ORAL PRESENTATION ABSTRACTS

SESSION 2A: Biomarkers – prognostic, predictive and disease monitoring roles

S01: INFLAMMATION IN CANCER

Stephen Clarke
Sydney Vital Translational Cancer Research Centre and Senior Staff Specialist in Medical Oncology, Royal North Shore Hospital

Cancer associated inflammation (CAI) contributes to the symptoms experienced by cancer patients including fevers, sweats and weight loss. When extreme, it results in the cancer cachexia syndrome, a major cause of cancer death. Our research over the last 10 years has focused on the impact of CAI on cancer treatment, including metabolism of cancer drugs and chemotherapy-induced toxicity as well as response and survival after treatment. We have shown that CAI results in reduced clearance of chemotherapy through hepatic drug clearance and transporter systems including CYP3A4. In addition, we have shown that evidence of CAI predicts for worse response and survival following treatment with chemotherapy in numerous malignancies including colorectal cancer, malignant mesothelioma, prostate, lung and head and neck cancer. A number of markers of inflammation have been used including white cell count, neutrophil to lymphocyte ratio (NLR) and the Glasgow Prognostic Score and each has its proponents. As yet the optimal inflammatory marker has not been defined. CAI is an obvious target for anti-inflammatory therapies designed to improve therapeutic outcomes. In addition, increased understanding of the biology leading to the development of CAI will provide further therapeutic options.

S02: POTENTIAL CLINICAL APPLICATIONS OF CIRCULATING TUMOUR DNA (CTDNA) IN COLORECTAL CANCER

Jeanne Tie[1,2,3], Hui-Li Wong[1], Rachel Wong[4], Luis A. Diaz Jr[5], Nickolas Papadopoulos[5], Robert Strausberg[6], Kenneth Kinzler[5], Bert Vogelstein[5], Peter Gibbs[1,2,3,6]
[1]*Walter and Eliza Hall Institute of Medical Research, Victoria, Australia,* [2]*Western Hospital, Victorian, Australia,* [3]*The Royal Melbourne Hospital, Victoria, Australia,* [4]*Eastern Health, Victoria, Australia,* [5]*Ludwig Center for Cancer Genetics and Therapeutics, Howard Hughes Medical Institute at Johns Hopkins Kimmel Cancer Center, Baltimore, USA,* [6]*Ludwig Cancer Research*

Prognostic and predictor markers in colorectal cancer (CRC) are urgently needed to optimize patient treatment and outcomes. As colorectal tumorigenesis are characterized by the accumulation of multiple genetic mutations, the detection of these molecular changes in patient's circulation represents an attractive way to monitor patient's disease status. The development of massively parallel sequencing and digital PCR technologies has enabled the identification/quantification of circulating tumour DNA (ctDNA) with high sensitivity and specificity.

In collaboration with the Vogelstein Laboratory at Johns Hopkins, several biomarker studies in CRC were initiated to assess the clinical validity and clinical utilities of ctDNA in multiple cohorts of CRC. The primary objective of our metastatic CRC study was to explore early changes in ctDNA concentrations during chemotherapy as a predictor of treatment response and survival. For the stage II colon cancer study, the main aim is to confirm that the presence of post-operative ctDNA is a marker of disease recurrence.

These prospective multi-centre studies collected serial blood samples for ctDNA and CEA analysis. Tumour and plasma were analysed for hotspot mutations in seven genes using massively parallel sequencing (Safe-SeqS).

In the metastatic CRC study, we found that ctDNA is detectable in a very high proportion of patients, and a significant drop in ctDNA concentration was seen after one cycle of chemotherapy. Early changes in ctDNA during chemotherapy are found to be independent predictors of tumour response (based on imaging) and progression-free survival. Preliminary data from the stage II study suggested that patients with detectable post-operative ctDNA after curative surgical resection had a shorter recurrence-free survival (median 231 days vs undefined, HR 25.73, log-rank $p < 0.0001$) and colon cancer-specific survival ($p < 0.0001$).

These early data suggest ctDNA is a promising marker of colorectal cancer disease status and if validated, have several clinical utilities in the management of patients with CRC.

S03: WHEREFORE ART THOU BIOMARKER(S)?: OPPORTUNITIES FOR PROTEOMICS

Mark Molloy
Macquarie University

Biomarkers to diagnose, determine prognosis and predict treatment response offer tremendous opportunity to improve the clinical care of cancer patients. Protein mass spectrometry has a unique role to play in biomarker analyses enabling the study of biomolecules that cannot be carried out using genomic techniques. Protein mass spectrometry is compatible with the analysis of biofluids, tissues and cells from cancer patients and is increasingly used to examine post-translational enzymatic modifications of proteins. During this presentation I will provide examples of how we have been applying mass spectrometry-driven proteomics for biomarker discovery in various cancer settings. In colorectal cancer (CRC) we have studied both patient tumours and plasma and identified candidate protein markers that predict response to systemic chemotherapy in node-positive patients. We recently extended this study in the ASCENT trial to search for plasma biomarkers of early toxicity and response to targeted VEGF blockade. Many well established protein biomarkers on the cell surface or in secretions (e.g. CEA) are augmented with glycans. These add great heterogeneity to the biomolecule and have been mostly overlooked for biomarker purposes. In the setting of CRC we have identified many new sites in proteins of N-linked glycosylation and begun the task of characterising the population of glycan structures resident here and will evaluate these for their biomarker potential compared with conventional biochemical assays. In thyroid neoplasms we developed a multiplexed, targeted mass spectrometry assay with utility for distinguishing benign disease from carcinoma. In melanomas mass spectrometry profiling is helping to understand the molecular drivers of resistance to MEK inhibitors. These examples highlight the opportunities for deploying advanced mass spectrometry methods at various points of cancer initiation and progression.

S04: STC1 EXPRESSION IS ASSOCIATED WITH TUMOUR GROWTH AND METASTASIS IN BREAST CANCER

Andy C-M Chang[1,2], Judy Doherty[3], Lily I Huschtscha[1,2], Richard Redvers[3], Christina Restall[3], Roger R Reddel[1,2], Robin L Anderson[3,4]
[1]*Cancer Research Unit, Children's Medical Research Institute, Westmead, New South Wales, Australia and* [2]*Faculty of Medicine, University of Sydney, Sydney, New South Wales, Australia,* [3]*Metastasis Research Laboratory, Peter MacCallum Cancer Centre, East Melbourne, Australia,* [4]*Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Australia*

Introduction: Stanniocalcin-1 (STC1) is a secreted glycoprotein implicated in several pathologies including cerebral ischemia, angiogenesis, inflammation and retinal degeneration. Aberrant STC1 expression has been reported in breast cancer but the significance is not clear.

Methods: High levels of STC1 expression were found in the aggressive 4T1 murine mammary tumour cells and in the MDA-MB-231 human breast cancer line. To investigate its significance, stable clones with

STC1down-regulation were generated in both tumour models. The mRNA expression of these clones and clones with a non-silencing vector was checked by northern blotting or PCR and confirmed with western blotting for protein expression. The consequences of STC1 down-regulation on cell proliferation, chemotactic invasion, tumour growth and metastasis were assessed. Microarray gene expression analysis was also completed to identify genes altered by STC1 down-regulation.

Results: Down-regulation of STC1 in the 4T1 murine mammary tumour cells had a major impact on mammary tumour growth. This observation was replicated in a second tumour model with the MDA-MB-231 human breast cancer line, with a significant reduction in primary tumour formation and a major inhibition of metastasis as well. Interestingly, in both models, proliferation *in vitro* was not affected. Subsequent gene expression profiling identified 30 genes to be significantly altered by STC1 down-regulation, the majority of which are associated with known hallmarks of carcinogenesis. Furthermore, bioinformatic analysis of breast cancer datasets revealed that high expression of STC1 is associated with poor survival.

Conclusion: This is the first study to show definitively that STC1 plays an oncogenic role in breast cancer, and indicates that STC1 could be a potential therapeutic target for treatment of breast cancer patients

S05: THE C-CIRCLE ASSAY AS A BLOOD TEST FOR ALT CANCER ACTIVITY

Joyce H Lee[1], International Sarcoma Kindred Study Consortium[2], Roger R Reddel[1], Jeremy D Henson[1]
[1]*Children's Medical Research Institute, Cancer Research Unit, Westmead, 2145, Australia,* [2]*The Peter MacCallum Cancer Centre, Research Division, East Melbourne, 3002, Australia*

Most cancers rely on a telomere lengthening mechanism (TLM) for continued growth and survival. Alternative Lengthening of Telomeres (ALT) is the mechanism used by approximately half of bone cancers and brain cancers. Although no ALT-specific proteins have been identified, C-Circles, a type of circular DNA, appears to be a useful marker for ALT activity, as they are found only in ALT positive (ALT+) cells, and not in healthy cells. They have also been detected in the blood of ALT+ osteosarcoma patients (1). A C-Circle blood test could potentially be useful for monitoring tumour size or response to treatments in patients with ALT+ bone cancer, or to assist in early diagnosis. This is particularly important for childhood cancers, where radiation from CT and bone scans need to be minimised. Here we tested the sensitivity and specificity of the C-Circle blood test for ALT cancer activity on plasma samples from patients with bone cancers. The ALT status of the tumours was determined by detection of ALT-associated PML Bodies (APBs) in tumour samples. Because TLMs may be activated in white blood cells during respiratory tract infections, blood samples were also taken from otherwise healthy volunteers. The C-Circle blood test results matched the tumour APB data 75% of the time. C-Circles were not detected in the healthy volunteers, nor the patients with ALT negative tumours. These results indicate the C-Circle blood test can be used in a clinical setting for the identification of ALT tumours.

1. Henson, J.D. et al., DNA C-circles are specific and quantifiable markers of alternative-lengthening-of-telomeres activity. *Nat.Biotechnol.* 27: 1181–1185, 2009.

SESSION 2B: Targeted therapies – new targets, new drugs

S06: ONCOGENIC TARGETS IN MELANOMA: WE ARE NOT DONE YET

Grant A McArthur
Peter MacCallum Cancer Centre, St Andrews Place, East Melbourne, Victoria

Targeting oncogenic drivers in cancer has become an established approach to improve survival and quality of life in cancer patients. This is clearly illustrated through the targeting of BRAF in melanoma. However in melanoma a number of additional oncogenic drivers have been identified that mediate tumour cell survival and proliferation either alone or in cooperation with other oncogenes like BRAF. We have been examining these additional oncogenic drivers that have been identified through genome sequencing projects to understand their cancer biology and develop strategies to target these molecules that include NRAS, CDK4, RAC1 and the RNA processing factor RQCD1. One approach to develop novel therapeutic strategies to target oncogenic drivers is the use of high throughput siRNA screens. We have performed such screens in melanoma cells and identified networks that open new therapeutic opportunities for cancer. The rapid process in sequencing of cancer genomes is opening profound opportunities for the development of novel therapies that require integrated translational research teams of cancer biologists, genome biologists, computational biologists , drug discovery and development experts and translational clinical researchers.

S07: CHALLENGES AND OPPORTUNITIES OF USING NEW TECHNOLOGIES IN CANCER MUTATION TESTING

Sandra O'Toole
Royal Price Alfred Hospital and Kinghorn Cancer Centre

In recent years there have been significant breakthroughs in the treatment of specific subgroups of cancer patients with the identification of driver mutations in oncogenes and the use of targeted therapies. In melanoma the use of BRAF inhibitors has lead to dramatic responses (at least in the short term) and in lung cancer the use of tyrosine kinase inhibitors against EGFR and ALK has resulted in better outcomes for patients in terms of progression free survival and quality of life.

New molecular biomarkers are being discovered at an increasing pace but these generally are observed in only a very small proportion of tumours, posing the challenge of identifying multiple, low incidence changes in a single limited sample. Thus it has become that there are major advantages in identifying all potentially actionable or clinically important changes in a broad range of oncogenes and tumour suppressors to allow optimal personalisation of effective treatment. However, but this poses significant challenges for routine diagnostic use.

Next generation sequencing technologies has the potential to identify all such mutations but there are significant barriers to its implementation in routine clinical practice including limited size and tumour content of tumour samples, DNA damage from routine formalin fixation and paraffin processing, cost and turn around pressures. This lecture will highlight advances and breakthroughs in this exciting field but will also focus on central issues required for the safe, cost effective and reliable implementation of molecular biomarker testing to ultimately improve outcome for cancer patients. It will also focus on some of the barriers to the discovery and translation of novel predictive biomarkers.

S08: TARGETED THERAPIES: NEW TARGETS, NEW DRUGS

Georgina Long
Melanoma Institute Australia and The University of Sydney

The median overall survival for patients with metastatic melanoma was <10 months until 4 years ago. Targeted therapies, particularly those targeting the MAPK pathway, and immunotherapies, have extended the median survival to beyond 2 years. Patterns of resistance differ between the two groups of therapies; primary resistance is common for immunotherapies (70% of patients treated with CTLA4 inhibitors and 30% for PD1 inhibitors) whereas almost all patients initially respond to MAPK inhibitors. Acquired resistance eventually occurs in 60–70% of patients treated with MAPK pathway inhibitors, mostly via re-activation of the MAPK pathway. BRAF inhibitors induce an immune infiltrate in melanoma biopsies taken early during treatment, which may be enhanced due to the paradoxical activation of BRAF wild type cells e.g. T lymphocytes by BRAF inhibitors. Translational studies of drivers of resistance and response suggest we can improve responses and survival to these drugs, however it will require combinations of therapies, and the work behind this rationale will be presented.

