ABSTRACT TEMPLATE

QMB Abstracts

M1: On the Road to Edward Jenner's Revenge: Lessons for TB Vaccines from a New Herpes Vaccine

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M2: Public Health Microbiology in the Genomics Era

Williamson, D, University of Otago, New Zealand & Institute of Environmental Science and Research, Wellington, New Zealand, New Zealand

M3: Coalition to Advance New Vaccines for Group A Streptococcus (CANVAS): A Trans-Tasman Initiative for Rheumatic Fever Prevention

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Group A Streptococcus (GAS) infections represent a major public health burden in both developing and developed countries. In Australia and New Zealand the GAS associated sequelae, Acute Rheumatic Fever (ARF), is a serious problem in Indigenous populations and a major cause of health inequality. Political recognition of these inequalities has provided impetus for strategies that reduce GAS disease and the development of a GAS vaccine has governmental support in both Australia and New Zealand. Stage I funding was approved and CANVAS commenced work on July 1st, 2014 towards three major deliverables as follows: performing a comprehensive assessment of regional GAS strain epidemiology; developing a robust assay for assessing vaccine antisera and; a health economics evaluation of GAS vaccination. This presentation will provide a progress update on CANVAS with respect to these deliverables and highlight the unique challenges and opportunities associated with developing a GAS vaccine “down-under”.

M4: Determining the microbial aetiology of pneumonia - will the real pathogen please stand up?

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The ability to determine confidently the cause of pneumonia remains challenging, despite recent improvements in diagnostic technology. It has become increasingly clear that the microbial aetiology of pneumonia is complex and that interactions between multiple micro-organisms play an important role in pneumonia pathogenesis. In particular, there is considerable evidence supporting the co-pathogenicity between respiratory viruses and bacteria, and the polymicrobial nature of pneumonia. Future research efforts to understand pneumonia aetiology and pathogenesis need to further explore the respiratory microbiome and host factors, and also utilise well-designed epidemiological studies.

M5: Staphylococcal pathogenesis and disease – is a vaccine possible?

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Staphylococcus aureus is the most common cause of hospital acquired infection and the increasing frequency of serious community infections is causing global concern. Emerging hypervirulent strains have resulted in a significant rise of life threatening illness. For instance 2 strains (USA300 and USA400) have been almost singularly responsible for a 10 year epidemic of fatal necrotizing-like infections throughout the USA. There is no effective vaccination strategy in sight with the latest vaccine trial ending when preliminary results revealed an increase of fatal infections in vaccinated individuals. Why is this? *S aureus* is unique for the sheer number of virulence factors and its seeming ability to modify its defense according to niche, meaning that there is no one vaccine target that is likely to protect against all types of infections. However it is becoming clear that a key to the organism's hypervirulence is how it increases survival within the phagocyte, the very cell that is designed to kill them. Thus vaccines that enhance phagocytosis, particularly of hypervirulent strains may enhance pathogenicity. I believe there are two major questions that require answers, identifying those host mechanism(s) that most efficiently kill *S aureus* and what, in a hierarchy of the many virulence factors is most responsible for pathogenicity and thus represents the best solution for a vaccine. The one bright light is the discovery of a new class of antibiotics that appears effective against all currently resistant strains of *S aureus*. I will discuss the important features of staphylococcal virulence in relation to enhancing pathogenicity in relation to potential vaccine strategies

M6: Controlling Zoonotic Pathogens: The Increasing Role Played By Molecular And Genomic Epidemiology

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Despite major advances in food and water safety, animal husbandry and the development of vaccines and antimicrobials, communicable diseases continue to impose significant health and economic impacts worldwide. It is estimated that at least 300 new human pathogens have emerged over the last 60 years - the majority of these are zoonotic and the rate of cross-over into humans appears to be increasing. This increase is attributed to changes in socio-economic, environmental and ecological factors that are collectively altering the infectious disease landscape. Previously treatable pathogens are developing resistance to antibiotics and changes in: food consumption patterns; agricultural intensification; climate change; human population growth; urbanization and encroachment into wild spaces, are all examples of escalating forces that are leading to the emergence and resurgence of zoonotic diseases.
Advances in our understanding of genomics, microbial population genetics, evolutionary biology and modelling, coupled with the increasing availability of pathogen whole genome sequence data and accompanying 'metadata' (e.g. host epidemiological and demographic data and pathogen phenotypic data), are set to transform epidemiology and public health, and make major contributions to the control of zoonoses. A major challenge is the integration of models of evolutionary ancestry and the transmission of infectious disease to understand and model how pathogens are transmitted between hosts. This includes refining our approaches to identifying the reservoirs and pathways for food and waterborne pathogens, and identifying host and geographical transition events. In this talk I will outline how recent advances in molecular epidemiology, whole genome sequencing and our understanding of pathogen evolution are improving public health, and highlight some of the challenges facing the emerging fields of phylodynamics and genomic epidemiology. A number of recent New Zealand examples will be discussed including the transmission and evolution of Shiga-toxin producing *Escherichia coli*, non-typhoidal *Salmonella* and multi-resistant *Campylobacter jejuni*.

M7: RePOOPulate and treating *C diff* infections

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M8: Gut microbiota in health and disease”

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M9: Understanding Bowel Bacteria

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The large bowel of humans is home to a complex bacterial community referred to as the bowel microbiota or microbiome. Although the composition of the bowel microbiota has been described thoroughly in terms of taxonomy by use of high-throughput DNA sequencing results, ecological and evolutionary understanding of the human-microbiota association is poor. It is clear, however, that the nutritional drivers of the bacterial community are mostly polysaccharides and oligosaccharides that are undigestible components of human diets that pass to the large bowel and become growth substrates for bacterial species. Current research, which is linked to the bowel microbiota of babies, suggests that syntrophic links are formed between bacterial species and that the resulting sharing of resources helps us to understand how the microbiota is formed following birth. This research is relevant to the development of better-formulated foods for babies.

