The 2015 Hunter Cancer Research Symposium

Program

Friday 27th November 2015, 8.00am to 6:00pm
Hunter Medical Research Institute Building,
John Hunter Hospital
A Message from the Scientific Committee

Welcome to the 2015 Hunter Cancer Research Symposium.

The Hunter Cancer Research Alliance (HCRA) has over 300 members, ranging from PhD students to clinicians, research fellows and leaders of major cancer research programs. This Symposium aims to foster collaborations among cancer researchers operating across basic science, clinical research, clinical practice, public health and health services research.

The overarching theme of this Symposium is “excellence in cancer research, innovation and implementation”. This Symposium will cover the full spectrum of the translational research-to-practice continuum from basic science to clinical research and implementation research. We believe bringing together expertise from diverse research areas will ensure an invaluable forum for all participants.

Thank you to our speakers, Professor Stephen Fox and Professor Bogda Koczwara for accepting our invitation and sharing their wealth of expertise regarding cancer research; we are certain our invited speakers will contribute to the high scientific quality of this symposium.

Thank you to our oral and poster presenters for providing such high quality research presentations for our symposium. Finally, a warm welcome to all our delegates and thank you for your participation in what promises to be a great forum to share knowledge and grow valuable collaborations.

Let the journey of learning, discoveries and collaborations begin.

Warm Regards
HCRA Symposium Scientific Committee
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Scientific Committee Membership

**Professor Stephen Ackland**, Director, Hunter Cancer Research Alliance, Senior Staff Specialist, Department of Medical Oncology, Calvary Mater Newcastle, Hunter New England Health.

**Dr. Allison Boyes**, NHMRC and Cancer Institute NSW Early Career Fellow, School of Medicine and Public Health, Priority Research Centre for Health Behaviour, University of Newcastle.

**Dr. Anoop Enjeti**, HCRA Clinical Fellow, Staff Specialist Haematologist, Department of Haematology, Calvary Mater Hospital Newcastle.

**Dr. Mike Fay**, Staff Specialist, Department of Radiation Oncology, Calvary Mater Newcastle, Conjoint Senior Lecturer, School of Medicine and Public Health, Faculty of Health and Medicine, University of Newcastle.

**Ms Susan Goode**, HCRA Centre Manager, School of Medicine and Public Health, Faculty of Health and Medicine, University of Newcastle.

**Dr. Gillian Gould**, Research Fellow, School of Medicine and Public Health, Faculty of Health and Medicine, University of Newcastle.

**Dr. James Lynam**, HCRA Clinical Research Fellow, Staff Specialist, Department of Medical Oncology, Calvary Mater Newcastle.

**Dr. Christopher Oldmeadow**, Senior Statistician, Clinical Research Design, Information Technology and Statistical Support (CReDITSS) unit, Hunter Medical Research Institute.

**Associate Professor Christine Paul**, HCRA Implementation Science Flagship Chair, Associate Professor, Senior Research Academic, Priority Research Centre for Health Behaviour, University of Newcastle.

**Professor Rodney Scott**, Deputy Director, Hunter Cancer Research Alliance, Head of the Discipline of Medical Genetics, School of Biomedical Sciences and Pharmacy, Faculty of Health, University of Newcastle.

**Dr. Rick Thorne**, HCRA Resource Manager, School of Biomedical Sciences and Pharmacy, Faculty of Health, University of Newcastle.

**Dr. Nicole Verrills**, Cancer Institute NSW ECR Fellow, School of Biomedical Sciences and Pharmacy, Faculty of Health, University of Newcastle.

**Dr. Nicholas Zdenkowski**, Breast Cancer Clinical Research Fellow, Australia and New Zealand Breast Cancer Trials Group and Department of Medical Oncology, Calvary Mater Newcastle, Hunter New England Health.

**Professor Xu Dong Zhang**, NHMRC Senior Research Fellow, Senior Brawn Research Fellow, Oncology and Immunology Unit, University of Newcastle.
Invited Speakers

**Professor Stephen Fox**

*Professor and Head of Molecular Pathology Laboratory and Director of Pathology at Peter MacCallum Cancer Centre*

Stephen Fox is Director of Pathology at the Peter MacCallum Cancer Centre, Professorial Fellow at the University of Melbourne and an NHMRC Practioner Fellow. He moved in Feb 2006 from the University of Oxford where he was Clinical Reader in Pathology. Dr Fox took an Honours degree and Medical degree at the University of Bristol, UK before completing Pathology training in Oxford. He holds a DPhil in Medicine at the University of Oxford and Fellowships of both the Royal College of Pathologists Australasia and UK. He is a Founding Fellow of the Faculty of Science of the Royal College of Pathologist, the Chair of kConFab and sits on the Scientific Advisory Board, Breast and Genetics groups to the Cancer Council of Victoria. His current research is focused on predictive markers of response to therapies in several tumour types using protein and DNA-based assays.

**Professor Bogda Koczwara**

*Medical Oncologist at the Flinders Centre for Innovation in Cancer in Adelaide and the NHMRC Translating Research into Practice Fellow.*

Prof Koczwara has clinical interests in management of breast cancer, survivorship care, psycho-oncology and supportive care and she has a particular interest in strengthening the interface between specialist and primary care for cancer patients especially in rural Australia.

Professor Koczwara leads the Survivorship Program at the Flinders Centre for Innovation in Cancer. She is the Lead in Survivorship for the South Australian Health and Medical Research Institute Comprehensive Cancer Consortium and she leads the development and implementation of the survivorship framework for cancer patients in South Australia.

Professor Koczwara is the past President of the Clinical Oncology Society of Australia (COSA), the peak cancer professional organisation in Australia and the past president of the Medical Oncology Group of Australia (MOGA), the national professional organisation of medical oncologists. She is the initiator and the immediate past Chair the Australia Asia Pacific Clinical Oncology Research Development, a collaborative of international cancer organisations aimed at improving cancer research capacity in Australia and Asia Pacific.

Professor Koczwara has been recognized as a Member of the Order of Australia in January 2015 for her services to oncology through clinical practice, education and research and through a range of professional organisations.
Venue and Map

The 2015 Hunter Cancer Research Symposium will be held at HMRI, John Hunter Hospital Campus, New Lambton Heights NSW. The Symposium venue is located on Level 4 (Caves Lecture Theatre/Breakout space) and is accessible by road, following Kookaburra Circuit past the main entrance to JHH and around to the rear of the hospital.

Address:
HMRI, Lot 1 Kookaburra Circuit
NEW LAMBTON HEIGHTS NSW 2305

Key Phone Contacts:
HMRI Reception: 02 4042 0000
Security: 02 4042 0007
HMRI Building Emergency Procedures

Evacuation Point
In the case of an emergency where the HMRI Building needs to be evacuated, all building occupants are to meet at the evacuation point located at the mid-tier of the three car parks.

Fire stairways are located at each end of the building, and at the front of the east wing, towards the centre of the building (adjacent to the Pod, Level 1 entry and goods lift).

The evacuation point for the HMRI Building is located on the middle tier of the three car parks.

Fire
If you discover a fire in the Building, use the R.A.C.E. acronym:

**REMOVE**
Remove yourself and others from danger.

**ALARM**
Raise the alarm:
- Notify the Chief Warden.
- Call Fire Service, from a safe place - Dial '000'.

**CONTAIN**
Contain the fire by using correct fire fighting equipment (if safe and you are trained).

**EVACUATE**
Evacuate if smoke or fire is dangerous:
- Take others with you.
- Close doors behind you.
- DO NOT lock doors.

First Aid
The First Aid Room is located on Level 4 east wing, near the rear entrance to the ‘Caves’ Lecture Theatre (as shown on the maps on page 6).

First Aid Kits are also located on each level of the building and with Security Services on Level 4 of the Pod.

A list of First Aid Officers and their contact details is displayed with each First Aid Kit.
General Information

Symposium Rooms

The conference will be held in the ‘Caves’ Lecture Theatre, Level 4, East Wing, HMRI Building, JHH. Poster Session will be displayed in the breakout space opposite the theatre.

Registration Desk

The registration desk is located on Level 4. All delegates will be required to sign in when entering the HMRI building. Registrations open from 8 am. NB: If presenting a poster, please arrive 15 minutes prior to registration time to allow enough time to display.

Session Chairs

Please ensure that you are available in the session room at least ten minutes before the start of the session. Please refer to the program guide for session times. Any questions or concerns, please report to the registration desk.

Delegate Entitlements

- Entry to all symposium lectures including invited speakers
- Coffee, tea and juice on arrival
- Morning and afternoon tea
- Lunch
- Canapés and poster session
- Symposium materials including program and presentation abstracts
- Awards for Best Oral and Poster Presentations

Refreshments

All morning tea, lunch and afternoon tea breaks will be provided in the breakout space outside the lecture theatre. Refreshments are included in the registration. Cocktail reception including canapés, drinks will also be served on Friday evening after the event commencing at 5pm.

Delegate Name Tags

For security purposes, delegates will be required to wear their symposium name tags at all times during the event.

Mobile Phones

Delegates are advised to switch their mobile phones to silent during sessions.

Awards

The following awards will be presented during the award presentation:

**Oral Presentations:** Excellence in Translational Research, Best Student/ECR and Best Rapid Fire.

**Poster Presentations:** Best in Biomarkers and Targeted Therapies, Best in Implementation Science and Best Student/ECR.

Awards will be valued at $400 each.
Acknowledgements

De Iuliis - a fresh approach to creating wines truly expressive of the Hunter Valley

As one of the Hunter Valleys top producers, the De Iuliis family aims to make wines that are unique yet highly identifiable with a sense of time and place.

Our secret is attention to detail with a modern small-batch approach to winemaking. What’s not a secret is a vast array of awards and great reviews bestowed on us over the last few years.

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ORAL PRESENTATION

ABSTRACTS

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Depersonalized cancer therapy: targeting MTH1 in melanoma
Jia Yu Wang,1 Hao Liu,2 Chen Chen Jiang,3 Xu Guang Yan,1 Yuan Yuan Zhang,1 Fen Liu,1 Chun Yan Wang,1 Su Tang Guo,1,4 Hamed Yari1 James S. Wilmott,5 Richard A. Scolyer,5 Lei Jin,3 Xu Dong Zhang1

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4. Department of Molecular Biology, Shanxi Cancer Hospital and Institute, Taiyuan, Shanxi, China
5. Discipline of Pathology, The University of Sydney, and Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney, NSW 2006, Australia

Background
Although a number of molecularly targeted agents that inhibit cancer cell survival and proliferation have achieved unprecedented responses in cancer patients, rapid development of resistance remains a major obstacle in the quest for curative treatment of advanced cancer. An alternative approach is to targeting more generic anomalies of cancer cells.

Aims
Cancer cells are critically dependent on the nucleotide pyrophosphatase MutT homolog 1 (MTH1) to sanitize oxidized dNTP pools, thus preventing cell death caused by incorporation of oxidized nucleotides into genomic DNA. The aim of this study was to define the effect of MTH1 inhibition on melanoma cell survival, and to determine how responses of cancer cells to MTH1 inhibitors can be predicted.

Methods
We used the MTH1 inhibitor TH588 and combined knockdown and overexpression as experimental tools, and melanoma cell lines, fresh melanoma isolates, and preclinical melanoma xenografts as experimental model systems.

Results
1) A threshold of oxidative stress is necessary for killing of melanoma cells by MTH1 inhibition; 2) TH588 kills melanoma cells through activating Bad and downregulating Bcl-2 and Mcl-1; 3) the endogenous levels of ROS dictate responses of melanoma cells to MTH1 inhibition; and 4) ROS modulates the response of melanoma growth to TH588.

Conclusions
1) Targeting MTH1 is a promising approach in the treatment of melanoma; 2) endogenous ROS are a potential biomarker predictive of responses of melanoma to MTH1 inhibition; 3) combinations of MTH1 inhibitors and oxidative stress inducers may be a valuable strategy to improve the therapeutic efficacy.
Translational research aspect
Given that clinical evaluation of MTH1 inhibitors is being planned, the results from this T1 and T2 study will soon be able to be tested in clinical settings (T3).
ProNGF as a New Biomarker in Thyroid Cancer

Sam Faulkner1,2,*, Severine Roselli1,2,*, Yohann Demont3, Genevieve Choquet4, Philippe Leissner4, Christopher Oldmeadow5, John Attia2,6, Marjorie Walker2,6 and Hubert Hondermarck1,2,*

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4. Biomarkers Department, bioMérieux Inc., 69280 Marcy l'Etoile, France.
5. School of Mathematical and Physical Sciences, Faculty of Science and Information Technology, University of Newcastle, Callaghan NSW 2308, Australia.
6. School of Public Health & Medicine, Faculty of Health and Medicine, University of Newcastle, Callaghan NSW 2308, Australia.

* Contributed equally to the study.

Background
Nerve growth factor (NGF) and its precursor proNGF are increasingly described for their role in cancer progression. Although NGF has been reported in thyroid cancer, the expression of proNGF is unknown and their clinicopathological significance is unclear.

Aims
Define the expression and clinicopathological significance of proNGF in thyroid cancer and determine its potential clinical value as a diagnostic or prognostic biomarker.

Methods
ProNGF protein expression was analysed by immunohistochemistry in two cohorts of thyroid tumours versus adenomas versus normal thyroid tissues.

Results
ProNGF expression was detected specifically in thyroid epithelial cells but not in other stromal cell types. In the two cohorts, there was a marked overexpression of proNGF in cancers as compared to adenomas and normal thyroid tissues (p<0.0001). High levels of proNGF were found in about 74% of cancers, particularly in the papillary and follicular forms, as compared to only 5% of normal tissue samples (p<0.0001). The area under the ROC curve was 0.90 (p<0.0001). There was no significant association with age, gender, tumour size, stage, lymph node invasion or nerve infiltration.

Conclusions
These data reveal that proNGF is increased in thyroid cancer and suggests its potential value as a diagnostic biomarker. Further studies are warranted to determine the mechanisms leading to this proNGF increase in thyroid cancer and its impact on tumour progression.

