Session one, August 24, 2018, 9:30 AM - 11:00 AM

**A common variation in the *IL6* promoter predicts time to metastasis for colorectal cancer and may indicate the mechanisms involved**

Munro, Fran1**,** Gimenez, Gregory2, Shepherd, Peter 3, Braithwaite, Antony2, McCall, John1, **Fleming, Nicholas2**  
  
*1Department of Surgical Sciences, University of Otago, NZ*

*2Department of Pathology, University of Otago, NZ  
3Department of Molecular Medicine and Pathology, The University of Auckland, NZ*

The rs1800795 single nucleotide polymorphism (SNP) resides within the interleukin 6 (IL-6) gene promoter and is reported to associate with the risk of inflammation related disorders and cancer initiation. IL-6 is also implicated in cancer progression, and we recently detected associations in public datasets between rs1800795 genotype and metastasis/invasion for a number of cancer types, including head and neck cancers, lung cancers, and colorectal cancers. We therefore proposed that it may have prognostic value.

We have now characterised rs1800795 status together with primary cancer gene mutation burden for 192 colorectal cancer patients from southern New Zealand. Rs1800795 status associated strongly with disease-free survival (DFS) in those patients who developed metastasis. Those who were GG developed metastasis in roughly half the time as those who were CC (~1.25 years vs. 3.2 years). Having any G allele (i.e. either GG or GC), or any C allele, was also associated with DFS. In addition, a strong relationship was detected between having any G allele and age of disease onset. The relationships with DFS were robust when age and sex were accounted for.

We propose that the SNP is functional, and directly alters regulation of the *IL6* promoter by tumour protein p63 (p63) and CCAAT/enhancer binding protein β (C/EBPβ). Using gene edited cancer cells, the SNP directly altered cooperative regulation of *IL6* by p63 and C/EBPβ. In addition, IL-6 expression was elevated to higher levels still by expression of the short isoforms of both p63 (ΔNp63) and C/EBPβ (LIP). In TCGA data, high expression of C/EBPβ was associated with shorter survival suggesting a dominant role for the LIP isoform.

These findings suggest that rs1800795 status has immediate value as a prognostic biomarker for colorectal cancer, and that it may predict what processes promote a patient’s recurrence. Relationships between patient rs1800795 genotype, metastasis, and response to relevant targeted therapies are being investigated.

Session one, August 24, 2018, 9:30 AM - 11:00 AM

**Proteomic analysis of breast cancer brain metastasis microenvironment in-vivo reveals a unique milieu intérieur of metabolic reprogramming**

**Kalita-de Croft, P.1,2**, Straube, J.2, Al-Ejeh, F.1,2,  Saunus, J.M.1,2,  Lakhani, S.R.1,3

*1University of Queensland, UQ Centre for Clinical Research, Brisbane, Queensland, Australia.*

*2Queensland Institute for Medical Research (QIMR) Berghofer, Brisbane, QLD, Australia.*

*3Pathology Queensland, Royal Brisbane Women's Hospital, Brisbane, Queensland, Australia.*

Brain metastasis (BM) is an unfortunate clinical complication that occurs in about 15-30% of the patients with metastatic-breast cancer[1]. Extremely poor prognosis and neurological impairments of sensory and cognitive functions are salient features of BM, with survival rates varying between 4-12 months post-diagnosis [2, 3]. Therefore, there is an urgent need of unravelling novel mechanisms of BM including treatment-resistance. The tumour-microenvironment (TME) provides both the framework and mechanism for metastatic outgrowth. Despite immense negative selection-pressure tumour-cells colonise using adaptive mechanisms, including: oxidative-stress resistance, repurposing neurotransmitters and mimicking neural traits[4]. These transformations could be clinically targetable and hence we set out to identify novel adaptations in breast cancer-brain metastasis by performing proteomic analysis of the mouse brain compartment of breast cancer brain xenografts.

MDA-MB-231 breast cancer cells were stereotactically injected into NOD/SCID mouse hosts (n=5). Mock-injected (PBS) and matching uninvolved brain (n=4) were used as controls. After three weeks, brain tissues (tumour-associated, mock and normal) were isolated using affinity-based magnetic bead separation (Miltenyi Biotec) and proteomics was performed by Mass Spectrometry (MS)-Swath at Australian Proteome Analysis Facility (APAF).

