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Identification of novel transcripts specific to triple negative breast cancer that are associated with lymph node metastasis

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Background: Triple negative breast cancer (TNBC) is characterised by the lack of receptors for estrogen, progesterone, and human epidermal growth factor 2. TNBC is known to be the most aggressive breast cancer subtype, with earlier and more frequent development of metastasis and disease relapse. Metastases are the major cause of cancer related death in TNBC patients. Due to the lack of hormone receptors there are no targeted therapies available as there are for other breast cancer subtypes, and new biomarkers/treatment targets are urgently required.

Aims: We aimed to identify novel TNBC specific transcripts that are associated with lymph node metastasis.

Methods: We used 49 invasive ductal carcinomas, from which we were able to compare 17 matched normal adjacent tissues and 15 matched lymph node metastases. Gene expression microarray analysis was used to identify differentially expressed transcripts between these three groups.

Results: We were able to identify and validate 99 transcripts that are significantly altered when comparing tumour samples versus normal adjacent samples. Out of these 99 transcripts 28 are specific to TNBC. Further, we identified 83 transcripts that are associated with lymph node metastasis, as they were differentially expressed in all lymph node positive tumours and not in lymph node negative tumours. The genes were associated with cell proliferation and cell death. Furthermore, these genes are associated with chromosomal instability, epigenetic changes and other known cancer related pathways.

Conclusions: We have identified a TNBC specific gene signature that appears to be specifically associated with metastasis.

Translational research aspect: The identification of specific transcripts for metastasis may serve as biomarkers or treatment targets for TNBC, and this warrants further investigation. (T1).
Aims: To investigate the limitations of mammography in women with high MD, in order to help women make informed healthcare decisions.

Methods: MD was assessed using Wald’s criteria (BMJ 1999) as a risk factor for screening. Issues surrounding mandatory reporting of MD in the USA, and the epidemiological and clinical aspects of MD were reviewed.

Results: Risk discrimination based solely on the RR of BC due to high/very high MD is too low to alter screening algorithms. MD masks cancer detection; very high MD is associated with high risk of interval BC (RR 17.8, 95% CI 4.8–65.9). Mandatory reporting of MD is impacting healthcare in the USA. BreastScreen Australia does not routinely report MD. Investigation of MD using different imaging and measurement techniques is ongoing.

Conclusions: Mandatory reporting of MD could improve health outcomes. Further research is needed to ascertain which imaging methods are best for screening women with dense breasts. Further research is needed to elucidate the biology of MD and its use as a factor in BC screening & risk assessment.

Translational research aspect: Despite nearly four decades of published data on MD as a masking and BC risk factor, translation of this information into clinical practice has been slow. This is mainly due to difficulties in imaging & measuring MD, as well as limited medical and public awareness (T1-T4).

OR4

Δ40p53 CAN ALTER BREAST CANCER CELL GROWTH BY MEDIATING THE ESTROGEN RESPONSE

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Background: Breast cancer is the most common cancer in women, and is the second highest cause of cancer-related deaths. p53, an important tumour suppressor gene, and Estrogen Receptor (ER) are crucial modulators of normal breast growth, and an imbalance in these pathways results in breast carcinogenesis. Isoforms of p53 are known to manipulate the overall effects of p53. Our previous studies have shown Δ40p53 to be the highest expressed isoform in breast cancer, however the functional significance of this is unknown.

Aim: We aimed to characterise the role of differential Δ40p53 expression on breast cancer growth and estrogen response.

Methods: Two breast cancer cell lines (MCF-7, ZR75-1) were transfected with siRNAs to knockdown the expression of Δ40p53. A stable overexpression cell line was also developed (MCF-7-Δ40p53). Cell growth was assessed (Promega) and the expression of ER and its target genes was characterised. Additionally, Kaplan-Meier survival analysis was performed to determine the effect of Δ40p53 expression in 118 ER-positive breast tumours.

Results: We found that knockdown of Δ40p53 caused a reduction in estradiol induced expression of ER and its target genes PR and pS2, and also resulted in a 10% and 20% loss of cell growth, in MCF-7 and ZR75-1 cells, respectively. Furthermore, we observed a 10% increase in proliferation in the Δ40p53-overexpressing cells, after treatment with estradiol. This was supported in survival analysis from ER-positive tumours.

Conclusions: These results propose that modulated expression of Δ40p53 is important in regulating ER signalling in breast cancer by significantly impacting on breast cancer cell growth, and is potentially associated with a worse outcome in ER-positive breast cancer patients.

Translational approach: This study highlights the importance of the Δ40p53 isoform in modulating the ER signalling pathway and breast cancer growth, and may lead to the use of Δ40p53 expression as a prognostic marker in stratifying ER-positive breast cancers.

OR5

THE FUNCTIONAL ROLE OF THE ENDOMETRIAL RENIN ANGIOTENSIN SYSTEM IN ENDOMETRIAL CANCER

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Background: Dysregulation of the normal renin angiotensin system (RAS) within the endometrium, which is involved in the regulation of angiogenesis, cell proliferation and adhesion, may contribute to the development and progression of endometrial cancer. Several studies have demonstrated that there is an upregulation of pro-angiogenic arm of the RAS in endometrial cancer (EC), however a profile of the entire RAS pathway has yet to be established.

Aims: To compare RAS gene expression and protein levels in human EC samples and adjacent normal endometrium. We hypothesised that the activation of the angiogenic/proliferative pathway of the RAS (REN, AGT, ACE1, AGTR1) is greater in tumour compared to adjacent endometrium.

Methods: RAS gene expression and protein levels were analysed in 30 human FFPE endometrial carcinomas and normal adjacent endometrium kindly donated by the Hunter Cancer Biobank.

Results: ATP6AP2, AGT and ACE1 were all significantly upregulated in tumour samples, whilst REN was undetectable (P<0.05, P<0.05 and P<0.05 respectively). Both AGTR1 and ACE2 were more abundant in tumour samples, however this failed to reach significance, whilst VEGF (an angiogenic marker) was not significantly different. There was no significant effect of tumor grade on RAS genes. AGT, ACE2 and (pro)renin receptor protein were all detected by immunohistochemistry and are very highly expressed in the glandular epithelium of the tumour samples.

Conclusions: This study is the first to characterise the expression and protein levels of the RAS within tumor and adjacent normal endometrium. Additionally, the upregulation of ATP6AP2, AGT and ACE1 expression in tumour tissue suggests a potential for RAS targeting drugs as anti-tumor therapies.

Research translational aspects: This research is translational because it provides a basis for an expression profile of the endometrial RAS in endometrial cancer that will aid in developing targeted anti-tumorigenic therapies. This research falls in the T1 phase of the translational pipeline.

OR6

MTOR: A NOVEL TARGET FOR TESTICULAR CANCER

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Background: P38K/Akt/mTOR signalling axis is an important regulator of cellular functions. Alterations in this pathway have been shown to cause cancer in various organs including breast and colon.

Aims: 1) To define the role of the mTOR pathway in human testicular cancer. 2) To test efficacy of mTOR inhibitors in testicular germ cell tumour cell lines.

Methods: Testicular tissues of 24 human patients suffering from testicular cancers and tissue array with 49 human seminoma samples were analysed for expression of members of the mTOR pathway (JKB1, PTEN, mTOR, pS6 and p4EBP1). The effect of mTOR inhibitors (Everolimus and BEZ235) on testicular cancer germ cell line (TCam-2) was examined.

Results: Our immunohistochemical study revealed loss of JKB1 in 48% of human testicular cancer patients and 94% of human seminoma patient samples in array revealing that deregulation in the mTOR pathway are common in testicular germ cell tumour patients. Our expression analysis results will further be confirmed with western blot analysis of protein
OUTCOMES OF A SMOKING CESSATION INTERVENTION DESIGNED FOR SOCIALLY DISADVANTAGED SMOKERS: A RANDOMIZED CONTROLLED TRIAL (RTC)

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Background: The prevalence of smoking within disadvantaged groups remains higher than the prevalence of smoking in the general population. However, few RCTs examining the effectiveness of smoking cessation programs have been carried out in disadvantaged groups.

Aim: This RCT aimed to evaluate the effectiveness of a case-worker delivered smoking cessation intervention at increasing smoking cessation rates amongst socially disadvantaged smokers.

Methods: The intervention group received brief advice and motivational interviewing during eight weekly sessions, free Nicotine Replacement Therapy (NRT), telephone quitline referrals and peer support. The control group received advice to quit smoking and the NSW Quitline phone number.

