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2016 Hunter Cancer Research Symposium
"Leading translational research for improved patient outcomes"
25th November 2016
Hunter Medical Research Institute
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HUNTER CANCER RESEARCH ALLIANCE

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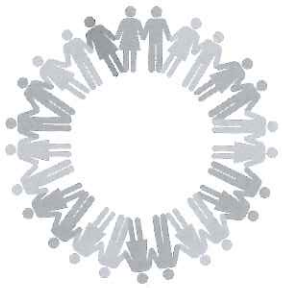

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A Message from the Organizing Committee

Welcome to the 2016 Hunter Cancer Research Symposium.

The Hunter Cancer Research Alliance (HCRA) has over 320 members, ranging from PhD students to clinicians, research fellows and leaders of major cancer research programs. This Symposium aims to foster collaborations among cancer researchers operating across basic science, clinical research, clinical practice, public health and health services research.

The overarching theme of this Symposium is "Leading translational research for improved patient outcomes" and will cover the full spectrum of the translational research-to-practice continuum from basic science to clinical research and implementation research. We believe bringing together expertise from diverse research areas will ensure an invaluable forum for all participants.

We wish to thank our invited speakers, A/Prof Nik Zeps and A/Prof Sarah-Jane Dawson for accepting our invitation to share their wealth of expertise with our local cancer research community. Their keynote addresses on integrating research into routine care and monitoring the cancer genome in the blood will contribute to our aim of promoting and encouraging high-quality translational research.

Our local researchers have contributed oral and poster presentations that will provide engaging and informative sessions highlighting the high-quality research being carried out in the Hunter New England Region. We are greatly appreciative of their commitment to our Symposium. Finally, a warm welcome to all our delegates, thank you for your participation in what promises to be a great forum to share knowledge and grow valuable collaborations.

Let the journey of research, innovation and translation begin.

Warm Regards

HCRA Symposium Organizing Committee

2016 Hunter Cancer Research Alliance Symposium "Leading translational research for improved patient outcomes"

Session 1a: Models of Care		
9:00-9:15	OR1	**Allison Boyes** *What models of peer support are most appealing to cancer patients? A cross-sectional survey.*
9:15-9:30	OR2	**Jan Shepherd** *Barriers to the provision of optimal care to patients dying in hospitals: Perceptions of nurses.*
9:30-9:45	OR3	**Shiho Rose** *Examining the association of stigma with treatment opinions among lung cancer patients.*
Session 1b: Breast Cancer		
9:45-10:00	OR4	**Jennette Sakoff** *Hi-jacking the aryl-hydrocarbon receptor pathway for the treatment of breast cancer.*
10:00-10:15	OR5	**Xiajie Zhang** *Δ40p53 regulates migration in the MCF-7 breast cancer cell line.*
10:15-10:30	OR6	**Nikki Verrills** *Reduced expression of the protein phosphatase 2A regulatory subunit B55α: Impact on luminal B breast cancer cells progression and DNA damage repair.*
10:30-11:00 Morning Tea		
Session 2: Keynote Presentations		
11:00-11:45	KN1	**Sarah-Jane Dawson** *Liquid biopsies: monitoring the cancer genome in blood.*
11:45-12:30	KN2	**Nikolajs Zeps** *Integrating research into routine clinical care: turning the dream of a self improving healthcare system into reality.*
12:30-1:30 Lunch and poster viewing		
Session 3: Cancer Biology		
1:30-1:45	OR7	**Matt Dun** *Quantitative, High-Resolution Proteomics for a Systems Biological Analysis of Acute Myeloid Leukaemia.*
1:45-2:00	OR8	**Trisha Al Mazi** *A Comparison between Data Dependant Analysis and High Resolution Accurate Mass Targeted Proteomics Approaches for the Quantification of Plasma Biomarkers in Colorectal Cancer.*
2:00-2:15	OR9	**Lei Jin** *A microfilament protein as a master switch at the intersection of survival signalling pathways in melanoma.*
2:15-2:30	OR10	**Judith Weidenhofer** *Prostate Cancer extracellular vesicles: friend or foe.*
Session 3: Prevention		
2:30-2:45	OR11	**Ashleigh Guillaumier** *Enforcement strategies for effective smoke-free policy implementation: A systematic review.*
2:45-3:00	OR12	**Yael Bar Zeev** *Assessing and Validating an Educational Resource Package for the Management of Smoking Cessation in Indigenous Pregnant Women.*
3:00-3:30 Afternoon Tea		
Session 4: Clinical Application		
3:30-3:45	OR13	**Kristen McCarter** *Eating As Treatment (EAT): A Health Behaviour Change Intervention to Improve Treatment Outcomes for Head and Neck Cancer Patients Undergoing Radiotherapy.*

Session 4: Clinical Application		
3:45-4:00	OR14	**Narges Miri** *A method for remote auditing of radiotherapy machines.*
4:00-4:15	OR15	**Nikola Bowden** *Repurposing chemotherapy to target the immune system in melanoma.*
4:15-4:30	OR16	**James Lynam** *The Incidence of Severe Thrombocytopenia in Glioblastoma Patients Undergoing Combined Chemoradiotherapy: A Single Centre Experience.*
Session 5: Science in 2 minutes		
4:30-4:32	P1	**Eliza Skelton** *Addressing tobacco smoking in a medically supervised injecting centre with an organisational change intervention: an acceptability study.*
4:32-4:34	P2	**Alix Hall** *Assessing the information needs of stage one testicular cancer patients and their carers.*
4:34-4:36	P3	**Todsaporn Fuangrod** *Treatment quality assessment using in-vivo electronic portal imaging device (EPID) dosimetry in radiotherapy.*
4:36-4:38	P4	**Nadine Berry** *HD-SNP Microarray Analysis of the Study 9 High Risk ALL Patients – providing key prognostic information using arrays.*
4:38-4:40	P5	**Yuan Yuan Zhang** *Apoptosis-regulating long non-coding RNAs in melanoma.*
4:40-4:42	P6	**Chloe Goldsmith** *The olive phenolic compounds apigenin, luteolin and oleuropein induce cell cycle arrest and apoptosis in pancreatic cancer cells in vitro.*
4:42-4:44	P7	**Subhransu Sahoo** *Influence of microenvironment in endometrial cancer progression.*
4:44-4:46	P8	**Heather Murray** *DNA-PK inhibition sensitises FLT3-ITD AML cells to cytarabine and sorafenib.*
4:46-4:48	P9	**Martine Cox** *Quantifying intervention engagement in a randomised controlled trial of online versus telephone-based information and support for lung cancer patients.*
4:48-5:00	P10	**Michelle Bovill** *'Wula': Voices of Aboriginal women on barriers to seeking and accepting smoking cessation support during pregnancy; findings from a qualitative study in Hunter New England district, New South Wales.*
5:00-6:15 Poster viewing and canapes		
6:15-6:25 Awards Presentations		
6:25-6:30 Closing Address		
6:30 Symposium Concludes		

Keynote Speakers

Associate Professor Sarah-Jane Dawson

Group Leader, Molecular Biomarkers and Translational Genomics Laboratory, Peter MacCallum Cancer Centre

Associate Professor Sarah-Jane Dawson is a clinician-scientist. She obtained her medical degree from the University of Melbourne, and trained as an oncologist in Melbourne, Australia. She completed her PhD at the University of Cambridge, UK. Following postdoctoral studies at the Cambridge Research Institute, she returned to Melbourne in 2014 to head the newly formed Molecular Biomarkers and Translational Genomics Laboratory at the Peter MacCallum Cancer Centre.

Her current research interests lie in understanding the genomic evolution of cancer and using this information to develop noninvasive molecular biomarkers for clinical application, including early detection, risk stratification and disease monitoring. The major focus of her research is the development of blood-based biomarkers ("liquid biopsies") through the use of circulating tumor DNA and circulating tumor cells to enable personalized disease monitoring and facilitate therapeutic decisions in both solid and hematological malignancies.

Title of Presentation: "Liquid Biopsies: Monitoring the Cancer Genome in Blood"

Adjunct Associate Professor Nikolajs Zeps

Director, Medical Research Network, St John of God Subiaco Hospital

Dr. Zeps is a PhD scientist involved in translational research in breast, gastrointestinal and gynecological malignancies. He is the Director of Research at SJG Health Care and head of a translational research program that has established a biobank and clinical registry as a part of routine multidisciplinary cancer care. He is an Adjunct Professor in the School of Health Sciences at Curtin University, the Centre for Comparative Genomics at Murdoch University and at Notre Dame Medical School. He is an Adjunct Associate Professor in the School of Surgery and the School of Pathology and Laboratory Medicine at the University of Western Australia.

He was a member of the Australian Health Ethics Committee from 2006 to 2012 and the Research Committee of the National Health and Medical Research Council of Australia from 2009 to 2015.

He is the chair of the Cancer Biology Group of the Clinical Oncology Society of Australia and a member of the Scientific Advisory Committee of the Australasian Gastro-intestinal Trials Group and of the Primary Care Cancer Collaborative Trials Group Executive committee. He is a founding director of the Australian Clinical Trials Alliance.

He is the Australian representative on the Ethics and Policy Committee of the International Cancer Genome Consortium (ICGC) and was recently appointed as Co-Chair of the Communication Committee of the ICGC-Precision Medicine initiative. He is a member of the Accountability Working Group of the Global Alliance for Genomic Health (GA4GH). He was the Australian member of the Steering Committee for the Global Summit.

Title of Presentation: "Integrating research into routine clinical care: turning the dream of a self-improving healthcare system into reality"

ORAL PRESENTATIONS

OR1

WHAT MODELS OF PEER SUPPORT ARE MOST APPEALING TO CANCER PATIENTS? A CROSS-SECTIONAL SURVEY

Allison Boyes[1,2], Heidi Turon[1,2], Alix Hall[1,2], Rob Sanson-Fisher[1,2]

[1] *Priority Research Centre for Health Behaviour, University of Newcastle, Callaghan, New South Wales, Australia*

[2] *Hunter Medical Research Institute, New Lambton Heights, New South Wales, Australia*

Background: Social support positively impacts upon cancer patients' outcomes. Peer support, which involves sharing experiences and empathy with others affected by cancer, is suggested to be a critical element in quality health care.

Aims: To examine cancer patients' preferences for different models of peer support.

Methods: Adult cancer patients were recruited from medical and radiation oncology clinics at five hospitals in NSW. A total of 172 participants completed a self-report questionnaire assessing their sociodemographic, disease and treatment characteristics; perceived social support; and preferences for cancer-related peer support.

Results: *Do patients want to connect with others?* One-third of participants reported not having someone to turn to about how to deal with a problem (34%) and not having someone to share their worries or fears with (30%). Two-thirds (62%) of participants wanted information about cancer-related peer support available to them. *Who do patients want to connect with?* Participants reported that peers who had received the same cancer treatment (56%) and were diagnosed with the same type of cancer (54%) were more important than connecting with those who were similar in age (42%), gender (38%) or culture (32%). *How do patients want to connect with others?* Peer support, which was provided one-to-one, was more preferable than a group-based format. Face-to-face modes of delivery were more preferred than telephone-based or web-based approaches. Factors associated with cancer patients' preferences for involvement in peer support will be reported.

Conclusions: Most cancer patients are interested in finding out about peer support. Despite the availability of innovative communication technology, patients preferred resource-intensive models of peer support. Better understanding of the barriers to cancer patients' involvement in more flexible and potentially low-cost models of peer support is needed.

Translational research aspect: This T3 research may inform the development and redesign of consumer-directed models of peer support.

OR2

BARRIERS TO THE PROVISION OF OPTIMAL CARE TO PATIENTS DYING IN HOSPITALS: PERCEPTIONS OF NURSES

Jan Shepherd[1], Amy Waller[1], Rob Sanson-Fisher[1], Katherine Clark[1,2]

[1] *University of Newcastle, Health Behaviour Research Group, Callaghan, New South Wales, Australia*

[2] *Calvary Mater Newcastle, Waratah, New South Wales, Australia*

Background: A widening gap between optimal and actual end-of-life care in hospitals is acknowledged in relation to symptom management, end-of-life discussions, access to palliative care and medication management. To develop interventions that improve care, we must understand the factors that hinder and facilitate care from the perspective of all stakeholders. Despite their pivotal role in delivery of end-of-life care, nurses' views are not widely reported.

Aims: To examine perceptions of nurses working in acute care wards regarding:

(1) Individual, social and system barriers to the provision of optimal end-of-life care to people dying in hospital.
(2) Potential enablers to increase the probability of providing optimal care to this population group.

Methods: A cross-sectional survey of 200 nurses from acute care wards across several hospitals. Nurses are asked to rate the importance of 47 barriers on a four-point Likert scale.

Results: A total of 84 nurses have been recruited to date. Data collection is expected to be completed by November 2016. Data on the most significant barriers identified by nurses across five domains (patient, family, nurse, doctor and system) will be presented. Factors that may increase the probability of providing optimal care will also be presented.

Conclusions: Findings will provide missing data on the extent to which essential elements of end-of-life care are occurring in hospitals, ways they are deficient and influential contextual factors from the perspective of nurses. Understanding the knowledge, attitudes and behavior of nurses in relation to these elements will help to inform development of interventions to support provider engagement and implementation of end-of-life care.

Translational research aspect: Delineating barriers and enablers is an important step in the development of behavior implementation science. Barriers may be patient- and provider-related, social- or system-related. Data will provide a baseline indication of current gaps between evidence and practice and factors that contribute to these gaps.

OR3

EXAMINING THE ASSOCIATION OF STIGMA WITH TREATMENT OPINIONS AMONG LUNG CANCER PATIENTS

Shiho Rose[1,2], Christine Paul[1,2], Allison Boyes[1,2], Brian Kelly[3,2], Martine Cox[1,2]

[1] *Priority Research Centre for Health Behaviour, University of Newcastle, Callaghan, New South Wales, Australia*

[2] *Hunter Medical Research Institute, New Lambton, New South Wales, Australia*

[3] *Centre for Brain and Mental Health Research, University of Newcastle, Callaghan, New South Wales, Australia*

Background: Patients who actively participate in their care report greater satisfaction and have better health outcomes. However, previous studies report lung cancer patients may be less active in their treatment decisions compared to other cancer patients. Perceived lung cancer stigma may influence patient's views about their treatment.

Aims: The study examined the relationship of perceived lung cancer stigma with: (i) treatment expectations and (ii) treatment attitudes. It is hypothesized that patients with greater perceived stigma will report less positive opinions about treatment.

Methods: A cross-sectional study was conducted. Lung cancer patients diagnosed ≤4 months were consecutively recruited via respiratory and oncology clinics in Australia. Consenting participants completed a survey with questions of perceived stigma (using the Cataldo Lung Cancer Stigma Scale) and treatment opinions (using adopted CanCORS study items and author-developed).

Results: The survey was completed by 134 patients from 21 clinics (males, 64.2%; mean age, 67.2±9.5 years). Patients reported mean stigma scores of 50.5±17.1 (of a possible 124). For treatment expectations, most agreed/strongly agreed that treatment would help them live longer (72.4%) and help with symptoms (60.0%), while some agreed/strongly agreed that it would cure their cancer (44.8%), others were unsure (37.3%). For treatment attitudes, more preferred treatment that extends life than relieve pain or discomfort (64.9% *vs* 17.1%). Associations between reported stigma, patient characteristics and treatment opinions will be presented.

Conclusions: Patients reported relatively low lung cancer stigma scores compared to other lung cancer populations, and appeared to have favorable

treatment opinions. Perceived stigma may need to be acknowledged when discussing treatment options.

Translational research aspect: This T3 research is directed toward developing new knowledge to build the evidence and identify possible targets for future interventions. The findings will be useful to assist in identifying strategies to ensure lung cancer patients are fully supported while making treatment decisions.

OR4

HI-JACKING THE ARYL-HYDROCARBON RECEPTOR PATHWAY FOR THE TREATMENT OF BREAST CANCER

Jennette Sakoff[1,2], Jayne Gilbert[1], Mark Tarleton[2], Trieu Nguyen Trinh[2], Geoff De Uillius[2], Adam McCluskey[2]

[1]*Calvary Mater Newcastle Hospital, Waratah, New South Wales, Australia*

[2]*The University of Newcastle, Callaghan, New South Wales, Australia*

Background: More than 3000 women die of breast cancer each year in Australia and the incidence is rising. Indeed, metastatic disease is incurable. Herein, we report a class of phenylacrylonitrile-based small molecules that are more than 250-fold more selective at killing breast cancer cells grown in culture than any other cell type; indeed, they have little to no effect on cells from other tumor types or on normal breast cells. The sensitive cell lines represent breast tumors from the molecular subtypes of luminal A, luminal B, human epidermal growth factor receptor 2 positive (HER+), basal and drug resistant.

Aim: The aim of our study is to determine the mode-of-action of this class of molecule.

Methods: Growth inhibition assays 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT), cell cycle analysis, western blotting techniques, kinase analysis and immunofluorescence imaging were exploited to characterize the mode-of-action of these compounds in breast cancer cell line models.

Results: Herein, we show that our compounds hi-jack the aryl-hydrocarbon receptor pathway (AhR). This pathway is well documented for the metabolism of environmental pollutants, the formation of carcinogenic compounds via cytochrome P450 (CYP1) activation and in the progression of breast cancer. Analysis of our most sensitive breast cancer cell line (MDA-MB-468) shows that our lead molecule (ANI-7) binds to the AhR, translocates to the nucleus, stimulates CYP expression, undergoes metabolic activation (via CYP1), halts cell cycle movement, activates the cell cycle checkpoint (CHK2) and induces DNA damage (γH2AX) and cell death. This is in contrast to all other standard breast cancer targeting therapies currently in use.

Conclusions: For the first time, we report that the phenylacrylonitrile ANI-7 targets breast cancer cells by activating the AhR pathway. This knowledge will build upon our endeavors to selectively target and treat breast cancers in the clinic.

Translational research aspect: This study represents the translation of knowledge from T1 to T2.

OR5

Δ40p53 REGULATES MIGRATION IN THE MCF-7 BREAST CANCER CELL LINE

Xiajie Zhang[1], Brianna Morten[1,2], Hamish Campbell[3], Antony Braithwaite[4], Rodney Scott[1,2,5], Kelly Avery-Kiejda[1,2]

[1]*Medical Genetics, Hunter Medical Research Institute, New Lambton Heights, New South Wales, Australia*

[2]*Priority Research Centre for Cancer, School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle, Newcastle, New South Wales, Australia*

[3]*Children's Medical Research Institute, University of Sydney, Sydney, New South Wales, Australia*

[4]*Department of Pathology, School of Medicine, University of Otago, Dunedin, New Zealand*

[5]*Hunter Area Pathology Service, John Hunter Hospital, New Lambton Heights, New South Wales, Australia*

Background: Breast cancer is the most common diagnosed cancer and the second leading cause of cancer-related death in Australian women. Metastases are the major cause of breast cancer mortality and the molecular mechanisms are largely unknown. The genome guardian p53 is rarely mutated in breast cancers, and loss of p53 or its functional inactivation contributes to metastasis processes such as epithelial-mesenchymal transition (EMT), migration and invasion. Several p53 isoforms have been identified and we have previously demonstrated that one of these, Δ40p53, is highly expressed in breast cancer where it is associated with an aggressive breast cancer subtype and worse prognosis, but nothing is known about its role in EMT or the metastatic cascade.

Aims: To determine whether Δ40p53 could regulate the migration of MCF-7 breast cancer cells and whether this was associated with altered expression of EMT markers, such as E-cadherin, which is crucial to maintain tissue integrity.

Methods: Δ40p53 was overexpressed (LeGO-vector) or knocked down (siRNA-mediated transient transfection) in MCF-7 cells. Proliferation, migration assays were applied. Real-time PCR and western blot were used to detect RNA and protein levels of E-cadherin and its negative regulator Slug. Immunofluorescence staining was used to detect E-cadherin localization.

