ABSTRACT BOOK TEMPLATE

QMB Abstracts

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Q1: Bringing Kiwi science to new heights: developing platforms for biological research in microgravity

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Microgravity protein crystallisation can be a valuable tool for generating high-resolution protein structures, with a recent meta-analysis indicating that over 90% of all crystals grown in the microgravity environment of Low Earth Orbit (LEO) exhibit superior quality over control experiments conducted on Earth. Despite the high-quality crystals and resulting structural data microgravity experimentation can provide, executing microgravity protein crystallisation is currently orders of magnitude more challenging than analogous experiments on Earth, with costs and extended experimentation timelines cited as leading reasons preventing most potential researchers from utilising microgravity platforms for their work. To address these challenges, our team is developing fully automated protein crystallisation facilities which will enable high-throughput screening and real-time monitoring of protein crystallisation, comparable to terrestrially-based services. Our partnership with world-leading Axiom Space will ensure regular, frequent, and cost-effective missions to both the International Space Station (ISS) in the near term and the first commercial space station from 2027. This talk will outline the success of New Zealand's first mission to the International Space Station in 2024 which validated our prototype facility and a range of protein experiments. The talk will also provide an overview of our team's upcoming opportunities for additional researchers to become involved in microgravity research.

Q2: Space Medicine, AI, and Earth-Independent Clinical Decision Support: Enabling Autonomy in Deep Space Missions

Brian Russell[1]

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Space is a stress test for the human body and mind. From molecular shifts in immune regulation and oxidative stress to tissue-level remodeling in muscle, bone, and vision, spaceflight exposes new dimensions of human biology. These changes are not just of academic interest—they have operational consequences that challenge how we maintain health and performance far from Earth. As such, space medicine is rapidly evolving into an applied field of molecular biology, integrating omics, physiology, and systems-level insights into real-time medical operations.

This presentation outlines recent work translating these insights into autonomous medical systems, including a Clinical Decision Support System (CDSS) for exploration-class missions. Developed with NASA's ExMC program and commercial partners, the CDSS is designed for Earth-Independent Medical Operations (EIMO), where evacuation is impossible, resupply is limited, and communication is delayed or absent. The system employs probabilistic reasoning, dynamic questioning, and embedded clinical knowledge adjusted to space environments to guide astronauts through diagnosis, monitoring, and treatment—even under degraded performance conditions.

We also present an AI-driven astronaut selection and waiver-assessment platform that uses large language models in a multi-agent system to perform structured interviews, identify medical risks, propose waivers (e.g., Med Volume A), and generate transparent, auditable clinical summaries. The system achieves 98% accuracy in findings and 87% sensitivity for waiver detection, dramatically reducing the burden on limited aerospace medical specialists.

These capabilities sit at the interface of molecular biology, human performance, and AI. They represent a shift toward adaptive, context-aware systems that respond to individual variability, mission constraints, and physiological stressors—including fatigue, radiation, and microgravity-induced changes.

As New Zealand deepens its engagement with space health, this work highlights how biology, computation, and clinical operations can merge to support safe, sustainable exploration—and improve care in extreme environments on Earth.

Q3: Cosmic radiation triggers thiol-based amyloid formation of the human tumour suppressor p16

Shelby G. Gray[1], Pierre de Cordovez[2], Emilie M. Hamzah[1], Karina M. O'Connor[2], Alex D. Botha[2], Daniel Mak[3,4], Patries M. Herst[5], Sarah A. Kessans[6,4], Christoph Göbl[1,2,4], Vanessa K. Morris[1,4]

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p16INK4A (also known as p16) is a critical regulator of the mammalian cell-cycle and is known to be mutated in many cancers. We have found that under oxidizing conditions, the single cysteine amino acid of p16 forms an intermolecular disulfide bond.[1,2] Formation of the disulfide-linked dimer leads to a dramatic structural rearrangement of the protein, from an all-alpha-helical structure to beta-sheet-based amyloid fibrils. Conversion to amyloid fibril structures prevents p16 from carrying out its normal function as a kinase inhibitor.[1] We recently had the opportunity to send samples to the International Space Station (ISS). Radiation is well known to generate reactive oxygen species, and thus we aimed to explore the effects of cosmic radiation and microgravity conditions aboard the ISS on the unique transition of p16. Analyses of the structural state and functionality of p16 following cosmic radiation exposure were carried out using a range of biochemical and biophysical assays. Results from this detailed analysis show intriguing differences between ISS samples compared to control samples. To further explore the effects of radiation, experiments were conducted at higher radiation exposures using caesium-137 radiation. Overall, this work contributes to our understanding of the mechanism and pathogenic roles of p16 amyloid formation.

1. Heath, S.G., Gray, S.G., Hamzah, E.H., O'Connor, K.M., Bozonet, S.M., Botha, A.D., de Cordovez, P., Magon, N.J., Naughton, J.D., Goldsmith, D.L.W., Schwartfeger, A.J., Sunde, M., Buell, A.K., Morris, V.K.* and Göbl, C.* (2024). *Amyloid formation and depolymerization of the tumor suppressor p16INK4a are regulated by a thiol-dependent redox mechanism*. Nature Communications. 15: 5535.

2. Göbl, C.*, Morris, V.K.*, van Dam, L.*, Visscher, M., Polderman, P.E., Hartlmüller, C., de Ruiter, H., Hora, M., Liesinger, L., Birner-Gruenberger, R., Vos, H.R., Reif, B., Madl, T. and Dansen, T.B. (2020). *Cysteine oxidation triggers amyloid fibril formation of the tumor suppressor p16INK4a*. Redox Biology. 28: 101316.

Q4: Sustainable Biofabrication in Space: Microgravity Production of Bacterial Nanocellulose via Synthetic Microbial Communities

David Hooks[1]

[1]AgResearch Ltd., Grasslands, Palmerston North, New Zealand

As humanity embarks on long-duration space missions, the need for in-situ resource utilisation, repurposing. and manufacturing capabilities becomes critical. Our new two-year research project addresses the challenge of sustainable material production in space through the development of bacterial nanocellulose (BNC) using synthetic microbial communities (SMC) powered by solar energy.

Our approach integrates photosynthetic microalgae with BNC-producing bacteria (*Komagataeibacter xylinus*) in a co-cultivation system. The microalgae, selected from space-tolerant species including *Chlamydomonas reinhardtii*, consumes CO_2 and generates carbohydrates that feeds the bacterial community. This minimises resource inputs, a crucial advantage for space applications.

BNC offers useful properties for manufacturing. It is lightweight, non-toxic, non-flammable, and biodegradable, with outstanding mechanical strength, thermal stability, and versatility. The material can be processed into various forms including films, membranes, and structural components, making it ideal for future space applications from habitat construction to life support systems.

Our project, starting in October 2025, will combine terrestrial optimisation with orbital validation. Lab-based research utilising High-Aspect-Ratio Rotating-Wall Vessel bioreactors to simulate microgravity conditions will optimise SMC cultivation parameters. Miniaturised spectroscopic techniques (NIR and FTIR) integrated with machine learning models will be designed and implemented to enable real-time, non-invasive monitoring of BNC production and physico-chemical characteristics.

The orbital phase, conducted in partnership with Helogen to build and deploy a miniaturised autonomous satellite via rideshare missions with companies such as SpaceX or Rocket Lab, will investigate how microgravity affects BNC microstructure and self-organisation. The absence of gravity and buoyancy forces may remodel the fibre networks and reduce aggregation, potentially unlocking novel material properties unavailable in terrestrial production.

The Biofabrication in Space project is a collaboration of BSI-AgResearch expertise in fermentation and biopolymers, Cawthron Institute microalgae biotechnology capabilities, and Helogen satellite engineering experience. It is supported by MBIE and the New Zealand Space Agency.

Expected outcomes include validated protocols for space-based BNC production, novel insights into microgravity effects on biomaterial synthesis, and demonstrated technologies for autonomous biological manufacturing in extreme environments.

Q5: Practical Pathways to Microgravity Research with Dawn Aerospace

Zach Preston[1]

[1] Dawn Aerospace New Zealand Ltd.

Microgravity access is scarce, slow, and expensive–yet this environment reveals biological and materials science phenomena impossible to study on Earth. Dawn's Aurora spaceplane creates microgravity on demand: two to three minutes of high-quality micro-g at aircraft-like cadence and cost, using reusable operations from New Zealand. Dawn will outline potential experiment classes suited to this window—protein crystallisation, cell and organoid assays, diffusion-driven formulation studies, and thin-film or semiconductor processes—and how rapid iteration de-risks orbital campaigns. Dawn will also share where Aurora is today (flight test progress, payload interfaces, environment control, vibration/acceleration profiles), the path to first research payloads, and practical steps for Canterbury researchers to get involved.