All participants were followed up at one and six months post baseline. Primary outcome was expired CO-confirmed continuous abstinence at six months.

Results: 919 people were screened, 433 people consented and were randomised into intervention (n = 193) and control groups (n = 242) with a 60% follow up rate at six months. Demographic and smoking related variables were similar across the intervention and control group. Based on complete case analysis, in the intervention and control groups, no statistically significant differences were detected in expired CO-confirmed continuous abstinence (3.2% versus 2.1%, OR = 1.07, 95% CI = 0.18, 6.31), or seven day point prevalence (2.1% versus 3.5%, OR = 0.39, 95% CI = 0.04, 3.37). Adjusted analyses found a statistically significant difference between intervention and control groups in number of cigarettes smoked per day (8 versus 13, p < 0.001).

Conclusions: This RCT was not effective at increasing smoking cessation rates amongst a sample of socially disadvantaged individuals, although a statistically significant reduction in the number of cigarettes smoked was observed.

Translational research aspect: The results of this study have the potential to influence future smoking cessation trials targeted at highly disadvantaged individuals (T2).

ENSURING RADIATION ONCOLOGY PROTOCOL COMPLIANCE IN AN INTERNATIONAL STUDY ON GASTRIC CANCER ... FROM TAMWORTH

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Background: The Trans-Tasman Radiation Oncology Group (TROG) and Australasian Gastro-Intestinal Trials Group (AGITG) study 08.08 “TOPGEAR” is a randomised phase III/III clinical trial of preoperative chemoradiation (CRT) and preoperative chemotherapy alone in the setting of resectable gastric cancer. The critical importance of protocol compliance in Radiation Oncology studies has previously been demonstrated. At present 73 centres around the world are participating, with pre-treatment protocol compliance assessments conducted by Radiation Therapists at the North West Cancer Centre (NWCC), Tamworth.

Aims: The protocol hypothesis is that preoperative chemoradiotherapy improves overall survival compared to preoperative chemotherapy alone in patients undergoing D1 dissection for resectable gastric cancer. Pretreatment review for patients on the CRT arm is conducted as the practice is uncommon and misadministration carries significant risks.

Methods: The study population is 752 patients with resectable gastric cancer, 376 randomised to receive preoperative chemoradiation. Pretreatment review is performed on de-identified 3D CT datasets in DICOM-RT format, using a TROG’s web-based centralised review system. Reviews are conducted by an international team of Radiation Oncologists and Radiation Therapists at the NWCC.

Results: The phase II component of the study has completed accrual (120 patients) and recruitment is accelerating as more international centres are activated. Reviews identified 25 major protocol deviations with all but 4 rectified prior to treatment delivery. Guidance provided by NWCC staff has facilitated treating centres in achieving this high level of compliance.

Conclusions: Consistent protocol compliance across multiple centres in a novel aspect of practice is being supported by web-based expert review.

Translational research aspect: T3 – Radiation Therapy for gastric cancer was uncommon prior to 2000, and is rarely used in the preoperative setting. This work provides centres pre-treatment confirmation that their implementation for study patients is appropriate.

WHY DO ONCOLOGY OUTPATIENTS WHO REPORT EMOTIONAL DISTRESS DECLINE HELP?

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Aims: Many patients experiencing significant distress do not seek help and little is known about the reasons for this. We explored reasons for declining help among patients reporting emotional distress.

Methods: Oncology outpatients reporting significant distress during routine screening were asked if they would like help. Those who declined help were asked their reasons for declining. Available demographic and clinical variables were used to identify factors associated with reasons for declining help.
Results: Of 311 patients with significant distress, 221 (71%) declined help and 215 of these gave a reason for declining professional help. The most common (n = 99, 46%) reason was “I prefer to manage myself”. Two other common reasons were “already receiving help” (n = 52, 24%) and not believing their distress was severe enough to require help (n = 50, 23%). Stigma was rarely cited as a reason for declining help in our sample (n = 1, <1%). Also uncommon were “I can’t afford the cost/money for treatment” (n = 1, <1%) and “I didn’t think anything could help” (n = 12, 6%).

Predictors for declining help were age and gender with younger patients and women more likely to decline help because they were more likely to already be in receipt of help. Distress score and PSYCH-6 scores were significantly lower among patients who rated their distress as not severe enough to require help. Nevertheless, there were patients who had maximal scores on distress and PSYCH in each group.

Conclusions: Two common barriers to patient uptake of available clinical services to help with distress are a preference for self-help and a belief that distress is not sufficiently severe to warrant intervention. These beliefs were held by a proportion of individuals who reported very high levels of distress. Qualitative research and subsequent interventions for overcoming these barriers are required to obtain the most benefit from distress screening programs.
TRANSLATIONAL RESEARCH ASPECT: This T1 research has identified a new target for the treatment of acute leukaemias. Further examination of this target, and the novel peptide inhibitor, may be useful therapeutically as a new strategy for the treatment of acute myeloid and acute lymphoblastic leukaemia.

CHARACTERISING A NEW TARGET FOR THE TREATMENT OF ACUTE LEUKAEMIAS

Aims: To elucidate resistance mechanisms of human colon cancer cells to HSP90 inhibitors, thus providing information for development of approaches to overcome the resistance.

Methods: BAALC expression was altered (siRNA knockdown, overexpression) in a panel of leukaemia cells. Effects on proliferation (resazurin) and survival (Annexin) were measured (n = 3). The sensitivity of this panel of cells, as well as AML patient samples, to C310, both as a single agent and in combination with chemotherapeutics was also determined (Annexin, resazurin, n = 3).

Results: We have shown that inhibition of BAALC expression in acute leukaemia cells significantly increases cell death and decreases proliferation. By contrast, overexpression of BAALC increases cell proliferation. Taken together, our data shows that BAALC is involved in controlling leukaemia proliferation and survival. Additionally, the BAALC inhibitor C310 kills a range of leukaemia cells and primary AML blasts, whilst leaving normal cells untouched, and this effect is at least additively enhanced via combination with various chemotherapeutics.

Conclusions: The targeting of BAALC offers a new strategy for the treatment of acute leukaemias, and due to the restricted expression of BAALC in normal cells, drugs directed against BAALC may offer more cancer specific effects than current therapies.
IDENTIFICATION OF ONCOGENIC SIGNALLING PATHWAYS IN ACUTE MYELOID LEUKAEMIA (AML) PATIENTS BY PHOSPHOPROTEOMICS

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**Background:** Acute Myeloid Leukaemia (AML) accounts for >30% of all leukaemia diagnoses in Australia and has the worst survival rate. Recent whole genome sequencing projects have identified a number of recurrent somatic mutations in AML. These mutations reside in genes encoding transcription factors, kinase signalling molecules and epigenetic regulators. For example, mutations in the receptor tyrosine kinase FLT3 occur in ∼35% of AML patients and cause constitutive activation of the receptor and of downstream signal transduction pathways. Currently the molecular consequences of these mutations are not well understood; therefore identification of pathways controlling transformation in these patients is needed to improve patient survival.

**Aims:** To identify novel molecular markers and drug targets in FLT3-ITD\(^+\) AML patients using quantitative phosphoproteomics.

**Methods:** RNA, DNA and protein were isolated from AML patient blasts. Mutations were identified by qBiomarker Somatic Mutation PCR Array and Sanger sequencing. Proteins isolated from 7 AML patients were labelled with iTRAQ8plex. The proteome and phosphoproteome was identified and quantified by LC-MS/MS.

**Results:** 4421 different phosphoproteins were identified across the 7 different patients, most with multiple phosphorylation sites. Significant phosphorylation of peptides associated with malignant transformation pathways in AML were identified; including PI3K, MAPK, mTOR, PKA, PKC and STAT, as well as known AML associated proteins such as nuclaphosmin (NPM1). Differential pathway analysis of FLT3-ITD\(^+\) and wildtype (wt)-FLT3 patients revealed altered activation of c-myc pathways, ribosome biogenesis pathways, and changes in a range of other proteins/pathways not previously associated with AML.

**Conclusions:** Global and site-specific analysis of in vivo phosphorylation sites by quantitative proteomics has resulted in the characterisation of activated signalling pathways in AML.

**Translational research aspect:** T1-T2. Linking these technologies to genetic mutations is providing important mechanistic information on FLT3-ITD\(^+\) mutations in AML, and highlighting potential targets for novel therapeutic approaches.