Results: Proliferation was not altered by Δ40p53. However, when Δ40p53 was highly expressed, MCF-7 cells migrated slower. In these cells, E-cadherin was upregulated, while Slug was downregulated. Migration assays showed that knocking down Δ40p53 had the reverse effect, in that cells migrated faster, though the expression of either E-cadherin or Slug was not significantly altered.

Conclusions: These studies have demonstrated a novel role for Δ40p53 in the migration of MCF-7 breast cancer cells and this has never been demonstrated.

Translational research aspect: Modification of Δ40p53 expression in breast cancer may provide new strategies to treat breast cancer.

OR6

REDUCED EXPRESSION OF THE PROTEIN PHOSPHATASE 2A REGULATORY SUBUNIT B55α: IMPACT ON LUMINAL B BREAST CANCER CELLS PROGRESSION AND DNA DAMAGE REPAIR

Abdul Mannan[1,2], Nikita Panicker[1,2], Richard Kahl[1,2], Matthew Dun[1,2], Kathryn Skelding[1,2], Nicole Verrills[1,2]

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[2]*School of Biomedical Sciences & Pharmacy, University of Newcastle, Callaghan, New South Wales, Australia*

Background: Breast cancer is the most frequent female cancer. The serine/threonine protein phosphatase PP2A encompasses a structural, regulatory and catalytic subunit. Previous work has shown that low level of the B55α subunit is associated with poor outcome in luminal B breast cancer patients – a subtype of patients that currently do poorly with standard therapies. Furthermore, molecular knockdown of B55α induces a tumorigenic phenotype in 3D cultures of normal mammary epithelial cells. B55α-containing PP2A complexes have previously been shown to be pivotal in homologous recombination-DNA double strand repair. Therefore, *we hypothesized that B55α-low tumors will be more aggressive, have impaired DNA damage repair and be more sensitive to DNA-damaging agents and/or PARP inhibitors.*

Aims: To determine the role of reduced B55α expression in breast cancer and DNA damage repair pathways.

Methods: B55α expression was inhibited using shRNA in the ZR-751 and BT474 luminal B breast cancer cell lines. Trans-well inserts (Corning, Massachusetts, USA) +/– matrigel (Trevigen®, Maryland, USA) were used to evaluate cell migration and invasion. For cytotoxicity and cellular survival in low-serum resazurin, metabolic assay was used. DNA damage repair

efficiencies were determined by immunofluorescence and confocal microscopy after bleomycin (radiomimetic) induced DNA damage.

Results: BT474-shB55α cells showed a marked change in cell morphology, with evidence of epithelial-mesenchymal transition, however, no changes were observed in ZR-751-shB55α cell morphology. BT474-shB55α cells showed significantly enhanced cell migration, matrigel invasion and survival in 0.2% serum media, and were significantly more sensitive to the PP2A-activating drug, AAL(S), compared with shRNA control cells (shCon). ZR751- and BT474-shB55α cells showed sustained γH2AX foci (double-strand DNA damage marker) post-Bleomycin treatment, compared to shCon cells. Prolonged activation of ATM (pSer1981) was also observed in ZR751-B55α knockdown cells.

Conclusions: B55α-low cells show an aggressive phenotype and have compromised DNA damage repair.

Translational research aspect: T1: If B55α-low tumors are sensitive to PP2A and/or DNA-damaging agents, this paves the way for novel therapeutic options for these poorly responding breast cancer patients.

OR7

QUANTITATIVE, HIGH-RESOLUTION PROTEOMICS FOR A SYSTEMS BIOLOGICAL ANALYSIS OF ACUTE MYELOID LEUKEMIA

Jonathan Sillar[1], Heather Murray[1], Juhura Al Mazi[1], David Skerrett-Byrne[2], Richard Kahl[1], Hayley Flanagan[1], Nathan Smith[3], Honggang Huang[4], Hubert Hondermarck[1], Andrew Wei[5], Charles de Bock[6], Jan Cools[6], Anoop Enjeti[7], Martin Larsen[4], Nicole Verrills[1], Matthew Dun[1]

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[4]*Department of Molecular Biology and Biochemistry, Protein Research Group, University of Southern Denmark, Odense, Denmark*

[5]*Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria, Australia*

[6]*University of Leuven, Department of Human Genetics, VIB, Leuven, Belgium*

[7]*Calvary Mater Hospital, Newcastle, New South Wales, Australia*

Background: Initiation and progression of cancer is regulated by a multistage process linked to the production of reactive oxygen species (ROS) that induce DNA damage. Patients diagnosed with recurring mutations to the FMS-like tyrosine kinase-3 (FLT3) receptor tyrosine kinase in acute myeloid leukaemia (AML) have a high rate of relapse and poor prognosis. FLT3-ITD (Internal Tandem Duplication) mutations are associated with the overproduction of ROS, leading to a state of hyper-genomic instability.

Aims: To determine the cooperation between phosphorylation and oxidation in AML patient samples to reveal improved drug targets.

Methods: Bone marrow-derived mononuclear cells from 16 AML patients were subjected to high-resolution data-dependent proteomic analysis. Validation of results was achieved using a panel of AML cell lines, by immunoblot and targeted mass spectrometry. The types and source of ROS were identified using flow cytometry. Novel drug targets were identified, and repositioned drugs tested using growth, survival and apoptosis assays. In vivo mouse models are being employed to determine the clinical utility of our novel therapies.

Results: High resolution proteomics facilitated the quantification of 2,678 unique phosphoproteins, and 4,029 proteins affected by oxidation across 16 samples. Patients expressing FLT3-ITD mutations (n = 6) showed significantly increased oxidation of tumour suppressor proteins compared to patients expressing the wild-type (FLT3-WT) receptor (n = 6). Significant activation of oncogenic kinases such as the proto-oncogene tyrosine-protein kinase (SRC), mitogen-activated protein kinase (MAPK), RAC-alpha serine/threonine-protein kinase (AKT) and pathways responsible for error-prone DNA repair were also observed. Interestingly, proteins used to maintain cellular homeostasis, such as antioxidants were differentially regulated between patient subtypes supporting the notion of REDOX dysfunction in ITD patients. FLT3-ITD AML cells were highly sensitive to pharmacological inhibition of REDOX signalling pathways.

Conclusions: For the first time, we reveal how recurring mutations to an oncogenic kinase increase oxidative stress, damage DNA, genomic instability and influence resistance to therapies. Inhibition of the pathways responsible for overproduction of ROS selectively sensitizes FLT3-ITD cells to therapies.

Translational research aspect: T1-2: This study provides never before seen proteomic coverage of the AML phosphoproteome and cysteine-oxidome and provides novel targets for new therapies.

OR8

A COMPARISON BETWEEN DATA-DEPENDENT ANALYSIS AND HIGH-RESOLUTION ACCURATE MASS TARGETED PROTEOMICS APPROACHES FOR THE QUANTIFICATION OF PLASMA BIOMARKERS IN COLORECTAL CANCER

Juhura (Trisha) Al Mazi[1], Nicole Verrills[1,2], Nathan Smith[3], Peter Pockney[4], Hubert Hondermarck[1], Matthew Dun[1,2]

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Background: Colorectal cancer (CRC) is the second most common cause of cancer-related mortality. Despite progress in treatment options for advanced staged disease, the clinical outcomes remain poor. Several plasma biomarkers are currently used for diagnosis, including carcinoembryonic antigen (CEA); however, the significance of CEA overexpression in CRC and its abundance in plasma remains controversial due to its expression in benign tumors. Therefore, improved detection and monitoring techniques coupled to better diagnostic and prognostic biomarkers are needed to improve the survival of these patients.

Aims: To determine the optimal collection and storage procedure for mass spectrometric analysis of CRC plasma specimens obtained from the Sequential Blood Collection initiative of the Hunter Cancer Biobank. Utilize high-resolution mass spectrometry to identify new and existing CRC biomarkers from patient's plasma samples pre- and postsurgery.

Methods: Plasma samples were obtained from the Hunter Cancer Biobank. Albumin depletion was achieved using the ProteoPrep Blue Albumin Depletion kit (Sigma-Aldrich, Saint Louis, MO, USA). Plasma proteins were digested using Trypsin/LysC enzyme mix. Data-dependent analysis (DDA) and targeted analysis (parallel reaction monitoring – PRM) were conducted on the HR/AM Q Exactive Plus (ThermoFisher Scientific, Carlsbad, CA, USA) mass spectrometer. Data analysis was performed using a combination of Proteome Discoverer (ThermoFisher Scientific, Carlsbad, CA, USA), Microsoft Excel (Microsoft, Redmond, Washington, USA), Skyline (MacCoss Lab, University of Washington, USA) and Prism (GraphPad Software, La Jolla, CA, USA).

Results: DDA quantitatively identified over 2000 plasma proteins with ~6000 unique peptides. Known CRC biomarkers, such as; Alpha-1-acid glycoprotein1, Gelsolin and Lumican were identified. Interestingly, novel markers such as Ficolin-3, 5-hydroxytryptamine receptor 2A and Plasma protease C1 showed increased abundance in patient samples pre-resection that no longer showed elevated expression post-surgery. Targeted PRM analysis identified

additional biomarkers not identified using DDA (CEA and the novel marker uPAR).

Conclusions: Our study provides quantitative data for the best method for collection and storage of blood samples for proteomics. Future directions will resolve the clinical utility of the new biomarkers we have identified to potentially aid in improved diagnosis and subsequent selection of personalized therapies.

Translational research aspect: Improved monitoring, diagnosis, prognosis and treatment selection in CRC will be aided by the development of better detection methods of plasma biomarkers. Our data span the T1–T2 spectrum of translational research.

OR9

A MICROFILAMENT PROTEIN AS A MASTER SWITCH AT THE INTERSECTION OF SURVIVAL SIGNALING PATHWAYS IN MELANOMA

Lei Jin[1], Hessam Tabatabaee[2], Xu Guang Yan[2], Jia Yu Wang[2], Yuan Yuan Zhang[1], Hamed Yari[2], Ting La[2], Fen Liu[2], Chun Yan Wang[2], Fu Xi Lei[2], Simonne Sherwin[2], Margaret Farrelly[2], Su Tang Guo[2,3], Chen Chen Jiang[1], Xu Dong Zhang[2]

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Background: We have previously shown that a microfilament protein (MP) is upregulated and promotes melanoma cell proliferation. Here, we reveal that this MP regulates activation of the serine-threonine protein kinase AKT and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) upon mitogen-activated protein kinase inhibitor (MAPKi) treatment, which contributes to resistance of melanoma cells to MAPK inhibition.

Aims: To define the role of the previously identified MP in regulating sensitivity of melanoma cells to MAPKi.

Methods and Results: Knockdown of the MP by shRNA increased melanoma cell death upon MAPKi treatment, which was associated with diminished activation AKT and NF-κB. However, the enhancement in killing was abolished by introduction of an active form of Akt (myr-AKT) or a constitutively active form of IκB kinase 1 (cIKK1) that resulted in hyperactivation of NF-κB. On the other hand, overexpression of the MP protected melanoma cells from MAPKi-induced cell death, which was correlated with elevation in AKT and NF-κB activation. Strikingly, the MP was physically associated with Akt in melanoma cells, driving membrane translocation and subsequent activation of AKT upon MAPK inhibition. Meanwhile, MAPKi treatment enhanced the binding between the MP and receptor-interacting protein kinase 1, promoting the activation of NF-κB. Our studies also showed that the expression of the MP was reversely correlated with the sensitivity of melanoma cells to MAPKi irrespective of their mutational status of *BRAF* and *NRAS*.

Conclusions: The identified MP protects melanoma cells from MAPKi-induced cell death through activation of NF-κB and Akt.

Translational research aspect: This study is currently at its T1/2 stages. The results will potentially lead to identification of the MP as a biomarker predictive of the response of melanoma cells to MAPKi. Whether the MP is targetable in the treatment of the disease needs further studies.

OR10

PROSTATE CANCER EXTRACELLULAR VESICLES: FRIEND OR FOE

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Background: Prostate cancer is the most common cancer diagnosed in males, and current treatments are associated with high rates of side-effects that compromise quality of life. Further, the lack of definitive biomarkers to identify men who need treatment from those with indolent disease means many men experience these side-effects unnecessarily. Noninvasive sources of biomarkers such as extracellular vesicles (EVs) hold promise for improving outcomes for prostate cancer; patients, however, remain poorly characterized to date. EVs are small spherical-shaped vesicles, which are secreted from their tissue of origin and contain high amounts of noncoding RNAs. Due to their role in cell–cell signaling, EVs are also proposed to drive metastasis through the delivery of cargo and thus their study may also identify novel therapeutic targets for metastatic disease.

Aims: The overarching aim is to identify components of EVs that are potential biomarkers or therapeutic targets for prostate cancer.

Methods: EVs were collected by ultraconcentration from media after 48 h of culture of a range of normal prostate, primary prostate cancer and metastatic prostate cancer cell lines. Characterization of the EVs has been conducted to identify components of interest. Nucleic acid cargo has been identified using Affymetrix whole transcriptome arrays, and lipidomics and proteomics being conducted. Functional analysis of EVs will be used to determine key EV molecules of significance in the identification and treatment of metastatic prostate cancer.

Results: Promising biomarkers have been identified within the nucleic acid cargo of EVs. In particular, a number of noncoding transcripts specifically discriminate EVs from cell lines generated from metastatic sites versus prostate cancer and normal cell lines. Differential incorporation of lipid classes including glycolipids and sphingolipids was also observed in EVs arising from metastatic versus normal cell lines. In addition, preliminary analyses of the proteome identified proteins with functions such as cell adhesion as differentially incorporated in exosomes.

Conclusions: EVs have the potential as a source of prognostic biomarkers that can distinguish metastatic prostate cancer from prostate cancer. Differences in protein cargo suggest that EVs are likely contributing to the metastatic process and therefore may be a future therapeutic target to prevent metastasis. Importantly, EVs could be collected from blood samples and thus reduce the need for invasive biopsy to identify metastatic prostate cancer.

Translational research aspect: This work is in the T1 stage, with the potential to be translated to prognostic or diagnostic biomarkers or therapeutic targets in the future.

OR11

ENFORCEMENT STRATEGIES FOR EFFECTIVE SMOKE-FREE POLICY IMPLEMENTATION: A SYSTEMATIC REVIEW

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Background: Enforcement strategies are often cited as critical to the initial success and adoption of a smoke-free policy; however, there is limited literature guiding their implementation and use.

Aims: A systematic review of the effectiveness of enforcement strategies that aim to facilitate the implementation of and compliance with smoke-free environment policies relating to both the person(s) responsible for the smoke-free space and to individual smokers was conducted.

Methods: Medline, Medline in Process, The Cochrane Library, Embase, PsycInfo and CINAHL databases were searched using MeSH and keywords for relevant studies published between January 1980 and September 2015. A

methodological quality assessment and narrative analysis of included studies was undertaken.

Results: Twenty-four studies were identified; 19 related to the person(s) responsible for the smoke-free space, 4 studies related to the behavior of the individual smoker and 1 related to both. Policy promotion and awareness raising activities, signage and enforcement officers or penalties for violations were the enforcement strategies most frequently cited as being associated with successful policy implementation. In terms of compliance, total smoke-free bans were easier to comply with compared to policies that had only partial restrictions. Additionally, workplaces were more likely to comply with smoke-free policies where they were aware of the laws, had nonsmoking management and lower staff smoking rates and were members of a network guiding the policy implementation.

Conclusions: This review outlines enforcement strategies necessary for the successful implementation of smoke-free policies as well as factors to consider that may impact on policy compliance.

Translational research aspect: Traditionally, the responsibility has been on the introduction of smoke-free policies across a range of environments and settings. However, there is limited information available to guide the inclusion of effective enforcement strategies that translate to increased policy compliance. This research is in T3 stage on the translational pipeline.

OR12

ASSESSING AND VALIDATING AN EDUCATIONAL RESOURCE PACKAGE FOR THE MANAGEMENT OF SMOKING CESSATION IN INDIGENOUS PREGNANT WOMEN

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Background: Indigenous pregnant women have a high smoking prevalence (47%). Health providers (HPs) report lack of adequate resources. Messages need to be tailored to ensure saliency, cultural-sensitivity and account for Indigenous population diversity. The ICAN QUIT in Pregnancy intervention aims to improve HP's management of smoking in Indigenous pregnant smokers. A resource package was developed collaboratively with two Aboriginal Community Controlled Health Services (ACCHS).

Aims: To assess the scientific accuracy, cultural acceptability, perceived useability and readability of the resources.

Methods: A multicentered community-based participatory process, with four ACCHS from NSW, SA and QLD. A four-step process included: (i) scientific review by a multidisciplinary expert panel (10 members); (ii) scoring for "Suitability of Materials" by two Aboriginal Health Workers. Mean overall score and inter-rater agreement will use Cohen's kappa coefficient; (iii) focus groups – two groups (HPs and community members) in each ACCHS will explore views about the resources and opportunities for improvement; and (iv) readability scores: an average level of grade 5 for patient's resources and grade 10 for HP's resources.

Results: Major themes from the scientific panel and suitability assessment of material (SAM) evaluation included "High attraction", "Simplifying the resources" and "Additional information (depression/e-cig/stress)." Average readability score was grade 6 (patient resources, range 0.2–12.5) and grade 9.4 (HP's resources, range 4.7–31.4). Results from focus groups discussions will be presented in reference to predefined themes. Resources will be adjusted accordingly.

Conclusions: This process will ensure that materials used for ICAN QUIT in Pregnancy are culturally sensitive and evidence-based. This formative evaluation technique has never been done in Australia. If effective, it could be adapted for other Indigenous interventions and culturally diverse programs.

Translational research aspect: This is a T2–T3 research using knowledge from previous research with Indigenous women and HPs, and evidence-based approaches to managing smoking in pregnancy, to develop and implement an intervention within ACCHS.

OR13

EATING AS TREATMENT (EAT): A HEALTH BEHAVIOR CHANGE INTERVENTION TO IMPROVE TREATMENT OUTCOMES FOR HEAD AND NECK CANCER PATIENTS UNDERGOING RADIOTHERAPY

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Background: Malnutrition is a significant problem in the head and neck cancer (HNC) population and is associated with an increase in complications due to side-effects of treatment as well as increased morbidity.

Aims: A dietitian-delivered health behavior change intervention was implemented to reduce malnutrition in HNC patients undergoing radiotherapy: Eating as Treatment (EAT).

Methods: A stepped wedge cluster randomized design was used. Dietitians were trained in the EAT intervention, including both intervention-specific skills and behavior change counseling (BCC) skills. Practice change strategies were also implemented to improve intervention adherence and care according to evidence-based dietetic guidelines.

HNC patients were recruited from radiotherapy departments in four Australian sites. The primary outcome of nutritional status, as measured by the Patient Generated Subjective Global Assessment, was analyzed using generalized linear mixed models. Dietitian adherence to BCC and study-specific techniques were assessed using a 20% random sample of audio recorded and coded dietetic sessions. Frequencies of patients of whom evidence-based guidelines were implemented were assessed via audiotape and medical record audits. The change in the odds of implementation was assessed via logistic regression.

Results: The intervention was effective in significantly reducing malnutrition $P = 0.025$. Relative to pretraining, application of both study-specific skills and BCC was significantly greater. For four of the evidence-based guidelines, the estimated odds ratio was significantly different to 1.

Conclusions: EAT is a potentially cost-effective intervention for changing the behavior of dietitians, promoting improved compliance with guidelines and improving cancer patient outcomes.

Translational research aspect: This trial tested the effectiveness of an innovative dietitian-delivered health behavior change intervention (T2) and included practice change strategies to improve system wide uptake of the intervention including care according to evidence-based guidelines (T3).