Session 2: Molecular Physiology Across Systems, Conway C2+C3, September 4, 2025, 10:30 AM - 12:00 PM

Q6: Death Becomes Them – Host Cells and their viruses

James P. Cooney[1,2], Ashley Hirons[5,6] , Natasha Jansz[5,6,7], Cody C. Allison[1,2], Peter Hickey[1,2,3], Charis E. Teh[1,2], Tania Tan[1,2], Laura F. Dagley[2,3], Jumana Yousef[2,3], David Yurick[5,6,9], Georges Khoury[5,6], Simon P. Preston[1,2], Kathryn A. Davidson[1,2], Lewis J. Williams[1,2], Stefanie M. Bader[1,2], Le Wang[1], Reet Bhandari[1,2], Liana Mackiewicz[1], Merle Dayton[1], William Clow[1], Geoffrey J. Faulkner[7,8], Daniel H. Gray[1,2],Lloyd Einsiedel[4§], Damian F. J. Purcell[5,6§], Marcel Doerflinger[1,2§], Marc Pellegrini[1,2,10§*]

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Satisfactory preventative or therapeutic drugs are lacking for Human T cell lymphotropic virus type -1 (HTLV-1), an infection which lags several decades behind its distantly related cousin HIV-1 in this regard. Consequentially, 5-10 percent of the approximately 10 million people infected with HTLV-1 will progress to serious complications.

This study investigated preventative and therapeutic agents against Human T cell lymphotropic virus type-1 subtype-C (HTLV-1c) infection. We established and characterised a humanized mouse model of HTLV-1c infection and identify that HTLV-1c disease appears slightly more aggressive than the prevalent HTLV-1a subtype, which may underpin increased risk for infection associated pulmonary complications in HTLV-1c. Combination antiretroviral therapy with tenofovir and dolutegravir at clinically relevant doses significantly reduced HTLV-1c transmission and disease progression *in vivo*. Single cell RNAseq and intracellular flow cytometry identified that HTLV-1c infection leads to dysregulated intrinsic apoptosis in infected cells *in vivo*. Pharmacological inhibition using BH3 mimetic compounds against MCL-1, but not BCL-2, BCL-xL or BCL-w, killed HTLV-1c-infected cells *in vitro* and *in vivo*, and significantly delayed disease progression when combined with tenofovir and dolutegravir in mice. Our data suggests combination antiretroviral therapy with MCL-1 antagonism may represent an effective, clinically relevant, potentially curative strategy against HTLV-1c.

Q7: Droplets that organise life

N. Amy Yewdall[1]

[1] School of Biological Sciences, University of Canterbury, New Zealand

Biomolecular condensates are droplet-like compartments that regulate several essential cellular processes, for example RNA processing, making ribosomes, and regulating gene expression. However, unlike conventional intracellular compartments within Eukaryotic cells, biomolecular condensates lack a membrane. Instead, favourable interactions between biomolecules (usually proteins and RNA) drive their phase separation to form dynamic droplets within the aqueous environment of the cell.
Condensate relevance echoes through different branches of biology: disrupted condensates are increasingly found to be a feature of diseases such as cancer, and in synthetic biology they can be used as hubs for controlling reactions.
In this seminar, I will introduce these enigmatic organisational hubs and highlight my research that covers unravelling the fundamental biology behind condensate properties and function. I will also give examples of how we are using condensates as tools to control biochemical processes, and give you an update on what my group is working on.

Q8: Dystrophin-deficiency disrupts skeletal muscle biomechanics

Natalia Kabaliuk[1,2], Pavithran Devananthan[1], Deirdre Merry[3], Rebecca Craven[1], Kellie Joe[1], Gretel S. Major[2,3], Jiayi Chen[3], Angus Lindsay[2-5]

[1]Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand**,** [2]University of Canterbury Biomolecular Interaction Centre, University of Canterbury, Christchurch, New Zealand, [3]School of Biological Sciences, University of Canterbury, Christchurch, New Zealand, [4]Department of Medicine, University of Otago, Christchurch, New Zealand, [5]Maurice Wilkins Centre for Molecular Biodiscovery, Auckland, New Zealand

Dystrophin protein structurally stabilises skeletal muscle cells. Genetic disruption to the dystrophin gene, commonly associated with Duchenne muscular dystrophy, compromises the biomechanical function of skeletal muscle – observations driven almost exclusively by *ex vivo* characterisation. We developed a platform, termed myomechanical profiling, that enables the *in vivo* biomechanical assessment of murine skeletal muscle viscoelasticity using rheology that conforms to *in vivo* constraints (e.g., the murine skeletal system, the isolation of live muscle for controlled load application, and the alignment of muscle fibre and fascicular organization with the directionality and characteristics of mechanical loading).

Dystrophin-deficiency increased stiffness in tibialis anterior skeletal muscle of mice *in vivo* in both static compression and compression strength testing and was associated with total collagen content of the muscle. Dystrophin-deficient tibialis anterior muscles were also less elastic and dissipated mechanical energy more than dystrophin-positive tibialis anterior muscles. When exposed to a series of damaging eccentric contractions, dystrophin deficient tibialis anterior muscles lost greater strength (85% vs. 30%), which further increased the stiffness of the muscle. Exposure to fatiguing isometric contractions also exacerbated stiffness of dystrophin-positive and dystrophin-negative tibialis anterior in response to compression and rotational strain.

These data indicate that the loss of dystrophin compromises the viscoelastic properties of skeletal muscle *in vivo*, fatiguing and damaging exercise stiffens skeletal muscle, and that myomechanical profiling represents an accurate, repeatable, and sensitive technology capable of assessing the biomechanical properties of skeletal muscle.

Q9: Integrated Multi-omics and Lipid-Protein Interactome Analysis to Characterise the Role of Aberrant Lipid Metabolism in Multisystem Mitochondrial Disease

Peng L.[1], Lee R. G.[2,3,4], Scott N. E.[5], Filipovska A.[1,2,3,4], Reid G. E. [1,6,7]

[1]Department School of Chemistry, The University of Melbourne, Parkville, VIC, Australia. [2]The Kids Research Institute Australia, Nedlands, WA, Australia. [3]Harry Perkins Institute of Medical Research, Nedlands, WA, Australia. [4]ARC Centre of Excellence in Synthetic Biology, Centre for Medical Research, QEII Medical Centre, The University of Western Australia, Nedlands, WA, Australia. [5]Department of Microbiology and Immunology, University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Parkville, VIC, Australia. [6]Department of Biochemistry and Pharmacology, The University of Melbourne, Parkville, VIC, Australia. [7]Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Parkville, VIC, Australia

Lipids, as fundamental components of cellular membranes, play crucial roles in maintaining plasma membrane and organellar structures, as well as regulating various biological processes through functional interactions with integral or peripherally associated proteins. Although the importance of many specific protein-lipid interactions has been elucidated, methods for the identification and functional characterization of the lipid-protein 'interactome' on a global scale are currently lacking. Here, an integrated multi-omics workflow for lipidome and proteome analysis has been used to characterise lipid metabolic reprogramming in mitochondrial disease patient samples resulting from defects in lipid metabolism, as well as in a cardiolipin synthase 1 (CRLS1) knockout cell model. Additionally, a co-fractionation mass spectrometry (CF-MS) technique for lipid-protein 'interactome' analysis, employing size exclusion chromatography (SEC) coupled with mass spectrometry (MS) was developed and applied to characterise alterations in membrane lipid-protein interactomes in a cardiolipin synthase-associated multi-system mitochondrial disease system. Non-denaturing membrane protein-lipid complex solubilization was carried out under an optimised mild detergent membrane solubilisation environment prior to SEC co-fractionation. To confirm the efficiency of solubilization and stability of solubilized membrane protein complexes and lipid-protein complexes, blue native gel, and quantitative MS was utilized. Co-fractionated lipid-protein interactions were then identified using an integrated lipid and protein extraction method followed by LC-MS/MS based lipidome and data-independent acquisition (DIA) proteome analysis. CF-MS lipid-protein interactome analysis were conducted on wild-type (*WT*) and cardiolipin synthase knockout (*CRLS1-KO*) CAL51 cell lines. Results showed that while cardiolipin species are co-fractioned with intact mitochondria respiratory chain protein complexes and supercomplexes in *WT* cell lines, significant disassembly of complex III subunits and mild disassembly of complex I subunit from mitochondria supercomplexes were observed in the *CRLS1-KO* cell line, highlighting the functional involvement of lipid-protein interactions in maintaining the assembly/stability and activity of mitochondrial membrane proteins, with potential implications for mitochondrial biology and inter-organelle communication.

Session 3: Commercialization in Life Sciences, Conway C2+C3, September 4, 2025, 1:30 PM - 3:30 PM

Q10: From Basic Research to Real World Impact

Tak W Mak[1,2]

[1]Princess Margaret Cancer Centre, University of Toronto, [2]Centre of Oncology and Immunology, University of Hong Kong

Q11: Navigating academic and industry uses of induced pluripotent stem cell-derived definitive haematopoiesis

Chambers, S.M.[1,4,5], Fstkchyan, Y.[1], Cheng, Q.[1], Zhang, J.[2], Lu, D.[1], Huang, G.[2], Dong, T.[3], Jones, L.[3], Kanke, M.[1], Hale, C.[1], Tarbell, K.[3], Li, C.-M.[1], Wang, S.[1]

[1]Research Biomics, Amgen Research, South San Francisco, CA, USA, [2]Genome Analysis Unit, Amgen Research, South San Francisco, CA, USA, [3]Oncology Research, Amgen Research, South San Francisco, CA, USA, [4]Brightfield Therapeutics, South San Francisco, CA, USA, [5]Department of Pathology, University of Otago, Christchurch, NZ.