Unsupervised hierarchical clustering exhibited forty-one differentially expressed proteins. We employed String and IPA analysis to further reveal Gene-Ontology (GO) terms associated with metabolic stress and extracellular vesicle transport such as extracellular exosomes and mitochondrial proteins (FDR <0.05 cut off) to be deregulated. Furthermore, they belonged to mitochondrial dysfunction, sirtuin signalling and apoptosis signalling pathways. These findings suggest that tumour associated brain exhibits metabolic reprogramming, evident from deregulation of exosomal and mitochondrial pathways. This indicates that the bioenergetics demand of the microenvironment has altered the *milieu intérieur* of the brain. Apart from validating these findings on additional mouse brain xenografts and clinical samples, future work will focus on studying these metabolic changes for targeting and therapeutic purposes.

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Session two, August 24, 2018, 11:20 AM - 12:40 PM

**Merkel Cell Polyomavirus status predicts outcome for Merkel Cell Carcinoma in a New Zealand cohort**

**Parker, Kate1**, Woodhouse, Braden1, Robb, Tamsin1, Houseman, Pascalene1, Restall, Paul2, Miller, Rose2, Low, Irene3, Hayward, Greg4, Knowlton, Nicholas1, Findlay, Michael1, Print, Cristin1, Lawrence, Ben1, Blenkiron, Cherie1

Affiliations

*1 Faculty of Medicine and Health Sciences, University of Auckland  
2 Auckland District Health Board  
3 Counties Manukau District Health Board  
4 Waitemata District Health Board*

Background: Merkel Cell Carcinoma (MCC) is a rare neuroendocrine skin cancer with a high mortality rate. Incidence in New Zealand is higher than in other parts of the world and is rising. In the Northern Hemisphere, Merkel Cell Polyomavirus (MCPyV) is found in ~50 to 90% of MCC. However, studies from Australia suggest a much lower rate of MCPyV positivity, and mutation signatures support a dominant role for ultra violet (UV) DNA damage in the etiology of MCC.

Methods: A register was established containing information on patients diagnosed with neuroendocrine tumours in NZ. Primary data source was the New Zealand Cancer Registry searched using ICD-03 codes. This was supplemented by searches of pathology and departmental records. Clinical data on each case was collected from medical records. The registry included 355 patients diagnosed with MCC. Of these 355 patients, tissue samples were obtained for 106 patients to test MCPyV status using droplet digital PCR (ddPCR, Bio-Rad) assays to amplify viral gene *LTA* in parallel with a viral protein immunohistochemistry (IHC) assay using the commercial CM2B4 antibody. Each MCC was therefore determined to be Virus positive or Virus negative.

Results: Viral positivity was observed in 29% (31/106) of patients. Virus negative MCC occurred more often in men (62.7%, P = <0.024). Virusnegative primary tumours were more common on the head and neck (53.3%, P = <0.0001). Some staging was conducted for 66 cases; virus negative cases were more often metastatic at diagnosis; of the cases where staging was conducted 8 (18.6%) had distant metastases at diagnosis compared with none of the virus positive patients. Median overall survival was consistently shorter for virus negative cases than virus positive cases, with lack of viral load associated with decreased survival (HR = 1.8, P = 0.015). Viral status was not associated with age at diagnosis.

Conclusions: This is the largest study of MCC patients in New Zealand, and the first examining MCPyV status. Analysis suggests that in NZ, as in Australia, a minority of MCC are driven by the MCPyV virus. UV exposure is an alternative explanation for NZ MCC and supported by the primary tumour site. Outcomes for virus negative patients and therefore NZ patients overall with MCC is poorer, and testing samples for MCPyV status at diagnosis would be prognostic. Our dataset provides a valuable resource of clinically annotated tissue that we will use to continue our research into MCC in New Zealand.

