QRW Abstracts: Cancer Meeting

C1: Filling a major gap: progress towards clinical proteomic data

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The proteome is a major determinant of the behaviour of cells and tissues, including cancers, and most drug treatments for cancer target one or more proteins. It is therefore expected that proteomic analysis of cancers will assist clinicians to predict outcomes and choose the most effective treatment for individual patients. However, for various technical reasons, quantitative proteomic analyses are not yet in routine clinical use (1).

To address this major gap in the data available to cancer clinicians, we are developing methods for mass spectrometric (MS) proteomic analysis of cancer tissues that can readily fit into existing clinical diagnostic workflows, are scalable, and produce reproducible data, and generating an evidence base to support its clinical use. We have devised a method for processing cancer tissues (formalin-fixed paraffin-embedded [FFPE] or frozen) that produces purified peptides ready for MS analysis in ~60 minutes (2). The MS step takes about 20 minutes, which means it should easily be possible to deliver proteomic data within the same time frame required for histopathology.

In parallel, we are analysing more than 100 cohorts of cancer samples – paediatric and adult – provided by many dozens of collaborating cancer research groups in 14 countries. For the great majority of the cohorts, clinical outcome data are already available, and for many of the cohorts other types of 'omic data have already been collected. Progress will be described toward the use of proteomic data to support treatment decisions.

1. Boys, E. L., Liu, J., Robinson, P. J., and Reddel, R. R. (2023). Clinical applications of mass spectrometry-based proteomics in cancer: Where are we? Proteomics 23, e2200238..
2. Xavier, D., Lucas, N., Williams, S. G., et al. (2024). Heat 'n Beat: A universal high-throughput end-to-end proteomics sample processing platform in under an hour. Anal Chem 96, 4093-4102.

C2: Role of H179 p53 mutation in driving aggressive tumours in patients

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TP53, a tumour suppressor gene is mutated in 50% of common cancers and associated with poor patient outcomes. Of the *TP53* mutations identified using genomic data from The Cancer Genome Atlas (TCGA), only six hotspot mutations (R175H, Y220, G245, R282, R273 and R248) have been characterised and 75% of other mutations remain uncharacterised. Better understanding of how these mutations affect tumour biology will enable identification of potential actionable targets and aid in guiding treatment strategies.

Our pan-cancer survival analysis for *TP53* mutations have identified that mutation at codon 179 is associated with poor patient outcome. To understand the biology driven by the H179 mutants, gene editing techniques were used to create stable lung, prostate and ovarian cancer cell lines expressing either H179R or H179Y mutant proteins. Functional characterisation demonstrated that H179R/Y mutant proteins localised in the nucleus, can form tetramers, have higher half-life compared to wild type (wt)-p53, but fail to induce canonical downstream wt-p53 genes and have increased cell viability. Taken together our data suggest that H179 mutants may activate biological pathways that differ from wt-p53. To identify these pathways, we performed RNA sequencing of the stable cell lines expressing H179R/Y mutant proteins. Gene expression analysis revealed majority of genes to be associated with epithelial to mesenchymal transition (EMT) and cholesterol/lipid transport pathway. Interestingly one of the genes elevated in cells expressing H179R/Y mutant p53 was apolipoprotein E (*APOE*), which is essential for lipid transport. Consistent with this, cells expressing H179R/Y p53 showed increased lipid content. Knockdown of H179R/Y p53 resulted in decreased APOE expression. Furthermore, using 3D collagen assays we demonstrated that cells expressing H179R/Y mutant p53 are more invasive than p53 null cells. Thus, taken together our results have identified that H179R/Y mutant p53 can promote elevated lipid levels and transport, leading to EMT and increased invasion.

C3: Investigating immune responsiveness in oestrogen receptor positive breast cancer

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Immunotherapies have revolutionised the treatment of some cancer types, particularly melanoma and lung cancer. Breast cancer has traditionally been viewed as an immunologically silent disease but, despite this, anti-tumour immune responses have been observed in some patients. However, response rates to immunotherapy are low and greater understanding of the mechanisms and determinants of response are needed. Our recent research suggests that commonly used anti-oestrogen therapies such as aromatase inhibitors may prime breast cancers to respond to immunotherapies. We have explored the use of immune checkpoint therapies and anti-tumour vaccination in combination with anti-oestrogen therapies in in vitro and animal models of breast cancer. Our work suggests that appropriate timing of administration of anti-oestrogen therapies may increase recruitment of immune cells to tumours and enhance responses. Translation of these findings into the clinic has the potential to improve outcomes for oestrogen receptor positive breast cancer.

C4: A Dark Matter: The lncRNA MALAT1 Contributes to the Transition from Drug Tolerance to Drug Resistance in Lung Adenocarcinoma

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Responses to targeted therapies are initially dramatic in patients with lung adenocarcinomas that harbour actionable mutations, but relapse is almost inevitable. Drug-tolerant persisters (DTPs) are a small fraction of cancer cells that survive treatment without genetic mutations and contribute to the emergence of acquired resistance, via adaptive mutability, a process that leads a heightened mutation rate in cells surviving treatment. Long non-coding RNAs (lncRNAs) are known to contribute to many processes thought to underpin DTPs, however their contribution to drug tolerance is unknown. Here, we investigate the role of lncRNAs in the emergence of DTPs.

EGFR-mutant PC-9 and $KRAS^{G12C}$-mutant H358 cells were treated with $>IC_{90}$ concentrations of osimertinib or sotorasib respectively, for 3, 7 and 19 days to induce drug tolerance. Bulk RNA-sequencing and RT-qPCR was performed to investigate RNA changes in DTPs. Several lncRNAs were differentially expressed in DTPs, including *MALAT1*, and *NEAT1*. DTPs also exhibited downregulation of DNA damage repair pathways (DDR) while upregulating error-prone polymerases, which are hallmarks of adaptive mutability. Combining ASO-mediated knockdown of *MALAT1* and *NEAT1* with targeted therapeutics partially reversed changes to DNA repair pathways in DTPs. To assess the impacts of *MALAT1* and *NEAT1*-KD on DDR function, plasmid-based reporters were used and analysed by flow-cytometry. In proliferation assays, *MALAT1*-KD in combination with drug treatment resulted in a greater reduction in proliferation when compared to drug alone. Finally, early data from long-term drug treatment following ASO transfection indicates that *MALAT1*-KD may delay the onset of drug resistance in PC9 cell lines.

This work has identified the lncRNA *MALAT1* as having a potentially important role in the development of the acquired drug resistance that emerges from drug tolerance. Further studies are ongoing to determine whether modulating *MALAT1* represents a potential approach to augment therapy in patients with lung adenocarcinomas undergoing treatment with targeted therapies.

C5: Targeting Cohesin Mutations in Leukaemia to identify druggable avenues

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Cohesin is a multiprotein complex essential for the three-dimensional (3D) organization of the genome. Mitotic cohesin consists of RAD21, SMC1A, SMC3, and STAG1/STAG2 subunits. Mutations in cohesin complex subunits are implicated in 10-20% of myeloid dysplastic syndromes and myeloid leukaemia, with a higher frequency (~50%) in Down Syndrome-associated acute myeloid leukaemia.

