THE 2015 CONTROLLING CANCER SUMMIT
ABSTRACTS

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Day 1:

Invited Speakers Abstracts

Cell-mediated anti-cancer immunotherapy; targeting chemotherapy-resistant malignant cells with personalized immunotherapy mediated by autologous and allogeneic cells
Professor Shimon Slavin, The International Center for Cell Therapy & Cancer Immunotherapy (CTCI), Weizman Center, Tel Aviv, Israel

High-risk and metastatic cancer remains incurable. Considering resistance of cancer stem cells to available anti-cancer modalities, innovative treatments to eliminate resistant malignant cells are urgently indicated. Cell-mediated immunotherapy can be effective for treatment of minimal residual disease (MRD). Such treatment can be easily accomplished at an early course of the disease following successful treatment with available conventional anti-cancer procedures. Control of MRD can then be successfully accomplished by personalized targeted autologous and allogeneic cell-mediated immunotherapy. Evidence for cure of otherwise incurable hematopoietic malignancies and metastatic solid tumors when patients are treated at an early stage of MRD will be presented.

Current status of minimally invasive diagnosis and staging of lung malignancies
Dr Jorge Pascual, MD, Assistant Professor, Mayo Clinic College of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Florida, USA

Lung cancer continues to be the highest cause of cancer deaths around the world. Optimal therapy for lung cancer is defined by the clinical stage of the disease and by newly identified specific genetic mutations. Imaging studies have progressed over the past decades, especially after introduction of PET scanners, but are not able to provide enough specificity, and histological diagnosis. Over the past decade new minimally invasive methods for sampling and staging lung cancer have been developed, reducing the number of futile surgical procedures, and allowing more individualized therapies based on genetic analysis of small samples.

Early detection of oral carcinogenesis: the biological fundaments of in vivo optical imaging
Professor Rui Amaral Mendes, The Catholic University of Portugal and Case Western Reserve University, Cleveland, OH, USA

The progression towards malignancy includes sequential pathological alterations ranging from hyperplasia through dysplasia to carcinoma in situ and invasive carcinoma and is determined by the accumulation of a series of genetic and epigenetic events.

Oral carcinogenesis must be seen as a molecular and histological multistage process featuring genetic and phenotypic markers for each stage, which involves enhanced function of several oncogenes and/or the deactivation of tumour suppressor genes, resulting in the alteration of several signal transduction pathways, which often produce dramatic changes in cell survival, proliferation, morphology, angiogenesis, longevity and other properties known to characterize cancer cells.

Still, genetically altered fields of cells are not always clinically or histologically evident. Fluorophores are specific tissue compounds that may be excited by higher-energy light so that they re-emit lower-energy light, thus making up the autofluorescence image of the tissue. Changes in fluorescence reflect a complex interplay of alterations to fluorophores in tissue and structural changes in tissue morphology. Direct fluorescence visualization (FV) is currently available for widespread use in the oral cavity. However, this method is still a matter of controversy regarding its poor specificity because of confounding benign conditions, including inflammation.

Some studies showing that new imaging tools may improve our ability to clinically distinguish normal from premalignant and malignant oral tissue in a real-time fashion, with some complementary lesion-focused assessments being accepted by some health authorities.

Selection of an optimum wavelength that may differentiate between oral cancers or premalignant lesions and confounders in a precise and objective manner remains of the utmost importance. Optical imaging technologies (e.g., in vivo confocal microscopy, molecular targeted optical contrast agents alone and in combination) must be integrated in the future with molecular findings to further advance our understanding of disease processes.
Overcoming Mechanisms of Therapeutic Resistance in Advanced Castration Resistant Prostate Cancer

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Taxane-based chemotherapy is the only clinically effective treatment for castration resistant prostate cancer (CRPC) via stabilization of microtubules. Previous studies identified that inhibitory effect of microtubule targeting chemotherapy on AR activity via blocking nuclear AR localization. The N-terminus of AR was identified as the tubulin-interacting domain that can be effectively targeted by the novel small molecule inhibitor, EPI-001/2. Taken together this evidence suggested that targeting AR nuclear translocation and activity by antiandrogen and taxane-based chemotherapy may optimize therapeutic response in advanced CRPC. The present study investigated the antitumor efficacy of a combination of EPI-001/2 with tubulin-targeting taxane, docetaxel chemotherapy in a model of CRPC. Our findings demonstrate that resistance to docetaxel can be potentially overcome by inhibition of the N-terminal domain for the AR via temporal cycling of EMT-MET. Impairing AR activity enables a new targeting platform for taxane-based chemotherapy during PCA progression and supports a combination strategy of ADT and tubulin-targeting chemotherapy towards an improved therapeutic outcome in patients with advanced CRPC.

