controlling sympathetic activity.

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Aberrant sympathetic activity exacerbates risk in hypertension and diabetes yet clinically remains poorly controlled. The hypertensive diabetic state is associated with increased reflex sensitivity and tonic drive from the carotid body (CB) adjunct to heightened sympathetic tone, the cause of which is unknown. Previously, we demonstrated that hypertension is critically dependent on CB input in the spontaneously hypertensive rat (SHR), a model that also exhibits a number of diabetic traits. We hypothesized that the CB sensitisation in the SHR may be linked to altered metabolism leading to dysfunctional reflex regulation in this model.

We used a hypothesis-free RNA-sequencing approach to investigate molecular pathways mediating CB sensitization and its regulation of sympathetic outflow in experimental hypertension (SHR). This led to the discovery of glucagon-like peptide-1 receptor (GLP-1R) expression in the CBs of rat and human where its decrease expression was associated with sympathetic hyperactivity in rats with cardiometabolic disease. Delivered to the CB, GLP-1 mimetics lowered its basal drive and attenuated chemoreflex-evoked blood pressure and sympathetic responses. Most importantly, hyperglycaemia-induced peripheral chemoreflex sensitisation was normalised by GLP-1R activation in the CB indicating a role in the homeostatic response to high blood glucose. We propose that GLP-1 signalling in the CB represent a novel gut-brain axis controlling sympathetic activity. Furthermore, we propose that targeting this pathway in the CB using clinically approved GLP-1R agonists may be used as a potential therapeutic strategy to alleviate aberrant sympathetic activity in metabolic syndrome.

MD6: Understanding amylin and its receptors for treating obesity and diabetes.

Hay, D.L.[1,2,3]

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Amylin is a pancreatic peptide hormone that controls blood glucose and body weight. One amylin mimetic, pramlintide (Symlin), is approved for clinical use for insulin-requiring diabetes but there is substantial scope for improvement by developing other amylin mimetic peptides with improved solubility and extended half-life. Amylin receptors are G protein-coupled receptors (GPCR) but are unusual in that they require accessory proteins, in addition to the core GPCR, to bind amylin with high affinity. Specifically, amylin receptors comprise the calcitonin receptor (CTR), together with receptor activity-modifying proteins (RAMPs). The three RAMPs with CTR form the AMY_1, AMY_2 and AMY_3 receptors, respectively. There are several splice variants of the CTR, and thus there are a large number of amylin receptor subtypes that could contribute to the mechanism of action of amylin. This presentation will outline the current status of research on amylin and amylin receptors. Progress towards the development of novel amylin mimetic peptides will also be discussed.

MD7: Hypothalamic Wnt/b-catenin signalling is required for normal metabolic homeostasis.

Grattan, D. R

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Human genome-wide association studies (GWAS) have revealed multiple genetic loci that confer susceptibility to the development of obesity and/or type-2 diabetes (T2D). Remarkably, at least 7 established genetic variants that associate with T2D are either components or targets of the Wnt signalling pathway, a pathway more commonly associated with embryogenesis and tumorigenesis. The strongest reported association with type-2 diabetes is a variant in TCF7L2, a binding partner of β-catenin in the canonical Wnt/β-catenin gene regulatory pathway. As the hypothalamus plays a key role in both bodyweight regulation and whole-body glucose homeostasis, we have been evaluating whether Wnt/β-catenin signalling may be involved in regulation of the neuronal circuits that regulate metabolism. We have previously shown that Wnt/β-catenin in specific hypothalamic regions is regulated by metabolic signals including feeding and leptin (1, 2). Here, we sought to determine whether β-catenin plays an critical role in the neuroendocrine regulation of body weight and glucose homeostasis. Using male and female β-catenin^{flox} mice, we performed bilateral injections of AAV2-mCherry-Cre into the hypothalamic arcuate nucleus to specifically delete β-catenin expression in that region in adult mice (MHB-β-cat KO). Surprisingly, on low-fat diet, MHB-β-cat KO mice were no different in body weight, despite equal caloric intake but increased energy expenditure ($P<0.05$). Nonetheless, the male mice did exhibit impaired glucose clearance ($P<0.05$). On high-fat diet, despite only a small difference in weekly caloric intake ($P<0.05$), the MHB-β-cat KO mice were markedly heavier than the control mice ($P<0.05$). This deficit seems to be a failure to show adaptive increase in energy expenditure seen in control animal that served to offset the increased calories by HFD. At this point both male and female had impaired glucose clearance, with the MHB-β-cat KO mice being highly glucose intolerant compared to control mice ($P<0.05$). Male MHB-β-cat KO mice displayed a significant reduction in both leptin sensitivity compared with control mice ($P<0.05$), but this effect was less pronounced in the females. This study highlights a critical role for β-catenin in the hypothalamic circuits regulating body weight and glucose homeostasis and reveals mechanisms by which genetic alterations in this pathway could impact on development of metabolic disease.

1) McEwen HJL, Cognard E, Ladyman SR, Khant-Aung Z, Tups A, Shepherd PR, Grattan DR. Feeding and GLP-1 receptor activation stabilize β-catenin in specific hypothalamic nuclei in male rats. J Neuroendocrinol. 2018 May 11:e12607. doi: 10.1111/jne.12607.

2) Benzler J, Andrews ZB, Pracht C, Stöhr S, Shepherd PR, Grattan DR, Tups A. Hypothalamic WNT signalling is impaired during obesity and reinstated by leptin treatment in male mice. Endocrinology. 2013 Dec;154(12):4737-45. doi: 10.1210/en.2013-1746. Epub 2013 Oct 8.

MD8: Catenin regulating the traffick: role of catenin proteins in the modulation of insulin vesicle trafficking in β-cells.

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Accumulating evidence indicates that adherens junctions play an important role in regulating the trafficking of vesicles to the plasma membrane. We have previously shown that adherens junction proteins, □-catenin and □-catenin could function as a rheostat to modulate insulin secretion. Next, we sought to understand how cadherin proteins regulate insulin secretion. First, we transfected rat pancreatic □-cell model INS-1E with siRNA targeting either E-cadherin or N-cadherin to modulate cadherin levels. Here we found that the individual depletion of either N-cadherin or E-cadherin does not affect insulin secretion; however simultaneous depletion of E-cadherin and N-cadherin significantly increases the basal insulin secretion indicating functional redundancy of these proteins. This double knockdown of cadherins also significantly reduced the levels of p120 catenin protein, which is involved in regulating cadherin internalization and turnover. We find that reduction in p120 catenin indeed destabilises both E-cadherin and N-cadherin along with a parallel decrease in □-catenin and □-catenin levels. Reduction in p120 catenin levels was also associated with increased levels of insulin secreted from the INS1E cells suggesting its involvement in the negative feedback mechanism in regulating glucose-stimulated insulin release. Further, we also found that the changes in actin remodelling and KCl stimulated calcium flux in p120 catenin-depleted cells are consistent with its effect on insulin release. These findings provide novel evidence to increase our understanding of how the proteins associated with adherens junctions regulate insulin secretion.

MD9: Are faecal microbes the magic pill for weight loss?

Wilson, B.C.[1], Vatanen, T.[1,2], Jayasinghe, T.N.[1], Leong, K.S.W.[1,3], Derraik, J.G.B.[1,3], Albert, B.B.[1,3], Chiavaroli, V.[1], Svirskis, D.M.[4], Beck, K.L.[5], Conlon, C.A.[5], Jiang, Y.[6], Schierding, W.[1], Holland, D.J.[7], Cutfield, W.S.[1,3], O'Sullivan, J.M.[1,3]

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What happens when you transplant faecal microbes from lean healthy individuals into a group of adolescents with obesity? This was the multi-million dollar question the Gut Bugs Trial team sought to answer. In a double-blinded randomised placebo-controlled trial, 87 adolescents with obesity received either multi-donor FMT (capsules containing the faecal microbiota of four healthy, lean, sex-matched donors) or placebo (saline capsules). Following a bowel cleanse, participants ingested a total of 28 capsules over two consecutive days. Clinical assessments and gut microbiome profiling were conducted at baseline and 6-, 12-, and 26-weeks after treatment.

We found that multi-donor FMT had no effect on body weight or total body fat percentage. However, we did find a reduction in the android to gynoid fat ratio, a marker of abdominal obesity, at all post-treatment timepoints. Most notably, we found complete reversal of metabolic syndrome in almost all (87%) of the treated participants who met the criteria for metabolic syndrome at baseline.