Using leukaemia cell lines edited to contain mutation in the cohesin-STAG2 subunit we found that cohesin mutation enhances stemness and adhesiveness, features that can promote survival of leukemic cells within the haematopoietic niche. We identified glycogen synthase kinase 3 (GSK3) and Bromodomain and Extra-Terminal (BET) protein inhibition as potential druggable targets in cohesin mutant cells. Using genome wide chromatin immunoprecipitation (Cut and RUN) we found that GSK3 inhibition alters the heterochromatin more extensively in the cohesin mutant cells. We found that BET inhibition dampens precocious expression of haematopoietic stem cell markers (*RUNX1*, *ERG*, *KIT*) in cohesin mutant leukaemia cells. In a genome wide CRISPR-Cas9 dropout screen we identified adhesion genes ADAM10 and MAEA as top synthetic lethal hits in cohesin mutant cells. Interestingly bulk RNA sequencing of cohesin mutant haemopoietic cells isolated from adult zebrafish also showed a similar enhancement of adhesion genes. This suggests that cohesin mutant cells might be upregulating adhesive features for survival and deletion of these targets might be beneficial to impede the growth of cohesin mutant cancer cells. Single cell RNA sequencing of the adult zebrafish haematopoietic cells revealed that cohesin mutation dysregulates erythroid differentiation and granulopoiesis and causes widespread transcriptional dysregulation in all haematopoietic cell types. Our results show that cohesin mutation create haematopoietic imbalances which can lead to preleukemia and contribute to development of haematopoietic malignancies. We are now further testing the efficacy of the druggable targets we identified in cohesin mutant cell line models *in vivo* using zebrafish models.

C6: Response to Chemoradiotherapy in Rectal Cancers: Profiling Protein Expression in Defined Tumour Tissue Structures

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The standard treatment of rectal cancer (RC) is surgery preceded by chemoradiotherapy (cRT). Patient response to cRT varies; complete responders will not require surgery, while non-responders will have their surgeries delayed if they undergo a cRT regimen. We therefore aimed to determine mechanisms of response to cRT in RCs, with the goal of understanding how this could help improve patient management.

Our previous work indicated an increase in B-cell activation and immunoglobulin production in complete responder (CR) tumours, compared to that of other responders (OR). We then investigated pre-treatement FFPE-tissues from 20 RC patients with different cRT responses (12 CRs, 8 ORs). We used Nanostring's GeoMx®-nCounter protein assay, which identifies spatial structures in the tissues, then subsequently measures protein expression in these structures. Based on our previous work, we chose PanCK (cancer marker), CD3 (T-cell marker), and CD19 (B-cell marker) to identify cellular structures in the tissues, then measured the expression of proteins from GeoMx®'s Immuno-Oncology protein panel from these structures alone, or together in a region of interest (ROI). We then compared protein expression in ORs vs CRs.

UMAP unsupervised analysis showed clustering based on response groups (CR vs OR), and that this may be driven by differences in the CD3- and whole ROI- marked structures. Differentially expressed proteins (*p-adjust <0.1*) in CD3 and whole ROI structures, include enrichment of ARG1 and CD56 proteins in ORs. ARG1 is associated with malignancy in CRCs, while CD56 is a natural killer (NK) cell marker, indicating a role of the immune system in cRT response. We also found increased expression of cleaved caspase 9 in CD3-marked structures of CRs, indicating apoptosis as a mechanism of complete response to cRT.

The results of this study, along with further analysis, will provide more comprehensive insights into mechanisms of response to cRT in rectal cancers.

C7: Genome based personalised cancer risk management

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Premature death from cancer is a significant health and economic issue. Risk-stratified early detection and intervention are critical to cost-effectively reducing the impact of cancer. Cancer is a genetic disease. Traditional family history-based eligibility for germline genetic testing is giving way to genome first identification. We initiated large cancer cohort studies (International Sarcoma Kindred Study; Genetic Cancer Risk in the Young study) to investigate hereditary predisposition. Translation of genetic insights into better risk management is pivotal to the value proposition for genomics. Whilst some organ specific screening is in place, little surveillance that accounts for high multi-organ cancer risk has been available. In 2013, we began the SMOC+ surveillance study and recently had the first MBS item number approved for whole body scans for early cancer detection. We aim to inform identification of those at greatest heritable risk, influence clinical risk management and lessen the burden of cancer on society.

C8: The University of Auckland Precision Medicine Initiative – projects, progress, proposals and prospects for the future

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The Precision Medicine Initiative, or the PMI, is a program established within the Auckland Academic Health Alliance at the University of Auckland. It aims to bring cutting-edge precision medicine practices to patients through clinical genomics and research. The program has been active since early 2022 with a focus on developing the infrastructure required to deliver benefits to New Zealand patients and researchers.

In this talk we will give an overview of the activities of the PMI to date and highlight some of the flagship projects currently underway. These projects include working with local clinical researchers, development of an Auckland based Molecular Tumour Board, implementing the use of the TSO500 gene panel for cancer research and collaboration with a Pūtahi Manawa (CoRE) funded research project that uses whole genome sequencing in patients and whānau affected by inherited cardiovascular diseases.

Alongside discussing our projects to date we want to highlight the ongoing investment in infrastructure for genetic research and clinical genomics in NZ. The PMI has recently purchased a NovaSeq 6000 and two Dragen servers which significantly increase the local capacity for sequencing and genetic analysis. We are actively looking for research projects where we can collaborate to answer research or clinical questions that have clear benefit to patients in NZ.

C9: Quantitative MRI and radiomics-based biomarkers for prostate Stereotactic Ablative Body Radiotherapy

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Prostate cancer is the most commonly diagnosed cancer amongst New Zealand men. Stereotactic Ablative Body Radiotherapy (SABR) is a high-precision form of radiation therapy (RT) that delivers treatment in fewer sessions than conventional RT. While prostate RT has high five-year tumour control rates, the risk of local recurrence increases after five years, and standard prostate-specific antigen (PSA) blood testing may delay detection. Additionally, PSA testing is prone to high false-positive rates and lacks spatial information. We hypothesise that radiomic features from quantitative MRI could more accurately identify early response to SABR than PSA testing.

Our team is conducting the Auckland Sequential-Imaging Biologically Targeted Radiation Therapy (SI-BiRT) clinical trial (ACTRN12621001118897) to develop imaging biomarkers for early SABR treatment response. We aimed to recruit a pilot cohort of 10 patients, scheduled for prostate SABR (36.25 Gray in 5 fractions) without androgen deprivation therapy. Multiparametric MRI is acquired pre-treatment and at 6- and 12-months post-SABR, including T2-weighted, diffusion-weighted imaging (DWI), dynamic contrast-enhanced (DCE) MRI, and R2* mapping. Quantitative MRI parameters and MRI radiomic features are extracted to quantify longitudinal changes. Blood samples are collected for PSA monitoring and to assess hypoxia, along with biopsy tissue which is analysed using immunohistochemistry.