Cancer Causation and Risk Communication: The gap between cancer knowledge and community perceptions

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Community-based surveys consistently indicate confusion regarding cancer causation; confusion which in some instances reflects current carcinogenicity data and its extrapolation to infer particular risks. Individual choice to smoke, drink alcohol or seek sun exposure illustrate circumstances where cancer causation is clear. Likewise, exposure to workplaces carcinogens and some environmental pollutants warrant immediate regulatory action to eliminate cancer risk. However, providing information to the community about cancer risk from food contaminants and through using particular consumer products is often challenging. A reasonable understanding of diverse risks is impaired because cancer causation is often been wrongly portrayed in the media.


Professor Peter Creighton Elwood, Cardiff University, Penylan, Cardiff, United Kingdom

There is convincing evidence from long-term follow-up randomised trials of a substantial reduction in both the incidence and mortality from colorectal cancer, and evidence of reductions by aspirin in other cancers is highly suggestive. There is also observational evidence that the taking of aspirin by patients with cancer, increases survival. Aspirin also increases the risk of gastrointestinal bleeding, but a review of the literature indicates that bleeds attributable to aspirin are less serious, are not fatal and their occurrence decreases markedly over time.

Prognostic value of repeat testing in population screening for CRC - for optimizing efficacy

Pavel Elsakov, MD PhD, State Research Institute, Innovative Medicine Center, Vilnius, Lithuania

Population screening for those average risk for CRC by FOBT every two years can reduce mortality from this cancer, when participation rate reach 45-60% of population. The choice of FOBT kits for screening impacts on participation rates and efficacy of such programs. From May 2009 using the FIT with automated processing (OC-Sensor™ test) screening started for a target population of 36,062 subjects – 14,559 (40,4%) males and 21,503 (59,6%) females between the ages of 50-74 years. Patients with an FIT value ≥100-ng Hb/mL of buffer underwent colonoscopy The participation rates for repeat testing is 26,1% less than the necessary minimum of - 45%, that is needed to be of benefit to reduce expected mortality rates.

Knowledgeable methods to assess and support older people with cancer; comprehensive care for older people with cancer (COCOC)

Professor Margot Ann Gosney, University of Reading, Clinical Health Sciences, Reading, UK

Older people account for 50% of all diagnoses of malignancy. They however, are often under investigated and under treated. Some of this discrepancy is due to patients having a number of co-morbidities, Giants of Geriatric Medicine and caring responsibilities. COCOC aims to fully assess older patients for reversible conditions, provide multidisciplinary input throughout the patient's treatment and emotional support in the form of buddies.
NANO-FORMULATION OF NOVEL OLEIC ACID CONJUGATE SUPPRESS MOUSE SKIN TUMORS BY REGULATING P53WT/MUT EXPRESSION

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ABSTRACT

Novel ester conjugate of oleic acid, 2,6-Diisopropylphenol-oleic acid (2,6P-OLA), has been observed as potent anticancer agent against panel of cancer cell lines (Khan et al., 2012). The present study describes development of a Nano-liposome-based approach for topical delivery of 2,6P-OLA on skin cancer in mice. The conjugate entrapped in liposomes were of 100-130 nm size and showed slow and sustained release pattern of the entrapped conjugate in the surrounding milieu. The nano-formulation showed visible therapeutic effect on skin tumor progression in experimental mice. The nano-formulation markedly reduced the surface nodule expression, an important parameter involved in cancer metastasis that is highly expressed in skin cancer. Histopathological studies also revealed positive recovery of general architecture and killing of cancerous cells by necrosis and apoptosis in skin tumor. The in-house nano-formulation was successful in significantly up-regulating of p53wt and down-regulating of p53mut eventually helping in better survival of cancer treated mice. Conclusively, the data demonstrates better efficacy of localized delivery of 2,6P-OLA entrapped in liposomes in the treatment of skin cancer in experimental murine model. The developed nano-formulation was found to possess necessary properties as revealed by size, zeta-potential and release pattern. The nano-formulation demonstrated strong inhibition of skin cancer in experimental mice. The conjugate entrapped in liposome showed therapeutic effect and was able to inhibit p53wt and p53mut factors that play a regulatory role in induction and progression of cancer. The site specific delivery of 2,6P-OLA entrapped in liposomes was highly useful with respect to safety as well as efficacy. The novel formulation is an effective means for the treatment of skin cancer and can pave the way for treatment of other forms of cancer.