S09: TARGETING THE DNA REPLICATION CHECKPOINT BY PHARMACOLOGIC INHIBITION OF CHK1 KINASE: A STRATEGY TO SENSITIZE APC MUTANT COLON CANCER CELLS TO 5-FLUOROURACIL CHEMOTHERAPY

Mariana Brocardo, Dr Estefania Martino-Echarri, Dr Beric Henderson
Westmead Millennium Institute

Colorectal cancer (CRC) is the second most common cancer in Australia for men and women and a major cause of cancer mortality. Current treatments most commonly involve surgery and chemotherapy, depending on stage and circumstance, and the single most common chemotherapeutic drug used at all stages of CRC is 5′-fluorouracil (5-FU). First-line treatment of CRC typically involves oral (capecitabine) or intravenous 5-FU plus leucovorin. A major clinical barrier to CRC modalities is relapse due to resistance of primary and secondary CRCs to the 5-FU treatment. The basis for this drug resistance is not well defined, but identifying at least one of the determinants of 5-FU resistance is essential to develop more effective 5-FU-based combination treatments. Truncating mutations in the adenomatous polyposis coli (APC) gene are known to be a major early driving force in CRC development, in > 60% of inherited and sporadic CRCs. We used a range of molecular-cell biology and immunofluorescence methods to show that colon cancer cells expressing truncated forms of APC exhibit a limited response to 5-FU and arrest without undergoing lethal damage. In SW480 APC-mutant colon cancer cells, 5-FU-dependent apoptosis was restored after transient expression of full length APC, indicating a direct link between APC and drug response. We found that inactivation of the Chk1 kinase by drug treatment allowed CRC cells to overcome the 5-FU induced replication block and undergo apoptosis. Our findings identify mutant APC as a tumor biomarker that determines resistance to 5-FU and importantly its presence contributes to the apoptotic Chk1 inhibitor response providing a selective strategy to sensitize CRC harboring APC mutations to 5-FU.

P10: A NEW TARGETED THERAPY FOR THE TREATMENT OF TRIPLE-NEGATIVE BREAST CANCER

Janet L Martin, Hasanthi C. de Silva, Carolyn D. Scott, Robert C. Baxter
Hormones and Cancer Division, Kolling Institute of Medical Research, University of Sydney, Royal North Shore Hospital, St Leonards, NSW 2065, Australia

Introduction: Triple-negative breast cancers (TNBCs) are characterised by the absence of estrogen and progesterone receptors (ER and PR), and lack of HER2 amplification, rendering them refractory to breast cancer therapies targeting these molecules. TNBCs typically express EGFR and insulin-like growth factor binding protein-3 (IGFBP-3), which potentiates growth-stimulatory signalling through the EGFR, mediated by upregulation of sphingosine kinase-1 (SphK1). We hypothesised that, because IGFBP-3 and EGFR are co-expressed in TNBC, combined inhibition of their signalling pathways may have potential as a novel treatment for TNBC.

Methods: A panel of TNBC cell lines representing the 6 subtypes of TNBC was studied. Expression of IGFBP-3 and signalling proteins was determined by RIA and Western blot, respectively, and cell proliferation was assessed using real-time imaging. IGFBP-3 signalling through SphK1 was inhibited using SKi-II or FTY720, and EGFR signalling using gefitinib. For *in vivo* studies, nu/nu mice were injected orthotopically with 5×106 cells, and i.p. treatment was started when tumours had reached ~100 mm3.

Results: Screening of 10 TNBC cell lines revealed IGFBP-3 expression ranging from 20 ng/ml to >900 ng/ml with the highest expression in basal-like cell lines. The different cell lines displayed markedly different proliferation rates under basal conditions. Proliferation of TNBC cells was inhibited by a combination of gefitinib and either SphK inhibitor when the drugs were used at concentrations that had minimal effect when used alone. Tumours in mice treated with the combination of gefitinib and FTY720 or SKi-II grew more slowly than those in mice treated with single agents.

Conclusions: The findings of this pre-clinical evaluation suggest that combined inhibition of EGFR and IGFBP-3 signalling through SphK1 may be of value as a novel treatment for TNBC. Because FTY720 and gefitinib are already approved for clinical use, rapid implementation is feasible. Supported by Cancer Council NSW.

SESSION 2C: Implementation research in cancer (1)

S11: USING GENOMICS TO MAKE A DIFFERENCE – CAN CLINICAL AND POPULATION HEALTH PRACTICE BE CHANGED SO THAT THINGS CAN BE "DONE BETTER"?

John L Hopper
School of Population and Global Health, The University of Melbourne

Since the early 1990s we have been conducting large scale population-based case-control-family studies of breast and colorectal with long term prospective follow-up. We have collected multi-generational family history data from multiple sources, including cancer verifications, measured lifestyle risk factors by questionnaire and measured a large number of known or putative genetic risk factors from blood samples, as well as molecular and other pathology features from tumour samples. These studies have produced insights not possible from other approaches, such as studying only highly-selected multiple-case families that have often challenged conventional wisdom.

The findings suggest ways that things could be "done better", but this implies a criticism of current clinical and population health practice and implementation has been inconsistent and problematic. I will discuss these successes and failures, and present new studies which will hopefully provide more and definitive information about how genomics might be used to lower the impact of these cancers. In particular, I will seek the audience's advice as to how implementation of future findings might be "done better".

S12: INTEGRATION OF SUPPORTIVE CARE AND CLINICAL RESEARCH – OVERCOMING BARRIERS TO IMPLEMENTATION

Kate White
Cancer Nursing Research Unit, The University of Sydney

The development of new therapies has led to significant benefits in survival, for both solid and haematological malignancies. Rapid translation into clinical care has been a priority, and occurs in cancer faster than most other clinical settings. However, there remain many examples of barriers to effective implementation of new treatments. One significant gap is the area of supportive care, and evidence for optimal management of side effects associated with new treatments. This paper will examine the role supportive care has in implementation of new treatments, and how to maximise opportunities to integrate supportive care research in parallel to new treatments.

S13: REMOVING THE CANCER EMPEROR'S CLOTHES: HOW RESEARCH MOVED INTO PRACTICE WITH PLAIN TOBACCO PACKAGING

Simon Chapman
Sydney School of Public Health, The University of Sydney

On December 1, 2012 Australian became the first nation to implement the plain packaging of tobacco products. Today, another six nations (Ireland, UK, New Zealand, Turkey, South Africa, France) have either passed legislation or announced that they plan to. The passage of the legislation saw massive resistance from the tobacco industry which continues today. On July 17, the AHIW released data showing that daily smoking in Australia had fallen to a record low of 12.8%, with the percentage decline between 2010–2103 being the largest ever and plain packaging being the only plausible variable in the three year between the surveys. In this presentation, I will summarise the role of research in providing the rationale for plain packaging, in defending it from attack and in evaluating its impact.

S14: SMOKING CESSATION AFTER CANCER

Freddy Sitas, Marianne Weber, Sam Egger, May Chiew, Sarsha Yap, Dianne O'Connell
Cancer Research Division, Cancer Council NSW, Woolloomooloo, NSW 2011, Australia

Aim: To illustrate the importance of smoking cessation at the time of diagnosis on cancer survival, using a simple modelling technique.

Background and Methods: Smoking cessation reduces overall mortality, therefore smokers diagnosed with cancer ought to benefit significantly if they quit. However oncologists and cancer control organisations do not often provide smoking cessation support at the time of a cancer diagnosis. This is possibly because there is very little evidence regarding the benefits of smoking cessation on cancer survival.

We calculated 8-year absolute survival of people who quit smoking around the time of a cancer diagnosis ("recent quitters"), ex-smokers, continuing and never smokers using recently published mortality rates and applying these to cancer survival statistics from Australia and the USA.

Results: Eight year absolute survival, across all cancer types, was 37% for smokers, 43% for recent quitters and 49% for never-smokers in Australia, and in the USA was 43%, 49% and 54% for smokers, recent quitters and never-smokers, respectively.

Conclusion: The benefits of quitting smoking after a cancer diagnosis compared to continued smoking are potentially very large. While large studies are needed to provide robust estimates of the effect of smoking cessation on cancer survival, the existing literature and our estimates suggest it is prudent to implement smoking cessation in treatment guidelines as an essential part of cancer care.

S15: HEALTH SERVICE UTILISATION AND INVESTIGATIONS BEFORE DIAGNOSIS OF CANCER OF UNKNOWN PRIMARY (CUP): A POPULATION-BASED NESTED CASE-CONTROL STUDY

Claire M Vajdic, Andrea Schaffer, Timothy A Dobbins, Jane Barrett, Robyn L Ward, Chuang Ching Er, Sallie-Anne Pearson
University of New South Wales, University of Sydney, CUP Action

Background: There are no population-based data on the whole-of-system health care prior to CUP diagnosis.

Aim: To compare the pre-diagnosis use of health services and diagnostic investigations for patients with CUP and metastatic malignancy of known primary.

Methods: Population-based nested matched case-control study using linked routinely collected health records for Australian Government Department of Veterans' Affairs (DVA) clients, 2004–2007. 281 DVA clients registered with a diagnosis of CUP (C809) and 1102 controls randomly selected from clients registered with a diagnosis of metastatic malignancy of known primary. Controls were matched by month/year of diagnosis, health care entitlement, and follow-up prior to diagnosis. Consultations/visits and diagnostic procedures in the three months prior and the month of diagnosis were analysed using logistic regression adjusting for socio-demographic characteristics and comorbid conditions.

Results: There were no differences in GP or allied health consultations and hospitalisations, but CUP patients were less likely to have a specialist consultation (odds ratio 0.50, 95% confidence interval 0.33–0.76), and more likely to have an emergency department visit (1.60, 1.18–2.17). CUP patients were less likely to have non-surgical resection (0.65, 0.48–0.87), surgical resection (0.40, 0.28–0.58), exploratory surgery (0.21, 0.08–0.60), or endoscopy (0.31, 0.22–0.44), and more likely to have a CT scan (2.16, 1.47–3.19), ultrasound (1.82, 1.33–2.49), and MRI (3.02, 1.61–5.68). Cytology (1.60, 1.10–2.32) and immunohistochemistry (2.51, 1.60–3.93) were more common and histopathology less common (0.41, 0.27–0.63) for CUP patients.

Conclusions: Compared to known primary, CUP is more likely after an emergency department visit, less specialist input, and fewer invasive diagnostic procedures. This pathway might suggest delayed recognition of cancer and thus scope for improvement in the medical management of high-risk individuals presenting to GPs. There is under-investigation in some CUP patients but this may reflect recognition of limited treatment options and poor prognosis and is consistent with clinical guidelines for CUP.

SESSION 4A: Experimental therapies & discovery (1)

S16: TARGETED EDVTMNANOCELLS AS VERSATILE VECTORS FOR DELIVERY OF THERAPEUTICS IN CANCER: TRANSLATING A PLATFORM TECHNOLOGY INTO HUMAN CLINICAL TRIALS

Jennifer MacDiarmid, Himanshu Brahmbhatt
EnGeneIC Ltd

Effective cancer therapy continues to be a daunting challenge due mainly to considerable tumor cell heterogeneity, drug-resistance and dose-limiting toxicity of therapeutics. We have developed a versatile nano-cellular delivery vehicle based on bacterial minicells, that can be packaged with therapeutically effective concentrations of chemotherapeutic drugs, siRNAs or miRNAs and can be targeted to tumors via bispecific (scFv) antibodies where one end attaches to the nanocell and the other end can be directed towards a tumour cell receptor. A range of EDV^{TM}nanocell-based therapeutics have shown highly effective tumor stabilization/regression in the murine xenograft model and more significantly, in 17 case studies in dogs with late-stage endogenous brain tumors. Recently, we have completed a First-in-Man study in 28 patients with a variety of late stage tumours. The patients were dosed once per week for five weeks (one cycle) with EGFR-targeted nanocells packaged with paclitaxel and the therapeutic showed an excellent safety profile. We have also completed a Phase 1 trial in 14 patients with recurrent glioma using a different therapeutic, being EGFR-targeted nanocells carrying doxorubicin. There were no significant toxicities at the doses evaluated and a recommended phase II dose was identified based on cytokine profiles. Despite the low numbers of patients, the overall survival data compels the further clinical development of $^{EGFR}EDVs_{dox}$ in this serious unmet need. Since the EDV^{TM}nanocell is a platform technology, we are pushing ahead into a number of early clinical trials including nanocells loaded with miR-16 for mesothelioma patients. Additionally, a "tailor-made" medicine trial protocol in late-stage patients with drug resistant tumours such as non-small cell lung cancer and adreno-cortical cancer has been submitted to Ethics. This trial aims to test EDV^{TM} nanocells loaded with a variety of cytotoxic drugs to effect the best outcome for patients who have run out of treatment options. We believe that the EDV^{TM}nanocell platform has important applications in personalized cancer medicine.

S17: PHOTOPROTECTION BY VITAMIN D COMPOUNDS

Rebecca S Mason, Wannit Tonkao-on, Mark Rybchyn, Eric Song, Vanessa Sequiera, Gary Halliday, Vivienne Reeve Katie Dixon
Bosch Institute, University of Sydney; Dermatology, University of Sydney; Veterinary Pathology, University of Sydney

The production of vitamin D in skin from 7-dehydrocholesterol by UVB is well known. Less well appreciated is that vitamin D is metabolized in skin to the active hormone, 1,25dihydroxyvitamin D (1,25D), as well as other metabolites, and appears to have important actions locally, including protection from UV-induced DNA damage and photocarcinogenesis. Topical application of 1,25D and other analogs reduce several types of UV-induced DNA damage in mice and human subjects. The mechanism of the photoprotective effect is not fully understood, but enhanced expression of p53 in the presence of D compounds, which would facilitate DNA repair, and reduced production of reactive nitrogen species, which would otherwise inhibit repair, may contribute. We have recent evidence that expression of key DNA repair proteins are enhanced with 1,25D. Analog studies as well as experiments with variant vitamin D receptors and knockout of ERp57 protein, indicate that both vitamin D receptor and ERp57 are required for photoprotection, but results are consistent with a non-genomic mechanism.

The studies to date support the hypothesis that the vitamin D system in skin contributes to photo-adaptation and suggest that vitamin D compounds may be usefully incorporated into a topical application such as a sunscreen or after sun lotion to reduce DNA damage.

