Te Aka Symposium Abstracts

Contents

Sandra Fitzgerald
University of Auckland,
Research Fellow,
Plenary;

Evolving genomic complexity unveiled in ctDNA analysis of cancer patients

Fitzgerald, Sandra1, 2, Blenkiron, Cherie1, 2, Somers-Edgar, Tiffany4, Rolfe, Gill3, Rykers, Alice1, Stephens, Rosalie4, Mathy, Jon A1, 5, Martin, Richard3, Jackson, Christopher6, Cocadiz, Judy Ann 7, Zou, Donghui 7, Eccles, Mike2, 7, Day, Rob7, Guilford, Parry7, Lawrence, Ben1,2, Lasham, Annette1, 2 and Print, Cris1, 2

1 University of Auckland, New Zealand, 2 Maurice Wilkins Centre, New Zealand, 3 Waitemata District Health Board, New Zealand, 4Cancer and Blood Service, Auckland City Hospital, New Zealand, 5Counties Manukau Health, New Zealand, 6Southern District Health Board, New Zealand, 7University of Otago, New Zealand

There is an increasing global focus on integrating minimally invasive "liquid biopsies", of mutation-bearing DNA that leaks out from tumours into the blood, into routine cancer care. DNA sequencing of tumour DNA within blood plasma can provide real-time information for patients and their clinicians about tumour type and optimal treatment, treatment response, the emergence of treatment resistance and tumour relapse after surgery, to facilitate more informed clinical decisions. In a NZ-wide project with Australian collaborators, we have developed a series of affordable and sensitive liquid biopsy next-generation sequencing assays for patients with melanoma, colorectal and lung cancer, focusing on potential use in remote clinics to address health system inequities. Circulating tumour (ct)DNA mutations identified in patients' plasma samples by these sequencing assays were almost universally confirmed when re-tested using droplet digital PCR. In this talk, we will discuss these assays and the complex tumour mutational heterogeneity evolving over time they have detected in advanced-stage melanoma patients. We will suggest that successful implementation of liquid biopsies into cancer care in New Zealand can make a significant difference to our patients, in terms of improving equity of access and outcome, informing timely management, and optimising capacity-constrained care. However, we first need to increase the robustness of laboratory ctDNA analysis systems to make this a reality.

Tamsin Robb
University of Auckland
Research Fellow

Genomics through a HoloLens: Cancer Evolution in Augmented Reality

Tamsin Robb[1], Yinan Liu[2], Rose McColl[3], Bianca Haux[3], Braden Woodhouse[1], Daniel Hurley[1], Cherie Blenkiron[1], Peter Tsai[1], Jane Reeve[4], Kate Parker[1], Mike Davis[2], Uwe Rieger[2], Cris Print[1], Ben Lawrence[1]

1 Faculty of Medical and Health Sciences, The University of Auckland

2 School of Architecture and Planning, The University of Auckland

3 Centre for eResearch, The University of Auckland

4 Auckland District Health Board, Auckland

Our incomplete understanding of cancer cells' ability to evolve is holding back our fight against metastatic disease. Studying many samples collected from metastatic tumours at autopsy provides a valuable opportunity to better understand the processes underlying the development of treatment resistance, relapse and metastatic dissemination, yet such datasets provide an interpretation challenge.

A patient with lung neuroendocrine tumour (NET) and 90 metastases requested and consented to donate her tumour tissues for research after death through rapid autopsy, providing a rare opportunity to investigate tumour evolution in a single patient. We constructed an n=1 research autopsy programme to accept this gift. We analysed 42 spatial sites through complementary genomic technologies including DNA whole exome sequencing.

We have developed an interactive 3D environment using Microsoft HoloLens augmented reality headsets to bring together spatial and temporal data with the aim of deeply understanding this unique dataset and making connections between clinical and genomic data that are difficult to make using traditional tools. At the centre of the HoloLens environment stands the patient model, her tumours represented with accurate volumetric renders from CT scans. Alongside the patient is an interactive 3D representation of the phylogenetic tree, allowing users to highlight genomically related tumour samples on the patient's body, visualising the anatomical distribution of three distinct genomic clades and hypothesise their routes to metastasis and the timing of dispersal of different clades. A time slider facilitates visualising how the patient's tumours have grown and shrunk over her disease course with respect to treatment, while genomic clades remain overlaid on tumour sample sites. Multiple users from intersecting disciplines can interact with the patient model collaboratively, enabling deep hypothesis generation.

We hope this project may spark future visualisation tools to integrate genomics with clinical data, to maximise the impact of genomics on our patients.

Dr Andrew Macann

Division of Oncology | Faculty of Medical and Health Sciences Te Aka Mātauranga Matepukupuku | Centre for Cancer Research

Radiation Oncologist

Plenary;

Sixty five % of patients with HPV negative head and neck squamous cell carcinoma (HNSCC) present with loco-regionally advanced disease. These patients are usually treated with extensive surgery, followed by adjuvant post operative chemo-radiation with a 3 year overall survival of 58%. Traditionally, advances in the management of HNSCC have been facilitated by adding novel treatment interventions onto the framework of existing standards of care. One approach has been adding immune checkpoint inhibitors (ICI) to surgery / chemo-radiation platforms. There is evidence that the regional lymphatic ablation integral to current surgical and radiation treatments compromises host immunity and the ability to respond to ICI. This raises a paradox. Do we need to revisit the paradigm of adding new therapeutics to existing standards of care ? These issues are driving the evaluation of neoadjuvant ICI interventions prior to surgery. Hypoxia is known to be a prognostic factor in HNSCC with evidence in tumours with hypoxia gene signatures that neoadjuvant ICI strategies are less effective. Tarloxotinib is a hypoxia activated pro-drug which releases an irreversible HER1-4 inhibitor under conditions of severe hypoxia, resulting in shutdown of EGFR signalling. Tarloxotinib combines well with stereotactic body radiotherapy (SBRT) which treats the gross tumour but avoids uninvolved regional lymphatics. We are evaluating the safety of this combination in advanced HPV negative HNSCC patients prior to surgery (involving delayed lymphatic ablation), with serial MRI imaging used to measure suppression of the hypoxic tumour microenvironment, and pathological response documented at subsequent surgery (along with proteo-genomic analyses). We will describe how this window of opportunity tarloxotinib / SBRT trial preludes a future therapeutic platform integrating ICI, and discuss the trial within a te whare tapa whā model of care. Our hypothesis is that suppression of the hypoxic microenvironment will improve outcomes in combination neoadjuvant strategies.