M10: Innate Factors in Early Clearance of *Mycobacterium tuberculosis*: validating a novel phenotype

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Progress towards a *Mycobacterium tuberculosis* vaccine has been stalled by poorly defined correlates of protection. To discover protective responses to *M. tuberculosis* we are studying highly exposed uninfected individuals. We hypothesise this group includes "early clearers" who mount a protective innate response to infection before *M. tuberculosis* specific T cell immunity develops.

The Innate Factors in Early Clearance of *Mycobacterium tuberculosis* (INFECT) study uses this approach to study early clearers in a cohort of contacts of sputum smear positive TB cases in Bandung, Indonesia. Each contact's exposure to *M. tuberculosis* is quantified by the grade of sputum positivity of their index case, and other measures of the intensity of their contact. *M. tuberculosis* infection is determined by Interferon Gamma Release Assay (IGRA) at baseline, and if negative, again at 14 weeks.

Early clearance could be achieved by enhanced alveolar macrophage recognition of *M. tuberculosis*, inflammatory cytokine signaling or intracellular killing, potentially mediated by Vitamin D. Other innate cells could augment early clearance. For example, neutrophils may promote infected macrophage disposal by apoptosis, limiting the propagation of *M. tuberculosis* to uninfected cells. To identify biomarkers of early clearance and identify priority mechanisms for further study we perform detailed immunological phenotyping at baseline as well as storing DNA, RNA and serum for future analysis using high throughput platforms.

Currently, we have recruited 251 index cases and contacts 718 contacts. We have validated that contact with a 2+ or 3+ smear positive carries a high risk of infection, and defined uninfected contacts of such cases as highly likely to be early clearers. This group will be the basis of biomarker discovery and validation studies.

An update will be provided on progress with this large cohort.

M11: LC3-associated phagocytosis restricts an intracellular bacterial pathogen in a process that involves both TLR2 signalling and ROS

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The relevance of Legionnaires' disease (LD) in New Zealand is commonly under appreciated. Recent rates of LD are comparable to those of Tuberculosis, Shigellosis and VTEC/STEC infections. Improved testing methods have uncovered a hidden disease burden in Canterbury, and widespread adoption of more relevant testing methods will likely lead to increased recognition of the disease. Significantly, the globally important pathogen Legionel/a pneumophila is not the main cause of LD in New Zealand. Although over 26 species of Legionel/a cause disease in humans, the virulence mechanisms of the majority of these species are unknown. Like L. pneumophi/a, non-pneumophila species possess mechanisms to inject bacterial proteins into host cells for the purpose of manipulating host defenses and cellular processes. However, how these pathogens survive inside hosts and whether differences in either their recognition by the host or their virulence arsenal accounts
for their ability to cause disease is unknown. Here we report on a mechanism that limits intracellular replication of Legionella dumoffii, but not L. pneumophila. LC3-associated phagocytosis (LAP) is a novel innate
immune response that is related to autophagy, which is a process for degrading and recycling cytosolic material including invading pathogens. Our novel findings include that (1) L. dumoffii lives in an ER-like vacuole that is devoid of ubiquitin, (2) a subset of pathogenic L. dumoffii are recognized and degraded by a process consistent with LAP, and (3) this process is dependent on both TLR2 signaling and reactive oxygen species (ROS) generation. These findings are supported by the modern technique of correlative light and electron microscopy (CLEM). Our novel insights extend knowledge in the field of innate immunity and support the notion that the various Legionella species have both shared and unique interactions inside human hosts. Whether or not these interactions impact disease severity is of key interest going forward.

M12: Methionine-less death in *Mycobacterium tuberculosis* – New opportunities for chemotherapeutic interventions.

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Multi-drug resistance, strong side effects and compliance problems in TB chemotherapy ask for new ways to kill *Mycobacterium tuberculosis (Mtb)*. Very little is known about the way this pathogen interacts metabolically with its host to achieve long-term persistence and antibiotic tolerance. We uncovered a previously unknown metabolic vulnerability of *Mtb*, the absolute requirement for methionine and S-adenosylmethionine for successful host infection and virulence. Inactivation of methionine biosynthesis in *Mtb* leads to unusually rapid cell death, a highly desired feature for chemotherapy. Bactericidal auxotrophies are rare in *Mtb* and so far their killing mechanisms have not been systematically characterized. Our study unravels a novel amino acid starvation-induced killing mechanism that leads to multi-target inhibition, opening up new avenues for anti-mycobacterial interventions.

M13: Application of the Henderson-Hasselbalch Equation to TB Drug Discovery

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Pyrazinamide (PZA) is an anti-TB pro-drug that was discovered more than 60 years ago. The active form of PZA appears to be pyrazinoic acid (POA). Administration of PZA is instrumental in reducing the duration of tuberculosis treatment from 9-12 months to six months; however, the precise mode of action is unclear. It has been reported that PZA inhibits ATP synthesis, trans-translation and pantothenate synthesis. PZA is unusual in that it is synergistic with nearly all other anti-TB drugs in the clinic. Understanding the basis of this synergy is the ultimate goal of the current research. PZA/POA is virtually inactive *in vitro* at physiological pH. The activity of PZA/POA increases with decreasing pH in *in vitro* assays and the minimal inhibitory concentrations can be predicted using the Henderson-Hasselbalch equation. Interestingly, POA has structural features that are similar to those of known chemical uncouplers of oxidative phosphorylation. The data presented demonstrate that POA collapses proton motive force in a manner similar to salicylic and benzoic acids. NMR experiments are used to demonstrate how the protonated and non-protonated acids partition in a reverse-micelle model of membranes. Results support the hypothesis that POA is the active form of the drug, and suggests that a pool of POA outside of the mycobacterial cell is important for the activity of the drug. However, determining if uncoupling is the source of the observed synergy of PZA with other drugs will depend on identification of compounds that are specific inhibitors of trans-translation, pantothenate synthesis, as well as, specific uncouplers.