GLOBAL DEMETHYLATION CAN RESTORE XPC EXPRESSION AND OVERCOME PLATINUM THERAPY RESISTANCE IN MELANOMA IN VITRO

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**Background:** Melanoma is resistant to platinum based chemotherapies such as carboplatin. Carboplatin induces DNA damage in the form of crosslinks resulting in apoptosis. This damage is recognised by the nucleotide excision repair (NER). The global genome repair (GGR) branch of NER is critical for recognizing DNA damage and triggering apoptosis. However melanoma does not induce GGR expression in response to carboplatin and may be a contributing factor in the resistance seen in melanoma. XPC, a key GGR gene may be silenced through methylation in melanoma. Decitabine, a DNA methyltransferase inhibitor, is a chemotherapy agent that results in global loss of methylation and re-expression of silenced genes. Restoring expression of XPC in melanoma using decitabine could overcome resistance to carboplatin-induced apoptosis.

**Aims:** This study is examining the effects of demethylation on the GGR pathway and response of melanoma to carboplatin. We hypothesise that demethylation will increase XPC expression in melanoma and induce expression in response to carboplatin, increasing susceptibility to apoptosis.

**Methods:** Melanoma cell lines were treated with decitabine or carboplatin alone, and in combination. Quantitative real time PCR was used to measure GGR transcript expression before and after treatments and apoptosis was quantified using Annexin V apoptosis kit and flow cytometry.

**Results:** Treatment of melanoma cells with carboplatin alone did not significantly induce XPC expression or increase apoptosis. Decitabine alone increased XPC expression and when combined with carboplatin showed a greater induction and significantly increased levels of apoptosis.

**Conclusions:** Silencing of XPC by methylation is a possible mechanism of platinum therapy resistance in melanoma and combination treatment of decitabine and carboplatin may be used restore GGR function and overcome resistance.

**Translational research aspect:** This research is T1 basic science that will directly transition into T2. The project has determined that decitabine and carboplatin combination therapy is feasible for melanoma.
DEVELOPING THE HMRI FRAMEWORK FOR MEASURING RESEARCH IMPACT

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Background: Healthcare accounts for approximately 9.7% of Australia’s GDP. The longevity of Australians suggests value is being extracted from this spending, yet many patients still do not receive evidence-based care while others receive unnecessary treatments. Improving transparency regarding the extent to which effective research outcomes are used in the community provides one potential method to address this challenge. Our project seeks to design a framework for measuring research impact. At its core will be an economic metric: social return on investment (SROI).

Aims: (1) Identify attitudes, barriers, and drivers to routinely measure research impact. (2) Develop a framework to demonstrate research translation and research impact (3) Develop an economic framework for measuring research impact based on SROI.

Methods: (a) Semi-structured interviews with HMRI researchers to identify attitudes, barriers and drivers for measuring research impact. (b) A review of economic approaches to measuring research impact. (c) Proof of concept studies to apply SROI.

Results: (a) There was strong support for measuring research impact. Concerns raised related to administrative burden, the measurement of basic science, the protection of ‘discovery’ and the interpretation by funding bodies. The main driver to encourage measurement was demonstration of research impact – an outcome that could help attract additional funding. (b) Economic techniques for measuring impact are cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA). The preferred technique; CBA, provides the basis for reporting SROI. (c) SROI was calculated for two projects (T1 and T2); both generated more benefit relative to cost.

Conclusions: Cost-effective research innovations must be used in the community for benefit to be generated. SROI captures this use and will be a component of the HMRI framework for measuring research impact.

Translational research aspect: The translation of research innovations to wider use will be facilitated by measuring the extent of translation. The HMRI framework will be applicable to measuring translation in T1, T2, T3 and T4.

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MIDKINE AS A PREDICTIVE MARKER IN METASTATIC COLORECTAL CANCER

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Background: Colorectal cancer (CRC) is the second most common cancer in New South Wales, with 4700 cases pa and 1700 deaths from metastatic disease. Chemotherapy +/- radiation and surgery has substantially improved survival. To determine if a patient is benefiting from treatment requires medical imaging and CEA, a conventional biomarker with low sensitivity for detecting progression or recurrence. New predictive biomarkers are urgently needed. Midkine (MK) is a retinoic acid-inducible heparin binding growth factor shown to be elevated in >90% of an unselected series of 25 CRC patients. Studies suggest MK is a superior biomarker to CEA in some other cancers.

Aims: A pilot study in patients undergoing chemotherapy for metastatic CRC to assess frequency of elevated MK compared to CEA in metastatic CRC; rapidity of change of MK levels after chemotherapy vs CEA; correlation of change in MK levels vs CT scan response.

Methods: Patients undergoing any line of treatment for metastatic CRC are eligible. Paired MK and CEA levels are assessed at baseline, 2 weeks, then every 3–4 weeks. Midkine is quantitated by ELISA. Routine clinical variables collected (CEA, CT scans etc).

Results: To date 19 of a planned 50 patients have been recruited, with 13 patients completed. At baseline 10/16 (63%) have elevated MK vs 15/19 (79%) have raised CEA.

Conclusions: Midkine represents a potential new predictive biomarker for patients undergoing treatment for metastatic CRC, with capacity to reduce use of futile treatment and replace CEA and reduced use of futile treatment.

Translational research aspect: Demonstrated clinical value as a biomarker will lead to incorporation into clinical management protocols for mCRC (T3). Further research will evaluate potential for application in other scenarios, such as monitoring of early CRC after treatment (T1, T2).

A PLATFORM FOR PHARMACOGENOMIC ANALYSIS OF ADVERSE DRUG REACTIONS IN CANCER

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Background: Adverse drug reactions (ADRs) account for ~10% of hospital admissions; in cancer management ADRs are often unexpected or severe (suADRs), with a significant burden on resources, as well as substantial morbidity and sometimes mortality. Strategies to predict suADRs to anticancer drugs are needed. Polymorphisms in genes involved in pharmaco- kinetics and metabolism or in genes involved in drug effect might account for suADRs.

Aims: To establish a NSW facility for evaluation of genomic predictors of suADRs to anticancer drugs. To determine pharmacogenomic predictors of severe or unexpected toxicity to 5FU, oxaliplatin, temozolomide and mTOR inhibitors. To establish an annotated DNA bank for future studies.

Methods: Clinicians in NSW will identify patients with a suADR to treatment and provide clinical data and a blood sample for genomic analysis. Controls will be patients similarly treated who did not have the ADR. Whole exome arrays will identify SNPs and CNVs in relevant genes.

Results: This study is about to be activated in the 8 PRIMe centres in NSW. Genomic and bioinformatic analysis will occur in HMRI.

Conclusions: It is anticipated that once this platform is established and validated with small studies of current drugs, it will be attractive to a wider range of cancer clinicians and researchers as well as agencies involved in drug development, clinical trials and drug evaluation.

Translational research aspect: This platform will create infrastructure and research projects to explain and predict chemotherapy toxicity, with direct clinical applications leading to better patient outcomes.

DEVELOPMENT OF INTEGRIN-DERIVED PEPTIDE-BASED ANTICANCER COMPOUNDS

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Background: Integrins are a class of cell-surface receptors leading to a transcripational signal transduction cascade affecting cell growth and migration. We have previously reported that a short amino acid sequence derived from the β3-integrin cytoplasmic domain inhibits cancer cell growth in vitro only under serum-free conditions. In the present study this peptide was modified to enhance its in vitro efficacy in the presence of serum.

Aims: To modify the anticancer integrin-based peptide in order to achieve inhibition of cancer cell growth in vitro in serum-containing media and, thereby, select candidates for further screening in kinase activity assays.

Methods: In vitro cell growth assays (MTT, MTS and trypan blue cell counts) were performed for screening of modified peptides against cancer cell lines followed by non-cell-based in vitro kinase assays.

Results: Initial peptide modifications resulted in compounds that inhibited cell growth in vitro in the presence of serum as assessed by MTT assays and further changes to the peptide structure resulted in low nanomolar (nM) IC50 inhibition of cell growth. In contrast, MTS and cell count assays revealed higher IC50 growth inhibitory effects approximating 1–2 μM. The activities of several kinases were inhibited at low-mid nanomolar IC50 concentrations by these modified peptides.

Conclusions: Notwithstanding differences identified in compound efficacy in the presence of serum between the various cell-based assays, the MTT assay provided a sensitive first-line screening tool by which to identify potentially effective anticancer compounds. The effects of these new compounds were confirmed in in vitro kinase activity assays which require further validation in cell-based kinase assays.