OR14

A METHOD FOR REMOTE AUDITING OF RADIOTHERAPY MACHINES

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Background: In radiotherapy, precise targeting is required to kill cancer cells and minimize impact on healthy cells. The dose delivered by radiation treatment machines is audited by independent organizations. Conventional audits are performed through site visits or mailing dosimeters to the centers, involving either high cost or increased measurement uncertainties.

Aim: This study lays the foundation for remotely auditing of radiotherapy machines. Using center images from readily available electronic imagers, it measures central pixel value (CPV) and gravitational sag of the imager and. It then models delivered dose.

Method: Images of eight centers were used in this pilot study. CPV: Two 10 × 10 cm^2 images with different collimator angles were used to determine CPV. Values of 50% points of each image width were calculated using linear interpolation and then, they were normalized to approximate CPV. Mean value of the points was considered as CPV. Sag: 10 × 10 images acquired at every 45° gantry angle were employed to model sag values. CPV of 0° image was calculated and compared with CPV of images acquired at other angles. The difference versus gantry angle showed best fit with first order of Fourier series. Finally, the corrections are used to model complex delivered dose distributions.

Results: CPV and sag were modeled for each center. Sag parameters were identified with 99.2% (SD: 0.94%) mean R-square fitting over the centers. Applying the corrections, delivered open field doses were modeled with mean isocenter dose discrepancy of 0.04% (SD: 0.11%).

Conclusion: The characterization method could be consistently applied to all centers. The remote audit approach is inexpensive and fast. It is feasible since all radiotherapy machines are equipped with similar imagers.

Translational research aspect: This project falls into the T1–T2 translational pipeline. Fundamental research on imagers resulted in a novel application for remote assessment of treatment delivery at various centers.

OR15

REPURPOSING CHEMOTHERAPY TO TARGET THE IMMUNE SYSTEM IN MELANOMA

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Background: Melanoma is difficult to treat once resistance to immunotherapies occurs. Overcoming resistance may be achieved by repurposing chemotherapy, such as carboplatin. Global genome repair (GGR) is critical for recognizing DNA damage caused by carboplatin. Xeroderma pigmentosum Complementation Group C (XPC), a component of GGR, is not induced in response to carboplatin in melanoma resulting in extreme resistance. There is evidence that methylation suppresses XPC. 5-aza-2'-deoxycytidine (decitabine) is a chemotherapy that results in global loss of methylation and re-expression of genes. We hypothesized that restoring expression of XPC in melanoma using decitabine could overcome resistance to carboplatin; while also increasing the tumor mutation load and expression of tumor neoantigens, reinstating immune sensitivity.

Aims: To investigate the effect of sequential decitabine and carboplatin XPC methylation, transcript expression and subsequent apoptosis in melanoma.

Methods: XPC mRNA and protein expression were quantified in 196 melanoma cases and the cancer genome atlas (TCGA) data. Melanoma cell lines were treated with decitabine or carboplatin alone, or in sequential combination. XPC transcript, apoptosis, proliferation, senescence, global and CpG island shore demethylation were quantified.

Results: XPC was low in melanoma tumors and correlated with poor survival. Carboplatin alone did not induce XPC or apoptosis. Decitabine decreased global methylation (–44.67%) and increased XPC (0.9–3.0 fold). Demethylation in the XPC CpG island shore was detected. After sequential decitabine/carboplatin, a greater XPC induction (1.5–7.6 fold) occurred with significantly increased apoptosis (1.6–2.2 fold), decreased proliferation and increased senescence.

Conclusions: Our results confirm that demethylation and DNA damage using decitabine and carboplatin elicits a response in vitro.

Translational research aspect: A pilot phase 2 clinical trial to test this combination has commenced. This will allow further analysis to determine if this combination can be used to reinstate immune sensitivity and response to immunotherapy.

OR16

THE INCIDENCE OF SEVERE THROMBOCYTOPENIA IN GLIOBLASTOMA PATIENTS UNDERGOING COMBINED CHEMORADIOTHERAPY: A SINGLE CENTER EXPERIENCE

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Background: Glioblastoma multiforme (GBM) is the most common primary brain tumor and has a poor prognosis. Standard treatment comprises Temozolomide chemotherapy combined with radiotherapy followed by temozolomide alone. The registration trial for temozolomide demonstrated a 14% incidence of severe thrombocytopenia (3% during chemoradiotherapy and 11% during chemotherapy alone). Anecdotal experience suggests that the incidence is higher and as such, a retrospective review at our institution was undertaken.

Aims: To determine the incidence of severe thrombocytopenia and its relationship to survival.

Methods: Patients with GBM treated at the Calvary Mater Newcastle between February 2009 and September 2015 were reviewed following ethics approval. Incidence, timing and CTCAEv4.0 grading (Gr 3: platelets 50.0–25.0 × 10^9/L; Gr 4: platelets <25.0 × 10^9/L) of severe thrombocytopenia were determined. Overall survival was assessed using the Kaplan–Meier function. Differences in time to death were estimated via a Cox proportional hazards regression model adjusted for age and sex.

Results: A total of 118 patients were reviewed. Nineteen (16%) patients develop severe thrombocytopenia. This was mainly Gr 4 (16 of the 19 patients). The majority (12 patients, 75%) of patients with Gr 4 thrombocytopenia developed this during chemoradiotherapy. All patients with Gr 3 thrombocytopenia developed this during chemotherapy alone. Median overall survival was similar between nonthrombocytopenic patients (15.6 m) and thrombocytopenic patients (14.9 m). Thrombocytopenic patients had a trend to increased hazard of death (HR = 1.36, 95% confidence interval 0.72–2.59, P = 0.34).

Conclusions: In a real-world population, the incidence of thrombocytopenia is greater and appears to occur sooner than in the registration trial for temozolomide. The incidence is significant and while it does not appear to affect survival, there are consequences from severe thrombocytopenia on patient's future treatment options, quality of life and implications on health resources. A predictive biomarker toxicity is needed.

Translational research aspect: T4. Real-world experience with temozolomide demonstrates more toxicity than expected.

POSTER PRESENTATION

P1

ADDRESSING TOBACCO SMOKING IN A MEDICALLY SUPERVISED INJECTING CENTER WITH AN ORGANIZATIONAL CHANGE INTERVENTION: AN ACCEPTABILITY STUDY

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Background: Among people who inject drugs (PWIDs), the rate of smoking exceeds 90% making this population particularly susceptible to tobacco-related illnesses and in need of smoking cessation care (SCC). The Medically Supervised Injecting Centre (MSIC) may be a potential setting to address tobacco smoking among PWIDs.

Aims: This study aimed to assess the acceptability of an organizational change intervention to integrate SCC into usual care practice at a MSIC. In addition, provision of SCC as reported by staff and clients was also explored.

Methods: Online cross-sectional surveys with staff and clients were conducted pre- and post-implementation of an organizational change intervention. The intervention consisted of six core components: engaging organizational support, identifying a SCC support champion, promoting the center's tobacco smoking policy, implementing a smoker identification system, providing education and evidence-based SCC treatments.

Results: Over 85% of staff agreed that it was acceptable to address client smoking as part of usual care. From pre- to post-intervention staff self-reported delivery of SCC strategies significantly increased for the provision of verbal advice ($P = 0.001$), offer of free nicotine replacement therapy ($P = 0.000$), referral to a GP ($P = 0.008$) and follow-up to check on quit smoking progress ($P = 0.005$). Nearly all (94%) clients agreed that it was acceptable to be asked by staff about their tobacco smoking and the majority held positive attitudes toward receiving SCC, agreeing that it was helpful to talk to staff about their smoking (89%). In the post-intervention period, more clients reported receiving SCC ($P < 0.05$).

Conclusions: The organizational intervention was well-received, with high acceptability from both clients and staff.

Translational research aspect: This research will provide novel information to shape program development for smoking cessation care in MSICs. This is T3 research.

P2

ASSESSING THE INFORMATION NEEDS OF STAGE ONE TESTICULAR CANCER PATIENTS AND THEIR CARERS

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Background: Chemotherapy or surveillance are recommended treatments for stage 1 testicular cancer patients, postsurgery. Both are equally effective, but have distinct pros and cons that may be valued differently, thus making treatment decisions preference sensitive. Decision aids are effective, and may help support these treatment decisions.

Aims: This is step 1 of a larger project aiming to develop and pilot test an online decision aid for testicular cancer patients, deciding between chemotherapy or surveillance postsurgery. This study aimed to assess the information preferences and needs of testicular cancer patients and their carers.

Methods: A retrospective, self-report survey of stage 1 testicular cancer patients, who attended one NSW-based treatment center in the last 12 months; and their carers. Eligible patients identified from clinical records were sent a questionnaire along with a questionnaire for their nominated carer. Participants could complete the questionnaire via pen-and-paper or online. Participants were also asked to consent to being contacted about future research. Those who agreed were invited to complete a semistructured telephone interview.

Results: Fourteen of 51 eligible patients (27%) and nine carers (18%) completed the questionnaire. All patients and carers indicated that they would have liked to receive information on the biological aspects of testicular cancer and possible treatment options. Over 90% of patients would have liked to receive information about: all possible side effects of cancer and treatment, available support services, signs, and symptoms to look out for and estimated life expectancy. Five patients and two carers completed an interview. Interview data emphasized that patients and carers would like written information about what to expect from treatment and cancer.

Conclusions: This information will be used to inform the development of a decision aid for testicular cancer patients.

Translational research impact: This is a descriptive study to inform a decision aid (T2/T3).

P3

TREATMENT QUALITY ASSESSMENT USING *IN VIVO* ELECTRONIC PORTAL IMAGING DEVICE (EPID) DOSIMETRY IN RADIOTHERAPY

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Background: Because of increasing complexity in modern radiotherapy, a comprehensive quality assurance (QA) practice is required. Traditional QA programs focus on the level of pre-treatment stage, which specifically ensures equipment's functionality and accuracy to meet the clinical standard expectation. However, QA at level of patient treatment delivery should be incorporated for treatment quality evaluation.

Aims: We aim to provide a quality assessment tools for: (1) individual patient treatment quality assessment and (2) identification of a "quality gap" from long-term treatment quality assessment. The ultimate goal of this research is to develop the treatment quality evaluation for continuous quality improvement for radiation therapy.

Methods: A statistical process control (SPC) was applied to evaluate treatment delivery using *in vivo* EPID dosimetry. A moving range control chart was constructed to monitor the individual patient treatment performance based on a control limit generated from initial data of 90 IMRT and 10 VMAT patient deliveries. A process capability index (Cpk) was used to evaluate long-term (September 2014–March 2015) treatment quality into three quality classes; treatment type-specific, linac-specific, and body site-specific.

Results: The determined control limits were 62.5% and 70.0% of the χ pass-rate (combination of dosimetric and geometric comparison matric) for IMRT and VMAT deliveries. Fourteen patients were selected for a pilot study, the results of which showed that about 1% of all treatments contained errors relating to unexpected anatomical changes between treatment fractions. Both rectum and pelvis cancer treatments at our center demonstrated Cpk <1, indicating the potential for quality improvement.

Conclusions: Assessing *in vivo* EPID dosimetry with SPC can be used to access the treatment quality in radiotherapy. Our proposed method is a valuable tool for assessing the accuracy of treatment delivery whilst also improving treatment quality and patient safety.

Translational research aspect: This project falls into the T1–T2 translational pipeline.

P4

HD-SNP MICROARRAY ANALYSIS OF THE STUDY NINE HIGH-RISK ALL PATIENTS – PROVIDING KEY PROGNOSTIC INFORMATION USING ARRAYS

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Background: Currently, standard clinical practice for the genomic investigation of paediatric acute lymphoblastic leukemia (ALL) utilizes bone marrow for standard G-banded karyotype, reverse transcription polymerase chain reaction (RT-PCR) or extensive fluorescence in situ hybridisation (FISH) testing translocations, rearrangements and ploidy changes. The characterization of such aberrations is often difficult and the abnormal clone(s) are missed using standard techniques such as karyotyping. SNP microarrays are useful in the detection of gains, losses and copy neutral loss of heterozygosity (cnLOH) not otherwise detectable using conventional karyotype in ALL and other hematological malignancies.

Aims

1. To identify additional genomic changes which were not detected by current clinical methodologies using SNP-HD microarray.
2. To assess the added value of SNP-microarray in a clinical setting for refining risk stratification.

Methods: A blinded pilot study performed on 23 high-risk ALL patients with DNA extracted from whole bone marrow (BM) taken at diagnosis and/or at relapse was supplied by the Lowy Research Institute. These samples are part of the Australasian arm of the Associazione Italiana di Ematologia Oncologia Pediatrica – Berlin-Frankfurt-Münster (AIEOP-BFM) ALL 2009 study.

High-density SNP-microarray was performed on the Affymetirx HD platform.

Data was analyzed blinded using the ChAS software supplied by Affymetrix.

SNP array results were compared to karyotype and FISH results supplied by the (AIEOP-BFM) ALL 2009 study.

Results: Abnormality detection rate increased from 57% (13/23) of samples karyotyped and 48% (11/23) of samples analyzed by FISH to 100% of samples analyzed by high definition single nucleotide polymorphism (HD-SNP)-microarray. Aberrations were defined with higher accuracy in terms of breakpoint analysis, complexity and clonal involvement utilizing the HD SNP-microarray. Important microdeletions, including IKZF1, PTEN, CDKN2A and the fusion forming microdeletions of STIL-TAL1 and CSF2RA-IL3RA were identified by HD SNP-microarray and not detected by karyotype or FISH. Also, numerous regions or whole chromosome cn-LOH were also observed.

Conclusions: SNP-microarray analysis has the ability to substantially increase and improve the detection of prognostic genomic aberrations in paediatric ALL. This technology complements the current clinical and laboratory techniques (including minimal residual disease) for risk stratification and treatment of ALL at diagnosis.

Translational research aspect: The implications of identifying these genomic aberrations can be significant in terms of treatment selection, particularly if they are considered a target for potential therapies and improved risk stratification.

P5

APOPTOSIS-REGULATING LONG NONCODING RNAS IN MELANOMA

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Background: Long noncoding RNAs (LncRNAs) are a family of transcripts that do not encode proteins but are involved in regulating gene expression through interacting with DNAs, mRNAs and/or proteins. There is increasing evidence demonstrating that lncRNAs play important roles in the pathogenesis of cancer. Although we have demonstrated that resistance of melanoma cells to apoptosis is a major barrier in the curative treatment of melanoma, the potential significance of lncRNAs in regulating the apoptotic response in melanoma cells remains unknown.

Aims: To define the functional significance of lncRNAs regulating the sensitivity of melanoma cells to apoptosis.

Results: We generated melanoma cell sublines resistant to apoptosis by prolonged exposure of ME4405 cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which activates the extrinsic apoptotic pathway, and the Mcl-1 inhibitor (UMI-77) that induces apoptosis by activating the intrinsic apoptotic pathway. RNA sequencing identified a panel of lncRNAs that were commonly upregulated or downregulated in TRAIL-selected and UMI-77-selected melanoma cells compared with the parental counterparts. SiRNA knockdown of two of the upregulated lncRNAs resensitized selected melanoma cells to apoptosis induced by TRAIL or UMI-77. Moreover, knockdown of these lncRNAs also enhanced TRAIL- or UMI-77-induced apoptosis in parental melanoma cell lines. We are currently using the capture hybridization analysis of RNA targets (CHART) assay to identify potential DNA and protein targets associated with these lncRNAs.

Conclusions: LncRNAs are involved in regulating the sensitivity of melanoma cells to apoptosis. In particular, the two identified lncRNAs play important roles in resistance of melanoma cells to apoptosis induced by activation of either the extrinsic or intrinsic apoptotic pathway. Targeting lncRNAs may be useful in overcoming resistance of melanoma to therapeutics that induce apoptosis.

Translational research aspect: This project is currently at its T1 stage. It has the potential to advance to T2 and subsequently T3/4 stages depending on results from follow-up experiments.

P6

THE OLIVE PHENOLIC COMPOUNDS APIGENIN, LUTEOLIN AND OLEUROPEIN INDUCE CELL-CYCLE ARREST AND APOPTOSIS IN PANCREATIC CANCER CELLS *IN VITRO*

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Background: Pancreatic cancer is a devastating disease with a 5-year survival rate of less than 5%. The heterogeneity of the disease, resistance to conventional treatment options and toxicity of current chemotherapy agents (FOLFIRINOX, gemcitabine) makes pancreatic cancer an important target for the development of novel therapeutic agents. Individual compounds isolated from olive products have been investigated extensively for their anticancer activity in cancers of the breast, colon, prostate and leukemia, however there is limited research into their effects against pancreatic cancer.

Aims: This study aimed to assess the antipancreatic cancer potential of individual olive phenolic compounds.

Methods: Pancreatic cancer (BxPC-3, CFPAC-1, MiaPaCa-2), and normal human pancreatic ductal epithelial (HPDE) cells were treated with oleuropein, hydroxytyrosol, myrictin, luteolin and apigenin. Cell viability was assessed using the CCK-8 viability assay. The induction of apoptosis was assessed by way of caspase 3/7 activation and cell-cycle analysis was performed using a MUSE flow cell analyzer.

Results: Most notable results include the IC_{50} values for luteolin and apigenin on BxPC-3 cells (10 and 12 μM, respectively) and CFPAC-1 cells (22 and 25 μM, respectively). Apigenin also induced G2-phase arrest in both CFPAC-1 and BxPC-3 cells. Interestingly, MiaPaCa-2 pancreatic cancer cells treated with a high dose of oleuropein (200 μM) resulted in viability of 4%, whereas no effect was observed for the normal pancreas (HPDE) cells at this concentration. After treatment of MiaPaCa-2 cells with 100 μM of oleuropein, a significant induction of apoptosis, as measured by increased activation of caspase 3/7, was observed.

Conclusions: Olive phenolic compounds demonstrate selective toxicity toward different pancreatic cancer cell lines, with oleuropein displaying no toxicity to normal pancreatic cells and, therefore, warrant further investigation.

Translational research aspect: This study aligns with the T1 translational pipeline in that is assessing the *in vitro* potential of novel chemotherapeutic agents for pancreatic cancer.

P7

INFLUENCE OF MICROENVIRONMENT IN ENDOMETRIAL CANCER PROGRESSION

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Background: The tissue microenvironment maintains the integrity of normal tissue architecture, whereas disruption of homeostasis between cells and surrounding stroma leads to tumor development and metastasis. However, the molecular signals derived from stromal cells and/or extracellular matrix (ECM) that are responsible for the modulation of indolent tumors to malignant state is currently unclear.

Aim: To investigate the signaling alteration in uterine stroma or ECM that promotes endometrial cancer (EC) growth and metastasis.

Methods: 3D culture, cell proliferation, survival and invasion assays, Western blot, immunofluorescence, RNA seq, Q-PCR, *in vivo* tumorigenicity assay and histopathological analysis of human EC patient tissue samples.

Results: 3D culture of 10 different EC cell lines revealed distinct glandular and non-glandular colonies. We investigated differentially expressed genes in 3D versus monolayer-cultured (2D) cells and identified that the members of TGFβ signaling pathway were most upregulated in EC spheroids forming nonglandular colonies than glandular colonies. Nonglandular cells displayed overexpression of pSmad2 (>2-fold) in 3D matrix suggesting ECM regulates TGFβ signaling. In 3D culture, TGFβ1 treatment increases pSmad2 protein expression in glandular cells. SB431542 (TGFβ signaling inhibitor) decreases basal level pSmad2 protein expression, proliferation and invasion of nonglandular cells ($P < 0.01$). 3D cultured endometrial cancer cells distinctly expressed EMT markers. TGFβ1 treatment disrupted polarized structure of glandular cells, whereas SB431542 treatment induced reverted glandular morphology of nonglandular cells. Suppression of TGFβ signaling in mouse xenograft model decreases aggressive EC metastasis. Overexpression of pSmad2 was observed in metastatic cancer tissue samples compared to primary endometrial tumors ($n = 50$; same patient or age matched).