All 10 patients have been recruited and completed baseline assessments, 8 have completed 6-month assessments while 6 have completed 12-month assessments. A significant increase in diffusion MRI parameters and a significant decrease in perfusion MRI parameters are shown 6-months post-SABR, indicating a favourable treatment response. Additionally, most patients have increased tumour oxygenation 6-months post-SABR.

This is the first New Zealand study to investigate SABR treatment response using imaging. Preliminary results supporting quantitative MRI for accurate and personalised evaluation of response. Robust imaging biomarkers would enable early interventions that target radio-resistant disease to limit the risk of disease progression.

C10: Evaluation of new DNA-dependent protein kinase inhibitors as radiosensitisers of head and neck cancer cells

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Despite advances in radiotherapy technologies and treatment scheduling, radioresistance occurs in subsets of cancer patients, including those with human papillomavirus negative (HPV-ve) head and neck squamous cell carcinoma (HNSCC). The dominant role of DNA-dependent protein kinase (DNA-PK) in repairing radiation-induced DNA double-strand breaks (DSBs) through the non-homologous end-joining pathway makes DNA-PK an appealing target for the development of radiosensitisers. We sought to characterise two new DNA-PK inhibitors (SN40318 and SN40905) as radiosensitisers in HNSCC cells. Mechanistic evaluation of SN40318 and SN40905 included assessment of their potency and selectivity for DNA-PK compared to related kinases with biochemical assays, inhibition of radiation-induced DNA-PK autophosphorylation with Western immunoblotting, and DNA-PK-dependent radiosensitisation of HAP1 wild type and DNA-PK knock out (*PRKDC*$^{-/-}$) isogenic cells with growth inhibition assays. Radiosensitisation by SN40318 and SN40905 was further evaluated in human (FaDu) and murine (MOC1 and MOC2) HNSCC cells using growth inhibition and clonogenic survival endpoints. Both SN40318 and SN40905 potently and selectively inhibited DNA-PK in biochemical assays, inhibited cellular DNA-PK autophosphorylation, and effectively radiosensitised HNSCC cells with no observable single-agent cytotoxicities. In clonogenic survival assays, 0.3 μM of SN40318 and SN40905 provided robust radiosensitisation of FaDu cells with sensitisation enhancement ratios at 10% survival of 3.1 and 4.5, respectively. This research provides compelling evidence for the application of SN40318 and SN40905 as radiosensitisers for the treatment of HPV-ve HNSCC. Further evaluation of the compounds *in vivo* is recommended.

C11: A long-acting biotherapeutic targeting the growth hormone receptor reduces tumour growth in a melanoma xenograft model (NZM79)

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Despite recent advances in treatment, metastatic melanoma is largely refractory to clinically available therapies, highlighting the need for novel therapeutics. Characterisation of a panel of 102 primary metastatic melanoma cell lines (NZM cell panel) demonstrated that the majority express *GHR* mRNA and are responsive to growth hormone (GH). GH contributes to cell proliferation, survival, and chemoresistance. Pegvisomant, the only clinically available GHR antagonist, is difficult to access for research so novel GHR antagonists are needed to investigate the role of GHR signalling in melanoma. This study evaluated the efficacy of an in-house generated GHR antagonist (GHA2) as a monotherapy in melanoma tumour models.

Recombinant GHA2 protein was expressed and purified from *E. coli* and conjugated with polyethylene glycol to extend the *in vivo* circulating half-life. *In vitro* bioactivity was confirmed using cell-based assays and inhibition of GHR-dependent signal transduction by western blot (STAT5 phosphorylation). Mouse melanoma B16-F10 syngeneic graft grown in C57BL/6J mice were treated daily with vehicle or GHA2 (30 mg/kg/day). Human melanoma NZM79 xenografts grown in immunodeficient NIH-III mice were treated daily with vehicle or GHA2 (30 mg/kg/day) ± human GH (2 mg/kg/day) for 2 weeks. Serum IGF-1 was measured by ELISA analysis as a surrogate biomarker for GHA2 activity.

GHA2 effectively inhibited GH-dependent cell viability in cell-based drug screening assays and STAT5 phosphorylation in melanoma cell lines. GHA2 treatment significantly reduced the serum IGF-1 concentration by 72% in C57BL/6J mice compared to vehicle control ($p<0.001$). A trend for decreased B16-F10 tumour volume was observed following GHA2 administration, although not statistically significant. In NIH-III mice, GHR antagonism with GHA2 significantly decreased the growth rate of NZM79 tumours versus vehicle or GH treatment ($p<0.05$).
GHA2 effectively antagonised GH signalling in melanoma cells and slowed melanoma tumour growth, highlighting its potential as a new therapeutic strategy for treating melanoma.

C12: Influence of SNP rs1800795 on macrophage polarisation, colitis, and response to emerging therapies

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Heritable variation in immune system function alters our risks for inflammatory bowel disease (IBD) and colorectal cancers (CRC), and likewise, responsiveness to treatments varies between individuals. Antagonists of interleukin 6 (IL-6) are potential therapies in both settings. IL-6 is predominantly produced by macrophages (Mφ) and alters their polarisation. Pro-inflammatory (M1) Mφ produce high IL-6, whilst the anti-inflammatory Alternative (Alt.) Mφ are promoted by IL-6. A single nucleotide polymorphism (SNP) called rs1800795 (-174G/C) in the IL6 gene promoter alters our IL-6 expression. We propose rs1800795 alters IBD and CRC risks by altering Mφ polarisation and may in turn, alter our responsiveness to IL-6 blockade.

We have established a novel mouse model of rs1800795, and report that it recapitulates its effects on disease risk. When colitis was induced chemically, the rs1800795:CC animals developed more severe IBD symptoms than GG animals, including greater weight loss, increased incidence of bleeding, and higher levels of IL-6. When immune cells (CD45+) were extracted from inflamed guts in this setting, greater expression of inflammation genes were detected in CC animals. In contrast, ex vivo differentiation of bone marrow cells from GG mice showed an increased IL6 expression compared to CC mice. We propose this effect favours Alt. Mφ polarisation and creates a protective effect against inflammation. Finally, when IL-6 trans-signalling was therapeutically blocked, mice with CC showed a better response than their GG siblings, while treatment with a Jak/Stat inhibitor favoured GG mice. Currently, the response of our mice against cancer treatments is being investigated.

These results substantiate the rs1800795 SNP as a reliable biomarker for personalising and facilitating the use of emerging drug treatments, and our novel mice provide a robust preclinical model for testing this.