Stephen Jamieson

Auckland Cancer Society Research Centre

Associate Professor

Plenary;

HER2-targeting antibody-drug conjugates (ADCs) are revolutionising the treatment of HER2-positive breast cancer. Trastuzumab emtansine (T-DM1, Kadcyla®) was the first ADC approved for the treatment of HER2-positive breast cancer, and more recently trastuzumab deruxtecan (T-DXd, Enhertu®) has shown improved efficacy over T-DM1 and also been approved in a new indication of HER2-low breast cancer. Despite their activity, intrinsic and acquired resistance remains a major problem and the mechanisms responsible are not well characterised. Therefore, we are utilising CRISPR/Cas9 functional genomics screens to discover genes responsible for sensitivity and resistance to HER2-targeting ADCs. Whole genome screens were carried out in HER2-positive cell lines transduced with Cas9 and the GeCKOv2 guide RNA (gRNA) library to identify gene knockouts enriched or depleted in response to T-DM1 or its effector DM1, with similar screens planned for T-DXd. Hit validation was carried out by secondary screens with a custom gRNA library and by single gene knockout. Our dual screening approach revealed candidate T-DM1 sensitivity and resistance genes, including known T-DM1 sensitivity genes: ERBB2 (HER2) and SLC46A3. Other top sensitivity hits were TSC1 and TSC2, which are negative regulators of mTOR complex 1. We generated TSC1 and TSC2 knockout clones, which were more resistant to T-DM1 in growth inhibition and competition growth assays than wildtype cells. Notably, gene knockout also promoted resistance to HER2-targeting tyrosine kinase inhibitors lapatinib and neratinib, suggesting the effect of TSC1 and TSC2 knockout was likely through mediating signalling downstream of HER2. Indeed, antiproliferative synergy was observed when T-DM1 was combined with the mTOR inhibitor everolimus. In summary, we have identified TSC1 and TSC2 as novel genes involved in T-DM1 sensitivity. Further knowledge of T-DM1 and T-DXd sensitivity and resistance may provide new combination strategies (e.g. with mTOR inhibitors) to overcome resistance or new predictive biomarkers to improve HER2-targeting therapy.

Dr. Hilary Sheppard

University of Auckland

Senior lecturer

Workshop;Panel;Innovative short format;

Immune checkpoint inhibitors (ICIs) have revolutionised the treatment of some cancers including melanoma. ICIs unshackle our immune cells to kill cancer. One type of ICI works by blocking the interaction of the PD-1 receptor on immune T cells with its ligand PD-L1 on the cancer cell. ICIs targeting the PD-1/PD-L1 axis are an effective treatment in approximately 30% of melanoma patients, however the underlying biology remains poorly understood. PD-L1 expression alone is a poor biomarker for patient response to ICIs. 30% of PD-L1+ patients fail to respond, while up to 15% of PD-L1- patients do respond to ICI therapy. Additionally, the role of a second PD-1 ligand (PD-L2) in the response to treatment is poorly characterised. Therefore, a fuller understanding of the PD-1 checkpoint pathway is needed to better predict which patients will benefit from ICI treatment.

Here we aim to fine-tune endogenous PD-1 and PD-L1/PD-L2 expression in primary human T cells and melanoma respectively, at physiologically relevant levels. We hypothesise that there are optimal expression levels of PD-1/PD-L1 axis proteins which tip the balance towards either immune escape or targeted cancer cell killing. MicroRNA based fine-tuning of endogenous gene expression is achieved through CRISPR/Cas9-mediated insertion of synthetic microRNA response elements into the 3'UTR of target genes.

We have achieved targeted insertion of a miRNA response element into the target genes PD-1 (65% editing rate) and PD-L1 (98% editing rate) in CD8+ T cells and melanoma cell lines, respectively. Flow cytometric analysis of PD-L1-edited cells showed a concurrent decrease in cell surface protein expression indicative of fine-tuned gene expression. Additionally, we have generated highly efficient (>90%) PD-L1 and PD-L2 knockout melanoma cells. Experiments are underway to assess the functional impact of melanoma PD-L1/PD-L2 modulation on melanoma-specific T cells. This research has implications for enhancing both cell based and drug based immunotherapies.

Alyona Oryshchuk

University of Auckland

PhD Candidate

Plenary;

Acute myeloid leukaemia is a devastating disease with poor prognosis. It is driven by leukaemia stem cells (LSCs) which sustain the disease, are able to survive treatment and drive relapse. This highlights the importance of identifying and characterizing LSCs. There are no known surface markers to identify them in patients. Targeting a signaling pathway that is common to LSCs could be a novel, promising treatment strategy. The aryl hydrocarbon receptor (AHR) pathway was shown to be critical for the self-renewal properties of normal hematopoietic stem cells (HSCs).

We used a murine bone marrow transplantation leukaemia model (CALM-AF10 minimal fusion gene-driven), to study the effect of AHR agonist (ITE) and AHR antagonist (CH-223191) treatment on LSCs. AHR modulation depleted LSC about 4 times (with ITE; LCS frequency of 1:163 versus 1:44 in a vehicle control) or to the level that could not be measured (CH-223191 resulted in no leukaemia dsevelopment). That is despite testing on a very aggressive AML model (LSC frequency of 1:4). RNA-Seq (n=90) revealed differential expression of many genes implicated in physiology of the stem cells (including haematopoiesis), cell proliferation, differentiation and apoptosis after AHR modulation. Among them were Arl11, Ccr2, Cxcl2, Esr1, Evi2, Heatr9, Hoxa9, Lin28a, Nanog and Zfp36 genes. To confirm that AHR antagonist treatment affects LSCs differently than normal HCS, we performed competitive repopulation assay (n=12). We observed an enhancing effect of CH-223191 on wild type HSCs (a steady increase in the percent of engraftment is observed over 47 weeks post transplantation compared with that of controls).

In summary, our data show that the LSCs react differently than normal HSCs to changes in AHR signalling. These differences suggest it might be possible to specifically inhibit LSCs while sparing normal HSCs, thus paving the way to develop strategies to treat leukemia based on manipulating AHR signalling.

Stephanie Chadd

University of Auckland

Masters in Health Psychology Candidate

Innovative short format;Plenary;

Developing CanACT – an Acceptance and Commitment Therapy (ACT) tool for rangatahi cancer survivors.

Stephanie Chadd1,4, Kirsten Ballantine2, Heidi Watson2, Meihana Douglas3, Sian Ellett1, Rachel Brown3, Anna Serlachius1.