M14: Emerging antimicrobial therapies for skin wound infections.

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Skin and soft tissue infections (SSTI), such as impetigo, abscesses, ulcers and surgical site infections, account for approximately 77% of all human infections. Microbial colonisation and subsequent biofilm production also impedes the repair process, contributing to the inflammation and ischemia associated with chronic wounds and burns. New Zealand has some of the highest rates of SSTI in the developed world, with over 15,000 patients hospitalised each year, while in the US, an estimated 5.5M patients require treatment for SSTI each year. As is seen with the majority of our front-line antimicrobial therapies, topical antibiotics and antiseptics are associated with the rapid emergence of resistance in bacterial pathogens. In addition, systemic antibiotics and many topical antimicrobials are unable to penetrate wound biofilms and their formulations are cytotoxic to cells, thus hindering the healing process and further limiting their use. The objective of this study is to identify an antimicrobial that targets SSTI without compromising natural healing responses. A number of natural and synthetic antimicrobial compounds that have potential as therapeutics for SSTI have been identified as part of a collaborative project. The minimum inhibitory concentration and minimum biofilm eradication concentrations of these compounds are being assessed against common wound pathogens using high throughput assays. The effects of these compounds on cell viability and key wound healing processes are being evaluated using cultured keratinocytes. In each assay, the potency and biocompatibility of the compounds are being compared to commonly-used topical antibiotics and wound healing products. We have also established an in vitro human skin equivalent, known as a skin raft culture. In response to injury, the skin equivalent mimics wound re-epithelialization in a manner consistent with the process in vivo. The next stage is to use this tool to study wound colonization and infection, and to assess the safety and efficacy of the lead antimicrobials when applied to the infected rafts at different stages of healing. By evaluating compounds in the context of a healing wound, valuable insights will be gained into how best to utilize antimicrobials therapeutically to target different SSTI

M15: Physiological and pharmacological roles of the diverse flavin/deazaflavin oxidoreductase superfamily in mycobacteria

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M16: Glutamate racemase as a target for antibiotic design in tuberculosis

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M17: Antibiotic resistance: what can the genome tell us?

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Multi-drug resistant (MDR) bacteria pose an urgent risk to global human health. Previously we characterized the genomes of ~100 *Escherichia coli* ST131 strains and discovered that this MDR clone had disseminated globally in little over a decade. Carbapenem resistant Enterobacteriaceae (CRE) are a growing problem in Australia and around the world and the acquisition of a carbapenem resistance gene by *E. coli* ST131 could render these superbugs resistant to all standard antibiotics. The long "reads" produced by Single Molecule Real Time (SMRT) genome sequencing enables the genetic context of antibiotic resistance genes on mobile genetic elements such as plasmids, integrons and transposons, to be accurately determined. Such elements are the key to understanding the origin, dissemination and expression of resistance genes but are generally difficult to analyse using standard shorter-read sequencing data. Here I report how we are using SMRT sequencing to investigate the genomic context of antibiotic resistance genes in *E. coli* ST131 and carbapenem resistant Enterobacteriaceae (CRE). As part of this study we determined the complete genome of a pandrug-resistant *Klebsiella pneumoniae* isolate, representing the first complete genome sequence of CRE resistant to all commercially available antibiotics. Remarkably, our analysis showed that the mobile element conferring resistance to carbapenem antibiotics is itself responsible for driving resistance to the last-resort antibiotic, colistin by insertional inactivation of another gene. These findings provide the first description of pandrug-resistant CRE at the genomic level, and reveal the critical role of mobile resistance elements in accelerating the emergence of resistance to other last resort antibiotics. Our experience with this isolate and several other CRE clinical isolates show that the SMRT platform readily produces high-quality, finished plasmid sequences that can discriminate plasmid diversity, and are indispensable for defining the genetic structure and position of complex resistance loci.

M18: Biomarkers for Resilience and Susceptibility to Mycobacterial Infection: Model studies in deer.

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While different breeds of cattle, deer and sheep display heritable resilience (R) or susceptibility (S) to Johne's disease (JD), little progress has been made to identify genetic markers that contribute to either R or S traits, in livestock.

Our 10 year study of an elite deer herd (>2,500 animals), tested 7 disparate breeds of European red deer (*Cervus elaphus*), from a herd that had been chronically infected with *M. paratuberculosis* for more than 5 years. Sires with a confirmed Resilient (R) or Susceptible (S) phenotype were used in an AI programme with crossbred females, and the phenotype of the progeny was confirmed immunologically, microbiologically and histopathologically, following experimental infection with virulent *M. paratuberculosis*. In a three year breeding programme, 21/26 progeny (81%) from R sires were confirmed as R and 23/26 S progeny (88%) expressed the S phenotype. Detailed RNA-seq and transcriptome analysis of R and S animals was used to determine the relative expression levels of immune genes, measured by qPCR. Multiple genes involved in functional pathways of innate and adaptive immunity have been evaluated using a 'systems biology' approach to target overall cell function.

Animals with a S genotype expressed significantly higher levels of pro-inflammatory genes; iNOS, IL-1, TNF- and IL-23p19 genes, genes associated with chemotaxis; CXCL10, CSF3, and CCL8 and type 1 interferons; RSAD2, IFIT1, IFIT2, ISG12, ISG15, USP18, and HERC6. Higher levels of adaptive immune genes; IL-2, IL-4, IL-12, GATA3, Foxp3 and increased levels of Apoptosis was seen in R animals.

Animals with S phenotypes express dysfunctional innate immunity and are less capable of clearing mycobacterial pathogens. By contrast, R animals express markers of adaptive immunity, that combined with adequate levels of innate immunity, promote protection.

M19: MAIT CELLS: KEY CELLULAR EFFECTORS IN ANTIBACTERIAL IMMUNITY?