C13: Optimising MRD-Seq: an improved method for measurable residual disease detection in acute myeloid leukaemia

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Acute myeloid leukaemia (AML) is a complex disease with a very poor prognosis, driven by several genetic mutations. With over 200 genes found to be mutated in AML, most patients present with unique mutation combinations. It is very important for the physician to know how well a patient's treatment is working. Therefore, being able to assess the number of remaining cancer cells (minimal residual disease, MRD) with high sensitivity is crucial to make appropriate treatment decisions. Using qPCR based MRD assays is very difficult, because a specific qPCR assay must be established and calibrated for each individual mutation. Thus, at present, sensitive MRD assays are not available to most AML patients. We aim to establish a new method of measuring MRD in AML using Next Generation sequencing (NGS) (MRD-Seq). MRD-Seq involves preparation of error-correcting PCR amplicons targeting a region of the genome that harbours a somatic mutation, followed by NGS. Amplicons were prepared from cell lines carrying NPM1-TypeA and IDH1R132H mutations. The sequencing reads were de-duplicated using UMItools, followed by counting the number of reads with and without specific mutation using the R- code developed in our lab. We have determined the sensitivity of NPM1-TypeA and IDH1R132H specific MRD assays to be 1 x 10-3. This approach should improve measurement accuracy and precision in monitoring AML. MRD-Seq can be easily adapted for any mutation by designing a mutation-spanning PCR, allowing MRD monitoring in most patients.

C14: The mechanisms through which αENaC negatively modulates breast cancer proliferation and metastasis

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In 2022, there were 2.3 million new breast cancer cases, while 666,000 died due to the disease. Australia/New Zealand is the region with the highest breast cancer incidence rates. While improvements have been made in detection, diagnoses and treatment of early-stage breast cancer, metastatic breast cancer remains incurable and the cause of breast cancer-related deaths.

Our lab investigated a role for the Epithelial Sodium Channel (ENaC) in breast cancer progression. Based on bioinformatic and in vitro analysis, it was discovered that the alpha subunit of ENaC (αENaC) inhibits breast cancer proliferation and metastasis. Further analyses have been performed that show αENaC mRNA expression is repressed in metastatic breast cancer. Also, lower expression of αENaC mRNA is associated with an increased probability of experiencing metastasis and relapse.

Various techniques are being employed to investigate the mechanisms through which αENaC influences proliferation and metastasis. RNA-sequencing was performed, using three clones of the MDA-MB-231 breast cancer cell line transfected to stably overexpress αENaC and a control MDA-MB-231 cell line. Analysis of the RNA-sequencing data uncovered 386 genes that were differentially expressed across all three clones due to overexpression of αENaC. These differentially expressed genes are being assessed to determine the functional processes that were altered. Using the MDA-MB-231 and MCF-7 cell lines, we are investigating how varied αENaC expression affects proliferation and migration, through alterations in cell cycle phase transitioning and calcium signalling respectively.

Efforts are also underway to investigate how at the protein level, αENaC expression relate to different breast cancer subtypes and its prognostic significance in New Zealand breast cancer cases. This study will help us understand the mechanism through which higher levels of αENaC inhibits breast cancer progression and present with molecular candidates that could be targeted therapeutically to improve breast cancer survival.

C15: Reduce, Reuse, Recycle: Drug Repurposing to Combat Drug Tolerant Persisters

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Resistance to targeted therapies contributes to treatment failure and relapse in cancer patients. Drug resistance can be preceded by drug tolerant persisters cells (DTPs). DTPs share characteristics with cancer stem cells (CSC) that allow them to enter a dormant state under drug treatment, eventually resulting in stable genetic resistance. There are no current drugs that specifically target DTPs, and developing new drugs is time-consuming and expensive. Drug repurposing uses approved drugs to treat diseases different from the original use. As the anti-parasitic ivermectin has been shown to target cancer stems cells, we explored whether it also targets DTPs.

To investigate the ability of ivermectin to inhibit DTPs, we treated $BRAF^{V600E}$-mutant A375 cells and EGFR-mutant PC9 cells treated with either DMSO, ivermectin only, the targeted therapy only or the combination of targeted therapy and ivermectin for 3- and 7-days to determine the effects on the cells. After 3- and 7-days melanoma DTP markers *NGFR* and *CD36* were downregulated in the combination treated A375 cells compared to cells treated with vemurafenib alone. Due to the similarity between DTPs and CSC, stem cell genes were measured. Both *NANOG* and *OCT-3/4* expression was decreased in A375 and PC9 cells.

Resistance can be controlled by pre-existing cells (early resistance) and the evolution of DTPs under selection pressure (late resistance). To investigate the long-term ability of ivermectin to inhibit late resistance under drug selection pressure, a long-term resistance assay was established. Preliminary results show that the combination of vemurafenib and ivermectin has decreased the emergence of resistant A375 clones compared to vemurafenib treatment alone.

These results suggest that the combination of ivermectin and targeted therapies to inhibit drug tolerant persisters is promising. By inhibiting DTPs, this combination has the potential to prevent the development of stable resistance and emergence of minimal residual disease, improving cancer outcomes.

C16: Characterising the Biology of Missense C176 Mutation in Tumour Suppressor p53

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The tumour suppressor p53 is encoded by the *TP53* gene, which is the most frequently altered gene across human cancers. The majority of inactivating mutations in *TP53* are missense mutations. Some missense mutations have shown to confer novel gain of function (GOF) effects which drive metastasis and treatment resistance. Frequently occurring "hotspot" mutants of p53 have been extensively characterised, however, all regions of *TP53* have been found to undergo mutation and the majority of missense p53 mutations have not been characterised. We analysed the pan-cancer dataset from The Cancer Genome Atlas (TCGA) to determine patient outcome in concordance with the mutation status of *TP53* in the tumour. We found that missense mutations at the C176 codon were significantly associated with poor prognosis in comparison to hotspot mutants, all other *TP53* missense mutants, and tumours which retained wildtype *TP53*. C176 is frequently altered to F/Y in this database. We characterised C176F/Y mutations *in vitro* to determine their contribution to poor prognosis. Plasmids with C176F/Y mutant *TP53* were transfected into p53-null cell lines (PC3 prostate adenocarcinoma, SKOV3 ovarian carcinoma, and H1299 lung adenocarcinoma). We found that C176F/Y mutant p53 is defective of several canonical wildtype functions such as cell death in our BFP reporter assay and inducing transcription of three known gene targets of p53 (e.g. *CDKN1A*, *MDM2* and *PIG3*). In contrast the C176F/Y mutant p53 retained tetramerization and the ability to localise to the nucleus similar to wildtype p53. Together our results suggest that C176F/Y may drive an alternative biology to wildtype p53. RNA-sequencing (RNA-seq) analysis of our H1299 stable cell lines showed C176F/Y mutations drive anti-apoptosis, mitotic fusion, and epithelial-mesenchymal transition. Therefore, these mutants may confer a gain of function, providing insight of how mutant p53 contributes to cancer progression which we are currently testing using functional assays.

C17: Reversing bone-specific immune suppression to combat metastasis

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The interactions between cancer cells and their microenvironment, including immune cells, dictates cancer persistence, invasion and metastasis. By modelling cellular interactions at the earliest stages of cancer invasion through to survival and outgrowth in metastatic tissues, we have identified and validated key signalling events that dictate risk of cancer progression, immune response against disseminated cells, and co-option of distant tissues, including bone. Use of preclinical models of bone metastasis and biospecimens from rapid autopsy samples, we have uncovered critical changes that specifically occur in the bone metastatic microenvironment that renders cancers poorly immunogenic. Our work to date has offered explanation as to why most therapies fail in the metastatic setting, due to the complete loss of innate interferon immune pathways in tumour cells that are critical in response to chemotherapy, radiotherapy and immunotherapy. These studies have uncovered biomarker platforms currently in development by international pharmaceutical companies for precision therapy, including immunotherapy. Additionally, we have uncovered new approaches to therapeutically restore tumour immunogenicity in metastatic tissues and are currently developing superior models to test these approaches in patient-derived metastases.