1Department of Psychological Medicine, The University of Auckland, Auckland, New Zealand

2Adolescent and Young Adult Cancer Network Aotearoa, Auckland, New Zealand

3National Hauora Coalition, Auckland New Zealand

4Tamaki Health, Total Health Care PHO, Auckland, New Zealand

Background on CanACT

In high-income countries like New Zealand and Australia cancer is the most common cause of disease-related death in adolescents and young adults (Wong et al., 2017). However, survivorship rates are high, over 84% in New Zealand, with a growing number of rangatahi living with the impact of cancer long-term (Ballantine, Moss, & Watson, 2020). Finishing treatment and remission is far from the end of the impact cancer has on a young person's life. Most rangatahi will adjust well to long-term survivorship however, research shows distress does not end when treatment finishes (Enskär & von Essen, 2007).

There are currently very few interventions developed to support survivors' psychological wellbeing and coping after cancer (Barakat, Galtieri, Szalda, & Schwartz, 2016). Without appropriate support there are serious implications for long-term psychological adjustment and wellbeing for rangatahi experiencing poor mental health (Lu et al., 2013; Sansom-Daly et al., 2012).

Investigating CanACT

The proposed study is to explore the usability, acceptability and cultural appropriateness of a brief, online Acceptance and Commitment Therapy (ACT) intervention for rangatahi cancer survivors aged between 16-24 years in New Zealand. The intention of this study is to collate feedback from rangatahi cancer survivors, adolescent and young adult cancer specialists, health care professionals, and whānau to explore their views of an online ACT intervention.

To our knowledge, there has never been a study that investigates an online wellbeing intervention targeting rangatahi cancer survivors in New Zealand. This study provides the opportunity to develop an engaging and relevant intervention supporting the wellbeing and quality of life for rangatahi throughout Aotearoa who are adapting to their lives as survivors of AYA cancer.

Maggie Kalev

University of Auckland

Senior Lecturer, Haematologist

Workshop;

Ethnic differences in haematologic malignancies remain poorly elucidated both in New Zealand and worldwide, hence research in this area is important. To this end, we conducted retrospective analysis for patients with acute promyeloctic leukaemia (APL) and classical Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) using data extracted from the New Zealand Cancer Registry (NZCR) and Auckland City Hospital (ACH).

For APL, we analysed 55 patients treated at ACH and 173 patients recorded in the NZCR for the period 2000–2017. We found that Polynesian patients presented at a younger age than Europeans (P = 0.005), showed higher blast counts (P = 0.033), and a marginally higher prothrombin ratio (P = 0.02). Treatment with all-trans retinoic acid was started faster in Polynesian patients, suggesting these patients were sicker at presentation but were managed accordingly, with no differences in short-term or long-term outcomes.

For MPN, we analysed 275 patients with polycythaemia vera (PV), 360 patients with essential thrombocythaemia (ET), and 152 patients with primary myelofibrosis (PMF) diagnosed between 2010-2017. We found that Polynesian patients with all MPN subtypes were younger than their European counterparts both at the time of diagnosis and death. Male gender was an independent risk factor for mortality from PV and PMF (hazard ratios (HR) of 1.43 and 1.81, respectively; P < 0.05), and Māori ethnicity was an independent risk factor for mortality from PMF (HR: 2.94; P = 0.006).

In conclusion, our results highlight a discrepancy in the presentation, severity, and outcomes of myeloid cancers between NZ Polynesian and European patients. Polynesian patients may have an increased genetic predisposition to myeloid malignancies or a unique risk factor profile, thus we advocate for modern genetic testing in this ethnic group and further epidemiologic analysis to identify the cause. More work is also required to identify modifiable risk factors for mortality.

Cristin Print

The precision oncology research-practice continuum

Genomic technologies serve whānau with cancer in two ways: by guiding current patient care, and by enhancing biological understanding of cancer in order to improve future patient care. In this session, Cris will summarise research by his team and their collaborators that uses genomic technologies synergistically with traditional pathology to enhance future precision oncology. He will discuss his own team's positive experiences partnering with Māori genomics leaders, clinical colleagues and industry experts across a range of cancers. His talk will raise questions about the next steps for genomics in New Zealand to support precision medicine.

Biography

Cris graduated in Medicine from the University of Auckland in 1989 and began research while working as a house surgeon in Dunedin, NZ. A PhD in the University of Auckland led to a four-year postdoctoral fellowship in the Walter and Eliza Hall Institute in Melbourne, Australia before six years in Cambridge University, UK. While there he co-founded a genomics and bioinformatics company and in 2005 he returned to the University of Auckland where he leads a cross-disciplinary research team of clinicians, cell biologists and data scientists who use genomics, systems biology and bioinformatics to better understand human disease, especially cancer. He leads the Genomics Into Medicine Strategic Research Initiative in Auckland and Chairs the Auckland Regional Biobank Scientific Advisory Board. He is Acting Chair of the NZ Institute of Environmental Science and Research (ESR) and one of the Principal Investigators of the Maurice Wilkins Centre and of the Genomics Aotearoa Rakeiora program. Previously, he served as President of the NZ Society for Oncology and was Director of the Bioinformatics Institute at the University of Auckland.

Richard Mithen

Liggins Institute University of Auckland

Professor of Nutrition

Plenary;Panel;

Prostate cancer is the most commonly diagnosed cancer in new Zealand, with around 4000 new cases diagnosed each year, and about 700 deaths. Men with organ-confined prostate cancer may choose a program of "active surveillance," in which radical treatment is delayed until there is evidence of cancer progression. As there are no approved therapeutic interventions for men who have chosen a program of active surveillance, dietary approaches to reduce risk of progression are an appealing option. Epidemiological evidence suggests that consumption of cruciferous vegetables such as broccoli is associated with reduced risk of prostate cancer progression, largely attributed to the biological activity of sulforaphane derived from glucoraphanin that accumulates in these vegetables. We undertook a 12 month doubled blinded RCT with men who has a diagnosis of organ confirmed prostate cancer in which the participants received a single weekly 300 mL portion of soup made from a standard broccoli (control) or from 1 of 2 experimental broccoli genotypes with enhanced concentrations of glucoraphanin, delivering 3 and 7 times that of the control, and underwent transperineal template biopsy procedures and dietary assessment at the start and end of the study. Gene expression in prostate tissues from each patient obtained before and after the dietary intervention was quantified by RNA sequencing followed by gene set enrichment analyses. In the control arm, there were several hundred changes in gene expression in non neoplastic tissue over the 12 month period that were associated with an increase in expression of potentially oncogenic pathways including inflammation processes and epithelial–mesenchymal transition. Changes in gene expression and associated oncogenic pathways were attenuated in men on the glucoraphanin-rich broccoli soup in a dose-dependent manner. Although the study was not powered to assess clinical progression, an inverse association between consumption of cruciferous vegetables and cancer progression was observed.