By utilising high-resolution metagenomic sequencing, we discovered that two donor microbiomes (one female, one male) dominated strain engraftment leading to durable shifts in the composition and metabolic potential of recipient gut microbiomes. However, engraftment rates were highly variable between recipients suggesting the host environment plays a critical role in mediating FMT receptivity.

We are now currently running three new FMT trials to better understand the role of the gut microbiome in metabolic syndrome, autism, and anorexia nervosa. We also intend to supplement these trials with experiments using human intestinal organoids to help in unravelling the mechanisms behind this exciting new microbial therapy.

MD10: Empowering Pacific-patient populations on the weight-loss surgery pathway: A co-designed evaluation trial.

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The condition of obesity meets all the criteria as a disease state1 and weight loss surgery is accepted as the most effective long-term treatment for obesity related diseases2. However, Pacific health consumers in New Zealand face both the highest rates of obesity and type 2 diabetes, and conversely, the lowest utilisation of weight loss surgery by population3. Systemic issues, gaps in patient knowledge of surgery benefits and risks, and lack of support from a cultural perspective have been identified as some of the factors contributing to Pacific-patients treatment ambivalence4. This presentation will explore a pre-surgery support programme co-designed with both the health professionals and previously successful Pacific patients. The resulting pre-surgery support programme may empower patients, and patients' families to engage with the treatment process resulting in higher overall retention rates and treatment satisfaction.

1. E. Pilitsi et al., *"Pharmacotherapy of obesity: available medications and drugs under investigation,"* Metabolism, vol. 92, pp. 170-192, 2019.
2. Nudel, J., & Sanchez, V. M. (2019). *Surgical management of obesity.* Metabolism, *92*, 206-216.
3. Rahiri, J. L., Lauti, M., Harwood, M., MacCormick, A. D., & Hill, A. G. (2018)1. *Ethnic disparities in rates of publicly funded bariatric surgery in New Zealand (2009–2014).* ANZ journal of surgery, 88(5), E366- E369.
4. Taylor, T., Wrapson, W., Dewes, O., Taufa, N., & Siegert, R. J. (2019). Preoperative bariatric surgery programme barriers facing Pacific patients in Auckland, New Zealand as perceived by health sector professionals: a qualitative study. *BMJ open*, *9*(11), e029525.

MD11: The Fructose in Schools Study (FiSS).

Conor O'Sullivan[1,2]
[1] The MOKO Foundation. [2] Maurice Wilkins Centre

Fructose, a dietary sugar has become an increasingly significant contributor to our diet. Importantly, though, there is a large degree of variability between individuals in their ability to absorb fructose, which is not the case for glucose.

The purpose of the Fructose in schools research programme is to understand whether there are significant differences in fructose absorption in New Zealand children and how this relates to the trajectory of obesity development. The study is being directed by a team of researchers affiliated with the Maurice Wilkins Centre for Molecular Biodiscovery, a Centre of Research Excellence based at the University of Auckland. Part of this study is being delivered however by Waharoa ki Te Toi, a community-based health research team located in Kaitaia since 2017. The Fructose in Schools Study (FiSS) is designed to give students a positive research experience and an opportunity to engage in a real-world scientific experiment that they do on themselves as well as being an innovative way to get dietary health messages into the community**.** The FiSS program has also become an example of how research programmes can be used as engagement points with schools and their communities to build further opportunities for young people looking to pathway into sciences. Through Fiss, the MOKO Foundation has been able to create initiatives prioritised for and reflective of the needs and desires of rangatahi Māori from the Te Hiku o te Ika to address barriers to accessing tertiary education.

Conor O'Sullivan will be talking about his experiences delivering the FiSS study to Kura Kaupapa Māori and mainstream schools in the Te Hiku o te Ika and beyond.

MD12: Carbohydrates in CVD prevention and management.

Reynolds, AN[1]

[1]Department of Medicine, University of Otago, Dunedin, NZ

Carbohydrates are a broad category of widely-consumed nutrients that include sugars, starches, and fibres. Despite this diversity, the contribution of total carbohydrate intake to health outcomes is often reported. This talk will briefly look at the evidence from meta for doing so, in terms of all-cause mortality, and then move on to consider health outcomes by carbohydrate type. Meta analyses on disease incidence will be discussed, as will new evidence on the role of dietary fibre as adjunct therapy in non-communicable disease management.

MD13: From Screening to Intervention: Vitamin C in the Pasifika Heart study.

Faatoese, A., .[1] Carr, A.,[2] John, C.,[3] Fakahau, T., [5] Maoate, B.,[4] Skidmore, P., and [6] Cameron, V.[1]

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Healthy dietary intake is associated with improving cardiovascular- and metabolic-health outcomes. Vitamin C (Vit C) is a potent antioxidant and a co-factor in many biological pathways. It is obtained by the consumption of fruit and vegetables. Food recall is used to calculate Vit C intake which may not necessarily reflect levels in circulation.

The Pasifika Heart study was designed to document cardiovascular risk factors for Pacific adults living in the Christchurch, NZ. A total of 200 adults, self-identified with any Pacific ethnicity, aged between 18-64 years underwent comprehensive cardiovascular risk screening, documentation of lifestyle behaviours. Random blood samples were collected for biomarker analysis. Levels of Vit C were measured in plasma using HPLC.

Recommended daily intakes of fruit of 2.0 (SD 1.3) servings were reached. Daily intake of vegetables consumption of 1.3 (0.8) serves were well below the recommended five serves a day. Mean circulating vit C levels were 30.7 (14.2) µM. Less than 10% achieved optimal vitamin C status of >50µM; 31% had levels <23 µM (hypovitaminosis C) and 8% were vitamin C deficient (< 11%). Current smokers had significantly lower levels compared to ex- and never smokers (current 23.7 (SD 14.8) uM vs. ex-smoker 32.4 (13.8) uM vs. never-smoker 32.0 (13.8)uM). Age, gender, BMI, diabetes and other risk factors and household income were not associated with vit C levels.

Findings from the Pasifika Heart study highlighted that literacy on healthy dietary intake requires effective approaches. Malie Le Loto, a pilot lifestyle intervention, was designed in partnership with a Primary Health Organisation. Using a family-focussed approach, a total of 50 adults will be recruited to participate in a 12-week intervention programme that is run in the community and Pacific-led. Pre- and post-intervention measures including Vit C will be measured, and evaluation of their experience with the study.

MD14: Update on rheumatic fever and rheumatic heart disease research in Aotearoa.

Rachel Webb[1]

[1]School of Medicine, Faculty of Medical and Health Sciences, University of Auckland.

MD15: Developing an intervention to optimise gestational weight gain.

Paterson H.[1] Coppell K.[2]

[1]Department of Woman's and Children's Health, Dunedin School of Medicine, University of Otago, NZ, [2]Department of Medicine, Dunedin School of Medicine, University of Otago, NZ.

Gestational weight gain has been extensively studied and gains in excess of the 2009 IOM guidelines appear to be associated with a higher incidence of adverse pregnancy outcomes. There have been multiple trials some of which have shown statistically significant reductions in weight gain but no change to clinical outcomes have been demonstrated.

We will describe our process through planned methodologies including RCT to our present case study proposal and the justifications of our journey.

MD16: Fish oil supplementation to rats fed a high-fat diet during pregnancy improves insulin sensitivity in the adult offspring.

Satokar VV[1], Vickers MH[1], Reynolds CM[1,2], Ponnampalam AP[3], Firth EM[1], Ramzan F[1], Garg ML[4], Barrett C[3], Cutfield WS[1,5], Albert BB[1,5]

[1]Liggins Institute, University of Auckland, Auckland, New Zealand, [2]University College Dublin Conway Institute of Biomolecular and Biomedical Research, Dublin, Ireland, [3]Manaaki Manawa - The Centre for Heart Research and the Department of Physiology, University of Auckland, New Zealand, [4]Nutraceuticals Research Program, School of Biomedical Sciences & Pharmacy, University of Newcastle, NSW, Australia, [5]A Better Start – National Science Challenge, University of Auckland, Auckland, New Zealand.