Human pluripotent stem cells (hPSCs) offer a tractable system to study early human hematopoietic development and model human diseases of the blood. Generating bona fide definitive hematopoietic stem and progenitor cells (HSPCs) in vitro has remained elusive. Here I present a highly efficient protocol to differentiate hPSCs into an aorta-gonad-mesonephros-like (AGM-like) definitive hemogenic mesoderm, achieving robust generation of HSPCs with multilineage potential. Leveraging a staged differentiation strategy, hPSCs were guided through mesodermal specification into an AGM-like hemogenic niche using defined cytokine cues. Limiting dilution analysis estimated one in five cells within the HSPC fraction were capable of robust multilineage in vitro colony forming potential. Gene expression profiling and single-cell RNA sequencing demonstrated clustering of the hPSC-derived HSPCs with gold standards of long-term hematopoietic stem cells (LT-HSCs). HSPCs were assessed in vitro directed differentiation and in vivo engraftment in immunodeficient mouse models demonstrate multilineage differentiation to specific cell fates including monocytes, macrophage, T-cells, NK-cells, B-cells.

This human model system of haematopoiesis can be useful in both academics and industry. Increasingly, public scientific funding has prioritized immediate application of research and commercialization over a more thorough curiosity-driven approaches to basic science research. Balancing the necessary risk to achieve basic science breakthroughs against the industry demand for rapid and incremental improvement can be tricky, making it important to find commonality between the two approaches. Data publication can be at odds with corporate public relations, trade secrets, and intellectual property ownership, yet to be most successful in both industry and academics, a publication track record is job one. This iPSC derived haematopoietic protocol will be used as framework to discuss philosophical differences and approaches to science in academics versus industry and a solution for how to bridge the gap.

Reference:
Yesai Fstkchyan et al. *A Highly Efficient Aorta-Gonad-Mesonephros-Like Definitive Hemogenic Endothelium From Human Pluripotent Stem Cells*. bioRxiv (2023) DOI: 10.1101/2023.06.26.546545

Q12: The development and commercialisation of recombinant dairy proteins

Miller I. [1], Freed N.E[1], La Grange D.[1], McIsaac E.C. [1], Govind B. [1], Miller, G. [1]

[1] Daisy Lab

Feeding a growing global population in a climate that is nearing planetary boundaries presents a huge challenge for humanity. Globally, animal agriculture is estimated to contribute 14% of human- caused greenhouse gas emissions, with a third of this attributed to dairy farming. To put this in perspective, it is 2.5 more emissions than global air travel. Intensive animal agriculture is also associated with air and water pollution, damage to soils and reduced biodiversity, as well as being linked to the spread of zoonotic diseases and antimicrobial resistance. Despite this, as income and population increase, more dairy products are expected to be consumed. This will put further strain on a food production system that is already at the limit of sustainable production. Daisy Lab has a solution – the familiar taste, nutrition, and functional properties of dairy without the need for cows. Since its inception in 2021, Daisy Lab made great progress in producing both bulk protein (beta-lactoglobulin) and lactoferrin (high-value neutraceutical). They currently move into their next stage of scale up and aim to enable existing dairy processing companies to diversity their supply chain and reduce greenhouse emissions through precision fermentation technology.

Q13: Commercialisation of a novel class of anti-parasitic compounds from nature

Hibbard T.[1], Styles K.[1], Burke L.[1], Nicholson M.[1], Parker E.[1,2]

[1]Bontia Bio Limited, Kelburn, Wellington, [2]Ferrier Research Institute, Victoria University of Wellington, Kelburn, Wellington, New Zealand

Bontia Bio is a Wellington-based synthetic biology startup, spun out from the Ferrier Research Institute at Te Herenga Waka — Victoria University of Wellington. The company implements the proprietary Fungal Factories™ platform whereby fungal strains are engineered to enable the production of potent natural compounds through enhanced industrial fermentation methods.
The company is named after *Bontia daphnoides*, a tropical shrub that has since been eradicated from Hawaii but is found naturally around the Caribbean. This ornamental plant is home to the endophytic fungus *Hypoxylon pulicicidum* which provides protection to its host via the production of a potent class of anti-parasitic compounds are not toxic to mammals. These compounds have the potential for use in a range of industrial and therapeutic applications.
Using patented technology for their biosynthesis, Bontia Bio is creating access to this novel class of anti-parasitic compounds and developing them for commercial use. Our first product will be an orally available flea and tick medication for companion animals that overcomes the limitations of existing products that are dominant in this market. Derived from nature, Bontia Bio's products will have a superior safety profile due to their selective mechanism of action and wide therapeutic window, a long duration of action, and will confer environmental benefits via their production in a sustainable system.

The journey from scientific innovation to successful biotech commercialization is full of technical, operational, and financial challenges, particularly for start-up companies navigating process development and scale-up. Our facility, located in the NZ Bioeconomy Science Institute (BSI) - Scion in Rotorua, specializes in partnering with emerging biotech ventures to accelerate their path from lab-scale proof-of-concept to robust, scalable manufacturing processes. We offer a unique ecosystem where start-ups can develop and optimize their bioprocesses in small-scale bioreactors, then seamlessly transition to pilot-scale systems using our state-of-the-art infrastructure. By hosting start-up companies and their bioreactors within our shared laboratory environment, we provide access to advanced equipment, expert technical support, and essential back-end lab services—dramatically reducing capital outlay and operational complexity for early-stage teams.

Q14: From Bench to Bioreactor: Collaborative Scale-Up Solutions for Biotech Start-Ups

Collet C.[1]

[1]Scion, New Zealand

The journey from scientific innovation to successful biotech commercialization is full of technical, operational, and financial challenges, particularly for start-up companies navigating process development and scale-up. Our facility, located in the NZ Bioeconomy Science Institute (BSI) - Scion in Rotorua, specializes in partnering with emerging biotech ventures to accelerate their path from lab-scale proof-of-concept to robust, scalable manufacturing processes. We offer a unique ecosystem where start-ups can develop and optimize their bioprocesses in small-scale bioreactors, then seamlessly transition to pilot-scale systems using our state-of-the-art infrastructure. By hosting start-up companies and their bioreactors within our shared laboratory environment, we provide access to advanced equipment, expert technical support, and essential back-end lab services—dramatically reducing capital outlay and operational complexity for early-stage teams.

Our collaborative model welcomes companies to work alongside our experienced staff in a vibrant, innovation-driven community, fostering knowledge exchange and accelerating scientific progress. We also offer flexible space and service arrangements, allowing start-ups to scale their operations and host their own personnel on-site as needed. By supporting the full trajectory from small-scale experimentation to larger-scale bioprocessing, we empower biotech entrepreneurs to de-risk their scale-up, achieve key milestones, and bring transformative products to market more efficiently. We invite start-up companies to join our lab, leverage our resources, and collaborate for successful scale-up and commercialization.

Q15: illumina™ Emerging Researcher Award 2025

Battling with double-edged swords: the importance of restraint in bacterial defence and phage counter-defence

Birkholz, N.[1-4], Kamata, K.[1], Feussner, M.[5], Wilkinson, M.E.[6-10], Cuba Samaniego, C.[11], Migur, A.[12], Kimanius, D.[13], Ceelen, M.[1], Went, S.C.[14], Usher, B.[14], Blower, T.R.[14], Brown, C.M.[15], Beisel, C.L.[12,16], Weinberg, Z.[5], Smith, L.M.[1,3,4], Fagerlund, R.D.[1-4], Jackson, S.A.[1-4], Fineran, P.C.[1-4]

[1]Department of Microbiology and Immunology, University of Otago, Dunedin, NZ, [2]Bioprotection Aotearoa, NZ, [3]Maurice Wilkins Centre for Molecular Biodiscovery, NZ, [4]Genetics Otago, University of Otago, Dunedin, NZ, [5]Department of Computer Science and Interdisciplinary Centre for Bioinformatics, Leipzig University, Leipzig, Germany, [6]Howard Hughes Medical Institute, Massachusetts Institute of Technology, Cambridge, USA, [7]Broad Institute of MIT and Harward, Cambridge, USA, [8]McGovern Institute for Brain Research, MIT, Cambridge, USA, [9]Department of Brain and Cognitive Sciences, MIT, Cambridge, USA, [10]Department of Biological Engineering, MIT, Cambridge, USA, [11]Computational Biology Department, Carnegie Mellon University, Pittsburgh, USA, [12]Helmholtz Institute for RNA-based Infection Research, Würzburg, Germany, [13]CZ Imaging Institute, Redwood City, USA, [14]Department of Biosciences, Durham University, Durham, United Kingdom, [15]Department of Biochemistry, University of Otago, Dunedin, NZ, [16]Medical Faculty, University of Würzburg, Würzburg, Germany.