Conclusion: ECM-derived chronic upregulation of TGFβ signaling promote aggressive EC metastasis.

Translational research aspect: Currently, patients with metastatic EC have a poor prognosis. Our results suggest that targeting TGFβ signaling might be of potential application to suppress EC metastasis and improve clinical outcomes in EC patients (T1, T2).

P8

DNA-PK INHIBITION SENSITIZES FLT3-ITD AML CELLS TO CYTARABINE AND SORAFENIB

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Background: Acute myeloid leukaemia (AML) carries a 5-year survival rate of just 24%. Current treatments include high-dose chemotherapy and bone marrow transplantation; however, development of chemotherapy resistance and relapse is common. Internal tandem duplication (ITD) mutation of the receptor tyrosine kinase FLT3 is the most recurrent driver mutation in AML, leading to poor prognosis and increased risk of relapse. Therapeutic inhibition of FLT3 has proven difficult to achieve, with FLT3 inhibitors displaying limited success as single agents.

Aims:

1. Characterize oncogenic signaling pathways downstream of FLT3-ITD.
2. Investigate drug ability of identified pathways.

Methods: The phosphoproteomes of six AML patient blast samples (three FLT3-ITD, three FLT3-wild type) were evaluated by mass spectrometry, and pathways differentially phosphorylated were identified using ingenuity pathway analysis. Validation of results was performed in a panel of AML cell lines using immunoblot. Drug sensitivity was tested using resazurin assay and synergy assessed using the method of Webb.

Results: Analysis of differentially expressed phosphoproteins in FLT3-ITD versus FLT3-wild type AML patient blasts revealed dysregulation of DNA repair pathways, with increased phosphorylation of the non-homologous end joining (NHEJ) pathway ($P = 0.0006$). Targeting NHEJ by inhibition of core component DNA-PK induced selective toxicity in FLT3-ITD cell lines. Cytarabine administration combined with DNA-PK inhibition elicited synergistic cell death in FLT3-ITD but not FLT3-wildtype AML cell lines. Similarly, the FLT3 inhibitor sorafenib displayed synergy in combination with DNA-PK inhibitors, in FLT3-ITD cells.

Conclusions: Our data shows that FLT3-ITD AML is associated with activation of the error-prone NHEJ pathway, which may contribute to

genomic instability. Targeting DNA-PK in combination with standard therapeutic agents has the potential to improve outcome for this AML subtype.

Translational research aspect: T1-2: This study provides phenotypic information about FLT3-ITD AML, and identifies potential novel treatment strategies which are currently being tested in animal models and may lead to clinical trial.

P9

QUANTIFYING INTERVENTION ENGAGEMENT IN A RANDOMIZED CONTROLLED TRIAL OF ONLINE VERSUS TELEPHONE-BASED INFORMATION AND SUPPORT FOR LUNG CANCER PATIENTS

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Background: Lung cancer patients commonly experience poorer prognosis, more severe physical effects and more prominent psychosocial distress than patients with other major cancers. The Cancer Council's Information and Support service in each state provides an easily accessible and ongoing source of tailored support for cancer patients. The service is underutilized by lung cancer patients, and similarly, despite the advantages and growing accessibility of online interactive cancer support services, many cancer patients still do not engage with these services. As part of a randomized controlled trial exploring the relative effectiveness of telephone versus online support, participants' engagement with the two forms of the service was examined.

Aims: To identify the proportion of participants allocated to the intervention (telephone and online chat) arms of the OPAL trial who interacted with service staff.

Methods: A total of 262 newly diagnosed lung cancer patients were recruited from cancer diagnosis and treatment services around Australia (31 clinics). The NSW Information and Support service was engaged to provide telephone and online-based support to lung cancer patients participating in the trial. Following randomization to the telephone or online support arms, participants will be sent an allocation letter notifying them of their allocation. For telephone arm participants, a trained oncology nurse consultant will attempt to conduct one or more outbound phone call/s. For online chat arm participants, a reminder email and phone calls will be conducted to encourage service engagement. Data extracted from Cancer Council databases were used to assess engagement with the telephone and online services. The proportion of participants who engaged with the telephone or online chat service will be reported.

Conclusion: Levels of engagement with online support are relatively low. Further study data will be used to identify the patient factors affecting engagement with telephone and online support services to provide additional insight into effective ways to increase utilization of cancer support services.

Translational research aspect: This study represents the provision of telephone and online information and support to cancer patients and is therefore a T3 translational research project.

P10

'WULA[1]: VOICES OF ABORIGINAL WOMEN ON BARRIERS TO SEEKING AND ACCEPTING SMOKING CESSATION SUPPORT DURING PREGNANCY; FINDINGS FROM A QUALITATIVE STUDY IN HUNTER NEW ENGLAND DISTRICT, NEW SOUTH WALES

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Background: Pregnant Aboriginal and Torres Strait Islander women's smoking prevalence rates remain high compared to their non-Indigenous counterparts. *The National Closing the Gap Campaign* includes two key targets: reducing the number of babies born with low birth weight and reducing tobacco smoking during pregnancy by 2030. These targets have the potential to decrease the prevalence of cancer and chronic diseases for Aboriginal and Torres Strait Islander peoples.

Aims: To capture the voices of Aboriginal women and collect their stories about smoking and becoming smoke-free during pregnancy and their recommendations for improved support.

Methods: One on one interviews with 20 pregnant and recently pregnant Aboriginal women, smokers and ex-smokers, were conducted by a female Aboriginal Research Assistant across the Hunter New England Local Health District. The semistructured interviews were audio-recorded and transcribed. Independently analyzed – coding – thematic development – emergent themes.

Results: Through dialogue and story-telling, barriers to accessing and accepting support to quit smoking emerged. Primary themes included several barriers to smoking cessation: reliance on reduction in smoking, attitudes toward nicotine replacement therapy, inconsistent health professionals' advice. In addition, the women recommended strategies to support aboriginal women to successfully quit smoking during pregnancy such as community based models of cessation care, including group support and elders engagement.

Conclusion: There is a significant need to address the overrepresentation of Aboriginal women continuing to smoke during pregnancy. Improvements can be made to current clinical support offered to Aboriginal mothers through the engagement of group-based models of support, engagement of local community and elders and the development of culturally responsive interventions.

Translational research aspect: This is T3 research to develop new knowledge designed to improve practices in health behavior research.

P11

HYPERACTIVE MTOR SIGNALING IN AGED UTERI LEADS TO ENDOMETRIAL HYPERPLASIA AND CANCER

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Background: Endometrial cancer is one of the most invasive gynecological cancers and affects approximately 1 in 69 Australian women before the age of 75 years. Aging increases the risk of disease development as majority of endometrial cancer patients are postmenopausal. mTOR signaling is a major regulator of aging as suppression of this pathway extends lifespan in model organisms. Emerging evidence has revealed the role of mTOR signaling pathway in endometrial carcinogenesis. However, the exact mechanism through which mTOR signaling contributes to the functional and morphological changes in uterus of aged women is currently obscure.

Aims

1. To investigate the role of mTOR signaling in hyperplasia and cancer in aged uterus.

2. To test the therapeutic efficacy of mTOR inhibitors against endometrial cancer.

Methods: To evaluate if overactive mTOR signaling is responsible for hyperplastic changes in aged uterus, tissue samples were collected from postmenopausal women and mouse models: *Pten* heterozygous ($N = 9$, 7–8 months old), aged *Pten* overexpressing ($Pten^{tg}$, $N = 5$; 26–27 months) and 9-month old mice ($N = 28$) treated with rapamycin, an mTOR inhibitor, for 12 months. Pharmacological suppression of pathway was achieved by treatment of human endometrial cancer cells with two FDA-approved drugs, Everolimus and NVP BEZ235.

Results: The hyperplastic endometrium of postmenopausal women and aged mice exhibited elevated mTOR activity as seen with increased expression of pS6. Analysis of uteri from *Pten* heterozygous mice confirmed that overactive mTOR signaling leads to glandular crowding and formation of *in situ* carcinoma. In contrast, analysis of uteri from $Pten^{tg}$ and rapamycin-treated mice showed a significant reduction in hyperplasia and cancer as compared to controls. Furthermore, treatment with mTOR inhibitors reduced colony size and proliferation of endometrial cancer cells in 3D culture.

Conclusions: Hyperactive mTOR signaling contributes to the initiation and progression of endometrial cancer.

Translational research aspect: Therapeutic targeting of mTOR pathway can be used to prevent endometrial cancer (T1–T2).

P12

A CELL BASED *IN VITRO* MODEL IN ASSESSING THE EFFECTIVENESS OF NAIL LACQUER IN PROTECTING AGAINST UV PENETRATION: A PRECLINICAL MODEL

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Background: Patients undergoing systemic taxane chemotherapy often develop nail toxicity affecting quality-of-life. Although taxane-induced onycholysis (separation of the nail plate from the nail bed) has not been clearly linked with ultraviolet (UV) light exposure, it has been recommended that patients wear dark-colored nail lacquer to prevent photo-induced onycholysis while on taxane therapy. We endeavor to test the hypothesis that nail lacquer protects the nail bed from taxane-induced onycholysis and explore whether a more subtle colour tone could be utilized.

Aims: Our first aim was to test whether a panel of standard nail lacquers with a broad colour spectrum could protect skin cells from UV exposure. The nail lacquer with the greatest UV protection and with the most subtle colour tone will be chosen for further clinical assessment.

Methods: The ability of the nail lacquers to protect cells from UV exposure was determined by culturing human skin cells in the laboratory in 96-well plates with plastic covers coated with the various lacquers ($n = 7$ differing colour tones from clear to black) and exposing them to UV radiation for 30–1800 s. Standard cell biology methods were used to assess the status of the skin cells after 72 h.

Results: The results showed that all colored lacquers including neutral-beige equally protected the cultured skin cells against UV damage; however, the clear lacquer was equivalent to no-lacquer resulting in total cell death when exposed to UV radiation for more than 5 min.

Conclusions: Using a cell-based *in vitro* model, neutral-beige nail lacquer protected skin cells from UV-induced cell death. The benefit of neutral-beige nail lacquer in ameliorating docetaxel-induced onycholysis in the clinical setting is currently being explored in a pilot study at the Calvary Mater Newcastle. Results of this will be reported in due course.

Translational research aspect: T3 project implementing EBS into clinical practice.

P13

PURE COMPOUNDS FROM VIETNAMESE MEDICINAL PLANTS SHOW PROMISING ANTI-PANCREATIC CANCER ACTIVITY *IN VITRO*

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Background: Pancreatic cancer is a devastating disease with a dismal survival rate of only 5%. This is due to late diagnosis and aggressive, metastatic disease. Currently treatment typically consists of surgery and/or treatment with gemcitabine, a natural product-derived chemotherapeutic which only prolongs survival for 5–6 months at best and is not a curative treatment. Traditional Vietnamese medicinal plants have been used to treat a number of diseases for several thousands of years. Therefore, there is a strong need for novel, naturally occurring therapeutic options for pancreatic cancer.

Aims: To determine if purified compounds from Vietnamese medicinal plants exert anticancer activity *in vitro*.

Methods: Normal pancreatic epithelial cells (HPDE) and various pancreatic cancer cell lines (BxPC3, MiaPaCa2 and CFPAC1) were treated with pure compounds from Vietnamese plants at different concentrations for 72 h; cell viability was assessed using CCK8 assay to determine the extent of anticancer activity.

Results: Treatment of pancreatic cancer cell lines with Pristimerin and CT1 resulted in significant growth inhibition, with substantially lower IC50 values compared to a normal pancreatic cell line. Pristimerin displayed an IC50 of 111 nM in HPDE compared to an IC50 value of 64, 103 and 77 nM in MiaPaCa2, BxPC3 and CFPAC1 pancreatic cancer cell lines, respectively. Treatment with CT1 resulted in an IC50 of 84.5 nM in HPDE cells, compared to MiaPaCa2 pancreatic cancer cells, which had an IC50 of 46.5 nM, and BxPC3 and CFPAC1 cells which displayed higher IC50 values of 300 and 170 nM, respectively.

Conclusions: Pure compounds from Vietnamese medicinal plants show significant pancreatic cancer growth inhibition *in vitro* at concentrations that have minimal effect on normal pancreatic cells and, therefore, show promise as novel anti-pancreatic cancer therapies.

Translational research aspect: This is a T1 study as it is assessing anticancer activity of compounds *in vitro*.

P14

COLLECTIVE AND NEGOTIATED DESIGN FOR A CLINICAL TRIAL ADDRESSING SMOKING CESSATION SUPPORTS FOR ABORIGINAL AND TORRES STRAIT ISLANDER MOTHERS IN NSW, SA, AND QLD - DEVELOPING A PILOT STUDY

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Background: Aboriginal and Torres Strait Islander mothers are four times more likely to continuing smoking through pregnancy than their non-Aboriginal counterparts. There is a range of factors influencing continual tobacco use including environmental context, lack of knowledge of smoking harms and cessation methods and lack of culturally targeted support.[1] A novel intervention was developed to improve health provider's skill and confidence in offering culturally appropriate supports to Aboriginal and Torres Strait Islander mothers during pregnancy.

Aims: This presentation will articulate how the "ten principles relevant to health research among Indigenous Australian populations"[2] informed the developmental phase of the Indigenous Counselling and Nicotine (ICAN) QUIT in Pregnancy intervention.

Methods: The "ten principles" include: addressing community priorities, respectful partnerships, capacity building, flexibility, acknowledging past research experiences, diversity, timelines, Indigenous leadership, community ownership and partnership management. These were applied as a reporting framework to articulate the developmental phase of the *ICAN QUIT in Pregnancy* pilot.

Results: Each of the "ten principles" are articulated, offering practical examples of how the ICAN QUIT in Pregnancy research practices influencing a pilot project design. This framework enabled us to assess the relevance, effectiveness and culturally respectful manner in which the research has engaged Aboriginal and Torres Strait Islander peoples and communities.

Conclusion: NHMRC and AH&MRC highlight the need to conduct research with Aboriginal and Torres Strait Islander people with community-driven and controlled participatory approaches. *ICAN QUIT in Pregnancy* reports how these approaches are put into practice to develop a pilot study.

Translational research aspect: This is a T2/3 research project, based on evidence from the general and indigenous populations, targeted to the indigenous context.

P15

QUANTIFYING THE UPTAKE OF DISTRESS SCREENING AND MANAGEMENT GUIDELINES IN AUSTRALIAN CANCER SERVICES: A PROTOCOL FOR A NATIONAL CROSS-SECTIONAL SURVEY

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Background: Distress screening and management is part of a comprehensive, patient-centered approach to cancer care. Despite the association with improved patient outcomes, it is unclear to what extent Australian cancer services complete distress screening and if these processes align with best-practice guidelines.

Aims: To identify the: (1) proportion of services which adhere to screening guidelines; (2) potential areas of improvement (i.e. use of validated screening measures or referral protocols); and (3) implementation strategies that are acceptable to services interested in improving screening practices.

Methods and Anticipated Results: A national cross-sectional survey of cancer services will be completed in two phases. In phase I, personalized study packages will be posted to clinic managers or leads of approximately 135 services. To maximize response rates, packages will include paper-based surveys with the option to complete online using service-specific Web-links; nonresponding sites will receive two mail and telephone reminders. In phase II, peak national organizations will circulate links to an online survey using member directories. To generate complete, comparable descriptions of screening processes, approximately 30 survey items were adapted from National Comprehensive Cancer Network screening audits. Participants will provide general service information and indicate any preferred implementation strategies. The survey will be pilot-tested with 5–10 service representatives. Survey data will be reported using descriptive statistics. We anticipate a low proportion of services (<50%) will conduct any distress screening with a smaller proportion reporting universal, repeated outpatient screening with established referral pathways.

Conclusion: Establishing or enhancing distress screening in Australian services is an opportunity to improve patient outcomes. The survey data will quantify the potential evidence-practice gap related to distress screening.

Translational research aspect: This study represents the preliminary stage of a larger implementation study (T3). Survey data will be used to tailor implementation strategies according to selected pilot sites' preferences and identified improvement areas.

P16

ALTERATIONS IN LIPID COMPOSITION OF NORMAL AND TUMOR-DERIVED PROSTATE EXTRACELLULAR VESICLES

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Background: Extracellular vesicles (EVs) have important roles in cell–cell communication throughout the body, achieved by the transfer of protein and nucleic acid cargo in a biologically active lipid membrane. In the tumor microenvironment, EVs facilitate the malignant transformation of cells and aide in tumor cell metastasis via the delivery of protumorigenic messages to target cells. The precise mechanisms controlling which cells receive these messages remain largely unknown, it is believed that by looking at the lipid composition of EV membranes from normal and tumorigenic cells will help in the understanding of cargo delivery by EVs.

Aims: This study aims to determine whether the lipid composition of EV membranes differs between normal and tumorigenic prostate cells.

Methods: EVs from a normal prostate cell line, RWPE1, and a tumorigenic derivative of this cell line, WPE1-NB26, were collected in triplicate from the culture media of cells using an ultrafiltration protocol. Lipids were extracted using a chloroform:methanol (2:1) mix, and freeze dried before resuspension in an LCMS loading buffer. LCMS was utilized for a targeted lipidomics approach to allow for the quantitation of 265 lipid metabolites to identify differences in composition.

Results: Data were analyzed using a Student's *t*-test with Benjamini–Hochberg correction following median normalization and log transformation of the raw data. There were 71 of the 265 detected metabolites deemed significantly different between the WPE1-NB26 and RWPE1 samples.

Conclusions: These results indicate that there is an identifiable difference in the lipid composition of normal and tumorigenic prostate EVs. Future work will focus on whether these differences can enhance the uptake of EVs by surrounding cells and will further help influence the development of nano-carriers for targeted drug delivery to prostate cancer cells.

Translational research aspect: This research is currently at the T1 stage with the potential to move toward clinical outcomes in the future.

P17

GENOME-WIDE METHYLATION RESPONSE TO COMBINED TREATMENT OF MELANOMA WITH DECITABINE AND CARBOPLATIN

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Background: Melanoma has an innate resistance to DNA damaging chemotherapy agents, including platinum-based chemotherapies such as carboplatin and cisplatin. Aberrant DNA methylation is a feature of many cancers and can silence genes. The demethylating agent decitabine can remove DNA methylation and restore gene expression and has been investigated in other cancers in combination with platinum therapy.

Aims: Here we test the effect of decitabine and carboplatin on the methylome of melanoma.

Methods: A panel of 16 melanoma cell lines were treated with decitabine, carboplatin and a sequential combination of decitabine/carboplatin. Genome wide methylation was identified using Illumina Infinium MethylationEPIC arrays. Data were normalized and analysis performed with the minfi R package.

Results: Global methylation levels in melanoma determined by ELISA were reduced by an average of 44.67% by decitabine. Carboplatin treatment alone resulted in small nonsignificant changes in methylation (<17%). A total of 136,808 CpG sites were significantly demethylated after decitabine treatment. Interestingly, 2340 sites significantly increased in methylation although at only a small rate. Treatment with carboplatin after decitabine resulted in further significant demethylation in 34,583 CpG sites whereas 162 were re-methylated. Preliminary analysis of differentially methylated regions identified enrichment for CpG islands in genes in pathways including melanogenesis, endocytosis, pathways in cancer and WNT signaling. Melanoma-related genes with differential methylation included MC1R, RAC1, PTEN and CDKN1A.

Conclusions: Further analysis will identify if these demethylation patterns influence the expression of key melanoma-related genes and how these pathways influence the response of melanoma to platinum chemotherapies.

Translational research aspect: This research is T1 basic science that will directly transition into T2. The project has determined that decitabine and carboplatin combination therapy is feasible for melanoma.