S18: ID4 CONTROLS MAMMARY STEM CELLS AND MARKS BREAST CANCERS WITH A STEM CELL LIKE PHENOTYPE

Simon Junankar[1,2], Laura Baker[1,2,5], Daniel Roden[1,5], Radhika Nair[1,2], Ben Elsworth[1], Sunil Lakhani[3], Peter Simpson[3], Chris Ormandy C[1,2], Sandra O'Toole[1,4], Alexander Swarbrick[1,2]
[1]*The Kinghorn Cancer Centre & Cancer Research Division, Garvan Institute of Medical Research, Darlinghurst, NSW Australia,* [2]*St Vincent's Clinical School, Faculty of Medicine, UNSW, Australia,* [3]*The University of Queensland, UQ Centre for Clinical Research, School of Medicine and Pathology Queensland, The Royal Brisbane and Women's Hospital, Herston, Brisbane, QLD, Australia,* [4]*Sydney Medical School, University of Sydney, Sydney, NSW, Australia,* [5]*These authors made an equal contribution*

Basal-like breast cancer (BLBC) is a heterogeneous poor prognosis disease, however its cellular origins and etiology are poorly understood. In this study, we show that ID4 is a key regulator of mammary stem cell self-renewal and marks a subset of BLBC with a putative mammary basal cell of origin. Using a novel ID4-GFP knock-in reporter mouse and single cell transcriptomics, we show that ID4 marks a stem cell-enriched subset of the mammary basal cell population. ID4 maintains the mammary stem cell pool by suppressing Notch, Brca1 and Elf5, key factors required for luminal differentiation. Furthermore, ID4 is specifically expressed by a subset of BLBC that possess a very poor prognosis and a transcriptional signature similar to a mammary stem cell. These studies identify a new mammary stem cell regulator, deconvolute the heterogeneity of BLBC and link a subset of mammary stem cells to the etiology of BLBC.

S19: LOSS OF VITAMIN D RECEPTOR IN BREAST CANCER CELLS ENHANCES BONE METASTASIS IN A MURINE MODEL OF BREAST CANCER

Konstantin Horas[1], Yu Zheng[1], Shu-Oi Chow[1], Colette Fong-Yee[1], Colin R. Dunstan[1], Hong Zhou[1], Markus J. Seibel[1]
[1]*Bone Research Program, ANZAC Research Institute, University of Sydney, Australia*

Breast cancer is one of the most prevalent malignancies and although diagnostic and therapeutic strategies have consistently improved over the past decades, up to 40% of patients will eventually develop bone metastases. We have previously demonstrated that vitamin D deficiency promotes the growth of human breast cancer cells implanted into the tibiae of nude mice. In the current study we aimed to define the role of the vitamin D receptor (VDR) in systemic breast cancer cell metastasis.

VDR expression was knocked down in the human breast cancer cell line, MDA-MB-231 ($MDA^{VDR-/-}$). Knock-down efficiency was ~80% compared to non-target (NT) controls. $MDA^{VDR-/-}$ and NT cells were transfected with a luciferase gene, and cells were injected into the left ventricle of female nude mice (n = 11 for each, $MDA^{VDR-/-}$ and NT). Systemic spread and growth of tumour cells were monitored by sequential *in vivo* bioluminescent imaging (BLI), high resolution X-ray and μ-CT imaging for a period of 30 days.

Compared to animals injected with NT-cells, mice receiving $MDA^{VDR-/-}$ cells developed more metastases at 5 ($p = 0.009$) and 10 days ($p = 0.03$) following intra-cardiac injection (Fig.1), with light emission measurements generating significantly higher values at all time points in $MDA^{VDR-/-}$ mice ($p < 0.01$). After 20 days, multifocal metastases were observed in all animals and tumours were visible on X-ray. However, mice injected with $MDA^{VDR-/-}$ cells had significantly larger bone lesions compared to control mice ($P < 0.01$).

We conclude that knockdown of the VDR in human breast cancer cells increases their systemic metastatic potential and promotes intra-skeletal growth, resulting in significantly greater tumour burden in mice injected with $MDA^{VDR-/-}$ cells. Our results indicate that the VDR itself impacts breast cancer cell invasiveness and growth.

S20: CAN ATRX DEFICIENCY BE EXPLOITED FOR ANTI-CANCER THERAPY?

Mingqi Han[1], Christine E Napier[1], Roger D Everett[2] and Roger R Reddel[1]
[1]*Cancer Research Unit, Children's Medical Research Institute, Westmead, NSW,* [2]*MRC-University of Glasgow Centre for Virus Research, Glasgow, Scotland, United Kingdom*

It has recently been found that many cancers which use alternative lengthening of telomeres (ALT) are deficient for ATRX. We are testing the hypothesis that ATRX deficiency may render cells susceptible to specific cellular stresses, which may make it possible to treat ALT cancers via a "synthetic lethal" approach. ATRX is a component of PML nuclear bodies (PML NBs), the functions of which include monitoring viral entry into the cell and defending against infection. This is referred to as intrinsic immunity, and is a third barrier to viral infection, together with innate immunity and adaptive immunity. This intrinsic antiviral resistance can be impaired if PML NBs are disrupted, and many viruses counter intrinsic resistance by expressing proteins which disrupt PML NBs in the early stages of virus infection. For example, herpes simplex virus type 1 (HSV-1) disrupts PML NBs by expressing a protein, ICP0, and consequently a mutant HSV-1 virus which is ICP0-null has severe difficulty in initiating viral replication in host cells. Previous knockdown studies showed that depletion of individual PML NB components could partially rescue the replication defects of ICP0-null HSV-1. We therefore hypothesized that ATRX-deficient ALT cells would lack resistance to ICP0-null HSV-1. To test this hypothesis, we compared the yields of wild-type (wt) and ICP0-null HSV-1 in a panel of 28 cell lines distributed in four categories: ALT/ATRX-, ALT/ATRX+, telomerase/ATRX- and telomerase/ATRX+. As expected, ICP0-null virus had a much lower plaque-forming efficiency than wt virus in telomerase/ATRX+ cells, but in many of the ALT/ATRX- cell lines the ICP0-null virus formed almost as many plaques as the wt virus. The data are consistent with the overall hypothesis that ATRX deficiency in ALT cells may render them more susceptible to specific cellular stresses.

SESSION 4B: Tumour immunology

S21: APPLICATIONS OF MONOCLONAL ANTIBODIES TO DENDRITIC CELLS FOR THE DIAGNOSIS AND TREATMENT OF HAEMATOLOGICAL AND OTHER MALIGNANCIES

Derek Hart[1], Georgina Clark[1], Zehra Elgundi[1], Phillip Fromm[1], Xinsheng Ju[1], Pablo Silveira[1], Kifah Shahin[1], Nirupama Verma[1], Douglas Joshua[2], Kenneth Bradstock[3]
[1]*Dendritic cell Biology and Therapeutics Group, ANZAC Research Institute, Sydney, Australia,* [2]*Institute of Haematology, Royal Prince Alfred Hospital, Sydney, Australia,* [3]*Blood and Marrow Transplant Service, Westmead Hospital, Westmead, NSW, Australia.*

Dendritic cells (DC) are specialized white blood cells involved in initiating, directing and regulating immune responses. Changes in DC have been documented in cancer and this knowledge is improving our understanding of how the development and progression of cancer evades the immune response. We have been developing monoclonal antibodies (mAbs) to DC surface molecules and studying the function of those molecules. This process has enabled us to define novel human DC subsets with unique functions and to develop DC diagnostic biomarkers. The potential to intervene at the induction of an immune response represents a novel therapeutic opportunity. We are developing monoclonal antibodies to DC that facilitate haematopoietic stem cell transplantation and maximize the intended therapeutic graft versus tumor effect. Human mAbs to CD300f are being engineered as potential therapeutics for acute myeloid leukaemia. Other mAbs are being developed to target DC for new therapeutic cancer vaccines.

S22: CELL AND GENE THERAPY UPDATE

John Rasko
Cell & Molecular Therapies, Royal Prince Alfred Hospital, Missenden Rd, Camperdown 2050; Gene and Stem Cell Therapy Program, Centenary Institute; Sydney Medical School, University of Sydney, Australia

It is an exciting time for genetic and cellular therapies. Since 1989 over 1500 Phase I/II studies of direct *in vivo* and cell-mediated gene therapy in diverse diseases have been completed (1). Substantial evidence of improved clinical outcomes has been shown in haemophilia B, immune deficiencies, haemoglobinopathies, immunotherapies and blindness. In the field of cellular therapeutics, applications have expanded beyond the foundation in autologous and allogeneic hemopoietic cell transplantation to mesenchymal and other adult cell therapy trials. Indeed, if pluripotent cells can be differentiated *ex vivo* to recreate and repair mature human tissues and organs then regenerative medicine will become a reality. However embryonic stem cells have been mired in controversy and clinical development has been forestalled (2). Medical and, in particular, stem cell tourism has become a billion dollar industry with increasing examples of false claims. Unregulated, untested or unsafe stem cell 'therapies' place the field at a challenging crossroad.

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2. Power C & Rasko JEJ. Will Cell Reprogramming Resolve the Embryonic Stem Cell Controversy? *Annals Int Med*, 2011 Jul 19;155(2):114–21

S23: CANCER IMMUNOTHERAPY – HOLY GRAIL OR PANDORA'S BOX?

Catriona McNeil
Chris O'Briene Lifehouse, Royal Prince Alfred Hospital

One of the hallmarks of cancer is the ability to escape regulation by the immune system. For decades, scientists and clinicians have attempted to intervene in the immune-regulation of cancer through a variety of strategies such as the administration of pro-inflammatory cytokines, vaccines, anti-tumour antibodies and adoptive cell transfer. In more recent years the development of immune modulating antibodies directed against the cytotoxic T-lymphocyte antigen 4 (CTLA4) and programmed cell death 1 (PD-1) checkpoints has led to a dramatic shift in how cancer clinicians treat traditionally refractory cancers such as melanoma and renal cell cancer, with flow-on effects for numerous other tumour types. While early phase clinical trials of such agents alone and in combination have shown unprecedented results, these treatments have been associated with a suite of new and sometimes life-threatening toxicities that require prompt recognition and management. However, the prospect of dramatically changing the outcomes for patients with a variety of solid tumours is now a distinct possibility with some commentators now raising the prospect of potential cure. This review will summarise the pros, cons and promise of cancer immunotherapy, with particular reference to melanoma.

S24: A SAFETY STUDY TREATING CANINE CANCER PATIENTS WITH AUTOLOGOUS VACCINES

Chris Weir[1], A. Ross[2], M. Alexander[2], V. Langova[3], P. Britton[4], P. Bennett[5], M. McClellan[6], R. Mullins[7], D. Thomson[8], S. Clarke[1], N. Pavlakis[1], R. Davey[1] and V.M. Howell[1]
[1]*Bill Walsh Translational Cancer Research Laboratory, Kolling Institute of Medical Research, Royal North Shore Hospital and the Sydney Medical School, University of Sydney, Sydney Australia,* [2]*Ku-ring-gai Veterinary Hospital, Sydney, Australia, Hospital,* [3]*Small Animal Specialist Hospital, Sydney, Australia,* [4]*St George Animal Hospital Sydney Australia,* [5]*Sydney University Veterinary Hospital, Sydney Australia,* [6]*Normanhurst Vet Practice, Sydney Australia,* [7]*Lane Cove Veterinary Hospital, Sydney Australia,* [8]*Regeneus Ltd, Pymble, NSW, Australia*

Introduction: Cancer is a major killer of dogs, accounting for more than one quarter of all deaths. With strong parallels between canine and human malignancies in terms of spontaneous development and frequency, dogs provide a potential resource to trial new treatments which have shown safety and efficacy in pre-clinical studies. Following establishment of our autologous cancer vaccine in a pre-clinical model (Weir et al, Cancer Immunol Res. 2014), we began a canine safety trial in February 2011.

Methods: Informed owner consent was obtained by participating vets prior to vaccination. Participation was irrespective of tumour type, other treatments, or age. Tumours were surgically removed, partially resected or, if inoperable, tumour tissue was obtained from a biopsy. Tissues were frozen (-20°C) immediately after excision and then processed according to our published method. Dogs received two or four doses at 3 weekly intervals and were monitored for signs of anaphylaxis for 15 minutes post vaccination. Health and tumour progression were monitored during veterinary consultations.

Results: To date, our safety trial has treated 70 dogs with a variety of malignancies including melanomas, sarcomas, adenocarcinomas and lymphomas. No cases of anaphylaxis occurred and only 2 other minor side effects were reported. Survival efficacy was determined from estimates based on the natural history of the cancers, comparing actual versus expected survival times, based on individual oncology reports or published literature outcomes with surgery alone or standard of care for the respective tumour type. Preliminary data suggest that up to 70% of our canine patients demonstrated survival benefit after autologous vaccine treatment.

Discussion: The study provides an excellent safety profile in administrating autologous vaccines to canine patients with evidence of survival benefit. Phase II canine studies will start in 2014 in Sydney and USA*, and a human Phase I study* in 2015 (*sponsor led by Regeneus Ltd).

S25: THE ETS TRANSCRIPTION FACTOR ELF5 IS A KEY DETERMINANT OF THE LETHAL PHENOTYPE IN LUMINAL BREAST CANCER, DRIVING THE ACQUISITION OF ANTIESTROGEN RESISTANCE AND METASTATIC ACTIVITY

Dr David Gallego Ortega, Ms Anita Ledger, Dr Daniel Roden, Ms Christina Cho, Ms Stephanie Allerdice, Dr Heather Lee, Dr Fatima Valdes-Mora, Mr Robert Salomon, Dr Samantha Oakes, Prof Christopher Ormandy
Garvan Institute of Medical Research

Key pathways driving normal mammary development are often hijacked and subverted by the carcinogenic process. This is the case for the ETS transcription factor Elf5, a master regulator of mammary alveolar development that specifies the formation of the estrogen receptor negative (ER-) secretory lineage during pregnancy. We have recently discovered that Elf5 acts during the specification of the basal breast cancer subtype by opposing estrogen action via direct transcriptional repression of FOXA1. This mechanism is also apparent in luminal breast cancer cells that have become resistant to anti-estrogen therapy. Basal and estrogen resistant breast cancers are characterised by a higher risk of metastasis and poor prognosis. Using our Elf5-inducible MMTV-PyMT mouse mammary tumour model and the human breast cancer MDA-MB-231 cells, we demonstrate that Elf5

regulates epithelial-to-mesenchymal transition (EMT), driving an epithelial status resulting in impaired cell invasion and distant seeding. At the same time, however, Elf5 orchestrates profound changes in the tumour microenvironment that largely override these cell autonomous effects, leading to a dramatic increase of pulmonary metastases. Elf5 over-expressing tumours exhibit increased angiogenesis and haemorrhage indicating abnormal vascular reorganization. This phenotype is associated to an expansion of tumour infiltrating Myeloid Derived Suppressor Cells (MDSC) (CD11b+/Gr1+) and a consequent suppression of CD8+ T-Cells, a major mechanism of tumour microenvironment-induced metastasis in PyMT tumours. We have identified an identical inflammation signature associated with Elf5 expression in breast cancer patient cohorts using The Cancer Genome Atlas (TCGA) database. Importantly, targeting MDSC using specific Ly6G antibodies efficiently reduced Elf5-driven metastasis opening the door to a future immunetherapy for metastatic breast cancer patients.