Bacteria are under constant attack from bacteriophages (phages), viral predators that drive the evolution of sophisticated defence mechanisms such as CRISPR–Cas and restriction–modification systems. In turn, phages employ counter-defences such as anti-CRISPR proteins to circumvent host immunity. However, the powerful weaponry on both sides of this microscopic conflict requires tight regulation to limit autoimmunity and toxicity. Here, I present examples from our research demonstrating how such control can occur. First, we discovered two antagonistic defences in the same bacterium; each provides protection against phage infection on its own, but their simultaneous activity would pose a lethal threat to the cell. Remarkably, this conflict is resolved through epigenetic silencing, where one defence mechanism suppresses the other. Second, we explored how a phage regulates the deployment of an anti-CRISPR protein to prevent toxicity from excessive expression and to optimize resource allocation throughout its life cycle. Notably, this regulation is mediated by a single, versatile helix–turn–helix repressor that binds both DNA and RNA. The resulting combination of transcriptional and translational regulation ensures tight control of anti-CRISPR production. Together, these findings underscore the delicate balance required in the deployment of bacterial defences and phage counter-defences, offering new insights into the dynamics of microbial immunity.

Q16: Ahakoa he iti, he pounamu – conducting relational microbiology

Essie Van Zuylen[1,2]

[1]Ngāi Tahu Research Centre, University of Canterbury, Te Whare Wānanga o Waitaha;

[2]Biomolecular Interaction Centre, University of Canterbury, Te Whare Wānanga o Waitaha.

Indigenous peoples contextualise their position in the world through reciprocal interactions with the surrounding environment. Importantly, microbes play a central role in maintaining balance between flora, fauna, geological systems, waterways, and the air. This kōrero will trace the thread that has inspired and connected my research projects as a Māori microbiologist, from anaerobic bacterial pathogens to indigenous psychoactive fungi. In pursuing ethical microbiology research, I employ a framework centered on the concept of relationality among Indigenous peoples, researchers, and microbes. Relationality links biological, social, land, food, and microbial systems, with accountability serving as the foundation of these relationships. Specifically, it seeks to address historical power imbalances that favour researcher perspectives and interests, while also creating space for Indigenous worldviews in the pursuit of Indigenous research sovereignty.

To illustrate this approach in practice, I will present a case study that implements this framework in the Ngā Puanga Pūtaiao research project, Ngā Harore Pōhewanga o Aotearoa; The Psychoactive Mushrooms of New Zealand, understanding our fungal taonga species. This kaupapa explores Māori relationships with indigenous psychoactive fungi and how this knowledge might inform culturally grounded, contemporary approaches to mental health care for whānau. Through the layering of archival ethnographic texts with iwi oral histories and scientific methods we seek to reconstruct our understanding of the whakapapa of endemic *Psilocybe* sp., an area with a history of colonial suppression and limited public understanding. Semi-structured interviews with Rongoā Māori practitioners, and a collaboration with Tū Wairua- the first marae-based clinical trial seeking to provide psilocybin-assisted therapy to whānau Māori suffering from methamphetamine use disorder in Te Tairāwhiti- will also inform this study.

Q17: Thermo Fisher Scientific award for excellence in molecular biology 2025

Fighting the invisible arms race – molecular strategies against antimicrobial resistance

Pletzer, D.[1]

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Antimicrobial resistance (AMR) is one of the greatest biomedical challenges of our time, threatening the effectiveness of antibiotics and impacting human, animal, and environmental health. While much is known about the bacterial “toolbox” of resistance, pathogens continue to outpace our therapeutic strategies. Addressing this molecular arms race requires both mechanistic understanding and translational innovation.

To investigate how bacteria survive antibiotic treatment, my team employs a combination of advanced *in vitro* assays, omics approaches, and novel *in vivo* models. Specifically, we developed a unique non-lethal murine skin abscess model, one of the first to enable dual-species infection studies under chronic conditions without mortality. These tools allow us to probe resistance, biofilm persistence, and host–pathogen interactions under physiologically relevant conditions. We also apply drug screening platforms to identify and optimize novel antimicrobials, including host-derived peptides, peptidomimetics, drug-nutrient conjugates, and prodrugs.

Our results have shown that antimicrobial peptides and their derivatives can potentiate last-line antibiotics and disrupt biofilms formed by WHO-priority pathogens. Using dual-species infection models, we demonstrated that peptide adjuvants can enhance colistin activity against mixed Gram-negative and Gram-positive infections. Prodrug strategies further demonstrated selective activation of antimicrobials at infection sites, offering new avenues to reduce systemic toxicity. This integrated approach has generated high-impact publications, attracted competitive national funding, and fostered collaborations across medicine, industry, and agriculture. In parallel, we are extending these approaches into One Health applications, recognising that AMR also affects food production and environmental safety.

Together, these findings advance both fundamental microbiology and translational therapeutics. By combining mechanistic insight, innovative models, and translational impact, our work exemplifies research excellence and leadership in AMR molecular biology, delivering strategies to extend the lifespan of antibiotics and mitigate AMR across sectors.

Q18: Exploring Aotearoa New Zealand's yeast diversity

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The geographical isolation of Aotearoa New Zealand (NZ) has supported the divergence of diverse evolutionary lineages and resulted in a large proportion of endemism in its flora and fauna. While endemism or local diversification has been shown for some microbial taxa there are also examples of international dispersal and connectivity. Comparatively less is understood about microbial diversity and their evolutionary histories compared to macro-organisms, despite their importance to ecosystem function and potential uses in biotechnology. Yeasts particularly play a pivotal role in the quality and style of fermented products with different species and strains imparting distinct flavours and aromas. The potential for high endemism in Aotearoa NZ provides the opportunity to leverage ecological knowledge of local yeast communities to develop unique products. Thus, we hypothesise there are distinct yeast lineages associated with native flora and fauna and these lineages harbour industrially coveted traits of value. Genetic analyses to date suggest agriculturally derived yeast isolates are recently connected to international sources and exhibit varying degrees of population structure and connectivity within Aotearoa NZ, although there is evidence of more diverged lineages from undisturbed environments.

Q19: Population structure in New Zealand *Rattus rattus*

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The ship rat, *Rattus rattus*, was introduced to New Zealand in the late 1800s and quickly outnumbered previously introduced species of rodents and spread across the country. Today, *R. rattus* continues to have a devastating impact on endemic taonga species, and is one of the targets of localised predator elimination efforts. Previous research, focusing on mitochondrial loci, supported several initial founding events with diverse, but widespread, haplotypes[1]. We assess population structure in New Zealand *R. rattus*, with an aim to determine population connectivity geneflow to inform future pest eradication efforts. Whole-genome resequencing data were generate from tissue samples collected from 98 rats across a broad geographic range spanning the length of New Zealand. Genotype likelihood analysis resulted in >60 million loci retained for downstream analyses. Population structure analyses revealed genetically distinct populations across large geographical distances and between geological barriers.

[1]Russell, J.C., Robins, J.H., Fewster, R.M. (2019) *Phylogeography of invasive rats in New Zealand.* Frontiers in Ecology and Evolution. 7:48

Q20: The structural basis of carnitine transport

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Carnitine is a nutrient central to metabolism in eukaryotes, facilitating the transport of long-chain fatty acids into mitochondria for β-oxidation. The transporter protein OCTN2 moves carnitine across the plasma membrane in most tissues, and is highly expressed in the kidney, heart, skeletal muscle and brain. OCTN2 dysfunction causes systemic primary carnitine deficiency (SPCD), a disorder that can be lethal if untreated. Despite its importance in metabolism, the mechanism by which OCTN2 achieves high-affinity, Na^+-coupled transport of carnitine is unclear. We report the first cryo-EM structures of human OCTN2 in occluded, ligand-free and drug-bound states. These structures reveal the molecular determinants of carnitine binding, alongside an idiosyncratic, allosterically-coupled Na^+-binding site. Combined with two-electrode voltage clamp electrophysiology data, we provide a framework for understanding variants associated with SPCD, and insight into how OCTN2 functions as the primary human carnitine transporter.

Q21: From Ice Age to Isolation: Historical Demography and Inbreeding Depression in New Zealand's Endemic Hector's and Māui Dolphins

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Hector's and Māui dolphins, endemic to Aotearoa, New Zealand, are small coastal dolphins facing significant anthropogenic threats. The IUCN lists the ~15,000 Hector's dolphins (Te Waipounamu/South Island) as endangered, while the Māui dolphin (Te-Ika-a-Māui/North Island), with only ~54 individuals, is critically endangered. We assessed the demographic history and population structure of both subspecies using whole genome data from 48 individuals. Palaeoceanographic trends have shaped contemporary admixture patterns and population structure, with the closure of Te Moana-o-Raukawa/the Cook Strait separating the Māui and Hector's dolphins during the LGM, and with productive regions (East/West Coast) acting as sources for less favourable habitats (South Coast). Māui dolphins diverged from Hector's dolphins ~12–16 kya and exhibit reduced genetic diversity, inbreeding depression, and higher genetic load, confirming the previously reported genetic decline in the Māui dolphin, which could severely impact its survival given their critically low population size. Similarly, the South Coast Hector's population shows elevated inbreeding compared to the larger, more diverse East and West Coast populations. Admixed individuals at population edges display higher genetic diversity, emphasizing the importance of protecting migratory corridors. Conservation strategies must prioritize migratory corridors while assessing adaptive variation and deleterious alleles in local populations to ensure the recovery of these subspecies.