Translational research aspect: This project (T1) aims to develop novel peptides for clinical use as commercially viable anticancer agents.
A HIGHLY POLYMORPHIC AG REPEAT IN THE UPSTREAM REGULATORY REGION OF THE ESTROGEN-INDUCED GENE EIG121 IS A POTENTIAL MODIFIER OF ENDOMETRIAL CANCER RISK

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Background: The estrogen-induced gene 121 (EIG121) encodes a transmembrane protein and has been associated with ovarian and endometrial carcinoma. In genome-wide investigations, we found that EIG121 contains a short tandem repeat (STR) located in the upstream regulatory region. Polymorphic STRs can alter levels of gene expression affecting transcription. This can have major consequences for disease risk and severity.

Aims: The aim was to analyse the variability of the EIG121 STR and to determine any association between its length and the risk of developing endometrial cancer.

Methods: In this study, DNA from 204 endometrial cancer patients and 220 healthy controls was analysed. STR length was determined by PCR and fragment analysis. Statistical analysis included Mann Whitney rank sum tests, Cox proportional hazard regression and Kaplan-Meier analysis.

Results: We found this repeat to be highly variable with a bimodal distribution. Statistical analysis revealed a trend towards an association between lower age at diagnosis for endometrial cancer and the length of the EIG121 STR short allele when adjusted for BMI. A longer short allele is correlated with earlier age at diagnosis with a one unit increase in STR length corresponding to a 5% increase in hazard (HR = 1.055, p = 0.019), and the median difference in age at diagnosis is 6 years when length of the STR is dichotomised around 37 repeats (p = 0.0085).

Conclusions: We have discovered a highly polymorphic STR in the upstream regulatory region of EIG121. When BMI was taken into account, a lower age at diagnosis was marginally associated with EIG121 STR short allele length. This novel, highly variable STR could be responsible for altered EIG121 expression and have implications for disease risk in endometrial cancer.

Translational research aspect: The study of STRs may provide a new avenue for estimating disease risk and improving diagnostic tools (T1).

IS IDENTIFICATION OF SMOKING, RISKY ALCOHOL CONSUMPTION AND OVERWEIGHT AND OBESITY BY GENERAL PRACTITIONERS IMPROVING? A COMPARISON OF DETECTION RATES IN AUSTRALIA BETWEEN 1982 AND 2011

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Background: Evidence-based strategies implemented to increase General Practitioner (GP) detection and intervention on lifestyle risk factors over the past 30 years have included the development of policies and clinical practice guidelines; education about the importance of detection in undergraduate medical curricula; and increases in remuneration for the provision of preventive healthcare. Despite this investment, little is known about whether GP detection of lifestyle risk factors has improved over time.

Aims: To compare results from four studies conducted in Australia between 1982-2011 to examine whether sensitivity and specificity of GP detection of smoking, excessive alcohol consumption and overweight and obesity has increased.

Methods: Demographic characteristics of patient and GP samples, the prevalence of each risk factor, and the sensitivity and specificity of detection of each risk factor was extracted from published studies. Differences between sample characteristics were examined using Pearson’s Chi-square and Exact tests. To identify trends over time in prevalence of risk factors and sensitivity and specificity of detection, the Cochran-Armitage test for trend was calculated for each risk factor.

Results: There were no statistically significant changes in the sensitivity of GP detection of smoking (p = 0.09) or overweight or obesity (p = 0.27) over time. There was a small decrease in the sensitivity of alcohol consumption risk detection (p = 0.02), and an increase in the specificity of alcohol consumption detection (p = 0.01). Specificity of detection of smoking increased significantly overtime from 64.7% to 98% (p < .0001). There was a significant decrease in specificity of detection of overweight or obesity from 92% to 89% (p = .01).

Conclusions: Detection of lifestyle risk factors by GPs remains low. Further examination of strategies to support the provision of preventive care in primary care, and ensure their implementation in practice, are needed.

Translational research aspect: This analysis highlights a clear gap in the translation of research evidence into changed clinician behaviour.

RETRANSPECTIVE DOSE EVALUATION OF PATIENT-SPECIFIC RADIOTHERAPY TREATMENTS USING 3DVH™ SOFTWARE

CHC Challenges
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Background: Complex radiotherapy techniques require comprehensive quality assurance to ensure safe and accurate treatment delivery. 3DVH™ software by Sun Nuclear provides the user an additional tool to predict 3D dose distributions in patients.
Aims: A retrospective patient study was performed to quantify the differences between 3DVH™ predicted dose-volume histograms and that predicted by the treatment planning system.

Methods: Treatment verification plans of 15 patients who received IMRT to the prostate were analysed after passing conventional quality assurance. The verification treatment plans were delivered to an ArcCheck™ cylindrical diode array phantom from Sun Nuclear.

Sun Nuclear’s 3DVH™ software were used to estimate dose-volume histograms from the ArcCheck™ measurements for organs at risk of radiation damage and the tumour sites. These were compared with the dose-volume histograms from the treatment planning system that were used for clinical treatment.

Gamma (1%, 1 mm) pass rates were used to compare the 3DVH results with that of the clinical treatment plans.

Results: The average number of voxels analysed per patient was 979,417 with a gamma (1%, 1 mm) dose match of 98.7% between the treatment plans and 3DVH™.

The average dose difference for the tumour target (prostate) was 0.4%. The organs at risk showed average dose differences of 0.4% for the femoral heads, 0.7% for the bladder and −0.2% for the rectum respectively.

Conclusions: The results of this study indicate that 3DVH™ is a practical tool, independent of the treatment planning system, which can provide radiation oncologists assurance of dose delivery accuracy. It potentially can assist clinical decision making to minimize the risk of radiation induced side effects such as fistula.

Translational research aspect: Translational pipeline T2: Incorporated routinely in clinical decision making may lead to an overall improvement in patient specific outcomes in radiotherapy.
ONCOGENIC ACTIVATION OF MEK/ERK PRIMES MELANOMA CELLS FOR ADAPTATION TO ENDOPLASMIC RETICULUM STRESS

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Background: Endoplasmic reticulum (ER) stress is characterized by accumulation and aggregation of unfolded and/or misfolded proteins in the ER lumen. Cells respond by activating a range of signaling pathways to alter transcriptional and translational programs. Cancer cells are commonly subject to chronic ER stress, which must be adapted for survival and proliferation. We report here that in melanoma cells intrinsic activation of the ER stress response/unfolded protein response (UPR) is, at least in part, caused by increased outputs of protein synthesis driven by oncogenic activation of MEK/ERK.

Aims: In this study, we examine the potential interaction between the constitutively activated MEK/ERK pathway and the UPR in melanoma cells.

Methods: Melanoma cell lines were treated with PLX4720, U0126 or vemurafenib and subjected to analysis by western blot, QPCR, or flow cytometry. Melanocytes were lentivirally transduced with BRAFV600E before being analysed by western blot, QPCR or flow cytometry.

Results: Inhibition of oncogenic BRAFV600E by PLX4720 or inhibition of MEK by U0126 attenuated activation of IRE1 and ATF6 signaling of the UPR in melanoma cells. This was associated with decreased phosphorylation of eIF4E and nascent protein synthesis, and was recapitulated by knockdown of eIF4E. In line with this, introduction of BRAFV600E into melanocytes led to increases in eIF4E phosphorylation and protein production, and triggered activation of the UPR. Paradoxically, treatment of melanoma cells with the clinically available BRAFV600E inhibitor vemurafenib resulted in induction of the UPR, an effect that may be independent of BRAFV600E inhibition.

Conclusions: MEK/ERK signaling is necessary and sufficient for intrinsic activation of the UPR as a consequence of ER stress triggered by enhanced protein synthesis in melanoma cells. These results indicate that potentiation of adaptation to chronic ER stress is another mechanism by which activation of the MEK/ERK pathway promotes the pathogenesis of melanoma. The contrasting effect of PLX4720 and vemurafenib on the UPR in this study raises questions pertaining to the role of the UPR and ER stress in melanoma patients treated with BRAF inhibitors.

Translational research aspect: T1: Basic Science

This study illuminates the effect of PLX4720 and vemurafenib on activation of the UPR, which may be useful in developing combinational therapies or reducing side effects in melanoma patients being treated with mutant BRAF inhibitors.

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the function of the inhibitory proteins, SET and ABP, we need to first understand the structure and the nature of the interactions that govern their roles in tumour suppressor deactivation.

Aims: By constructing complexes of the tumour suppressor PP2A with putative protein inhibitors can we identify avenues for the development of 2nd generation or novel drug therapeutics? Using a molecular modelling approach we aim to construct complexes of PP2A with two separate inhibitors in order to understand the specific molecular interactions.