P18

DEVELOPMENT OF A SENSITIVE AND QUANTITATIVE MASS SPECTROMETRY-BASED ASSAY FOR THE QUANTITATION OF DNA DAMAGE REPAIR PATHWAYS IN HUMAN CANCERS

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Background: Breast cancer is a major national and global health concern. Although the overall survival for breast cancer has significantly improved, outcomes for patients with triple negative (TNBC) or Luminal B subtype tumors remains poor. Recent studies show that some TNBCs display inactivation of key DNA damage repair (DDR) pathways, which renders them hypersensitive to specific DNA damaging chemotherapy. Whether other breast cancer subtypes also have altered DDR pathways is not known, in part because an effective tool for quantifying the activity of DDR pathways is not available.

Aims: Develop a robust and sensitive assay to quantitate the activity of DDR pathways in breast cancer.

Methods: DDR pathways are regulated by phosphorylation of key proteins, therefore we used a targeted proteomics approach to simultaneously quantitate phospho- and total levels of DDR proteins in a multiplexed manner, using high-resolution liquid chromatography-tandem mass spectrometry (LC-MS/MS) for parallel reaction monitoring (PRM). To optimize the assay, we utilized human breast cancer cells, BT474, treated +/− bleomycin to induce double-stranded DNA breaks (DSBs) and activate DSB repair pathways, and tested a range of cell lysis, protein digestion, and peptide enrichment strategies.

Results: Using our optimized protocol of sodium carbonate extraction and titanium dioxide enrichment, we identified increased phosphorylation of H2AX, a key marker of DSBs, in response to bleomycin. We further found increased phosphorylation of Protein Kinase B (AKT) at S123, T307 and S473, checkpoint kinase 2 (CHK2) at Thr386 and the ataxia–telangiectasia mutated (ATM) protein (double phosphorylation at Y175 and S179). In contrast, pThr68-CHK2 and pS367-ATM was reduced.

Conclusions: This was obtained from 1 μg of peptides, therefore we believe this assay will be useful for primary patient tissues, which we are beginning to test.

Translational research aspect: Despite improvements in detection and treatment, around 3,000 Australian women lose their lives to breast cancer every year. Our study aims to develop a new test to identify which high-risk breast cancer patients are likely to respond to a specific type of chemotherapy. If successful, this would pave the way for improved outcomes for these high-risk patients.

P19

RESPONSES TO THE HEALTH EDUCATION IMPACT QUESTIONNAIRE (HEIQ) TO DESCRIBE LEVELS OF EMPOWERMENT IN A COHORT OF RECENTLY DIAGNOSED LUNG CANCER PATIENTS

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Background: Chronic diseases such as cancer are the leading causes of fatal burden of disease in most age and gender groups and are the leading cause of illness, disability and mortality in Australia. The Health Education Impact Questionnaire (heiQ) is an Australian-developed validated survey tool for evaluating the effectiveness and influence of health education and self-management programs for patients with chronic disease. This tool can be used to describe levels of empowerment among patients. The heiQ contains eight survey subscales: (1) Health-directed behavior; (2) Positive and active engagement in life; (3) Emotional well-being; (4) Self-monitoring and insight; (5) Constructive attitudes and approaches; (6) Skill and technique acquisition; (7) Social integration and support and (8) Health service navigation. Little use has been made of the tool with cancer patients, and no Australian data with lung cancer patients have been published using the heiQ.

Aims: To examine lung cancer patients responses, the prevalence of each of the factors on the heiQ in a cohort of recently diagnosed lung cancer patients.

Methods: A total of 262 newly diagnosed lung cancer patients were recruited from cancer diagnosis and treatment services around Australia (31 clinics). Upon recruitment, patients are provided with a baseline survey. A total of 196 participants completed a paper questionnaire, which included the 42-item heiQ scales. Respondents were asked to indicate the degree to which they agree or disagree with each survey item on a six-point Likert scale. Standardized subscale scores (from 1 to 6) will be calculated, with higher scores indicating better functioning.

Conclusion: There is a need to improve levels of engagement and empowerment among lung cancer patients.

Translational research aspect: This study relates to the T3 end of the research translation pipeline given the focus on implementing psychosocial support for cancer patients.

P20

THE EFFECTIVENESS OF A POINT OF CARE INTERVENTION TO IMPROVE UPTAKE OF COLORECTAL CANCER SCREENING AMONG PRIMARY CARE PATIENTS

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Background: Studies conducted in the United States indicate that general practitioner endorsement of colorectal cancer (CRC) screening and provision of fecal occult blood test (FOBT) can improve CRC screening uptake. The effectiveness of these strategies in improving uptake of CRC screening among Australian primary care attendees has not yet been examined.

Aims: To examine the effectiveness of a multicomponent intervention for improving CRC screening uptake and CRC knowledge among primary care patients.

Methods: A randomized control trial based in two primary care clinics. Primary care patients aged 50–75, at average risk of CRC that have not had a FOBT in the past 2 years or had a colonoscopy in the past 5 years are eligible for randomization. Self-report data on screening uptake is collected via touchscreen survey (baseline) and telephone follow-up (6 weeks post baseline). The proportion of patients completing CRC screening at the follow-up time point will be compared using a logistic regression model. Differences in knowledge scores between the usual care group and the intervention group will be determined by ordinal logistic regression. For all tests we will use two-sided *P*-values with a 5% significance level.

Results: Data collection is in progress. Preliminary analyses on the uptake and impact of the intervention will be presented.

Conclusions: We anticipate the intervention will result in a significant increase of CRC screening in the intervention group. If effective, this intervention has the potential to be incorporated into routine general practice and act as a "booster" to the current National Bowel Cancer Screening Program.

Translational research aspect: Despite general practice guidelines recommending regular FOBT there remains an evidence-practice gap with colorectal cancer screening rates lower than desirable levels. This T3 research will test an intervention to close the "evidence-practice" gap in CRC screening participation.

P21

PARTICIPATION IN FOBT AND COLONOSCOPY AMONG AUSTRALIAN PRIMARY CARE PATIENTS: RESULTS OF A CROSS-SECTIONAL STUDY

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Background: The National Bowel Cancer Screening Program (NBCSP) offers fecal occult blood test (FOBT) to Australians turning 50, 55, 60, 64, 65, 70, 72 and 74. Only 36% of invites return a completed kit. There is no systematic method to capture FOBT participation outside the NBCSP or the reasons people choose to not participate in the NBCSP.

Aims: To examine, among primary care patients: (1) rates of FOBT use within and outside of the NBCSP; (2) characteristics associated with undertaking FOBT within the NBCSP; and (3) reasons for nonparticipation in the NBCSP.

Methods: We conducted a cross-sectional survey of primary care patients aged 50–75 years from three general practice clinics in NSW. Self-reported data for CRC screening participation, family CRC risk, knowledge of CRC screening recommendations and demographics was collected via touchscreen survey while patients waited for their appointment.

Results: Of the 200 respondents, approximately one third ($n = 76$) reported completing a FOBT in the past 2 years, 43% ($n = 33$) of those completing a FOBT sourced their kit from outside the NBCSP, mostly from their general practitioner. The most common reason for nonparticipation in NBCSP was having had a colonoscopy within the past 5 years, followed by perceiving the test as unpleasant.

Conclusions: The effectiveness of the NBCSP is limited by suboptimal participation rates. This study demonstrates that screening via FOBT is occurring outside the program and that the general practitioner is an important resource to promote CRC screening. Further analysis will determine whether screening outside of the NBCSP using colonoscopy is in accordance with the National Health and Medical Research guidelines.

Translational research aspect: This study collected epidemiological data to identify evidence-practice gaps in colorectal cancer screening (T3). This data will be used to inform an intervention designed to increase appropriate CRC screening in general practice patients.

P22

CIRCULATING MICROVESICLES ARE LESS PROCOAGULANT BUT CARRY MORE MIRNA CARGO IN MYELODYSPLASIA

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Background: Microvesicles (MV) are membrane bound circulating particles usually in size range of 100–1000 nm and products of cell activation or apoptosis. Myelodysplasia (MDS) is a preleukemic condition characterized by bone marrow failure and increased apoptosis of bone marrow precursors within their niche. The role of circulating MV in MDS has not been studied.

Aims: We undertook to evaluate the number and function, including small RNA content, of circulating MV in MDS.

Methods: Citrated blood samples were collected from 35 patients with myelodysplasia and 15 age similar controls after receiving informed consent. MV subsets were enumerated by Flow cytometry (BDFACS Canto) after staining with specific antibodies for platelets (CD41), endothelial cells (CD105), white blood cells (CD45), monocytes (CD14) and red cells (CD235a) as well as tissue factor (CD142) and phosphatidyl serine (Annexin V binding). MV were labeled with Qtracker 655 for Nanotracking (NanoSight NS500) under

scatter and fluorescent settings. Pro-coagulant function was assessed by the XaCT assay on a BCS analyzer and by thrombin generation (ETP) using a Calibrated Automated Thrombogram (CAT). Small RNA was extracted and quantitated on an Agilent bioanalyzer.

Results: The mean age of the normal subjects was 65 years (range 60–73), whereas the mean age of MDS subjects was 78 years (range 56–91). The CD41 expressing platelet MV were highest MV in normal subjects with a median of 166 μL^{-1} (interquartile range or IQR of 24–617). The MV in MDS were uniformly low with CD235 red cell MV being most abundant with a median MV level of 22 μL^{-1} (IQR of 22–45). Nanotracking measurements were not different between normal and MDS subjects in either mode. The median ETP was 2190 RFU (relative fluorescence units)/min (IQR 1611- 2660) in normal compared to 1094 RFU/min (IQR of 933–1212) in MDS. The pro-coagulant function by XaCT and ETP was significantly lower in MDS ($P < 0.0001$ for both). The small RNA and miRNA content was significantly higher in MDS samples ($P = 0.0005$ and 0.02, respectively).

Conclusions: Circulating MV in MDS show reduced pro-coagulant functional activity but significantly increased small RNA content when compared to age similar normal controls.

Translational research aspect: Circulating MV and miRNA content varies significantly between normal and MDS subjects with potential to be a biomarker for MDS (T1).

P23

CLINICOPATHOLOGICAL SIGNIFICANCE OF PRONGF RECEPTORS IN THYROID CANCER

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Background: The receptors for the neurotrophic factor proNGF, specifically the pro-neurotrophin receptor sortilin, the neurotrophin receptor $p75^{NTR}$ and the receptor tyrosine kinase TrkA (NTRK1), are all emerging biomarkers and therapeutic targets in oncology, but their clinicopathological significance in thyroid cancer is unknown.

Aims: Define the expression and clinicopathological significance of proNGF receptors in thyroid cancer and determine their potential clinical value as diagnostic or prognostic biomarkers as well as their utility as therapeutic targets.

Methods: Sortilin, $p75^{NTR}$ and TrkA were analyzed by immunohistochemistry in a cohort of thyroid cancers versus adenomas and normal thyroid tissues. Thyroid cancer cell lines were also analyzed in real-time RT-PCR and Western-blotting.

Results: Sortilin and $p75^{NTR}$ were overexpressed in cancers compared to adenomas and normal thyroid tissues. Sortilin was not detected in normal thyroid tissues but was expressed in 33% of adenomas and 62% of thyroid cancers ($P < 0.0001$). In contrast, $p75^{NTR}$ was detected in epithelial cells for the majority of normal thyroid, adenoma and thyroid tumors, however, there was a clear overexpression in over 50% thyroid cancer cases ($P < 0.0001$). TrkA exhibited a distinct expression pattern suggesting a prominence in stem cells in relation to cancer expansion. ProNGF receptors were also expressed in nerves and may therefore be involved in the nerve-cancer cell crosstalk. The expression of neurotrophin receptors was confirmed using thyroid cancer cell lines.

Conclusions: These data reveal sortilin, $p75^{NTR}$ and TrkA as potential clinical biomarkers in thyroid cancer. Further functional investigations are warranted to determine the interest of these receptors as therapeutic targets.

Translational research aspect: This research is applicable to the T1 translational pipeline.

P24

DEVELOPMENT OF A SIMPLE LCMSMS METHOD FOR THC AND METABOLITES IN PLASMA

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Background: There is growing interest in the use of medicinal cannabis around the world. However, there is limited human pharmacokinetic data available to make decisions about what doses to use in patients. Most current routine methods measure only the metabolite carboxy tetrahydrocannabinol (THC) in urine. In order to monitor THC and its metabolites hydroxy THC, carboxy THC and cannabidiol (CBD) in plasma a method needs to be developed.

Aims: To develop an LCMSMS method for the analysis of THC, and its metabolites, hydroxy THC, carboxy THC and cannabidiol (CBD), in plasma.

Methods: Plasma samples (50 μL) were prepared by adding twice the volume of acetonitrile containing deuterated internal standards. The samples were vortexed then centrifuged and the supernatant was transferred to a vial and injected onto the LCMSMS. The LCMSMS system consisted of a Shimadzu UHPLC with a SCIEX 6500QTrap, a Kinetex Biphenyl column and using a gradient of 0.1% formic acid and acetonitrile.

Results: THC and its metabolites were linear over the following ranges: THC 0.5–500 ng/mL, OH-THC 0.5–50 ng/mL, COOH-THC 0.5–500 ng/mL and CBD 0.5–500 ng/mL. Intraassay precision was between 3% and 12% and intraassay bias was between −15% and 12%. Interassay precision was between 5% and 13% and interassay bias was between −11% and 15%. The limit of quantitation for all compounds was 0.5 ng/mL.

Conclusions: A validated LCMSMS method for THC and its metabolites was developed using a small volume of plasma and a simple acetonitrile extraction with a limit of quantitation of 0.5 ng/mL. This method will be used for the analysis of THC and metabolites in clinical studies.

Translational research aspect: This work will support clinical studies looking at the effectiveness of medicinal cannabis in cancer patients. Evaluating the effectiveness of new treatments in patients is consistent with T2 in the translational pipeline.

P25

PHARMACOKINETICS OF A NOVEL FORMULATION OF 5-FLUOROURACIL (5FU) AND LEUCOVORIN (LV): (DEFLEXIFOL) IN A PHASE I TRIAL

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Background: 5FU with or without its biomodulator LV is still widely used in clinical oncology. Physical incompatibilities between 5FU and LV necessitate the infusion of each component separately, often through a central line due to high pH, resulting adverse events including phlebitis, catheter blockage and sepsis which lead to poor outcomes due to treatment interruption and discontinuation.

Aims: We have developed Deflexifol, an all-in-one injectable reformulation of 5FU/LV at physiological pH, as an alternative to serial administration of 5FU and LV in a high pH solution (Locke JM, Anticancer Drugs 2009). Preclinical testing demonstrated that Deflexifol is stable, bioequivalent to 5FU with reduced side effects (Stutchbury TK Anticancer Drugs 2011).

Methods: An open label phase I dose escalation study is underway in two schedules (bolus weekly and 46-hour infusion every 2 weeks) to assess the safety and tolerability in 33 patients (16 bolus, 17 infusion) with advanced malignancy after failure of standard treatment. Limited sampling PK of 5FU and dihydroFU is being conducted (three at each of five dose levels, doses one and six) in both schedules to assess PK variability and adequacy of dosing in comparison to previous reports.

Results: With bolus 5FU dose levels one to four (375–525 mg/m^2), AUC was ~25–70% of that expected to cause any toxicity, whereas dose level 5 (575 mg/m^2) was similar to expected. 5FU AUC for infusional levels 1–3 (1200–2400 mg/m^2/46 h) was 5–30% of expected. More data on levels 4 and 5 (3000 and 3600 mg/m^2/46 h) are pending.

Conclusion: 5FU exposure with Deflexifol is similar to 5FU alone at the same dose. PK analysis suggests that the MTD may be reached at dose levels 4 or 5. A phase II randomized study is in planning.

Translational research aspect: This project (T2–T3) leads to new drugs in clinical oncology.

P26

TO EVALUATE THE FEASIBILITY OF MAGNETIC RESONANCE IMAGING (MRSI) USING SEMI-LASER GRADIENT OFFSET INDEPENDENT ADIABATICITY (SLASER-/GOIA) REFOCUSING PULSES FOR THE HUMAN PROSTATE

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Background: Magnetic resonance spectroscopic imaging (MRSI) provides metabolic information about tissue *in vivo*, such as citrate (Cit), creatine (Cr), choline (Cho) and polyamine (PA). Among many MRSI acquisition techniques, point resolved spectroscopy (PRESS) is the most common sequence for prostate. In conventional PRESS, a volume of interest (VOI) is excited by RF refocusing pulses with low bandwidth. One of the main drawbacks of MRSI prostate image are the long acquisition time and the low signal-to-noise ratio (SNR). Although a large external magnetic field (Bo) increase SNR and spatial resolution, chemical shift displacement error (CSDE) increase linearly with Bo and causes lipid contamination in the VOI.

Aims: Feasibility of gradient offset independent adiabaticity (GOIA) semi-LASER sequence as a new MRSI sequence for prostate. Comparison of the SNR, CSDE and metabolism ratios of the PRESS and GOIA sequences of the human prostate.

Methods: Four healthy volunteer underwent Skyra 3T MR imaging with phase array coil and without endorectal coil. The 3D MRSI was obtained from VOI using (1) GOIA semi-LASER sequence with high bandwidth and 50% lower RF power refocusing pulses and (2) PRESS sequences. (Cho+Cr)/Cit was measured in the same voxels of VOI and spectra quality compared.

Results: The results demonstrated the higher SNR, a lower lipid contamination and improved volume selectivity for GOIA sequence compared to PRESS. For the same voxel, the amount of Cit for GOIA and PRESS were 4.33 and 0.29 absolute units, respectively. In addition, (Cho+Cr)/Cit ratio for the same voxel for GOIA and PRESS were 0.314 and 0.034, respectively.

Conclusions: GOIA MRSI can overcome the limitations of PRESS MRSI in prostate and improve the application of MRSI for prostate cancer prediction.

Translational research aspect: This study falls into the T3 translation pipeline. GOIA can improve application of MRSI for prostate cancer detection and response to treatment.

P27

CALIBRATION OF APPARENT DIFFUSION COEFFICIENT (ADC) VALUE ON TWO DIFFERENT WHOLE BODY MAGNETIC RESONANCE (MR) SCANNERS USING ICE–WATER PHANTOM

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Background: Apparent diffusion coefficient (ADC) value is an important biomarker to evaluate cancer and response to treatment. The ADC value depends on many parameters including kinetic energy of the specimens under investigation. Standardizing the ADC measuring parameters means that the ADC value will be identical even after changing MRI sequence and/or scanner. ADC value of tap water at just above 0 is1.1×10^{-3}mm^2/s.

Aims: Standardization of ADC value in two MR centers using a specially designed phantom at controlled temperature to find a quantitative agreement for cancer prediction.

Methods: The ice–water phantom consisted of a 1.5 L polypropylene wide-mouth jar and a 30 mL polypropylene tube. The tube was filled with tap water .The jar was filled with ice and water and left approximately 0.5 h to reach thermal equilibrium. The phantom was scanned at 3T Skyra MRI scanner at Calvary Mater hospital and 3T Prisma MRI scanner at HMRI using torso coil. The ADC value was measured in a circle (1-cm diameter) inside of the tube along the artifact-free axial slices.

Results: The mean ADC value of Skyra and Prisma were 1.115 ± 0.025 and 1.121 ± 0.008 mm^2/s, respectively. There was no significant differences between ADC values measured in two centers ($P = 0.608$). The drift of ADC from theoretical ADC might be due to many reasons including RF inhomogeneity as well as gradient non-linearity which might in turn be related to gradient bore size.

Conclusions: This study demonstrated reproducibility of ADC values in two centers using the same acquisition protocol. These values confirmed that ice-water phantom can be used as a practical and low cost method for

standardization of ADC values across different magnets. Standardization of ADC values improve the prediction of cancer aggressiveness.