Kirsten Ballantine

AYA Cancer Network Aotearoa

Research & Data Lead

Plenary;Panel;

Background

Every year 190 adolescents and young adults (AYAs) aged 12-24 years are told that they have cancer. New Zealand's AYA survival rates published in 2013 lagged behind what was being achieved internationally. In 2014 the AYA Cancer Network Aotearoa was established to ensure that rangatahi have equitable access to the best cancer care and age-appropriate supports available.

Aotearoa's relatively small AYA case numbers present significant challenges; how can we achieve consistency of care and equity for AYAs who undergo treatment in different regions and across multiple services? Here we describe how our national focus on AYA cancer research and data is helping to drive improvements for rangatahi.

Methods & Results

Research informed the eighteen priorities outlined in the Network's first AYA Cancer Action Plan 2020-2025. Our updated survival analysis showed significant survival gains but inequities remain - particularly for Māori and Pasifika - that must be addressed. Additional priorities, such as fertility preservation and survivorship, strongly emerged from 'Whakarongo Mai', our patient experience survey.

The Network has established a national AYA cancer data set to support clinical case management, service planning, and performance monitoring. We receive weekly notifications from the New Zealand Cancer Registry, ensuring timely referrals of rangatahi to their regional AYA Cancer Key Worker for support.

We conduct research in partnership with NGOs, academic institutions, and clinicians or lend support to studies in specific areas such as recruitment, reducing the risk of over-burdening AYAs with research invitations. All Network research is undertaken in consultation with our AYA Consumer Group. A research directory on our website promotes awareness of AYA cancer research in Aotearoa and encourages the cross-pollination of ideas.

Conclusion

The establishment of a national network has led to an increased focus on research and supported greater innovation, consumer involvement, and collaboration across the sector.

Jeff Smaill

University of Auckland

Associate Professor, Auckland Cancer Society Research Centre

Discovery of FGFR-targeted therapeutics with an improved therapeutic index

Many cancers that disproportionately affect Māori are caused by amplifications, mutations or fusions in the Fibroblast Growth Factor Receptor 1-4 (FGFR1-4) family. Systemic administration of selective FGFR1-4 inhibitors is associated with common adverse reactions such as hyperphosphatemia, alopecia, diarrhea, nail toxicity, fatigue, dysgeusia, nausea, constipation, stomatitis, vomiting, arthralgia, abdominal pain and dry eye. Many of these toxicities are derived from on-target inhibition of FGFR1/3 in normal tissues and often result in dose reductions and interruptions. Consequently, these toxicities compromise efficacy in the majority of cancer patients. Consistent with this, the pan-FGFR inhibitor erdafitinib gained FDA accelerated approval in 2019 based on a modest 32% overall response rate (ORR) in urothelial carcinoma patients with FGFR2/3 mutations. Subsequently, two further pan-FGFR inhibitors (pemigatinib and infigratinib) have gained FDA accelerated approval in cholangiocarcinoma patients with FGFR2 fusions or other rearrangements, based on a 36% and 23% ORR, respectively.

Over the last decade, we have been collaborating with Jinan University (Guangzhou, China) to develop two alternate strategies that will address FGFR-dependent cancers while avoiding systemic toxicities. Firstly, the discovery of tumour-targeted irreversible pan-FGFR inhibitors, and secondly, the design of FGFR4-selective kinase inhibitors. We have designed SN38180, a hypoxia-activated prodrug of a pyrido[2,3-d]pyrimidin-7(8H)-one irreversible pan-FGFR inhibitor, that covalently targets cysteine 488 in the p-loop of FGFR1-4. We are currently evaluating SN38180 in preclinical models of cancer, relative to erdafitinib, to demonstrate the promise of this approach. In addition, we have identified promising novel FGFR4-selective kinase inhibitors for advanced biological evaluation. Through covalent targeting of a poorly conserved cysteine (Cys552) situated in the hinge region of FGFR4, these agents spare FGFR1-3 and achieve exceptional kinome-selectivity. This project is currently in hit-to-lead optimization to identify a clinical candidate for the treatment of FGF19/FGFR4-amplified hepatocellular carcinoma.

Dean Singleton

The University of Auckland

Senior Research Fellow

Workshop;Innovative short format;

Lower-grade gliomas (grade II-III) are primary diffuse brain cancers with an intermediate survival expectancy (median survival of 3-10 years, depending on classification). Genomic discoveries have shown that 80% of lower-grade gliomas are caused by missense mutations at the arginine 132 codon in the gene encoding the metabolic enzyme isocitrate dehydrogenase 1 (IDH1). Biochemically this mutant protein acquires a neomorphic activity: reductive NADPH-dependent catalysis of αKG to (R)-2-hydroxyglutarate [(R)-2-HG]. (R)-2-HG interferes with the function of αKG-dependent epigenetic modifiers, resulting in extensive epigenetic remodelling that impairs cellular differentiation and promotes gliomagenesis. Strategies for selectively targeting cells with IDH1 mutation offer promise for improved treatment over the standard modalities of surgery, chemotherapy and radiotherapy.

We have conducted whole-genome CRISPR/Cas9 knockout screens to identify gene dependencies in an IDH1 mutant glioma cell line. We discovered that glucose-6-phosphate dehydrogenase (G6PD), an enzyme involved in the pentose phosphate pathway (PPP), is needed for viability of mutant IDH1 brain cancer cells. The PPP is the main producer of cytosolic NADPH that is used for de novo lipogenesis, maintenance of antioxidants and production of (R)-2-HG by mutant IDH1. Previous reports suggest that IDH1 mutant cells increase PPP flux to support these processes.

We have validated this dependency using G6PDi-1, a cell-active inhibitor of G6PD. Growth inhibition (IC50) assays demonstrated that IDH1 mutant glioma cells were three times more sensitive to G6PDi-1 than WT cells. Further work is underway to quantify effects of G6PDi-1 on redox status and cell death. To enable these studies, we have developed more physiological cell culture conditions by delipidating serum to more closely mimic the conditions within the central nervous system. These findings highlight the potential of G6PD inhibition as a targetable vulnerability in mutant IDH1 gliomas.

Nishi Karunasinghe

University of Auckland

Senior Research Fellow

Performance of prostate cancer diagnoses in Auckland region during 2006-2013.

Nishi Karunasinghe1, Lynnette R Ferguson2 and Jonathan Masters3

1.   Auckland Cancer Society Research Centre, FMHS, University of Auckland; 2. Emeritus Professor, University of Auckland; 3. Consultant Urologist, Whangarei Hospital

Introduction

New Zealand (NZ) is among the countries recording higher rates of prostate cancer incidence in the world. Whether this is due to better diagnoses or otherwise need assessment.