Translational Research Aspect
This research is applicable to the T1 translational pipeline.
Identification and synergistic targeting of FLT3-activated pathways in Acute Myeloid Leukaemia

Matthew D. Dun\textsuperscript{1,2}, Heather C. Murray\textsuperscript{1}, Juhura Al-mazi\textsuperscript{1}, Richard G.S. Kahl\textsuperscript{1}, Hayley M. Flanagan\textsuperscript{1}, Nathan D. Smith\textsuperscript{3}, Anoop K. Enjeti\textsuperscript{4}, Martin R. Larsen\textsuperscript{5}, Nicole M. Verrills\textsuperscript{1,2}

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\textsuperscript{5}. Department of Molecular Biology and Biochemistry, Protein Research Group, University of Southern Denmark, Odense, 5230, Denmark.

Background
Acute Myeloid Leukaemia (AML) is the most lethal form of leukaemia, carrying a 5-year survival rate of 21%. Current treatments include high dose chemotherapy and bone marrow transplantation; however development of chemotherapy resistance and relapse is common. Internal Tandem Duplication (ITD) mutation of the receptor tyrosine kinase FLT3 is the most frequent driver mutation in AML (~35%), and is associated with poor prognosis. Due to development of resistance mechanisms, targeted FLT3 inhibitors have displayed limited therapeutic success in AML. Characterisation of the oncogenic signalling pathways activated in FLT3-mutant AML patients is required to develop improved therapeutic strategies.

Aims
1. Identify differentially expressed phosphoproteins in FLT3-ITD+ and FLT3-wildtype AML patients
2. Investigate the utility of the identified proteins as novel biomarkers and drug targets

Methods
AML blasts were isolated from 7 patients (3 x FLT3-wildtype, 4 x FLT3-mutant). Protein was extracted and labelled with iTRAQ8plex, and the phosphoproteome subsequently quantified by LC-MS/MS. AML cell lines MV4;11 (FLT3-ITD+) and HL-60, Kasumi-1, and THP-1 (FLT3-wildtype) were utilised to assess drug toxicity through resazurin assay. Drug synergy was evaluated using the method of Chou-Talalay.

Results
Phosphoproteomic analysis in AML patients identified significant overrepresentation of oncogenic pathways including PI3K, MAPK, mTOR, PKC, and STAT. Comparison of FLT3-ITD+ versus FLT3-wildtype patients revealed differential activation of c-myc, and ribosome biogenesis pathways; along with novel AML-associated proteins including DNA-PK. Targeting of DNA-PK with specific inhibitor NU7441 displays synergistic lethality with low doses of AML chemotherapy agents cytarabine and daunorubicin in FLT-ITD+, but not FLT3-wildtype AML cell lines.

Conclusions
Combining targeted inhibition of FLT3 signalling pathways with standard chemotherapy agents in FLT3-ITD+ AML has the potential to improve response to therapy in this poor responding AML subtype.
Translational research aspect
T1-2: Quantitative phosphoproteomic analysis has provided phenotypic information about FLT3-ITD+ AML; identifying potential targets for novel treatment strategies.
EphA2 antibody increases sensitivity of U87 glioblastoma cells to irradiation

Michael Fay 1,2,3, Jennette Sakoff 2,4, Jennifer Martin 2,4, Stephen Rose 5,6, Stuart Crozier 5, Andrew Boyd 5,7, Klaus Dittman 3, Hans-Peter Rodemann 3.

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2. Calvary Mater Hospital, Newcastle, Australia  
3. Eberhard Karls Universität, Tübingen, Germany  
4. University of Newcastle, Newcastle, Australia  
5. University of Queensland, Brisbane, Australia  
6. Biomedical Imaging, Health and Biosecurity, CSIRO, Brisbane, Australia  
7. Queensland Institute of Medical Research, Herston, Brisbane, Australia

Background
Glioblastoma is a poor prognosis brain tumour with median survival typically around a year. EphA2 is a membrane bound tyrosine kinase thought to be important in mediating cell-to-cell interactions. An imbalance in EphA2 signalling appears to be associated with a particularly malignant phenotype in glioblastoma patients. Our research team has developed a monoclonal antibody that specifically targets EphA2 with the purpose of investigating the ability of this antibody to synergise with adjuvant radiation treatment.

Aims
To investigate the cytotoxicity in glioma cells of a specific EphA2 antibody when given with radiotherapy.

Methods
U87 glioma cells were chosen for study as they are known to express EphA2 and grow readily in cell culture. U87 glioma cells were treated with EphA2 antibody or an isotype control IgG and treated with 2Gy 16h later and assessed for colony formation after 2 weeks using Comassie blue staining. Western blotting strategies were also exploited to investigate the content of EphA2 in glioma cells following treatment.

Results
Treatment of glioma cells with EphA2 antibody significantly reduced the content of EphA2 and phosphorylated EphA2 in glioma cells, within 16h. Treatment of glioma cells with EphA2 antibody alone had minimal effect on the growth of cells, however, when used in combination with radiotherapy the ability of glioma cells to form colonies decreased by 80% (radiation plus EphA2). This effect was significantly greater than the effect of radiotherapy alone (50% reduction), indicative of a synergistic interaction.

Conclusions
We have shown that pre-radiation treatment with EphA2 antibody leads to a markedly decreased colony forming ability in glioma cells. We intend to expand upon this data and investigate the role of this tyrosine kinase in radiation sensitivity with the purpose of exploring this therapy in the clinical arena.

Translational research aspect
This is a T1/T2 translational project.
Aiming For The Right Quality Improvement Target: Cross-Sectional Data Exploring Outpatients’ Priorities And Preferences For Quality Improvement In Tertiary Clinics.

Elizabeth A. Fradgley¹, Christine L. Paul¹, Jamie Bryant¹,², Christopher Oldmeadow³

¹. Priority Research Centre for Health Behaviour (University of Newcastle) and Hunter Medical Research Institute. Level 4 West. University of Newcastle, Callaghan, New South Wales, Australia.
³. Public Health Research Program, Hunter Medical Research Institute. HMRI Building, University of Newcastle, Callaghan, New South Wales, Australia

Background
Patient-experience tools have not been designed specifically to inform health service change. Use of this data as a quality improvement mechanism has proven difficult with limited effects. To provide clear and actionable improvement messages, detailed evidence on patients’ preferences and priorities for service change is needed.

Aims
To report the: proportion of outpatients selecting each general quality improvement initiative; detailed initiatives corresponding to commonly-selected (>10%) general initiatives; and, commonly-selected initiatives in order of relative priority.

Methods
Outpatients completed a touch-screen survey in three tertiary clinics, including two medical oncology clinics. Participants selected up to 23 general initiatives that would improve in-clinic experiences. Using novel survey software, participants could select an additional 110 detailed initiatives and complete relative prioritization exercises.

Results
A total of 541 outpatients participated (71.1% consent, 73.1% completion), including 336 (62.0%) oncology outpatients. In order of relative priority, examples of commonly-selected general initiatives included: up-to-date information provision (15.0%); access to information at home (12.8%); reduced wait-times (19.8%); and information on medical emergencies (11.1%). To address general initiatives, 40 detailed initiatives were selected. For example, to improve up-to-date information provision, participants selected: providing information on treatment steps (72.8%) and condition progress when possible (67.9%); and, to receive test results quickly (58.0%). Participants selected access to a list of trust-worthy sources (45.1%) to improve information provision at home. To manage medical emergencies, participants selected information on emergency symptoms (71.7%) and information for family (61.7%) as specific initiatives.

Conclusions
Information-based initiatives were commonly-selected and are of relatively greater perceived priority. Improved wait-times was commonly selected but was a relatively lower priority.

Translational research aspect (T3)
Using this survey approach, patients are able to specify and prioritise strong quality improvement preferences. This data provides clear improvement messages and assists health services to strategically allocate resources to changes of greatest value to patients.
The tobacco smoking profile of clients attending a medically supervised injecting centre

Eliza Skelton¹, Billie Bonevski¹, Flora Tzelepis¹, Anthony Shakeshaft², Ashleigh Guillaumier¹, William Wood³, Marianne Jauncey³

1. The University of Newcastle
2. National Drug and Alcohol Centre [NDARC] The University of New South Wales
3. Sydney Medically Supervised Injecting Centre

Background
Medically supervised injecting centres offer a professionally supervised environment that is legally sanctioned for clients to inject pre-obtained illicit drugs. Among people who inject drugs (PWIDs), the rate of smoking exceeds 80% making this population particularly susceptible to tobacco-related illnesses and in need of intervention. The Medically Supervised Injecting Centre (MSIC) may be a potential setting to address tobacco smoking among PWIDs.

Aims
The aim of this study is to examine MSIC clients’ tobacco smoking-related behaviours.

Methods
An online cross-sectional survey was conducted in November 2015 to January 2016. Eligible individuals were current MSIC clients aged ≥18 years, self-reported tobacco smoker, who had satisfactory English comprehension and were able to provide informed consent.

Results
Of the 214 eligible individuals, 202 consented to participate (94%); 200(99%) were daily smokers who were moderately to heavily nicotine dependent (n=156, 77%). Most (n=186, 83%) had made at least one quit attempt in their lifetime. Previous quit attempts were largely unaided relying mostly on will power (n=52, 70%). The majority (n=138, 68%) indicated that they would like to quit smoking and would like to receive access to smoking cessation strategies while at a MSIC.

Conclusions
MSIC clients are highly nicotine dependent, interested in quitting smoking and would like their smoking to be addressed.

Translational research aspect
This research will provide novel information to shape program development for smoking cessation care in MSICs. This is T1 research.
Development of action limits for patient error detection for an EPID-based real-time delivery verification system
Todsaporn Fuangrod¹, Peter B Greer²,³, Richard Middleton¹.

1. University of Newcastle, School of Electrical Engineering and Computer Science, Newcastle NSW, Australia.
2. University of Newcastle, School of Mathematical and Physical Sciences, Newcastle NSW, Australia.
3. Calvary Mater Newcastle, Radiation Oncology, Newcastle NSW, Australia.

Background
The application of in vivo dosimetry using electronic portal imaging device (EPID) has been clinically implemented to improve the quality of treatment in external beam radiotherapy (EBRT). EBRT is a complex radiation treatment technique, which uses non-intuitive fluences, and large dose can be delivered to the patient. The traditional and routine quality assurance (QA) programs are used to prevent treatment errors. However, the main drawback of most of the QA programs used in the clinic is that they are unable to detect some serious errors during treatment, such as patient anatomy changes, data transfer issues, accidental plan modification, wrong patient position setup, failed dose delivery, and immobilization issues. We developed and clinically implemented an EPID-based real-time patient treatment verification, comparing predicted EPID image to measured EPID image in real-time. Our proposed system can ensure the quality of radiation treatments.

Aims
The aims of this study is to develop statistically based evaluation tools for error detection during real-time EPID-based patient treatment verification for IMRT and VMAT based on verification results.

Methods
The real-time verification system (Watchdog) utilises a comprehensive physics-based model to generate a series of predicted transit cine EPID image as a reference data set, and compares these to measured cine-EPID images acquired during treatment. The agreement between the predicted and measured transit images is quantified using chi-comparison (currently 4%, 4 mm) on a cumulative frame basis.

Cine-EPID images were acquired from the first two fractions of 137 IMRT patients to generate the lower control limit using Statistical Process Control (SPC) technique; 82 Prostate treatments, 37 head and neck treatments, and 18 Rectum treatments. An action limit was determined based on an integration of real-time verification result and the calculation of process capability index. The action limit sensitivity were tested to ensure the system is able to detect patient position misalignment, dose delivery errors, wrong patient treatment, and wrong plan. For clinical study, 15 IMRT Patients were treated and operated with Watchdog used to evaluate the treatment outcome as well as to determine the source of error.

Results
The derived lower control limits (4%, 4 mm) after 2 seconds of image acquisition for prostate, head and neck, and rectum IMRT were 75.62%, 71.29%, and 71.11% respectively. For a clinical study of 15 patients, on average 7% of the entire treatment failed under the action limit and were identified for further investigation regarding the source of error (see figure a). A case study of a head and neck
patient patient (see figure b), showed an error detected toward the end of the treatment course that was correlated with weight loss shown on CBCT scans.

Conclusions
We have developed an evaluation method for a real-time EPID based treatment verification system (Watchdog). These action limit are designed to be applied to real-time verification during treatment with immediate intervention during SBRT treatments and post-delivery investigation during standard fractionation. Initial results found that the system detected significant changes in patient contour due to weight loss for a head and neck treatment.
Assessment of blood transfusion practices in patients with myelodysplastic syndromes in the era of hypomethylating agents.

Asma Ashraf, Anoop K Enjeti, Milton Hasnat, Philip A Rowlings.

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Background
Myelodysplastic syndromes (MDS) are heterogeneous group of primary bone marrow disorders characterized but ineffective or reduced blood cells production. Supportive management comprising of blood transfusion is still the corner stone of the management of MDS. Around >80% of patients with myelodysplasia develop anaemia at diagnosis or during course of disease and will need transfusion. Hypomethylating agents like azacitidine has been developed with the aim of reducing the transfusion burden and hence risk of transfusion associated complications. Clinical trials have shown efficacy of azacitidine in reducing the frequency of blood transfusion but the benefit has not been established outside clinical trials.

Aims:
Evaluation of usage and change in frequency of blood products in Hunter area since the availability of azacitidine for treatment in MDS.

Methods
A cross sectional study of 256 transfusion dependent MDS patients from 1st January 2008 to 31st May 2015 has been undertaken at the haematology department Mater hospital. Patients have been divided into groups as per treatment with or without azacitidine. Blood transfusion data has been collected from blood bank at Pathology north for assessment.

Results
The analysis has shown reduction in the blood transfusion frequency in transfusion dependent MDS patients. However, it has been demonstrated that reduction in blood transfusion is not a sustained response and after six to eight months of azacitidine, the requirement for blood product increases again.