Translational research aspect: This study falls into the T1 translation pipeline.

P28

DESIGNING *INDIGENOUS COUNSELING AND NICOTINE (ICAN) QUIT IN PREGNANCY* PROGRAM WITH THE BEHAVIOR CHANGE WHEEL: IMPROVING HEALTH PROVIDER SMOKING CESSATION CARE FOR INDIGENOUS PREGNANT WOMEN

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Background: In Australia, smoking rates among pregnant Indigenous women are 47%, and slow to decline. Previous strategies in this population suffered from design challenges.

Aims: To develop an intervention to meet the needs of the target population, and improve culturally-competent smoking cessation care (SCC) for pregnant Indigenous smokers, by training providers at Aboriginal Medical Services. The behavior change wheel (BCW) – a parsimonious model governing capability, opportunity and motivation for behavioral interventions – provided a theoretical framework for the Indigenous Counselling and Nicotine (ICAN) QUIT in Pregnancy development.

Methods: We identified evidence-practice gaps through: two systematic literature reviews on provider attitudes and interventions for SCC in pregnancy; a national survey of clinicians; and gathering stories of smoking and quitting from Aboriginal mothers. These studies facilitated the development of this targeted intervention.

Results: Areas identified for performance improvement included: capability (psychological skills), motivation (optimism), and opportunity (resources/time). Using the BCW, we targeted: capability by training clinicians in pharmacotherapy to assist women to quit; opportunity by structuring the consultation using a flipchart and prompts, and using a whole-of-service approach; and optimism for success by presenting recent evidence, and positive testimonials from patients and clinicians. Webinar brings the training to the services to accommodate time and location constraints, and diversify responsibilities to providers other than clinicians. A Stakeholder and Consumer Aboriginal Advisory Panel was consulted on developing intervention materials.

Conclusions: The formative development of ICAN QUIT in Pregnancy demonstrates how it is uniquely designed to improve the implementation of SCC for expectant mothers attending Aboriginal Medical Services. Training was designed to improve gaps identified from several robust studies, and includes improved counseling skills and pharmacotherapy management. The intervention has implications for reducing the risk of cancer from tobacco exposures to mother and child.

Translational research aspect: This T2/3 research translates evidence-based approaches through a theoretical framework, to the context of Australian Indigenous maternal smoking cessation.

P29

DECISION-MAKING PREFERENCES AND SATISFACTION OF STAGE ONE TESTICULAR CANCER PATIENTS

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Background: Involving patients in the treatment decision making process is an important aspect of patient-centered care. However, patient's preferences for involvement are not always met.

Aims: This was a retrospective survey study, which assessed a range of factors concerning the treatment decision making process of testicular cancer patients. This abstract reports the following outcomes:

1. The percentage of patients who achieved their preferred level of involvement in treatment decision making.
2. Patient's level of satisfaction with their treatment decision.

Methods: A retrospective, self-report survey of stage 1 testicular cancer patients, who had attended a NSW-based treatment center in the preceding 12 months. Eligible patients were identified from clinical records and sent a questionnaire pack. Participants completed the survey via pen-and-paper or online. Involvement in treatment decision-making and decisional satisfaction were assessed using an adapted version of the control preference scale (CPS) and the satisfaction with decision scale (SWD), respectively.

Results: Fourteen of 51 eligible patients (27%) completed the survey. Half (50%) of patients indicated an exact match on the CPS scale, between their preferred and perceived role in treatment decision making, 29% were less involved, and 21% were more involved than they preferred. The median level of satisfaction with their treatment decision was 4.7 (range: 3–5), out of a possible score of 5.

Conclusions: Involvement of testicular cancer patients in treatment decision making could be improved to better align with their preferences. However, patient satisfaction with their treatment decision was high. Because of the small sample size the results of this study should be interpreted with caution.

Translational research impact: This is part of a descriptive study that will inform the development of a decision aid to support testicular cancer patients (T2/T3).

P30

EXAMINING WHERE RESEARCH EFFORTS ON CANCER-RELATED DECISION AIDS HAVE BEEN MADE

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Background: Decision aids are designed to help patients make difficult healthcare decisions. There is substantial evidence to support decision aids' effectiveness in improving patient outcomes. Despite their apparent effectiveness, decision aids are not commonly used in clinical practice.

Aims

I. To examine the number of studies published in 2000, 2007, and 2014, which tested the effectiveness of decision aids in improving cancer patient outcomes, coded by type of cancer and decision type being targeted.
II. To compare these numbers with the number of studies examining, the effectiveness of implementation strategies to increase the adoption of decision aids by healthcare providers.

Methods: We undertook a literature review of intervention studies and searched Medline, Embase, PsychInfo and Cochrane Database of Systematic Reviews. The search was limited to human studies published in English,

French or German. One reviewer assessed the abstracts against eligibility criteria. A random sample of 20% was checked by a second.

Results: Over the three time points assessed, an increasing number of studies has tested the effectiveness of decision aids ($P < 0.0001$). The volume of research on cancer screening or prevention decision aids increased statistically significantly ($P < 0.0001$); the volume of research on cancer treatment decision aids did not ($P = 1.00$). Most studies tested decision aids for prostate, breast or colon cancer. Only two studies examined the effectiveness of implementation strategies.

Conclusions: More research is needed on other cancer populations and other decision types, such as treatment decisions, to establish decision aids' effectiveness in different patient populations. This evidence then needs to be translated into meaningful benefits for patients by implementing decision aids into routine cancer care.

Translational research aspect: This review focuses on research testing the effectiveness of interventions and implementation strategies to improve service delivery in cancer care (T2/T3).

This abstract is based on a paper which has recently been published in BMC Medical Informatics and Decision Making ("Wilfully out of sight? A literature review on the effectiveness of cancer-related decision aids and implementation strategies," URL: https://bmcmedinformdecismak.biomedcentral.com/articles/10.1186/s12911-016-0273-8)

P31

TETRASPANIN CD9 MODIFIES EXTRACELLULAR VESICLE NUCLEIC ACID CARGO IN PROSTATE CELL LINES

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Background: Prostate cancer has one of the highest incidence rates of all cancers in Australia. Although 5-year survival rates are high, this is generally attributed to most prostate cancers either exhibiting a slow progression toward metastasis or being indolent. However current treatments for localized disease have devastating effects on quality of life and the biomarkers that are currently available are not accurate enough. This has resulted in many men with indolent disease being unnecessarily treated. Therefore, it is essential to identify new prognostic biomarkers that are accurate, sensitive and able to be tested for, in noninvasive ways. Tetraspanins have been shown to be involved in cellular processes including, adhesion, invasion, migration and cell signaling, all of which play key roles in cancer. Studies have shown that expression levels of tetraspanins CD9 and CD151 correlate with tumor type, stage and patient outcome in prostate cancer. Extracellular vesicles (EVs) have gained interest as a promising avenue for cancer biomarkers in recent years. EVs are small spherical shaped vesicles, which are secreted from their tissue of origin and contain high amounts of noncoding RNAs.

Aims: The overarching aim is to identify EV cargo specifically incorporated as a response to altered tetraspanin expression that can be used to enhance the potential of tetraspanins as prognostic biomarkers for prostate cancer.

Methods: CD9 expression was decreased in RWPE1 (normal prostate cells) and increased in PC3 (bone metastasis from prostate cancer) to manipulate resultant incorporation of CD9 into EVs from these cells. EVs were collected by ultraconcentration from cell culture media devoid of supplements after 48 h. Total RNA was extracted with Trizol and evaluated using total RNA Agilent 2100 bioanalyzer chips. RNA was converted to labeled cDNA and hybridized to Affymetrix Human Transcriptome arrays. Data were normalized using expression console and analyzed using transcriptome analysis console.

Results: Increasing the expression of the metastasis suppressor CD9 in prostate cancer cells resulted in 1413 transcripts being differently incorporated in to extracellular vesicles, conversely decreasing CD9 resulted in 237. These transcripts represent a variety of RNAs such as, mRNA, miRNA, snRNA, snoRNA, tRNA and lncRNA. Comparing total numbers of transcripts between increase CD9 and decrease CD9 expression, of these changes, 50 transcripts were common.

Conclusions: The increased and decrease of CD9 expression does effect the nucleic acid cargo of EVs of normal and prostate cancer cells. Several transcripts had significantly different abundance levels that discriminated between EVs released from cells of CD9 decreased and increased expression, showing potential as biomarkers. Therefore, in the future it may be possible to identify a biomarker signature that will improve outcomes for prostate cancer patients.

Translational research aspect: This work is in the T1 stage, with the potential to be translated to prognostic or diagnostic biomarkers or therapeutic targets in the future.

P32

IDENTIFICATION OF A NOVEL TRANSCRIPTION FACTOR COMPLEX IN CLASS I HDACS-MEDIATED UPREGULATION OF PD-L1 IN CANCER CELLS

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Background: The expression of programmed death-ligand 1 (PD-L1) is an important mechanism of immune evasion of cancer. However, how PD-L1 expression is regulated in cancer cells remains less understood.

Aims: We have found that histone modification is essential in controlling PD-L1 expression. In this study, we aimed to elucidate the mechanism by which inhibition of histone deacetylases regulates PD-L1 expression in cancer.

Results: Inhibition of class I HDACs upregulated PD-L1 in diverse types of cancer cells suggesting the involvement of these HDACs in suppressing PD-L1 expression. This was confirmed by siRNA knockdown of the individual HDACs. Mechanistically, a transcription factor complex was required for transcriptional activation of PD-L1 when one or more class I HDACs were inhibited. Moreover, this complex appeared necessary for the constitutive expression of PD-L1 and its upregulation in response to INFγ. Of note, the transcription factors within this complex were physically associated and knockdown of one of them diminished the effect of the other on PD-L1 expression, indicating that their interaction is required for transcriptional activation of PD-L1. Functional studies showed that class I HDAC inhibition in melanoma cells attenuated IFNγ production and reduced viability of lymphocytes, which were reversed by the addition of a PD-L1 Fc chimeric protein, in a mixed lymphocyte and tumor cell culture system. Cotreatment with class I HDAC inhibitor and anti-PD-1 antibody significantly retarded the growth of mouse melanoma *in vivo*.

Conclusions: These results reveal the critical involvement of a transcription factor complex in transcriptional activation of PD-L1 and identify class I HDACs as important regulators of PD-L1 expression in cancer cells.

Translational research aspect: This project is currently at T1–T2 stages. Nevertheless, the project will potentially be preceded to T3/4 as the results indicate

that clinical evaluation of targeting class I HDACs in augmenting responses to anti-PD-1 and anti-PD-L1 antibodies in melanoma is warranted.

P33

TOWARDS TARGETING QUIESCENT MELANOMA CELLS

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Background: Although most malignant cells are fast-dividing, a small population of so-called quiescent cancer cells do not proliferate. These cells are not sensitive to cell death induced by anti-cancer drugs and are closely associated with cancer recurrence, especially following long periods of remission after treatment. However, the molecular mechanism responsible for the resistance of these cells to cell death remains unknown. This is largely due to the lack of specific cell surface markers that precludes isolation of intact quiescent cancer cells for laboratory studies. Quiescent cells express high levels of p27, which is degraded by proteolysis mediated by KPC at G0–G1 transition and SCF at S/G2/M phase.

Aims: To isolate intact quiescent melanoma cells and to determine the mechanism by which these cells are resistant to cell death.

Methods: mVenus-p27K$^-$ (a p27 mutant that lacks binding affinity to CDK) and mCherry-hCdt1(30/120) (FUCCI (Fluorescence Ubiquitin Cell Cycle Indicator)) were cotransduced into B16 mouse melanoma cells. Propidium iodide and Ki-67 staining was used to verify the quiescent status of the resulting cells, which were then purified using FACs cell sorting.

Results: A mVenus-p27K$^-$ and mCherry-hCdt1 (30/120) cotransduced B16 mouse melanoma subline was established. Propidium iodide and Ki-67 staining confirmed that mVenus$^+$/mCherry$^+$ cells were at G0 phase. We are in a process to characterize the isolated G0 cells in comparison with G1 cells with particular attention to differentially expressed noncoding RNAs.

Conclusions: Intact quiescent melanoma cells can be isolated by using ectopically expressed mVenus-p27K$^-$ and mCherry-hCdt1 (30/120) as a marker. This will potentially lead to better understanding of the resistance mechanism of these cells to treatment.

Translational research aspect: This T1 basic science research may lead to T2 and subsequently T3/T4 studies to improve the response of cancer to treatment.

P34

RIPK1 PROMOTES MELANOMA CELL SURVIVAL UPON MAPK INHIBITION

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Background: Receptor-interacting protein kinase 1 (RIP1) mediates both cell survival and death signaling and is emerging as an important determinant of cell fate in response to cellular stress. We have previously shown that RIP1 functions as an oncogenic driver through activation of NF-κB in human melanoma cells, and regulates survival of melanoma cells upon endoplasmic stress. However, the potential impact of RIP1 on the response of melanoma cells to MAPK inhibitors, which have become the standard of care for patients with late-stage mutant BRAF melanomas, remains unknown.

Aims: To elucidate the potential role of RIP1 in regulating sensitivity of melanoma cells to MAPK inhibition.

Results: Although the RIP1 kinase inhibitor necrotatin-1 did not affect the sensitivity of melanoma cells to MAPK inhibitors, knockdown of RIP1 enhanced reduction in cell viability caused inhibition of MAPK. Moreover, knockdown of RIP1 killed melanoma cells selected for resistance to the BRAF inhibitor PLX4720. Intriguingly, the expression of RIP1 was markedly unregulated in PLX4720-selected melanoma cells at the protein level but remained unaltered at the mRNA level. We are currently investigating the mechanism by which RIP1 promotes melanoma cells from MAPK inhibition and the mechanism responsible for upregulation of RIP1 in melanoma cells selected for resistance to BRAF inhibitors.

Conclusions: These results reveal that RIP1 plays a role in promoting melanoma cell survival independently of its kinase activity when MAPK is inhibited, and identify upregulation of RIP1 as an adaptive mechanism of melanoma cells upon long-term exposure to MAPK inhibitors

Translational research aspect: This project is currently at its T1 stage. It has the potential to advance to T2 and subsequently T3/4 stages depending on results from follow-up experiments.

P35

DEVELOPMENT OF A HIGHLY SENSITIVE AND SPECIFIC TARGETED MASS SPECTROMETRY ASSAY FOR PSA IN PROSTATE CANCER

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Background: Prostate cancer (PCa) is one of the most prevalent cancers in Australia. The PCa serum biomarker prostate specific antigen (PSA) has revolutionized diagnosis and prognosis of the disease. To date, immunoassay is the most accepted methodology for quantifying serum levels of PSA. In spite of efforts to standardize the antibodies for PSA, lack of specificity and reproducibility in immunoassay still exist. A reliable antibody-free methodology to quantify PSA in the serum of PCa patients with increased confidence would represent an improvement.

Aims: To design a new highly sensitive and specific assay of PSA by targeted proteomics.

Methods: Parallel reaction monitoring (PRM) in mass spectrometry, using a high resolution, accurate mass Orbitrap mass spectrometer (Q Exactive Plus) coupled to nanoflow liquid chromatography system (LC-MS/MS). We have detected and optimized PSA peptide precursor:product ion pair transitions in PCa serum after Trypsin digestion. Then we have used the identified peptides to quantify PSA by PRM mass spectrometry in a cohort of 60 serum samples obtained from the Australian Prostate Cancer Bio-Resource (APCB). The cohort was composed of 20 benign prostatic hyperplasia (BPH) and 40 PCa.

Results: A total of eight PSA tryptic peptides could be detected in PRM mass spectrometry. Two highly specific peptides at 636.84^{++} Da and 510.74^{++} Da, and presenting no similarities with other human proteins (after BLAST search) were selected for PSA quantification. Quantification of these two peptides was based on 21 and 8 ionic transitions (observed in positive ion mode) respectively. The results indicated a high reproducibility of the PRM assay and a correlation with clinicopathological parameters.

Conclusions: This study demonstrates that PRM mass spectrometry can be efficiently used to quantify PSA in PCa serum and may improve upon the performance of currently used immunoassays.

Translational research aspect: T1.

P36

MAPK REGULATES CD47 EXPRESSION IN MELANOMA CELLS

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Background: Inhibition the MAPK pathway is a valuable therapeutic approach in the treatment of melanoma. However, the benefits are often of limited duration due to the rapid development of acquired resistance. On the other hand, immune checkpoint antibodies can result in long-lasting melanoma regression, but only a subset of patients benefit from these agents. Because activation of the MAPK pathway in melanoma cells contributes to the immunosuppressive microenvironment and inhibition of the pathway triggers melanoma-specific immune responses, combining MAPK pathway inhibitors and immunotherapy that activates the T-cell response appears promising to improve the therapeutic efficacy.

Aim: To investigate the potential impact of MAPK activation in melanoma cells on the innate immune response and its role in the response of melanoma to MAPK inhibition.

Results: Inhibition of the MAPK pathway by pharmacological or genetic approach upregulated the CD47, a "self-marker" that transmits "don't eat me" signaling upon binding signal-regulatory protein α (SIRPα) on the surface of phagocytic cells, in melanoma cells. This was due to a transcriptional increase and was mediated by the transcription factor Nuclear respiratory factor 1 (NRF-1). Although inhibition of CD47 by a blocking antibody triggered phagocytosis of melanoma cells by macrophages, cotargeting CD47 and the MAPK pathway resulted in an enhanced therapeutic effect in a mixed macrophage and melanoma cell culture system.

Conclusions: These results suggest that upregulation of CD47 in melanoma cells may counteract the immune response elicited upon MAPK inhibition, and that simultaneous or sequential inhibition of MAPK and CD47 is a promising combined approach in the treatment of melanoma

Translational research aspect: This project is currently at its T1 stage. It has the potential to advance to T2 and subsequently T3/4 stages depending on results from follow-up experiments.

P37

HOW CAN WE ENHANCE PATIENT-CENTERED COMMUNICATION AT THE END OF LIFE? PROOF-OF-CONCEPT RCT

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Background: Advance care planning (ACP) can help people to discuss and document their preferences for future medical care. However, uptake of ACP is low and variable. There is a need to develop and test the feasibility and acceptability of low-burden strategies that promote ACP participation.

Aims: To develop and test the feasibility and acceptability of an enhanced strategy to assist cancer patients to discuss and document preferences for medical care.

Methods: Adult medical oncology outpatients were recruited from a treatment center in NSW. Participants were randomized to receive either usual care or an intervention which included a DVD of an oncologist and patient discussing ACP, links to an ACP website, and a prescriptive letter encouraging them to use the resources. A follow-up survey was undertaken at 6 weeks.

Results: A total of 82 patients consented (68% of eligible). There were no significant differences between the groups at baseline. At baseline, 30% of patients had talked to a clinician about their end of life wishes and 51% had talked to their family. Only 12% had an advance directive; 36.6% had appointed an enduring guardian. Follow-up data on feasibility, acceptability and uptake will be presented.

Conclusions: Successful implementation of strategies to increase ACP uptake relies on the ability to operate within available resources, and be acceptable to the target population. Participants felt the materials were easy to use, a helpful way to provide information and covered the main points about ACP in the right detail.

Translational research aspect: End of life discussions are identified as one of five priority evidence-to-practice gaps in end of life care by ANZSPM. This trial tested a novel strategy to encourage patient participation in ACP that could be easily integrated into routine practice.

P38

EXPLORING THE IMPLEMENTATION OF PSYCHOSOCIAL CARE GUIDELINES IN A RADIATION ONCOLOGY TREATMENT CENTRE

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Background: Uncertainty about treatment processes, side-effects and outcomes, contribute to the high rates of psychological distress among cancer patients receiving radiotherapy. To optimize supportive cancer care during radiotherapy, there is a need to explore and enhance uptake of guidelines for detecting and managing psychosocial issues, in radiation oncology treatment centers.