C18: Putting the STING back into BH3-mimetic drugs for therapy of aggressive blood cancers

Diepstraten, S.T.[1,2], La Marca, J.E.[1,2,3,4], Yuan Y.[1,2,5], Whelan, L.[1], Young, S.[1], Chang, C.[1], Ross A.M.[1], Fischer K.C.[1,2], Litalien, V.[1], Brown, F.C.[1,2], Roberts A.W.[1,2,5], Wei A.H.[1,2,5], Strasser A.[1,2] & Kelly G.L.[1,2]

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Survival rates for many blood cancers have improved significantly over the last decade; however, those with mutations in the tumour suppressor gene p53 remain a major clinical challenge. 50% of cancer patients have p53 mutations, and these blood cancers are aggressive and associated with poor outcomes[1].

BH3-mimetic drugs, a new class of anti-cancer therapy, inhibit pro-survival BCL-2 family proteins to induce apoptosis in cancer cells. The leading BH3-mimetic venetoclax has been approved for therapy of certain blood cancers, but we and others have found that p53 mutations blunt the effectiveness of BH3-mimetic drugs[2].

To address this, we have discovered a novel way to boost apoptosis induced by BH3-mimetic drugs - even in aggressive blood cancers with p53 mutations – by directly activating the DNA-sensing protein STING[3]. While STING agonists have been investigated as immune modulators, we showed that this drug class can directly induce apoptosis in blood cancer cells. Combining BH3-mimetics and STING agonists was incredibly effective at killing aggressive human blood cancers *in vitro* and *in vivo*, even those with currently dismal prognosis like natural killer/T-cell lymphoma and p53-mutant acute myeloid leukaemia.

As STING agonists have already been shown to be safe in humans, this combination therapy represents a novel therapeutic direction that can be fast tracked to the clinic for treatment of aggressive blood cancers.

1. Stengel A., *et al.* (2017). *The impact of TP53 mutations and TP53 deletions on survival varies between AML, ALL, MDS and CLL: an analysis of 3307 cases.* Leukemia 31, 705–711.
2. Nechiporuk T., *et al*. (2019). *The TP53 Apoptotic Network Is a Primary Mediator of Resistance to BCL2 Inhibition in AML Cells.* Cancer Discov 9(7), 910-925.
3. Diepstraten S.T., *et al.* (2024) *Putting the STING back into BH3-mimetic drugs for TP53-mutant blood cancers.* Cancer Cell 42(5). 850-868.

C19: Developing T-Cell Immunotherapy for Epithelial Ovarian Cancer

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Effective immune therapies enable T cells within the patient's body to attack and kill their cancer cells. Even the most advanced cancer may be cured by immune treatments; however, only a small percentage of cancer patients respond to currently accessible immune therapies.
Ovarian cancer is one of the cancers that respond poorly to anti-PD-1/L1. For many patients with ovarian cancer, spontaneous T-cell responses against their tumours are absent or weak. Indeed, approximately 40% of women have no sign of T cells within their tumours, so checkpoint inhibitor drugs like anti-PD-1/L1 are very unlikely to work. The relative lack of responses to anti-PD-1/L1 has led us to explore other forms of immunotherapy, particularly Adoptive Cell Therapy (ACT), where cancer-specific T cells are grown in the laboratory and infused into patients as a therapeutic product. To this end, we have been rationally developing a T cell product derived from patient peripheral blood to target residual disease following first-line therapies.

Using a multiplex digital pathology system, we investigated the interactions between myeloid cells and invading lymphocytes, the levels of checkpoint receptor expression, and the targetable proteins expressed in the tumour. We have identified three targetable proteins (PRAME, NYESO-1, and Mage-A4) demonstrating overlapping expression in our New Zealand cohort. These results allow us to target proteins that are more homogenously expressed in ovarian cancer and help us understand how tumour interactions may influence the efficacy of our treatments.

In tandem with our investigation of the tumour site, we are utilising immunological profiling from peripheral blood to identify which circulating populations differ in patients with ovarian cancer and how these variations influence the ability to produce a tumour-specific T-cell product.

By combining our cell therapy knowledge and the information gained from high-dimensional patient profiling, we aim to build a therapy that will rationally target epithelial ovarian cancers and improve progression-free survival for New Zealand patients.

C20: Can YB-1 expression levels be used to classify immunotherapy responses of chromosomal instable tumours based on cGAS-STING activity?

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Chromosomal instability (CIN) is a feature of 60-80% of human tumours and is increasingly being recognised as an important driver of tumour evolution. CIN refers to an ongoing process of chromosome mis-segregation during late mitosis and cytokinesis, leading to the accumulation of cytosolic DNA, which results in increased cGAS-STING signalling. The cGAS-STING pathway plays an important role in anticancer therapy, especially in response to immunotherapy. Chromosomal instable tumours with active cGAS-STING signalling are likely to respond to immunotherapy as cGAS-STING signalling attracts immune cells, and CIN results in the presence of cancer neoantigens that are potential targets for cytotoxic T cells. Chronic cGAS-STING signalling in chromosomally unstable tumours is thought to facilitate immune evasion through the action of an immunosuppressive noncanonical NF-kB pathway. Our recent work has demonstrated that the cold-shock Y-box binding protein-1 (YB-1) is critical for the assembly of microtubules required for the segregation of chromosomes in cancer cells. Thus, we hypothesise that tumours with high YB-1 levels are chromosomally instable and activate aberrant cGAS-STING signalling, resulting in an immunosuppressive environment. To test this hypothesis, we used Cancer Genome Atlas and stratified lung, prostate and ovarian tumours based on YB-1 mRNA levels. Our results showed that tumours with high YB-1 mRNA levels are associated with a significantly higher fraction of their genome altered (a marker of chromosomal instability), enrich for low cGAS-STING expression, and have increased expression of noncanonical NF-kB signalling compared to tumours with low YB-1 mRNA levels. Together, these findings suggest that YB-1 levels can potentially be used as a predictive biomarker of immunotherapy. We have developed tetracycline-inducible YB-1 cancer models to test the efficacy of clinically used immunotherapies and identify neoantigens likely to be present in high-YB-1 tumours. Results from these studies have the potential to develop novel immunotherapeutic ways to target high-YB-1 tumours.

C21: The mucinous menace: combating an insidious disease

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Mucinous ovarian carcinoma (MOC) is a rare cancer type with several distinct features that make it unique. We need to better understand this cancer to develop new treatments. We have undertaken in-depth genomics and transcriptomic characterisation of MOC, including some single-cell multi-ome analyses, and here will discuss some of the key findings. In addition, we have developed and profiled pre-clinical models of this disease, including tumour organoids and patient-derived xenografts. These models accurately reflect the parent tumours. We have performed in vitro drug screening and will present these data along with preliminary correlations with the genomic profiles. Our ongoing research aims to find therapies for MOC that are actually effective, in contrast to the current standard of care for this chemo-resistant disease.