Conclusions
Azacitidine reduces the blood transfusion burden after commencement secondary to improvement of bone marrow function. However this response is not sustained and with continuation of treatment this response is lost. This phenomenon has not been demonstrated in the clinical trials.

Translational research aspect: this project is T2 research as it will help to further structure the blood bank according to the requirements of the patients to reduce the wastage of blood products. Our study results need confirmation from larger prospective studies in future.
Predictors of MDT review and the impact on lung cancer survival for HNELHD residents treated in the public sector
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2. Calvary Mater Hospital
3. Cancer Services Directorate Hunter New England LHD

Background
Review by an MDT has been shown to lead to increased rates of surgical resection, radiotherapy, chemotherapy and timeliness of care. Most recently, the Victorian lung cancer patterns of care study have found that MDT review is an independent predictor of lung cancer survival.

Aims
1. To examine predictors of lung cancer MDT
2. To determine if MDT review is an independent predictor of survival

Methods
Hunter New England residents diagnosed with lung cancer between January 1st 2009 and June 30th 2013 obtained from the Clinical Cancer Registry linked to MDT surveys obtained from ARIA. Logistic regression was used to estimate predictors of MDT review and proportional hazards regression modelling was used to analyse survival.

Results
Of the 2,167 individuals with lung cancer 411 or 20% were reviewed at the MDT. The odds of MDT review were higher for stage II patients; if cytological or histologically verified; four times more likely if treated at Calvary Mater or John Hunter; if undergoing radiotherapy and if seen by a specialist nurse. Lower odds of MDT review occurred for patients with stages III and IV, or unstaged; those referred to Palliative Care and those who died within a month of diagnosis. MDT review was found to be an independent predictor of survival with a 21% lower hazard of death (HR 0.79 95% CI 0.20-0.90) after adjustment for covariates. Further stratification by stage showed that stage III patients had the most marked survival advantage HR (0.59 95%CI 0.45-0.77) followed by stage IV with a 20% reduction in the hazard of death HR (0.80 95%CI 0.66-0.97).

Conclusions
Current guidelines recommend that all lung cancer patients be reviewed at an MDT given that this is not feasible

Translational research aspect (T3) targeting stage III patients would appear to confer the greatest survival advantage.
Monte-Carlo simulations of the clinical benefits from therapeutic drug monitoring of sunitinib in patients with gastrointestinal stromal tumours
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2. Centre for Human Drug Research, Leiden, The Netherlands

Background
Therapeutic drug monitoring (TDM) is being considered to individualize cancer treatment with tyrosine kinase inhibitors like sunitinib. However, TDM’s potential benefit for eligible patients in terms of clinical outcomes, such as time to tumor progression (TTP), remains unclear.

Aims
To estimate the expected improvement of TTP from a TDM program in patients with gastrointestinal stromal tumors (GIST) treated with sunitinib at a starting dose of 37.5 mg/day.

Methods
A Monte-Carlo simulation of 10,000 patients was performed, using published models of the pharmacokinetics and pharmacodynamics of sunitinib. The simulation included two TDM-guided dose increases of 12.5 mg/day on day 21 and 42, for patients with total (sunitinib + metabolite SU12662) trough levels (TTL) below the pharmacokinetic target of 50 ng/ml.

Results
Without TDM, only 45.3\% of patients had a TTL of at least 50 ng/ml, but two rounds of TDM increased this proportion to 76.2\%. The TDM program increased median time to tumour progression in initially underdosed patients from 214 to 285 days.

Conclusions
This simulation study does not take dose-limiting toxicity into account; in a clinical setting, not all patients will tolerate a TDM-guided dose increase. However, this Monte-Carlo simulation study suggests that an improvement in time to tumor progression might be achieved with TDM in underdosed patients that tolerate dose increases.

Translational research aspect
This work suggests clinical outcome in eligible patients with GIST can be improved by implementing a TDM program. Evaluating the clinical benefit of a TDM intervention \textit{in silico} is consistent with T2 in the translational pipeline.
Panel Testing for Breast Cancer Risk Assessment: is it just because we can rather than should?

Ella R Thompson\textsuperscript{1,2}, Michelle Wong-Brown\textsuperscript{3}, Simone M Rowley\textsuperscript{1,2}, Susan Dooley\textsuperscript{4}, Na Li\textsuperscript{1,2}, Michael Hipwell\textsuperscript{4}, Simone McInerny\textsuperscript{1,2}, Cliff Meldrum\textsuperscript{4}, Lisa Devereux\textsuperscript{1,2}, David Mossman\textsuperscript{4}, Alison H Trainer\textsuperscript{1,2}, Briar-Rose Millar\textsuperscript{4}, Gillian Mitchell\textsuperscript{2,5}, Cate Smith\textsuperscript{1,2}, Paul A James\textsuperscript{1,2}, Ian G Campbell\textsuperscript{1,2}, Rodney J. Scott\textsuperscript{3,4}

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Since the identification of BRCA1 and BRCA2 a number of other genes have been reported to be associated with an increased risk of breast cancer. Many of these genes have now appeared on commercial massively parallel sequencing (MPS) panels and are increasingly used for assessing breast cancer risk in women who developed disease at unusually young ages. Apart from BRCA1 and BRCA2 where there is considerable evidence associated with disease risk as well as strategies to mitigate the effects of mutation carriage there is little if any information about the consequence mutations in the more recently identified breast cancer susceptibility genes. This includes knowledge about the histopathology conferred by the loss of expression of a particular gene, the influence of environmental factors on disease risk as well as the most effective treatment strategies for disease prevention or disease treatment. For many of the genes listed on commercial panels knowledge about disease frequency in affected populations compared to control populations is lacking thereby undermining the veracity of breast cancer susceptibility claims.

To help address the shortfall in information about some of the more recently identified genetic risk factors to breast cancer we undertook a study of 2000 cases and 2000 controls to estimate the prevalence of mutations in a panel of genes that are commonly included in commercial testing. The results reveal that MPS panel testing must continue under a research setting so that more information can be gathered to understand what is meant by the term “genetic predisposition” to breast cancer for a large proportion of genes that are currently under scrutiny. At present only four genes can be used unequivocally in a diagnostic setting for the assessment of genetic risk of disease in most countries.
Patient perspectives on issues of access to cancer care across the care continuum

Christine Paul

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Differences in cancer incidence and mortality are associated with inequalities at each step in the process of preventing or developing cancer, diagnosis and care provision. Patient perspectives are an important part of gaining a full understanding of how the care continuum operates. These data can assist us in identifying priority opportunities for change.

This presentation will explore Australian data regarding patient perspectives on their access to care from the prevention of cancer, to obtaining a diagnosis and treatment. Data regarding perceptions on the quality of care received, preferences for change, affordability and financial impacts of cancer will be described.

An understanding of these issues allows us to consider where our research efforts might focus in order to translate evidence into practice in an equitable way and deliver a more equitable and patient-centred care.
POSTER PRESENTATION ABSTRACTS

NOTE: Some authors did not give permission for their abstract to be published in this handbook and have been purposefully omitted from the publication.
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Development of novel multiple reaction monitoring (MRM) assay for biomarker quantitation in cancer cells
Juhura Al-mazi¹, Matthew Dun¹, Nathan Smith¹, Nicole Verrills ¹.

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Background
Multiple reaction monitoring (MRM) is an emerging branch of targeted mass spectrometry. It exploits the unique mass of a molecule to detect it in biological samples with immense specificity and sensitivity. MRM assays can be customised to monitor any number of cancer biomarkers and biochemical pathways, allowing biomarker detection in individual patients for diagnosis, prognosis, and therapy using blood or tumour samples.

Aims
1. Establish MRM assays for quantitation of novel biomarkers in acute myeloid leukaemia (AML)
2. Establish a multiplexed MRM assay for quantitation of active DNA damage repair pathways in breast cancer cells

Methods
(i) Using discovery proteomics, we have detected differential expression of proteins and their phosphorylation status in AML patient blasts with varying genetic mutations. To validate these changes, MRM assays were developed using human AML cell line, MV4-11 ± kinase inhibitors. This assay will be applied to a panel of AML patients to determine if the phospho-biomarkers are associated with specific clinical features, mutations and/or disease outcome. (ii) A panel of DNA damage biomarkers were analysed using MRM in breast cancer cells (MCF7) subjected to DNA damage (Belomycin, γ-irradiation, Cisplatin). For both analyses cells were lysed, digested using Trypsin/LysC and analysed on a triple quadrupole, QTRAP 6500 mass spectrometer.

Results
Using MRM 52 peptides have been detected and quantified using ≤ 200 µg of protein extract from MV4-11 and MCF7 cells. Differential expression of protein biomarkers correlated well with orthogonal experiments.

Conclusions
This study established a powerful mass spectrometry based assay that can be used for a variety of applications in cancer research. Future studies will focus on clinical implementation of MRM targeting cancer biomarkers in patient blood samples.

Translational research aspect
MRM assays will enable speedy monitoring of treatment efficacy in patients undergoing therapy, and fits primarily in the T1-T2 phase of translational research.
Assessment of epidemiologic profile of patients with myelodysplastic syndromes in Hunter region.
Asma Ashraf,1,2,3,4 Anoop K Enjeti1,2,3,4, Milton Hasnat3,4, Philip A Rowlings1,2,3

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2. Haematology department, Pathology North.
3. University of Newcastle.
4. Hunter Medical Research Institute

Background
Myelodysplastic syndromes, are heterogeneous groups of primary bone marrow disorders characterized by morphologic dysplasia, inefficient haematopoiesis and development of peripheral cytopaenias. They harbor increased risk for leukemic transformation. The incidence of MDS increases with age with median age at diagnosis of 71 years. The incidence in general population is about 5 per 100.00 people per year. MDS was regarded as a reportable disease in 2001 when WHO included it under the category of malignancy. It is estimated that of 17.2% of patients > 65 year of age with “undiagnosed anaemia”, at least 5.8 % of patients had features of MDS on blood film.

Aims
Explore the loco-regional demographic profile of patients diagnosed with MDS from January 2000 – January 2015 in Hunter region.

Methods
Using the diagnostic and procedural ICD-10 codes, records from the Health information and coding department at the Mater hospital, ARIA database and bone marrow biopsy records will be collected for the number of myelodysplastic syndrome patients diagnosed along with demographic profile.

Results
The analysis has shown increase in the incidence of disease as well as in the prevalence of disease secondary to availability of newer therapeutic agents. Prevalence has also increased secondary to improvements associated with best supportive care measurements including blood transfusions and antibiotics.

Conclusions
The prevalence of MDS is increasing with increasing age with 7-35 per 10^5 for individuals age 60 or above. It is also contemplated that increasing number of long term cancer survivors with the more successful treatment for lymphomas and breast cancer with chemotherapeutics like anthracyclines and etoposide has resulted in the development of secondary myelodysplasia.

Translational research aspect
This project is T2 research as it will help to study the epidemiologic profile of MDS in the hunter region and will help in future to design health care resources accordingly.
The Provision of Smoking Cessation Care for People with a Mental Illness: ‘Carers’ Expectations of Health and Community Services

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Background
Smoking prevalence remains high among people with a mental illness, who experience high levels of smoking-related morbidity and mortality and reduced life expectancy as a consequence. Health care services are considered to represent important avenues to provide smoking cessation care (SCC) for smokers with a mental illness. ‘Carers’ play an increasingly critical role in the care and support of people with a mental illness. Research has not explored the expectations of carers regarding the provision of SCC for people with a mental illness.

Aims
To determine ‘carer’ expectations of SCC provision for people with a mental illness across four types of health and community services.

Methods
In the Hunter New England region, NSW, 144 carers of a person with a mental illness were surveyed by self-administered questionnaire regarding their expectations of the provision of SCC by specialist mental health care services, general practice and non-government organisations (NGOs) to people with mental illness. Possible associations with socio-demographic and attitudinal variables were explored using multivariate analysis.

Results
Of all participating carers, 68.8% reported that they cared for a smoker, and a majority considered that SCC should be provided by each type of service: mental health hospitals (71.4%), community mental health services (78.0%), general practice (82.7%), and NGOs (56.6%). The belief that smoking cessation could positively impact mental health was associated with an increased expectation of SCC.

Conclusions
Carers expect SCC from health and community services; reinforcing the need for such services to provide SCC for clients in an effective and systematic manner.

Translational research aspect
New knowledge (T1) has been reported which may improve patient outcomes through informing strategies to reduce smoking among people with a mental illness. Carers’ expectations of SCC may suggest a possible role for carers in supporting and/or extending SCC provision for people with a mental illness.
The effects of altered CD9 and CD151 expression on prostate exosomes

Joshua Brzozowski\textsuperscript{1,2}, Belinda Coldie\textsuperscript{1,2,3}, Helen Jankowski\textsuperscript{1,2}, Danielle Bond\textsuperscript{1,2}, Christopher Scarlett\textsuperscript{1,2}, Matthew Dun\textsuperscript{1,2}, Kathryn Skelding\textsuperscript{1,2}, Judith Weidenhofer\textsuperscript{1,2}

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\textsuperscript{2} Hunter Medical Research Institute (HMRI), NSW, Australia
\textsuperscript{3} Kyoto University, Kyoto, Japan

Background

The tetraspanins CD9 and CD151 have effects on cellular functions including cell adhesion and motility, predominantly through interactions with integrins. The expression of these tetraspanins becomes altered during the progression of prostate cancer to metastasis where CD9 decreases and CD151 increases in expression. These tetraspanins are also abundantly recovered on exosomes.

Aims

This study aimed to identify whether CD9 and CD151 expression on exosomes correlated with the tetraspanin expression on the parent cell and how altered expression of these tetraspanins can affect the function of exosomes when used as a treatment on a normal cellular population.

Methods

The normal, non-tumorigenic prostate cell line RWPE1 was modified to express either low CD9 (CD9\textsuperscript{LOW}) or high CD151 (CD151\textsuperscript{HI}) levels. Exosomes were collected from the culture media of cells. Correlations between cell and exosome tetraspanin expression was determined using western blot. Exosomes were tested for their effects on cell adhesion, migration and proliferation in cellular assays. Furthermore, the proteome of exosomes with differential tetraspanin expression was investigated.