In rats, a maternal high-fat diet (HFD) leads to an adverse phenotype in the adult offspring[1] similar to the children of mothers with obesity during pregnancy[2]. A high dose of fish oil (FO) given to rat dams fed a HFD prevented the development of insulin resistance in the adult offspring[3]. A study was conducted to determine whether supplementation with a human-relevant dose of FO to pregnant rats can prevent the long-term adverse metabolic effects of maternal HFD on adult offspring.

Female rats (N=100, 90 days old) were assigned to either a HFD or a control diet (CD) prior to mating and following mating, they received a gel containing 0.05ml of FO (human-equivalent 2-3ml) or a control gel on each day of pregnancy and lactation. This produced 4 groups, CD-control gel, CD-FO gel, HFD-control gel and HFD-FO gel. Primary outcome was insulin sensitivity derived by Matsuda index in adult offspring. Metabolic parameters, body composition, liver and gonadal adipose tissue for morphology and gene expression were also assessed in the adult offspring.

In the adult offspring, a maternal HFD impaired insulin sensitivity ($p \leq 0.005$) in addition to greater food consumption, adipocyte hypertrophy, hepatocyte microsteatosis and alterations in gene expression. FO supplementation to dams fed HFD prevented the reduction in insulin sensitivity ($p<0.05$), and led to smaller adipocyte size, a trend to a decrease in liver microsteatosis and prevention of the pro-inflammatory effects on gene expression. FO supplementation to dams on CD, led to impaired insulin sensitivity ($p<0.01$), greater body weight, adipocyte hypertrophy, liver micro-steatosis and reduced ejection fraction.

FO was beneficial to the offspring if the mother consumed a HFD, but deleterious if the mother consumed a CD. This study suggests that supplementation with FO should be targeted to women expected to have abnormalities of metabolism such as those with overweight and obesity.

1. Srinivasan, M., et al., *Maternal high-fat diet consumption results in fetal malprogramming predisposing to the onset of metabolic syndrome-like phenotype in adulthood.* Am J Physiol Endocrinol Metab, 2006. **291**(4): p. E792-9.
2. Kaar, J.L., et al., *Maternal obesity, gestational weight gain, and offspring adiposity: the exploring perinatal outcomes among children study.* J Pediatr, 2014. **165**(3): p. 509-15.
3. Albert, B.B., et al., *Fish oil supplementation to rats fed high-fat diet during pregnancy prevents development of impaired insulin sensitivity in male adult offspring.* Sci Rep, 2017. **7**(1): p. 5595.

MD17: A sex specific risk factor for cardiovascular disease: Preeclampsia and the role of placental extracellular vesicles.

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[1]Department of Physiology, University of Auckland, Auckland, NZ, [2]Department of Obstetrics and Gynaecology, University of Auckland, Auckland, NZ, [3]The Liggins Institute, University of Auckland, Auckland, NZ, [4]Hub for Extracellular Vesicles Investigations (HEVI), University of Auckland, Auckland, NZ.

Preeclampsia is often considered a disorder limited to pregnancy, however women who experience preeclampsia are at an increased risk of developing cardiovascular disease later in life. There is growing evidence that the endothelial dysfunction associated with preeclampsia persists post-pregnancy contributing to the progression of cardiovascular disease. Our research team is examining the hypothesis that extracellular vesicles (EVs) derived from the placenta are essential in mediating both the normal cardiovascular responses to pregnancy, but also the potential for abnormal remodelling resulting in preeclampsia and later cardiovascular disease.

Using rodent models, we have examined the vascular responses to placental EVs. When pregnant mice are exposed to nano-EVs derived from first trimester placenta their mesenteric arteries are pro-dilatory, consistent with the decrease vascular resistance seen in early pregnancy. When exposed to EVs obtained from early onset preeclamptic placenta obtained at time of delivery, the mesenteric arteries displayed an increased response to vasoconstrictors, and reduced response to vasodilators, compared to those exposed to normal placental EVs. Additionally, we have shown that exposure to placental EVs can modify the cardiovascular disease trajectory, with hypertensive rats showing a greater increase in arterial pressure when exposed to EVs obtained from preeclamptic placenta vs normal placenta.

Together our results are suggesting the placental EVs can influence the maternal vasculature, both reducing vascular tone as part of the normal cardiovascular responses to pregnancy and increasing vascular tone in preeclampsia. Additionally, the exposure to EVs obtained from preeclamptic placenta has the potential to result in long-term changes, contributing to the increase in cardiovascular risk seen in women who have experienced preeclampsia.

MD18: How androgen excess shapes the polycystic ovary syndrome (PCOS)-like brain.

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[2]Department of Anatomy and Centre for Neuroendocrinology, University of Otago, School of Biomedical Sciences, NZ

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder seen in the clinic and impacts approximately 1 in 10 women of reproductive age. PCOS is characterised by androgen excess, impaired menstrual cycles , abnormal ovarian morphology and, in some cases, a metabolic syndrome, including obesity and hyperinsulinemia. Elevated luteinising hormone secretion is evident in most women with PCOS and implicates abnormal steroid hormone feedback to circuits in the brain that regulate fertility. Although the eitiology of PCOS remains unclear, exposure to androgen excess in early life is associated with PCOS development. To understand how androgen excess mediates PCOS pathophysiology, our group utilises two mouse models of androgen excess that reflect the lean and obese phenotypes of PCOS. In this talk, I will compare the effect of androgen excess in different developmental windows on specific brian circuits associated with reproductive function. I will also introduce recent evidence implicating androgen-induced impairments in microglia pruning of developing synapses as a mechanism by which PCOS pathology may develop.

MD19: Using mice to understand how the CREBRF variant drives larger size and lower diabetes risk.

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A coding SNP (p.Arg457Gln) in the CREBRF gene, found in ~25% of Māori and peoples of the Pacific islands, is associated with a large increase in BMI, yet paradoxically, it is also associated with an approximately 50% reduction in the incidence of type-2 diabetes [1,2]. The mechanism by which this variant drives these associated phenotypes is unknown and CREBRF itself has been subject to minimal study. Despite this, we know CREBRF is involved in regulation of bZip transcription factors that are ubiquitously expressed and have roles in several key cellular processes. We are working in a large NZ-wide collaboration to study CREBRF and our work is focused on molecular mechanism. Body size and glucose metabolism are regulated by the synchronous activities of many organs; requiring us to use a whole-body model system. Due to strong conservation in the CREBRF gene, we are able to use mice carrying the orthologous SNP to study this variant. We focused phenotyping on older mice as well as looking at global and targeted gene expression in tissues and mouse embryonic fibroblasts. Our in vitro work has confirmed the variant changes levels of CREBRF-regulated mRNA; basally and in response to stimuli. This data indicates glucocorticoid receptor activity is affected by the variant which may have clinical implications considering this is a target of commonly-prescribed anti-inflammatory drugs. We have characterised 20-month-old mice and show there are differences in body composition that manifest at this age and in males this is accompanied by increased grip strength and rotarod performance as well as lower serum myostatin levels [3]. Body composition changes are accompanied by improvements in glucose metabolism; improved insulin responsiveness accompanied by lower serum insulin in response to stimuli. The SNP does not lead to phenotypic outcomes that are seen in CREBRF genetic ablation models. Our mouse models will be useful for further exploring the molecular mechanisms by which the CREBRF variant can confer metabolic protection.

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MD20: Protective role of a Polynesian-specific variant of the CREBRF gene against gestational diabetes mellitus (GDM): mouse model.

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During pregnancy, the mother needs to provide the growing fetus with a constant supply of glucose, requiring major adaptations in maternal glucose homeostasis. Dysfunction of glucose regulation, particularly when β-cells fail to compensate for the insulin resistance of late pregnancy, can lead to gestational diabetes mellitus (GDM). Recently, a Polynesian-specific variant (R457Q) of the *CREBRF* gene was shown to be markedly protective against the development of GDM. To investigate the mechanisms underlying this protection we used a novel mouse line generated to model the Polynesian-specific gene variant. In mice, pregnancy-induced adaptations of β-cells are dependent on the pituitary hormone prolactin and deletion of the *Crebrf* gene in mice causes marked suppression of prolactin secretion. We hypothesized that the CREBRF variant 'knock in' (KI) mice may display a 'gain of function' resulting in elevated prolactin during pregnancy, thus providing protection against GDM. Since mice do not naturally develop GDM we utilized a model of diet-induced obesity to challenge glucose homeostasis during pregnancy. Mice fed a high fat diet (HFD) had impaired glucose tolerance both before and during pregnancy compared to mice on a control diet but there was no difference between genotypes. As hypothesized, a significant increase in prolactin level was detected in pregnant KI mice, in both the HFD-fed and control groups. To explore how this CREBRF variant may influence prolactin levels, the expression of the *Crebrf* gene was assessed using RNAscope *in situ* hybridization in the brain region which contains neurons that regulate prolactin secretion. However, KI mice and control mice had similar levels of *Crebrf* gene expression during pregnancy. Overall, these data suggest that increased prolactin levels are observed in mice containing the R457Q CREBRF gene variant, and this is consistent with the hypothesis that enhanced prolactin could contribute to the protection from gestational diabetes.