Methods

NZ prostate cancer cases (n=515) and control (n=572) cohorts were recruited between 2006-2013 from the Auckland region and clinical, health, lifestyle, biomarker, and genetic factors were collected, and risk factors were assessed. Diagnoses performance was assessed against two US cohorts (European American [US-EA] and African American [US-AA]) and two Taiwanese cohorts (advanced prostate cancer cohort [TW1] and localised prostate cancer cohort [TW2]) recruited during comparable time periods.

Results

Comparison between NZ prostate cancer case and control cohorts showed that risk increased in association with ever-tobacco smoking and lower serum Se levels. Risk was also associated with a panel of genetic polymorphisms including those in the antioxidant, androgen, and lipid metabolism pathway genes and those near the putative oncogenes.

Compared to US cohorts, NZ cases and controls recorded higher PSA levels at diagnosis and recruitment respectively. Median Gleason sum score was the lowest among the US-EA cases compared to other cases cohorts. Percentage of NZ cases recording high-risk prostate cancer with a prognostic stage of >IIB were comparable with the US-EA cases. However, the cumulative % of high-risk prostate cancer detection among NZ cases shows significantly lower diagnosis rates at lower PSA levels compared to both US groups. These delays were further compounded by smoking status and genetics.

A NZ cases sub-cohort undergone radical prostatectomy (RP) showed lower over-diagnoses, and higher under-diagnoses rates compared to world averages. In addition, Māori and Pacific men recorded poor prostate pathology features compared to other NZ ethnic groups. Poor mortality rates were recorded for this sub-cohort compared to averages seen internationally.

Discussion

There is potential to improve diagnoses for better management of our patients.

Hayley Reynolds

Auckland Bioengineering Institute

Senior Research Fellow

Workshop;Panel;
TITLE: Advancing precision oncology using medical imaging and bioengineering

Recent technical advances in artificial intelligence, big data and radiomics are driving rapid growth in medical imaging research. The Cancer Imaging Research Group at the Auckland Bioengineering Institute (ABI) is taking advantage of these by developing advanced tools for precision treatment of melanoma, breast cancer and prostate cancer, three of the most common cancers in NZ. This includes development of predictive software tools for melanoma and breast cancer to indicate likely sites of metastatic spread, providing decision support systems for medical practitioners and patients. In addition, quantitative imaging biomarkers for prostate cancer are being developed using radiomics and artificial intelligence for their ability to indicate response to radiotherapy, which would early interventions to be given if recurrent disease is detected. Medical imaging expertise spans various spatial scales and types of imaging, from digital pathology through to multiparametric MRI, PET/CT, SPECT/CT, and near infrared lymphography. Our aim is to build upon existing expertise to develop predictive software tools and imaging biomarkers for other solid tumours such as head and neck cancer, and those with poor prognosis such as pancreatic and liver cancer. We are keen to discuss potential collaborative opportunities with others in the oncology space who have related research questions and interests.

Adam V Patterson

Auckland Cancer Society Research Centre

Associate Professor

Plenary;

Tarloxotinib amplifies the therapeutic efficacy of immune checkpoint inhibitors through multiple mechanisms.

Immune checkpoint inhibitors (ICI) are monoclonal antibodies that block the interactions between inhibitory receptors and their ligands, thereby relieving T-cells from negative regulation. ICI are capable of eliciting robust and durable anti-tumour immune responses in advance-staged cancer patients, but only in a minority of patients and malignancies, indicating underlying resistance mechanisms. Accumulating evidence suggests that pathophysiological hypoxia within the tumour microenvironment can suppress the anti-tumour immune response via multiple pathways. Tarloxotinib is a hypoxia-activated prodrug of an irreversible EGFR/HER2 inhibitor (Tarloxotinib-TKI), that may improve the efficacy of ICI through lowering of the tumour hypoxic fraction and thus relief from hypoxia-mediated immunosuppression.

Tarloxotinib treatment inhibited EGFR signalling in the syngeneic murine cancer cell line MB49, both in vitro and in vivo, significantly delaying the growth of subcutaneous MB49 tumours, and lowering the hypoxic fraction. In vivo the combination of tarloxotinib with ICI led to much improved anti-tumour efficacy when compared to the respective monotherapies. Flow cytometric analysis revealed that combination treatment increased the tumour infiltration of effector T-cells while enhancing their activation and function. Further, T-cells were demonstrably rescued from exposure to the hypoxic tumour microenvironment. Treatment also led to enhanced cytokine production and changes in transcriptional activity of multiple immune-related genes. Mechanistically the observed combinatorial activity required both functional release of tarloxotinib-TKI within the tumour and direct inhibition of the PD-1/PD-L1 pathway by ICI. The observed synergy was demonstrated to be CD8+ T-cell and MyD88-dependent. These results illustrate the therapeutic potential of combining tarloxotinib with ICI, leading to greatly improved anti-tumour activity.   Word count: 264 (including title)

Michael Alexander Pudjiahrtono

University of Auckland

PhD student

Workshop;

Genome-wide association studies (GWAS) have identified 76 genomic loci associated with melanoma risk. However, most of these loci are in the non-protein-coding part of the genome, making functional interpretation difficult. While previous studies have developed various approaches to tackle this problem, most have focused on identifying close-range connections (e.g. in the promoter or other nearby regions). Here, we integrated information from melanoma GWAS with tissue and cell-specific markers of the 3D DNA structure (Hi-C), expression quantitative trait loci (eQTLs), and other co-localising enhancer features (e.g. histone acetylation; H3K27ac) to identify the genes dysregulated by non-coding mutations in skin and melanocytes. Our integrative approach identified 151 genes regulated by non-coding variants in 42 melanoma GWAS loci through both close and long-range connections. Collectively, these non-coding mutations impact genes involved in various biological processes such as regulation of cell death and modifiers of skin pigmentation. Many of these genes have not been associated with melanoma before. Notably, a substantial proportion of these genes are regulated via long-range connections. A long-range connection from a risk locus at 9p21.3 to the LRP1B gene on 2q21.2 highlights a novel link between germline predisposition and somatic mutational processes in melanoma. Our study highlights putative biological implications of long-range regulation by melanoma risk loci and provides a starting point for further experimental validation of functional variants and disease-related genes.