Session five, August 25, 2018, 9:00 AM - 10:40 AM

**Identification of MRP2 as a targetable factor limiting oxaliplatin accumulation and response in gastrointestinal cancer**

**Li, Yan**1, Myint, Khine2, Biswas, Riya1, Jong, Nancy2, Jamieson, Stephen2, Liu, Johnson3, Han, Catherine2, Squire, Christopher2, Merien, Fabrice1, Lu, Jun1, Nakanishi, Takeo4, Tamai, Ikumi4, McKeage, Mark2

*1Auckland University of Technology, Auckland, New Zealand*

*2University of Auckland, Auckland, New Zealand*

*3University of New South Wales, Sydney, NSW, Australia*

*4Kanazawa University, Kakuma-machi, Kanazawa, Japan*

Oxaliplatin is important for the clinical treatment of colorectal cancer and other gastrointestinal malignancies, but tumour resistance is limiting. Several oxaliplatin transporters have been previously identified but their relative contributions to determining oxaliplatin tumour responses and gastrointestinal tumour cell sensitivity to oxaliplatin remains unclear. We studied clinical associations between tumour expression of oxaliplatin transporter candidate genes and patient response to oxaliplatin, then experimentally verified associations found with MRP2 in models of human gastrointestinal cancer. Among 18 oxaliplatin transporter candidate genes, MRP2 was the only one to be differentially expressed in the tumours of colorectal cancer patients who did or did not respond to FOLFOX chemotherapy. Over-expression of MRP2 (endogenously in HepG2 and PANC-1 cells or induced by stable transfection of HEK293 cells) decreased oxaliplatin accumulation and cytotoxicity but those deficits were reversed by inhibition of MRP2 with myricetin or siRNA knockdown. Mice bearing subcutaneous HepG2 tumour xenografts were sensitised to oxaliplatin antitumour activity by concurrent myricetin treatment with little or no increase in toxicity. In conclusion, MRP2 limits oxaliplatin accumulation and response in human gastrointestinal cancer. Screening tumour MRP2 expression levels, to select patients for treatment with oxaliplatin alone or in combination with a MRP2 inhibitor, could improve outcomes from treatment of gastrointestinal cancer.

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Session five, August 25, 2018, 9:00 AM - 10:40 AM

**Co-targeting BRAF and VEGF receptors synergistically inhibited the growth of BRAF-mutant and BRAF wild-type melanomas**

**Tran, Khanh1**,2,3, Shih, Jen-Hsing1,2, Wang, Qian1,2, Jamieson, Stephen1,3, Print, Cristin1,3, Tsai, Peter2, Blenkiron, Cherie2, Seyfoddin, Vahid2, Kolekar, Sharada1, Buchanan, Christina2,3, Hunter, Francis1,3, Baguley, Bruce1,3, and Shepherd, Peter1,2,3

1Auckland Cancer Society Research Centre, University of Auckland, New Zealand

2Department of Molecular Medicine and Pathology, University of Auckland, New Zealand

3Maurice Wilkins Centre, University of Auckland, New Zealand

**Background**BRAF inhibitors such as vemurafenib (VEM) are only effective as single agent melanoma therapy in BRAF-mutant melanomas and resistance to the treatment develops within 6 to 12 months. We investigated whether targeting VEGF receptors could increase the efficacy of the BRAF inhibition therapy.

**Method**We measured levels of VEGF-A secretion from our unique NZM panel of melanoma cell lines, including BRAF- and RAS-mutant lines and lines with neither BRAF nor RAS mutations (nonBRAF/nonRAS lines). Variations of the VEGF pathways in these cells were analysed by exome sequencing, RNA-Seq and western blotting. Xenograft and syngeneic models were used to investigate efficacy and safety of a combination of VEM and the VEGFR2 inhibitor axitinib (AXI) *in vivo*. Species-specific tumour RNA sequencing was performed to identify pathways uniquely affected by the drug combination in tumour cells and host stroma. RNAscope and immunohistochemistry were used to further analyse effects of the drugs in the tumours.