MD21: Accelerated DNA Methylation epigenetic age in vascular disease.

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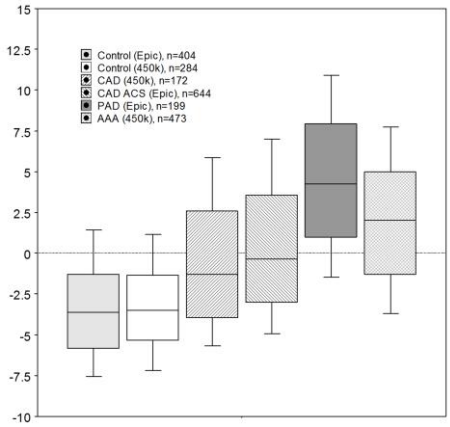
Accelerated epigenetic age has been suggested as a means of predicting a range of later-life health outcome related events, including time to heart disease or death.

This talk will present the epigenetic clock scores of several Aotearoa New Zealand patient cohorts with different forms of cardiovascular disease (abdominal aortic aneurysm; AAA, coronary artery disease; CAD and peripheral artery disease; PAD) and compare these with healthy elderly controls. Externally weighted epigenetic clocks scores were calculated using data derived from Illumina DNA methylation (450k or EPIC) arrays.

DNA methylation 'GrimAge' (adjusted for chronological age) was the most significantly different score between disease and control groups. Amongst vascular disease cohorts, more accelerated epigenetic age was observed in peripheral artery disease patients when compared to those with coronary artery disease. Although these associations were partially confounded by smoking history, there was no strong association with diabetes. The association between epigenetic GrimAge and vascular diseases remained significant in a comprehensive multivariate regression model, which included other cardiovascular risk factors (age, sex, smoking, hypertension, BMI, dyslipidaemia, diabetes). Accelerated epigenetic (GrimAge) age had an area under the curve of 0.91 (95% CI 0.88-0.93), with a sensitivity of 82% and specificity of 86%, in ROC analysis.

Epigenetic age scores are significantly, but differentially, increased in those with a range of vascular disease phenotypes. The incorporation of epigenetic risk scores into 'conventional' cardiovascular disease risk prediction scores warrants further investigation.



This study was funded by grants from the Health Research Council of New Zealand, The Healthier Lives, National Science Challenge and Genomics Aotearoa (a New Zealand Ministry of Business, Innovation and Employment funded research platform).

MD22: Predicting progression from coronary artery disease to heart failure.

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Many patients surviving acute coronary events incur later adverse sequelae, especially heart failure. In our own cohorts ~10% of patients develop ischaemic heart failure within 5 years after an acute coronary event. However, the rate and extent of remodelling is influenced by many factors and varies considerably between patients, making it difficult to identify those at risk. We have derived a clinical risk model to predict heart failure after an acute coronary event that combines clinical factors with cardiac biomarkers. Although strongly predictive, this model does not predict heart failure in all patients, and we are now investigating whether including genetic predictors in a multi-variable model could help identify those at risk.

First, we are developing a pragmatic clinical risk model (including variables typically collected in research cohorts) to predict progression to heart failure in 30,000 patients with coronary artery disease from NZ, the United Kingdom (UK Biobank) and Iceland. Second, in the same cohorts, we are undertaking a genome wide association study to identify genetic variants that differ in frequency between patients who develop heart failure compared with those who do not, so as to develop a genetic risk score. Finally, we will validate our clinical and genetic models in 20,000 patients from independent cohorts from the GENIUS consortium (www.genius-chd.com) and in 2,000 patients from contemporary NZ cohorts including 400 Māori patients. Our project will identify whether a genetic risk score has the potential to improve prediction of heart failure beyond established clinical predictors and may help identify high-risk patients who would benefit from intensified monitoring and treatment.

We gratefully acknowledge funding from the Health Research Council, the Heart Foundation and the Christchurch Heart Institute Trust.

MD23: Understanding genetic impact on metformin efficacy to guide clinical treatment in diabetes.

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Metformin is the first line treatment for type-2 diabetes and achieves its effects by increasing the ability of the body to dispose of glucose. This involves a range of mechanisms including increased GDF15 production in the gut which affects food intake a direct effect on liver and muscle to improve the efficacy of insulin. SLC22A3 is a cation transporter that is involved in the uptake of metformin from the gut and into cells. Genetic variants have been identified in SLC22A3 which affect the rate of these into cells. While most of these reduce the rate of metformin transport in *in vitro* systems, the Thr44Met coding variant (rs8187715) increases transport of metformin in these systems. Since this coding variant was rare in European populations it was not pursued further but here, we report it is present in up to 25% of Māori and Pacific peoples. Therefore, to study this variant in a physiological context we made an orthologous knock-in mouse model. These studies show the variant does increase the rate of uptake of metformin into the blood. Acute dosing studies with metformin showed the variant was associated with reduced weight loss, loss of metformin effects on food intake and increased insulin sensitivity. To reconcile these findings with recent evidence indication a role for GDF15 in metformin's actions, we measured GDF15 levels and found while metformin increased GDF15 in wild type mice, it did not do so in knock-in mice. Together this is consistent with a model in which accelerated rate of metformin uptake increases actions on insulin sensitive tissues to increase insulin sensitivity while reducing the effects of metformin in the gut. Therefore, these studies show that the T44M variant as a pharmacogenomic marker that has potential to guide response to metabolic disease development and treatment in Māori and Pacific peoples.

MD24: Precision medicine in Diabetes: Type 2 diabetes medication Which One is Right Here? (WORTH) study.

Rebecca Brandon[1,2], Yannan Jiang[3,4], Rui Qian Yeu[1,2], Ry Tweedie-Cullen[1,2], Kate Smallman[5], Glenn Doherty[6], Kerry A Macaskill-Smith[7], Rebekah J Doran[7], Penny Clark[7], Allan Moffitt[8], Troy Merry[2,9], Norma Nehren[10], Frances King[11], Jennie Harré Hindmarsh[11], Megan Leask[2,12,13], Tony R Merriman[2,12,13], Brandon Orr-Walker[14], Peter R Shepherd[2,15], Ryan Paul[2,16], Rinki Murphy[1,2]

Aims: To investigate comparative glycaemic lowering by vildagliptin and pioglitazone among people (a) of Māori and/or Pacific ethnicity (b) with obesity and/or hypertriglyceridemia (OHTG) or (c) with *CREBRF rs373863838* (p.Arg457Gln) A-allele.

Methods: A randomised, open-label, two-period crossover trial was conducted in New Zealand adults with type 2 diabetes, HbA1c>58mmol/mol (>7.5%), who received 16 weeks of either pioglitazone [P] (30mg) or vildagliptin [V] (50mg) daily, then switched over for another 16 weeks of treatment. Differences in HbA1c [P vs V] were tested for interaction with ethnicity, OHTG or genotype, controlling for baseline HbA1c using linear mixed models. Secondary outcomes included weight, blood pressure (BP), side effects and diabetes treatment satisfaction.

Results: 346 participants were randomised (55% M/P) between February 2019 to March 2020. Overall, HbA1c after pioglitazone was lower than after vildagliptin (mean difference -4.9mmol/mol [0.5%]; 95% CI -6.3,-3.5; p<0.0001). Primary intention-to-treat analysis showed no significant interaction effect by Māori and/or Pacific vs other ethnicity (1.5mmol/mol [0.1%], 95%CI -0.8, 3.7), and per-protocol analysis (-1.2mmol/mol [0.1%], 95% CI -4.1, 1.7). An interaction effect was found by OHTG status (interaction effect -4.7mmol/mol [0.5%], 95% CI -8.1, -1.4), but not by *rs373863828* genotype. Weight gain after pioglitazone relative to vildagliptin was lower among those with the A allele vs those homozygous for the GG genotype (interaction effect -2kg, 95%CI -3.4, -0.6).