GENOMIC ANALYSIS AND BETA-PAPILLOMAVIRUS INFECTION IN CUTANEOUS SQUAMOUS CELL CARCINOMA DURING ADVANCED MELANOMA BRAF-INHIBITION THERAPY

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Targeted melanoma therapy by BRAF-inhibition (BRAFi) carries a high rate of cutaneous squamous cell carcinoma (cSCC) and rarely emergence of leukemia and recurrence of RAS-mutant solid tumors. Ultraviolet (UV) radiation drives cSCC in healthy individuals. While α-genus human papillomavirus (α-HPV) infection causes SCC of the oropharynx, larynx and cervix, β-genus HPV are believed to commensally reside in human skin. We sought to test the hypothesis that somatic mutation, environmental factors and β-HPV coexist in BRAFi-cSCC.

Experimental Design: DNA isolated from BRAFi-cSCC tumors were assessed for the presence of viruses and cancer gene mutations. Ion Torrent next generation sequencing with Sanger confirmation in available samples was employed. HPV and Merkel Cell Polyomavirus (MCPyV) PCR primer sets were utilized for cloning and detection. Biopsy site, a surrogate for UV exposure, and clinical course were statistically analyzed in relation to histopathology.

Results: Twenty-nine patients contributed 69 cSCC lesions from the Vanderbilt-Ingram Cancer Center and the Sarah Cannon Research Institute (Nashville, TN). Next-generation and Sanger sequencing revealed 63% of evaluated BRAFi-cSCCs harbored RAS mutations with PIK3CA, CKIT, ALK and EGFR mutations also detected. Twenty-two percent of BRAFi-cSCC displayed wart-like features (WF) and β-genus HPV-17, HPV-38, and HPV-111 were isolated at a significantly higher rate than reported for cSCC in otherwise healthy individuals (39% vs 13.5%, p-value < 0.0001). Controlling for gender, histomorphology and UV exposure, a multivariate model revealed that, on average cSCC-WF arose 11.6 weeks sooner than conventional cSCC (conv.-cSCC) among patients receiving Vem therapy (p-value=0.03).
Conclusions: UV-radiation, cancer gene mutation and β-HPV are significantly associated with BRAFi-cSCC and may synergize with pharmacologic inhibitors of mutant-BRAF to accelerate keratinocyte neoplasia.

SEXUAL FUNCTION OF MEN ON A PHASE III RANDOMIZED STUDY OF HIGH VERSUS STANDARD DOSE 3D-CRT/IMRT IN PATIENTS TREATED FOR LOCALIZED PROSTATE CANCER

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Background: Multiple randomized phase III trials have supported an improvement in biochemical progression free survival, local control, and distance metastasis with higher vs. lower doses of external beam radiotherapy (RT). However, the impact upon overall survival and quality of life including erectile dysfunction (ED) is less clear which led to the creation of RTOG 0126. Primary outcomes are reported elsewhere, briefly, biochemical failure was significantly less in the 79.2Gy vs 70.2Gy arm (30% vs 44%, p<0.0001). However, overall survival was not significantly different between arms.

Purpose: To report on differences in ED of men treated with 3D-CRT/IMRT dose of 70.2 Gy versus 79.2 Gy for prostate cancer.

Methods: Men with localized, intermediate risk prostate cancer with no previous cancer or RT were eligible. Sexual function was assessed with the International Index of Erectile Function (IIEF). IIEF question 1 (“How often were you able to get an erection during sexual activity?”) is scored from: none/almost never (response 0-1) or ≤ half the time (response 2-3) to most times/always (response 4-5). A response of 0 to 3 on question number 1 of the IIEF was considered to be ED. This endpoint was designed with 90% power to detect a 10% difference in ED at 1 year with a 2-sided alpha of 0.05. Based on previous literature at time of protocol development it was assumed that 71% of patients would have baseline erectile function and of those 80% would have 1 year compliance. Comparisons of the proportion of patients without ED at baseline and with ED at one year by treatment arm were performed using a chi-square test.