Results

A correlation between exosomal and cellular CD9 and CD151 expression was observed. No significant differences were observed in assays between control RWPE1 and CD9\textsuperscript{LOW} exosome populations, however, limited but significant differences were observed with CD151\textsuperscript{HI} exosomes on adhesion and migration. Further, proteomics identified limited but selective sorting of proteins into exosomes. Validation of proteomics data is currently being undertaken.

Conclusions

Tetraspanin expression on exosomes is correlated to the level of parental cell surface tetraspanin, and affects exosome composition. High expression of CD151 leads to the production of exosomes that modify normal cells to have increased migration and adhesion, which would increase metastatic capacity. Thus modifying tetraspanin levels may be a new therapeutic strategy for cancer treatment and identification of tetraspanin levels on circulating cancer exosomes might have prognostic or diagnostic significance.

Translational research aspect

This research is currently at the T1 stage with the potential to influence clinical decision making in the future.
Is VTE prophylaxis safe in haematological cancers undergoing autologous transplantation?

Aisling Carville¹, Anoop Enjeti¹,²,³,Emily Dunn¹, Eleanor Stephens¹, Cathie Milton¹.

1. Department of Haematology, Calvary Mater Hospital, Waratah, Newcastle, NSW.
2. Hunter Cancer Research Alliance and Hunter Medical Research Institute
3. University of Newcastle
4. Pathology North Hunter

Background

Patients with haematological malignancies have an increased risk of VTE however are often also thrombocytopenic. This results in the management dilemma of whether VTE prophylaxis in thrombocytopenic patients will increase the risk of major bleeding.

Aims

Autologous stem cell transplant (ASCT) patients on LACE regimen receive VTE prophylaxis with low molecular weight heparin(LMWH) despite severe thrombocytopenia due to the risk of veno-occlusive disease with lomustine. A retrospective analysis was undertaken to determine the risk of major bleeding in these patients.

Methods

Retrospective data from 41 patients who underwent a LACE transplant at the Calvary Mater Hospital, Newcastle between January 2010 and February 2015 was undertaken. Any bleeding episodes including WHO grading along with age, preexisting anticoagulant use, use of LMWH prophylaxis, platelet count and need for platelet transfusion was analysed.

Results

Twenty-five bleeding events were recorded in 41 patients. Twenty-three events were WHO grade 1 or 2. Grade 4 bleeding was seen in 1 patient; however VTE prophylaxis had been ceased 3 days prior to the bleed. Three patients (3/41) did not receive any VTE prophylaxis with one of these patients experiencing a grade 3 bleeding event. There was no clear correlation between severe thrombocytopenia and bleeding with 10 of the 25 bleeding events occurring at platelet counts greater than 20 x 10⁹/L.

Conclusions

This local experience provides vital pilot data indicating that the use of prophylactic LMWH in the LACE transplant group does not increase the incidence of major bleeding despite severe thrombocytopenia in these patients.

Translational research aspect

(T2): This pilot project provides data on use of thromboprophylaxis in severely thrombocytopenic patients. This is useful because many patients with haematological cancers have venous thrombosis - in this group of patients it appears that low dose LMWH can be used safely without significant increase in bleeding risks.
Techniques for Improving Emotional Content of Online Communications – A Systematic Review
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Background
Online forms of communication are increasingly being used to provide both information and psychosocial support to cancer patients. Written or typed forms of communication carry particular challenges in conveying emotional content, both for the consumer and the provider.

Aims
A systematic review was conducted to identify: techniques used to convey emotion in written or typed online communications and the effectiveness of the identified techniques in influencing the nature of the interaction, consumer perceptions of the interaction, participant satisfaction and impact on consumer psychosocial outcomes such as distress or anxiety.

Methods
An electronic search was conducted of databases including PubMed, Medline, CINAHL, PsychINFO, Embase and the Cochrane Library. Searches were also conducted using Google Scholar, manual searching of article reference lists and manual searching of tables of contents for selected relevant journals.

Results
A small number of techniques were identified including emotional bracketing and use of emoticons. Very few rigorous studies were identified which provide any empirical data regarding the effectiveness or impact of techniques for enhancing the emotional content of online communication techniques.

Conclusions
Techniques to facilitate communicating emotional content in an online setting do appear in the literature, but empirical data to support their effectiveness and use is scarce.

Translational research aspect
As many health-based organisations are moving to incorporate online information and support services, there is a need for empirical examination of online communication techniques in the context of the provision of information and support in the health context. This review provides a foundation for translation of online communication techniques into practice in regards to the provision of information and support to cancer patients and is therefore a T3 translational research project.
Advancing collaborative quality improvement in tertiary settings: Do chronic disease outpatients and health professionals identify similar types and numbers of quality initiatives?

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Background
Very few studies have directly compared patients’ and health professionals’ priorities for quality improvement in tertiary care. Quantifying the ways in which priorities vary can identify potential obstacles to collaborative improvement while areas of agreement are strategic targets to address both groups’ preferences.

Aims
This cross-sectional study compared the number and types of quality improvement initiatives selected outpatients and health professionals.

Methods
Outpatients and health professionals were recruited from three tertiary clinics, including two medical oncology clinics. Participants selected up to 23 initiatives to improve in-clinic experiences. The number and types of initiatives selected by each group were compared using summary statistics and Chi-square tests. The ten most-frequently selected initiatives are listed and compared for each group.

Results
A total of 541 outpatients (71.1% consent, 73.1% completion) and 124 professionals (47.1% response) participated, including 336 (62.0%) oncology outpatients and 67 (52.3%) professionals with an interest in cancer. On average, outpatients selected 2.4 (median=1, IQR=1-3) initiatives; professionals selected 10.7 (median=10, IQR=6-15) initiatives. Compared to outpatients, a greater proportion of professionals selected each initiative (p<0.001). Information-based initiatives were included in both groups’ top ten most-frequently selected. Initiatives relating to service accessibility were included in outpatients’ top ten only, patient communication and care coordination were only included in professionals’ top ten.

Conclusions
Outpatients selected few improvement targets potentially reducing the complexity of service change and resources required. Comparatively, professionals indicated a greater degree of change is needed and emphasised aspects related to daily practise.

Translational research aspect (T3)
Government policy mandates patient engagement in health evaluation and professionals’ support is essential to sustained quality improvement. However, patients and professionals vary in the degree and type of change desired. A collaborative model is needed to translate both groups’ preferences into improved chronic disease care.
Therapeutic Drug Monitoring for cancer patients receiving chemotherapy
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Background
With many anticancer drugs, both interpatient and intrapatient pharmacokinetic (PK) or pharmacodynamic variability can account for treatment failure or excess toxicity, due to under- or over-dosing. Tailoring drug treatment regimens can provide better outcomes by maximising drug benefit and minimising toxicity, especially in patients with extreme phenotypes such as obesity, advanced age or organ dysfunction. This is specifically so with newer oral therapies which have pharmacokinetics affected by diet in addition to changing PK parameters during treatment.

Aims
To establish Therapeutic Drug Monitoring (TDM) facility at Calvary Mater Newcastle Hospital.

Methods
HPLC, LC-MS and LC-MS/MS methodologies have been developed to measure various chemotherapy drugs and their metabolites in patient blood samples.

Results
Our validated methodologies can support clinical decisions by measuring several chemotherapy drugs and their metabolites in patient samples: mitotane, fluoropyrimidines, anthracyclines, taxanes, vincas, uracil, and some tyrosine kinase inhibitors (pazopanib, sunitinib). In adrenocortical cancer, we used TDM of mitotane and metabolites in 15 patients to facilitate achievement of ideal concentrations (14-20μg/ml) in 11 patients and support dose-reduction in 6 patients with toxic levels. In a phase I study of a new formulation of 5FU and folinic acid (Deflexifol), PK parameters in each patient are determined to achieve rapid dose escalation. In adjuvant therapy of breast cancer, we will monitor blood levels of anthracyclines, taxanes, 5FU and cyclophosphamide to determine if PK differences explain worse outcomes in obese as compared to normal weight women. In renal and other cancers, we will assess PK of pazopanib and sunitinib to identify patients needing dose modification.

Conclusions
TDM is an under-utilised translational tool in cancer chemotherapy, with significant capacity to optimise dosing and explain variability in outcomes. This facility can be adapted for other drugs and clinical situations.

Translational research aspect
This project (T2-T3) leads to clinical decisions for dose adjustments.
Background
Genetic alterations in Wnt signalling are a common event in endometrial cancer. Approximately 30% of type 1 endometrial cancer patients show nuclear accumulation of β-catenin, which is indicative of overactivation of Wnt signalling pathway. Type 1 endometrial cancer is caused by unopposed oestrogen and accounts for approximately 85% of all endometrial cancers. However, the mechanism by which oestrogen and hyperactive Wnt signalling drive endometrial cancer is currently unclear.

Aims
To elucidate the role of unopposed oestrogen and hyperactive Wnt signalling in endometrial cancer

Methods
Human endometrial cancer patient samples were analysed for alterations in Wnt signalling pathway. We have developed a unique doxycycline-regulated endometrial cancer model. To evaluate the role of steroid hormones in endometrial cancer, we treated ovariectomised mutant mice with hormonal pellets (E2, E2+P4 and vehicle) (N=4/group).

Results
Analysis of human endometrial cancer patients revealed alterations in Wnt ligands in 62% of patients (N=232). Further analysis of downstream targets of Wnt signalling revealed that 31% of 232 patients had activating mutations in β-catenin.

Examination of mutant mouse uteri from E2 treated group with constitutive activation of β-catenin showed development of endometrial cancer. However, the E2+P4 treatment group did not develop endometrial cancer, although hyperplasia and cystic growth were observed in these mice. The vehicle treated group showed endometrial hyperplasia but did not develop endometrial cancer.

Conclusions
Our results suggest that unopposed oestrogen along with dysregulated Wnt signalling in uterine epithelium drives endometrial carcinoma. This explains the presence of activating mutations in the Wnt pathway in type 1 endometrial cancer patients.

Translational research aspect
Our study will help in designing personalized treatment for type 1 endometrial cancer patients (T1).
Evidence-Practice Gaps for Australian General Practitioners (GP) in Assisting Pregnant Women To Quit

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Background
Smoking prevalence among Indigenous pregnant women is high at 49%. Evidence-based smoking cessation interventions have not been effectively translated into the maternal Indigenous context.

Aims
To explore GPs’ knowledge, attitudes and practices of managing smoking in pregnant women.

Methods
A random sample of 500 members of the RACGP National Faculty of Aboriginal and Torres Strait Islander Health were invited to an on-line survey. Inclusion criteria were GPs who consult with pregnant women. The response rate was low at 8% (N=42), however alternative recruitment is ongoing.

Results
One-third of the sample worked in Indigenous organisations; 62% of respondents were women. Most GPs (81%) always asked and gave brief advice about smoking in pregnancy. Less GPs (62%) always provided cessation support, assessed dependence (55%), discussed the psychosocial context of smoking (33%), followed up within 2 weeks (14%); 5% referred to the Quitline. Only 21% always recommended/prescribed nicotine replacement therapy (NRT), despite 93% agreeing that using NRT in pregnancy was safer than smoking; 71% believed NRT was moderately effective, and 69% were confident to prescribe NRT. More GPs in Indigenous organisations, compared to mainstream, agreed that discussing smoking benefits their relationship with pregnant clients (p<0.05). Discussing psychosocial contexts was positively associated with prescribing NRT (p<0.05). Only 10% GPs trained in smoking cessation for pregnancy; 83% agreed training was warranted, over two-thirds agreed access to oral NRT should be improved.

Conclusions
Smoking cessation is a high priority for cancer prevention. NRT can be offered to pregnant smokers unable to quit. Low levels of assisted quitting may relate to scarcity of training for pregnancy, and policies governing access. Caution is advised due to small sample size.

Translational research aspect
Training GPs in smoking cessation for pregnant women, and improving NRT access, may progress T2/3 translation of evidence-based methods for smokers in high prevalence groups.
Indigenous Counselling and Nicotine (ICAN) QUIT in Pregnancy – developing an evidence-based intervention for smoking cessation for Indigenous pregnant women

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Background
Smoking prevalence among Indigenous pregnant women is four times the rate in non-Indigenous women (49% vs. 12%). An evidence-practice gap exists in evidence-based primary care approaches for Indigenous pregnant smokers.

Aims
To develop a culturally appropriate intervention to improve the provision of evidence-based smoking cessation care to pregnant women attending Aboriginal Community Controlled Health Services (ACCHS). The presentation will discuss the collaborative development of the intervention and the protocol.

Methods
We developed a culturally competent evidence-based guide for smoking cessation care specific to Indigenous maternal smokers, with a multi-component intervention called ICAN QUIT in Pregnancy. The approach aims to empower women and involve them in shared decision making, using ABCD (Ask, Brief intervention, Cessation, and Discuss the psychosocial context), and recommends the expedited use of nicotine replacement therapy. The resources for provider training and clients were collaboratively developed with ACCHS in Hunter New England. The intervention, including provider training, will be pilot tested, and then a cluster randomised controlled trial will determine the efficacy of the ICAN QUIT approach. Primary outcomes will be provider practices relating to an offer of NRT to Indigenous pregnant women (measured by audit of NRT prescription). Secondary outcomes will be mean scores on client checklists of care they received, and items of smoking cessation care recorded on client notes.

Results
The outcomes of the collaborative development of the intervention will be discussed. The pilot study is planned to commence in 2016.

Conclusions
Evidence-based smoking cessation interventions have not yet been effectively translated into the maternal Indigenous context. The authors aim to meet a vital need to improve the provision of culturally competent best-practice approaches by training and supporting ACCHS, GPs and multidisciplinary teams.

Translational research aspect
If successful the approach could be scaled up and potentially standardise the care of Indigenous maternal smokers.
Background
Lung cancer (LC) development is currently poorly understood. A combination of environmental factors and genetic susceptibility is thought to result in uncontrolled cellular growth and tumorigenesis. Current treatments are poorly effective. Clinically relevant animal models are urgently needed to increase our understanding of LC pathogenesis, as well as to test novel therapeutic compounds.