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Mucosal associated invariant T (MAIT) cells are a recently recognized innate-like T lymphocyte population in humans. They are abundant, comprising ~5% of the lymphocyte population in blood and are enriched in the liver and mucosal tissues. They are restricted by MR1, a non-polymorphic, highly evolutionarily conserved MHC class I-like molecule. It has recently been shown that MR1 presents a metabolic precursor of riboflavin synthesis and consistent with this MAIT cells are activated by a wide range of bacteria. *In vivo* mouse models suggest that MAIT cells may play a non-redundant role in antibacterial immunity.

In this presentation, I will discuss our recent findings on the role of MAIT cells in antibacterial immunity in humans and a preliminary assessment of their role in *Mycobacterium avium* subsp. *paratuberculosis* infection in deer.

M20: *Salmonella* Enteritidis lineages: from broad host range generalists to highly adapted human invasive strains

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Salmonella enterica serovar Enteritidis is responsible for a global epidemic of poultry associated gastroenteritis. It is also the second largest cause of invasive nontyphoidal salmonella disease (iNTS), a prominent cause of bloodstream infection in Africa with a fatality rate of 20-25%. Epidemics of iNTS are associated with the emergence of multidrug resistance in Malawi.

We whole genome sequenced 679 strains of Enteritidis isolated between 1948-2013, 73% of which were from Africa. The phylogenetic structure reveals strong evidence for three epidemics as well as a globally circulating lineage. The epidemic lineages showed strong geographically structuring and were characterised by their increase in invasiveness and drug resistance – for instance the Central/Southern African epidemic was invasive in 95% of cases, 97% had some form of drug resistance and 82% were multi-drug resistant. Bayesian temporal analysis allowed us to identify the most recent common ancestors of these epidemics.

Analysis of the accessory genome revealed striking differences in virulence potential. The globally circulating, non-epidemic clade which includes the reference strain P125109, were characterised by the φSE20 prophage which is known to be essential for poultry invasion. The invasive epidemic clades have lost this prophage and, furthermore, we could characterise each of these epidemics by their unique prophage and plasmid repertoire. These included known virulence determinants and sources of drug resistance.

We tested these genomic differences using an infection model and confirm that the African epidemic strains have lost the ability for invasion and colonisation. This suggests that genomic degradation is a signal for host adaptation, in contrast to the behaviour of *S.* Typhimurium.

These results identify recent lineages of *S.* Enteritidis with invasive, multi-drug resistance phenotypes, a genome characterised by its prophage and plasmid repertoire and host adaptation to humans.

M21: Revisiting the NZ meningococcal disease epidemic using whole genome analysis

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From 1991 to 2008 New Zealand (NZ) suffered a *Neisseria meningitidis* epidemic, caused by a group B strain (NZMenB) with a novel porA type that had not been detected in disease-associated meningococcal strains in NZ before 1991. The NZMenB epidemic caused over 200 deaths and 5000 hospitalisations. With the introduction of a strain-specific vaccine in 2004, disease cases lowered greatly. It is thought the NZ epidemic strain is highly virulent. Molecular typing showed that NZMenB belonged to the hypervirulent clonal complex CC41/44 with three sequence types (ST) represented, ST41, ST42 and ST154. ST42 and ST154 were more common than ST41 strains. Epidemiological and molecular analysis raised questions regarding the epidemic that remain to be answered; how did the NZMenB strain arise in NZ and what is the relationship among the three STs found in NZMenB. We decided to use whole-genome sequencing (WGS) to answer these questions, as other molecular typing techniques do not represent the full diversity among the NZMenB strain isolates.

As a pilot study we used WGS to analyse 96 NZMenB genomes from 1991 to 2011. Years 1991 to 2011 cover the emergence, the height of the epidemic, post-vaccination and post-epidemic periods. Preliminary phylogenomic analyses suggested isolates clustered according to STs but no correlation to year or geography were found. Our preliminary findings do not support the hypothesis of a recent clonal expansion of a single NZMenB strain, as genetic diversity at the beginning of the epidemic is similar to that at the end. Instead it indicates that genetic diversity was already present before the epidemic started. We compared NZMenB sequences to other cc41/44 isolates from rest of the world and found NZMenB isolates were more closely related to each other. In addition we compared the genomes of isolates pre- and post-vaccination and found that major meningococcal antigens (those present in the newly licensed MenB vaccine) remained stable after vaccine introduction. Interestingly, all post-vaccination isolates analysed so far contained a loss-of-function mutation in the IgA protease gene, a major virulence factor in meningococci. To gain knowledge regarding immune evasion and host adaptation, we also analysed the genomes of isolates collected from different sites of the same patient at the same time, and from individuals who suffered NZMenB disease multiple times.

M22: Whole-genome sequencing of multidrug-resistant *Mycobacterium tuberculosis* from Myanmar

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Drug-resistant tuberculosis (TB) is a major threat to global health. Rapid detection of drug-resistant strains of *M. tuberculosis* is essential to treat patients with drug-resistant TB. Conventional laboratory procedures for drug susceptibility testing (DST) take several weeks due to the requirement for bacterial culture followed by laborious phenotypic testing. In an attempt to overcome this rate-limiting step, several genotypic DST assays such as the Xpert MTB/RIF diagnostic test have been developed. Unfortunately, these assays only interrogate the most frequent resistance mutations for a limited number of antibiotics. Whole-genome sequencing (WGS) has the potential to overcome this limitation and can be used to identify patients with drug-resistant tuberculosis. While WGS is being considered for routine diagnosis and management of drug-resistant TB in well-resourced, low-TB burden, settings, it is also important that new tools with the potential to improve TB control are adopted as early as possible where they are needed the most. We, therefore, conducted a preliminary evaluation of the potential utility of WGS and this talk will provide insights into the potential incorporation of WGS into routine clinical management of drug-resistant TB in Myanmar, one of the 22 high-burden tuberculosis countries, with a high prevalence of multidrug resistant-TB.