Results: Of 1499 eligible patients on study, 479 (64%) on the 70.2Gy arm and 456 (61%) on the 79.2Gy arm completed IIEF question 1 at both baseline and 12 months. Treatment arms were well balanced for sociodemographic and disease factors. Mean age was 67.1 years and 86% were white. Patient completion of the IIEF was associated with white race and Zubrod score of 0. Only 37% of patients had good erectile function (most times/always) at baseline, lower than previous reports. Among those patients who had erectile function at baseline, 46% and 52% on the 70.2Gy and 79.2Gy arms respectively reported ED at 12 months (p=0.28).

Conclusions: The literature indicates that risk of sexual dysfunction plays a major role in prostate cancer treatment decisions for many men. This study reports 1) a higher than previously reported baseline ED rate, 2) higher rates of ED at 12 months than previously reported, and 3) dose escalation may not significantly increase the risk of ED. Differences in baseline rates may be related to improved and validated methods of evaluating ED using patient self-reported measures.

LAYING THE FOUNDATION FOR A DICYCLOPLATIN CLINICAL TRIAL FOR CANCER CHEMOTHERAPY IN THE UNITED STATES

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Dicycloplatin (DCP), a new platinum compound approved by the Chinese FDA in March of 2012, shows better water solubility, greater stability, and lower toxicity, compared to cisplatin and carboplatin. Preclinical in vitro and in vivo studies and a phase I clinical trial demonstrated that DCP possesses greater antitumor activity and lower adverse events than carboplatin. A randomized, controlled and open phase II clinical trial using dicycloplatin plus paclitaxel in NSCLC had a 1-year survival rate of 54.8% in the experimental group, versus 20.1% in the control group (treated with carboplatin plus paclitaxel; p=0.028). Recently, a clinical study involving 10 prostate cancer patients treated with DCP alone found that PSA level
CAUSES OF UNEQUAL OUTCOMES IN WOMEN WITH BREAST CANCER

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Background.
One way of identifying ways to improve the outcomes of patients with cancer is to identify the causes of inequalities. We have used a study of New Zealand women with breast cancer to quantify the contribution of different factors that are responsible for the unequal outcomes for Māori women compared with non-Māori.

Methods
The study population included women with invasive breast cancer diagnosed between 1999 and 2012 from the Waikato region of New Zealand. Key variables recorded included age, ethnicity, stage of disease, method of diagnosis (screening or symptomatic), biological markers such as grade, ER/PR and HER2 status and treatment. The key outcome was breast cancer specific survival. Contributions of different factors towards the survival disparity were quantified with Cox proportional hazard modelling.

Results.
Of the total of 2791 women included in this study, 2260 (80.1%) were NZ European and 419 (15%) were Māori. Compared with NZ European women, Māori had a significantly higher age adjusted cancer specific mortality (HR =2.02, 95% CI, 1.59-2.58) with significantly lower 5-year (86.8% vs. 76.1%, p<0.001) and 10-year (79.9% vs. 66.9%, p<0.001%) crude cancer specific survival rates. Stage at diagnosis explained approximately 40% while screening, treatment and patient factors (i.e. comorbidity, obesity and smoking) contributed by approximately 15% each towards the survival disparity. The final model accounted for almost all of the cancer survival disparity between Māori and NZ European women (HR=1.07, 95% CI, 0.80-1.44).

Conclusions.
For Māori women the late presentation to the health system is the single largest contributor to the inequalities in outcomes. It would seem that further investigation of the reasons for late presentation and how primary care can reduce the barriers for Māori would be most productive in improving outcomes. It is likely that this approach is relevant to other disadvantaged populations.

Poster Presentation Abstracts
Poster abstracts will be finalised weeks before the event

THE ADHESION-GPCR GPR56 COMPLEXES WITH CD9/CD81 AND ACTIVATES IL-6 PRODUCTION IN MELANOMA CELLS FOLLOWING RECEPTOR LIGATION

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GPR56 belongs to the adhesion-class G protein-coupled receptor (adhesion-GPCR) family characterized by a hybrid structure of a large N-terminal extracellular domain (ECD) and a seven-pass transmembrane (7TM) region. The adhesion-GPCRs are commonly proteolytically processed at a consensus GPCR proteolysis site (GPS) motif located within an extracellular GPCR autoproteolysis-inducing (GAIN) domain. GPR56 was first identified in melanoma cells where its gene expression level was correlated inversely to the metastatic potential. It has been reported recently that GPR56 inhibits melanoma growth and metastasis by binding to and promoting the internalization and degradation of tissue transglutaminase.
However, other alternative molecular mechanisms mediated by GPR56 remain unexplored. In this report, we show that ligation of GPR56 in melanoma cells by specific mAbs induces the production of IL-6, which promotes cell migration and invasion. The effect of GPR56-mediated IL-6 production is critically dependent on the GPS proteolysis and the 7TM domain. The tetraspanins CD9 and CD81 form receptor complexes with GPR56 via the ECD and are required for Ab-induced GPR56-mediated IL-6 production. Interestingly, overexpression of the GPR56-7TM domain alone also activates IL-6 production. We conclude that the GPR56-ECD acts as a tethered inverse agonist of the 7TM region by binding to CD9 and CD81. Ab ligation removes the ECD from the 7TM domain, which transduces the signaling activity for IL-6 production. Our results provide a novel insight into the role of GPR56 in melanoma progression.