Methods: A range of molecular modelling software was employed to predict and validate likely protein-protein interactions, forming protein complexes.

Results: Both SET and ABP form strong interactions with PP2A and the drugs that reactivate PP2A by targeting SET and ABP have significant interactions with PP2A trimmer itself.

Conclusions: This finding clearly indicates that further approaches to develop new strategies or second generation drugs to re-activate the tumour suppressor, should be based not only the single protein inhibitors, but on the total PP2A-inhibitor complex.

Translational research aspect: Developing a functional platform which utilises in silico analysis will facilitate anti-cancer drug target identification and lead to rational design of improved targeted therapies.

### SIDE EFFECTS OF ANDROGEN DEPRIVATION THERAPY FOR PROSTATE CANCER: ECONOMIC IMPLICATIONS

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**Background:** Cancer, the leading cause of disease burden in Australia, represents significant costs to the individual, community and the economy. Prostate cancer (PCa) is the most commonly diagnosed cancer in men with one of the highest five year survival rates after diagnosis of 92%. The prevalence of PCa increases with age and with a demographic transition towards an ageing population, and greater uptake of prostate specific antigen (PSA) screening, the cost burden of PCa is likely to increase. Androgen deprivation therapy (ADT) is the standard first-line therapy for metastatic PCa and also improves survival in men with non-metastatic, locally advanced or high-risk localised PCa. Thus, ADT and the numerous side effects associated with it, represent a considerable cost burden.

**Aims:** The aim of this research is to identify the side effects of ADT, their prevalence and treatment, for the preparation of a cost study and subsequent economic analyses.

**Methods:** A systematic review of the literature published from 2000 to September 2014 was undertaken. Databases included MEDLINE, EMBASE, Cochrane Library, Inforrnit Health Collection, PsychInfo, Scopus and Web of Life.

**Results:** The side effects associated with ADT are numerous, debilitating and potentially life threatening. They include metabolic changes, risk of cardiovascular disease, type 2 diabetes, osteoporosis, sexual dysfunction, hot flushes, etc. Exercise has been shown to slow PCa progression, reverse side effects, and improve the wellbeing and quality of life of prostate cancer patients.

**Conclusions:** The side effects associated with ADT, and their treatment, represent significant costs to patients, community and the economy. Clinical uptake of exercise has the potential to translate into health and economic benefits in improved quality of life and fewer complications, resulting in savings to the health care system, enhanced productivity and reduced patient and carer burden.

Translational research aspect: This research is T3 research for its potential to impact on policy and clinical practice.

### PRONGF AND SORTILIN EXPRESSION AND FUNCTION IN PANCREATIC CANCER

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**Background:** Nerve growth factor (NGF) and its receptors TrkA and p75NTR are expressed in pancreatic cancer and stimulate perineural invasion, thus contributing to cancer-associated pain. In the nervous system, the precursor of NGF, namely proNGF, and its receptor sortilin have a biological effect (neuronal apoptosis) that is distinct from NGF (neuronal growth). However, in pancreatic cancer, proNGF and sortilin have not been reported.

**Aims:** Examine the expression and role of proNGF and sortilin in pancreatic cancer.

**Methods:** The expression of proNGF and sortilin was investigated in a pancreatic cancer TMA (n = 40) using immunohistochemistry, and in vitro using qPCR and Western-blotting on immortalized human pancreatic ductal epithelial cells (HPDE) and cancer cell lines (PANC-1, Mia PaCa-2, BxPC-3, PaCa-44). The effect of proNGF was tested on cancer cell proliferation and invasion.

**Results:** In normal pancreas, proNGF was strongly expressed in acini and glandular tissues and sortilin predominantly localized in Langerhans islets. In pancreatic cancer, proNGF and sortilin were both expressed in cancer epithelial cells. In vitro, the production of proNGF and sortilin by both pancreatic cancer cells and HPDE cells was observed. ProNGF levels were on average 50-fold higher than that of NGF, indicating that the major NGF gene product in pancreatic cancer is actually proNGF and not NGF. However, blocking antibodies against proNGF had no effect on pancreatic cancer cell proliferation and invasion.

**Conclusions:** High level expression of proNGF and sortilin were detected in pancreatic cancer but blocking proNGF did not affect cancer cell proliferation/invasion. Recently we have reported that proNGF stimulates nerve infiltration in prostate cancer (Pundavela et al. Am J Pathol 2014, PMID: 23285721). Thus the high levels of proNGF levels produced by pancreatic cancer cells could stimulate perineural invasion, an effect previously attributed to NGF. We are now investigating this hypothesis.

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

### CLINICAL STUDY OF MITOTANE PHARMACODYNAMICS IN ADRENOCORTICAL CANCER IN CHILDREN AND ADULTS

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**Background:** Adrenocortical carcinoma (ACC) is a highly malignant, often metastatic tumour with a dismal five year survival. Mitotane is the only recognised effective systemic therapy. Benefit depends on maintenance of
adequate plasma drug levels >14 μg/ml and toxicity occurs at >20 μg/ml. The relationship between steady state level and dose administered is variable with up to 5–10 fold inter-patient variation.

**Aims:** To define therapeutic drug monitoring (TDM) strategy to achieve ideal levels quickly and to determine the relationship between levels and toxicity. We will identify factors that account for variability in mitotane kinetics.

**Methods:** Patients will have plasma mitotane levels determined serially by HPLC with dose adjustment advised to rapidly achieve and then maintain therapeutic levels. Anthropomorphic and patient factors will be evaluated to determine their contribution to variability.

**Results:** To date we have conducted >50 mitotane levels on 74 patients (44/30 F/M) from Australia and New Zealand (median age 50, range 11–81, 3 children). Empirical recommendations were provided to adjust dose, and were variably followed. Mitotane starting dose varied from 1–8 g/day; 42 patients (24/18 F/M, 3 children), achieved therapeutic range and the dose required to achieve therapeutic range was 6.1 ± 3.2 (mean±SD) g/day. It took adult patients 5.9 ± 3.7 months of therapy to acheive therapeutic range while it took children 1.5 ± 0.1 months. 21 patients (14/7 F/M) including all children, recorded toxic levels.

**Conclusions:** It takes a variable time (2–6 months) to achieve therapeutic range with the current practice and some patients overshoot despite TDM. This project (T2) will lead to clinical guidelines for mitotane dose adjustment.

**Translational research aspect:** This project (T2) will lead to clinical guidelines for mitotane dose adjustment.

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**PP16**

**ANTI-PROLIFERATIVE CAPACITY OF OLEUROPEIN RICH OLIVE LEAF EXTRACTS AGAINST PANCREATIC CANCER CELLS**

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**Background:** Olive leaves are an agricultural waste product with a high concentration of phenolic compounds, including the bioactive compound oleuropein. Oleuropein has been shown to exhibit anti-proliferative activity against a number of different cancer types. Pancreatic cancer is a devastating, heterogeneous disease with significant resistance to the limited conventional treatment options and high toxicity of current chemotherapeutic agents. Clearly there is an urgent need for the development of novel therapeutic strategies.

**Aims:** This study investigated the oleuropein content of olive leaf extracts, and assessed their anti-proliferative activity against pancreatic cancer cells.

**Methods:** The oleuropein content of two varieties of olive leaf extracts were prepared from 3 different extraction protocols. The oleuropein content of the extracts was assessed and their anti-proliferative capacity against primary pancreatic cancer cells (MiaPaCa-2) and normal pancreas cells (HPDE) was compared to gemcitabine.

**Results:** Despite differences in the oleuropein content of the different olive leaf extracts, there was no difference between their anti-proliferative capacity (p > 0.05). Furthermore, all extracts (200 μg/ml) significantly decreased the viability of pancreatic cancer cells (MiaPaCa-2) compared to the chemotherapeutic agent gemcitabine (p < 0.05). Importantly, there was no difference in the toxicity of the extracts towards the normal pancreas cells (HPDE) compared to gemcitabine (p > 0.05).

**Conclusions:** Olive leaf phenolic compounds warrant further investigation into their potential anti-pancreatic cancer activity.

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

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**PP17**

**A QUALITATIVE STUDY EXPLORING AUSTRALIAN SOCIOECONOMICALLY DISADVANTAGED SMOKERS’ RESPONSES TO INCREASING CIGARETTE PRICES**

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**Background:** Substantial research supports increasing tobacco taxes to achieve smoking cessation among low socioeconomic status groups. However, few studies have explored the resulting experience of deprivation and financial stress among those who maintain smoking despite increasing costs.