M23: STRUCTURAL STUDIES OF THE MEMBRANE PROTEIN CYP51 REVEALS RESISTANCE MECHANISM AGAINST SHORT-CHAIN AZOLE ANTIFUNGALS

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Lanosterol 14α-demethylase (CYP51, Erg11p) is a CYP51 cytochrome P450 membrane-spanning mono-oxygenase required for sterol biosynthesis and is the target of azole antifungal drugs. It is a bitopic, membrane-anchored protein and converts its substrate, lanosterol, into a precursor of ergosterol, the essential cell membrane sterol. Resistance to commonly administered azole antifungal drugs has arisen through mutations that reduce their binding affinity for the fungal enzyme. Mutations that have been reported to confer resistance in clinical isolates of the human pathogens *Candida albicans* and *Aspergillus fumigatus* as well as in agricultural phytopathogens have been the focus of this study. The mutation of a tyrosine to either phenylalanine or histidine residue adjacent to the haem and bounding the active site has been introduced into *Saccharomyces cerevisiae* CYP51 (Y140F/H) and the high-resolution X-ray crystal structures of the full-length enzyme determined. Structures of Y140F with four azole drugs and a further two structures of Y140H complexed with azole antifungal drugs have revealed the mechanism of resistance against short-chained azole drugs. This occurs via the disruption of a key water-mediated hydrogen bonding network when compared with the wild-type *S. cerevisiae* CYP51 in complex with the short-chain azole fluconazole. Cells containing the mutations also became resistant to short-tailed, but not long-tailed, azoles. Structures of numerous agricultural compounds in complex with *S. cerevisiae* CYP51 have revealed that they are also susceptible to resistance via the same mechanism due to the similar chemical features of the antifungals used in both man and agriculture. These findings provide the basis for avoiding resistance of this type in the development of new antifungal agents.

M24: Ribonuclease HI – a new candidate for drug development for *Mycobacterium tuberculosis*

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Ribonuclease HI (RNase HI) activity is found in all eukaryotes and prokaryotes. RNases HI degrade the RNA strand of an RNA:DNA hybrid. This fundamental housekeeping function is necessary to eliminate the hybrids that occur when transcripts invade the genome, causing single-stranded DNA bubbles. Persistent R loops can lead to gene silencing and double strand breaks. Aberrant R-loop formation in eukaryotes has been linked to cancer and ageing.

In *M. tuberculosis* (Mtb), the gene encoding RNase HI (Rv2228c) is essential[1]. A whole cell screen of small molecule inhibitors previously identified a known RNase HI inhibitor as possessing inhibitory activity for *M. tuberculosis* [2] suggesting that RNase HI in Mtb is a viable drug target. Since RNases H are ubiquitous and have a conserved fold and active site, we asked whether sufficient differences exist between Mtb and human RNases HI that the Mtb enzyme could be targeted selectively.

As proof of principle, we screened known inhibitors of human RNase HI for inhibition of Mtb RNase HI, and found compounds that either also inhibited Mtb RNase HI, had little effect on Mtb RNase HI, or enhanced RNase HI activity, demonstrating that sufficient differences exist that these two enzymes can be targeted specifically. One of these compounds showed good activity against Mtb RNase HI (IC_{50} =1.6 µM), inhibited growth of Mtb at an MIC of 25 µM but possessed little toxicity for HL-60 human cells (IC_{50} >100).

1. Griffin, J.E, Gawronski, J.D., DeJesus, M.A, Ioerger, T.R., Akerley, B.J., et al. (2011) *High-Resolution Phenotypic Profiling Defines Genes Essential for Mycobacterial Growth and Cholesterol Catabolism*. PLoS Pathog 7(9): e1002251.
2. Altaf, M., Miller, C.H., Bellows, D.S. and O'Toole, R. (2010) *Evaluation of the Mycobacterium smegmatis and BCG models for the discovery of Mycobacterium tuberculosis inhibitors.* Tuberculosis. 90(6):333-7.

M25: A plant-like PPR protein controls RNA cleavage in the Plasmodium remnant chloroplast

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The malaria parasite, Plasmodium sp. is one of the world's deadliest pathogens, around 200 million people are infected every year, resulting in 655 000 deaths, mainly in children under 5. Interestingly, this intra-cellular parasite has a photosynthetic ancestry and retains a remnant chloroplast termed the apicoplast. Although no longer photosynthetic the apicoplast carries out essential biochemical functions and is a target for existing anti-malarial drugs. As with the plant chloroplast, the apicoplast has its own (although greatly reduced) genome. This 35 kb genome contains around 60 genes, most of which are required for transcription and translation of the genome. Transcription within the apicoplast is polycistronic and characterisation of transcripts using circularised RNA identified potential processing sites. We have identified several nuclear encoded proteins in Plasmodium that are predicted to be apicoplast targeted that play important roles in transcription and post-transcriptional processing. One of which belongs to the pentatricopeptide repeat (PPR) protein family, which play essential roles in RNA stabilisation, splicing and editing in the plant chloroplast. We have characterised the PPR protein from Plasmodium falciparum and show it to be localised to the apicoplast and bind to specific RNA sequences at the identified processing sites to protect transcripts from degradation. The unique 'plant-like' nature of the PPR proteins could provide an avenue for the development of future anti-malarial drugs to combat emerging drug resistance to current therapies.

M26: The Complete Genome of PSA – *Pseudomonas syringae* pv. *actinidiae* – and the recent emergence of antibiotic resistance in New Zealand

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The economically significant pathogen *Pseudomonas syringae* pv. *actinidiae* (PSA) causes severe bacterial canker on kiwifruit (*Actinidia* sp.). To support efforts to study the origin, transmission and ongoing evolution of PSA, our group has generated the first complete PSA genome. This assembly was based on Illumina reads (500bp) and SMRT reads (PacBio, 10,000 – 40,000bp), each being required for the finished genome. The assembly method involved iterative read mapping of the SMRT reads to a series of draft genomes to identify areas that had not assembled correctly. The final assembly was then SNP corrected using the higher accuracy Illumina reads. This new assembly method has low computational load, can overcome systemic errors in sequence platforms, and allowed for genome completion at less than $10,000.