**Results**V600E-mutant melanoma cell lines secreted VEGF at significantly higher levels compared to cell lines with RAS mutations or nonBRAF/nonRAS lines. VEM downregulated VEGF secretion in V600E-mutant cell lines but not in RAS-mutant or nonBRAF/nonRAS cell lines. We found in two separate BRAF-mutant xenograft models that the VEM + AXI combination synergistically inhibited the tumour growth. Interestingly, the combination also inhibited the growth of two separate NRAS-mutant xenograft models and a nonBRAF/nonRAS model. A similar trend was found in the syngeneic B16 murine melanoma model, suggesting the combination was also effective when an intact immune system was present. When AXI was replaced with our in-house VEGFR2 inhibitor SN35332, we found the combination also provided the synergistic effect, which suggests the combined effects were likely pathway specific rather than drug specific. Pathway-related synthetic lethality was identified in two key pathways of the tumour cells when VEM and AXI were combined: upregulation of the endothelial-mesenchymal transition and downregulation of the p53 pathways. Furthermore, synthetic lethality was also found in the tumour stroma in the combination group where the two essential tumour-promoting pathways TGF-beta and angiogenesis were significantly downregulated. Consistent evidence was also observed when tumour sections were examined using RNAscope. Finally, we developed a cell line acquired resistant to vemurafenib and showed that the combination of VEM + AXI resensitized the tumours to BRAF inhibition therapy.

**Conclusion**Together, this study suggests an important link between the VEGF axis and BRAF signalling in melanoma biology and co-targeting those two axes could enhance the efficacy of BRAF inhibition therapy not only in BRAF-mutant but also in BRAF wild-type tumours.

Session five, August 25, 2018, 9:00 AM - 10:40 AM

**Targeting DNA-dependent protein kinase for tumour-selective radiosensitisation**

**Wilson, William R.**1**,**2, Wong, Way W.1, Dickson, Benjamin D.1, Hunter, Francis W.1,2, Lee, Tet-Woo 1,and Hay, Michael P. 1,2

*1Auckland Cancer Society Research Centre, University of Auckland, Auckland, New Zealand.*

*2Maurice Wilkins Centre for Molecular Biodiscovery, University of Auckland, Auckland, New Zealand.*

The ability of cells to repair DNA double strand breaks has a major influence on the sensitivity of individual tumours to radiotherapy. DNA-dependent protein kinase (DNA-PK) plays a key role in non-homologous end-joining repair of radiation-induced double strand breaks, but its exploitation as a target for radiosensitisation may be limited by effects on normal tissue within the radiation field. With the objective of exploiting tumour hypoxia to achieve tumour selectivity we synthesised SN38023, a 2-nitroimidazolyl prodrug of the DNA-PK inhibitor (DNA-PKi) IC87361. SN38023 was markedly deactivated (800-fold) relative to IC87361 in a cell-free assay for DNA-PK catalytic activity (IC50 560 vs 0.7 nM). We showed that metabolic reduction of SN38203 in HCT116/POR cells results in hypoxia-dependent formation of IC87361. IC87361 (10 µM, 1 hr before and 30 min after irradiation) strongly inhibited DNA-PKCS Ser2056 autophosphorylation in oxic UT-SCC-54 and HCT116/POR cell lines by western immunoblotting. In clonogenic assays, IC87361 markedly radiosensitised oxic UT-SCC-54C, HCT116 and HCT116/POR cells incubated with the DNA-PKi for 24 hr post-irradiation (sensitiser enhancement ratios, SER, of 2.05, 1.73 and 2.08, respectively). In contrast prodrug SN38023 had no significant effect on radiation-induced DNA-PKcs phosphorylation or cell killing under oxic conditions, but was highly active following incubation with cells for 3 hr under anoxia prior to irradiation (e.g. SER 1.54 and 2.28 for UT-SCC-54C and HCT116/POR cells, respectively). We also demonstrated that the prodrug radiosensitises hypoxic cells efficiently in an HCT116 multicellular spheroid co-culture model, but the latter studies showed the lack of a bystander effect (i.e. inability of the released DNA-PKi to diffuse out of cells in which it is generated). This likely reflects the high intracellular/extracellular concentration ratio (~400) of IC87361 in monolayer cultures, determined by HPLC, whether generated from SN38023 under anoxia or during incubation with the DNA-PKi itself. This study has demonstrated the potential for hypoxia-activated prodrugs of DNA-PKi to target selectively the most radioresistant (hypoxic) subpopulation within tumours, but has also identified limitations of IC87361 in this context. We are currently exploring novel DNA-PKi with potential to exploit tumour hypoxia for selective radiosensitisation through this prodrug strategy.