Conclusions: Comparative glucose-lowering by pioglitazone and vildagliptin does not differ in Māori and/or Pacific compared to those of other ethnic groups. OHTG is a useful predictor for stratified glucose response to these medications.

MD25: Sympathetic modulation of pressure, flow and capacitance – implications for cardiovascular control.

Fiona D McBryde

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A tightly controlled relationship between blood pressure (BP) and organ blood flow is vital for matching an organ's metabolic needs to the delivery of oxygen and nutrients. However, the nature of the pressure-flow relationship is complex and governed by multiple control systems, including local autoregulatory mechanisms at the level of the individual organ, as well as neural and hormonal modulation. To fully understand how pressure-flow relationships operate in health, and may be altered in pathological settings, we have made direct, long-term assessments of BP and blood flow to "consumer" organs such as the brain, and "reservoir" organs such as the mesenteric bed, in conscious rats. We have assessed the relationships between pressure and flow in rats with normotension and in hypertension, where sympathetic drive is chronically elevated.

We have found that blood flow to the brain is highly affected by experimentally induced decreases in BP. This contrasts the traditional view that brain blood flow is kept constant via cerebral autoregulation. Resting brain blood flow was significantly lower in hypertensive rats, and similarly sensitive to falls in BP. This suggests that brain blood flow may be more vulnerable to dynamic changes in hypertensive rats with reduced cerebrovascular reserve. This may be particularly important in situations such as ischemic stroke, where protecting collateral blood flow is essential to avoid poor outcomes.

We also found that SHR have higher venous tone and reduced capacity to accommodate excess volume within the mesenteric vascular bed. Reductions in sympathetic drive reduced venous tone and improved the ability to accommodate volume load. Inhibiting sympathetic activity may provide a novel therapeutic opportunity to restore venous mesenteric capacity and potentially ameliorate hypertension.

MD26: Using stem cell-derived kidney organoids for disease modelling.

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The ability to reprogram adult cells back to an induced pluripotent stem cell (iPSC) state has revolutionised how human diseases are studied and treated. iPSCs have the potential to generate any of the body's ~200 cell types and thus provide a limitless supply of human tissue to be used to model human diseases *in vitro*. Our lab has generated the first human iPSC lines in NZ and developed a protocol for growing kidney organoids from these cells. We have previously shown that these mini-kidneys are susceptible to drug-induced injury similar to the human kidney, and can be used for toxicity screening of clinical drugs.

With the ease and efficiency of CRISPR/Cas9 genome-editing, we have also modified kidney-associated genes in iPSCs in order to recapitulate genetic kidney defects in the organoids. I will present our latest work on polycystic kidney disease (PKD), which is characterised by progressive development and enlargement of kidney cysts and can lead to kidney failure. Metabolically, PKD kidneys show alterations that include defective glycolysis, mitochondrial function and fatty acid synthesis. PKD accounts for ~10% of dialysis patients worldwide, yet a shortage of safe and effective treatment options remains. We have generated knockout iPSC lines for *PKD2*, the gene responsible for autosomal dominant PKD. We found that *PKD2*-deficient organoids develop large fluid-filled cysts that resemble those in PKD patients. Our approach to address the need for new PKD therapies is to screen the cystic organoids with a novel type of library that consists of conjugates of small molecule nutrients. Slowing or reversing cyst growth by targeting altered metabolic/nutrient pathways in PKD could represent a new therapeutic strategy, with the benefit of such conjugated nutrients exhibiting more predictable safety profiles than unnatural drugs.

MD27: Beyond blood pressure and glucose lowering: SGLT 2 inhibition and diabetes kidney disease.

Dr Jasmine Tan,

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Diabetic kidney disease is defined by the presence of chronic kidney disease and/or sustained proteinuria in patients with diabetes. Patients who suffer from this condition have an elevated risk for cardiovascular disease which contributes to 45% of all-cause mortality in this population.

To modify cardiovascular risk in patients with diabetic kidney disease, standard treatment with renin-angiotensin aldosterone system (RAS) blockers have been used. It is well-recognised that RAS blockers modify cardiac remodelling, resulting in a reduction in cardiovascular associated death and congestive heart failure hospital admissions. In addition, these medications confer renal protection beyond blood pressure lowering, reducing the development of end stage renal disease.

Recently, addition of sodium–glucose cotransporter 2 (SGLT 2) inhibitors to standard therapy, have shown further improvement in cardiovascular and renal outcomes. These include reductions in cardiovascular death (38% reduction), heart failure hospitalizations (39% reduction) and end stage renal disease development (60% reduction). The greatest benefit is observed in patients with significant proteinuria.

Mitigating glucose, sodium, and chloride hyperabsorption at the proximal renal tubules, predominantly via SGLT 2 receptor inhibition, has been widely accepted as the principal mechanism behind this cardiorenal risk reduction. However as there are only modest improvements in glycated haemoglobin (HbA1c) and blood pressure, alternative pathways of action of SGLT 2 inhibitors have been investigated, suggesting that an extensive extra-renal effect of SGLT 2 inhibition likely contributes to the cardiorenal benefit demonstrated clinically.

MD28: Neurocardiac aspects of the long QT Syndrome- a sympathetically triggered arrhythmia.

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Long QT syndrome (LQTS) is the most common cause of unexplained sudden cardiac death in New Zealand youth. Life-threatening LQTS arrhythmias are typically triggered by the sympathetic “fight or flight” response, however, the cellular mechanisms underlying sympathetic triggering of LQTS arrhythmia remain incompletely characterised.

The most common LQTS subtype is LQT1, caused by loss-of-function variants in the *KCNQ1* gene that encodes the Kv.7.1 potassium channel, leading to prolonged cardiac repolarisation and increased arrhythmia risk. *KCNQ1* function-loss is also associated with neuronal pathologies causing sudden death. The LQT1 sympathetic neuronal phenotype is unstudied in human cells.

Here we aimed to study human induced pluripotent stem cell (hiPSC)-derived sympathetic neurons (SNs) to evaluate neuronal functional phenotype in LQT1. We generated hiPSC-SNs from two LQT1 patients with a history of sympathetically triggered arrhythmia and *KCNQ1* loss-of-function genotypes (c.781_782delinsTC and p.S349W/p.R518X). Characterisation of hiPSC-SNs was performed using immunohistochemistry, enzyme-linked immunosorbent assay and whole-cell patch clamp electrophysiology, and functional LQT1 hiPSC-SN phenotypes compared to healthy control (WT) hiPSC-SNs. hiPSC-SNs stained positive for tyrosine hydroxylase, peripherin, KCNQ1, and secreted noradrenaline. hiPSC-SNs at 60±2.2 days in vitro had healthy resting membrane potentials (-60±1.3 mV) and fired rapid action potentials with mature kinetics in response to stimulation. Significant hyperactivity in LQT1 hiPSC-SNs was evident via increased noradrenaline release, increased spontaneous action potential frequency and reduced afterhyperpolarisation, compared to age-matched WT hiPSC-SNs. A significantly higher action potential frequency upon current injection and larger synaptic current amplitudes in compound heterozygous p.S349W/p.R518X hiPSC-SNs compared to heterozygous c.781_782delinsTC hiPSC-SNs was also observed, suggesting a potential genotype-phenotype correlation. Together our data reveal increased neurotransmission and excitability in heterozygous and compound heterozygous patient-derived LQT1 sympathetic neurons, suggesting that the cellular arrhythmogenic potential in LQT1 is not restricted to cardiomyocytes.

MD29: Insights into metabolic disease in CHamoru in Guam, Western Micronesia.

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It has long been understood that Māori and Pacific people living in Aotearoa New Zealand suffer a higher burden of gout, type 2 diabetes and other metabolic conditions compared to people belonging to other ethnic groups. While structural inequities contribute to the increased prevalence genetic studies have shown that shared genetic ancestry contributes. But how recent is this genetic ancestry and can we see similarly high burdens of disease in ancestrally-related populations from other parts of the Pacific?

Methods

We recruited 152 CHamoru (the indigenous people of Guam) from Western Micronesia to participate in our study. Information about metabolic history, lifestyle behaviours, height and weight, blood pressure, and non-fasting blood and urine, in addition to DNA, were collected. Low pass genome sequencing has been undertaken to investigate genetic contribution to disease.