The complete PSA genome has created new opportunities to analyse New Zealand field isolates – so far being used to identify new plasmids and the genetic basis of the recently emerged Streptomycin and Copper resistance in the Bay of Plenty region. This will allow targeted diagnostics to be developed for these resistant isolates of PSA.

M27: Transcriptional response of human bladder cells to UPEC 536 membrane vesicles.

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[1]Department of Molecular Medicine and Pathology, [2]Department of Surgery, [3]School of Biological Sciences, Auckland University, New Zealand; [4]Maurice Wilkins Centre for Molecular Biodiscovery, New Zealand.

Introduction: Uropathogenic E. coli (UPEC) has been reported in literature to use secreted membrane vesicles (MVs) to deliver toxins into human cells. Whilst phenotypic effects of individual MV-associated toxins on human cells have been described no study to date has evaluated uroepithelium transcriptional response to UPEC MVs as a whole.
Objective: To determine the transcriptional response of human bladder epithelial cell to MVs released by UPEC.
Methods: MVs were isolated from UPEC 536 cultures by filtration and ultracentrifugation and visualised using transmission electron microscopy. MV uptake into bladder cells was investigated with confocal microscopy by labelling vesicle membranes with a fluorescent dye PKH67 and bladder cells with a nucleic acid (DAPI) and cytosol (CellTracker Red CMTPX) dyes. Effects of MVs on bladder cell viability were measured using the MTT assay. Transcriptional response of bladder cells to UPEC 536 vesicles was investigated using GeneChip® PrimeView™ Human Gene Expression Arrays. Quantitative real time PCR was used to validate changes in expression of bladder cells genes identified from the microarray analysis.
Results: Secretion of MVs by UPEC 536 was confirmed by electron microscopy. Fluorescent microscopy showed that MVs can enter cultured human bladder cells whilst phenotypic assays showed a negative effect of MVs on bladder cell viability. Exposure of bladder cells to MVs upregulated expression of a range of genes responsible for an early response to infection and pathways responsible for xenobiotic metabolism.
Conclusions: Our study has provided insights into the complex events underlying uropathogenesis by identifying pathways involved in bladder cell response to the cytotoxic MVs produced by UPEC.

M28: Sub-lethal effects of commercial formulations of herbicides on bacteria. A link to the creeping antibiotic resistance?

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In the last year, both the World Health Organization and the U.S. Centers for Disease Control and Prevention issued stern reports on the continuing and growing problem of antibiotic resistance. While antibiotics have existed in nature for billions of years, the resistance of human pathogens only emerged in force since the middle of the last century. This phenomenon corresponds to the beginning of the commercial use of antibiotics in medicine and agriculture.

Biocides, compounds that kill organisms, are routinely tested for their toxicity on microbes, even if they are not the intended target. However, sub-lethal effects are usually not considered. A variety of common substances (e.g. aspirin) are known to induce an adaptive response in bacteria leading to a multiple antibiotic resistance (mar) phenotype when bacteria are exposed to the chemical and an antibiotic simultaneously. This reversible resistance can be due to the overexpression of efflux pumps, reduction in the synthesis of outer membrane porins, or both.

We have shown that commercial herbicide formulations Kamba (dicamba), 2,4-D, and Roundup (glyphosate) induce varied but significant changes in antibiotic resistance, in a manner resembling the mar phenotype. I will present data on the effects of the three herbicides on antibiotic resistance towards five antibiotics from different classes in two potential pathogens, *Escherichia coli* and *Salmonella enterica* serovar Typhimurium.

The magnitude and direction of the induced response varied, but the effects may undermine the treatment of bacterial infections in humans and animals as it can change the dose needed to eliminate an organism.

M29: The pathogenesis of influenza A virus in histone deacetylase 6-knockout mice

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In response to virus infection, host cells produce many antiviral proteins that inhibit virus infection. We recently identified host histone deacetylase 6 (HDAC6) as an antiviral protein that inhibits influenza virus infection using a cell culture model [1]. Consistent with these findings, we report herein that influenza virus is more pathogenic in HDAC6-knockout mice. Age- and weight-matched wild type (WT) and knockout (KO) C57BL/6 male mice (8-10 weeks old) were inoculated intranasally with influenza virus A/PR/8/34/H1N1 strain, and their weight and survival were monitored over two weeks. Both WT and KO mice started losing weight from day 4 post virus inoculation. The WT mice, by day 8, lost only 12% of their body weight and started recovering from day 9, and by day 14 they had recovered 100% of their original body weight. Conversely, KO mice lost 20% of their body weight by day 8 and continued to lose weight until day 9 (22%). From day 10, KO mice started recovering, but by day 14 they could only recover 91% of their original body weight. Further, only 47% of the KO mice survived the influenza virus infection as opposed to 76% of the WT mice. These data indicate that HDAC6 play an important part in the host defence against influenza virus infection. Further experiments are underway to determine the lung viral load, lung pathology, and cytokine profile towards understanding the anti-influenza virus mechanism of HDAC6. The HDAC6, a class II HDAC, mainly deacetylates various non-histone proteins. Consequently, it regulates several cellular pathways and is a therapeutic target of multiple human diseases, especially cancer [2]. Therefore, HDAC6 modulators could be employed to develop a new therapeutic strategy against influenza virus.