Session six, August 25, 2018, 11:10 AM - 12:50 PM

**Investigating Tumour Evolution in a Single Patient with Disseminated Cancer**

**Tamsin Robb1**, Cherie Blenkiron1, Peter Tsai1, Kate Parker1, Alexei Drummond2, Mik Black3, Alex Gavryushkin4, Braden Woodhouse1, Pascalene Houseman1, Esther Coats1, Paula Shields1, Sandra Fitzgerald1, Deborah Wright5, Rexson Tse5, Nicole Kramer5, Claire Barker5, Yvonne Triggs5, Simon Stables5, Lucy Modahl5, Jane Reeve5, Phillip Shepherd1, Ben Lawrence1\*, Cris Print1\*

Affiliations

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

2 *Faculty of Science, The University of Auckland*

3 *Department of Biochemistry, University of Otago*

4 *Department of Computer Science, University of Otago*

5 *Auckland District Health Board, Auckland*

\* Cris Print and Ben Lawrence have contributed equally to the leadership of this study

For cancer biologists, understanding the evolution and resulting genomic heterogeneity of multiple tumours in a single patient is an important goal. For oncologists, genomic maps of multiple tumours in each patient, when combined with histology and imaging studies, could bring a step change to precision oncology. Therapeutic targets universal to all of a patient’s tumours could be selected, private resistance mechanisms found only in individual metastases could be identified, and metastasis-specific ctDNA biomarkers for better disease monitoring could be selected.

A patient with a primary lung neuroendocrine tumour and 88 metastases requested and consented to rapid autopsy, providing a rare opportunity to study tumour evolution and heterogeneity in a single patient. We have embarked on a multi-layered genomic investigation, augmenting clinical notes and imaging, to build a personalised evolutionary model of the disease progression. Following comprehensive ethical consultation the patient and her extended family provided informed consent to collection of tumours through rapid autopsy. Both formalin fixed, paraffin embedded (FFPE) and fresh frozen samples were collected from the 89 lesions, annotated comprehensively and lesions sampled extensively where large and there was likely heterogeneity. From an initial 30 FFPE tumour samples, representing a broad spatial distribution of the patient’s total tumour burden, DNA whole exome sequencing (WES), transcriptome mRNA sequencing and RNA microarray analysis was completed, to provide a bank of genomic information to guide evolutionary investigations. We have built statistical evolutionary phylogenetic models from differences observed across the genomic data to produce a broad evolutionary picture encompassing single nucleotide variants (SNVs), indels, copy number variants (CNVs), and RNA expression.

Overall, the 30 tumours were generally homogenous in terms of SNVs, indels and CNVs, mirroring histopathological observations of homogeneity. However, key differences in SNVs that may have driven metastatic events were found and used to infer tumour lineages and evolutionary progression. The data suggests that multiple ancestral lineages within the primary tumour may have been responsible for seeding different metastatic tumours. The analysis is facilitated by anatomical and temporal information from clinical notes, and also allows inferences to be made in timing of evolutionary progression.

This generous donation by a patient represents an opportunity to draw on well-annotated clinical history alongside a substantial bank of multi-layered genomic data to investigate biological drivers of tumour evolution.

Session six, August 25, 2018, 11:10 AM - 12:50 PM

**An increase in effector Tregs is a classifying feature of the immune landscape in colorectal tumours**

**Norton, Sam1,** Ward-Hartstonge, Kirsten1, McCall, John1, Leman, Julia1 Shen, Shirley1 Taylor, Edward1 Munro, Fran1 Black, Mik1 Fazekas De St Groth, Barbara2, Mcguire, Helen2, Kemp, Roslyn1.