**Aims:** This study aimed to explore how socioeconomically disadvantaged smokers manage smoking costs on limited budgets, and the impact this has on material deprivation, financial stress and cessation cognitions.
Methods: Qualitative semi-structured interviews were conducted with 20 smokers recruited from a Social and Community Service Organisation providing crisis welfare assistance to disadvantaged people in New South Wales, Australia. Interviews explored the perceived impact of tobacco costs among socioeconomically disadvantaged smokers, including the effects on essential household expenditure, smoking behaviour and quit cognitions. Interviews were audio-taped, transcribed verbatim and analysed using thematic framework analysis.

Results: Limited budgeting and financial planning led to instances of smoking-induced deprivation and financial stress. Participants reported struggling to pay bills and going without meals or substituting food choices. Use of price-minimisation strategies, such as switching product types and reducing consumption were viewed as short-term solutions when money was tight. Participants reported tobacco price increases were good for preventing uptake, but that larger price rises and subsidised cessation aids were needed to help them quit smoking.

Conclusions: Socioeconomically disadvantaged smokers may reduce essential living and household spending to maintain smoking as tobacco prices rise. Tobacco control policy should consider impact on the financial and material well-being of socioeconomically disadvantaged smokers who may find it difficult to quit unassisted.

Translational research aspect: Highly disadvantaged groups face significant tobacco-related health and welfare inequalities, and there is a need for T2 research to understand the strategies these groups use to maintain smoking in order to develop socially responsible policy.

MULTIFUNCTIONAL NANOMEDICINES BASED ON ALBUMIN FOR TARGETED BREAST CANCER THERAPY

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Background: The membrane Trk receptors are increasingly regarded as therapeutic targets in oncology. Unlike conventional chemotherapeutics, the molecularly targeted Trk inhibitors are expected to be more specific to tumors and less harmful to normal tissues. However, the clinical use of Trk inhibitors still confront with the challenges of low bioavailability and potential adverse effects arising from high systemic absorption of drugs.

Aims: Small Trk inhibitor GNF-5837 had recently shown anti-tumour activity in tumor xenografts derived from RIE cells. This research is set to investigate the efficacy of GNF-5837 on breast cancer and develop novel targeted delivery systems to concentrate drugs at tumors and enhance their uptake by tumor cells.

Methods: Albumin was used to formulate nanocarriers for GNF-5837 due to its unique advantages in cancer therapy. The resulting nanomedicines were extensively characterized in terms of drug loading and physicochemical properties. The anticancer efficacy was investigated by measuring cell proliferation, cell apoptosis and Trk inhibition on a panel of breast cancer cell lines representative of different breast cancer subtypes.

Results: The albumin nanocarriers were around 180 nm with a narrow size distribution (PdI: 0.17) and a drug loading efficiency of approximately 90%. Nanocarriers alone were well tolerated by breast cancer cells and showed no apparent toxicity. In contrast, nanocarriers with GNF-5837 showed effective inhibition of the growth of breast cancer cells, which was about 2 times more efficient than the drug alone. Furthermore, the IC50 for breast cancer cells was significantly lower than that for the normal HME cell line.

Conclusions: These nanomedicines may hold great promise for the development of targeted breast cancer therapy. Future studies are required to examine their efficacy in vivo in xenograft model.

Translational research aspect: This research focuses on developing treatments and interventions (T1). The targeted therapy not only represents a translatable approach to improve treatment efficacy and patient tolerance, but also opens up the field for new line of molecularly targeted approaches to treat patients who no longer benefit from conventional therapies.

BREAST DENSITY MEASUREMENTS

INTROOBSERVER INTRA- AND INTER-METHOD RELIABILITY IN BREAST DENSITY MEASUREMENTS

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Background: Mammographic (breast) density is a risk factor for breast cancer. Many methods to quantify mammographic density (MD) require human input, and hence are subject to user variability. User differences in MD assessment affect detection of meaningful longitudinal change in MD.
Aims: We wished to quantify the variability in a single-user’s assessment of percent density (PD) using Cumulus (defacto ‘gold standard’) and visual methods, and examine differences between these techniques.

Methods: 130 cranio-caudal view film-screen mammograms from participants in the IBIS-II breast cancer prevention trial were digitised on an Array laser digitiser. Mammograms were assessed by a single user one month apart using both assessment methods (Cumulus and visual). Intra-class correlations (ICCs) and Bland-Altman plots were utilised to compare techniques.

Results: Intra-technique correlation was high: Visual Percent Density (VPD) ICC 0.95 (95% CI 0.93–0.97); Cumulus PD (CPD) ICC 0.97 (95% CI 0.96–0.98). The limits of agreement (LOA) were ±13% VPD and ±8% CPD. A bias (mean difference) of −12% (95% CI −13% to −11%) between average VPD and average CPD was found. Visually assessed PD is not equivalent to Cumulus assessed PD. CPD is more time consuming to complete, but has improved repeatability compared to VPD.

Conclusions: Cumulus assessed PD has less variability with single-user assessments compared to visually assessed PD. Variability with CPD is still high, and is approximately equivalent to the smallest meaningful change in PD (10%) associated with a clinical difference in breast cancer outcomes. Methods with less variability would improve assessment of longitudinal changes in breast density.

Translational research aspect: This project confirms previous research that methods with improved repeatability are needed to assess breast density; this is especially true in the longitudinal context where small, but potentially meaningful changes in density may be obscured by measurement variability (T2 – method efficacy).

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**PP22**

**ENHANCING RADIATION EFFECTS FOR THE TREATMENT OF BRAIN CANCER**

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Background: Glioblastoma multiforme (GBM) is the most common primary brain tumour, the most lethal and difficult to treat. Even with optimal therapy (temozolomide plus radiation) the median survival is 40–60 weeks. The DNA alkylating activity of temozolomide and the subsequent G2/M cell cycle arrest induced by this agent is believed to underlie the radiosensitizing ability of this treatment. We have identified dynamin II (Dyn II) as an important protein in cytokinesis, the final step in mitosis. Inhibition of Dyn II induces cytokinesis failure with cell cycle arrest in G2/M. We have identified two drugs that inhibit Dyn II and cause cell growth inhibition in various brain-derived cancer cell lines.

Aims: To examine the ability of our lead Dyn II inhibitors to enhance radiation effects in our cell line models of glioblastoma.

Methods: MTT assays together with a colony-forming assay will be exploited to determine the ability of our lead dynamin inhibitors to enhance the effect of radiation treatment in glioblastoma cell lines. Our cell lines will be exposed to our lead compounds or the standard radiosensitizer, temozolomide for 24 h before radiation (2–8 Gy) and tested for growth and colony-forming efficiency 10–14 days post treatment.

Results and Discussion: Our lead Dyn II inhibitors significantly reduce cell growth in a wide panel of cancer cell lines including glioblastoma cells, with GI50 values of 5–10 μM after 72 h exposure. We have established and optimised the in vitro model system, so we can now assess the ability of our compounds to enhance radiation effects using temozolomide as a comparator. The ability of our compounds to enhance radiation effects will be presented in comparison to temozolomide.

Translational research aspect: This is a T1 lab-based study for the development of better treatments for brain cancer.
THE IMPACT OF INTEGRATING SYSTEM CHANGES INTO ROUTINE HEALTHCARE PRACTICES VIA MODIFICATION OF EXISTING PROCESSES: A LOOK AT BIOBANKING CONSENT IN THE HUNTER REGION

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Background: As part of a Cancer Institute NSW (CINSW) Biobanking Stakeholder Network initiative, Hunter Cancer Research Alliance, together with the Hunter Cancer Biobank, developed a unique, pre-operative process for embedding biobank consent into routine hospital practice. In 2014, a 12 week pilot was conducted that incorporated consent into existing pre-surgical forms.

Aims: The growth of institutional biobanks has been met with many challenges over the past few decades. With a clear disjunction between end users (researchers) and facilitators (health care providers), and an increase in demand of high quality specimens linked to clinical data, a major challenge has been in developing efficient systems for capturing biobank consent, allowing clinical data linkage to specimens. This project proposed embedding consent as part of routine practice through integrating biobank consent into existing pre-surgical consent practices.

Methods: A model for pre-operative consent was developed and multidisciplinary stakeholders were engaged across the John Hunter Hospital to identify issues, provide education, and canvass support for biobanking. A 12-week pre-operative consent pilot was completed by Gastrointestinal Surgery and Gynaecological oncology tumour streams. The pilot embedded biobank consent wording (via a sticker) into the existing state-wide, pre-surgical ‘Request for Admissions’ (RFA) booklet. Compliance was determined by assessment of number of operations and consents obtained. System integration was determined through analysis of weekly consent rate.