Petr Tomek

Auckland Cancer Society Resesrch Centre, University of Auckland
Research Fellow

Banishing immunosuppressive kynurenine for sensitising cancer patients to immunotherapies

Arresting the production of an immune-suppressive tryptophan metabolite called kynurenine generated by enzymes IDO1 and TDO is a key strategy for sensitising cancer patients to curative immunotherapies. That is because elevated kynurenine levels are present in most cancers and undermine immunotherapies. Further, immunotherapies themselves can elevate kynurenine production as part of the natural immune-regulatory response. Over 20 years of drug development efforts, however, have not yet generated an approved IDO1/TDO inhibitor. That is likely due to challenges in blocking both IDO1 and TDO simultaneously in the absence of toxicities caused by their tendency to bind vital haemoproteins other than IDO1/TDO such as haemoglobin.

This talk will outline two strategies being developed in my group to circumvent these limitations and arrest kynurenine production safely and effectively. To address haem-related toxicities and increase potency, we aim to design a Trojan Horse, a molecule that sticks exclusively to the inactive haem-free form of both IDO1 and TDO simultaneously, thereby preventing enzyme activation by the haem co-factor. From the screen of 15,000 compounds in IDO1/TDO-expressing cancer cells, we have discovered many unique chemicals for the Trojan Horse development and identified molecular fingerprints of cellular IDO1 and TDO selectivity.

The second approach explores the possibility of arresting kynurenine production by inactivating an understudied enzyme called arylformamidase (AFMID) required by IDO1/TDO to produce kynurenine. AFMID inactivation offers advantages to IDO1/TDO blockade as AFMID has no confirmed isozymes, lacks haem and its loss is well tolerated in mice. We have evidence indicating that exclusively AFMID drives kynurenine production in cancer. This warrants further explorations and uncovering whether AFMID inactivation safely sensitises mouse tumours to immunotherapy.

Successful development of Trojan Horse or anti-AFMID drugs in the future holds promise to sensitise patients, particularly Māori people who have higher incidence of malignancies addicted to kynurenine, to immunotherapies.

Aldric Khoo

The Liggins Institute

Masters of Biomedical Science student

Novel gene regulatory patterns linked to previously identified lung cancer SNPs

Lung cancer is the leading cause of cancer deaths worldwide. Understanding how one's genome might contribute to lung cancer risk is one key aspect to predict who is at risk. Genome-wide association studies (GWAS) have identified lung cancer risk loci, but most GWAS SNPs lie in non-coding regions, making the interpretation of GWAS SNP function challenging. The impact of GWAS SNPs on distal genes within the three-dimensional genome is one way to attribute these SNPs to the genes and molecular mechanisms upon which they impact. In this study, we accounted for lung-specific chromatin interactions via Hi-C (long-distance chromatin connections) and gene expression levels via expression quantitative trait loci (eQTL) in lung tissue to identify novel interactions between GWAS SNPs and distal genes. We identified spatially constrained connections between 119 SNPs targeting 191 genes. Novel findings included the additional role of rs2853677 in ADCY2 dysregulation (along with its previous link to TERT) and the role of rs9322193 targeting tumour suppressor gene LATS1 (instead of its previous attribution to RPS18P9 and KATNA1). Pathway enrichment analysis identified several functional networks involving the gene targets. For example, after accounting for the oversaturated signal of HLA, caffeine metabolism, DNA IR-double strand breaks and cellular response via ATM, and nicotine effect on dopaminergic neurons were pathways enriched in our list of gene targets. Our results highlight the robustness of accounting for long-distance chromatin interactions when assessing the SNP-gene relationship in lung cancer, which serves as a potential platform for experimental validation.

Cho Rong Hong

University of Auckland

Research Fellow

Plenary;

DNA-dependent protein kinase (DNA-PK) is central to the process of non-homologous end joining (NHEJ) repair of radiation-induced DNA double strand breaks. Thus DNA-PK acts as a resistance mechanism to radiotherapy, so its selective inhibition has potential to improve clinical outcomes. The DNA-PK inhibitor AZD7648 has been shown to potentiate radiotherapy in xenografts and is being evaluated in phase I clinical studies.

Extreme sensitivity to radiation has been shown in SCID mice which have a loss of function mutation in DNA-PK catalytic subunit, and in patients with genetic deficiencies in NHEJ components. Thus DNA-PK inhibitors pose a potential risk of normal tissue radiosensitisation. However, there is currently little information on effects of DNA-PK inhibitor on normal tissues. In the present study we evaluate activity of AZD7648 against radioresistant hypoxic tumour cells and compare radiosensitisation of tumour and normal tissues by AZD7648 in mice after single-dose whole-body irradiation.

First, we investigated radiosensitisation by AZD7648 in head and neck squamous cell carcinoma cells (SCCVII, UT-SCC-54C) showing potent radiosensitisation under both normoxic and anoxic conditions. AZD7648 diffused rapidly through multicellular layer cultures. Using a Fick's second law diffusion model, we calculated that AZD7648 can reach 90% of plasma concentration in hypoxic regions (100 µm from blood vessels) within 12 min, which is much less than the pharmacokinetic half-life. These observations suggest that AZD7648 will be effective in radiosensitising hypoxic cells.

Radiosensitisation of SCCVII tumours by AZD7648 was measured by ex vivo assay of clonogens and compared with radiosensitisation of regenerating stem cells in the oral mucosa and small intestine labelled with 5-ethynyl-2'-deoxyuridine (EdU). Radiosensitisation was similar for tumour and the normal tissues, with radiation dose modifying factors of approximately 2.1-2.5, indicating that AZD7648 enhances normal tissue and tumour radiosensitivity similarly. This suggests that strategies for reducing normal tissue damage will be needed to enhance the therapeutic index of DNA-PK inhibitors when combined with radiotherapy.

Jack Flanagan

Department of Pharmacology and Clinical Pharmacology, and Auckland Cancer Society Research Centre, and Maurice Wilkins Centre for Biodiscovery

Associate Professor

Panel;Workshop;Plenary;Innovative short format;

Cells respond to their environment through the action of kinases. Cell signalling kinases phosphorylate proteins and lipids as well as scaffold larger protein complexes to change activity states. Through these functions, kinases start and stop intracellular programs that drive the machinery to effect some form of response. Mutations in kinases that uncouple kinase activity from normal environmental regulation is one of the mechanisms that allows cancer cells to hijack proliferation and survival pathways. The identification of mutant kinases started the discovery and development of kinase targeted medicines that can be applied based on cancer genotypes. Developments in immuno-oncology have very clearly demonstrated that kinase activity in immune cells in the tumour microenvironment are also sites of therapeutic intervention. We are interested in discovering new molecules that can modulate the function of kinases (and other proteins) found only in cancer cells or immune cells involved in the regulation of cancer cell survival. To do this we combine an atomistic level understanding of proteins with cancer drug pharmacology using data science, medicinal chemistry and in vitro assays to discover and develop new compounds with new modes of action. More general goals include continued development of cancer therapeutics by expanding the range of novel ligands for known target proteins, discovering new compounds that can interrogate the therapeutic potential of novel target proteins, and application of structure guided drug design to uncover new mechanisms of drug action.