Q22: Boiling over Bad Smells: Harnessing Thermophilic Enzymes to Sniff out Volatile Sulfur Compounds in Wine

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Have you ever tasted a wine and been hit with an unpleasant aroma, maybe an old cabbage or rubbery sulfidic smell? The cause behind these unpleasant aromas is a group of compounds known as volatile sulfur compounds (VSCs). We used headspace-solid phase microextraction gas chromatography-mass spectrometry to identify the VSCs in New Zealand Sauvignon Blanc wines. Several compounds, such as dimethyl sulfide, carbon disulfide, benzothiazole, and methionol were consistently present above detection limits. While these compounds are well understood in terms of their effect on wine flavour and aroma, the reactions during fermentation that underpin their creation is poorly understood. Accurately quantifying these compounds during winemaking is difficult without expensive and technically complex equipment, thus there is a need within the industry for novel, cheap, and accessible detection tools.

Interestingly, we found that some VSCs in wine are also prolific in geothermal hot springs. New Zealand geothermal hot springs are rich in a broad range of microorganisms which can survive at high temperatures, low pH, and utilise sulfur compounds for growth. Some of the most thermostable and technologically feasible enzymes are sourced from hot springs due to their unique characteristics that make them an excellent tool in a range of bio-engineering applications. We have isolated and sequenced the DNA of several microorganisms from these geothermal environments and identified several enzymes of interest utilised by these microorganisms to bind VSCs within their native environment. These enzymes show promise as the basis for novel detection tools to be used on the winemaking floor throughout the fermentation process as an affordable and simplistic alternative to previous VSC detection methods.

Q23: Towards Dissecting the Molecular Mechanisms Underlying GCN2 Activation – A Protein Kinase with Known Links to Health and Disease.

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The protein kinase GCN2 is a critical sensor of cellular stress conditions, including nutrient starvation and oxidative stress.1 The GCN2 signalling pathway is evolutionarily conserved from yeast to humans, where it has acquired additional roles such as long-term memory formation, antiviral defence, regulation of immune responses, metabolic homeostasis, and inflammation.1,2 Not surprisingly, the GCN2 pathway has been increasingly implicated in diverse physiological and pathological conditions, including cancer, neurodegeneration, and immune disorders.1,3
Activation of GCN2 leads to phosphorylation of the eukaryotic initiation factor 2 alpha (eIF2α), triggering a broad reprogramming of gene expression at both translational and transcriptional levels to promote cellular adaptation. Moreover, the multifaceted functions of GCN2 imply that it must be subject to complex regulatory mechanisms1 to ensure tissue-specific functionality. Despite its recognized importance in health and homeostasis, the detailed molecular mechanisms governing GCN2 activation and regulation remain poorly understood. However, this knowledge is essential for elucidating how dysregulation of GCN2 contributes to disease pathogenesis, and for identifying potential therapeutic strategies. Using baker's yeast as an in *cellula* 'test tube', and molecular genetic studies, we here show that ribosomal proteins are critical for full activation of GCN2 in response to stress.

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Q24: The application of heparan sulfate as a human therapeutic

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A human therapeutic derived from porcine mucosal heparan sulfate[1] has been developed to accelerate wound repair. The key attribute is the ability to moderate specific growth factors activity in the wound site.

Sulfated glycans are the most negatively charged natural polymers and arguably the most information-rich biomolecule in nature. However, while only mast cells produce Heparin, and it is present in our body in very small amounts, *every* cell generates the closely related heparan sulfate. As heparan sulfate is ubiquitous in the body it exhibits perfect biocompatibility; therefore, such a technology should direct cellular repair and speed tissue regeneration without any undesirable side-effects.

The characterization of these sulfated polysaccharides,[2] application in a wound repair technology[3] and research towards wholly synthetic variants[4,5] will be discussed.

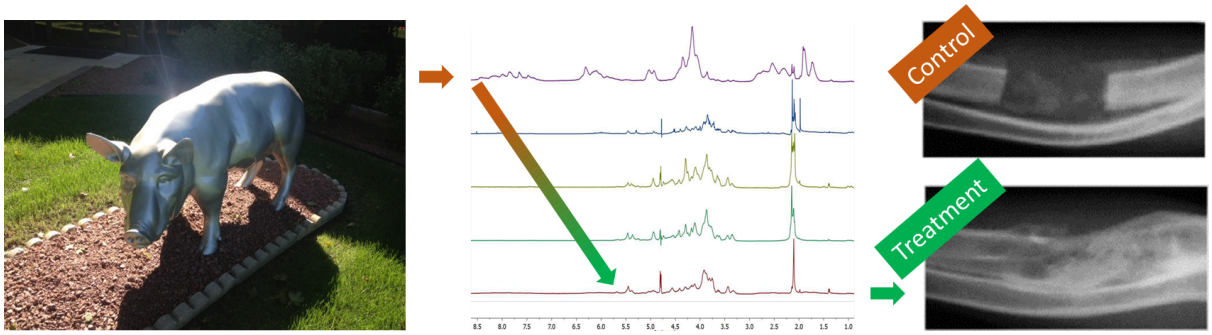

Figure 1. Porcine derived heparan sulfate with processing can promote rapid bone repair.

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Q25: Māu Tēnā Kīwai o te Kete, Māku Tēnei: Equitable Application of Circulating Tumour DNA to the NZ Māori Population.

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For patients living with cancers in Te Tairāwhiti (East Coast of the North Island), there is a strong desire for services that can reduce cost, travel, and the amount of care that must be received in clinical settings. Circulating tumour DNA is DNA released by a tumour into the bloodstream and represents a novel class of blood marker for cancer-specific detection and surveillance. ctDNA testing is a minimally invasive procedure that requires only a simple blood draw for real-time analysis of patient-specific markers that can determine tumour burden, size, type, prognosis, response to therapy, and risk of recurrence.

However, before ctDNA testing can be integrated into clinical practices in Aotearoa and a kaupapa Māori approach must be used to inform the appropriate clinical use of ctDNA testing. In this project, a laboratory workflow for detection of tumour-specific structural variants from fresh-frozen tissues was designed. Additionally, cancer patients living in Te Tairāwhiti, their whānau, and their healthcare providers were interviewed. The laboratory workflow provides an option for Tairāwhiti-based precision medicine delivery and the main themes analysed from the interviews will inform the co-design of clinical protocols for ctDNA testing in Te Tairāwhiti to ensure that opportunities for ctDNA to benefit these communities specifically are optimised, and tikanga is retained in future ctDNA use.

‘Māu tēnā kīwai o te kete, māku tēnei’ is a whakataukī (Māori proverbial saying) that roughly translates to “You take that handle of the basket, I will take this one.” It builds the project on a foundation of Indigenous knowledge and speaks to the responsibilities of both the community and the researchers within this project. It highlights that for outcomes to improve, a change in both community mindset and engagement with health services and research and the integration of mixed methodologies by biomedical scientists are required.

Q26: Optimised high rates of gene editing for skin engineering applications

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Epidermolysis bullosa (EB) is a severe group of monogenic fragile skin conditions, that currently lack a permanent treatment option. We used gene editing on patient derived skin cells to repair mutations in type VII collagen which cause recessive dystrophic EB, and laminin-332 which cause junctional EB. The edited cells were used to engineer gene-edited, patient-specific skin substitutes *in vitro*. These could be used in the future to permanently cover chronic EB wounds.

Cell editing was achieved by nucleofection of an optimised formulation of CRISPR/Cas9 complexes delivered as ribonucleoproteins. We achieved high rates of targeted editing using clinically translatable methods in both major skin cell types, primary keratinocytes and fibroblasts. We achieved up to 95% non-homologous end joining (NHEJ)-mediated repair efficiencies in patient-derived skin cells. We used these methods to restore type VII collagen function by excising disease-causing defective exons in the *COL7A1* gene in cells derived from NZ patients.

We have also developed editing methods that allow for exceptionally high rates of homology directed repair (HDR)-mediated gene repair. To the best of our knowledge, our HDR rates are the highest reported to date in primary human skin cells. Targeting the *COL7A1* gene, we achieved Cas9-mediated HDR in up to 75% of cells in a population of patient-derived keratinocytes and >20% in a fibroblast cell population. Using Cas9 nickases to target the *LAMB3* gene we achieved 60% HDR. Nickases offer advantages over Cas9 nucleases with higher levels of safety by avoiding double-stranded DNA breaks and increased levels of on-target specificity. In each case robust off-target analysis (using nanopore sequencing) did not detect any unintended editing events. We further demonstrated correct gene expression, localisation and functionality by incorporating edited skin cells into lab-grade 3D skin equivalents. We are now working towards clinical translation by engineering gene edited cells into bilayered skin substitutes.

Q27: The contribution of gene-gene and gene-environment epistasis to polygenic risk predictions for common, complex diseases

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Current polygenic risk scores (PRS) for complex diseases capture only a fraction of their potential heritability and lack standardized approaches for integrating environmental factors, limiting their clinical utility. Some of the missing heritability in PRS can be attributed to higher-order gene-gene (GxG) epistatic interactions not captured in traditional GWAS studies.