1. Husain M, Cheung C. *J Virol.* 81:11229-11239 (2014).
2. Li Y, Shin D, Kwon SH. *FEBS J.* 280:775-7793 (2013).

M30: Zinc Daggers - Killing Group A Streptococcus In A Different Way

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Streptococcus pyogenes (Group A Streptococcus; GAS) is a Gram-positive human pathogen responsible for a wide spectrum of diseases ranging from pharyngitis and impetigo, to severe invasive diseases including necrotizing fasciitis and streptococcal toxic shock-like syndrome. Zinc is recognized as an important metal ion in relation to nutritional immunity and zinc deficiency is linked to increased susceptibility to bacterial infection. Zinc stress impairs glucose metabolism through the inhibition of the glycolytic enzymes phosphofructokinase and glyceraldehyde-3-phosphate dehydrogenase. In the presence of zinc, a metabolic shift to the tagatose-6-phosphate pathway allows conversion of D-galactose to dihydroxyacetone phosphate and glyceraldehyde phosphate, partially bypassing impaired glycolytic enzymes to generate pyruvate. Additionally, zinc inhibition of phosphoglucomutase results in decreased capsule biosynthesis. To investigate the role of zinc in innate immune defense against GAS, we analyzed the clinically important GAS M1T1 wild-type strain, and the phenotypes of two isogenic mutants and corresponding complemented mutants. The targeted GAS czcD gene encodes for a putative zinc efflux pump and the adjacent gczA gene encodes a putative Zn-dependent activator of czcD expression. Compared to wild-type and complemented cells, both mutants exhibited reduced ability to grow in the presence of zinc. Transcriptional analyses indicate that gczA up-regulates czcD in response to zinc. The gczA regulator also induces galactose metabolism, circumventing zinc-induced blockage of glucose uptake, and the zinc susceptible CTP synthase. Both czcD and gczA are up-regulated in contact with human neutrophils. Zinc efflux plays a critical role in GAS pathogenesis, as both czcD and gczA mutants displayed increased susceptibility to killing by human neutrophils and reduced virulence in a murine infection model. Taken together, these results demonstrate that zinc homeostasis is an important contributor to GAS pathogenesis and innate immune defense against infection. Strategies to manipulate zinc homeostasis in order to reduce GAS infection are discussed.

Summary of Abstracts for the Poster Session Template

No.	Title	Presenter	Institutions
M31	Novel Naturopathic Remedies: New Method for Screening of New Zealand Fungi for New Antibiotics	Uy, B.[1], Dalton, J. [1], Weir, B. S. 2, Swift, S. [1]	[1]Department of Molecular Medicine and Pathology, University of Auckland, Auckland, NEW ZEALAND, 2Landcare Research, Auckland, NEW ZEALAND
M32	Phenotypic changes in pathogenic bacteria during the transition from iron starvation to iron sufficiency	Dauros-Singorenko, P.[1], Vesty, A.[1], Rowe, M,[1] Swift, S.[1]	[1]Department of Molecular Medicine and Pathology, University of Auckland, Auckland, NEW ZEALAND
M33	Through a Mouse, Brightly: *in vivo* experimental evolution of the pathogenic bacterium *Citrobacter rodentium*	Read, H[1], Johnson, S.[1], Hanage, W.[2], Goddard, M.[3], Wiles, S.[1]	[1]Department of Molecular Medicine & Pathology, University of Auckland, Auckland, NEW ZEALAND, [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA, UNITED STATES OF AMERICA, [3]School of Biological Sciences, University of Auckland, Auckland, NEW ZEALAND.
M34	Characterization of Mycobacterial Membrane Vesicles	Chang V [1], Dalton J [1], Blenkiron C [1], Phillips A [2,3], Dauros Singorenko P [3], Wiles S [1] and Swift S[1]	[1]Department of Molecular Medicine and Pathology, University of Auckland, Auckland, NEW ZEALAND. [2]School of Biological Sciences, University of Auckland, Auckland, NEW ZEALAND. [3]Department of Surgery, University of Auckland, Auckland, NEW ZEALAND.
M35	Regulation of the Type I-F CRISPR-Cas system by CRP-cAMP and GalM controls spacer acquisition and interference	Adrian G. Patterson, James T. Chang, Corinda Taylor and Peter C. Fineran	Department of Microbiology and Immunology, Otago School of Medical Sciences, University of Otago, Dunedin, NEW ZEALAND

M36	Investigating the mode of Action of The Type IV AbiE toxin-°©-antitoxin Phage resistance system.	Hampton. H. G., Jackson. S.A.,Vogel. A.I.M.,Dy. R.L., Fineran, P.C	Department of Microbiology and Immunology, Otago School of Medical Sciences, University of Otago, Dunedin, NEW ZEALAND
M37	Identification of key genetic differences between *Campylobacter concisus* genomospecies.	Nicole E. Wheeler[1], Angela J. Cornelius[2], Stephen L.W. On[2], Paul P. Gardner[1]	[1] School of Biological Sciences, University of Canterbury, NEW ZEALAND [2] Institute of Environmental Science and Research Ltd (ESR), NEW ZEALAND
M38	Novel mode of action for a new TB drug	Kiel Hards[1*] and Gregory M. Cook	Department of Microbiology and Immunology, Otago School of Medical, University of Otago, Dunedin, NEW ZEALAND *Presenting author, to whom correspondence should be addressed; Email:kiel.hards@otago.ac.nz
M39	The Rangipo cluster: a highly virulent *M. tuberculosis* strain in New Zealand?	Mulholland C. V.[1], Ruthe A.[1], Cursons R. T.[1], Arcus V. L.[1]	[1] School of Science, University of Waikato, Hamilton, NEW ZEALAND
M40	Herbicide ingredients sometimes sufficient to cause herbicide-induced multiple antibiotic resistance in human pathogens	P S Gibson[1], B Kurenbach[1], W Godsoe[2] and J A Heinemann[1].	[1]School of Biological Sciences, University of Canterbury, Christchurch, NEW ZEALAND. [2]Bio-Protection Centre, Lincoln University, Lincoln, NEW ZEALAND
M41	Building a framework for OXPHOS inhibitor discovery: the structure and mechanism of type II NADH dehydrogenase	Heikal A.[1, 2], Nakatani Y.[1], Dunn E.A.[1], Hards K.[1], Tee Z.S.[1], Lott J.S.[2, 3] and Cook G.M.[1, 2.]	[1]Department of Microbiology and Immunology, University of Otago, Dunedin, NEW ZEALAND. [2]Maurice Wilkins Centre for Molecular Biodiscovery, The University of Auckland, Auckland, NEW ZEALAND. [3]School of Biological Sciences, University of Auckland, Auckland, NEW ZEALAND.