William Schierding

Liggins Institute, University of Auckland

Senior Research Fellow

Plenary;Panel;

Proposal:

I would like to propose a session focused on novel studies on cancer genetics, with topics ranging from machine learning in mutation detection to novel detection of germline cancer risk loci. My group's work, primarily featuring gene regulation in melanoma and lung cancer, would be one sub-section of the session, focusing on gene regulatory networks and their use in tying germline risk to somatic driver genes.

My science abstract:

Every individual has an underlying genetic susceptibility for cancer development. Across all cancer types, the full complement of events driving tumour development still defies identification and, in many cases, no genetic drivers are found. Detecting such alterations with standard tools is fundamentally and technically challenging due to the combinatorially enormous number of ways that a genome can be altered. However, my group uses machine learning to better understand how markers of epigenetic gene regulation (chromatin conformation, Hi-C) and gene expression (eQTL) can be combined to predict the genomic elements active in driving common cancer types. We have found that regulatory elements altered in those with elevated germline risk are also interacting with genes which confer somatic cancer risk (driver genes). These gene regulatory networks provide functional interpretation of the impact of non-coding genetic variation, genome structure, and gene expression.

Barbara Lipert

Auckland Cancer Society Research Centre
Research Fellow
Workshop;Panel;Innovative short format;

CRISPR screens to explore synthetic lethality within DNA damage response pathways

Authors: Lipert B., Wilson W.R., Lee T.W., Hay M.P.

Affiliation: Auckland Cancer Society Research Centre, University of Auckland, Auckland, New Zealand

DNA double-strand breaks are the main cytotoxic lesions associated with replication stress or radiotherapy. Two complementary pathways are primarily responsible for repairing double-strand breaks: homologous recombination repair (HRR) and non-homologous end-joining (NHEJ). The reliance on HRR and NHEJ repair pathways provides a compelling therapeutic opportunity - the synthetic lethality approach, where a targeted pharmacological inhibition of DNA-repair machinery combined with pre-existing mutations in a tumour renders cells incapable of repairing DNA and leads to cell death in response to radiotherapy or replication stress.

DNA-dependent protein kinase (DNA-PK) is a key component of NHEJ, and loss of DNA-PK function results in severe radiosensitisation. As such, DNA-PK has been identified as a credible drug target. We recently identified a novel, potent and selective inhibitor of DNA-PK, SN39536. We seek to identify genes whose inactivation provides synthetic lethal combinations for SN39536 alone or in combination with radiotherapy. To this end, we carried out CRISPR/Cas9 functional genomic screening in a cancer cell line (UT-SCC-54C) using a custom DNA damage response library comprising 3370 plasmids that target 852 genes involved in the DNA damage response and cell cycle. We transduced this library into 54C-Cas9 expressing cells achieving >1000 representation of cells per plasmid. These cultures were exposed to the SN39536 alone or SN39536 + intermittent radiotherapy for 22 days. At the screen completion, enrichment/depletion of gene knockouts in each population was determined by targeted sequencing on Illumina NextSeq 500. Bioinformatic analysis identified the genes whose knockout increased sensitivity to the treatment, providing a list of likely synthetic lethal interactions for DNA-PK inhibition with SN39536.

Marta Seretny

University of Auckland/ADHB
Senior Lecturer/Anaesthetist
Plenary;

Retrospective cohort study investigating the influence of anaesthetic technique on breast cancer recurrence.

Background:

During breast cancer surgery, patients receive medicines to alter consciousness and allow them to 'sleep' or become 'unconscious' for the time of the operation. This is called general anaesthesia or GA. Recently; studies have suggested that the medications given during GA may affect the cancer itself. None of these studies were conducted on an Aotearoa New Zealand (NZ) population.

In NZ, we have several large databases that contain all the information needed to look at if the choice of GA affects breast cancer recurrence. This study will use deidentified data from existing datasets held by the Auckland District Health Board (ADHB), Ministry of Health (MOH), and Breast Cancer Foundation. We will explore possible links between the type of GA given and patient outcomes, such as breast cancer recurrence and mortality. A subgroup analysis investigating the effects of ethnicity on the research question is planned.

Study Design: Retrospective cohort study

Objectives: The aim of this study is to explore whether independent predictors for cancer recurrence can be determined, and to evaluate the association between GA technique (propofol TIVA vs volatile anaesthetic) and breast cancer recurrence in a New Zealand patient cohort.

Number of Participants: ~ 1500

Eligibility Criteria:

Inclusion:

• All patients undergoing primary breast cancer surgery who have outcome data available in the

NMDS//Te Rēhita/SaferSleep.

Exclusion:

• recurrent or metastatic breast cancer surgery, • reoperation due to acute complications,

• palliative surgery for metastatic disease,

• patients below the age of 18years old,

• ASA status >3

Measures:

Primary Outcome:

• Any breast cancer recurrence • Mortality

Secondary Outcome:

• Days alive and out of hospital (DAOH90)

Data Sources: New Zealand Ministry of Health administered databases, Breast Cancer Foundation Register and electronic anaesthetic record dataset (SaferSleep). These are large databases that have a wide capture of cases included in this study.

Statistical Analysis: Propensity scores to match groups and Directed Acyclic Graphs (DAGs) to explore interactions will be used. The Kaplan-Meier method and the Cox proportional hazard model will be employed to assess any association between anaesthetic technique and breast cancer recurrence. Finally, binary logistic regression will be used to determine independent predictors of cancer recurrence in the study cohort.

Results: Pending but will be available in time for the conference in November 2022

Bill Wilson

Auckland Cancer Society Research Centre, University of Auckland
Emeritus Professor
Plenary;

A novel inhibitor of DNA-dependent protein kinase for radiosensitisation of hypoxic cells in tumours

William R. Wilson, Way Wua Wong, Benjamin D. Dickson, Lydia Liew, Cho Rong Hong, Stephen M.F. Jamieson & Michael P. Hay

Radiation therapy kills cancer cells through the generation of DNA double-strand breaks (DSB) which give rise to lethal chromosome aberrations. The two most important intrinsic resistance mechanisms in radiotherapy are suppression of initial DSB formation by hypoxia in the tumour microenvironment, and rapid repair of DSB by non-homologous end-joining (NHEJ). DNA-dependent protein kinase (DNA-PK) is activated by binding to DSB and coordinates NHEJ. DNA-PK is a well-validated target for tumour radiosensitisation. However, we and others have shown that systemic inhibition of DNA-PK radiosensitises normal tissues as well as tumours. Thus, the objective of our programme is to provide tumour-selective radiosensitisation by developing a prodrug that releases a small molecule DNA-PK inhibitor (DNA-PKi) selectively in hypoxic cells.