Our discovery indicates that an anti-ELF5 therapy may act to maintain sensitivity to antiestrogens and simultaneously suppress the metastatic phenotype in luminal A breast cancers. Patterns of Elf5 expression may provide a marker predicting antiestrogen-insensitive metastasis in luminal breast cancer.

SESSION 4C: Quality of life, patient reported outcomes & survivorship issues

S26: DERIVING CANCER-SPECIFIC UTILITY WEIGHTS FROM THE QLQ-C30: A DISCRETE CHOICE METHODS EXPERIMENT

Madeleine King, Richard Norman, Daniel Costa, Neil Aaronson, Peter Fayers, Georg Kemmler, Deborah
Street, Galina Velikova, Tracey Young, Rosalie, Viney
University of Sydney, Centre for Health Economics, Norwegian University, Department of Psychiatry and Psychotherapy, Innsbruck Medical University, University of Technology

Aims: We aimed to assess the feasibility of using a discrete choice experiments (DCE) to generate utility weights for a preference-based measure derived from the widely- used cancer-specific quality of life questionnaire, the EORTC QLQ-C30, and to assess two DCE presentation formats in terms of clarity, difficulty and respondent preference.

Methods: The DCE was run in an Australian online panel. Respondents answered 16 choice pairs. Two presentation formats were tested, each in half of the choice pairs, with order of format randomised. In the "highlight" format, all domains were tabulated and domains which differed in level between a pair of choice options were highlighted in yellow. In the "text and table" format, domains with the same levels in the two choice options were described in text, and only domains that differed were tabulated. Ease and clarity of the choice task was explored for each format using Likert scales, and respondents were asked which format they preferred. Conditional logit analysis was performed on responses from each format and for the pooled dataset. Semi-structured telephone interviews (N = 8) explored respondents' approaches to the choice task and their reasons for format preference.

Results: 449 individuals were recruited to the valuation task; 430 completed at least one choice set and 422/449 (94%) completed all 16 choice sets. Respondents found 10 domains difficult but manageable, and many adopted simplifying heuristics to make the task easier. Results for the clarity and difficulty questions were identical between presentation formats, but the "highlight" format was preferred by 68% of respondents. Conditional logit parameter estimates were monotonic within domains, bolstering our confidence in respondents' ability to complete the DCE sensibly, yielding valid results.

Conclusions: The DCE was feasible. The "highlighted" presentation format will be used in definitive valuations planned for Australia, UK, Europe, Canada and USA.

S27: AUSTRALIAN IMPLEMENTATION OF SCALP COOLING FOR PREVENTION OF CHEMOTHERAPY INDUCED ALOPECIA

Frances Boyle, Lina Pugliano, Julie Winstanley, Kerrie Andrews, [1]Boyle F, [1]Pugliano L, [1]Dear R, [1]Winstanley J, Andrews K.
Patricia Ritchie Centre for Cancer Care and Research, Mater Hospital North Sydney 2060 and, [1]University of Sydney Medical School

Background: Chemotherapy induced alopecia (CIA) is one of the most feared consequences of cancer therapy. Scalp cooling has been widely used in Europe for amelioration of this side effect over the last decade, but uptake in Australia has been minimal. We report a single institution experience with implementation of scalp cooling in patients with early breast cancer over 3 years, and outline barriers, facilitators and current research.

Methods: We audited our results with 3 scalp cooling devices over a 3 year period, and surveyed staff and patients. International support was accessed from leaders of the Dutch Scalp cooling registry.

Results: The Penguin Cold Cap® system requires frequent cap changes, significant staff time, space and patient discomfort. Results were promising (approximately 50% grade 2 or less alopecia with anthracycline/taxane sequential adjuvant regimens). The newer Dignitana® and Paxman® coolant circulating systems avoid many of these difficulties and have similar success rates. Post-infusion cooling time requires attention to scheduling and chair utilisation to avoid delays in commencing therapy. Donors have been enthusiastic to support purchase of the equipment. Current research, in collaboration with international groups, will address improved measurement tools for assessing quality of life, online data collection systems to support a national registry, staff educational and translational issues influencing efficacy.

Conclusions: Scalp cooling is feasible, effective and welcomed by breast cancer patients in our unit. Wider implementation in Australia is a supportive care priority.

Acknowledgements: This work was supported by The Friends of the Mater Foundation and Dr Corina Van den Hurk of the Dutch scalp cooling registry.

S28: COGNITION AFTER CHEMOTHERAPY: AN OVERVIEW

Janette Vardy
Concord Cancer Centre, University of Sydney

Up to 70% of cancer survivors report changes in their cognition after undergoing chemotherapy. Studies that have formally tested neuropsychological function in women with breast cancer show that ~20–30% of survivors have cognitive impairment prior to receiving any chemotherapy, and 20–50% have impairment after chemotherapy. The cognitive domains most affected are: processing speed, learning and memory and executive function. There is a poor association between self-reported cognitive function and neuropsychological performance on formal cognitive testing. Cognitive symptoms are strongly associated with fatigue, anxiety and depression, and impaired quality of life; but these symptoms are not correlated with neuropsychological impairment on cognitive testing. The underlying mechanisms of cognitive impairment in cancer survivors are unknown, but hypotheses include: direct neurotoxicity, release of cytokines, hormonal changes, blood clotting in small cerebral vessels, and genetic predisposition. There are no proven interventions to prevent the cognitive impairment from occurring or to treat it.

An overview of seminal studies will be presented ranging from preclinical to our recent longitudinal cognitive study in colorectal cancer patients. Studies evaluating interventions will also be reviewed.

S29: A NEW CONCEPTUAL FRAMEWORK AND CLINICAL STRATEGIES TO MANAGE AND ENHANCE FAMILY INVOLVEMENT IN CANCER CONSULTATIONS

Rebekah Laidsaar-Powell, Phyllis Butow, Stella Bu, Cathy Charles, Amiram Gafni, Wendy Wing Tak Lam, Jesse Jansen, Kirsten McCaffery, Martin Tattersall, Ilona Juraskova
The University of Sydney

Introduction: Family members are often considered valuable members of the multidisciplinary team. However, their involvement in consultations can be challenging; disagreements about decisions may occur and patients' autonomy and privacy can be reduced. In three studies we explored patient, family and physician views on family roles, the roles they actually assume, and reviewed the evidence on this topic. We utilised this research to develop a novel conceptual framework and have proposed practical consultation strategies.

Methods: A brief overview of the three studies we conducted will be presented. 52 papers were identified in a systematic review exploring physician-patient-family communication and/or decision-making. Interviews were audiotaped, transcribed, and analysed with 30 patients, 34 family members, 10 nurses and 11 oncologists, regarding their attitudes and experiences. 20 audiotaped triadic oncology consultations were analysed and on the basis of all of the above a triadic interaction analysis coding system was developed and applied to 72 audiotaped cancer consultations.

Results: Health professionals possessed positive attitudes towards family involvement, despite sometimes finding their involvement challenging. Conflicting patient-family treatment wishes were particularly difficult. Health professionals stated that they utilise an array of strategies in triadic consultations. However, consultation analyses revealed that physicians rarely initiated interaction with family members and never clarified expectations or preferences for family members' role. In light of the results from the three studies, we will discuss a new conceptual framework for decision-making which includes family members. In addition, practical strategies for how health professionals can best manage and enhance family involvement will be proposed.

Conclusion: The involvement of family members is variable and dynamic, and can be helpful or challenging. A triadic decision-making conceptual framework may help guide future research about ethical family involvement in consultations. Additionally, dissemination of practical strategies or development of triadic skills training to improve consultation communication may be beneficial.

S30: WHAT'S IN A NAME: HOW DIFFERENT TERMINOLOGY IMPACTS COMMUNITY CONCERN AND TREATMENT PREFERENCES FOR DCIS

Brooke Nickel, Kirsten McCaffery, Jolyn Hersch, Ray Moynihan, Alex Barratt, Armando Teixeira-Pinto, Les Irwig
Screening and Diagnostic Test Evaluation Progra, The University of Sydney; Faculty of Health Sciences, The University of Sydney

Introduction: Ductal carcinoma in situ (DCIS) is a pre-malignancy of the breast. There is growing debate about whether the terminology used for DCIS may contribute to the desire for more aggressive management and overtreatment. We aimed to investigate the effect of using different terms for DCIS on perceived level of concern and management preferences.

Methods: We carried out a telephone survey among 500 Australian adults, using a randomised design and recruited participants via random digit dialling. Participants were given a hypothetical scenario of a DCIS diagnosis described as either abnormal cells (arm A) or pre-invasive breast cancer cells (arm B). Outcomes were hypothetical level of concern and management preference (treatment vs. watchful waiting). For each arm the terms were then switched and outcomes reassessed.

Results: The survey response rate was 47.5%. There was a high level of concern in both arms in response to a DCIS diagnosis (51.1% extremely concerned) and a strong preference for watchful waiting rather than treatment overall, 67.2%. There were no differences in initial concern or management preference by trial arm. However, women in arm A (who were given the abnormal cells terminology first) were significantly more concerned when given the alternative term (pre-invasive breast cancer cells) than woman in arm B who received the alternative order (52.0% vs. 66.7%, $p = 0.001$). 17.8% of women and 24.0% of men in arm A showed an increased preference towards treatment when the terminology was switched from abnormal cells to pre-invasive breast cancer cells, while only 5.4% of women ($p = 0.005$) and 2.1% of men ($p < 0.001$) changed their preference to watchful waiting.

Discussion: Given the growing evidence surrounding the overtreatment of DCIS, understanding how terminology plays a role is important. This study found that changing the terminology for DCIS can influence people's hypothetical level of concern and management preferences.

SESSION 5: Plenary

S31: BIG DATA LINKAGES: THE MAGIC BULLET FOR CANCER HEALTH SERVICE RESEARCH?

Sallie-Anne Pearson
Pharmacoepidemiology and Pharmaceutical Policy Research Group, The University of Sydney

Routinely collected health databases are used increasingly in cancer health services research. Established primarily for performance measurement or billing purposes, these databases capture millions of records of patients' interactions with the health care system. By virtue of Australia's universal health care arrangements, we are in a unique position to undertake large-scale, observational cancer research. We have comprehensive data on medical care, emergency department visits, hospitalisations and medicines dispensed in the community. Linkage of these health administrative datasets with other routinely collected data such as cancer and death registrations creates a powerful and comprehensive tool to investigate pathways to cancer diagnosis, patterns and outcomes of cancer treatment and end-of-life cancer care. Australia's capacity to undertake whole of health care research has been limited to date, due primarily to strict privacy legislation and the challenge of linking Commonwealth and State-based data collections. However, in recent years, significant investment has been injected into building infrastructure and processes to facilitate cross-jurisdictional data linkages for health service evaluation and research. In her presentation, Sallie will outline the health data linkage landscape in Australia, discuss the challenges and opportunities for undertaking population-based cancer health service research and highlight the potential of Australian cancer health services research using key examples of cross-jurisdictional research studies.

SESSION 6A: Experimental therapies & discovery (2)

S32: WHOLE GENOME METHYLATION SEQUENCING IDENTIFIES POTENTIAL EPIGENETIC- BASED CANCER BIOMARKERS

Susan Clark
Garvan Institute of Medical Research

Epigenetic alterations in the cancer methylome are common in cancer and provide novel options for tumor stratification. There are over 28 million CpG sites in the human genome and the challenge to date has been to assess the methylation state of each of these sites in different cell types and disease states in order to fully understand the role of DNA methylation in epigenetic-based molecular function. Advances in genome-wide DNA methylation technology have now enabled more comprehensive mapping of CpG methylation and identification of potential epigenetic diagnostic and prognostic cancer biomarkers. We recently performed whole genome methylation capture sequencing on DNA isolated from formalin-fixed, paraffin-embedded breast and prostate cancer and identified differentially methylated regions (DMRs) that were both cancer specific and had prognostic potential. Here, I will discuss the main protocols used for

methylome studies and compare genome coverage of promoters, genes and intergenic regions, capacity to quantitate individual CpG methylation states and finally summarise the extent of cancer methylomes that have been generated using genome-wide approaches.

S33: MICROTUBULE TARGETS IN CANCER: POTENTIAL OF NANOTECHNOLOGY-BASED THERAPEUTICS

Maria Kavallaris
Children's Cancer Institute

Background: Lung cancer is the most common cancer in the world and non-small cell lung cancer (NSCLC) accounts for 80% of all cases. The majority of patients are diagnosed with advanced stage disease that is poorly responsive to treatment and five-year survival rates are dismal. NSCLC is commonly treated with radiation therapy and/or a platinum based DNA damaging agent and a tubulin-targeted agent. High expression of the tubulin protein, βIII-tubulin (encoded by *TUBB3* gene) is strongly linked with clinical resistance and more aggressive disease in NSCLC and other epithelial-derived cancers such as ovarian and breast. We have previously shown that RNAi mediating gene silencing can sensitise NSCLC cell lines to not only tubulin-binding agents, but also to DNA damaging agents. Importantly, βIII-tubulin increased *in vivo* drug sensitivity and decreased tumour formation in NSCLC. Our goal has been to develop approaches to use RNA interference (RNAi) to silence *TUBB3 in vivo* and chemosensitise NSCLC tumours to current therapy.

Methods: We have established orthotopic human xenograft models of NSCLC that recapitulate the tumour environment and closely mimic the human disease state. We are using both siRNA and shRNA approaches to silence the *TUBB3* gene *in vivo*. For delivery of RNAi we have optimized nanoparticle-based delivery systems that can efficiently and potently silence *TUBB3 in vitro* and *in vivo*.

Results: Both siRNA and shRNA targeting of *TUBB3* can efficiently silence expression of this gene in orthotopic lung tumours. Importantly, *in vivo* suppression of the *TUBB3* gene sensitises the NSCLC tumours to chemotherapy, significantly prolonging survival.