Aims:

(1) To assess radiation oncology treatment center staff awareness of, agreement with, adoption of, and adherence to, psychosocial care guidelines.
(2) To develop, implement and test (based on staff and patient perceptions) a strategy for improving uptake of psychosocial care guidelines in radiation oncology settings.

Methods: *Design:* Quasi-experimental pre–post test (without control group).

Sample: Healthcare providers and patients attending a radiation oncology treatment center.

Data collection: Phase 1 (and 3 if required): Radiation oncology department staff will complete an online survey assessing uptake of psychosocial guideline recommendations. Patient's perceptions of their psychosocial care will also be assessed. Phase 2: If required, a psychosocial guideline implementation enhancement package will be developed and implemented, targeting any gaps in psychosocial guideline uptake that are identified by staff and patients.

Data analysis: Descriptive statistics will be used to inform development of the psychosocial guideline implementation enhancement package. Nonparametric statistics will be used to compare pre- and posttest staff-reported and patient-perceived psychosocial care.

Results: A project update and preliminary findings will be presented at the 2016 Hunter Cancer Research Symposium.

Conclusions: This study will progress translational research in psycho-oncology, in turn reducing psychosocial distress among radiation oncology patients.

Translational research aspect: This project fits within the T3 research component of the HCRA Second Flagship (Implementation Research), as it is expected that the research team and site-based working party will develop an implementation strategy aimed at decreasing an evidence-practice gap in cancer care (the provision of guideline adherent psychosocial care for adults in oncology settings).

P39

DNA METHYLATION PROFILE OF TRIPLE NEGATIVE BREAST CANCER-SPECIFIC GENES COMPARING LYMPH NODE POSITIVE PATIENTS TO LYMPH NODE NEGATIVE PATIENTS

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Background: Triple negative breast cancer (TNBC) is the most aggressive breast cancer subtype with no targeted treatment available. Our previous study identified 38 TNBC-specific genes with altered expression comparing tumor to normal samples.

Aims: This study aimed to establish whether DNA methylation contributed to these expression changes in the same cohort as well as if disease progression from primary breast tumor to lymph node metastasis was associated with changes in the epigenome.

Methods: We obtained DNA from 23 primary TNBC samples, 12 matched lymph node metastases, and 11 matched normal adjacent tissues. These were assayed for differential methylation profiles using Illumina HumanMethylation450K BeadChip arrays. The results were validated in an independent cohort of 70 primary TNBC samples.

Results: The expression of 16/38 TNBC-specific genes was associated with alteration in DNA methylation. Novel methylation changes between primary tumors and lymph node metastases, as well as those associated with survival were identified. Altered methylation of 18 genes associated with lymph node metastasis were identified and validated.

Conclusions: This study reveals the important role DNA methylation plays in altered gene expression patterns of TNBC-specific genes and lymph node metastases.

Translational research aspect: The novel insights into progression of TNBC to secondary disease may provide potential prognostic indicators for this hard-to-treat breast cancer subtype (T1).

P40

BREAST CANCER MOLECULAR PORTRAITS OF INTRINSIC SUBTYPES AND INTEGRATIVE CLUSTERS IN THE METABRIC DATA SET

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Background: Breast cancers have been stratified according to their molecular profiles. Microarray gene expression cohorts in the early 2000s have been used to classify the disease into five intrinsic subtypes: luminal A, luminal B, HER2-enriched, normal-like, and basal-like. More recently, a novel classification approach has further expanded the transcriptomic architecture by integrating this data with a spectrum of genomic aberrations, defining ten integrative clusters (IntClusts). Both classification, however, show a limited overlap that reflect the different means of stratification.

Aims: In this study, we aim to review and to reconcile the classification of intrinsic subtypes and IntClusts, and the underlying differences in the disease outcome.

Methods: We explored the genomic and transcriptomic signature of over 2000 samples disclosed by the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC). Labels in the data were considered for relevant comparisons in terms of reliability and accuracy of breast cancer classification. The t-SNE approach is then used to determine the position of each sample in a two-dimensional layout, based on the expression of 48 803 probes. This method also exposes the accuracy of the labels previously assigned.

Results: The t-SNE provided an overview of the labels' distribution for the five intrinsic subtypes, clearly differentiating independent entities based on their molecular profile, clinical data and survival outcome. The IntClust labels, however, showed a humble distribution of clusters that compromised the assessment of clinicopathological markers ER, PR and HER2. Although genomic aberrations were found associated to some transcriptomic variants, there was limited overlap between these independent sources for defining intrinsic subtypes – recognized clinical independent entities – and IntClusts.

Conclusions: Complementary bioinformatics strategy is therefore required to further investigate the relevance of both labels. The combination of "multi-omics" data source (genomics, transcriptomics, epigenomics, proteomics) may also contribute to improving the breast cancer classification and the disease understanding.

Translational research aspect: In this study, we investigated the classification of breast cancer disease within the context of their molecular profile, clinico-pathological information and survival outcome. We focused on fundamental research (T1) with the alignment of group-based approaches with potential clinical implications. This investigation is part of a major project entitled "The integration of bioinformatics, cheminformatics and toxicogenomics methods: a new approach for the identification of combination tailored therapies and novel drug targets in breast cancer," from Cancer Institute of New South Wales, Big Data Big Impact Grant 13/DATA/1-03.

P41

EFFECT OF (P)RR KNOCKDOWN AND RAS INHIBITORS ON ENDOMETRIAL CANCER GROWTH

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Background: Endometrial cancer is the most common gynecological malignancy. Australia has one of the highest rates of endometrial cancer in the world and its incidence is increasing. Tissue renin angiotensin systems are known to stimulate angiogenesis, cell proliferation and migration. All these actions potentiate cancer growth and spread. We have previously demonstrated that endometrioid endometrial cancers express both prorenin and prorenin receptor (P)RR mRNA and have significantly greater levels of these proteins than normal adjacent endometrial tissue. Prorenin acting via the (P)RR can activate both RAS dependent and independent signaling pathways.

Aims: To examine the effects of prorenin receptor (P)RR knock down and RAS inhibitors on endometrial cancer cell proliferation and viability.

Methods: Prorenin receptor (P)RR knockdown was done by transfection of (P)RR siRNA in three endometrial cancer cell lines at 24, 48, 72 and 96, mRNA expression was carried out by qPCR. Effect of (P)RR siRNA and RAS blockers on cell viability was carried out by Resazurin assay at 48 h.

Results: All three endometrial cancer cell lines expressed (P)RR and renin mRNA, but levels of (P)RR were much higher in Ishikawa cells. Transfection into the three cell lines with a (P)RR siRNA which resulted in 90% knockdown of PRR mRNA reduced cell viability of both Ishikawa and AN3CA but not HEC-1A cells. Aliskiren a (renin inhibitor) reduced cell viability of all three cell lines (Ishikawa, AN3CA and HEC-1A), whereas in AN3CA cells VTP-27999 alone reduced cell viability. Perindopril (an ACE inhibitor) reduced cell viability of all three cell lines. The angiotensin II type 1 receptor (AT1R) inhibitor, losartan, had no effect on cell viability in any cell line. Another AT1R antagonist, telmisartan, which also acts as a selective modulator of peroxisome proliferator-activated receptor gamma (PPARγ), did, however, reduce cell viability in all three cell lines (Ishikawa, HEC-1A and AN3CA).

Conclusions: The prorenin receptor/prorenin angiotensin system may be functionally important for endometrial cancer growth and development. Thus, these signaling pathways may be therapeutic targets for treating endometrial cancer.

Translational research aspect: There is evidence that expression of the renin angiotensin system (RAS) is dysregulated in patients with endometrial cancer. As well patients undergoing treatment for hypertension with ACE inhibitors have a decreased incidence risk of cancer. This raises the possibility that repositioning existing antihypertensive drugs that target the RAS pathway could be used in the treatment of endometrial cancer.

P42

SEROUS OVARIAN CANCER: A SYNCHRONY OF MUTATIONS AND HORMONES

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Background: Women with BRCA1/2 mutations have a genetic predisposition to ovarian cancer, but not all (~50%) of these women develop the disease. Epidemiological findings show that lifestyle factors such as contraceptive use and pregnancy, a progesterone dominant state, decrease the risk of getting ovarian cancer in both the general population and in BRCA1/2 mutation carriers. In opposite, infertility and nulliparity increases the risk of developing ovarian cancer.

Aims: To decipher the molecular mechanisms of the early serous ovarian carcinogenesis and to understand the role of ovarian hormones in progression of serous ovarian cancer (SOC).

Methods: We collected whole fallopian tubes from 11 patients who underwent risk-reducing prophylactic salpingo-oophorectomy (RRSO) from the Hunter Cancer Biobank and performed extensive sectioning to detect SOC precursor lesions. We developed a unique mouse model activating β-catenin in the secretory cells of the fallopian tube epithelium. The mouse model was subjected to ovarian hormones by placing estrogen and/or progesterone pellets subcutaneously to assess their effects on the initiation and growth of SOC.

Results: We found Wnt signaling activations specifically in the SOC precursor lesions of the Fallopian tubes of BRCA1/2 mutation carriers. Activating the Wnt signaling in the mouse fallopian tube secretory cells resulted in the formation of lesions phenocopying gross morphology and immunophenotype of the early SOC. Estrogen promoted and progesterone suppressed the growth of these lesions in our mouse model.

Conclusions: Our study deciphers Wnt activation as one of the drivers of early SOC. Our mouse model is the first *in vivo* proof of concept for the benefits of progesterone in suppressing SOC progression.

Translational research aspect: Our study provides *in vivo* evidence that progesterone or progestin-based therapy decreases the onset of SOC and might be a beneficial alternative to RRSO in women with increased risk of developing ovarian cancer (Translational pipeline T1, T3).

P43

PPP2R2A LOSS AND ITS ROLE IN GROWTH, DEVELOPMENT, AND BREAST CANCER

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Background: Protein Phosphatase 2A (PP2A) is a tumor suppressive serine/threonine phosphatase that is inactivated in numerous diseases, including breast cancer. Recent findings indicate loss of the regulatory subunit B55α (*PPP2R2A* gene) is associated with a large proportion of poor outcome breast cancers. Our laboratory has shown that reduced B55α induces a tumorigenic phenotype in breast epithelial cells *in vitro*. However, lack of a B55α knockout mouse has impaired the ability to study the role of this protein *in vivo*.

Aims: To generate *Pppr2ra* knockout mice and characterize *in vivo* the functional role of PP2A-B55α in normal growth and as a tumor suppressor.

Methods: C57/Bl6 *Pppr2ra* knockout mice were generated using targeted CRISPR/Cas9 technology. Heterozygous breeding pairs were established, mice were sacrificed at various developmental stages, mammary glands collected, fixed and stained to analyze whole structure and protein expression analyzed by Western blotting. Mammary glands of pregnant mice and their 10.5-day-old embryos were also collected, and genotyped with PCR and gel electrophoresis.

Results: No homozygous knockout pups (out of over 200) have been born from heterozygous breeding pairs, suggesting embryonic lethality. Analysis of 10.5-day-old embryos identified Mendelian ratios of all genotypes, minus knockouts. *Ppp2r2a* heterozygous mice are viable, and demonstrate decreased

B55α protein expression in various organs, especially the mammary glands. Preliminary data suggests these mice have aberrant mammary gland structural branching compared to wild-type mice.

Conclusions: This is the first study to generate *PPP2R2A* knockout mice, and shows it is embryonic lethal, emphasizing the importance of this protein in normal growth and development. Potential changes to the mammary gland in heterozygous mice, paired with future experiments to backcross with tumor susceptible FVB/N mice will better inform the functional role of *PPP2R2A* loss in breast cancer.

Translational research aspect: T1; the novel findings of this study may lead to *in vivo* testing of various chemotherapeutics in *Ppp2r2a*-low mice with breast tumors.

P44

AN ACUTE MYELOID LEUKAEMIA PROGNOSTIC BIOMARKER CONTROLS CELL SURVIVAL AND SENSITIVITY TO CHEMOTHERAPEUTICS

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Background: Acute myeloid leukaemia (AML) accounts for ~30% of leukaemia diagnoses in Australia, and is the most common acute leukemia in adults. The 5-year survival rate for AML is 24%, and the majority of patients who enter remission will relapse. Primary refractory disease occurs frequently in AML, with 33% of patients aged <65 years, and 57% of patients over 75 years exhibiting primary induction failure. Overexpression of brain and acute leukaemia, cytoplasmic (BAALC) is associated with poor patient prognosis, specifically decreased overall and relapse-free survival, as well as increased incidence of primary refractory AML. We have previously shown that BAALC overexpression increases AML cell proliferation and decreases cell sensitivity to chemotherapeutics. However, precisely how BAALC controls these cellular functions remains unknown.

Aims: The main aim of this study was to identify how BAALC overexpression controls AML cell proliferation and survival.

Methods: BAALC was overexpressed in a panel of AML cells, and reciprocal co-immunoprecipitations were performed to identify proteins that interact with BAALC. To elucidate the cellular functions mediated by these interactions, the expression of each interacting protein was reduced via siRNA transfection. Following this, effects on proliferation and survival were examined (cell counts, resazurin, Annexin assays).

Results: We have identified three novel proteins that interact with BAALC, and have shown that some of these interactions are responsible for the BAALC-mediated control of AML cell survival and proliferation.

Conclusions: BAALC is a potential target for the treatment of AML. Because BAALC has restricted expression in normal cells, drugs that target BAALC or its binding partners may present more cancer cell–specific effects than existing chemotherapeutics.

Translational research aspect: This T1 research has identified a new target for the treatment of AML. Further examination of this target may be useful therapeutically as a new strategy for the treatment of primary resistant AML.

P45

A NOVEL SCREENING TEST FOR PROSTATE DISEASE USING NUCLEAR MAGNETIC RESONANCE (NMR)

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Background: Identification of a more reliable biomarker for prostate disease is an unmet need. Nuclear magnetic resonance (NMR) spectroscopy is an established molecular technology with a proven ability in many diseases which could identify a molecular fingerprint of disease using metabolomics, the study of metabolic processes in biological systems. NMR gives a spectral signature for nearly every present chemical in a 0.5 mL serum sample. It has been shown that cancer metastases, in cellular profiling, exhibit profound metabolic shifts, leading to large changes in NMR profiles. This is supported by NMR metabolomic studies of patient serum and urine samples showing the possibility of delineating between healthy, benign and malignant conditions in ovary and breast.

Aims: Search for a novel and reliable prostate cancer biomarker from blood serum using NMR-based metabolomics.

Methods: Serum samples were subjected to data acquisition in 5 mm precision NMR tubes at 37°C. For statistical analysis, spectral pointwise segmentation between 0.02 and 10.00 ppm was used. The search for a robust and reliable fingerprint was performed using Aurelia-Amix.

Results: We found that peaks representing glucose, glutamate, threonine, glutamine and lysine were downregulated in disease patients when compared with healthy controls whereas phenylalanine and 3-hydroxyisovalerate were upregulated with disease subjects when compared with healthy controls. In addition, HDL, isoleucine, VLDL, and LDL were found to be upregulated in PCa compared to BPH.

Conclusions: NMR metabolomics detected differences in serum metabolites with potential discrimination between healthy and prostate disease, and offers potential biomarkers and therapeutic target in prostatic cancer.

Translational research aspect: This T1 research has demonstrated NMR metabolomics as novel screening test for prostate cancer that may provide clinicians with useful information to help make a more accurate decision about patient diagnosis, treatment and progress.

P46

OVARIAN TUMORS PRESENT AUTONOMIC AND SENSORY INNERVATION

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Background: The coexistence of cancer cells and nerves is increasingly reported in human tumors and is associated with a more aggressive cancer phenotype (Jobling et al., Cancer Res., 2015). Epithelial ovarian cancer is one of the most lethal gynecological cancers worldwide. We previously evidenced axons in ovarian tumors but the origin (sympathetic, parasympathetic, sensory) remains to be determined.

Aims: In this study we aim to further characterize the neuronal populations that invade ovarian tumors.

Methods: Tissue microarrays (TMAs) from human ovarian cancers were analyzed by immunohistochemistry. Antibodies against the vesicular acetylcholine transporter (VAChT), substance P (SP) and neurokinin receptor 1 (NK1) were used.

Results: NK1 immunoreactivity (IR) was present in 8/10 tumors and two normal ovary sections. Substance P-IR was observed in 8/18 of normal ovarian sections and 35/202 tumors. SP–IR was observed in axons, immune cells and neuroendocrine cells. VAChT-IR was observed in 150/202 ovarian tumors where it was expressed in axons, intrinsic neurons, cancer cells and other cells within the stroma.

Conclusions: Our data suggest that autonomic cholinergic and sensory (peptidergic) signaling is part of the ovarian tumor microenvironment and these pathways may offer novel biomarkers and therapeutic targets.

Translational research aspect: Tumor microenvironment and genetic makeup directly affects cancer progression. Our results indicate that nerves have to be considered as part of the tumor microenvironment in ovarian cancer. The interaction pathways between nerves and cancer cells may enclose valuable therapies and, cancer models may provide new representations of neuronal development.

P47

STIGMA-RELATED EXPERIENCES IN NONCOMMUNICABLE RESPIRATORY DISEASES: A SYSTEMATIC REVIEW

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Background: The stigma of non-communicable respiratory diseases (NCRDs) can be an important element of a patient's experience of his/her illness and a contributing factor to poor psychosocial, treatment and clinical outcomes.

Aims: This systematic review examines the evidence regarding the associations between stigma and patient outcomes, and compares findings across a range of common NCRDs.

Methods: Electronic databases and manual searches were conducted to identify original quantitative research published to December 2015. Articles which focused on adults diagnosed with asthma, chronic obstructive pulmonary disease, cystic fibrosis, lung cancer or mesothelioma; and included a measurement of stigma, were eligible for inclusion. Included articles were explored for study characteristics, stigma scores, correlates between stigma and patient outcomes, and methodological rigor.

Results: Twenty-five articles were included in the review, with four out of five related to lung cancer. No articles for cystic fibrosis were identified. Twenty unique stigma scales were used, with low to moderate stigma scores reported overall. Higher levels of stigma were experienced by chronic obstructive pulmonary disease and lung cancer patients. Stigma significantly correlated with all 6 patient-related domains explored (psychosocial, quality of life, behavioral, physical, treatment and work), which were investigated more widely in chronic obstructive pulmonary disease and lung cancer samples. No studies adequately met all criteria for methodological rigor.

Conclusions: The stigma literature was most common for lung cancer, which may suggest this population is more vulnerable to stigmatization compared to the other NCRD groups. The inter-connectedness of stigma to other aspects of patient experiences highlight that an integrated approach is needed to address this important issue. Future studies should adopt more rigorous methodology, including streamlining measures, to provide robust evidence.

Translational research aspect: This T3 research is directed toward exploring how the evidence may be applicable for recommendations or guidelines in general practice.

P48

LYNCH SYNDROME MUTATION SPECTRUM IN NEW SOUTH WALES, AUSTRALIA, INCLUDING 55 NOVEL MUTATIONS

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Background: Lynch syndrome, the most frequent hereditary colorectal cancer syndrome, is caused by defects in mismatch repair genes. Genetic testing is important in order to identify mutation carriers who can benefit from intensive surveillance programs. One of the challenges with genetic testing is the interpretation of pathogenicity of detected DNA variants. The aim of this study was to investigate all putative pathogenic variants tested for at the Division of Molecular Medicine, Pathology North, in Newcastle, Australia, to establish whether previous variant classification is in accordance with that recently performed in the InSiGHT collaboration.

Aims: To gain insight into whether local mutation interpretation is similar to that defined by a new internationally accepted classification scheme.