Results: Education was provided to the surgical tumour groups in February 2014 with the pilot being conducted from March to May 2014. A total of 118 surgeries were conducted by Gastrointestinal Surgery (61%) and Gynaecological oncology (39%) during the pilot period. The success of capturing biobank consent following the introduction of our consent sticker was 52% (36/72) in Gastrointestinal Surgery and 65% (36/56) for Gynaecological oncology. Week to week consent rates showed Gastrointestinal Surgery had a slow increase in system integration, peaking at 100% by week 10, in comparison, Gynaecological oncology achieved full system integration by week 5 and levels were maintained throughout the pilot period. Both tumour-streams had 100% compliance to consent when forms included the new biobank consent sticker.

Conclusions: The ease in access to biobank consent played a vital role in facilitating the consent process for surgical teams with limited resources. Embedding consent as part of routine practice utilising the existing pre-surgical consent forms successfully indicated a 100% compliance rate for both groups. While compliance to the proposed process was high, the reduced consent rate (61%, 72/118) was attributable to the lag-time/failure of implementing the consent sticker into the pre-existing RFA.

Translational research aspect: This project will provide knowledge for further investment into standardising biobanking consent for public institutions at a state level.

CORRELATES OF THE DETECTION OF CANCER RISK FACTORS BY GENERAL PRACTITIONERS

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Background: One of the key responsibilities of primary health care is the provision of preventive care services. Clinical practice guidelines recommend that general practitioners (GPs) regularly screen for health risk factors such as smoking, risky alcohol consumption and obesity. GPs also have an important role in facilitating routine screening for cancers (e.g. breast, bowel and cervical cancers). However, delivery of preventive care within primary care settings remains low.

Aims: This study aimed to identify the patient, GP and practice level factors associated with increased GP detection of risk factors.

Methods: Patients aged at least 18 years presenting for appointments at 12 practices across NSW and Victoria. Patient demographic characteristics, health risk factors, and cancer and cardiovascular risk screening practices were collected by self-report. GPs were asked to report their perceptions of whether these patients had health risk factors and had undergone recommended screening tests. Mixed effects logistic regression was used, with the proportion of patient-reported risk factors and the proportion of GP-reported risk factors as the binomial outcomes.

Results: On average, 33% of patients reported at least one health risk factor, while GPs detected 36% of these risk factors. GPs were more likely to detect risk factors in patients who had lower education, held a health care card, and did not have private health insurance.

Conclusions: These results suggest that risk factors are more likely to be detected in individuals of lower socioeconomic status (SES). However prior research shows that lower SES is associated with increased prevalence of health risk factors and chronic diseases. This suggests an urgent need to translate risk factor identification into effective management of these risk factors in disadvantaged populations.

Translational research aspect: This research fits in the T2 component of the translational pipeline as the findings may be translated to inform practice.

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PREVALENCE OF TOBACCO SMOKING 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 continue to smoke after diagnosis and this behaviour affects radiotherapy treatment efficacy and survival.

Aims: This study aimed to describe the prevalence of continued smoking within a sample of head and neck cancer patients about to undergo radiotherapy.

Methods: As part of an NHRC funded randomised controlled trial, head and neck cancer patients from four Australian radiotherapy departments completed baseline assessments and data were collected on smoking characteristics. Nicotine dependence was measured via The Fagerstrom Test for Nicotine Dependence (FTND). Biochemical verification (CO breath analysis > 10 ppm = smoker) of smoking status was also conducted.

Results: The mean age of patients (n = 142) was 58 years and 82% were male. 13% of patients identified as current smokers and these results were consistent with the CO verification measure. The majority of current smokers fell in the low to moderate range of nicotine dependence. 78% of patients had been smokers in their lifetime and 41% of these reported to have smoked in the last 6 months.

Conclusions: This is the first Australian study to biochemically verify self-report of smoking in head and neck cancer patients about to undergo radiotherapy. Our results indicate that further investigation is needed using qualitative methods to elucidate head and neck cancer patients’ reasons for quitting as well as reporting the prevalence of smoking relapse. This reduction which may be reflective of decreasing smoking rates nationally as a result of public health initiatives such as tobacco price increases, mass media campaigns and plain packaging.

Translational research aspect: The current and past smoking rates in this sample will help to develop interventions in this population which may need to address relapse prevention post treatment (T1).

FACTORS PREDICTING RESPONSE AND SURVIVAL IN COLORECTAL CANCER PATIENTS RECEIVING ADJUVANT 5-FUOROURACIL CHEMOTHERAPY: 10-YEAR FOLLOW-UP OF A PROSPECTIVE PATIENT COHORT

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Background: 5-fluorouracil (5FU) is the backbone of adjuvant chemotherapy for stage III and high-risk stage II colorectal cancer (CRC) patients. Despite a number of prognostic attempts to better select patient groups more likely to benefit from adjuvant chemotherapy, there are still significant differences in long-term outcomes.

Inter-patient variations in drug metabolism (pharmacokinetic) and drug effect (pharmacodynamic) may account for differences in toxicity and tumour response. In addition, a number of demographic characteristics such as age, gender and comorbidities, may contribute further to the differences in outcome.

In a prospective cohort of 73 CRC patients treated with 5FU, we previously showed that a number of pre-treatment factors predict for clinical toxicity, including short WBC telomere length (TL), high platelet-lymphocyte ratio (PLR), low starting neutrophil count, age and gender. Some 5FU PK parameters (AUC, half-life, and clearance) also correlated with toxicity (Garg et al, Br J Cancer 2012). In this study, we evaluate the predictive factors for long-term survival of patients involved in the original study.

Aims: To determine factors predicting response and survival in colorectal cancer patients receiving adjuvant 5FU chemotherapy.

Methods: Baseline patient demographics were collected. TL was measured from peripheral blood mononuclear cells using southern blotting. Plasma 5FU, U, FUH2 and UH2 concentrations were measured using high-performance liquid chromatography – mass spectrometry (HPLC-MS).

Long-term survival and relapse data are collected from electronic and physical patient records. Univariate and multivariate analyses will be performed using disease free survival and overall survival as dependent variables.

Results and conclusion: Analysis is ongoing.

Translational research aspect: This analysis has potential to explain variability in outcomes after chemotherapy, and thereby lead to better decision-making in clinical settings (T2, T3).

PERIPHERAL NERVES ARE ASSOCIATED WITH SOME OVARIAN TUMOURS

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Background: Epithelial ovarian cancer represents 90% of all ovarian cancers. This cancer is categorised into serous, endometrioid, mucinous and clear cell carcinomas, according to histological characteristics. It has been demonstrated that autonomic nerves grow into some prostate tumours and their density correlates with cancer aggressiveness. Our laboratory has shown that nerves grow into breast tumours and this correlates with lymph node invasion.

Poster Abstracts

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Aims: Investigate potential nerve infiltration and the role of nerve growth factor in ovarian cancer.

Methods: Tissue microarrays (TMAs) were purchased from US Biomax, Inc. To determine overall nerve density we used antiserum directed against protein gene product (PGP) 9.5 as a general marker for nerves. Antiserum directed against nerve growth factor (NGF) was also used.

Results: PGP9.5 immunoreactivity (IR) was observed in 101/208 cases. PGP9.5 was expressed by nerve fibres (axons), but also by cancer cells and fibroblasts. PGP9.5-IR axons were observed in 14% of tumours, fibroblasts in 19% and cancer cells in 37%. NGF-IR cells were found in 90% of tumour sections mostly associated with cancerous cells.

Conclusions: This data shows for the first time that nerves infiltrate some ovarian tumours and that expression of PGP9.5 is not restricted to axons. NGF was also observed in ovarian tumours providing a potential driver for axon growth. The subtypes of nerves in these tumours remain to be determined, as do the neurotransmitters that may influence tumour growth.

Translational research aspect: Tumour progression is reliant upon both the genetic makeup of cancer cells and their surrounding microenvironment. We now demonstrate here that nerves have to be considered as part of the tumour microenvironment in ovarian cancer. This finding uncovers a number of new potential therapeutic targets.

Effects of INPP4B on Pancreatic Cancer

Aims: Investigate potential nerve infiltration and the role of nerve growth factor in ovarian cancer.