Aims
To develop a clinically relevant mouse model of LC that is induced by cigarette smoke/tobacco carcinogen (NNK – nicotine derived nitrosamine ketone) exposure in a genetically susceptible strain that recapitulates typical drivers of tumorigenesis.

Methods
A/J mice were administered NNK and chronically exposed to cigarette smoke in a variety of protocols. The development of LC was assessed by histological and molecular analysis.

Results
100% of mice administered NNK and exposed to cigarette smoke for 8 weeks (with equivalent rest period after smoke cessation) developed autochthonous tumours, with an average of 7.5 tumours per lung. Tumours rarely developed in non-NNK treated smoke-exposed controls. These were early stage tumours (adenomas) with alterations in specific tumour-associated gene transcripts and miRNAs.

Conclusions
We have established a novel, clinically relevant mouse model(s) LC. It will provide a platform for the discovery and functional characterisation of factors that may be important biomarkers or therapeutic targets for preventing early development and progression of LC. Future investigations will assess tumour types and genomic mutations, and we hope to translate our findings into screening of high-risk patients for early detection and LC intervention.

Translational research aspect
Our development of a clinically relevant short-term mouse model of tobacco carcinogen/cigarette smoke-induced LC will potentially be a powerful tool to study its development and progression, as well as test therapeutic compounds (T1), which would result in better translation of results into the clinic.
Prostate Cancer Biomarkers: Are Extracellular Vesicles the Solution?

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Background
Prostate cancer has one of the highest incidence rates of all cancers in Australia. Most prostate cancers exhibit a slow progression towards metastasis or are in fact indolent, meaning 5-year survival rates are high. However, current treatments for localised disease have devastating effects on quality of life and current biomarkers are not accurate enough leading to many men with indolent disease being unnecessarily treated. Extracellular vesicles (EVs) have gained interest as a promising avenue for cancer biomarkers in recent years. EVs are small spherical shaped vesicles, which are secreted from their tissue of origin and recoverable from most bodily fluids including urine and plasma, making them ideal candidates for biomarker discovery.

Aims
To identify new prognostic biomarkers that are accurate, sensitive and able to be tested for in non-invasive ways.

Methods
EVs from a panel of 20 prostate cell lines are being investigated by Affymetrix Human Transcriptome arrays to identify nucleic acids that contribute to the development of metastasis by comparison with EV and cellular function.

Results
Preliminary analysis of nucleic acid content showed that the amount of mRNA, miRNA and lncRNA packaged into EVs varies between cell lines.

Conclusions
Further analysis is ongoing to identify which mechanisms contribute to the packaging of nucleic acid into EVs in prostate cells and specific nucleic acid changes that could be used as novel biomarkers. Further work relating the nucleic acid cargo to metastasis related functions will have the potential to identify novel therapeutic targets.

Translational research aspect
This work is in the T1 stage, with the potential to be translated to prognostic or diagnostic biomarkers or therapeutic targets in the future.
A New Venture for the Hunter Cancer Biobank- Establishment of Sequential Blood Collection for Brain Cancer Research

PP16

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Background
The Hunter Cancer Biobank (HCB) was established in 2012 to meet the needs of cancer researchers for high quality tissue specimens linked to clinical data. The HCB collects a range of tumour and adjacent normal tissue from adult patients having cancer-related procedures in the Hunter New England (HNE) region. Now with support from the Mark Hughes Foundation the HCB has established a dedicated Brain Cancer Biobank to create a high value resource for future brain cancer research.

With recent technical advances in molecular biology, computing and bioinformatics allowing for the detection of trace amounts of patients’ cancers circulating within blood samples, the biobank is investigating the feasibility of collecting sequential blood samples from patients with brain cancer.

Aims
Test the feasibility of collecting and storing sequential blood samples for the Brain Cancer Biobank.

Methods
Banking sequentially collected blood samples, together with solid tumour samples, adds power and utility, but also complexity, to the biobanking process. Innovative procedures were developed for:

- patient recruitment and tracking to collect samples at multiple clinically relevant time-points during their cancer treatment;
- use of specialised tubes for blood collection;
- prospective clinical data collection to accompany samples;
- timely processing of blood samples and appropriate storage to maximise their utility for future research;
- testing the range of utility of stored blood samples.

Results
Since June 2015, blood samples sequentially collected from patients with brain cancer have been processed and stored as aliquots of plasma and buffy coat.

Data will be presented on the key performance indicators used in establishing the processes for patient consent and tracking, collection of multiple blood samples, processing techniques and sample utility.

Conclusions
The Brain Cancer Biobank has been successful in establishing processes to collect and store sequential blood samples and is working to ensure the utility of these samples for future research.

Translational research aspect
The infrastructure being developed will be used in T1 basic science research.
PP17 Sifting data from the clinical coalface: Datamining in Radiation Oncology to aid clinical decisions
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Background
Recent applications for datamining in radiation therapy, notably from our collaborators in the MAASTRO Clinic and the NSW radiation oncology datamining network, develop predictive models and decision support systems (DSS). (Dekker et al. 2014) In the MAASTRO approach, using ‘distributed learning’, the model with its parameters travels between institutions while the patient data remains at each institution.

Aims
Implement local datamining system, develop data selection and cleaning methods to increase number of complete datasets available for analysis, as incomplete datasets potentially introduce a bias.

Methods
Our institution has recently built a datamining system linked to the developing NSW datamining network, supported by MAASTRO and Sydney University collaborators. Clinical data sets were exported, anonymized and prepared for analysis with the MAASTRO DSS. Two year survival is determined relative to start of radiation treatment using the date of death (DoD). Data for the DSS’ five predictive factors are obtained: (1) Tumour volume is calculated with an in-house script deployed remotely to Eclipse (2) Forced Exhale Volume (FEV) and (3) ECOG status are found in free text search. (4) Gender is available in the database. (5) The number of positive lymph nodes is inferred from tumour stage.

Results
With 4285 initially retrieved patients, data preparation is in progress: Selection was made for NSCLC patients, stages I-III, and available DoD. Tumour volume calculation with a previously developed script was adapted for data mining; results are compared to those using the MAASTRO approach. Free text search for FEV and ECOG are ongoing.

Conclusions
Completing datasets for datamining is feasible and requires a team approach with sophisticated computer science components. Efforts should be made to prospectively keep all relevant patient data in a structured format.

Translational research aspect
The work falls into categories T2 and T3.

References
Determining the mechanism of leukaemogenesis induced by Shwachman-Diamond Syndrome (SDS) using comparative and quantitative proteomics

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Background
Shwachman-Diamond Syndrome is an autosomal recessive, multisystem disorder characterised by haematopoietic dysfunction. Point mutations in the SBDS gene introduce premature stop codons resulting in the expression of truncated SBDS isoforms. Defects in both myeloid and lymphoid cell lineages are observed suggesting SDS affects early hematopoietic stem cells (HSC). Importantly, these mutations induce leukaemic transformation. Myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) are estimated to occur in 36% of SDS patients by the age of 30. Currently very little is known about the function of wild type SBDS or indeed its truncated isoforms. We hypothesise that generating SDS-like myeloid progenitors cells will help us to determine the mechanisms of leukaemogenesis in SDS.

Aims
To test these hypotheses we aim to; i) generate myeloid progenitor cell stably expressing knockdown (KD) of wild type SBDS and overexpressing its isoforms, then ii) confirm the altered expression. iii) Study the effect these mutations have on cell proliferation and survival, and iv) perform comparative and quantitative proteomic analysis to help us determine their functional role.

Methods
Stable SBDS KD was achieved by shRNA transduction in mouse FDC.P1 myeloid progenitor cells. KD cells were transfected with lentiviral constructs expressing SBDS isoforms. Pure populations of mutant cells were isolated via fluorescence-activated cell sorting and SBDS expression confirmed via Western blotting. Comparative and quantitative proteomics will be used to determine signalling pathways regulated by SBDS.

Results
Mutant cells expressing both SBDS-KD and isoforms overexpression were generated and SBDS expression confirmed. Cellular proliferation, factor dependence and altered signalling pathways analyses are ongoing.

Conclusions
Our sophisticated model systems are designed to help us characterise the effect SBDS isoforms have on the myeloid progenitor cells that give rise to AML. This will provide us new information to help develop improved treatments for SDS and AML.

Translational research aspect - T1.
**Background**

The tumour suppressor phosphatase 2A (PP2A) is a serine-threonine phosphatase that is involved in cell proliferation, DNA-damage, apoptosis and cell cycle. Many interacting proteins contribute to the function of PP2A by binding and regulating its substrate specificity and sub-cellular location. PP2A is functionally inactivated in many cancers, including AML. In some cases the PP2A inhibition is caused by overexpression of the SET or CIP2A oncoproteins, both of which bind to and inhibit PP2A activity. However the mechanism/s of PP2A inactivation in many cancers is still unknown. Detailed investigation of proteins that regulate PP2A activity will help us understand how PP2A inactivation contributes to cancer development and progression, and will aid in the development of novel PP2A activating anti-cancer drugs.

**Aim:** To cross-link PP2A interacting proteins together and use chemical proteomic approaches to identify novel inhibitory proteins in AML cell lines.

**Methods**

PP2A interacting proteins were identified by Western blotting and LC-MS/MS using orthogonal cross-linking approaches:

a. In vivo: AML cell lines exhibiting PP2A inhibition and control myeloid progenitor cells were incubated with membrane permeable cross-linkers prior to protein extraction.

b. In vitro: Protein complexes were isolated from AML cell lines and control cells followed by protein cross-linking.

**Results**

This study is developing robust methodologies to identify and characterise PP2A interacting proteins in AML. We have optimised an *in vivo* and *in vitro* chemical cross-linking procedure using AML cell lines and are currently performing mass spectrometry to identify PP2A interacting proteins. Proteins identified will be validated using Western blotting, targeted proteomics and gene interference studies to determine their utility as new drug targets for the improved treatment of AML.

**Conclusion**

Our *in vivo* and *in vitro* chemical cross-linking method has the potential to help us characterise PP2A inhibition in AML and to identify new drug targets.

**Translational aspect:** T1.
A Survey Of Medical Students’ Understanding and Attitude Towards Medical Oncology: A Pilot Study.
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Background
Medical oncology is a rapidly expanding and developing sub-specialty. With an ageing population, treatment advancements and molecular/translational research in this field, there will be much future demand for medical professionals to join.

Aim
We seek to assess medical students’ current understanding and attitude towards medical oncology teaching and training in the university curriculum. The aim is to improve delivery of education, to both attract interests and train competent future medical oncologists. Further to enhance our knowledge of the challenges and opportunities for better rural resource governance.

Methods
Fifth year medical students who had been rotated at North West Cancer Centre and interns at Tamworth Rural Referral Hospital from May 2013 to August 2015, advised to participate voluntarily in an online 16-point questionnaire. The project was approved by Human Research Ethics Committee of the University of New England. Questions were on introduction of Medical Oncology in medical school,

Results
94 participants were from 11 different universities across Australia and one participant obtained a medical degree in the UK. We noted non-uniformity on introduction of medical oncology subject during medical schooling from first year to fifth year. Duration of rotation was one to five weeks which was combined with other sub-specialty as per half of the responders. Lack of clinical exposure, resources and limited consultant teaching sessions were the main reasons for unsatisfactory training. Surprisingly, lack of awareness on medical oncology at undergraduate level was the main reason for not considering further training in it; however 55% of responders rated medical oncology high for a future career. Around 44% of responders were interested more in clinical applications and unfortunately no participants emphasized on learning molecular biology, pathology and treatment approaches.

Conclusions
We recognized need for additional robust training in medical oncology for medical students.
**Role of reduced Protein Phosphatase 2a subunit, B55α, expression in luminal B Breast cancer cell line DNA damage repair pathway**

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**Background**
Breast cancer is the most cancer in women and a leading cause of cancer related deaths. The serine/threonine protein phosphatase PP2A consists of a structural, a regulatory and a catalytic subunit. Our lab has shown that low expression of the \textit{PPP2R2A} gene—encoding the B55α regulatory subunit—associates with poor outcome in luminal B subtype breast cancer patients, and its short-hairpin RNA (shRNA)-mediated knockdown in normal mammary epithelial 3D cultures induces a tumourigenic phenotype. Earlier studies show that B55α-containing PP2A complexes are pivotal for Homologous Recombination (HR)-mediated DNA double strand repair, therefore we hypothesized that tumours with low B55a will have impaired DNA damage repair and be more sensitive to DNA damaging agents and/ or PARP inhibitors.

**Aim**: To investigate the effect of reduced B55α expression on the DNA damage repair pathways of luminal B subtype breast cancer cell lines, and if this can be used as a novel target in B55α-low patients.

**Methods**: shRNA mediated B55α knockdown was performed in ZR-751 and BT474 luminal B breast cancer cell lines. DNA damage was induced with 10uM Bleomycin and repair efficiencies were examined by immunofluorescence and in-cell-western.

**Results**: ZR-751–B55α knockdown cells showed no changes in cell morphology or proliferation, but exhibited sustained expression of gamma H2AX foci (double strand DNA damage marker), and delayed and prolonged activation of ATM (pSer1981) post Bleomycin treatment. B55α knockdown in BT474 cells resulted in a marked change in cell morphology, with evidence of epithelial-mesenchymal transition (EMT). Further experiments examining DNA repair pathways, EMT marker expression, and sensitivity to DNA damaging drugs are currently in progress.

**Conclusion**: B55α-low cells have compromised HR repair.

**Translational Research Aspect**
\textbf{T1-T2}: If the current study shows that reduced B55α expression sensitises cells to DNA damaging agents, this will lead to clinical trials on clinically available DNA damaging drugs.
A clinical practice change intervention to increase dietitian provision of depression screening and referral for head and neck cancer patients
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Background
Given the prevalence and adverse effects of psychological distress on treatment outcomes, clinical practice guidelines recommend dietitian screening and referral of head and neck cancer patients for psychosocial distress. However, research suggests that the provision of this care is sub-optimal.