Results

Of the 152 CHamoru participants, we found that self-reported metabolic conditions included: diabetes (19.7%), gout (28.9%), hypertension (34.9%), dyslipidemia (17.8%), and heart conditions (9.9%). Compared to females, more males reported gout (40.5% versus 18.7%; P=0.003) and were hypertensive (48% versus 21.1%; P<0.0001), had hyperuricaemia (64.4% versus 31.6%; P<0.0001), and obese (77.3% versus 46.1%; P<0.0001).

Conclusions

The CHamoru population of Guam have a high burden of metabolic disease, similar to what is seen among Māori and Pacific people in Aotearoa New Zealand. This is consistent with our hypothesis that that there is a shared Pacific-wide genetic predisposition to metabolic conditions such as gout, though more data is still necessary and genetic analyses are ongoing.

MD30: FGF-2 reverses myofibroblastic activation of diseased valvular interstitial cells.

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In healthy people, valvular interstitial cells (VICs) maintain structure and function of the heart valves. Like all interstitial cells, VICs can differentiate into myofibroblasts in response to changes in their environment. Excessive myofibroblastic activation is the pathological process behind aortic valve sclerosis and calcification—a disease affecting a quarter of over-65s. Aortic valve calcification is widely prevalent in older adults and increasing life expectancies worldwide are set to drastically increase the incidence of this disease. Despite this, the molecular cues governing the activation of VICs is poorly understood.

We isolated human VICs from calcified aortic valves and cultured them in medium containing fibroblast growth factor 2 (FGF-2) and nitric oxide. Myofibroblastic activation was assessed by cell morphology and alpha-SMA staining at 48 and 96 hours. Cell viability and proliferation was measured by resazurin assay. We also compared expression of 24 genes associated with myofibroblasts, osteogenesis, and matrix production.

We found 10ng/mL FGF-2 inhibited the development of myofibroblastic morphological changes, including a significant decrease in area and circularity, and increase in aspect ratio. Proportion of cells 'strongly' positive for alpha-SMA approached 0% in the treatment groups. Resazurin assay showed no effect on proliferation. Without treatment, VICs showed a pro-fibrotic pattern of gene expression, and when treated with FGF-2, this effect was reverted to a quiescent-type pattern. In particular, expression of collagen and matrix metalloproteases was significantly reduced.

This study is the first instance of treating diseased human cells with FGF-2. We have demonstrated that FGF-2 is a powerful inhibitor of myofibroblastic activation in VICs and is able to reverse the pathological changes seen in diseased valve cells, constituting an *in vitro* therapeutic effect.

MD31: The Māori and Pacific specific type 2 diabetes protective gene variant, *CREBRF* rs373863828, is associated with greater early phase insulin response to a glucose stimulus.

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[11] *Waitemata District Health Board*

Obesity and type 2 diabetes (T2D) are major health concerns. Genetics has a role in these conditions. The *rs373863828* minor A allele in the *CREBRF* gene is of interest because it is uniquely found in up to 25% of Māori and Pacific people, and is associated with an approximately 1.4 units increase in BMI [1,2] but paradoxically, 40-60% lower risk of type 2[1] and gestational diabetes[2]. Given T2D is characterised by impaired insulin action and impaired □-cell function, we investigated the impact of *rs373863828* on these metabolic components in young, overweight but otherwise healthy, men of Māori and Pacific ancestry. In response to both an oral (mixed meal tolerance test) and intravenous (intravenous glucose tolerance test and two-step hyperglycemic clamp) glucose challenge, *rs373863828* minor A allele was associated with a greater increase in plasma insulin during the early phases of both tests. Typically, greater plasma insulin is indicative of insulin resistance, yet we found the variant to have no effect on insulin sensitivity index or glucose disposal during a hyperinsulinemic-euglycemic clamp. We found no association of the *CREBRF* rs373863828 minor A allele with response to arginine stimulation test, a proxy measure of □-cell mass. This work suggests that the T2D protective effect of *rs373863828* minor A allele may be due to enhanced □-cell insulin secretory responsiveness or resilience of □-cells to metabolic stress. Understanding how this influences metabolic disease risk could play a key role in developing treatment and prevention strategies tailored to Māori and Pacific peoples.

MD32: Identifying novel mitochondrial derived peptides from utilising natural variations in mtDNA.

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Introduction

Mitochondrial derived peptides (MDPs) are newly discovered regulators of metabolism that are encoded as short open reading frames (ORFs) of the mitochondrial DNA (mtDNA). There are >700 ORFs within the mtDNA, while only eight MDPs have been identified. Unique SNPs in the mtDNA could be a useful tool to identify other MDPs. Therefore, the aim of the study is to identify potential biologically active MDPs by correlating SNPs with the prevalence of metabolic diseases and test their effects on metabolism.

Method

mtDNA sequencing analysis was conducted on 2407 participants with Polynesian ancestry. Stratifying the cohort revealed that for West Polynesians, the SNP A6905G was associated with diabetes (OR=1.52, p=0.034). A6905G is synonymous in the COX1 gene, but alters the sequences of three putative MDPs: 34A, 29B, and 59C.

10 week old C57BL/6 male mice were fed a high-fat diet for 10 weeks with daily intraperitoneal injections (5mg/kg) of 34A, 29B, 59C, or vehicle control (n=8 per group, n=7 in 59C). Over the course of treatment, mice were challenged with several metabolic tests and culled to collect metabolically active tissues.

Results

After 10 weeks of treatment, mice did not show any significant difference in body weight or tissue weights. Blood glucose changes from a glucose tolerance test, insulin tolerance test, and fast-refeed did not differ between groups. Resting energy expenditure and oxygen consumption were also not different between groups.

Conclusion

Unfortunately, we did not observe any metabolic phenotype differences after treatment with the three MDPs. However, as these peptides have never been tested before, it is possible that the study design was not able to capture any metabolic effects. Possible reasons for this could be the disease-inducing diet, duration of study, or dosage. Further investigation on i*n vitro* models will provide some insight to their function.

MD33: A novel protocol for the enrichment of exosomes yield from biological fluids.

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Exosomes are extracellular nanovesicles released by cells and mediate cell to cell communications and are considered as intercellular wireless communicators [1-3]. Recently, exosomes have gained interest due to their association in many physiological and pathophysiological processes, proving to be a novel therapeutic agent [1, 4-12]. However, there is no reproducible protocol available that can be adapted for the isolation of concentrated pure exosomes for therapeutic use. [8, 13, 14]. Therefore, the aim of this study is to optimize and develop a protocol for the isolation of exosomes from biological fluids.

Pericardial fluid was used as the biological fluid for this study. Exosomes were isolated by 3 techniques (precipitation, size exclusion chromatography (SEC), and a combination of precipitation and SEC). Isolated exosomes were characterised by western blot analysis, transmission electron microscopy (TEM), immuno gold labelling and dynamic light scattering to confirm their purity. Among all three methods, exosomes isolated by precipitation were highly concentrated, however, they were also contaminated with cellular debris and large vesicles. Western blot analysis confirmed the expression of exosome surface markers (CD63, HSP60 and Alix) in all three isolation groups. However, exosomes isolated from the precipitation groups were positive for Calnexin, a marker for non-exosomal components. TEM analysis of precipitated exosomes showed aggregated exosomes. SEC resulted in pure exosomes within the size range (10-150µm), however, at low concentrations. Interestingly, combination of precipitation followed by SEC resulted in pure concentrated exosomes, with TEM showing no aggregation.

We have established a novel reproducible protocol for isolation of pure exosomes from biological fluids that have low exosomal counts. This has laid foundation to test the therapeutic efficacy of pure exosomes in various diseases.

MD34: Administration of alpha-1-antitrypsin attenuates hepatic steatosis and escalation to non-alcoholic steatohepatitis in mice.

D'Souza RF.[1,2], Puliuvea C [2,3], Chan AHC [1,2], Woodhead JST [1,2], Zheng X [1], MacRae C [1], Hedges CP [1,2], Merry TL [1,2].