M42	Global transcriptomic response to nitrogen limitation in Mycobacterium smegmatis	Michael Petridis[1], Andrej Benjak[2], Chelsea Vickers[3], Vickery L. Arcus3, Zhi Shean Tee[1], Gregory M. Cook[1]	Department of Microbiology and Immunology, Otago School of Medical Sciences, University of Otago, Dunedin, NEW ZEALAND
M43	Serological Evidence for Repeated Group A Streptococci Exposures in Siblings with Acute Rheumatic Fever	Raynes, J.M.[1,2], Frost, H.R.[1], Williamson, D.A.[2,3], Young, P.G.[1,2], Proft, T.[2,4], Atatoa-Carr, P.E.[5,6], Bell, A.[5,7], Moreland, N.J.[1,2].	[1]School of Biological Sciences, University of Auckland, NEW ZEALAND, [2]Maurice Wilkins Centre, NEW ZEALAND, [3]University of Otago, Wellington, NEW ZEALAND, [4]Institute of Environmental Science and Research, Wellington, NEW ZEALAND, [5]University of Otago, Dunedin, NEW ZEALAND, [6]School of Medical Sciences, University of Auckland, NEW ZEALAND
M44	Influenza A virus dysregulates host histone deacetylase 1 to efficiently replicate	Nagesh P T, and Husain M,	Department of Microbiology and Immunology, University of Otago, Dunedin, NEW ZEALAND
M45	Defining the Bacitracin-Resistance Network in *Enterococcus faecalis*	Herron, R.L.[1], Gebhard, S.[2], Cook, G.M.[1]	[1]Department of Microbiology and Immunology, University of Otago, Dunedin, NEW ZEALAND, [2]Department of Biology and Biochemistry, University of Bath, Bath, UNITED KINGDOM
M46	Identification and molecular characterisation of chlorhexidine resistance in national *Staphylococcus aureus* isolates.	Tiong, A. I.[1,2], Ren, X. [1]	[1]Department of Pathology and Molecular Medicine, University of Otago, Wellington, NEW ZEALAND, [2]Institute of Environmental Sciences and Research Ltd, Porirua, NEW ZEALAND.

M47	The Evolution of Poxvirus Immuno-modulatory Proteins	Elham Torbati [1], Kurt L. Krause [1], Chris M Brown [1]	[1] Department of Biochemistry, University of Otago, Dunedin, NEW ZEALAND
M48	Determining the molecular effects of 5-fluorocytosine on the virulence of *Pseudomonas aeruginosa*	Jessica Thomson[1], Iain Lamont[1]	[1]Deparment of Biochemistry, University of Otago, Dunedin, NEW ZEALAND
M49	Metabolic profiling reveals the likely mechanism of *Mycobacterium tuberculosis* cell killing by fluorinated anthranilates.	Reese Hitchings[1], Nurul Islam[1], Genevieve L. Evans[2], Dean C. Crick[1] and J. Shaun Lott[1,2]	[1]Mycobacteria Research Laboratories, Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, UNITED STATES OF AMERCIA; [2]School of Biological Sciences and Maurice Wilkins Centre for Molecular Biodiscovery, The University of Auckland, Auckland, NEW ZEALAND.
M50	Role of innate-like lymphocytes in pneumonia pathogenesis	Hannaway, R.[1], Murdoch, D.[2], and Ussher, J.[1]	[1]Department of Microbiology and Immunology, University of Otago, Dunedin NEW ZEALAND, [2]Department of Pathology and School of Medicine, University of Canterbury, Christchurch, NEW ZEALAND
M51	Characterization of PvdF, interaction studies of PvdA and PvdF, enzymes involved in pyoverdine biosynthesis in *Pseudomonas aeruginosa*	Priya Philem[1], Sigurd Wilbanks[1], Iain Lamont[1]	[1]Biochemistry Department, University of Otago, NEW ZEALAND
M52	Role of mucosal associated invariant T (MAIT) cells in cervine Johne's disease	Joshua Lange[1], James Ussher[1], Rory O'Brien[1], Rachel Hannaway[1]	[1]Department of Microbiology and Immunology, University of Otago, Dunedin, New Zealand
M53	A Breath of Clean Air: the potential use of conductive polymers as an anti-tuberculoid agent in facemasks	Julia Robertson[1,3], Marija Gizdavic-	[1]Department of Molecular Medicine and Pathology, [2]School of Chemical Sciences, and [3]Hybrid Polymers

		Nikolaidis[2], James Dalton[1] and Simon Swift[1,3]	Programme, School of Chemical Sciences, University of Auckland, Auckland, NEW ZEALAND
M54	Developing a diagnostic test for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome based on the anti-viral immune protein Protein Kinase R	Sweetman, E. C[1], Tate, W. P.[1]	[1]Department of Biochemistry, University of Otago, Dunedin School of Medicine, NEW ZEALAND
M55	Swabbing beef for contamination: testing methodology using meat spiked with *Serratia marcescens*	Honney, C.[1], Vanholsbeeck, F.,[2] Swift, S[1].	Department of [1]Molecular Medicine and Pathology and [2]The Dodds-Walls Centre for Photonic and Quantum Technologies & Department of Physics, University of Auckland, Auckland, NEW ZEALAND