C22: Whole-genome CRISPR-Cas9 screens identify *SHOC2* as a genetic dependency in *NRAS*-mutant melanoma cell lines

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Melanoma is the most lethal form of skin cancer, with over 300,000 new cases worldwide every year. Specifically, melanoma with *NRAS* mutations are of particular clinical concern due to their association with a poor prognosis and lack of specific treatment options. Therefore, there is a pressing need for novel approaches to address the treatment of *NRAS*-mutant melanoma. A current approach to identify novel drug targets is based on the genetic concept of induced essentiality, where functional interactions that occur in response to oncogene addiction create a dependency on another gene.

To identify genetic dependencies in *NRAS*-mutant melanoma, whole-genome CRISPR-Cas9 knockout screens were conducted in 6 *NRAS*-mutant and 7 *NRAS*-wildtype (wt) melanoma cell lines that were established from New Zealand melanoma (NZM) patients. The NZM cell lines were stably transduced with the whole-genome Brunello lentiviral single guide (sg) RNA library and screened for up to 35 days. BAGEL (Bayesian Analysis of Gene Essentiality) analyses of the NZM whole-genome knockout screens, alongside CRISPR-Cas9 screening data using the Avana sgRNA library from an additional 28 melanoma cell lines, available on the Cancer Cell Line Encyclopaedia (CCLE) database, revealed 45 prospective candidates that exhibit greater detrimental effects on the fitness of *NRAS*-mutant cell lines compared to the *NRAS*-wt lines. Further validation through *in vitro* individual gene knockout studies demonstrated that knockout of *SHOC2*, a scaffold protein essential for activation of the MAPK signalling pathway, results in the prevention of ERK phosphorylation and a more substantial reduction in cell proliferation in *NRAS*-mutant NZM cell lines when compared to *NRAS*-wt lines. We are currently exploring targeting the protein-protein interaction between SHOC2 and RAS proteins. Our findings will contribute to the development of SHOC2 inhibitors, which may be beneficial in treating *NRAS*-mutant melanoma, an area where greater treatment options are urgently needed.

C23: Advanced CRISPR knockout and activation mouse models as tools for genome screening and the investigation of cancer biology

La Marca, J.E.[1,2,3,4], Jin, W. [1,2,3,4], Deng, Y.[1,2,3,4], Diepstraten, S.T.[3,4], Lelliott, E.J.[1,2,3,4], Tai, L.[1,3], Kueh, A.J.[1,2,3,4], Potts, M.A.[1,2,3,4], Heidersbach, A.[5], Snetkova, V.[5], Dorighi, K.M.[5], Hoberecht, L.[6], Haley, B.[5,7], Fortin, J.-P.[7], Kelly, G.L.[3,4], Herold, M.J.[1,2,3,4]

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Now more than a decade after its first revolutionary descriptions, CRISPR technology has hit its stride. Our groups have contributed to this maturation via the generation of two CRISPR mouse models: a CRISPR-dCas9 activation mouse, and a new CRISPR-Cas12a knockout mouse. We have successfully utilised our dCas9 activation mouse to generate a new model of “double-hit” diffuse large B cell lymphoma, and to conduct whole-genome screens for resistance factors to drug treatment using novel sgRNA libraries [1]. Our Cas12a knockout mouse is still quite new, but we have characterised its efficacy, and conducted whole-genome screens using two novel crRNA libraries in a model of pre-B/B cell lymphoma [2]. These mice should have utility for a wide-range of cancer research, and we are excited to share them with the scientific community.

[1] Deng, Y., Diepstraten, S.T., Potts, M.A., Giner, G., Trezise, S., Ng, A.P., Healey, G., Kane, S.R., Cooray, A., Behrens, K., Heidersbach, A., Kueh, A.J., Pal, M., Wilcox, S., Tai, L., Alexander, W.S., Visvader, J.E., Nutt, S.L., Strasser, A., Haley, B., Zhao, Q., Kelly, G.L., Herold, M.J. ‘Generation of a CRISPR activation mouse that enables modelling of aggressive lymphoma and interrogation of venetoclax resistance.’ Nature Communications, 2022. 13(1): 4739, DOI: https://doi.org/10.1038/s41467-022-32485-9.

[2] Jin, W., Deng, Y., La Marca, J.E., Lelliott, E.J., Diepstraten, S.T., Snetkova, V., Dorighi, K.M., Hoberecht, L., Whelan, L., Liao, Y., Tai, L., Healey, G., Shi, W., Kueh, A.J., Haley, B., Fortin, J.-P., Herold, M.J. ‘Advancing the genetic engineering toolbox by combining AsCas12a knock-in mice with ultra-compact screening.’ bioRxiv, DOI: https://doi.org/10.1101/2024.05.30.596755.

C24: A New Zealand experience: Targeted Next Generation Sequencing in Acute myeloid leukaemia and its impact in disease management

Kakadia, P.M.[1], Child, L.[2], Chien, J.[1], Bye, S.[1], Tan, T.[1], Ghallyan, N.[2], Ruskova, A.[2], Browett, P. J.[1,2], Bohlander S. K.[1]

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The advent of Next Generation Sequencing (NGS) has enabled extensive sequencing of acute myeloid leukaemia (AML) exomes and genomes and has broadened our understanding of the genetic changes driving leukaemogenesis. This led to advances in the classification, prognostic stratification, treatment and response assessment of AML. We established a myeloid NGS panel (MGP) and performed sequencing of diagnostic samples of AML patients from Auckland to improve clinical care.

101 consecutive AML patients were sequenced from January 2019 until December 2020 using a capture based custom gene panel targeting the coding exons of 78 genes commonly mutated in myeloid malignancies. The samples were sequenced to a depth 200x mean target coverage on an Illumina NextSeq500 machine. The bioinformatics and variant curation pipelines were optimized to detect somatic variants. Of the 101 patients studied, 95 had a somatic mutation in one or more of the 78 genes examined. The number of mutations detected in each sample ranged from 1-14 (median 3.36). Our MGP detected at least one molecular lesion in all the AML cases with a normal karyotype (n=47) and allowed us to risk stratify 32.7% of cases more precisely using a new genomic classification of AML. An NGS marker suitable for Minimal Residual Disease (MRD) assessment was detected in 95% of cases and in 53.5% of patients at least one druggable target was identified. Surprisingly, this study detected 4 cases of familial *DDX41* mutations and one case with a germline *CEBPA* mutation.

The finding of a high prevalence of AML cases with an inherited predisposition was unexpected and has considerable implications for management. In summary, when used as part of the diagnostic work up for AML, the MGP altered the classification, risk stratification, management and assessment of treatment response in more than 1/3 of the AML patients in our study.