*1 The University of Otago, Dunedin, New Zealand*

2 *The University of Sydney,* *Sydney, Australia*

Colorectal cancer (CRC) has the third highest incidence rate of any cancer in New Zealand. Immune cells play an important role in determining CRC disease progression. T cell infiltration, in particular, is associated with disease outcome and has been incorporated into a new prognostic test called the Immunoscore. However, T cell populations are highly diverse and recent work in our laboratory has demonstrated that the infiltration frequency of specific population of regulatory T cells (Tregs) improved prognostic stratification. This population of Tregs expresses the transcription factor BLIMP-1. The underlying mechanism of protection, however, has not yet been elucidated.

The advent of new technologies, such as mass cytometry, for studying immune cells requires the development of new techniques to analyse these populations. This substantial increase in data dimensionality limits the use of standard analysis techniques. Clustering and dimensionality reduction techniques have therefore been developed to visualize these complex datasets.

Here, mass cytometry was used to assess the frequency and phenotype of BLIMP-1+ Tregs in tumour and non-tumour bowel (NTB) obtained fresh from CRC patients undergoing bowel resection at Dunedin Hospital. This data was analysed using network cluster analyses including SCAFFoLD, VORTEX and CITRUS. These analyses revealed a significant increase in the frequency of both total Tregs (a validation of previous work in our lab) and BLIMP-1+ Tregs in the tumour compared to NTB. Further, CITRUS analysis revealed that an increase in BLIMP-1+ Tregs was a classifying, significant feature of the tumour tissue compared to NTB; two of seven T cell populations that were present at a greater abundance in the tumour than the NTB were BLIMP-1+ Tregs. These analyses also revealed expression of ICOS, CD45RO and a variety of exhaustion markers on BLIMP-1+ Tregs indicating a more activated phenotype than conventional Tregs.

Together, this work highlights the complexity of T cell responses in colorectal cancer and demonstrates the strength of mass cytometry and network analyses for resolving these populations. Further, this work lays a significant scaffold for developing future prognostic tools to improve patient care.

Session six, August 25, 2018, 11:10 AM - 12:50 PM

**Survival after Breast Conserving Surgery (BCS) Compared to Mastectomy (MTX) in Early Stage Breast Cancer.**

Mr Shoaib Abrahimi1, Dr Sandar Tintin1, Professor Mark Elwood1, Associate Professor Ian Campbell1,2, Professor Ross Lawrenson3

1The University of Auckland , Auckland , New Zealand, 2Waikato Hospital , Hamilton West, New Zealand , 3The University of Waikato , Hillcrest, New Zealand

**Abstract**

**Background**

Earlier randomised control trials illustrate equal survival outcomes after breast conserving surgery plus radiotherapy (BCS+RT) and mastectomy (MTX) in women with early stage breast cancer (ESBC) whereas more recent observational studies suggest BCS+RT is better or at least equal to MTX.

**Aims:**

To compare breast cancer specific mortality and overall mortality after BCS, BCS+RT, MTX and MTX+RT in New Zealand women with early stage breast cancer.

**Methods**

This population-based study involves all women who were diagnosed with ESBC (Stage I-IIb) in the four health regions between 1st January 2000 and 30th June 2014 and had undergone one of: BCS, BCS+RT, MTX or MTX+RT as their primary treatment. Kaplan Meier estimator and Cox proportional hazard modelling were used to compare hazards of breast cancer specific and overall mortality across the four types of surgical treatment, and demographic, clinical and systemic treatment factors were adjusted.

**Results**

10,289 women were analysed: 5154 (50.1%) received BCS+RT, 1042 (10.1%) BCS, 3069 (29.8%) MTX and 1024 (10.0%) MTX+RT.

Compared to women who received BCS+RT, those who received other types of surgical treatment had a higher DSS risk (adjusted HR: 1.78 (95%CI: 1.47-2.14) for BCS; 1.49 (95%CI: 1.20-1.83) for MTX; 1.50 (95% CI: 1.16-1.94) for MTX+RT) as well as OS (adjusted HR: 1.47 (95% CI: 1.47-2.14) for BCS; 1.59 (95% CI: 1.38-1.83) for MTX; 1.49 (95% CI: 1.22-1.82) for MTX+RT.

**Conclusion**

BCS+RT is associated with better survival outcomes in New Zealand women with early breast cancer. The findings could be assessed in future randomised trials.