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Non-alcoholic fatty liver diseases (NAFLD) are a spectrum disorder and the leading cause of liver transplants worldwide. Whilst NAFLD usually presents as a benign accumulation of liver lipids, it can spontaneously escalate to more serious non-alcoholic steatohepatitis (NASH) which includes hepatic steatosis, immune-cell infiltration, fibrosis development and also loss of liver function. Currently there are no clinically approved therapeutics for the treatment of NAFLD. However, emerging evidence suggests neutrophils may play a central role in the early escalation of NASH via the proteolytic activity of secreted neutrophil serine proteases (NSPs). As such, we hypothesised that treatment of mice with an endogenously produced inhibitor of NSP activity, alpha-1-antitrypsin (A1AT), may be a therapeutic for early NASH development. Firstly, we validated a diet model of NASH, showing that feeding mice a diet that is choline-deficient amino acid defined and high in fat rapidly drives hepatic lipid accumulation, inflammation and fibrosis in C57Bl6J mice. We then fed mice this diet for 10 weeks and treated with vehicle or A1AT (i.p 3x weekly 2mg/mouse) and assessed the effects on hepatic neutrophil infiltration and hepatic lipid accumulation, markers of fibrosis and inflammation as indicators of NASH. A1AT treatment did not affect blood neutrophils levels, but did lower the most abundant NSP, neutrophil elastase. Furthermore, mRNA reflective of neutrophils and NSPs were lower in livers from A1AT treated mice. In addition, A1AT-augmentation reduced liver NAFLD severity scores, it also attenuated the shift in the ratios of collagen type III to collagen I suggesting an attenuation in liver fibrosis. This was reflected in reduced concentration of the plasma liver damage marker, ALT, in A1AT treated mice. These results indicate that targeting hepatic neutrophil accumulation under conditions of metabolic stress, potentially via A1AT treatment, may be a therapeutic strategy to prevent NASH escalation.

MD35: Phosphorylation of RyR2 by CK2 is anti-arrhythmic.

Valeria Mereacre, Peter Jones.

Department of Physiology, University of Otago, School of Biomedical Sciences, NZ

The ryanodine receptor 2 (RyR2) is located within the membrane of the sarcoplasmic reticulum, where it plays an essential role in cardiac excitation-contraction coupling, releasing the bulk Ca2+ required for contraction. However, inappropriate release of Ca2+ through RyR2 (termed Ca2+ sparks) can also trigger arrhythmias. We have recently identified that RyR2 is phosphorylated by casein kinase 2 (CK2), and that in vitro loss of this phosphorylation increases Ca2+ sparks. This project aimed to determine the role of CK2 phosphorylation of RyR2 in vivo. This was achieved using phospho-specific mutant mice, which expressed a variant of RyR2 unable to be phosphorylated by CK2 (S2692A/S2693A ++). To determine if loss of phosphorylation increases Ca2+ sparks, line-scan imaging was performed on isolated cardiomyocytes from S2692A/S2693A ++ and wildtype controls. Cells isolated from S2692A/S2693A ++ animals exhibited 4.64 sparks/100µm/s which was significantly greater than in control animals 2.21 sparks/100µm/s (45=cells, 8=animals per group respectively, p=0.0007). Next, to determine if this increase in Ca2+ spark frequency translated to an increased risk of arrhythmias, electrocardiograms were recorded before and after a pharmacological stress trigger, an intraperitoneal injection of caffeine (120 mg/kg) and epinephrine (1.6 mg/kg). In control animals this procedure increased the heart rate but had little effect on arrhythmogenicity, with brief changes in sinus rhythm occurring in only 2 out of 9 animals. In contrast, S2692A/S2693A ++, animals experienced a significant increase (7 out of 10 animal) in severe and prolonged non-sinus rhythm (p=0.0173). Combined these data show that phosphorylation of RyR2 by CK2 is essential for normal channel function and Ca2+ release, and that loss of phosphorylation increases Ca2+ leak and the susceptibility of arrhythmia. Clinically, this may offer a new target to treat one of the leading causes of death in New Zealand.

MD36: Inhibition of PI3K to promote weight loss.

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Obesity is a major health concern, both in New Zealand and globally. Present lifestyle and pharmacological interventions for weight loss show relatively modest effects in the long term (>1 year), thus there is a need for alternative intervention options. Insulin is an anabolic hormone released in response to increased blood glucose levels, and one of the actions of insulin is to promote glucose uptake into adipose tissue, where it can be stored as lipid. Phosphoinositide-3-kinase (PI3K) is involved in the insulin signalling pathway, and we have previously shown in mice that chronic PI3K inhibitor consumption in a chow diet resulted in mild weight loss. Therefore, we tested the effectiveness of PI3K inhibitor treatment as a potential weight-loss therapeutic in an obesity setting.

Mice were made obese by high-fat diet feeding for ~10 weeks, after which mice were assigned to high-fat diet containing either 0.3g/kg of BYL-719 (PI3Ki), or Vehicle (0.5% DMSO). PI3Ki treatment resulted in rapid and sustained weight loss in diet-induced obese mice, occurring predominantly from decreased fat mass. Additionally, hepatic lipid accumulation was evident in vehicle treated mice, but was absent in PI3Ki treated mice. Indirect calorimetry assessment shows PI3Ki resulted in increased in energy expenditure, and decreased in RER, suggesting elevated fat metabolism. PI3Ki treatment did induce hyperglycaemia, a known on-target effect of PI3K inhibitors. Co-treatment with the SGLT2 inhibitor Empagliflozin prevents this hyperglycaemia, without affecting the magnitude of weight loss. Our current experiments are focusing on understanding the mechanisms leading to weight loss, and how side effects can be managed. However, these investigations suggest inhibition of PI3K is a promising therapeutic candidate for effective weight loss treatment.

MD37: Neural plasticity in the innervation of the heart and its potential role in cardiac arrhythmias.

Montgomery, J.M.[1], Ashton J.[1], Smith J[1], Anderson M[2], Argent L.[1], Tedoldi A.[1], Lever N[2], Ramanathan I[2].

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Atrial fibrillation (AF), is the most common serious cardiac arrhythmia with an overall prevalence of 1.7% in the New Zealand population. AF burden is significantly higher in Māori and Pacific people in New Zealand, resulting in higher risk of stroke. Modulation of neural input into the heart is emerging as a novel therapeutic option for AF management: specifically the sympathetic and parasympathetic nervous systems control heart rhythm and the hearts susceptibility to arrhythmias. Parasympathetic fibres form synapses onto clusters of neurons on the heart surface, termed “ganglionated plexi” (GP) or “little brains”. These neurons are the final site of neuronal input to the heart and are known to play a critical role in initiating and maintaining AF. Little is known about the functional properties of these neurons however, and how their electrical activity could contribute to AF. We have performed the first whole cell recordings from GP neurons in epicardial tissue isolated from both a rodent model of hypertension and AF (spontaneously hypertensive rats), and patients with and without AF undergoing open heart surgery at Auckland City Hospital. In rodent tissue, our data show significantly increased frequency of spontaneous synaptic activity and action potential firing in SHRs over controls, as well as increased synaptic density, cholinergic neurons, and noradrenergic glomus cells. In human patient tissue samples, human GP neurons showed increased complexity in dendritic morphology compared with rodent tissue, and fired both continuous and accommodating action potential firing patterns. Preliminary data from AF patients suggests more depolarised resting membrane potentials and lower thresholds for action potentials, suggesting that GP neurons have increased excitability in AF. Together our data show evidence of structural and functional plasticity occurring in the innervation of the heart, suggesting that neural plasticity contributes to the substrate for atrial arrhythmia.

MD38: Role of calcium in arrhythmias

Pete Jones

Department of Physiology and HeartOtago, University of Otago, Dunedin, NZ.

Cardiac contraction depends on the cyclic release of calcium into individual cardiomyocytes. The bulk of this calcium is released from the sarcoplasmic reticulum (SR) through the cardiac ryanodine receptor (RyR2). The magnitude and timing of calcium release is critical to control both the strength and timing of contraction. Consequently, inappropriately timed release of calcium through RyR2 can lead to abnormal contractions and arrhythmias. The function of RyR2 is has been proposed to be regulated by several signalling pathways as well as the ultrastructural arrangement of individual channels within the SR.

We have identified that several forms of posttranslational modification, including phosphorylation, oxidation and O-GlcNAcylation, all modify the activity of RyR2 and can lead to abnormal 'spontaneous' calcium release. This presentation will highlight some of our key findings on posttranslational regulation of RyR2 that will be expanded upon by the relevant lead researcher in other presentations and posters at this meeting.

MD39: Autonomic dysfunction, arrhythmic risk, and rheumatoid arthritis.