We developed an interactive PRS pipeline incorporating both GxG and gene-environment (GxE) interactions to identify distinct risk subgroups beyond traditional single-SNP approaches. This method was applied to two contrasting complex diseases: type 2 diabetes (T2D), characterized by high heterogeneity and strong environmental components, and celiac disease (CD), with lower heterogeneity and fewer molecular pathways.

The inclusion of higher-order interactions identified an additional 27% of total cases in the validation set for T2D cases and 10% of CD cases compared to traditional methods, demonstrating that epistatic interactions significantly contribute to genetic risk prediction. Further analysis quantified epistatic contributions within established T2D molecular pathways and revealed enrichment of high-risk cases providing insight into some of the heterogeneity underlying five well-known T2D subtypes.

This research advances the field of precision medicine, demonstrating that higher-order GxG and GxE interactions are essential considerations for accurate risk assessment with the potential to improve clinical risk prediction and enable more precise therapeutic targeting.

Q28: Neutrophils produce hydrogen cyanide and cyanogen chloride during inflammation

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Neutrophils are the major white blood cell in humans. They ingest and kill pathogens using the enzyme myeloperoxidase. This haem enzyme oxidizes chloride and thiocyanate to hypochlorous acid and hypothiocyanite, respectively. We now show that hypochlorous acid and hypothiocyanite react with each other at close to the diffusion-controlled limit. The products include the toxic gases hydrogen cyanide and cyanogen chloride. When myeloperoxidase concurrently oxidized chloride and thiocyanate, cyanide was produced, chelated the enzyme's ferric heme iron, and inhibited its activity. Cyanogen chloride was also produced by myeloperoxidase and cyanylated lysine and cysteine residues on peptides to form *N*-cyanolysine and *S*-cyanocysteine. Glutathione - an important antioxidant - was also cyanylated. To show that neutrophils produce hydrogen cyanide and cyanogen chloride during inflammation, we analysed lung lavage fluid from children with cystic fibrosis for *S*-cyano-glutathione. Lung inflammation in cystic fibrosis is dominated by neutrophils that release myeloperoxidase and produce large amounts of hypochlorous acid. Using liquid chromatography with mass spectrometry, we identified *S*-cyano-glutathione in the lung lavage fluid from the children with cystic fibrosis. We propose that hydrogen cyanide and cyanogen chloride are natural products of activated neutrophils that are likely to play important roles in the inflammatory cascade.

Q29: Using Advanced Genome Editing Techniques to Reprogramme T-cells for Cancer Immunotherapy

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Historically, autologous T-cell receptor engineered T-cells (TCR-T) and chimeric antigen receptor (CAR) T-cells for cancer immunotherapy have been produced using retroviral gene insertion. Non-viral CRISPR-based editing may be a better approach, enabling physiological receptor expression and reducing insertional mutagenesis risk. CRISPR/Cas9 editing in primary human T-cells is in its early stages globally, and large-insert editing often yields low insertion rates and high toxicity, limiting therapeutic cell populations. The type of template DNA used in large-insert genome editing affects toxicity, insertion rates, and off-target DNA integration. We aim to assess the optimal template DNA type and optimise editing conditions to maximise the therapeutic T-cell population.

We have sequenced melanoma-targeting TCRs from a library of CD8+ T-cell clones using TCR sequencing protocols we developed. We plan to use optimised gene editing tools to insert these novel TCRs into the endogenous TCR locus. To optimise large-insert gene editing protocols, we are working with the insertion of a large green fluorescent protein (eGFP) tag. A proof-of-principle experiment yielded >40% insertion of eGFP into HEK293T cells. Now, to develop and assess efficient T-cell editing methods, we are:

- Developing protocols to generate linear and circular dsDNA and ssDNA templates to compare how template type affects insertion rates and T-cell viability after editing.
- Assessing the effect of DNA-sensing inhibition on T-cell viability following large-insert gene editing.
- Evaluating the ability of CRISPR-edited TCR-T cells to recognise target antigens and kill cancer cells.

This research could advance T-cell immunotherapy and support the development of a platform to generate T-cells targeting tumour-specific antigens. The scope of this work extends beyond melanoma, as we can sequence TCRs from our CD8+ T-cell clone library targeting viral, cancer germline, and other neoantigens. Additionally, methods developed through this research may be broadly applicable to all large-insert T-cell editing and editing in other cell types.

Q30: Bioprinting of 3D *in vitro* Organoid Models for Investigating Tissue Fusion in Healthy and Diseased Microenvironments

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Biofabrication technologies, including extrusion bioprinting, are enabling generation of engineered constructs that replicate the complex 3D organization of native tissues via automated precise placement of cell-laden bioinks, organoid modules, and/or bioactive factors. Regenerative Medicine strategies aim to repair damaged or diseased tissues via stimulating new tissue formation and integration with host native tissue, however, robust lateral integration is challenging. Therefore, there is a critical need to explore 3D models and mechanisms that drive successful tissue formation and fusion within healthy and diseased microenvironments. Here, we describe a modular bioprinting approach to spatially pattern healthy and diseased (osteoarthritic) cartilage tissue spheroids, enabling investigations into mechanisms of spheroid fusion, and ability of cell-instructive biomolecules (vitreous humour (VH), hyaluronic acid (HA), thiolated-heparin (Hep-SH)) to enhance cell differentiation and integration.

Healthy tissue spheroids (TS, Ø1mm) were formed by centrifugation of human articular chondrocytes (hACs). Mildly diseased, TS(M), and severely diseased, TS(S), spheroids were obtained by exposing TS to cytokines (IL-1β+TNF-α) and/or hypertrophic conditioned culture media. Healthy and diseased cartilage spheroids were then bioassembled adjacent to one-another and cultured for 14 days. Single, fused, and biomolecule supplemented (VH, HA) tissue-spheroids were evaluated both quantitatively (GAG/DNA, qPCR) and qualitatively (Safranin-O, Alizarin red, IHC:Collagen I/II/X staining). TS displayed homogeneous GAG and collagen-II deposition, while TS(M) and TS(S) displayed significantly reduced GAGs and collagen-II/I ratio. Integration was accelerated when fusing healthy TS spheroids with diseased spheroids (compared to TS-TS alone), however, the quality of fused tissue worsened with greater disease severity. Supplementation with VH significantly improved fusion between healthy and diseased TS, evidenced by increased GAG formation and cell migration in the integration region.

Expanding this approach, we describe further examples applying photocrosslinking to 3D bioassembly platforms for probing fundamental kinetics of multicellular organoid fusion, and tissue-tissue integration mechanisms in healthy and diseased tissues, with specific examples of new paradigms for high-throughput screening in tumour microenvironments, and disease modelling.

Q31: Can activation of an oncoprotein do good things?

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PIK3CA, the gene encoding the p110α catalytic subunit of PI3Kα is one of the most frequently mutated genes in cancer. Therefore, inhibition of PI3Kα has been a major target in anticancer drug discovery. However, the therapeutic potential of activating PI3Kα, and kinases in general, remains largely unexplored. PI3Kα pathway activation has been extensively linked to cardioprotection and neuro-regeneration, with a positive role for PI3Kα recently demonstrated in protection against ischaemia reperfusion injury and axonal regeneration using genetic approaches. To explore the potential of pharmacological PI3Kα activation in this context, our laboratories have recently reported in *Nature* the discovery of UCL-TRO-1938, a small molecule direct activator of PI3Kα. Our crystal structure showed that UCL-TRO-1938 binds the PI3Kα complex at the junction of multiple domains. The activator binding opened a pocket on the surface of the enzyme complex, producing a conformational change resembling changes elicited by natural activators, such as oncogenic mutations and binding to phosphorylated tyrosine-kinase receptors. UCL-TRO-1938 is highly selective for PI3Kα over other PI3K isoforms, and multiple protein and lipid kinases. It transiently activates the PI3K signalling pathway in cells, leading to increased cell viability and proliferation. In animal models, UCL-TRO-1938 enhances neurite outgrowth in dorsal root ganglia, and accelerates neuro-regeneration after peripheral nerve injury, for which there are currently no therapeutic agents. The discovery of UCL-TRO-1938 causes a paradigm shift from investigating the therapeutic potential of kinase inhibitors to kinase activators, and opens up new fields of research and opportunities not only in nerve regeneration, but also in other areas of tissue protection such as ischaemia reperfusion injury.

Q32: Decoding protein degradation with structural biology and machine learning

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The post-translational modification of proteins with ubiquitin has a central role in all eukaryotic cells. As a result, disruption of ubiquitin transfer is associated with many illnesses including cancer, diabetes, and neurological disease. Ubiquitin modification regulates the fate of substrate proteins, often by directing them for destruction by the proteasome. I use a combination of structural and computational methods to understand how ubiquitin signals are generated, and develop new tools to control ubiquitin signaling.

Here I will discuss how we use phage display, protein-design tools, structural biology, and biochemical assays to discover and design protein-based inhibitors of the ubiquitin cascade. Our targets include enzymes that are central to ubiquitin transfer that play an essential role in promoting degradation of substrate proteins, such as p53, as well as being involved in the development neurodegenerative disease. Some of the discovered inhibitors are potent and specific, and structural and biochemical analyses allowed us to establish how they can block activity. Overall, our results may form a framework for development of new therapeutics—such as PROTACs or molecular glues—and useful research tools.