Aims
This study describes a clinical practice change intervention that aims to improve the provision of depression screening and referral by dietitians in head and neck cancer patients undergoing radiotherapy.

Methods
The study employs a multi-site, stepped-wedge randomised controlled trial design. The intervention will be implemented across four Australian radiotherapy departments who provide care to patients with head and neck cancer. The intervention to facilitate depression screening and referral will include the following evidence based clinical practice change strategies: executive support, staff training, academic detailing, systems and prompts, performance audit and feedback and provision of tools and resources. The primary outcome is the increase in depression screening and referral by dietitians in head and neck cancer patients at initial session, which will be assessed via audiotape of dietitian clinical consultation with patients and medical record audits. Dietitian ratings of how helpful the intervention components are will also be evaluated.

Results
Preliminary results indicate that 0% (n=162) of control (pre-intervention) patients were screened for distress by dietitians. The intervention has been implemented at all four sites and is ongoing. The intervention components, including staff visits, feedback reports, resources and supervision have been well received and rated positively by the participating dietitians.

Conclusions
This study is the first to implement a multi-component clinical practice change intervention in increasing the provision of dietitian depression screening and referral in head and neck cancer patients.

Translational research aspect
If effective, the intervention could serve as a model for improving the implementation of guidelines in other outpatient clinics in Australia and internationally (T3).
Continued tobacco smoking, alcohol use and depressive symptoms in a sample of head and neck cancer patients about to undergo radiotherapy


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Background
Available evidence indicates that approximately one-third of patients with head and neck cancer (HNC) continue to smoke after diagnosis. Continued tobacco and alcohol use as well as depressive symptoms may affect quality of life, treatment efficacy and survival.

Aims
This study aimed to describe the rates of comorbid smoking, alcohol use and depression within a sample of HNC patients about to undergo radiotherapy.

Methods
As part of a NHRMC funded, stepped-wedge randomised controlled trial, baseline data on smoking characteristics, alcohol use and depressive symptoms were collected from a sample of HNC patients from four Australian radiotherapy departments. Self-reported smoking status and biochemical verification were assessed. Alcohol use was measured via The Alcohol Use Disorder Identification Test (AUDIT). Depressive symptoms were measured via the Patient Health Questionnaire 9 (PHQ9).

Results
The mean age of patients (n=269) was 58 years and 80% were male. 13% (n=35/267) and 63% (n=169/267) of patients identified as current and former smokers respectively. However, a newly recommended CO cutoff of >3ppm identified 34% (n=83/246) of patients as current smokers. 31% of patients met criteria for harmful drinking. 38% of patients met criteria for at least mild depressive symptoms. 10% of patients met criteria for comorbid harmful drinking and at least mild depressive symptoms.

Conclusions
The rate of self-reported current smoking status in our sample is lower than reported in existing HNC literature. However, the rate of current smokers when applying newly recommended cutoffs to biochemical verification indicates that some patients may be continuing to smoke despite self-reporting abstinence. The results also indicate that some smokers may have quit post diagnosis and may be vulnerable to relapse.

Translational research aspect
The current and past smoking rates in this sample will help to develop interventions in this population that may need to address relapse prevention post treatment (T1).
Basal-Like Breast Cancer Subgroups Uncovered by Genomic and Transcriptomic Profiles and Overall Survival Outcomes

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Background
Basal-like breast cancers (BLBCs) form an important clinical group characterised by the lack of hormone receptors oestrogen (ER) and progesterone (PR), and human epidermal growth factor receptor-2 (HER2). The outcome of patients diagnosed with basal-like subtype is, however, contradictory. Most patients show increased risk of death within 5 years, as opposed to other individuals that have a long-term survival of over 10 years.

Aims
In this study, we aim to identify survival markers able to define subgroups with distinct disease outcomes.

Methods
We explored the genomic and transcriptomic signature of 449 basal-like samples from the METABRIC cohort and ROCK data set. Two filters were designed to identify gene signatures associated with varying survival outcomes: the Differential filter separates cancer-related features by comparing basal-like and control samples and the Survival filter defines the probes affecting patients’ survival. The hierarchical clustering analysis is then applied to group samples with divergent outcomes.

Results
The 80-genes signature lead to identification of two main subgroups, named Basal I and II. These groups showed distinct characteristics as regard to the gene expression profile, copy number aberration (CNA), clinical data and survival outcome. High centrality genes, including HCST, ANKRD22, PSMG3, C3AR1, TPX2 and LAP3 are key elements for differentiating BLBCs. These genes most closely characterise the cancer immune response, epithelial-mesenchymal transition and cell cycle. Additionally, chromosomes 1q, 3q, 7q and 8q increased percentages of gains, and 4q, 8p, 13q and Xp, of losses; underlying the intrinsic genomic instability in both training and validation sets.

Conclusions
The predictive survival markers support that a prognostic differentiation exists across BLBCs. Recognizing the aggressive phenotype improves the clinical decision-making, with the administration of effective tailored therapy for patients at high risk of relapse, and conversely avoid aggressive treatments in those at low risk.

Translational research aspect
In this study, we defined two main subgroups of BLBCs based on the analysis of transcriptomic and genomic data, with divergent survival outcome. Defining subgroups is an important issue in breast cancer research due to its impact on the disease characterization and management. The study focuses on fundamental research (T1) with the alignment of patients’ outcome, with potential clinical implication.
Background
Approximately 50% of cancer patients receive radiation therapy either curatively or palliatively. IMRT (Intensity Modulated Radiation Therapy) is a complex technique to deliver highly conformal dose distributions to tumours while sparing normal tissues and reducing toxicity. The accurate planning and delivery of these sophisticated treatments is essential for optimal patient outcomes and multi-centre clinical trials.

Aim
The aim of this work is to develop a method for remote assessment of IMRT treatments performed in some clinical centres using electronic portal imaging device (EPID) images.

Method
The centres are provided by two CT data sets and an instruction to make their own plans for a virtual cylindrical phantom using their treatment planning system (TPS). Then, the centres deliver the plans in air to their EPIDs and send the recorded images to a central site for analysis. At the central site, the images are combined using a model to calculate the 3D dose distribution inside the phantom. The calculated dose is compared to the planned dose in sagittal, coronal and transverse planes using Gamma analysis with criterion of 3%, 3 mm with a 10% threshold.

Results
The study assessed treatments of four centres having different combination of linear accelerator and TPS. The mean pass rates of the centres were 98.2%, 98.3% and 99.4% for sagittal, coronal and transverse planes, respectively while the average of mean gamma for each plane was respectively 0.38, 0.34 and 0.33.

Conclusion
The method delivers an efficient method of remote evaluating treatments of different centres. It is fast, remote, inexpensive and accurate so, it could be used as a standard method for multi-centre credentialing.

Translational research aspect
This project falls into the T1-T2 translational pipeline. Basic research on EPID dosimetry methods led to a new application of remote evaluation of treatment accuracy at centres is being tested.
Association of the polymorphic intron 3 16bp duplication in TP53 (rs17878362) with a low Δ40p53:p53 ratio and better outcome in breast cancer.

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Background
Breast cancer is the most common cancer in women, but surprisingly it has relatively low rates of TP53 mutations, suggesting other mechanisms are responsible for p53 inactivation. Our group is specifically interested in the Δ40p53 isoform which we have shown is highly expressed in breast cancer, and may be one mechanism contributing to p53 inactivation (Carcinogenesis 2014;35(3):586–96). It can be produced by either alternative splicing in intron 2, or alternative initiation of translation. The alternative splicing of the TP53 transcript can be regulated by the formation of G-quadruplex (G4) structures in TP53 intron 3 from which the nucleotides forming these structures overlap with a common intronic polymorphism (rs17878362). rs17878362 alters p53 splicing to decrease fully-spliced p53 mRNA in vitro following ionising radiation and this in turn alters Δ40p53:p53. Therefore, the presence of this polymorphism may be an important mechanism used by cells to regulate the ratio of Δ40p53 to full-length p53.

Aims
This study aimed to determine if the rs17878362 polymorphism was associated with altered Δ40p53:p53 expression and outcome in breast cancer.

Methods
We sequenced TP53 in breast tumour specimens from 139 patients and compared this to Δ40p53 and p53 mRNA expression.

Results
We found that the ratio of Δ40p53:p53 was significantly lower in tumours that were homozygous for the polymorphic rs17878362 (A2) allele compared to those who were wild-type (A1/A1). Furthermore, there was a lower proportion of breast cancers carrying the A2 allele from patients who subsequently developed metastasis compared to those who did not. Patients whose tumours carried the polymorphic A2 allele had significantly better disease-free survival.

Conclusions
These results show that the rs17878362 polymorphism is associated with a low Δ40p53:p53 expression in clinical breast cancer specimens and that this is associated with better outcome.

Translational research aspect
This is basic science T1 research, and translationally may be useful as a novel prognostic indicator in patients whose breast cancers express different Δ40p53:p53 ratios.
Abstract

Biobanking of human cancer tissues is vital for translational research for novel biomarker discovery, identifying new targets for therapy and developing personalised medicine. The Hunter Cancer Biobank (HCB) supports cancer research by providing researchers with access to high quality validated, annotated biospecimens linked to clinical outcomes data. The HCB was established (2012) in partnership with the Anatomical Pathology Department of Pathology North HNE. This relationship has allowed HCB to integrate its operations into core pathology processes utilising anatomical pathology expertise as the natural custodians of formalin fixed paraffin embedded tissue collections.

Anatomical pathologists have integrated Biobanking into routine practice. By selecting the tumour and normal tissue to be banked, the pathologist ensures that the diagnostic specimen and the patients’ clinical care are not compromised. Pathologists provide quality assurance by digitally validating and annotating H&E sections taken from each block. These quality measures allow researchers to know exactly what type of tissue they are receiving as the pathologist annotates areas of malignancy in context with other cellular changes such as inflammation, degenerative change or hormonal effects. HCB pathologists collaborate with researchers and clinicians to provide pathological expertise and interpretation of research needs ensuring efficacious use of HCB specimens. Via his process HCB have provided over 11,000 tissue specimens to 10 projects in the last 2 years.

An important additional benefit of the partnership has been the experience anatomical pathology registrars have gained in characterising cancer tissue, utilising digital pathology and importantly, working in a research environment. For biobanks to continue to offer the highest quality specimens to researchers and contribute to successful translational cancer research the contribution of anatomical pathologists must be valued and their role recognised as a critical step in the biobanking process. Furthermore, anatomical pathology registrars should be encouraged to contribute to research as they progress through their training.
Reduced expression of Protein Phosphatase 2a subunit, B55α, in Breast Cancer DNA damage repair pathways
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Background
Breast cancer is the most common female cancer and the second-leading cause of cancer-related death nationally. Clinical outcome differs based on a tumour’s molecular subtype, with the luminal-B subtype associated with early relapse and poor prognosis. Currently no markers are available to predict which luminal-B patients will/will not respond to treatment. Work from our laboratory revealed low expression of the PPP2R2A gene (encoding the regulatory B55α subunit of the serine/threonine phosphatase PP2A) predicts for poor outcome in luminal-B patients. PP2A is a tumour suppressor, and complexes consisting of B55α are essential for cellular DNA damage repair via the Homologous Recombination (HR) repair pathway. Therefore we hypothesize that breast tumours with low B55α expression will have impaired DNA damage repair and heightened sensitivity to DNA damaging agents and/or PARP inhibitors.

Aims
To investigate the role of reduced B55α expression in the DNA repair pathways of breast cancer cells and whether this is a potential treatment target for low-B55α luminal-B tumours.

Methods
Short-hairpin RNA mediated knockdown of B55α was achieved in MCF7 and ZR751 breast cancer cells. DNA repair efficiency was examined by immunoblotting post Bleomycin-induced DNA damage. Cell survival and proliferation were examined using long term clonogenic assays post DNA damage (ɣ-irradiation, Bleomycin, Cisplatin, ABT888).

Results
In B55α-low cells, Bleomycin induced prolonged increase of γH2AX (marker for Double Strand Breaks), increased BRCA1 phosphorylation and decreased Chk2 phosphorylation in the HR repair pathway. Clonogenic assays revealed no significantly increased sensitivity to DNA damaging agents in the MCF7 B55α-low cells compared to controls. Similar analyses in ZR751 cells are ongoing.

Conclusions
HR repair is impaired in B55α-low breast cancer cells.

Translational Research Aspect
T1-T2; if this study finds B55α-low breast tumours are hyper-sensitive to clinically available DNA damaging agents this will lead directly to clinical trials for poor outcome luminal-B patients.
BAALC can control the sensitivity of AML cells to chemotherapeutics

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\textbf{Background}
Acute myeloid leukaemia (AML) is the most common acute leukaemia in adults and has a five year survival rate of 2-9\% in adults \geq 65 years of age. Despite advances in treatment of AML over 50\% of older adults die within two months of treatment and most will relapse. Furthermore, primary refractory disease occurs frequently in AML with 30-60\% of patients exhibiting primary induction failure. Primary resistance to chemotherapeutics increases with age and affects 33\% of those aged less than 65 years and 57\% of patients over 75 years. Overexpression of the brain and leukaemia, cytoplasmic (BAALC) gene is associated with increased incidence of primary refractory AML. However, precisely how overexpression of BAALC is controlling sensitivity to chemotherapeutics is unknown.

\textbf{Aims}
The main aims of this study were to demonstrate that BAALC overexpression is directly controlling chemosensitivity in AML cells, and to identify the mechanisms involved in BAALC-mediated chemosensitivity.

\textbf{Methods}
BAALC was overexpressed in a panel of AML cells and their sensitivity to commonly used chemotherapeutics was measured (resazurin and clonogenic assays). Reciprocal co-immunoprecipitations were performed to identify BAALC binding partners.