**SENESCENCE-INDUCING STRESS PROMOTES PROTEOLYSIS OF PHOSPHOGLYCERATE MUTASE VIA UBQUITIN LIGASE MDM2**

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Enhanced glycolysis is a characteristic feature of cancer, referred to as the Warburg effect. Despite its well-documented clinical significance, it remains unclear how the aggressive glycolytic rates of tumor cells might contribute to other hallmarks of cancer, such as bypass of cellular senescence. Primary somatic cells suffer a permanent cell cycle arrest, called cellular senescence. The senescent phenotype could be induced by telomere erosion, while it can also manifest prematurely, upon exposure to various stresses. Stress-induced senescence is now considered as a defence mechanism against tumorigenesis.

We previously reported that glycolytic enzyme, phosphoglycerate mutase (PGAM) can bypass the cellular senescence in mouse embryonic fibroblasts (MEFs), while knock-down of PGAM expression induces premature senescence (Kondoh et al, Cancer Res, 2005). We find that, during oncogene- or DNA damage-induced senescence, Pak1-mediated phosphorylation of PGAM predisposes to ubiquitin-mediated degradation. We identify Mdm2 as a direct binding partner and ubiquitin ligase for PGAM in cultured cells and *in vitro*. Mutations in PGAM and Mdm2 that abrogate ubiquitination of PGAM restored the proliferative potential of primary cells under stress conditions and promoted neoplastic transformation. We propose that Mdm2, a downstream effector of p53, attenuates the Warburg effect via ubiquitination and degradation of PGAM (Mikawa et al, J Cell Biol, 2014).

**CYTOKINE-RICH MACROPHAGE CONDITIONED MEDIA INCREASES THE EXRESSION OF RhoC GTPase, A METASTASIS-ASSOCIATED ONCOGENE, AND THE MIGRATION OF INFLAMMATORY BREAST CANCER**

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Inflammatory breast cancer (IBC) is the most lethal form of breast cancer due to its propensity for quick progression and the high prevalence of distant metastases at diagnosis. IBC has higher incidence in African Americans who experience worse outcomes from breast cancer. Investigating the biological basis for IBC stands to contribute to addressing disparities by providing new anti-IBC strategies. RhoC GTPase, overexpressed in 90% of IBC tumors, is known to be an important protein in cell motility. The mechanism(s) that upregulate RhoC remain undetermined, however, tumor associated macrophages (TAMs) have been found to facilitate the movement and invasion of many breast cancers. Therefore, as a component of the immune system attracted to sites of inflammation, we hypothesized that TAMs play a role in increasing RhoC expression in IBC cells, consequently leading to IBC’s severe migratory and metastatic potential.

We found the expression of RhoC significantly increased in two different IBC cell lines, SUM149 (African American) and SUM190 (Caucasian), after culturing with conditioned media (CM) from the macrophage-differentiated U937 monocytic cell line. This increase was not detected in either the normal-like MCF-10A breast epithelial cell line or the non-IBC MDA-MB-231 basal-like breast cancer cell line. A novel microfluidic device created by our team was used to measure the migratory phenotype of IBC cell lines in response to CM. As predicted, IBC cells migrated away from a serum-free control towards serum. CM also promoted migration. Interestingly, in the presence of both CM and serum, the cells exhibited an extreme migratory phenotype and migrated roughly twice the distance of the serum-only control. This suggests that the CM might act to “prime” the migration capability of the IBC cells in order to manifest an amplified response to the serum chemoattractant. In a time-course experiment, the increase in RhoC was observed to happen between 3 and 8 hours of exposure to CM. Further, stimulating IBC cells with CM for 8 hours
before the migration then exposing the cells to serum resulted in a similar migration phenotype to those cells exposed to both CM and serum simultaneously. These data strongly support that macrophages have a lasting effect on IBC migration, a key event in determining its lethality.