Fisher, J.P.[1]

[1]Manaaki Mānawa – The Centre for Heart Research, Department of Physiology, University of Auckland, Auckland, NZ.

Rheumatoid arthritis (RA) is a chronic inflammatory condition associated with increased cardiac morbidity and mortality, including the risk of sudden cardiac death. The presence of traditional cardiovascular risk factors in RA does not fully explain this increased cardiovascular risk, and autonomic dysfunction and abnormal ventricular repolarisation have been implicated. Heart rate corrected QT interval, a marker of cardiac repolarisation that predicts cardiovascular mortality, is positively correlated with inflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, IL-10) in RA (1). The prevalence of autonomic dysfunction in patients with RA is ~60%. This has principally been characterised as impaired cardiovascular reflexes and reduced heart rate variability derived indices of cardiac parasympathetic activity (2). Our recent work has also identified increases in directly recorded central sympathetic outflow in RA patients, in comparison with healthy age- and sex-matched controls (3). In the same study, sympathetic baroreflex sensitivity was observed to be preserved in RA, while cardiac baroreflex sensitivity was reduced by ~50%. The elevated sympathetic nerve activity and reduced cardiac baroreflex sensitivity were associated with raised inflammatory markers (serum high sensitivity C-reactive protein) and patient reported pain. Collectively, such observations support the concept that lowering inflammatory burden and ameliorating pain in RA may reduce cardiovascular risk.

1. Adlan AM, Panoulas VF, Smith JP, Fisher JP & Kitas GD. (2015) *Relationship between QTc interval and inflammatory cytokines in rheumatoid arthritis. J Rheumatology*. 42(3):421-8.

2. Adlan AM, Lip GY, Paton JFR, Kitas GD & Fisher JP. (2014) Autonomic Function and Rheumatoid Arthritis - A systematic Review. Seminars in Arthritis and Rheumatism 44(3).

2. Adlan AM, Paton JFR, Lip GY, Kitas GD & Fisher JP. (2017) *Increased sympathetic nerve activity and reduced arterial baroreflex sensitivity in rheumatoid arthritis*. J Physiol. 595(3):967-981

Summary of Abstracts for the Poster Session

No.	**Title**	**Presenter**	**Institutions**
MD40	Circulating erythroferrone in the diagnosis of acute decompensated heart failure in patients with comorbidities.	Appleby, S	Christchurch Heart Institute
MD41	CaMKII inhibition decreases atherosclerosis in middle aged ApoE$^{-/-}$ mice.	Ashley, Z	Department of Physiology, School of Biomedical Sciences, University of Otago
MD42	Effect of obesity on human epicardial adipose tissue induced arrhythmic susceptibility in human atrial myocardium.	Bingham, K	Department of Physiology and HeartOtago, University Of Otago
MD43	Using 'turn-on' fluorescent probes to study the cellular target and delivery of carbon monoxide using novel organic releasing molecules.	Bland, A	Department of Pharmacology and Toxicology, School of Biomedical Sciences, University of Otago
MD44	Untangling purinergic cardiac regulation through the stellate ganglion.	Bussey, C	Manaaki Manawa Centre for Heart Research, Department of Physiology, Faculty of Medical & Health Sciences, University of Auckland
MD45	How the ratio of RyR2 and CSQ2 play a role in pro-arrhythmogenic Ca2+ release.	Cruz, H	Department of Physiology & HeartOtago, University of Otago
MD46	Representation of Māori and Pacific Island patients in cardiac research requiring tissue collection in the Southern District Health Board region in Aotearoa.	de Jonge, W	Department of Physiology - HeartOtago, School of Biomedical Sciences, University of Otago
MD47	Neural Network Phenotyping of Open Source PCOS Accounts.	Emanuel, R.H.K	Department of Mechanical Engineering, University of Canterbury

MD48	Endocrinologic modelling of dysregulated hormonal pathways in PCOS.	Emanuel, R.H.K	Department of Mechanical Engineering, University of Canterbury
MD49	Placental extracellular vesicles as a mediator of maternal cardiovascular disease following preeclampsia.	Feng, Y	Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, University of Auckland
MD50	RXFP4 is expressed in gut enterochromaffin cells and may regulate serotonin synthesis and secretion	Fernando, S	University of Auckland
MD51	The effects of Amiloride on Diabetic Cardiac Fibrosis	Herath, B	University Of Otago
MD52	CK2-mediated hyperphosphorylation of RyR2: Can it protect against cardiac arrhythmia?	Hintz, M	University of Otago
MD53	Characterisation of t-tubules and dyads in human atrial myocytes	Iposu, A	University of Otago
MD54	Identifying Functional Variants Associated with High Lipoprotein (a) Phenotypes.	Ismail, L	Biochemistry Department, University Of Otago
MD55	Soluble Urokinase Plasminogen Activator Receptor (suPAR) in the convalescent phase of acute coronary syndrome predicts all-cause mortality and adverse cardiovascular outcomes.	Keys, T	Christchurch Heart Institute
MD56	Regulation of RyR2 by O-GlcNAcylation.	Khaing, E	Department of Physiology and HeartOtago, University of Otago
MD57	Characterising inflammatory endotypes of individuals after an attack of pancreatitis using hierarchical clustering.	Kimita, W	[1]School of Medicine, University of Auckland
MD58	Aryl hydrocarbon receptor ligands can modulate fructose-induced hepatic	King, J	[1]University Of Otago

	insulin resistance.		
MD59	Placental extracellular vesicles can induce changes in maternal resistance arteries persisting 22 weeks after original exposure.	Lau, S	[1]Department of Obstetrics and Gynaecology, University Of Auckland
MD60	Assays specific for BNP1-32 and NT-proBNP exhibit a similar performance to two widely used assays in the diagnosis of heart failure.	Lewis, L	University Of Otago
MD61	Pharmacological inhibition of PI3K induces weight loss in diet-induced obese female mice.	Macrae, C	Department of Nutrition and Dietetics, University of Auckland
MD62	Proteomic analysis of 4-phenylbutyrate treated HepG2 cells expressing endogenous ATP-binding cassette transporter A1 (ABCA1).	Munir, J	Department of Biochemistry, School of Biomedical Sciences, University of Otago
MD63	Assessment of plasma risk markers for acute kidney injury in patients with acute decompensated heart failure using a multiplex immunoassay.	O'Connor, K	University Of Otago, Christchurch
MD64	Do placental extracellular vesicles cause cardiovascular changes in preeclampsia?	Paek, S.Y	Department of Obstetrics and Gynaecology, The University of Auckland
MD65	Investigating the effectiveness of a novel therapeutic to improve Diabetic wound.	Paul, S	Department of Physiology, University of Otago
MD66	Carbon Monoxide Release by oCOm-21 Enhances Ca2+ Sensitivity of the Cardiac Myofilament.	Payne, F	Department of Pharmacology and Toxicology, University of Otago
MD67	CK2 Phosphorylation of RyR2 in Heart Failure Patients.	Pirker, T	Department of Physiology, School of Biomedical Science, University of Otago
MD68	Human Cardiac neuron characterization via large tissue imaging.	Prince, B	Department of Physiology, University of Auckland

MD69	Understanding the gene-regulatory mechanisms behind Juvenile Idiopathic Arthritis (JIA).	Pudjihartono, N	Liggins Institute, University of Auckland
MD70	Role of loss of CaMKIIδ in atherosclerosis in aging ApoE-/- Mice.	Roberts-craig, F	Department of Physiology, School of Biomedical Sciences, University of Otago
MD71	Determining the functional effect of CSQ2 glycosylation on calcium-handling and heart failure.	Sibbles, E	University Of Otago & HeartOtago
MD72	Cardioprotection using organic carbon monoxide donors.	Thwaite, S	Department of Pharmacology and Toxicology, School of Biomedical Sciences
MD73	Effects of synthetic miRNA cocktail for activation of endogenous progenitor cells in the diabetic heart	Tonkin, D	Department of Physiology, HeartOtago, School of Biomedical Sciences, University of Otago
MD74	Elucidating the Role of miRNAs Underlying Chronic Pain in Rheumatoid Arthritis.	'Uluaki'afua, K	Department of Physiology, HeartOtago, School of Biomedical Sciences, University of Otago
MD75	Preparation of functional human atrial slices and multi-day tissue culture.	Waddell, H	Department of Physiology and HeartOtago, University of Otago