\textbf{Results}
We have shown that overexpression of BAALC, but not an empty vector (EV) control, decreases sensitivity to daunorubicin, vincristine, and cytarabine, but not etoposide. We have also identified several BAALC binding partners that may affect BAALC-induced sensitivity to chemotherapeutics.

\textbf{Conclusions}
BAALC is a potential target for the treatment of refractory AML. Since BAALC has restricted expression in normal cells, drugs that target BAALC or its binding partners may present more cancer cell specific effects than current chemotherapeutics.

\textbf{Translational research aspect}
This T1 research has identified a new target for the treatment of acute myeloid leukaemia. Further examination of this target may be useful therapeutically as a new strategy for the treatment of acute myeloid leukaemia.
A novel combinatorial optimisation approach for feature selection via integration of information from multiple datasets
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Background
Meta-analysis of gene expression datasets has become a popular method for identifying novel biomarkers in the field of cancer research. Integrating available information from different dataset to generate a combined result seems reasonable and promising; however, different factors make it difficult.

Aims
We propose a new combinatorial optimisation based method that aims to find a set of classifying genes, whose expression level may be used to answer the research question in hand. In addition, we develop a integration method for combining datasets at its probe level.

Methods
We have used six prostate cancer datasets belonging to different platforms and combined those datasets using the proposed method which is a simple alignment strategy to combine probes across platforms depending on the hg19-GRCh37 version of the Genome Browser’s table. The combined datasets have 16157 combined probes with 319 samples. The proposed feature selection method- Coloured (α,β)-k-Feature Set approach- is a generalised version of the (α,β)-k-Feature Set problem. We have applied this new methodology on the combined dataset, also compared our results to the popular meta-analysis method called RankProd.

Results
The integrated study resulted with more informative and significant signatures than the RankProd and individual analysis results. The set of genes identified is highly significant in relation to prostate cancer. Lists of 120 genes that are over or under expressed in all the six datasets have been identified. The two most dysregulated pathways that are identified in our combined study are Integrin signalling pathway and focal adhesion.

Conclusions
The results of our study suggest that the proposed method is an efficient meta-analysis method that is capable to identify biologically relevant genes that other methods fail to identify.

Translational research aspect
As the number of cancer related studies increases we will be able to use this novel method to find more significant genes and pathways related to cancer that may provide new insights to the disease mechanism and makes a contribution towards understanding, preventing and cure.
Characterisation Of A Novel PP2A Inhibitory Oncoprotein In Acute Myeloid Leukaemia (AML)

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Background
In Australia ~900 AML diagnoses are made each year. AML is responsible for most leukaemia-associated deaths with a dismal 5-year survival rate of <25%. To improve AML survival new drug targets are needed. The tumour suppressor PP2A is a critical regulator of growth and survival; however its function is commonly inhibited in cancers, including AML. We have identified a novel PP2A interacting protein coined Tumour Suppressor Repressor (TSR). The function of TSR is not well characterised; however, we have shown it associates with PP2A and binds to PP2A activating drugs. We hypothesise that TSR is an endogenous inhibitor of PP2A and a target for novel PP2A-activating drugs.

Aims
To test this hypothesis we aim to i) determine PP2A activity and characterise altered signalling pathways in TSR knockdown AML cells. ii) Visualise co-localization between TSR and PP2A in AML cells, and iii) determine the effects of TSR knockdown on cell proliferation, survival and sensitivity to PP2A activators.

Methods
Stable TSR knockdown (KD) was achieved by shRNA transduction into human and mouse AML-model cell lines. TSR-KD cells were assayed for PP2A activity (phosphatase assay), cellular proliferation, survival and apoptosis (resazurin, clonogenic, and apoptosis assays). Signalling pathways were examined by western blotting and co-localisation of PP2A-subunits, TSR and TSR-binding partners were determined using Proximity Ligation Assays (PLA).

Results
TSR-KD increased PP2A activity and sensitised cells to PP2A activating drugs AAL (S) and FTY720. Incubating PP2A-complexes isolated from AML cells expressing KD-TSR with recombinant-TSR reinduces PP2A inhibition to the level of scramble-KD control. Signalling pathway analysis, cell survival and PLA co-localisation assays are ongoing.

Conclusions
We have identified a novel PP2A inhibitory protein highly expressed in AML that may be a cellular target for clinically relevant PP2A re-activating compounds.

Translational research aspect
T1. Identification of underlying mechanisms in AML and characterisation of new chemotherapeutics.
The protein phosphatase inhibitor cantharidin, potentiates the effect of all-trans retinoic acid in acute promyelocytic leukemia cells.

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Background
Acute promyelocytic leukaemia (APML) is characterised by a reciprocal translocation (15:17) that produces a fusion between retinoic acid receptor-α (RAR-α) and promyelocytic leukaemia (PML) genes. The resulting hybrid protein binds to DNA, enhancing interaction with the nuclear co-repressor molecule and histone deacetylase to block transcription and differentiation of granulocytes. All-trans-retinoic acid (ATRA) is the primary treatment and triggers the dissociation of co-repressors and the association of co-activators to restore gene transcription; however, ATRA-resistance does occur. Since co-repressor and co-activator action is intricately regulated by signal-dependent phosphorylation mechanisms, we examined the ability of protein phosphatase inhibition to enhance the action of ATRA in APML cells. The protein phosphatase inhibitor chosen for study is cantharidin, an analogue of which recently entered phase 1 clinical trials for advanced tumours (ClinicalTrials.gov NCT01837667).

Aims
To investigate the effect of combining ATRA with cantharidin in ATRA-sensitive and -resistant APML cells (NB4, positive for the PML/RAR-α translocation).

Methods
Two ATRA-resistant cell lines, NB4-7 and NB4-6, were developed from parental NB4 cells via long term dose escalation in 10⁻⁷M and 10⁻⁶M ATRA, respectively. The MTT growth inhibition assay, Giemsa and Hoechst staining, and flow-cytometric methods were exploited to characterise growth inhibition, differentiation and apoptotic cell death. Drug interaction indices and synergistic effects were also calculated.

Results
The combination of ATRA and cantharidin induced a striking synergistic effect on growth inhibition followed by apoptotic death in all cell lines with interaction indices as low as 0.43. Importantly, cantharidin (1.5μM) in combination with ATRA abrogated the resistance of NB4-6 cells to ATRA and induced growth inhibition comparable to that induced by ATRA alone in the parental cells.

Conclusions
A greater understanding of this novel interplay between ATRA signalling and protein phosphatase activity will provide an opportunity to clinically enhance ATRA treatment in APML patients.

Translational research aspect: this is a T1/T2 translational project.
Enhancing the efficacy of tyrosine kinase inhibitors through bio-polymeric albumin hybrid nanoparticles in breast cancer

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Background
The application of biocompatible nanoparticles (NPs) has shown great promise for cancer drug delivery in recent decades. By virtue of their unique physicochemical properties and localized tumor targeting, NPs have solved several challenges such as poor solubility, low bioavailability, low therapeutic index and dose-limiting side effects faced by most conventional therapeutics.

Aims
This research was set to investigate the ability of NPs in promoting the efficacy of a selective small molecule inhibitor (GNF-5837) of the tyrosine kinase receptor A (TrkA) in different breast cancer subtypes. The poorly soluble GNF-5837 was incorporated in novel albumin hybrid NP to potentially increase its antineoplastic efficacy while alleviating non-specific distribution through systemic administrations.

Methods
Bio-polymeric hybrid NP was designed through a unique polyelectrolyte complexation method of core drug-loaded albumin/dextran sulfate (DS) and a pH sensitive DS/chitosan matrix. The resulting nanomedicine was extensively characterized in terms of drug loading and physicochemical properties. The anticancer efficacy, TrkA downregulation and signalling was investigated through various cellular studies including proliferation, apoptosis, invasion and western blotting.

Results
The hybrid NP was characterized with a hydrodynamic diameter of 150 nm, a narrow size distribution and high drug loading efficiency (~ 80%). Breast cancer cells treated with either free drug or drug-hybrid NP showed efficacious reduction in cell viability, invasion, TrkA phosphorylation and the associated downstream MAPK activation inducing an apoptosis boost compared to those treated with control groups. Remarkably, these effects were more potently observed for drug-hybrid NP while the non-cancerous cells were more resistant to the therapies.

Conclusions
The combination of GNF-5837 with optimally designed albumin hybrid NP had much stronger anticancer efficacy in vitro than the free GNF-5837 therapy, then representing a promising strategy for preclinical evaluation in vivo.

Translational research aspect
This research focuses on developing treatments and interventions (T1). The targeted therapy with this type of all-natural polymeric transport system represents a translatable approach to improve the clinical outcomes that were not achievable by the conventional formulations of free drugs.
Pathways to Smoking Care Implementation Project: Stage 2

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Background
For cancer patients, smoking status is a powerful clinical risk indicator that merits the full attention of the health care team and the patient. However, the limited evidence suggests smoking cessation care for patients is likely to be poor. There is little rigorous research on the extent to which cessation support is offered to Australian consumers with cancer.

Aims
The objective of this research is to assist in achieving routine clinician delivery of smoking cessation care for cancer patients in NSW. Stage 2 of the work will identify the degree to which smoking cessation care is provided to cancer patients and will describe opportunities for and barriers to improving care. Data from Stage 2 will be used to inform and refine a pilot care-implementation intervention.

Methods
Three hundred and fifty cancer patients from 7 hospitals across NSW will be invited to complete an anonymous survey while waiting for their scheduled medical, radiation or surgical oncology appointment. All medical, nursing and allied health staff at the same hospitals will receive an email from a senior member of staff inviting them to complete an anonymous online survey.

Results
Descriptive statistics from approximately 150 patient and 100 staff surveys at three hospitals providing cancer care will be presented.

Conclusions
Smoking status is a powerful risk indicator for cancer patients, with adverse clinical outcomes associated with continued smoking after diagnosis. Ascertaining the prevalence of existing smoking cessation care is important, not only to ensure that patients are receiving optimal care, but to also help identify where clinical practices can be improved.

Translational research aspect
This project will provide a sound foundation for a large scale trial to implement routine smoking cessation care as part of routine practice and is therefore a T3 translational research project.
Comparing digital versus visual scoring methods for immunohistochemical staining: a case study in the Hunter Cancer Biobank

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Background
Tissue microarrays (TMAs) combined with pathological and clinical data are a powerful tool for evaluating cancer biomarkers. However, increasing sample throughputs via TMAs also increases analysis workloads. Replacing visual scoring with a digital analysis workflow offers to redress this workload issue; with published reports comparing these methods generally favourable for implementing digital approaches. To supplement our services the Hunter Cancer Biobank (HCB) has implemented a centrally available digital analysis platform (HALO, Indica Labs).

Aims
The objective of this study was to compare the outputs of this digital resource with traditional visual scoring methods for immunohistochemistry (IHC).

Methods
TMAs consisting of intraductal and intralobular breast carcinoma (IDC and ILC, respectively, n=160/group) were stained by IHC for the prospective biomarker, NGF. After slide digitisation, staining was evaluated by two observers (pathologist and scientist) with the level and percentages of diaminobenzidine staining classified as categories (Path score; 0-3). Using HALO, TMAs were segmented automatically and the Area Quantitation Algorithm (HALO) used to determine H-scores (0-300).

Results
NGF staining was determined to be significantly increased in IDC compared to cases of ILC using either visual Path scores (1.10+/−0.81 vs. 0.68+/−0.74; p<1E-6) or digital H-scores (84.8+/−40 vs. 33.9+/−21.7; p<1E-17). Comparing measures by ROC curve analysis showed that H-scores were significantly better at discriminating breast carcinoma as IDC or ILC than Path scores (AUC 0.918 vs. 0.620, respectively; p<0.0001).

Conclusions
The digital pathology workflow produced similar findings to visual assessment but with improved accuracy. Moreover, the digital approach allowed data generation, formatting and analysis in a greatly reduced timeframe. In addition, along with better sensitivity, digital assessment also has the inherent advantage of alleviating intra- and inter-observer variations.

Translational research aspect
In the context of biobanking services for research, the application of digital IHC scoring can help reduce burden on professional pathology time.
How Intrinsic are Luminal Breast Cancer Subtypes?
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Background
Even though luminal tumours comprise about two thirds of all breast cancers, there is no consensus on their separation into molecular subtypes A or B.

Aims
In this study we aim to analyse the relations between these tumours and identify the molecular signature of patients at risk.

Methods
We investigated genomic and transcriptomic data of 2147 luminal samples from the METABRIC and ROCK data sets. The MST-kNN clustering based on 10000 probes related to tumour development the most, provided insights about the connections between cancer and control samples. A further hierarchical clustering of 500 probes related to varying survival outcomes was employed to obtain patient groups at risk. All results were validated across data sets and platforms Illumina and Affymetrix.

Results
The MST-kNN approach revealed that Luminal A samples are closely related to each other, while Luminal B tend to diverge from them. The clustering based on survival related genes lead to a molecular signature associated to cell cycle and extracellular matrix, for which the transition between luminal cancers is approximately continuous from low- to high-risk patients. Additional support for these findings came from copy number aberration analysis, where the latter group shows significantly higher percentage of gains and losses on chromosomes 8, 11, 17 and 20.

Conclusions
The separation of luminal breast cancers into two intrinsic subtypes is ambiguous; they should rather be considered as one highly heterogeneous group with variable proliferation states.

Translational research aspect
The panel of genes identified in this study represents a robust and accurate definition of the disease state, important for guiding therapy. Moreover, the Ki-67 marker, currently used for Luminal A or B subtype determination, also represented by this list, can already be applied in clinics as a stage indicator instead.
Revision of Molecular Breast Cancer Subtypes

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Background
The latest studies revealed luminal breast cancers should be considered a single heterogeneous group, questioning the current separation of all breast cancers into five intrinsic molecular subtypes.

Aims
In this study we aim to investigate all breast tumours with the goal to determine distinct groups, and provide insights about their relations to each other and control samples.