Conclusions: *In vivo* suppression of the *TUBB3* gene sensitises NSCLC tumours to chemotherapy, highlighting this as a promising therapeutic strategy for the treatment of NSCLC.

S34: CANCER PROGRESSION AND RECURRENCE: WHAT WE CAN LEARN FROM EVOLUTIONARY BIOLOGY

Guy Lyons, Dr Erwin Lobo, Vanisri Raviraj, Vyomesh Patel, Nicole S. Bryce, Paul W. Sou, Cathy A. Payne,. Gary M. Halliday, J. Silvio Gutkind,.. Mary R. Myerscough
Dermatology, The University of Sydney; School of Mathematics, The University of Sydney; Nasopharyngeal Cancer Research, Cancer Research Initiatives Foundation

The progression from normal tissue to cancer and the resistance of cancers to therapies are generally accepted to be evolutionary processes, driven by the acquisition of mutations that confer a selective advantage on the cells. This is often seen as a simple process in which a lineal succession of ever-more malignant clones of cells dominate the tissue, culminating in a malignant clone that has accumulated all of the mutations needed for malignancy. However, in biological systems composed of whole organisms, evolution frequently develops through symbiotic relationships, in which adaptation to the environment depends on interactions between two or more organisms. Similarly, the adaptation of cancer cells to their microenvironment can be influenced by interactions with each other. For example, this can occur when distinct mutations in different cancer cell clones are mutually beneficial, enabling them to cooperate with respect to proliferation, dissemination or both. The existence of several evolutionary pathways that can be taken by cancers has important implications for their diversity, development and treatment. To explore the impact of clonal interactions on the early stages of cancer, we have developed biological and mathematical models to investigate the evolution of cancer cell clones in head and neck squamous cell carcinomas. We demonstrate that cooperation between genetically and phenotypically distinct clones of keratinocytes strongly influences the incidence and aggressiveness of tumours that arise from them.

S35: EXPLOITING HSA TO STIMULATE THE DELIVERY AND ANTI-TUMOUR ACTIVITY OF THE ANTI-CANCER THIOSEMICARBAZONE, DP44MT, TO CANCER CELLS

Angelica M. Merlot Ashleigh M. Fordham, Sumit Sahni, Namfon Pantarat, Danuta S. Kalinowski, Des R. Richardson
Molecular Pharmacology and Pathology Program, Department of Pathology and Bosch Institute, The University of Sydney, Sydney, Australia

Introduction: Di-2pyridylketone 4,4-dimethyl-3-thiosemicarbazones (Dp44mT) overcomes multi-drug resistance and demonstrates potent and selective *in vitro* and *in vivo* anti-cancer and anti-metastatic activity (*PNAS* 2006;103:14901–06; *EMBO Mol Med* 2012;4:93–108). Recently, we have discovered that 14C-Dp44mT enters tumour cells *via* a specific receptor (*Mol Pharmacol* 2013;84:911–24). Considering that human serum albumin (HSA) binds drugs to affect their pharmacokinetics, 14C-ligand uptake was assessed in HSA-containing medium to model the tumour milieu. This was important to assess considering that this class of thiosemicarbazones has recently been commercialized by our laboratory and will enter clinical trials in 2015.

Methods: 14C-Dp44mT and 125I-HSA were employed to assess membrane transport mechanisms using human SK-N-MC neuroepithelioma cells. Studies were compared to the more lipophilic thiosemicarbazone, 14C-2-benzoylpyridine 4-ethyl-3-thiosemicarbazone (14C-Bp4eT).

Results: Interestingly, unlabelled HSA significantly ($p < 0.01$–0.001) increased 14C-Dp44mT cellular uptake in SK-N-MC cells and a range of tumour cells. In contrast, HSA significantly ($p < 0.001$) decreased 14C-Bp4eT uptake. The augmented uptake of 14C-Dp44mT was specific to HSA, considering bovine serum albumin and the serum protein, transferrin, did not significantly alter 14C-Dp44mT uptake. Importantly, in contrast to Bp4eT, the anti-proliferative activity of Dp44mT (IC50: 40 ± 2 μM) was significantly ($p < 0.001$) increased in the presence of HSA relative to the ligand alone (IC50: 66 ± 4 μM). Moreover, HSA enhanced the apoptotic activity of Dp44mT, increasing the cleavage of poly(ADP-ribose) polymerase, while inhibiting that of Bp4eT. Subsequently, drug-protein binding studies demonstrated that these drugs bind to HSA, with Bp4eT binding more avidly than Dp44mT. Furthermore, 125I-HSA uptake occurred *via* an initial saturable transport process that was not altered by unlabelled Dp44mT or Bp4eT.

Discussion: These findings demonstrate that, in contrast to Bp4eT, the interactions of Dp44mT with HSA stimulate its uptake into cancer cells, enhancing its anti-tumour activity. As Dp44mT targets the lysosome to mediate it anti-cancer effects, HSA may aid uptake of Dp44mT by the specific Dp44mT receptor. Considering the clinical development of these drugs, the development of HSA-containing nanoparticles that increase their uptake could be a therapeutic option.

S36: METASTASIS SUPPRESSOR, N-MYC DOWNSTREAM REGULATED GENE 1 (NDRG1), INHIBITS PRO-SURVIVAL AUTOPHAGIC PATHWAY IN CANCER CELLS

Sumit Sahni, Dong-Hun Bae, Danuta S. Kalinowski, Patric J. Jansson, Des R. Richardson
Molecular Pharmacology and Pathology Program, Department of Pathology and Bosch Institute, University of Sydney, Sydney, New South Wales, Australia

Introduction: N-myc downstream regulated gene 1 (NDRG1) is a potent metastasis suppressor with an undefined role in the stress response. Autophagy is a pro-survival pathway and can be regulated via the PERK/eIF2α-mediated endoplasmic reticulum (ER) stress pathway. Hence, we

investigated the role of NDRG1 in stress-induced autophagy as a mechanism of inhibiting metastasis via the induction of apoptosis.

Methods: NDRG1 over-expression and silencing models were employed to assess its effects on autophagy in human pancreatic and colon cancer cells. Late stage autophagy inhibitor, Bafilomycin A1, was used to study the effect of NDRG1 on autophagy initiation. Selective silencing of PERK was performed using siRNA. The protein levels were probed by western blot analysis. Stress was induced using variety of stressors, such as iron chelators, serum starvation and tunicamycin.

Results: We observed increased expression of the autophagic marker, LC3-II, on incubation of cancer cells with variety of stress stimuli such as iron chelators, serum starvation and tunicamycin. This stress induced increase in LC3-II was dependent on activation of the PERK/eIF2α axis, as silencing PERK prevented LC3-II accumulation. NDRG1 over-expression inhibited basal autophagic initiation and the ER stress-mediated autophagic pathway via suppression of the PERK/eIF2α axis. Moreover, selective knockdown of NDRG1 resulted in increased accumulation of stress induced LC3-II levels. Notably, NDRG1 over-expression led to increased susceptibility of the cells towards stress induced apoptosis, potentially due to the ability of NDRG1 to suppress pro-survival autophagic pathway.

Conclusion: This study establishes the mechanistic relationship between NDRG1 and ER-stress mediated autophagy. This process occurs through an interaction between NDRG1 and the PERK/eIF2α axis. The observed suppression of autophagy could be important for ability of NDRG1 to induce apoptosis. Hence, this study further extends our understanding of mechanism via which NDRG1 exert suppression of metastasis.

SESSION 6B: Developing novel drugs for new targets

S37: NON-MUTATED PROTEINS AS TARGETS FOR CANCER THERAPY

Kenneth O'Byrne
Princess Alexandra Hospital and Queensland University of Technology, Queensland

The hallmarks of cancer comprise 10 biological capabilities of malignant disease that are acquired during the multistep development of human tumours. There are, however, only two major features of cancer that underpin all others – DNA instability and immune privilege.

The crucial role that DNA instability plays in malignant disease is underpinned by the knowledge that virtually all known mutations that predispose to the development of cancer, including those affecting BRCA1, BRCA2 and ATM, are DNA repair proteins. Furthermore, many of our cytotoxic agents function, at least in part, by increasing DNA damage and instability with the aim of inducing apoptosis or necrosis of the malignant cells.

In normal cells DNA damage leads to cell death. If this does not occur, however, DNA instability occurs and gives the cell an advantage, allowing genetic drift, spontaneous evolution and the development of heterogeneity. Ultimately this leads to changes in gene expression, development of driver oncogenes and loss of tumour suppressor activity responsible for the observed progression of malignant disease and the development of resistance to systemic therapies.

Recent work has identified a gene, human single stranded DNA binding protein (hSSB)1, that is the initial sensor of DNA damage and appears to have a similar key role in the detection and initiation of repair of oxidised nucleotides. This protein is overexpressed in solid tumours, is functionally normal and when targeted, in combination with irradiation (IR), results in dramatic cell death at non-therapeutic IR doses. A number of other rarely mutated proteins have likewise been identified that appear to be essential for cancer cell survival. These 'cancer permissive genes/proteins' are potential targets for therapy.

Increased understanding of the processes that underpin cancer immunity has likewise lead to the identification of a series of non-mutated proteins in cancer and immune cells that, when targeted, permit identification and destruction of cancer cells by the immune response.

As a result of these observations the current focus of therapeutic drug development targeting oncogene drivers in small subsets of patients will shift to those agents targeting normal proteins overexpressed in a large number of tumours that are key for cancer cell survival. This approach, underpinned by the evidence from immune therapeutics, will not only improve survival but cure some patients of their disease, often with fewer side-effects than from currently available therapies.

S38: DETERMINING THE EFFECTIVENESS OF TARGETED THERAPIES: CHALLENGES, STRATEGIES AND PITFALLS

John Simes
NHMRC Clinical Trials Centre and Sydney Catalyst Translational Research Centre, University of Sydney

With the ever increasing development of new therapies targeting specific pathways or tumour subtypes, the challenge to reliably determine which treatments are effective for which patients continues to grow. The problem is compounded by i) the shrinking patient numbers within each patient subpopulation ii) the increasing numbers of genetic or molecular profiles to define each potential subpopulation and iii) the multiplicity of potential research questions being tested across the many clinical trials evaluating these therapies.

Some design approaches to tackle this problem have included adaptive trial designs and/or enrichment designs with relevant subgroups. Underpinning the successful development of novel targeted therapies has usually been a very strong basic science or biological rationale. In addition, 3 approaches are now being advocated more routinely in the screening / assessment of new drugs: i) a greater use of non-randomised data to more rapidly assess new treatments ii) the search for reliable intermediate biomarkers as potential surrogates of efficacy and ultimately net clinical benefit and iii) the use of clinical trials of mutation-specific or biomarker specific profile across multiple tumour types to effectively increase patient numbers.

Each of these approaches has some potential to improve trial efficiency but at a cost of increasing false positive results, as illustrated by some recent examples. However, provided these strategies are combined with subsequent confirmatory randomised trials they are likely to play an increasing role in assessment of targeted therapies.

S39: USING PATIENT-DERIVED XENOGRAFTS TO DEFINE ACTIONABLE ABERRATIONS IN HIGH-GRADE SEROUS CANCER

Clare Scott
Walter and Eliza Hall Institute of Medical Research

Unfortunately, the major treatment regimens and poor survival outcomes for high-grade serous cancer (HGSC) have changed little in the last twenty years. Pre-clinical models have centred around cell lines which have recently been shown to poorly reflect human disease. In contrast, we and others have shown that patient-derived xenograft (PDX) models provide relevant, accurate and tractable models for pre-clinical testing. In addition to testing the "prognosis" of a particular HGSC, by demonstrating its response to the standard therapy, cisplatin, we can determine response to new therapeutics, such as PARP inhibitors and determine modes of drugs resistance.

We can also address utility of new next generation sequencing panels, by testing response of PDX to therapeutics indicated by potential molecular aberrations identified by next gen sequencing. This approach will help to clarify the utility of such testing and the potential role for it in the clinic. Barriers exist in that it is not yet routine for patients with relapsed ovarian cancer to undergo biopsy, let alone molecular testing. If choice of therapy can be altered by next gen sequencing testing, that could dramatically change the way we manage patients with ovarian cancer.

S40: RESTORING EXPRESSION OF MIR-7 BY TARGETED BACTERIAL MINICELLS INHIBITS THE MAPK/ERK PATHWAY AND OFFERS A NOVEL THERAPY FOR ADRENOCORTICAL CANCER

Anthony Glover, Jing Ting Zhao, Jocelyn Weiss, Natasha Vanegas, Glen Reid, Bruce Robinson, Patsy Soon, Himanshu Brahmbhatt, Jennifer MacDiarmid, Stan Sidhu
Kolling Institute of Medical Research, EnGeneIC, University of Sydney, The Ingham Institute

Background: Metastatic adrenocortical cancer (ACC) has a poor prognosis with limited treatment options. Pilot studies from our lab have identified a number of micro-RNAs, including microRNA-7 (miR-7) that are significantly under-expressed in ACC versus normal adrenal cortex, implying the involvement of microRNAs in the pathogenesis of ACC and its potential as a therapeutic target.

Aims: To establish the role and mechanisms of miR-7 as a tumour suppressor in ACC and to assess the role of miR-7 replacement therapy, delivered via bacterial minicells as a novel treatment.

Methods: miR-7 replacement was performed in ACC cell lines (H295R, SW-13) in 2D and 3D cell culture systems. A mouse xenograft model was established using the H295R cell line and primary cell cultures and systemic microRNA replacement therapy was administered in bacterially derived EGFR targeted EnGeneIC delivery vehicles (EDVs)/minicells.

Results: The role of miR-7 as a tumour suppressor in vitro was confirmed after replacement lead to reduced cell proliferation and cell migration ($P < 0.05$). Cell cycle analysis showed this to be due to G1 arrest ($P < 0.05$) with no difference in the rates of apoptosis. miR-7 predicated targets, EGFR and C-Raf were found, following replacement to have reduced mRNA and protein expression ($P < 0.05$). Luciferase reporting assays confirmed EGFR and C-Raf seed binding sequences as miR-7 targets. miR-7 replacement therapy in a mouse xenograft model caused significantly reduced tumour growth compared to control treated mice with no evidence of toxicity and reduced mRNA expression of C-Raf and mTOR ($P < 0.05$).