C25: Mutational analysis of the gene *DDX41* in myelodysplastic syndromes and acute myeloid leukaemia

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Background: More than 200 genes have been reported to be somatically mutated in Myelodysplastic syndromes (MDS) and acute myeloid leukaemia (AML). Co-occurrence of a somatic and a germline mutation in the DEAD-box RNA helicase-1 (*DDX41)* are associated with familial MDS and AML, and are found in about 5% of MDS/AML patients. In 12 out of 19 *DDX41* mutation positive samples analysed in the LBCRU, using a targeted gene panel, both germline and somatic variants were detected. However, in 7 samples only germline *DDX41* mutations were detected and no somatic second-hit mutations.

Objective: To identify the second hit *DDX41* mutations in those 7 samples and determine the spectrum of *DDX41* mutations and co-operating mutations in other genes in the *DDX41* mutation(s) positive MDS/AML patients. Additionally, we also aim to study the impact of *DDX41* mutations in AML development by analysing a loss-of-function *DDX41* leukemic zebrafish model.

Method: Long-range polymerase chain reaction (LR-PCR) to amplify the *DDX41* locus from genomic DNA (gDNA), followed the by preparation of next-generation sequencing (NGS) libraries, sequencing and analysis and restriction enzyme digestion to detect bigger genetic changes like deletions, inversions or translocation. Using existing gene panel data to determine the mutation spectrum in the LBCRU *DDX41* positive MDS/AML cohort. For zebrafish analysis, we will monitor the progeny of a cross between a *DDX41* heterozygous mutant zebrafish line and our leukemic CALM/AF10 line.

Result and Discussion: The *DDX41* LR-PCR and library preparation protocols were successfully established and optimized to enable *DDX41* focused NGS analysis. Our *DDX41* focused NGS method yields even coverage across the exons and introns of the DDX41 gene. The *DDX41*-focused NGS method can be used to identify bigger rearrangements and potentially pathogenic variants in *DDX41*. Our method will provide clinicians with crucial information to guide the management of patients.

C26: Preventing evolution of cancer drug resistance by inhibiting DNA-specific cytosine deaminase APOBEC3A

Harjes, S.[1], Kurup, H.M.[1], Rieffer, A.E.[2], Filitcheva, J.[1], Hale, T.K.[1,3], Filichev, V.V.[1,3], Harjes E[1,3], Harris R.S.[4,5], Jameson GB[1,3]

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Tumour cells develop drug resistance when mutations accumulate in their genome that drive phenotypic diversity. Normally, cytosine deaminase APOBEC3A[1] is part of antiviral defence, mutating C-to-U on single-stranded DNA. However, many drug-resistant tumours exhibit a mutagenic signature associated with increased activity of APOBEC3A.[2] Therefore, inhibition of APOBEC3A could potentially extend efficacy of front-line anticancer therapies. Within the genome, potential DNA-hairpin structures are hotspots for mutagenesis.[3]

Here we reveal through X-ray structures of APOBEC3A (wild-type and its inactive E72A mutant) in complex with hairpin inhibitor and substrates the structural basis of (i) enhanced activity of hairpin-DNA with a 3-nucleotide TTC-loop, compared to linear single-stranded DNA, (ii) pyrimidine and purine preferences, respectively, either side of the TC-recognition motif, and (iii) potent inhibition of APOBEC3A by hairpin-DNA bearing 2'-deoxy-5-fluorozebularine in place of the cytidine in the TC-recognition motif (K_i=116 ± 15 nM).

Importantly, the nuclease-resistant derivatives of these inhibitors maintain *in-vitro* potency against APOBEC3A, and when transfected into cancer cells localise to the nucleus, where they potently inhibit mutagenic activity of APOBEC3A.[4]

This suggests a key role for these inhibitors and others[5] to study APOBEC3A activity in cells, with potential application as therapeutics, working alongside and improving efficacy of existing cancer therapies.

1. Harris, R.S., et al. (2003) *DNA deamination mediates innate immunity to retroviral infection*. Cell 113: 803-809.
2. Law, E.K., et al. (2020) *APOBEC3A catalyzes mutation and drives carcinogenesis in vivo*. J Exp Med 217: e20200261.
3. Langenbucher, et al. (2021) *An extended APOBEC3A mutation signature in cancer*. Nat Commun 12: 1602.
4. Harjes, S., …, Hale, T.K., Filichev, V.V., Harjes, E., Harris, R.S., Jameson, G.B. (2023). S*tructure-guided inhibition of the cancer DNA-mutating enzyme APOBEC3A*. Nat Communications, 14: 6832.
5. Kurup, H.M., et al. (2022) *Design, synthesis, and evaluation of a cross-linked oligonucleotide as the first nanomolar inhibitor of APOBEC3A*. Biochemistry 61: 2568-2578.

C27: Leveraging Chemical Tools to Unlock the Potential of Antibody-Drug Conjugates for cancer therapy

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Antibody–drug conjugates (ADCs) have rapidly emerged as a leading class of drugs in oncology, capitalising on the precision of monoclonal antibodies (mAbs) and the potency of cytotoxic drugs to effectively target and eliminate cancer cells.[1] With the projected growth of the ADC market from $7.82 billion in 2022 to approximately $17.13 billion by 2030, ADCs are becoming one of the most intensively researched areas in biotechnology. Currently, 14 ADCs have gained market approval globally, and the clinical investigation of more than 100 ADC candidates is actively progressing, highlighting the ongoing growth and development of this promising field. This dynamic landscape reflects a continuous evolution, with a strong focus on broadening the applications of ADCs not only in oncology but also in non-oncological indications and exploring their potential in combination therapies.

A critical step in developing ADCs is the synthesis of linker-payloads. The conventional method for synthesising cathepsin B-labile dipeptide linkers, commonly used in ADC development, involves the solution-phase assembly of cathepsin B-sensitive dipeptides, followed by the installation of self-immolative para-aminobenzyl carbonate to facilitate the attachment of potent cytotoxic payloads. However, this approach is often low yield and laborious, especially
when extending the peptide chain with components like glutamic acid to improve mouse serum stability or charged amino acids or poly(ethylene glycol) moieties to enhance linker hydrophilicity.

We have recently developed a novel approach utilising late-stage desulfurisation chemistry, enabling safe, facile, and cost-effective access to the cathepsin B-cleavable linker on resin for the first time.[2] This innovative method promises to streamline the synthesis process, potentially overcoming current limitations and accelerating the development of more effective ADC therapies.

(1) Tong, J. T. W.; Harris, P. W. R.; Brimble, M. A.; Kavianinia, I. *An Insight into FDA Approved Antibody-Drug Conjugates for Cancer Therapy*. Molecules **2021**, *26* (19), 5847. https://doi.org/10.3390/molecules26195847.

(2) Ahangarpour, M.; Brimble, M. A.; Kavianinia, I. *Late-Stage Desulfurization Enables Rapid and Efficient Solid-Phase Synthesis of Cathepsin-Cleavable Linkers for Antibody–Drug Conjugates*. Bioconjugate Chem. **2024**. https://doi.org/10.1021/acs.bioconjchem.4c00199.