Methods: Tissue microarrays (TMAs) were purchased from US Biomax, Inc. To determine overall nerve density we used antiserum directed against protein gene product (PGP) 9.5 as a general marker for nerves. Antiserum directed against nerve growth factor (NGF) was also used.

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Translational research aspect: Tumour progression is reliant upon both the genetic makeup of cancer cells and their surrounding microenvironment. We now demonstrate here that nerves have to be considered as part of the tumour microenvironment in ovarian cancer. This finding uncovers a number of new potential therapeutic targets.

A NATURAL PRODUCT DRUG DISCOVERY PIPELINE FOR NOVEL PANCREATIC CANCER THERAPIES: A NEW CANCER RESEARCH HUB FOR THE HUNTER REGION OF NSW

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Background: The diagnosis of pancreatic cancer (PC) has dire consequences as it presents late and is rapidly progressive. Due to the significant heterogeneity, PC is one of the most devastating of human cancers. Treatment options are limited to surgery and/or treatment with gemcitabine, and regardless of intervention, patient outcomes are modest at best. Novel approaches and new treatments are urgently required, and natural product-derived compounds, such as taxol/paclitaxel, irinotecan and gemcitabine provide justification for their continued investigation for novel drug discoveries.

Aims: New therapeutic interventions begin in the laboratory. At the University of Newcastle’s Central Coast Campus, we are aiming to commission an Australian PC screening facility as part of a PC translational treatment pipeline. Our focus is to exploit the unique evolutionary adaptations that natural products have developed to identify biologically active compounds that target aberrant mechanisms driving pancreatic carcinogenesis.

Methods: Terrestrial and marine flora from Australia and Vietnam, as well as marine invertebrates from Australian temperate seas, are ethnobotanically collected for further investigation. Using optimised extraction chemistry techniques, we are extracting, isolating and identifying biologically active compounds and assessing their anti-PC activity in vitro.

Results: We have extracted numerous compounds (as isolated compounds and within crude extracts). To date we have assessed the activity of >50 natural product extracts (including fractions containing phenolic compounds, saponins and terpenoids) from 12 terrestrial flora historically used for their traditional medicine properties. We have also established a pipeline for the extraction of complex cytotoxic molecules from marine invertebrates. Significant efficacy at low dose concentrations against PC cell lines have been observed (single compounds <1 μM; crude extracts <200 μg/mL) while exhibiting only limited toxicity towards normal pancreatic cells.

Conclusions: This unique drug discovery pipeline utilises powerful bioactive natural chemical compounds from an unmatched and untapped natural products source as well as a unique resource of PC cell lines and expertise (cancer biology, natural product chemistry and chemical synthesis capability) to identify, develop and assess novel therapeutic agents for PC.

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.
as a tumor suppressor in some other tissues. These results reveal that INPP4B can regulate PI3K signaling positively or negatively and thus differentially affects cell proliferation and survival in a tissue type-specific manner. Therefore, the role of INPP4B in the development, progression, and response to treatment of different types (subtypes) of cancers needs to be defined discretely.

Translational research aspect: This project is currently at T1-T2 stages. Nevertheless, the results are expected to lead to identification of upregulation of INPP4B as a biomarker of colon cancer pathogenesis, and to development of inhibitors of INPP4B in the treatment of colon cancer, which will be taken into T3-T4 studies.

WHAT ARE THE MOST IMPORTANT BARRIERS TO QUITTING SMOKING? A CROSS-SECTIONAL SURVEY OF PERCEPTIONS OF HIGHLY DISADVANTAGED SMOKERS

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Background: Understanding the barriers to quitting smoking faced by socially disadvantaged groups may help to improve their smoking cessation rates.

Aim: This study aimed to identify the most frequently reported barriers to smoking cessation and the top three barriers to cessation ranked as most important within a sample of Australian welfare recipients.

Methods: A cross-sectional survey of adult welfare recipients who were current smokers was carried out in two welfare agencies in NSW, Australia from October 2013 to July 2014. Smoking status, smoking-related variables and barriers to cessation were assessed. Participants were presented with a randomised list of 38 barriers to quitting and asked to rate each item on a scale of zero (not a barrier) to three (large barrier). Of those barriers rated as “large”, participants were asked to rank the top three most important barriers to address in order for participants to quit smoking.

Results: In total, 384 current smokers consented (85% consent rate). Females made up slightly more of the sample (59%), mean age = 40 years. The most frequently reported “large” barriers were addiction to smoking (54%), smoking to deal with stress (47%), smoking to manage anxiety or depression (39%), too many stressful life events (39%) and smoking for relaxation (38%). The top three “large” barriers identified as most important in order for participants to quit smoking were addiction (38%), dealing with stress (12%) and enjoyment (8%).

Conclusions: By addressing addiction, stress and mental health when encouraging disadvantaged smokers to quit smoking, the primary perceived barriers to quitting will be tackled.

Translational research aspect: This research will allow the design of targeted approaches to increasing smoking cessation rates in disadvantaged welfare recipients through addressing the most important perceived barriers to quitting smoking (T2).
REGULATION OF SENSITIVITY OF HUMAN MELANOMA CELLS TO KILLING BY THE HUMAN MUT T HOMOLOG1 INHIBITOR

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Background: Cancer cells often have dysfunctional redox regulation that produces high levels of intracellular reactive oxygen species, which oxidizes dNTPs leading to damage to DNA. MTH1 hydrolyzes oxidized dNTPs thus protecting cells from DNA damage. Inhibition of MTH1 by specific inhibitors is emerging as a promising approach in the treatment of various types of cancer. However, the effect of MTH1 inhibitors in human melanoma remains less understood.

Aims: To define the effect of inhibition of MTH1 on melanoma cell survival, and to determine the therapeutic potential of MTH1 inhibitors in the treatment of melanoma.

Results: While MTH1 was commonly upregulated in melanoma cells in vitro and in vivo, treatment with the MTH1 inhibitor TH588 potently induced cell death in the majority of melanoma cell lines tested. Killing of melanoma cells by TH588 was associated with activation of the mitochondrial apoptotic pathway and the caspase cascade, and was inhibitable by the general caspase inhibitor z-VAD-fmk, indicative of induction of apoptosis. Moreover, differential regulation of pro-apoptotic Bcl-2 family proteins appeared to play an important role in determining sensitivity of melanoma cells to TH588-induced apoptosis. Induction of apoptosis by TH588 was consolidated in fresh melanoma isolates and melanoma cells grown in 3-dimensional cultures.

Conclusions: The above results indicate that MTH1 expression is upregulated in melanoma cells, and that the MTH1 inhibitor TH588 is a promising therapeutic agent in the treatment of melanoma.

Translational research aspect: This project is currently at T1 stage. However, it is expected to be taken into pre-clinical studies in near future, which will be followed by evaluation in clinical trials.

PICNIC: TREATMENT OF PANCREATIC ENZYME INSUFFICIENCY IN PATIENTS WITH PANCREATIC CANCER (TRIAL IN PROGRESS)

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Background: With current best practice, patients with advanced pancreatic cancer can expect to live for around 11 months. This condition is characterised by progressive cachexia, refractory pain and symptoms of malnutrition. Pancreatic cancer causes enzyme insufficiency (PEI) by: pancreatic duct obstruction; replacement of pancreatic tissue by tumour; or pancreatic tissue autodigestion. Patients with PEI have poorer quality of life and shorter survival. PEI can be treated with creon, an oral pancreatic enzyme replacement therapy. Previous work has shown that creon reduces weight loss and improves quality of life in patients with pancreatic cancer and a biliary stent in situ.

Aims: To determine if patients with advanced pancreatic cancer experience less weight loss, better quality of life and better nutrition when given pancreatic enzyme replacement therapy, compared with those who are given placebo.

Methods: PICNIC is a randomised phase II placebo controlled trial enrolling patients with advanced or metastatic pancreatic cancer and a life expectancy of >2 months. Key exclusion criteria are symptoms of active PEI or currently receiving creon. The initial dose is 2 capsules with meals and one with snacks, of creon 25,000 units or matched placebo with dose escalation if symptoms of PEI develop, followed by unblinding if symptoms persist. Outcome measures are weight, quality of life (QLQ C30 and PAN26 module), nutrition (PGSGA) and overall survival.

Progress to date: 18 patients have been randomised with a median time on study of 119 days. Adherence has been high, and the pill burden does not appear to be a significant barrier. Screen failure reasons include performance status, rapid progression and already taking creon. The recruitment target is 40 patients. If this study regimen is feasible with a preliminary signal of efficacy, it will provide rationale for a fully powered study.

Translational research aspect: This represents T2 research.
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