Conclusions: miR-7 acts a tumour suppressor in ACC by inhibiting the MAPK/ERK pathway and replacement therapy when delivered via targeted minicells offers a potential major advance in the treatment of this deadly malignancy.

S41: TUMOUR SUPPRESSOR FUNCTIONS OF MIR-192 AND MIR-193A-3P IN MALIGNANT PLEURAL MESOTHELIOMA

Marissa Williams, Michaela B Kirschner, Yuen Yee Cheng, Casey Wright, Jacky Hanh, James Edelman, Michael Vallely, Sonia Klebe, Nico van Zandwijk and Glen Reid
Asbestos Diseases Research Institute

Introduction: Malignant Pleural Mesothelioma (MPM) is an aggressive cancer caused by asbestos. The tumour arises in the pleural lining of the thoracic cavities and has a poor prognosis with limited treatment options. Previous studies have identified several microRNAs (miRNAs) to be differentially expressed between MPM and lung adenocarcinoma, however, their functional significance has not yet been investigated in MPM. The current study aimed to assess their potential as novel therapeutic targets.

Methods: RT-qPCR was utilised to test the expression of a panel of miRNAs in 64 tumour samples and 23 normal pleura controls. Down regulated miRNAs were re-expressed using synthetic mimics in 4 mesothelioma and 1 representative mesothelial cell line, after which the expression of target genes was measured using RT-qPCR and western immunoblot. Changes in cell growth, cell cycle and apoptosis were examined using standard growth assays and flow cytometry.

Results: We found that miR-192 and miR-193a-3p were both consistently down regulated in tumour samples compared to normal pleura controls. Following miRNA mimic transfection, the mRNA and protein expression of the target genes TYMS, MCL1, E2F1 and SRSF2 was reduced 2 to 3-fold. Cell proliferation in mesothelioma cell lines was markedly inhibited upon re-expression of miR-193a-3p and miR-192. Cell growth was unchanged in the mesothelial cell line. miR-192 and miR193a-3p re-expression resulted in disruption to the cell cycle, i.e. G1 arrest. Re-expression of miR-193a-3p also induced cell death, necrosis and apoptosis. This was most notable in the biphasic cell line MSTO, where apoptotic cells were increased by 15% and necrotic cells by 50%.

Discussion: This study has shown miR-192 and miR-193a-3p to be consistently down-regulated in MPM tumour samples compared to normal pleura. Re-expression of these miRNAs in MPM cells reduced cell growth, arrested the cell cycle and negatively regulated oncogenic targets making them suitable therapeutic candidates in MPM.

SESSION 6C: Implementation research in cancer (2)

S42: THE PROMPT-CARE PROJECT: EHEALTH SYSTEM UTILISING PATIENT REPORTED OUTCOMES TO INFORM PERSONALISED CANCER TREATMENT AND CARE

Afaf Girgis[1,2], Geoff Delaney[1,2,3], Anthony Arnold[1,4], Andrew Miller[4,5], Martin Carolan[1,4,6], Stephen Della-Fiorentina[7], Nasreen Kaadan[3], Sandra Avery[3], Nick van Domburg[8], Weng Ng[3], Kevin Spring[1], Cathelijne Van Kemenade[1], Ashley Maher[9] *
[1]*Ingham Institute for Applied Medical Research, Liverpool NSW 2170 Australia,* [2]*South Western Sydney Clinical School, UNSW Medicine, The University of New South Wales, Liverpool NSW 2170 Australia,* [3]*Liverpool Cancer Therapy Centre, Liverpool Hospital, Liverpool NSW 2170 Australia,* [4]*Illawarra Cancer Care Centre, Wollongong Hospital, Wollongong NSW 2500 Australia,* [5]*Centre for Oncology Informatics, University of Wollongong, NSW 2500 Australia,* [6]*Illawarra Health and Medical Research Institute, University of Wollongong, NSW 2500 Australia,* [7]*Macarthur Cancer Therapy Centre, Campbelltown Hospital, Campbelltown NSW 2560 Australia,* [8]*Information Services Department, Liverpool Hospital, Liverpool NSW 2170 Australia,* [9]*Didymo Designs, North Sydney NSW 2059 Australia*
**Funded by the Cancer Institute NSW Patient Reported Experience Collaborative Project Grant*

Introduction: Patient reported outcomes (PROs) are increasingly important in informing patient-centred care, with evidence of impact on patient care and outcomes for sub-groups of patients. Yet their collection in the clinic does not occur routinely.

Methods: Our newly developed eHealth decision-support platform facilitates collection and analysis of PROs (physical, psychosocial) from cancer survivors over time to inform patient self-management, with online evidence-based information and resources enabling patients to take an active role in decision making and in managing ongoing care and recovery. The system will be fully integrated into the existing hospital oncology information systems (OIS), providing clinicians with real-time reports of the PRO results, with evidence-based recommendations for addressing issues of concern, thereby promoting timely, PRO-tailored cancer care.

Results: The project is guided by a Steering Group and Technical and Clinical Advisory Groups, with consumer consultation. The PROs included in the pilot are symptoms (Edmonton Symptom Assessment Scale), distress (Distress Thermometer and checklist) and unmet needs (SCNS-ST9). We have developed algorithms to inform PRO intervention thresholds for self- and clinical-management; and clinician PRO feedback reports (summaries and longitudinal data); have collated patient self-management resources; and undertaken the IT programming to transfer PRO data in real-time to the OIS to support clinical decision making. Evaluation of feasibility and acceptability of this system-level strategy will inform the wider implementation of this system in clinical practice.

Discussion: This research will investigate implementation of evidence into "real world" clinical practice, through development of an efficient and user-friendly eHealth system to facilitate a) PRO data capture; b) data linkage and retrieval to support clinical decisions; and c) data retrieval to support ongoing evaluation and innovative research. Accumulated data will inform a) population level needs of cancer survivors to identify potential care gaps and b) impact of changes in service delivery over time.

S43: A SYSTEMATIC APPROACH TO CLOSING EVIDENCE GAPS IN CANCER CARE

Tim Shaw, Nicole Rankin, Deborah McGregor, Kate White, Jane Phillips, Phyllis Butow, Jane Young, Lyndal Trevena, Sallie Pearson, Sarah York
Sydney Catalyst Translational Cancer Research Centre, The University of Sydney, Australia

Background: Catalyst Translational Cancer Research Centre is a 5 year program funded by the Cancer Institute NSW. Catalyst covers a number of major research and cancer service centres across NSW. A key aim of Catalyst is to promote Implementation Science. Catalyst has funded a 2 year flagship project to address gaps in lung cancer.

Method: The Flagship Program has taken a systematic approach to creating a Implementation Program in Lung Cancer. This has included: a review of implementation frameworks to underpin a systematic approach; an gap analysis around lung cancer care using literature and local and international data; a priority setting process across three clinical centres (Lifehouse, St Vincent's and Orange); a process mapping exercise; and the establishment of implementation initiatives across these sites that is integrated into existing quality improvement programs matched to priority areas.

Results: The gap analysis identified seven evidence-practice gaps in lung cancer care. The prioritisation process (n = 42 participants) highlighted two priority gaps to target for implementation: reducing the time from first presentation of symptoms to diagnosis and referral for treatment, and improving early referral to palliative care services. The process mapping exercise resulted in detailed maps that show the patient journey from entry points into cancer services via primary care and emergency department admissions, routes to diagnosis and referral for treatment, through to survivorship or palliative care. These maps highlight the delays (e.g. symptom presentation), bottlenecks (e.g. interventional radiology) and complexities for patients navigating health services, particularly for those living in regional and rural areas (e.g. travel to Sydney for surgery).

Conclusion: Taking a systematic and structured approach based on evidence has resulted in engaged clinical teams, identified and prioritised gaps in cancer care, substantial capacity building in implementation science and a sustainable program that has attracted additional funding.

S44: LUNG CANCER REFERRAL INTERVAL TIMES: A MIXED METHODS STUDY

Geraldine Largey, Peter Briggs, Tracey Tobias
Southern Melbourne Integrated Cancer Service

Introduction: This study compares lung cancer referral intervals with agreed target measures across three public health services in Victoria and provides an insight into the experiences of clinicians in the diagnosis and treatment of lung cancer.

Methods: A retrospective medical record audit of 98 patients with a new diagnosis of lung cancer and 19 semi structured interviews with expert lung Multidisciplinary Teams (MDT's) members were conducted. A Likert scale of 1 (strongly disagree) to 10 (strongly agree) was used to establish a mean level of agreement with the influence of factors and initiatives on management of lung cancer. Interviews recordings were transcribed and thematically analysed.

Results: Approximately 70% of patients [n = 74] had a diagnosis of new lung cancer confirmed within the referral to diagnosis interval target of ≤28 days. About 50% of patients [n = 81] achieved the diagnosis to first treatment interval of ≤14 days. Indeed 29 cases waited longer than 30 days from diagnosis to first treatment. Only 31% [n = 6/19] of surgical, 42% [n = 8/19] of chemotherapy and 55% [n = 11/20] of radiotherapy patients achieved the referral to first treatment target of ≤42 days. Some records audited had insufficient pathway detail for analysis. Emerging themes highlighted systemic delays in the role and functioning of the lung MDT. The mean level of agreement with the influence of the key initiatives included: single point of referral contact [9.31]; escalation triggers [8.42]; MDT personnel to manage referral breaches [8.31]; greater consistency in measurement of referral times [7.84] and more robust definitions of target measures (7.47).

Discussion: This study demonstrates significant delays in the referral to first treatment interval, and identifies the aspects of the care pathway that have an adverse impact on timely treatment, including MDT decision making. Moreover, it provides expert consensus on a blueprint of initiatives to address impediments to timely patient treatment pathways which are transferrable to the wider arena.

S45: AN INTERNATIONAL SURVEY OF AWARENESS OF GENETIC RISK IN THE CLINICAL SARCOMA COMMUNITY

Kate A McBride, Tim Schlub, David Thomas, Martin Tattersall
The University of Sydney and The Kinghorne Cancer Centre

Introduction & Aims: Integration of clinical genetics into oncology is variable. For some cancers, genetic literacy is high. This is not the case for most cancers. Sarcomas have a strong genetic component, with 1/30 patients carrying germline mutations in TP53. We aim to define genetic risk awareness amongst sarcoma clinicians.

Methods: An online survey was emailed to membership of the Connective Tissue Oncology Society and the Australian Sarcoma Study Group, comprising a diverse group of clinicians working in the field of connective tissue tumours. 159 of 1200 recipients from 21 countries responded to the survey (13%). One hundred and twenty four sarcoma clinicians participated. Other respondents include researchers (9%), pathologists (6%).The primary outcome was attitudes towards genetic testing, levels of cancer risk, and awareness of risk reduction measures.

Results: 96% of clinicians indicated that they routinely take a family history during the initial consultation. 40% favoured routine TP53 mutation testing in children regardless of family history, increasing to 80% if a family history was present, and 87% if multiple primary cancers were present, regardless of subspecialisation. The likelihood of TP53 mutation carriers developing cancer approaches 80% by 50 years of age. 41% of clinicians estimated cancer risk accurately, while 37% thought the risk was less than 40%. Risk estimates were lower in older clinicians, surgeons, and in clinicians from the Asia-Pacific region (including Australia). 3% of clinicians were not aware that screening of at-risk individuals may identify some cancers at an earlier, more curable stage. 57% of clinicians were not aware that reproductive strategies exist to reduce the chance of passing on a mutation to offspring, although most clinicians (75%) considered these options acceptable. No significant differences were observed according to gender, subspecialisation, or age.

Conclusions: Because clinical genetics is not yet standard of care for multidisciplinary management of sarcoma, awareness of genetic risk is critical amongst the sarcoma clinical community. Although attitudes amongst the sarcoma community were generally positive, education on the implications and opportunities for genetic risk modification may improve quality of care.

S46: USING A MULTI- DISCIPLINARY PROGRAM OF CANCER CARE AS A VEHICLE FOR MORE EFFECTIVE RESEARCH TRANSLATION

Tracy Robinson[1,2], Anna Janssen[1,2], Tim Shaw[1], Paul Harnett[2]
[1]*University of Sydney, Sydney, Australia,* [2]*Sydney West Translational Cancer Research Centre, Westmead, Australia*

Background: Multi disciplinary teams (MDTs) are the model of cancer care in Australia and the UK. However, there is considerable variation in their performance and in the way they interact with research across the translational space from discovery to practice and policy. This study focuses on how to build systemic capacity for implementation science via a program of MDT cancer care.

Objectives: The study explored the factors that support MDTs to conduct more effective research translation in cancer care. In particular, we identified resources and tools that assist MDTs translate new evidence and improve the quality and coordination of care for people living with cancer.

Methods: The study used mixed methods to identify organizational systems and structures that support MDTs. Semi structured interviews were conducted with MDT leaders and champions to collect baseline information about how teams interact with and how they generate research and implementation initiatives. In addition, observations of MDT meetings were also undertaken to identify strategies for increasing the research output of MDTs and to improve quality of care for people with cancer in western Sydney. Subsequently, a process mapping exercise was used as an implementation technique to highlight areas for improvement and to identify structures and systems that support implementation effectiveness.

Results: The presentation will report on findings from interviews, the process mapping exercise and the observations of MDT meetings. Despite considerable variation in the way MDTs interact with and generate research, process mapping and observation are effective and powerful tools for implementation studies.

SESSION 8A: Advances in technologies for patient treatment

S47: TISSUE ENGINEERED HUMANIZED BONE SUPPORTS HUMAN HEMATOPOIESIS IN VIVO

Dietmar Hutmacher
Queensland University of Technology

Our work shows that it is possible to engineer a humanized ossicle in vivo which hosts a fully functional hematopoietic system and recapitulates both the morphology and function of an organ bone. We show, to our knowledge, for the first time that humanized bone is supportive of the lodgement and maintenance of human HSCs. After transplantation via the retro-orbital plexus, human HSCs preferentially home to the humanized ossicles, resulting in a significant higher level of bone marrow humanization than in the mouse femur. This new model makes it possible to unravel the interactions between human HSCs and their native niche within a murine host and could be an easy-to-use screening system for personalized therapeutic approaches.