C28: Post-diagnostic statin use and breast cancer-specific mortality: a population-based cohort study

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Purpose
Statins are the most widely prescribed cholesterol lowering medications and have been associated with both improved and unchanged breast cancer outcomes in previous studies. This study examines the association between the post-diagnostic use of statins and breast cancer outcomes (death and recurrence) in a large, representative sample of New Zealand (NZ) women with breast cancer.

Methods
Women diagnosed with a first primary breast cancer between 2007 and 2016 were identified from four population-based regional NZ breast cancer registries and linked to national pharmaceutical data, hospital discharges, and death records. Cox proportional hazard models were used to estimate the hazard of breast cancer-specific death (BCD) associated with any post-diagnostic statin use.

Results
Of the 14,976 women included in analyses, 27% used a statin after diagnosis and the median follow up time was 4.51 years. Statin use (vs non-use) was associated with a statistically significant decreased risk of BCD (adjusted hazard ratio: 0.74; 0.63–0.86). The association was attenuated when considering a subgroup of 'new' statin users (HR: 0.91; 0.69–1.19), however other analyses revealed that the protective effect of statins was more pronounced in estrogen receptor positive patients (HR: 0.77; 0.63–0.94), postmenopausal women (HR: 0.74; 0.63–0.88), and in women with advanced stage disease (HR: 0.65; 0.49–0.84).

Conclusion
In this study, statin use was associated with a statistically significant decreased risk of breast cancer death, with subgroup analyses revealing a more protective effect in ER+ patients, postmenopausal women, and in women with advanced stage disease. Further research is warranted to determine if these associations are replicated in other clinical settings.

Summary of Abstracts for the Poster Session - Cancer

No.	Title	Presenter	Institutions
C10	Evaluation of new DNA-dependent protein kinase inhibitors as radiosensitisers of head and neck cancer cells	Sophia O'Brien-Gortner	University of Auckland
C11	A long-acting biotherapeutic targeting the growth hormone receptor reduces tumour growth in a melanoma xenograft model (NZM79)	Minah Kim	University of Auckland
C12	Influence of SNP rs1800795 on macrophage polarisation, colitis, and response to emerging therapies	Jildou van der Werf	University of Otago, Dunedin
C13	Optimising MRD-Seq: an improved method for measurable residual disease detection in acute myeloid leukaemia	Mariam Alhilali	University of Auckland
C14	The mechanisms through which αENaC negatively modulates breast cancer proliferation and metastasis.	Elijah Atta Manu	University of Otago, Dunedin
C15	Reduce, Reuse, Recycle: Drug Repurposing to Combat Drug Tolerant Persisters	Madeleine Thompson	University of Otago, Dunedin
C16	Characterising the Biology of Missense C176 Mutation in Tumour Suppressor p53.	Polina Shevchuk	University of Otago, Dunedin
C29	Primary Intracranial Malignant Melanoma diagnosed on squash smear cytology in Indian Subcontinent: A Rare Case Report	Madhu Kumar	King George's Medical University, Chowk 226003, lucknow, uttar Pradesh, India
C30	Epigenetic and Genetic Biomarkers for Long COVID and ME/CFS: Developing a Robust Molecular Diagnostic Panel	Sayan Sharma	University of Otago, Dunedin
C31	Epigenetic drivers of early onset of cancer	Aniruddah Chatterjee	University of Otago, Dunedin
C32	Epigenomic profiling of paired colorectal cancer samples to identify drivers of early metastasis	Euan Rodger	University of Otago, Dunedin
C33	Precision methylation editing as a tool to modulate MGMT Expression and alter drug sensitivity	Janhavi Gujadhur	University of Otago, Dunedin

C34	Cautionary tale: Potential of false hits in CRISPR screens through editing of close proximity genes	Marcella Flinterman	University of Auckland
C35	Epigenetic profiling and analysis of transrectal ultrasound-guided prostate biopsy tissue	Angela Yee	University of Otago, Dunedin
C36	Developing a multi-omic signature for prediction of early prostate cancer recurrence following radical prostatectomy.	Jim Smith	University of Otago, Dunedin
C37	DMAP2: A pipeline for analysis of whole genome-scale DNA methylation sequencing data	Peter Stockwell	University of Otago, Dunedin
C38	Identifying epigenetic markers for early detection of prostate cancer	Bayley Knofflock	University of Otago, Dunedin
C39	Establishing a DNA methylation biomarker panel for prostate cancer detection	Atreyi Dutta	University of Otago, Dunedin
C40	The role of miR-21 in Drug Tolerance	Nina Simmons	University of Otago, Dunedin
C41	Tackling Resistance to HER2-Targeted Antibody-Drug Conjugates in Breast Cancer	Queenie Yong	University of Auckland
C42	A CRISPR/Cas Methylation-Editing Screen to Identify Epigenetic Drivers of Cancer	Nicholas Keestra	University of Otago, Dunedin
C43	Investigating a minimal custom targeted enrichment gene panel for lung cancer mutation detection in circulating tumor DNA	Mia Hillock	University of Otago, Dunedin
C44	Epigenomic and transcriptomic profiling of drug resistant lung cancer	Safia Farry	University of Otago, Dunedin
C45	Evaluation of cfEM-Seq and cfRRBS for cell-free DNA Methylation Profiling	Mark Ezegbogu	University of Otago, Dunedin
C46	Inhibiting Adaptive Mutability to Prevent the Emergence of Drug Resistance in Non-Small Cell Lung Cancer	Olyvia Gill	University of Otago, Dunedin
C47	Development of ctDNA methylation analysis for non-invasive colorectal cancer detection	Morgan Jones	University of Otago, Dunedin

C48	Integrating Methylation and DNA Sequencing data using DNAmBERT model for Non-Invasive Cancer Diagnosis	Maryam Yassi	University of Otago, Dunedin
C49	α-ENaC influence on sensitivity towards chemotherapy drugs in breast cancer and immune response	Priyanka Singh	University of Otago, Dunedin
C50	Advancing Precision Oncology: Artificial Intelligence's Remarkable Success in Predicting Early-Stage NSCLC Recurrence	Ghazal Mehri-kakavand	University of Auckland
C51	Effect of epithelial sodium channel level on breast cancer cell response to docetaxel	Israa Abosaleek	University of Otago, Dunedin
C52	A systematic review of the recent trends in the prevention, early detection and treatment options for breast cancer in NZ	Maran Muthiah	University of Auckland
C53	YB-1 Mediated Modulation of Chromosomal Instability in Cancer	Selena Wang	University of Otago, Dunedin
C54	Investigating mechanisms of epigenetic change in colorectal cancer: the role of immune cell oxidants and gut bacteria	Annika Seddon	University of Otago, Christchurch
C55	Modelling Early Lung Squamous Cell Carcinoma	Sam Siljee	Gillies Mcindoe Research Institute
C56	A new approach to targeting cancer: Dual action construct which simultaneously targets two microRNAs commonly dysregulated in lung cancer	Alex McDonald	University of Otago, Dunedin
C57	Generation of Oestrogen Receptor Positive Breast Cancer Models with Enhanced Metastatic Potential	Hunter Dickson	University of Otago, Dunedin