Methods: Prediction programs and available literature were used to classify new variants or variants without classification.

Results: We identified 333 mutation positive families, in which 211 different putative pathogenic mismatch repair mutations were found. Most variants with an InSiGHT classification (141 out of 146) were in accordance with our classification. Five variants were discordant, of which one can definitively be reclassified according to the InSiGHT scheme as class 5. Sixty-four variants had not been classified by InSiGHT, of whom 55 have not been previously reported.

Conclusion: We found that our classifications were mostly in accordance with the InSiGHT scheme. In addition to already known MMR mutations, we have also presented 55 novel pathogenic or putative pathogenic mutations.

Translational research aspect: Increased confidence in screening large numbers of patients can be gained by ensuring appropriate cross-referencing is undertaken so that patients are provided with as accurate knowledge as possible about their personal risk of developing colorectal and other cancers associated with Lynch syndrome.

P49

OVERCOMING BARRIERS FACED BY CANCER PATIENTS AND CLINICIANS TO ACHIEVE SMOKING CESSATION: STUDY PROTOCOL

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Background: The clinical relevance of quitting smoking following a cancer diagnosis is becoming an internationally recognized translational priority, yet the limited evidence suggests that the implementation of smoking cessation for cancer patients in Australia is poor. Our previous research suggests that is

in part due to health providers lacking context-specific knowledge and ready-made tools to assist patients to quit.

Aims: The proposed study aims to:

(1) Identify the facilitators and barriers unique to patients with cancer who are trying to quit smoking.
(2) Develop tailored smoking cessation education tools which address barriers to quitting, designed for oncology clinicians to use to providing smoking cessation care.
(3) Pilot test the developed tools to evaluate the acceptability and utility of the resources for both cancer patients and oncology clinicians.

Methods and Anticipated Results: The study will consist of:

(1) Qualitative interviews of cancer patients (current smokers or smoking at diagnosis, $n = 12–20$). The interview will elucidate the barriers and/or facilitators to quitting smoking.
(2) Production of a cessation handout for both clinicians and patients. The resources will be developed to assist in overcoming or utilizing the identified barriers/facilitators and will be refined via Delphi-style review.
(3) Pilot testing of resources – the clinician and patient resource will be piloted at three sites. Up to 30 patients and 10 clinicians will participate in qualitative interview to assess the utility of the resource.

Conclusions: There are few resources available for Australian oncology clinicians to provide personalized smoking cessation care to patients undergoing treatment. Testing the acceptability and efficacy of these novel resources holds immediate and direct implications for improving patient care.

Translational research aspect: By addressing the clear gap between the knowledge of the clinical benefits of smoking cessation, and the degree to which smoking cessation care is delivered, the project aligns with the T3 framework.

P50

SMOKING CESSATION CARE FOR CANCER PATIENTS: PATIENT PERSPECTIVES

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Background: Cancer patients who continue to smoke can face a host of deleterious treatment outcomes. Consequently, smoking cessation care for cancer patients has been as a translational priority. Despite this, there is little rigorous research on the extent, or quality, to which cessation support is offered to Australian cancer patients.

Aims: To identify the degree to which cancer patients report receiving smoking cessation care, and to describe patient beliefs regarding the appropriateness of such care.

Methods: Adult patients, regardless of smoking status, diagnosed with any cancer within the previous 6 months were invited to complete an anonymous paper or online survey while waiting for their scheduled oncology outpatient clinic appointment.

Results: A total of 281 patients completed the survey (35 [12.6%] current smokers, 117 [41.64%] former smokers). Eighty-three percent of all patients reported being asked about their smoking status, and approximately half of the current smokers and those who smoked at diagnosis ($n = 62$) reported being offered help to quit at least once. The majority of all patients supported smoking cessation care; with 93.9% agreeing that smokers should be offered to help quit as part of their treatment.

Conclusions: Patients report being asked about smoking status, yet there is limited opportunity to engage in provider-driven smoking cessation care activities beyond this initial point. Despite this, patients are generally receptive to information about smoking, and believe that there is a need to refer patients who do smoke to additional or external supports. Given the importance of smoking cessation for this population, methods to link patients with greater support need to be identified and tested in a clinically relevant manner.

Translational research aspect: Data from this project provided a sound foundation for a large-scale trial to implement routine smoking cessation care as part of routine practice and is therefore a T3 translational research project.

P51

PRECLINICAL INVESTIGATION OF A NEW CLASS OF DRUGS FOR THE TREATMENT OF GLIOBLASTOMA MULTIFORME

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Background: Glioblastoma multiforme (GBM) is the most common and aggressive form of brain cancer. The median survival time for patients with GBM is 14.6 months. As such, there is an urgent need to develop new therapies for GBM. However, few targeted therapies for GBM exist, and new targets suitable for the development of such therapies need to be identified. We propose that the protein brain and acute leukaemia, cytoplasmic (BAALC) is one such novel target. BAALC has restricted expression in normal cells, but is overexpressed in GBM.

Aims: The main aim of this study was to examine the preclinical effectiveness of BAALC inhibitors in GBM models *in vitro*.

Methods: Screening procedures with OpenEye software were used to search virtual libraries of over 4.5 million drug-like compounds for promising hits. Immunoprecipitations were performed to confirm binding to BAALC. The sensitivity of a panel of GBM cells to these molecules was determined (Annexin, resazurin, $n = 3$).

Results: Using computer modeling, we identified a druggable binding pocket in BAALC. Using our *in silico* screen, we identified 100 compounds that were predicted to bind within this pocket. We chose 20 compounds for further analysis, and showed that 7 of these compounds could bind to this BAALC binding pocket *in vitro*. Additionally, these BAALC-targeting drugs, as well as our peptide inhibitor (C310) killed a range of GBM, but not normal, cells *in vitro*.

Conclusions: The targeting of BAALC offers a new strategy for the treatment of GBM, and due to the restricted expression of BAALC in normal cells, drugs directed against BAALC may offer more cancer specific effects than current therapies.

Translational research aspect: This T1 research has identified a new target for the treatment of GBM. Further examination of this target may be useful therapeutically as a new strategy for the treatment of GBM.

P52

THE POTENTIAL OF ORGANIZATIONAL CHANGE INTERVENTIONS TO INCREASE THE DELIVERY OF SMOKING CESSATION CARE IN THE ALCOHOL AND OTHER DRUG TREATMENT SETTING: A SYSTEMATIC REVIEW

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Background: Smoking rates of clients in alcohol and other drug (AOD) treatment is high, an estimated 84% yet the assessment of smoking status is variable and provision of smoking cessation care (SCC) is low. Organizational change interventions aim to build the capacity of services by modifying current processes to ensure routine assessment and treatment of tobacco smoking. There is a developing body of research detailing organizational change interventions to increase the provision of SCC. This study aims to consolidate and examine the evidence of organizational change interventions in the AOD setting on: the provision of SCC practices and client smoking cessation.

Aims: This study aims to consolidate and examine the evidence of organizational change interventions in the AOD setting on: the provision of SCC practices and client smoking cessation.

Methods: MEDLINE, PsycINFO, CINAHL, EMBASE and Scopus were searched using keywords and MeSH terms from each database's inception to July 2016. Studies employing an organizational change intervention with the aim of increasing the delivery of SCC in the AOD setting were included. Two authors independently assessed studies for inclusion and extracted data.

Results: Of the 4625 identified studies, seven publications were included describing five unique studies. The study methodology of included studies was generally of poor quality and low level evidence (IV). Only one study reported changes to staff provision of SCC practices though staff self-reported provision was found to be non-significant, clients reported receiving more SCC and this was found to be highly significant ($P < 0.00001$). Client smoking cessation ranged from 7.5% to 41%, however only one study validated client self-reported abstinence.

Conclusions: Organizational change interventions have the potential to increase the provision of SCC and assist client smoking cessation though further research that employs more rigorous study methodology and validated measures are warranted.

Translational research aspect: This is T3 research.

P53

DO HEMATOLOGICAL CANCER PATIENTS GET THE INFORMATION THEY NEED ABOUT THEIR CANCER AND ITS TREATMENT?

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Background: Effective information provision can have a significant impact on psychosocial outcomes for cancer patients. In addition to legal and ethical imperatives for informed consent, appropriate information can influence patients' role and choices in decision-making regarding treatment. Information provision has been found to reduce psychological distress prior to cancer treatment, and improve anxiety, depression and quality of life when self-managing the symptoms and side-effects of cancer.

Aims: This study aimed to explore the experiences of hematological outpatients in obtaining information about their cancer and its treatment.

Methods: A cross-sectional questionnaire of adult hematological cancer outpatients was conducted in three metropolitan hospitals. Research assistants recruited eligible patients in outpatient clinic waiting rooms. Consenting participants completed two pen-and-paper questionnaires: the first examined demographics and disease characteristics and was completed at the time of consent; the second was completed by mail 4 weeks later. Participants indicated whether they received the information they needed about preparation for potentially threatening medical procedures and self-management, experiences regarding doctor-patient communication, and self-efficacy in seeking information and support. Items were derived from clinical practice guidelines where available.

Results: A total of 293 (84%) patients consented to take part in the study, with 171 (58%) completing both questionnaires. Overall, information experiences were largely positive and in accordance with guidelines. Areas identified as requiring improvement included: insufficient information regarding strategies for managing stress and anxiety related to medical procedures (20%); difficulty recalling information provided by their doctor (28%); information overload (26%); and insufficient opportunity to ask questions (23%).

Conclusions: There is room for improvement in the provision of guideline-recommended psychosocial care for hematological cancer patients. Findings emphasize the need for implementation of evidence-based strategies to aid recall of information post-consultation and minimize information overload.

Translational research aspect: This T3 research explored the experiences of patients in receiving guideline-recommended psychosocial care.

P54

RARE IMMUNE SUBSETS AS BIOMARKERS FOR IMMUNOTHERAPY TREATMENT RESPONSE IN METASTATIC MELANOMA PATIENTS

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Background: Until recently, the survival rate for metastatic melanoma was very low. With the advent of new immunotherapies and targeted therapies, some patients now have enduring disease free period. But for a large portion of patients, there is no response to these therapies and for some that do respond, the disease free time is short-lived. The current method of monitoring patients on immunotherapies is RECIST scores modified for immunotherapy. We propose a blood immune biomarker panel to ascertain patient response to immunotherapy in real-time. This would involve blood collected with the patients' usual monitoring bloods samples to investigate subsets of T cells, B cells and monomyeloid series. During tumor progression, circulating monocytes and macrophages are actively recruited into tumours. By monitoring the passage of these immune cells and the patients T cell and B cell response, a definitive visualization of the patients' response is identified.

Aims: To validate a panel of immune cell surface markers reflecting a patient's response to immunotherapy. These will include but not limited to T_{reg}, activated and naïve T cells, and tracking chemokines at three time points. To correlate clinical indicators of response with an immune cell surface panel.

Methods: Metastatic melanoma patients about to commence immunotherapy will be asked for permission to enroll in the study. Blood will be collected before treatment commencement, 21 and 42 days after initial drug dosage. A minimum of 30 patients will be enrolled in the study. Fluorescent bound antibodies to immune cell surface markers will be added to the whole blood

sample and incubated. Lysis buffer will be added, the sample washed and the fluorescence measured on the FACS CantoII. Gating for parent and daughter populations will be analyzed. The difference in cell populations between the three collections date will be analyzed for statistical significance between surface markers and collection points. These results will be correlated with clinical indicators of response.

Results: The predictive results of this study will reveal the subtle changes occurring in T- and B-cell populations in response to immunotherapy. The change in expression of surface cell markers such as PD-1 on CD8+ T cells and their circulating numbers reflect the intratumor microenvironment.

Conclusions: Patients with metastatic melanoma undergoing immunotherapy treatment do not know the results unless their tumors have been biopsied or undergo expensive MRI or PET scans. By identifying predictive T and B cell signature changes in the blood of metastatic melanoma patients, their response to immunotherapy can be measured. This will aid the patient as essential time will be saved and alternate therapies can be administered. The overall result will be to reduce the costs, stress and inconvenience to patients, by validating a blood biomarker profile that reflects the response to treatment early in the course of therapy.

Translational research aspect: This study is a T2 research strategy that will provide pilot data on the proposed blood biomarkers as indicators of response to immunotherapy. If successful, the blood biomarker panel can be translated into practice rapidly at low-cost.

P55

REACTIVATION OF ERK AND AKT CONFERS RESISTANCE OF MUTANT BRAF COLON CANCER CELLS TO THE HSP90 INHIBITOR AUY922

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Background: Oncogenic mutations of BRAF occur in approximately 10% of colon cancers and are associated with their resistance to clinically available therapeutic drugs and poor prognosis of the patients. Heat shock protein 90 (HSP90) plays an essential role in maintaining stability and activity of its clients, including many proteins that regulate signalling pathways involved in the pathogenesis of cancer. Targeting HSP90 has received considerable attention in the development of novel agents in cancer treatment.

Aims: To determine the potential effect of oncogenic mutations of BRAF on the response of colon cancer cells to HSP90 inhibitors.

Results: We found that colon cancer cells with mutant BRAF were more resistant to the heat shock protein 90 (HSP90) inhibitor AUY922 than those carrying wild-type BRAF, and that this was caused by rebound activation of ERK and Akt. Although AUY922 triggered rapid reduction in ERK and Akt activation in both wild-type and mutant BRAF colon cancer cells, activation of ERK and Akt rebounded shortly in the latter leading to resistance of the cells to AUY922-induced apoptosis. Reactivation of ERK was associated with the persistent expression of mutant BRAF, which, despite being a client of HSP90, was only partially degraded by AUY922, whereas reactivation of Akt was related to the activity of the HSP90 co-chaperone, cell division cycle 37 (CDC37), in that knockdown of CDC37 inhibited Akt reactivation in mutant colon cancer cells treated with AUY922.

Conclusions: These results identify that reactivation of ERK and Akt associated respectively with the activity of mutant BRAF and CDC37 renders mutant BRAF colon cancer cells resistant to AUY922, with implications of co-targeting mutant BRAF and/or CDC37 and HSP90 in the treatment of mutant BRAF colon cancers.

Translational research aspect: This project is currently at its T1 stage. It has the potential to advance to T2 and subsequently T3/4 stages depending on results from follow-up experiments.

P56

REACTIVE OXYGEN SPECIES DICTATE THE APOPTOTIC RESPONSE OF MELANOMA CELLS TO TH588

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Background: Cancer cells often have dysfunctional redox regulation that produces high levels of reactive oxygen species (ROS), which oxidize dNTPs leading to DNA damage. MutT homolog 1(MTH1) hydrolyses oxidized dNTPs thus protecting against DNA damage-induced cell death. Although MTH1 inhibition has been proposed to be a promising approach for cancer treatment, its effect on cancer cell survival has been elusive.

Aims: To define the mechanism by which the first-in-class MTH1 inhibitor TH588 kills melanoma cells and to identify predictive biomarkers of responses of melanoma cells to TH588.

Results: TH588 killed melanoma cells through apoptosis independently of its inhibitory effect on MTH1. Induction of apoptosis by TH588 was not alleviated by MTH1 overexpression or introduction of the bacterial homologue of MTH1 that has 8-oxodGTPase activity but cannot be inhibited by TH588. Of note, treatment with the oxidative stress inducer elesclomol also enhanced TH588-induced apoptosis, whereas a ROS scavenger or an antioxidant attenuated apoptosis triggered by TH588. Indeed, the sensitivity of cultured melanoma cells and fresh melanoma isolates to TH588 was correlated with endogenous levels of ROS. Mechanistically, killing of melanoma cells by TH588 was due to apoptosis, which was mediated by activation of Bad and downregulation of Bcl-2 and Mcl-1.

Conclusions: The results demonstrate that TH588 kills melanoma cells through induction of apoptosis by ROS and define the levels of endogenous ROS as a promising biomarker of the response of melanoma to TH588. These results suggest that TH588 alone or in combination with oxidative stress inducers is potentially useful in the treatment of melanoma.

Translational research aspect: This project is currently at T1/2 stages. Given that clinical evaluation of TH588 is being planned, the project will be potentially instructive for clinical application of the compound.

P57

TARGETED RESEQUENCING OF *BRCA1* AND *BRCA2* IN FAMILIAL BREAST CANCER

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Background: Inherited loss-of-function mutations in *BRCA1* and *BRCA2* predispose to high risk of breast cancer. Since the discovery of these breast cancer genes 20 years ago, there have not been any other genes identified that play a significant role in predisposition to inherited breast cancer. A large

proportion of individuals with inherited breast cancer are negative for *BRCA* mutations and despite numerous research efforts, further breast cancer susceptibility genes still remain elusive.

Aims: We hypothesize that potentially deleterious mutations may reside in the less-researched noncoding sequences. This study aims were to identify genetic anomalies in the *BRCA* genes by completely re-sequencing 200 kb surrounding *BRCA1* and *BRCA2* using next-generation sequencing.

Methods: For this study, DNA was used from 10 individuals referred for genetic testing after meeting the criteria for inherited breast cancer, and had been screened for *BRCA1* and *BRCA2* mutations by the Hunter Area Pathology Service (Newcastle, NSW, Australia). All individuals used for this study did not harbor causative genetic changes in the coding regions of *BRCA1* or *BRCA2*. Targeted sequencing of the entire *BRCA1* and *BRCA2* genes was performed.

Results: Common SNPs were removed from further analyses. Single nucleotide variants (SNVs) and insertions/deletions (indels) were identified in most individuals tested in regions that had previously remained unexplored, such as the noncoding regions, 5'-UTR, 3'-UTR and promoter sites.

Conclusions: The aim of this study is the increase in current knowledge of the genetic variations that results in the development and/or progression of inherited breast cancer, and aid in the management of individuals with breast cancers by providing a more specific diagnosis of disease risk.

Translational research aspect: Our results could be used as argument that it is important to screen the entire BRCA genes as mutations in "noncoding" regions could affect transcript expression and may predispose to breast cancer. This research fulfills T2 (Clinical Research), in which we can implement this diagnostic testing in the clinical setting to improve current screening practices

P58

AN ONCOGENIC LONG NONCODING RNA IN HUMAN COLON CANCER

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Background: Colon cancer is the second leading cause of cancer-related death worldwide. However, curative treatment of metastatic colon cancer remains an unmet health need. Long noncoding RNAs (LncRNAs) are a family of transcripts that do not encode proteins but are involved in regulating gene expression through interacting with DNA, RNAs, and/or proteins. There is increasing evidence showing that lncRNAs play important roles in the pathogenesis of cancer. Although a large number of human lncRNAs have been already identified, only less than 1% has been experimentally characterized.

Aims: To profile dysregulated lncRNAs and to define the functional significance of the identified lncRNAs in colon cancer cells.

Methods: Paired colon cancer and adjacent noncancerous colon epithelial tissues were subjected to transcriptome microarray. QPCR was used to confirm the changes in the expression of identified lncRNAs. ShRNA knockdown by lentiviral transduction was performed to inhibit the expression of selected lncRNAs. Colonogenic and MTS assays were used to reveal the impact of the lncRNAs on colon cancer cell proliferation and survival.

Results: One of the lncRNAs that were differentially expressed between colon cancer and normal colon epithelial tissues was markedly increased. Knockdown of this lncRNA significantly inhibited colon cancer cell proliferation. We are currently using the capture hybridization analysis of RNA targets (CHART) assay to identify its DNA and/or protein targets. The mechanism responsible for regulation of colon cancer proliferation will also be investigated.

Conclusion: We have found in this study that an array of lncRNAs are dysregulated in colon cancer cells, and have identified a lncRNA that plays important oncogenic roles in colon cancer cells.

Translational research aspect: This project is currently at its T1 stage. It has the potential to advance to T2 and subsequently T3/4 stages depending on results from follow-up experiments

1. "Wula" translates to "voice, a sound, a call" in Wiradjuri Aboriginal language.

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