S48: NOVEL ANTIBODY SCAFFOLDS FOR THERAPY OF SOLID TUMOURS

Andrew M. Scott
Ludwig Institute for Cancer Research, Olivia Newton-John Cancer Research Institute, and Dept. of Nuclear Medicine and Centre for PET, Austin Hospital, Melbourne, Australia

Background: The gene mutation changes responsible for many cancers are frequently associated with phenotype changes that involve changes in cell surface receptors and intracellular signalling processes, which can be abrogated by antibody therapeutics for clinical benefit. The engineering of antibodies for optimal targeting and therapeutic effect through signalling abrogation, immune effector function, and payload delivery, has emerged as a critical factor in the success of this approach in the clinic.

Methods and Results: We have explored the biology and therapeutic antibody approaches targeting EGFR in glioma, colon, head and neck and lung cancer using a novel antibody which binds to a conformationally exposed epitope of EGFR (mAb806). Validating the targeting of humanised 806 in preclinical models has been extended to human Phase I/II trials, where we have shown that imaging of biodistribution and tumour uptake can identify patient populations suitable for therapy. In conjunction with AbbVie, a tumour selective approach to payload delivery has been developed utilising an auristatin-antibody conjugate (ABT-414), and in a Phase I trial in GBM patients (NCT01800695) we have seen major clinical responses. Multi-centre clinical trials of ABT-414 are ongoing.

Optimisation of antibody size and structure may also enhance in-vivo behaviour and therapeutic ratio. We have developed in conjunction with Avipep a novel diabody approach to payload delivery, and have validated ^{124}I-PEG-AVP0458 for PET imaging of TAG-72 expression in tumour models[5]. This novel construct has been evaluated in a first-in-human Phase I trial (ACTRN12612000802808), which will have results available for presentation at the conference.

Conclusions: Novel engineered antibodies have improved therapeutic effects in cancer patients, and warrant further clinical studies.

S49: APPLICATIONS OF PATIENT-DERIVED SUBRENAL CAPSULE TUMOUR XENOGRAFT MODELS IN MICE

Aiqun Xue, Sohel Julovi, Thomas Hugh, Jaswinder Samra, Anthony Gill, Ross Smith
Kolling Institute of Medical Research, Royal North Shore Hospital, The University of Sydney

Objective: Patient-derived tumour xenografts (PDTX) may more faithfully emulate the molecular diversity, heterogeneity and histology of human tumours than traditional cell lines.

Methods: We have successfully established PDTX models by implanting fresh tumour in subrenal capsules of NOD/SCID mice and studied the stabilisation of the PDTX. The applications of this preclinical model for predicting gemcitabine response and novel combinations of anticancer drugs were also investigated.

Result: The passage of 5 generations of PDTXT tumour grafts demonstrated similar morphological features in terms of both architecture and cytology and there was a more than 90% success rate for xenografting. Those 5 generations of xenografts also consistently expressed similar levels of the proliferation marker Ki-67, cytokeratins 7 and 20, and SMAD4.

PDTX from 28 pancreatectomy patients who went on to receive adjuvant gemcitabine were established. Xenografts retained the histological and cytological features of the original counterparts. 7 patients' xenografts responded to gemcitabine similar to clinical observations (10, disease-free time >18 months after surgery). Xenografts from 14 of 18 patients who developed recurrence/metastasis were nonresponsive.

In PDTX subrenal capsule ($n = 90$) and sub-passaged ($n = 22$) xenografts, erlotinib (EGFR inhibitor) plus NVP-BYL-719 (BYL, PI3K-alpha inhibitor) significantly reduced tumour volume ($P < 0.005$). Strong pEGFR and pAkt immunostaining (2+/3+) in primary tumours was correlated with high and low responses respectively to erlotinib and erlotinib plus BYL.

Conclusion: The PDTX subrenal capsule xenografts are biologically stable at the molecular and genetic levels. The ability to passage fresh tumour tissue from individual patients through large numbers of mice holds promise to better predict treatment response to individual therapies and therefore improve the delivery of personalized medicine.

S50: QUANTITATIVE BIOLOGICALLY GUIDED CANCER TREATMENT USING MULTI-NUCLEAR MAGNETIC RESONANCE IMAGING

Yves De Deene
Macquarie University

In modern conformal radiation therapy, as much radiation dose as possible is delivered to the tumor while sparing the healthy tissue that surrounds it. Innovative radiation delivery techniques and dedicated software developments combined with increasing computer power enable the prediction of dose distributions obtained with these different treatment modalities. Uncertainties with respect to the position of the treatment target are further reduced by incorporating imaging techniques on the treatment machine (Image Guided Radiotherapy). As the radiation dose can now be delivered to the tumor volume more precisely with steep dose gradients between the tumor and the surrounding healthy tissue, other important challenges arise. Until now, in the practice of radiation therapy, the tumor has been considered as a solid homogeneous body that is invariant over time. However, it is well recognized by the (radiation) oncology community that this does not correspond with the actual situation. First of all, a physical tumor is biologically heterogeneous and secondly, the tumor changes, partially as a response to the fractionated radiation treatment.

Reoxygenation, redistribution, repopulation and tumor shrinkage may all modify the initial spatial and functional pattern on which the prescribed radiation dose distribution is based.

In order to translate the biological data to a prescription radiation dose, more quantitative detail on the tumor biology is required. Our research is directed towards the development of quantitative non-invasive magnetic resonance imaging (MRI) techniques that can map cellular density, oxygen concentrations (pO_2), pH, vascular density, blood fraction, molar metabolite concentrations in three dimensions. The combination of these techniques enables biologically adaptive and patient individualized radiotherapy called "dose painting". This is a research field that is highly multi-disciplinary and is not restricted to the life sciences but benefits largely from the input of physicists, software developers and biomedical engineers.

S51: DISTINCTIVE WATER DIFFUSION PROPERTIES OF EPITHELIA MAY BE THE KEY TO BETTER CANCER IMAGING TECHNIQUES

Roger Bourne, Carl Power, Aritrick Chatterjee, Gary Cowin, Nyoman Kurniawan, Geoffrey Watson
University of Sydney, UNSW, University of Queensland, RPA Hospital, Sydney

Introduction: Diffusion-weighted magnetic resonance imaging (DWI) has high sensitivity and specificity for cancer detection, most likely because because water diffusion is strongly affected by the same tissue architecture features that are used to define and grade solid cancers at histopathology. In clinical DWI cancer tissue exhibits a lower water apparent diffusion coefficient (ADC) than normal tissue, however, the responsible tissue structure changes are poorly understood and often misattributed to "high cellularity".

Methods: Formalin fixed human breast, prostate and skin tissue samples were imaged in a 16.4 Tesla magnetic resonance microscopy scanner using diffusion sensitive methods. Morphometric analyses of H&E stained sections of prostate tissue were performed to measure relative volumes of epithelium, stroma, and lumen space in samples of normal tissue and Gleason patterns 3, 4 and 5.

Results: The epithelial cell layers in prostate, breast and skin have lower ADC than their supporting stroma. Similar results have been reported for human oesophagus. Morphometric analysis of prostate tissue revealed much stronger correlations between volume of epithelium, stroma, and lumen space and cancer Gleason pattern than between cellularity measures and Gleason pattern.

Discussion: We hypothesize that the low ADC of cancer seen in clinical studies results from proliferation of low ADC epithelial cells rather than a higher cell density *per se*. Understanding and exploiting the distinctive water diffusion properties of normal and malignant epithelia may be the key to development of new clinical and preclinical cancer imaging techniques that probe both the tumour an its microenvironment.

SESSION 8B: Cancer genomics & pathways

S52: OESOPHAGEAL ADENOCARCINOMA GENOMICS

Andrew Barbour
Translational Research Institute

Oesophageal adenocarcinoma (OAC) incidence is rapidly increasing in Western countries. A better understanding of OAC underpins efforts to improve early detection and treatment outcomes. With a 5-year survival rate of ~15%, the identification of new therapeutic targets for EAC is greatly important. Statistical analysis of exome data has identified 26 significantly mutated genes, including previously implicated genes (TP53, CDKN2A, SMAD4, ARID1A and PIK3CA) and new significantly mutated genes including chromatin-modifying factors and candidate contributors SPG20, TLR4, ELMO1 and DOCK2. The majority of recurrently mutated genes in OAC are also mutated in the precursor lesion, non-dysplastic Barrett's oesophagus. Only TP53 and SMAD4 mutations occurred in a stage-specific manner, confined to Barrett's oesophagus with high grade dysplasia and OAC, respectively. While these sequencing efforts to date have found recurrent loss of function mutations, oncogenic driving events have been under-represented. Using a combination of whole genome sequencing (WGS) and SNP-array profiling, genomic catastrophes are frequently identified in OAC. These findings suggest that genomic catastrophes play a significant role in the malignant transformation of OAC.

S53: KNOW THY ENEMY: USING GENOMICS TO UNDERSTAND MOLECULAR SUB-TYPES OF EPITHELIAL OVARIAN CANCER

Anna De Fazio
Sydney West Chair in Translational Cancer Research; Obstetrics, Gynaecology and Neonatology, Westmead Clinical School; and Westmead Millennium Institute for Medical Research

Epithelial ovarian cancer is a poor-prognosis cancer and there has been little improvement in survival in recent decades. One reason is likely to stem from the fact that ovarian cancer has traditionally been treated as a single disease using a 'one-size-fits-all' approach, despite the fact that ovarian cancer is a heterogeneous disease, by several criteria. We have utilized the resources of the Australian Ovarian Cancer Study and the Gynaecological Oncology Biobank at Westmead, totalling over 3,000 patients, to investigate profiles that are predictive of treatment response and patient outcome in patients with ovarian cancer. Previously unrecognized patient sub-sets, and molecular subtypes, have been identified through analysis of genome-wide gene expression, SNP arrays (gene copy number variation) and next-gen sequencing. We have identified novel treatment targets, including *ANKRD1*, expressed in a sub-set of chemo-resistant ovarian cancer and screened drug libraries to find drug combinations that are able to sensitize ovarian cancer cell lines to treatment. In addition, we have investigated rare subtypes of ovarian cancer, namely low-grade serous ovarian cancer, which often occur in younger women and are not responsive to standard chemotherapy. We have found that Ras pathway mutations are more frequent in this group, including mutations in *NRAS*. This is in contrast with the most common ovarian cancer subtype, high-grade serous cancer, where mutations are usually in *TP53*. We have Phase 2 clinical trials underway using pathway-targeted agent in patients with the low-grade serous subtype. The outcomes of these and similar trials, and further development of predictive markers, will determine the likelihood of moving these targetted treatments into mainstream care. The recognition of sub-sets of ovarian cancer, with different molecular drivers and different treatment targets is an important step forward in improving clinical outcome through individualized cancer care.

S54: TARGETED THERAPY RESISTANCE AND IMPLICATIONS FOR PERSONALISED THERAPY IN MELANOMA

Helen Rizos
Macquarie University

The discovery of oncogenic mutations and pathways that drive melanoma progression has led to the development of selective small molecule inhibitors with significant clinical activity. Potent inhibitors of $BRAF^{V600}$ mutant protein, dabrafenib and vemurafenib, have produced response rates of 50–60%, and prolong the progression-free and overall survival of $BRAF^{V600E}$ melanoma patients, compared to chemotherapy. Despite this activity, 50% of patients treated with these inhibitors develop disease progression 6 to 7 months after starting treatment.

We have systematically screened over 80 $BRAF^{V600}$ mutant melanoma metastases derived from 40 patients treated with BRAF inhibitors alone or in combination with the downstream MEK kinase inhibitor trametinib. Acquired resistance mechanisms were identified in 67% progressing tumors and MAPK reactivation occurred in 84% tumours. Of patients with multiple independently excised biopsies we noted evidence of resistance heterogeneity and we also observed heterogeneity of resistance mechanisms within single progressing tumours. Further, we found that most melanomas carried additional oncogenic mutations at baseline (e.g. RAC1 and AKT3) that

activate the MAPK and PI3K pathways and are predicted to diminish response to MAPK inhibitors. Thus, durable responses in BRAF-mutant melanoma patients may require combination first-line therapy that selectively inhibits multiple proliferative and survival pathways.

S55: A NEW BETA-CATENIN REGULATORY PATHWAY AS A POTENTIAL TREATMENT TARGET IN COLON CANCER

Laurent Pangon[1], Dessislava Mladenova[1], Nicola Currey[1], Patrick Lecine[2], Jean-Paul Borg[2], Maija R J Kohonen-Corish[1,3]
[1]*Kinghorn Cancer Centre, Garvan Institute of Medical Research, Sydney, Australia,* [2]*Inserm U1068, CRCM, 27, Bd Lei Roure, 13009 Marseille, France,* [3]*St Vincent's Clinical School, UNSW Medicine, UNSW Australia*

Introduction: Mutated in Colorectal Cancer (MCC) is a multifunctional tumour suppressor gene showing loss of expression or mutations in colorectal and liver cancers. MCC is known to regulate several cellular pathways, such as beta-catenin signalling, which is hyperactivated in 90% of colon cancers. We aim to identify the pathway that mediates this function of MCC, which is independent of APC-mediated degradation of beta-catenin.

Methods: We used a yeast two-hybrid approach to identify new MCC-interacting partners and the TOPFlash reporter assay to monitor changes in beta-catenin signalling when MCC or its interacting partners are manipulated in colon cancer cell lines. Subcellular localization of proteins was determined with confocal microscopy.

Results: We identified Deleted in Breast Cancer-1 (DBC1) as a new MCC-interacting partner. DBC1 has either oncogenic or tumour suppressor activity in different types of cancer. Re-expression of MCC or knockdown of DBC1 repressed beta-catenin signalling in colon cancer cells. The tumour-derived MCC-R506Q mutation impaired the ability of MCC to bind DBC1 and to repress beta-catenin hyperactivity. RNA interference experiments further showed that the presence of DBC1 is required for MCC-mediated beta-catenin repression. DBC1 is the main inhibitor of Silent information regulator 2 homolog 1 (SIRT1), which is a known epigenetic repressor of beta-catenin signalling. Therefore, we next tested whether MCC re-expression can regulate acetylation of beta-catenin-K49, a SIRT1 target. Re-expression of MCC-WT, but not the MCC-R506Q mutant, reduced beta-catenin-K49 acetylation and caused DBC1 cytoplasmic relocalisation in RKO cells. Treatment of cells with the SIRT1 inhibitor nicotinamide reversed MCC-induced K49 deacetylation.