Q33: Thiolate oxidation of ankyrin repeat proteins triggers transition into amyloid structures.

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Ankyrin repeat (AR) proteins are conserved across all three kingdoms of life and are composed of tandem motifs, each consisting of two α-helices separated by a loop—forming a characteristic helix–loop–helix structure. These motifs stack to form an elongated AR fold that provides a versatile surface for mediating protein–protein interactions. Many AR-containing proteins play essential roles in signalling pathways critical to cellular function.

Among the many AR-containing proteins are the INK4 tumour suppressors, including $p15^{INK4b}$, $p16^{INK4a}$, $p18^{INK4c}$, and $p19^{INK4d}$. These proteins inhibit cell division and are often mutated in various cancers. We recently identified a novel oxidation-dependent mechanism majorly affecting the function of the INK4 protein $p16^{INK4a}$. Here, we have expanded this finding and we investigated this cysteine dependent amyloid fibril formation in homologous proteins $p15^{INK4b}$ and $p18^{INK4c}$. We discovered that under oxidative conditions, the proteins form disulfide-linked homodimers through its single cysteine residue, which subsequently assemble into inactive amyloid fibrils. Amyloid fibrils are traditionally associated with neurodegenerative diseases, characterized by a cross β-sheet structure and this is the first example of oxidation-induced amyloid formation.

We have also identified specific protein regions that drive amyloid formation (Heath et al., 2024). Our discovery prompted us to investigate whether this mechanism extends beyond the INK4 family. We identified further sequence-homologous AR proteins harbouring these motifs, such as integrin-linked kinase (ILK) and myotrophin (MTPN), also contain cysteines and form amyloid fibril structures.

Our study introduces the novel concept of oxidation-induced amyloid formation, emphasizing the existence of different structural and functional states in the INK4 family of tumour suppressors and scaffold related proteins ILK and MTPN. Our study suggests the existence of a second stable structural states for a family of proteins and expands our understanding of protein folds, their stability and functions.

(1) Heath, S. G., et al (2024). *Amyloid formation and depolymerization of tumor suppressor p16INK4a are regulated by a thiol-dependent redox mechanism.* Nature Communications, 15(1), 5535. https://doi.org/10.1038/s41467-024-49581-7

Q34: Mechanosensitive endonuclease ANKLE1 processes chromatin bridges by cleaving mechanically strained DNA

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Maintenance of genome integrity is one of the main functions of living cells. Despite the existence of a highly complex mitotic spindle that ensures the precise distribution of identical copies of genetic material between daughter cells during cell division, errors can still occur that result in missegregation of sister chromatids, causing the formation of chromatin bridges between daughter cells. Uncontrolled disruption of these stretched chromatin bridges by actomyosin contractile forces during cytokinesis leads to detrimental consequences such as genomic instability. To prevent catastrophic damage to the genome due to uncontrolled rupture of chromatin bridges, cells have developed special mechanisms to handle them. Here we reveal the unique property of ANKLE1, a midbody-associated endonuclease involved in chromatin bridge processing, to recognize and respond to DNA tension during cell division. Single-molecule analysis using magnetic tweezers showed that stretching force applied to DNA can significantly accelerate the DNA-cleaving activity of ANKLE1. This activity can be further enhanced by DNA supercoiling. Although ANKLE1 was found to cleave only one DNA strand of positively supercoiled and/or torsionally relaxed DNA, under high stretching forces (5 pN) it predominantly cleaved both strands of negatively supercoiled DNA. The latter reflects conditions under which stretched chromatin bridges lose histones and expose negatively supercoiled DNA. These findings suggest a previously uncharacterized role for ANKLE1 as a DNA tension sensor that resolves stretched chromatin bridges. Our study highlights the importance of mechanical forces in the DNA bridge processing, expanding our understanding of the role of mechanobiological process in maintaining genome integrity during cell division.

Q35: Martini3-NMR: empowering coarse-grained simulations with AI-predicted NMR observables.

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Beyond structure, protein dynamics shapes cellular functioning. By exploiting nuclear resonance as a proxy of chemical environment and conformation, NMR spectroscopy is key to investigate molecular motions. Nonetheless, by collecting average molecular behaviour, NMR is limited in yielding detailed conformational states and is often coupled to all-atom molecular dynamics (MD) simulations to provide high-resolution protein ensembles.[1] While integrating NMR and MD allows to sample NMR-complying ensembles, simulating biologically relevant molecular sizes and timescales remains challenging.

As opposed to all-atom MD, by clustering groups of atoms into beads, coarse-grained simulations (CG-MD) facilitate the investigation of larger molecules over longer timescales. Being linked to atomic nuclei, the integration of NMR observables in CG-MD has however so far been thought impossible.

We challenged this apparent impossibility by training a neural network (NN) to predict NMR chemical shifts (CS) from coarse-grained representations of proteins.

We then differentiate the predicted CS with respect to coarse-grained coordinates and restrain protein motions towards experimentally valid ensembles. Our approach thus allows the incorporation of NMR CS into CG simulations of proteins boosting the biological relevance of CG-MD.

We name this framework Martini3-NMR as we implemented it on Martini3: a widely used force field for CG-MD. We show that Martini3-NMR can reproduce NMR-sound ensembles for a wide range of proteins: from soluble to membrane-bound and amyloidogenic conformational states. To overcome known limitations of Martini3 in preserving protein packing, we additionally incorporate long-range distance restraints from Nuclear Overhauser Effect (NOE) NMR signals. Overall, Martini3-NMR ultimately allows the investigation of protein motions on longer timescales for ever larger molecular systems, empowering a simulation-driven understanding of biologically relevant events.

References

1. Robustelli,P. Using NMR Chemical Shifts as Structural Restraints in Molecular Dynamics Simulations of Proteins. Structure 18, 923–933 (2010).

Q36: Targeting antioxidant defence mechanisms in *Streptococcus pneumoniae*

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Streptococcus pneumoniae is a leading cause of death from infectious disease. The bacterium generates large amounts of hydrogen peroxide during its normal metabolism. In the presence of thiocyanate (SCN-) in the respiratory tract, this hydrogen peroxide is converted to hypothiocyanous acid (HOSCN) by the host enzymes lactoperoxidase and myeloperoxidase. We have shown that *S. pneumoniae* has a high tolerance to HOSCN. The aim of our research is to understand how *S. pneumoniae* copes with this oxidant and to develop strategies to neutralize its HOSCN defences.

We identified two essential components of the pneumococcal HOSCN defence: 1) a flavoprotein disulfide reductase that directly breaks down HOSCN, named hypothiocyanous acid reductase (Har), and 2) a membrane transporter that enables the bacteria to import glutathione from their host environment. We showed that genetic deletion of both systems renders the bacteria completely incapable to grow in the presence of HOSCN. Importantly, loss of either Har or the glutathione importer results in an attenuated phenotype in mouse models of pneumococcal infection, with a lower bacterial burden observed in the lungs and blood.

We generated recombinant Har and showed that it reduces HOSCN with near diffusion-limited catalytic efficiency. We identified a potent inhibitor of Har by screening a pool of known flavoprotein disulfide reductase inhibitors. Encouragingly, this Har inhibitor was able to increase *S. pneumoniae* susceptibility to HOSCN.

We also purified the glutathione-scavenging component of the pneumococcal glutathione importer and investigated its interaction with glutathione using NMR chemical shift perturbation assays and differential scanning fluorimetry. Our results indicate that electrostatic interactions between lysine and arginine residues in the protein's ligand binding site and the carboxylate groups of glutathione are critical for binding. Collectively, our research lays the foundation for inhibiting the HOSCN reductase enzyme and disrupting glutathione import in *S. pneumoniae*.

Q37: Caspase-8 amyloid aggregation: A redox-driven switch in cell fate

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Caspase-8 is a key regulator of programmed cell death, directing cells into apoptosis or necroptosis depending on environmental signals. While apoptosis is non-inflammatory, necroptosis promotes inflammation which can damage nearby tissue. Regulatory mechanisms that determine which pathway is activated have been elusive. Our recent work identified hypothiocyanous acid (HOSCN), an oxidant produced by immune cells, as a modulator of caspase-8 through formation of an inhibitory disulfide, but the structural consequences of this oxidation were unknown.[1] This study investigated the cellular and molecular impact of caspase-8 oxidation by HOSCN.

In human cell models, treatment with HOSCN altered the pattern of cell death, shifting responses away from classical apoptosis. Caspase-8 was converted into high molecular weight aggregates, with a loss of its normal enzymatic function. To investigate the underlying mechanism, purified recombinant caspase-8 was exposed to HOSCN, resulting in rapid disulfide bond formation. This oxidative modification led to the formation of large, stable aggregates that resisted disassembly even under reducing conditions. Electron microscopy and biophysical analysis revealed that these aggregates exhibited fibrillar morphology consistent with amyloid-like structures, which are typically associated with protein misfolding and pathological aggregation. Other apoptotic caspases, including caspase-3, -6, -7, and -9, were also susceptible to HOSCN. Like caspase-8, caspase-9 formed fibrils, suggesting a broader role for redox-triggered aggregation in the regulation of initiator caspases.