To achieve this objective, we have undertaken a screening campaign to identify a novel, potent DNA-PKi with functionality suitable for derivatisation as a hypoxia-activated prodrug (HAP). Our initial DNA-PKi lead, SN39536, provided highly selective DNA-PK inhibition in biochemical and cell-based assays, potently radiosensitised parental HAP1 cells but not an isogenic knockout of PRKDC (encoding the DNA-PK catalytic subunit), and radiosensitised UT-SCC-54C cells both in vitro and as tumour xenografts. The corresponding 2-nitroimidazole HAP, SN39884, is metabolised selectively in hypoxic cells to generate SN39536 in vitro, efficiently penetrates through hypoxic tumour tissue as assessed using multicellular layer cultures, and significantly radiosensitises UT-SCC-54C tumours in NIH-III mice at well-tolerated doses. However, the limited metabolic stability of SN39884 in mice led us to explore HAPs with an ether rather than carbamate link between the 2-nitroimidazole unit and DNA-PKi, providing compounds with clearly superior in vivo activity as tumour radiosensitisers. We are currently comparing tumour and normal tissue radiosensitisation by these second-generation HAPs and their corresponding DNA-PKi in mice, which will provide a critical test of our hypothesis that hypoxia-dependent generation of the DNA-PKi will enhance tumour selectivity.

Dr Saem Park

On digital pathology and spatial transcriptomics; Saem's leading the MWC"s initiatives in this space and has been sponsored by industry to talk about this at Queenstown Research Week

Saem is a Research Fellow in the School of Biological Sciences, University of Auckland. Since completion of her PhD in 2015 she has become a go-to expert in molecular tissue imaging technologies including the Vectra Polaris system. Her research has been predominantly focused on immunology including cancer immune responses. Her combination of imaging expertise, in-depth immunology understanding and cancer research experience suit her well for this role

Dr Saem Park

Dr Alicia Didsbury on our T cell therapy programme, generating new T cells to cancer-specific molecules; this is what we'll be discussing soon in the "CAR-T" meeting you scheduled

In this project we propose to fine-tune our current immunotherapy product by growing tumour-specific T cells that will migrate into ovarian tumours and kill cancer cells without attacking their healthy cells. This work will lead directly to clinical trials of T cell therapy using our clinical grade tissue culture suite to efficiently produce cancer-specific T cells as a personalised cancer therapy. This project also provides an opportunity for the applicant as an early career researcher to make major contributions to the field of immuno-oncology, with immediate potential to benefit New Zealand patients suffering from cancer.

Gynaecological cancers are often diagnosed late due to a range of features including lack of distinctive symptoms and a reluctance to discuss (gynaecological cancer remains a taboo subject among the public). Part of the funding for this project will be allocated to establishing relationships with key stakeholders, including patient-led advocacy groups, as well as bringing together clinical teams to raise the profile both of Ovarian Cancer and onco-immunotherapy.

Here's some of her recent public commentary on immunotherapy: https://www.newshub.co.nz/home/new-zealand/2022/05/immunotherapy-proves-game-changing-cancer-treatment-for-patient.html

And here's something a bit more personal on her journey to get here: https://www.auckland.ac.nz/en/news/2020/11/03/ten-years-on--uni--drop-out--becomes-doctor.html

Novel Cleavable Linkers for Antibody-Drug Conjugate Targeted Cancer Therapy

Juliana T. W. Tong[1,2], Iman Kavianinia[1,2,3], Paul W. R. Harris[1,2,3], Margaret A. Brimble [1,2,3]

[1] *School of Chemical Sciences, The University of Auckland 1010, New Zealand*

[2] *Maurice Wilkins Centre for Molecular Biodiversity, The University of Auckland 1010, New Zealand*

[3] *School of Biological Sciences, The University of Auckland 1010, New Zealand*

Antibody-drug conjugates (ADCs) are a class of targeted therapeutics that leverage the specificity of antibodies to selectively deliver potent cytotoxic payloads to antigen-expressing targets, such as cancer cells. They have garnered widespread attention in recent years, as discrimination between healthy and malignant tissues or cells can be achieved. While 11 ADCs have thus far received approval from the US Food and Drug Administration and more than 90 others are undergoing clinical investigations for a range of malignancies, the road to ADC success has been far from straightforward. Extensive research over the past decade has highlighted the critical nature of the linker technology adopted for attachment of the payload to the antibody. In particular, reducible disulfides are the most prominent class of chemically cleavable linkers, and they exploit elevated glutathione levels inside tumour cells for selective payload release. Unfortunately, clinical use of these ADC linkers has been hindered by several drawbacks, the most significant being disulfide instability and thus premature payload release. Herein, we report a novel class of cleavable linkers that can simultaneously achieve improved linker stability in circulation and efficient payload release in the target tumour cell.

Parry Guildford

'Implementing cancer genetics research in Aotearoa NZ'.

Abstract: Bringing change to a financially stressed and conservative health system is challenging. Using Hereditary Diffuse Gastric Cancer and ctDNA as examples, this talk will explore the pathways for the successful implementation of biomedical research in Aotearoa NZ.

Parry Guildford

Stephen Fox

Clinical utility of genomics in cancer pathology

Peter Mac Pathology

Clinical cancer molecular diagnostics is undergoing a transformation, the result of a shift towards using targeted therapies that are matched to mutations, coupled with the widespread availability of affordable high throughput sequencing (HTS). This new standard of care in the management of cancer patients holds the promise of a step change in our understanding of fundamental biology with an impact on disease and patient care reminiscent of the introduction of the microscope in the 1840s. Tumour classification previously underpinned by morphology now in many tumour types are reliant on classification using a combination of morphology and molecular, and indeed in some circumstances are solely dependent on the molecular characteristics of the underlying molecular profile/change. Increasing information can now be extracted from genomic information that is clinically useful to help identifying cancers of unknown origin and new entities. This has had profound effect on the delivery of pathology such that anatomical pathologists now need to acquir additional skill sets to prosecute their role with technologies leading to collision of disciplines. The future of pathology will continue to combine morphology and molecular with the exciting potential of merging into digital spatial technologies and use of AI/ML algorithms for decision support.