Conclusions: Taken together, these data suggest that cytoplasmic MCC-DBC1 interaction sequesters DBC1 away from the nucleus, thereby removing a brake on DBC1 nuclear targets, such as SIRT1, which can lead to deacetylation of beta-catenin. This study has discovered a new beta-catenin inhibitory pathway with potential therapeutic applications in cancer.

S56: POTENTIAL DRIVER GENES OF OVARIAN CARCINOGENESIS IDENTIFIED BY SLEEPING BEAUTY MUTAGENESIS

Emily K. Colvin[1], Emily Fuller[1], Jizhou Cheng[1], Anthony Gill[1,2], Deborah J. Marsh[1], Viive M. Howell[1]
[1]*Hormones and Cancer Division, Kolling Institute of Medical Research, University of Sydney, NSW 2065, Australia,* [2]*Royal North Shore Hospital, NSW 2065, Australia*

Introduction: Serous Epithelial ovarian cancer (SEOC) is the most lethal gynaecological malignancy in women. Germline mutation of *BRCA1* is the best known risk factor for developing SEOC, while somatic mutation of *TP53* is the most common genetic change in SEOC. However these changes individually, or combined, are insufficient to induce SEOC in mouse models, suggesting that additional unknown genetic factors are required for ovarian carcinogenesis. To identify these additional genetic factors we utilised Sleeping Beauty (SB) insertional mutagenesis.

Methods: The following genetically engineered mice were generated and cross bred: homozygous floxed *SB* (STOCK *Rosa26-LsL-DSB11; T2/Onc2*,TG6113), homozygous floxed *Brca1* knock-out (C57BL/6.*Brca1*^{tm2Brn}) and *Tp53* mutant (C57BL/6-*Trp53*^{tm1Tyj}/*J*). To delete *Brca1* and activate SB mutagenesis in the ovarian surface epithelium, adenoviral CRE recombinase was injected under the ovarian bursal membrane of mice. Tumours were assessed for SB transposase activity by immunohistochemistry. DNA extracted from ovarian tumours underwent high-throughput sequencing for T2/Onc2 insertion sites (Illumina, University of Iowa).

Results: Ovarian tumours were observed at low penetrance starting from 30 weeks post-surgery in SB$^{flox/+}$Tp53$^{mut/+}$ mice and SB$^{flox/+}$Brca1$^{flox/flox}$ p53$^{mut/+}$ mice. No tumours were observed in *SB*$^{flox/+}$*Brca1*$^{flox/flox}$ *or* SB$^{flox/+}$Brca1$^{flox/+}$ mice. Sequencing of insertion sites identified mutations in several genes, of which 67 were also altered in 10–30% of human cases from The Cancer Genome Atlas SEOC dataset (N = 316). This gene-set was enriched for kinases including *Fgfr2*, *Dyrk1a* and *Gsk3b,* and small GTPase regulators including *Smap2, Trio* and *Dock10*. Other genes of interest included tumour suppressor genes *Wwox, Arid1b, Cdh4.*

Conclusions: This screen identified several novel potential driver genes of ovarian cancer. In addition, genes previously associated with ovarian cancer were identified, providing proof of principle for this approach. Further investigation of several of these novel genes is currently underway and will lead to further insights into the pathogenesis of ovarian cancer.

SESSION 8C: Public health and translational research

S57: TRANSLATING EPIDEMIOLOGICAL RESEARCH IN GYNAECOLOGICAL CANCER INTO CANCER CONTROL

Penelope M Webb
Population Health Division, QIMR Berghofer Medical Research Institute, Brisbane, Qld, AUSTRALIA

Background: More than 3,500 women were diagnosed with ovarian or endometrial cancer in Australia in 2010, a doubling in the number of endometrial cancers (EC) and a 30% increase in ovarian cancer (OvCa) since 1990. The fundamental goal of epidemiology, the study of health states and application of this knowledge to control health problems, is clearly one of translation and we seek to achieve this through prevention and improving outcomes. This presentation will consider if, and how we are meeting this goal.

Methods: Primary data from national population-based case-control studies of ovarian (AOCS, 2002–6) and endometrial (ANECS, 2005–7) cancer and a national ovarian cancer patterns of care survey will be put into context with information from recent reviews and pooled analyses.

Results: One third of ECs may be attributable to obesity; reducing obesity rates would almost certainly reduce EC incidence, if not mortality rates. Options for prevention of OvCa are more limited although age-standardised rates in Australia are falling. This is likely due in part to use of the oral contraceptive pill (OCP) which prevents OvCa but is not without risk and cannot be recommended solely for cancer prevention. While standard health recommendations regarding breastfeeding, not smoking and body weight may prevent some OvCa, effects are likely to be modest. If we cannot prevent OvCa, can we improve outcomes? A national study found 50% of women did not receive the recommended dose/frequency of chemotherapy. Obese women may be more likely to receive reduced doses and also have worse survival. Evidence regarding other non-clinical options that might improve outcomes, quality of life and/or survival, is currently limited.

Conclusions: Practical options for prevention of OvCa are limited although addressing obesity will help control EC. Understanding how variations in care and modifiable aspects of lifestyle impact outcomes has potential to inform patient management.

S58: SURVIVORSHIP CARE FOR PEOPLE WITH COLORECTAL CANCER: A POPULATION-BASED SURVEY OF PATIENTS' EXPERIENCES AND PREFERENCES

Jane Young[1,2], Ivana Durcinoska[1], Kris Rogers[2], Mikaela Jorgensen[2], Michael Solomon[1,3]
[1]*Surgical Outcomes Research Centre, Royal Prince Alfred Hospital, Camperdown, NSW, Australia and School of Public Health, University of Sydney, Sydney, NSW, Australia,* [2]*Cancer Epidemiology and Cancer Services Research (CESR), Sydney School of Public Health University of Sydney, Sydney, NSW, Australia,* [3]*Discipline of Surgery, University of Sydney, Camperdown, NSW, Australia*

Background: Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with almost 1.4 million new cases in 2012. The number of cases is increasing with population growth and ageing. As a result of improved screening, earlier detection, and increased treatment efficacy, relative survival has improved markedly so that CRC is currently the second most prevalent cancer worldwide, with over 3.5 million survivors alive at 5 years after diagnosis. This increasing prevalence, together with substantial differences in individual patients' response to cancer and its treatment and a paucity of rigorous evidence about effective and cost-effective models of service delivery, means that the provision of survivorship care is a major challenge for cancer services.

Survivorship care includes surveillance for recurrent and new cancers, management of late and long term side-effects and secondary prevention. This study investigated received and recommended survivorship care among a population-based sample of colorectal cancer survivors across New South Wales (NSW) as part of the NSW Bowel Cancer Care Study.

Methods: Patients with newly diagnosed colorectal cancer, notified to the NSW Central Cancer Registry between 29 November 2012 and 31 May 2013 and who were 4–6 months post-diagnosis were asked to complete questionnaires on study enrolment and at 12 months post-diagnosis. Questions about experiences of, and preferences for, survivorship care were included in the follow up questionnaire.

Results: Of 1027 patients contacted, 560 participated (55%) at baseline. Respondents had a mean age of 68 years, 60% were male and 28% had rectal cancer. Follow up questionnaires were received from 484 participants (86% of baseline participants, 47% of invited sample). Patterns and predictors of guideline-recommended survivorship care, and patients' preferences for ongoing care, will be presented.

Conclusions: These findings will provide an empirical basis for the development of targeted strategies to improve the implementation of evidence-based survivorship care.

S59: IMPACT OF COMMON GENOMIC VARIANTS ON MELANOMA RISK PREDICTION

Anne E Cust[1], Minh Bui[2], Chris Goumas[1], Elizabeth A Holland[3], Graham J Mann[3], Mark A Jenkins[2] and Australian Melanoma Family Study Investigators
[1]*Cancer Epidemiology and Services Research (CESR), Sydney School of Public Health, Sydney Medical School, The University of Sydney, Australia,* [2]*Centre for Epidemiology and Biostatistics, Melbourne School of Population Health, University of Melbourne, Australia,* [3]*Westmead Institute for Cancer Research, University of Sydney at Westmead Millennium Institute and Melanoma Institute Australia, Sydney, Australia*

Background: Genome-wide association studies have identified numerous common genomic variants associated with increased susceptibility to melanoma, but there is limited knowledge about the utility of adding them to risk prediction models for melanoma.

Aim: To evaluate the contribution of common genomic variants to melanoma risk prediction, among young Australian adults.

Methods: The sample included 552 cases with invasive cutaneous melanoma diagnosed between ages 18–39 years and 405 controls from an Australian population-based, case-control-family study. *MC1R* genotype was sequenced, and through a genome-wide association study we obtained genotype data for single nucleotide polymorphisms from 18 selected gene regions. Measures of discriminatory accuracy included the area under receiver operating characteristic curves (AUC) and net reclassification improvement (NRI), calculated based on predicted probabilities of melanoma from unconditional logistic regression models. We used 10-fold cross-validation and bootstrap methods to assess internal validation.

Results: Compared to a demographic model containing age, sex and city of recruitment (AUC 0.69; 95% CI 0.65–0.72), the combined contribution to the AUC of common genomic variants was the same as that contributed from traditional self-reported risk factors for melanoma (UV exposure, pigmentation phenotype, nevi, etc) – both AUCs increased to 0.77 (95% CI 0.74–0.80). An inclusive model containing demographic, genetic and non-genetic (traditional) risk factors had an AUC of 0.81 (95% CI 0.78–0.84). Inclusion of genomic variants in the multivariate model improved the quartile classification of predicted risk (NRI) by a net 17% (95% CI 9–24) compared to the non-genetic (traditional) model.

Conclusions: Our results suggest that common genomic variants could considerably improve risk prediction models for early-onset melanoma, and may have a role in primary prevention of melanoma.

S60: INFORMING WOMEN ABOUT OVERDETECTION OF BREAST CANCER: RANDOMISED TRIAL OF A MAMMOGRAPHY SCREENING DECISION AID

Jolyn Hersch, Jesse Jansen, Les Irwig, Alexandra Barratt, Nehmat Houssami, Kevin McGeechan, Haryana Dhillon, Gemma Jacklyn, Kirsten McCaffery
The University of Sydney

Introduction: Mammography screening can cause overdetection of breast cancers that would not present clinically during the woman's lifetime. This RCT investigates the effects of information about overdetection on women's decision making about breast screening.

Methods: We developed an evidence-based decision aid explaining overdetection and other screening outcomes (breast cancer mortality reduction, false positives) with pictographs illustrating how often these occur among 1000 women screened for 20 years. We refined content and presentation through 49 user-testing interviews before starting a community-based RCT evaluation. Women aged 48–50 years (n = 1032) were randomised to receive the intervention described above or a control decision aid (mortality reduction and false positives only). The primary outcome is informed choice (adequate knowledge, and screening intentions consistent with attitudes) assessed via telephone interview 2 weeks post-intervention. Secondary outcomes include decision process and psychosocial variables.

Results: User-testing phase: Women found both decision aids clear and helpful, subsequently demonstrating good knowledge of general screening concepts (95% accuracy) whereas numerical knowledge was less accurate. Most women (91%) recognised that screening increases the likelihood of a diagnosis, though there was some confusion about the distinction between overdetection and false positives. Screening attitudes remained positive overall, with 85% of women intending to be screened.

RCT: Recruitment to the RCT was completed in early July, with data analysis to follow shortly. Main findings to be presented include the proportion of women making an informed choice, comparing the intervention and control groups.

Discussion: Mammography screening services worldwide are considering how to deal with overdetection, in the context of a broader international discussion concerning overdiagnosis and overtreatment. This RCT addresses the need for evidence about how best to accurately and sensitively inform women. Findings will help ensure that information on overdetection may be communicated clearly and effectively, using an evidence-based approach, to women considering screening.

S61: WHY ARE TWO IN FIVE PROSTATE CANCER CASES RECORDED AS HAVING "UNKNOWN" STAGE OF DISEASE IN AN AUSTRALIAN POPULATION-BASED CANCER REGISTRY? A STUDY OF HEALTH SERVICE FACTORS

Qingwei Luo, Xue Qin Yu, David Smith, David Goldsbury, Dianne O'Connell
Cancer Council NSW

Aims: To identify possible explanations for why stage at diagnosis was recorded as "unknown" for prostate cancer cases in an Australian population-based cancer registry.

Methods: Linked data for prostate cancer cases registered in the NSW Central Cancer Registry (CCR) in 2001–2007 and the NSW Admitted Patient Data Collection for 2000–2008 were used. Stage at diagnosis was recorded as localised, regional, distant or "unknown" by the CCR, using information received up to 4 months after diagnosis. We examined the distribution of cases with "unknown" stage at diagnosis by hospital cancer services for up to one year after diagnosis and used multivariable logistic regression to examine factors associated with "unknown" stage.

Results: Of all 35213 prostate cancer cases, 40.9% were recorded as having "unknown" stage. Of cases without a hospital diagnosis of prostate cancer within 4 months after diagnosis, 76.5% had "unknown" stage. For cases with a hospital-reported prostate cancer diagnosis up to 4 months after diagnosis, the proportion of patients with "unknown" stage was lowest for cases who had a radical prostatectomy (RP) in that time (6.8%). Of the remaining cases, 88.4% received non-RP procedures ≤4 months after diagnosis and 33.3% had "unknown" stage. Factors related to having "unknown" stage were: having prostate-related procedures other than "imaging and transurethral resection of the prostate (TURP)" (e.g. biopsy or TURP only, adjusted OR range: 1.37–1.86); attending a private hospital (adjusted OR range 1.48–2.03); or having a day only admission (adjusted OR = 1.19, 95% CI: 1.05–1.35).

Conclusions: Nearly 60% of cases with "unknown" stage could be explained by a lack of a prostate cancer diagnosis in hospital records or by a lack of notified episodes of care for prostate cancer occurring up to 4 months after diagnosis. However, a significant proportion of patients with "unknown" stage could not be explained using available data.