Together, these findings suggest that caspase inactivation and aggregation by HOSCN may shift cell fate toward necroptosis and inflammatory outcomes. This redox-sensitive control of caspase function reveals a novel layer of regulation within the cell death machinery and may have implications for inflammation-associated conditions such as inflammatory bowel disease.

1. Bozonet SM, Magon NJ, Schwartfeger AJ, Konigstorfer A, Heath SG, Vissers MCM, et al. Oxidation of caspase-8 by hypothiocyanous acid enables TNF-mediated necroptosis. J Biol Chem. 2023 May;104792–104792.

Summary of Abstracts for the Poster Session Template

No.	Title	Presenter	Institutions
P1	Characterisation of p15(INK4b) amyloid formation	Ramana J[1], Hamzah E[2], Magon N[1], Morris V[2,3], Göbl C[1,2,3]	1 - Department of Pathology, University Of Otago, 3 - Biomolecular Interactions Centre , 2 - School of Biological Sciences, University of Canterbury
P2	Disrupting the oligomeric structure of peroxiredoxin 2 in cancer cells promotes cell death	Pace P, Helem S, Austad S, Peskin A, Winterbourn C, Hampton M	Mātai Hāora - Centre for Redox Biology and Medicine, University of Otago Christchurch
P3	Exploring the functional role of amyloid formation by the cell cycle regulator p18ink4c in Zebrafish Development	Greene G[1], Sethi A[1], Darroch H[2], Magon N[1], Horsfield J[2], Morris V[3,4], Göbl C[1,3,4]	4 - Biomolecular Interaction Centre, University of Canterbury, 1 - Mātai Hāora Centre for Redox Biology and Medicine, University of Otago Christchurch, 2 - Department of Pathology, University of Otago, 3 - University of Canterbury
P4	Exploring the TREM2-glycosaminoglycan binding site using solution NMR	Kumar S[1] , Sheen C[2], Göbl C[3], Morris V[1]	3 - Mātai Hāora - Centre for Redox Biology and Medicine, University of Otago Christchurch, 1 - School of Biological Sciences, University Of Canterbury, 2 - Canterbury Health Laboratories
P5	Folding-limited nucleation of curli suggests an evolved safety mechanism for functional amyloid production	Claridge J[1,2,3], Martens C[4], Sleutel M[2,3], Pradan B[2,3], Sobott F[5], Remaut H[2,3]	1 - Agresearch Ltd., 3 - Structural and Molecular Microbiology, Structural Biology Research Center, VIB, 5 - School of Molecular and Cellular Biology & Astbury Centre for Structural Molecular Biology, University of Leeds, 4 - Structure and Function of Biological Membranes - Chemistry Department, ULB, 2 - Structural Biology Brussels, Vrije Universiteit Brussel
P6	How allosteric tuning influences enzyme promiscuity and host adaptation	Given F, Ho T, Allison T, Bulloch E, Jiao W, Fries A, Mazzaferro L, Muller M, Johnston J	University Of Canterbury
P7	Hugh Green Technology Centre - an integrated core facilities approach to solving high-complexity genomics questions	Handley A[1], von Daake S[1], Moloney-Geany K[2], Price K[1]	2 - Malaghan Institute of Medical Research, 1 - Hugh Green Technology Centre at the Malaghan Research Institute of Medical Research
P8	Insights into the mechanism of the Streptococcus pneumoniae glutathione import system	du Toit S[1], De Cordovez P[1], Dickerhof N[1],	1 - University Of Otago, 2 - University of Canterbury

		Dobson R[2], Göbl C[1,2]	
P9	Insights into the structure and the oxidation-induced amyloid formation mechanism of the tumour suppressor protein p16	Gölitz A[1], de Cordovez P[1], Hamzah E[2], Morris VK[2], Göbl C[1,2]	1 - University Of Otago, 2 - University of Canterbury
P10	Investigating PHA synthases for better bioplastic production	Bailey M[1,2], Hoang V[1,2], Ho T[1,2], Given F[1,2], Nazmi A[1,3], Allison T[1,2], Johnston J[1,2]	2 - School of Physical and Chemical Sciences University Of Canterbury, 1 - Biomolecular Interaction Centre University Of Canterbury, 3 - School of Product Design University of Canterbury
P11	Investigating Promoter Methylation as a Driver of Opiate Receptor Gene Expression Using CRISPR SunTag Editing	Manning E[1], Osborne A[1], Dobson R[1]	1 - University Of Canterbury
P12	Investigating relationships between the microbiome and methylation profiles in colorectal cancer	Kinder C[1,2], Sulit A[1,2], Wiggins G[1,3], Purcell R[1,2]	1 - University Of Otago, Christchurch, 2 - Department of Surgery and Critical Care, 3 - Department of Pathology and Biomedical Science
P13	Investigating the anti-cancer properties of portimine	Helem S[1], McDonald C[1], Faville S[1], Seddon A[1], Pace P[1], Selwood A[2], Harwood T[2], Kumar A[3], Kleffman T[3], Hampton M[1]	1 - Mātai Hāora – Centre for Redox Biology and Medicine, Department of Pathology and Biomedical Science, University of Otago Christchurch, 2 - Cawthron Institute, 3 - Centre for Protein Research, University of Otago
P14	Investigating upstream open reading frames in Arabidopsis thaliana	Gibbon A[1], Macknight R[1], Lim C[1]	1 - University Of Otago
P15	Low maternal dietary vitamin C intake during pregnancy in guinea pigs results in an altered behavioural and metabolic phenotype in offspring and induces TET-dependent tissue-wide methylation changes	Vissers M[1], Smith-Diaz C[1], Coker S[3], Dyson R[3], Berry M[3], Hore T[4], Das A[2]	3 - University of Otago, Wellington, 2 - Walter and Eliza Hall Institute, 4 - University of Otago, 1 - University of Otago, Christchurch
P16	Nuclear Magnetic Resonance Analysis of Reflex Tear Metabolites in Parkinson's Disease	Coldicott R[6], Jemima Ganderton[1,2,3,4], Briana Smith[2,6], Tim Anderson[4,5], John Dalrymple-Alford[1,4,5], Christoph Göbl[3,6], Vanessa K. Morris[2,3]	1 - Department of Psychology, University of Canterbury, 2 - School of Biological Sciences, University of Canterbury, 3 - Biomolecular Interaction Centre, University of Canterbury, 4 - New Zealand Brain Research Institute, 5 - Department of Medicine, University of Otago, 6 - Mātai Hāora - Centre for Redox Biology and Medicine University of Otago Christchurch, 7 - Department of Neurology, Christchurch Hospital
P17	Oxidation of caspase-9 by hypothiocyanous acid triggers formation of amyloid-like aggregates that influence cell death outcomes	Austad S[1], Schwartfeger A[1], Hampton M[3], Göbl C[2,3], Morris V[1,3]	1 - School of Biological Sciences, University Of Canterbury, 3 - Biomolecular Interaction Centre, University of

			Canterbury, 2 - Mātai Hāora - Centre for Redox Biology and Medicine, University of Otago Christchurch
P18	Swimming against the tide: Ovarian fluid protects sperm from oxidative stress during external fertilisation	Helem S[1], Smith B[1], Hampton M[1], Rosengrave P[2]	2 - Department of Nursing, University of Otago, 1 - Mātai Hāora – Centre for Redox Biology and Medicine, University of Otago Christchurch
P19	Understanding a novel oxidation-induced amyloid formation mechanism of the tumour suppressor protein p16INK4a	de Cordovez P[1], Gray S[2], Heath S[1], Bird S[3], Demeler B[3,4], Morris V[2], Göbl C[1]	4 - University of Montana, 2 - University of Canterbury, 1 - University of Otago Christchurch, 3 - University of Lethbridge
P20	Unravelling the functional impact of the zebrafish P18ink4c transition into amyloid fibrils	Sethi A[1], Darroch H[2], Greene G[1], Magon N[1], Horsfield J[2], Morris V[3,4], Göbl C[1,4]	4 - Biomolecular Interaction Centre, University of Canterbury, Christchurch, New Zealand, 2 - Department of Pathology, University of Otago, Dunedin, New Zealand, 3 - University of Canterbury, Christchurch, 1 - Mātai Hāora Centre for Redox Biology and Medicine, University of Otago Christchurch
P21	Unravelling the oligomeric forms of the membrane-interacting EsxE-EsxF complex	Viet Anh Hoang	University of Canterbury
P22	How do independent coarse-grained models converge on defining accurate ensembles of intrinsically disordered proteins?	Ung V[1], Cullen M[1], Mercadante D[1]	University Of Auckland
P23	Ascorbate uptake and its effects on phenotype and cytokine expression in human monocyte-derived macrophages Dr. Stephanie Bozonet Mātai Hāora – Centre for Redox Biology and Medicine Group, Department of Pathology and Biomedical Science, University of Otago	Dr. Stephanie Bozonet	Mātai Hāora – Centre for Redox Biology and Medicine Group, Department of Pathology and Biomedical Science, University of Otago