Methods
We investigated genomic and transcriptomic data of 2130 samples from the METABRIC data, split into a training and a validation set. The hierarchical clustering based on 179 probes whose expression is associated to copy number aberrations and multimodal distributions, identified groups of samples with distinct characteristics. Further, the relative neighbourhood graph (RNG) calculated for 10000 probes mostly differentiating between tumours and controls, visualised the connections between samples belonging to these groups. The results were validated on 993 samples.

Results
The hierarchical clustering lead to a definition of 6 groups of tumours with distinct copy number aberration profiles and survival outcomes: basal-like, Her2-enriched and luminal c1, c16, c8 and c17. Remarkably, the IHC ER positive luminal c17 subgroup shows a similar gain on 17q12 as the Her2-enriched. The RNG supported the existence of these groups, and revealed that luminal samples are closely connected to each other, while luminal c17 are related to Her2-enriched, which are in turn the closest relatives of basal-like. Interestingly, the control samples are attached at the meeting point between these four major groups.

Conclusions
The results indicate that luminal c1, c17, Her2-enriched and basal-like tumours can diverge from healthy cells, while luminal c16 and c8 tend to connect via luminal c1.

Translational research aspect
This study suggests a separation of breast cancers into four major groups: luminal IHC HER2 negative, luminal IHC HER2 positive, Her2-enriched and basal-like, where each of them can directly diverge from a healthy cell.
The effectiveness of the Public Direct Access Colonoscopy Service implemented at John Hunter hospital
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1. University of Newcastle
2. John Hunter Hospital
3. Cancer Services Directorate Hunter New England LHD

Background
The Public Direct Access Colonoscopy Clinic (PDACC) was introduced to reduce the time from the GP referral to colonoscopy by replacing a specialist surgeon or gastroenterologist with assessment and booking by a specialist nurse.

Aims
1. To investigate time-to-colonoscopy for people with a positive FOBT attending the PDACC relative to the normal service. 2. To investigate the proportion of patients who meet the recommended triage category of 30 days from GP referral to colonoscopy. 3. To investigate the clinical and health service dependent time components.

Methods
Patients with a positive FOBT were identified from Provation or from PDACC database as having a colonoscopy in 2014 at John Hunter, Belmont or Calvary Mater hospitals. Time-to-colonoscopy was measured in days using three dates: the date on the GP letter of referral, the date on the request for admission (RFA) and the date of the colonoscopy. All analysis was conducted in SAS 9.4. Kaplan Meier and multivariable Cox Proportional Hazards models examined time-to-colonoscopy.

Results
There were 628 patients in 2014, 313 referred to PDACC for triage and 315 normal service patients: 8.8% of PDACC and 6.6% of normal service patients had their colonoscopy within 30 days. The median time from GP referral to colonoscopy was 43 days (95% CI 41-49) for the PDACC and 84 days (76-92) for the normal service patients. The primary impact of PDACC was to reduce the clinical component time from GP referral to RFA from 39 days (95% CI 34-34) for normal service patients to 7 days (95% CI 6-8) for PDACC patients (p<0.0001).

Conclusions
To our knowledge this is the first Australian study to evaluate the PDACC or report time to colonoscopy.

Translational research aspect (T3)
Lessons learned can be applied to patients who have a colonoscopy for symptomatic and monitoring purposes and to other LHDs.
Background
Recent work from our laboratory and others has highlighted the importance of inactivation of the tumour suppressor, protein phosphatase PP2A, in myeloid leukaemias. The PP2A activating drugs FTY720, and its closely related structural analogue, AAL(S), enhance the activity of PP2A to induce cell death of AML cells by a mechanism that is not fully understood. We have recently identified a novel cellular target of these compounds (coined: the Tumour Suppressor Repressor, TSR), and shown that TSR associates with PP2A complexes in AML cells. Therefore we hypothesize that TSR is a novel inhibitory protein of PP2A in AML.

Aims
To determine the effect of TSR overexpression on; PP2A activity, cellular proliferation and sensitivity to PP2A activating drugs.

Methods
Using retroviral transduction to induce gene overexpression followed by fluorescence-activated cell sorting, the human TSR gene was introduced into growth factor dependent FDC.P1 mouse myeloid cells and FDC.P1 cells expressing the oncogenic D816V mutation of human c-KIT, which are growth factor independent. Overexpression was confirmed by Western blotting. Cell proliferation was performed using resazurin assays, and PP2A activity assay were performed. Co-immunoprecipitation was also performed to confirm the PP2A and TSR interaction.

Results
Stable cell lines overexpressing TSR were generated. TSR overexpression was monitored by flow cytometry over 6-8 weeks revealing a progressive decrease in expression over time in mutant c-KIT+ cells. TSR overexpression had no effect on cell proliferation, however reduced PP2A activity. Sensitivity of these cells to AAL(S) and FTY720 is still ongoing.

Conclusions
TSR is a novel PP2A inhibitory protein and may contribute to AML development.

Translational research aspect
T1-T2. PP2A activating drugs targeting TSR are poised to enter clinical trials for AML and other cancers. These data reveal the cellular target of these drugs which may help these compounds enter phase I clinical trials.
PP42 Development and testing of a decision aid for women considering neoadjuvant systemic therapy for operable breast cancer (study in progress)
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Background
Neoadjuvant systemic therapy (NAST) has gained popularity for women with larger or more proliferative, operable breast cancer in routine care and as part of a clinical trial. It adds complexity which limits women’s ability to engage fully in the decision-making. Patients report either not being offered NAST, or not being as involved in the decision as they would like. Clinicians report typically directing the decision about NAST, and are interested in offering a decision aid (DA). Patient DAs can increase patients’ involvement in decision-making, but a systematic review did not identify a neoadjuvant breast cancer DA.

Aims
To develop a patient DA for NAST and test its acceptability, feasibility and impact on decision-related outcomes.

Methods
The design and content of the DA was based on: interviews with patients, a survey of clinicians; literature review; expert consensus; and the International Patient Decision Aid Standards criteria for DA development. The DA includes: a balanced description of the advantages and disadvantages of systemic therapy followed by surgery, or the reverse sequence; graphical and written representation of outcome probabilities; and a values clarification exercise. The DA is currently being evaluated in a prospective single-arm pre-post study. Primary endpoints are DA acceptability to patients and clinicians, and feasibility of use. Secondary endpoints include decisional conflict, knowledge, information and involvement preferences, control preferences, distress, anxiety, satisfaction and regret.

Results
Between July and September 2015, 8 NAST candidates out of a sample size of 50 have registered to this ongoing study at 4 sites in Newcastle, Sydney and Melbourne.

Conclusions
This study intends to provide a new resource designed to be implementable within routine clinical practice to improve decision-making, and support clinicians to offer NAST to eligible patients.

Translational research aspect
T2-T3 research: the development and testing of a new intervention; and facilitating quality evidence-based treatment.

Impact of Chronic Soy-derived Isoflavones (sISO) Exposure on Mammary Glands of Ovary-intact ACI Rats (Morphological and Immunohistological Aspects)

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Background
Breast cancer is the second leading cause of female cancer-related mortalities in most western countries, whereas this incidence appears lower in East Asian countries, where a high amount of soy is consumed. It has been reported that pre-pubertal soy-consumption may be protective against mammary gland (MG) malformation. However, the effect of long-term sISO-exposure on MG development is not known.

Aim
To investigate how a chronic sISO-exposure influences the MG development of ovary-intact August Copenhagen Irish (ACI) rats.

Methods
Female ACI were exposed to 476 parts-per-million sISO pre-natally until certain post-natal days (PND): PND 21 (pre-puberty), PND 50 (post-puberty) and PND 81 (adolescence). The #4 left MG was used for morphological investigation and immunohistological detection of certain protein levels: 1) estrogen receptor alpha (ESR1) and progesterone receptor (PGR), because estrogen and progesterone are the main regulating hormones of MG development; 2) KI67 (proliferative index).

Results
Morphological analyses of whole mount MGs revealed no diet-dependent differences with regard to epithelial tree elongation and area measurements. The highest number of terminal end bud (TEB) was found on PND 50, but chronic sISO-exposure reduced its number. ESR1-expression levels were increased in sISO-exposed immature MG epithelia, where it also showed higher KI67-expression. In addition, PGR-expression in epithelial cells appeared earlier.

Conclusions
In response to the long-term sISO-exposure, MG epithelial of immature animals expressed a higher ESR1-expression, indicating a higher susceptibility to estrogenic substances, and a higher KI67-expression, indicating more proliferative cells. And early PGR expression suggested an early ductal morphogenesis. The high proliferative TEBs were reduced during puberty. Altogether, the chronic sISO-exposure accelerates the MG development, which can probably lead to minimizing the breast cancer risk.

Translational research aspect
More developed MG is associated with decreased risk of breast tumorigenesis. Hence, chronic soy diet may protect against breast cancer.
The search for novel treatment agents for Pancreatic Cancer: Tales from the land and sea

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Background
Pancreatic cancer (PC) is a disastrous disease with a dismal survival rate of only 5%. The current standard of care for PC patients consists of surgery and/or treatment with gemcitabine, a natural product-derived chemotherapeutic which has been shown to have a modest effect for some patients, however it is not a long-term curative treatment and results in many unwanted side effects. Natural therapies have the advantage of being relatively inexpensive to manufacture and are usually very tolerable and effective. Therefore, there is a strong need for novel, naturally occurring therapeutic options for PC.

Aim
To determine if crude extracts and/or purified compounds from various Australian and South East Asian flora and fauna (Vietnamese medicinal plants, Blueberry ash, bitter melon, Eucalyptus and marine invertebrates) exert anti-cancer activity in vitro, with an emphasis on pancreatic cancer.

Methods
Pancreatic cancer cell lines (BxPC3, MiaPaCa2 and CFPAC-1) and normal human pancreatic epithelial cells (HPDE) were treated with varying doses of crude extracts and purified compounds over a range of treatment times. Cell viability was assessed using CCK8 and MTT viability assays to determine the extent of anti-cancer activity due to growth inhibition and/or apoptosis.

Results
Significant growth inhibition of pancreatic cancer cells was observed with the purified compound pristimerin (from 2 Vietnamese medicinal plants), which displayed an IC₅₀ of <2.7μM in pancreatic cancer cell lines compared to 4.9μM in normal HPDE cells. Crude extracts also showed significant selective efficacy at concentrations below 100 μg/mL; such as blueberry ash extract with IC₅₀ values of 38.53μg/mL and 57.34μg/mL in BxPC3 pancreatic cancer cells and HPDE cells respectively; saponin enriched bitter melon extract IC₅₀ values were 11.02 μg/mL and 54.60 μg/mL for MiaPaCa2 and HPDE cells, respectively; while specific Eucalypt crude extracts showed very low IC₅₀ values (7-11 μg/mL in MiaPaCa2 cells). Further, 2 semi-purified compounds from a marine invertebrate had IC₅₀ values <12.5 μg/mL for MiaPaCa2 cells and >25 μg/mL for HPDE cells.

Conclusions
Purified compounds and crude extracts from plants and marine invertebrates show significant selective pancreatic cancer growth inhibition in vitro at concentrations with minimal effect on normal pancreatic cells, therefore showing promise as novel anti-pancreatic cancer therapies.

Translational research aspect
This is a T1 study as it is assessing ant-cancer activity of compounds \textit{in vitro}, however it has the potential to move through the translational pipeline into T2 research in the future.
A bispidinone analogue induces an apoptosis-mediated cytotoxic effect on pancreatic cancer cells in vitro

Melanie J. Predebon¹, Danielle R. Bond¹,⁴, Joshua Brzozowski²,⁴, Helen Jankowski²,⁴, Fiona M. Deane³, Mark Tarleton¹, Adam McCluskey³, Michael C. Bowyer¹, Judith Weidenhofer²,⁴ and Christopher J. Scarlett¹,⁴.

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4. Cancer Program, Hunter Medical Research Institute (HMRI), New Lambton, NSW, 2305, Australia.

Background
Pancreatic ductal adenocarcinoma (PDAC) is a disease with a very poor prognosis and limited therapeutic options. Current therapies and clinical trials have failed to improve survival outcomes. Due to the known complexity and heterogeneity of PDAC there are potential significant benefits in the continued discovery of novel targeted drug treatments, and bispidinone analogues have yet to be investigated as cytotoxic agents against pancreatic cancer cells.

Aim
This study investigated the cytotoxicity of bispidinone analogue FD5006, (2S,2S’)-1,1’-(9-oxo-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonane-3,7-diyl)bis(2-amino-2-(1H-indol-3-yl)ethanone).4HCl, against pancreatic cancer cell lines.

Methods
The cytotoxic effect of FD5006 was assessed against 3 pancreatic cancer cell lines (MiaPaca-2, CFPAC-1, and BxPC-3). Viability was assessed using a CCK-8 colorimetric assay, and apoptotic cell death was confirmed using fluorescence microscopy, fluorescence/luminescence assays and flow cytometry.

Results
Initial viability screening results revealed significant cytotoxic activity from analogue FD5006 treatment (concentration range 1µM-100µM) on all three cell lines compared to a no treatment control. A logarithmic dose-response analysis calculated IC₅₀ values for MiaPaca-2, BxPC-3, and CFPAC-1 (16.9µM, 23.7µM, and 36.3µM respectively). Cytotoxic treatment time-response (4h, 24, and 48h) from multiple viability assay replicates revealed a 24h treatment time was sufficient to produce a cytotoxic effect on all cell lines in this study. Further investigations for markers of apoptosis on FD5006 treated MiaPaca-2 pancreatic cancer cells revealed dose-dependent characteristic apoptotic morphological changes using light microscopy images, and fluorescent DAPI staining. Further fluorescence/luminescence assays and flow cytometry confirmed apoptotic cell death by findings of dose-dependent activated caspase-3/-7.

Conclusions
This study showed that the bispidinone analogue FD5006 induced an apoptosis-mediated cytotoxic effect on MiaPaca-2 cell lines, and significant cytotoxicity on CFPAC-1 and BxPC-3 cell lines, in a dose- and time-dependent manner. This study paves the way for further investigations into the precise cellular mechanisms of action necessary for potential development into pre-clinical trials.

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

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