Cytokine array studies showed CCL2, CCL5, IL-8, PAI-1, and MIF to be key mediators in the macrophage CM. Western blotting proposes that CCL2, CCL5, and IL-8 stimulation causes the greatest increase in RhoC. Further pathway analysis suggests a role for p38 in the intracellular signaling responsible for the increase in RhoC expression and migration capability. Studies involving RhoC inhibitors are ongoing and could yield promising therapies for the prevention of metastasis of IBC. By understanding the specific mechanism of TAMs’ effects on IBC, we hope to learn how to control the lethal metastatic nature of IBC and improve outcomes for patients of all ethnicities.

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TREATMENT OF NEUROBLASTOMA CELLS WITH CISPLATIN (CDDP) OR TOPOTECAN (TOPO) RESULTS IN DOWN-REGULATION OF ITPR1, ITPR3 AND RYR3 BUT IS NOT ASSOCIATED WITH ALTERED DNA METHYLATION OF THE PROMOTER REGIONS OF THESE GENES

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Current treatments for neuroblastoma need improvement, especially for the therapy of high risk tumors. Present treatment schemes include platinum compounds such as CDDP and topoisomerase I inhibitors such as TOPO. We have previously shown that chemotherapy of neuroblastoma cells is able to modify the intracellular calcium $[Ca^{2+}]_{i}$ homeostasis and trigger cell death by apoptosis. In this study we investigated whether expression of IP3 and ryanodine receptors (ITPR1, ITPR3, RYR1, RYR3) is changed upon chemotherapy of neuroblastoma cells (SH-SY5Y, IMR32, NLF) with CDDP (0.1-10µM) or TOPO (0.1nM-1µM). Furthermore, we investigated whether focal DNA methylation plays a role in the regulation of ITPR1, ITPR3 and RYR3 by chemotherapy. For this investigation we used RT-PCR to measure the changes in mRNA expression of each candidate gene as well as pyrosequencing of sodium bisulfite-modified DNA to analyse the methylation of their promoter regions. Methylation of LINE1 was determined as indicator of global DNA methylation.

The results show that baseline expression of the ITPR1, ITPR3, RYR1 and RYR3 was different in the neuroblastoma cells tested: while ITPR1 was expressed at highest levels in NLF cells followed by SH-SY5Y and IMR32, the expression of ITPR3 and RYR1 was highest in SH-SY5Y cells followed by IMR32 and NLF. Nevertheless, mRNA expression of RYR3 was the highest in IMR32 followed by SH-SY5Y and NLF. Analysis of the global methylation marker LINE1 showed that NLF had the highest baseline level of global methylation followed by IMR32 and SH-SY5Y cells.

Chemotherapy of SH-SY5Y, IMR32 and NLF neuroblastoma cells confirmed that concentrations of 0.1-10µM CDDP and 0.1nM-1µM TOPO were able to decrease cell viability in a time- and concentration-dependent manner. Gene expression analysis of ITPR1, ITPR3, RYR1 and RYR3 in neuroblastoma cells treated for 72h with chemotherapy revealed that ITPR1 and ITPR3 were down-regulated upon 10µM CDDP or 0.1µM-1µM TOPO exposure while RYR3 was down-regulated upon 10µM CDDP or 0.1µM TOPO treatment. However, reduced expression of these genes following chemotherapy was not associated with changes in methylation of their promoter regions. Thus, other mechanisms appear to be involved in their chemotherapy-induced down-regulation, e.g. altered expression of miRNAs or transcription factors. Thus, further research is necessary to understand the mechanisms of chemotherapy-induced deregulation of IP3 and ryanodine receptors in neuroblastoma cells.
Epigenetic changes are key factors in the pathogenesis of cancer including childhood neuroblastoma. Therefore, pharmacological modification of neuroblastoma-associated epigenetic changes might lead to an improved effect of traditional chemotherapy. Current treatment strategies include derivatives of platinum: cisplatin (CDDP) or carboplatin. Here we investigated whether the DNA methyltransferase inhibitor 5-AZA and the histone deacetylase inhibitor TSA are able to induce cytotoxicity in SH-SY5Y, IMR32 and NLF human neuroblastoma cells, either as single drugs or in combination with CDDP. Furthermore, we checked whether 5-AZA and TSA are able to interfere with calcium homeostasis and may modify gene expression and focal methylation of genes encoding [Ca^{2+}]−-regulating proteins, including calcium channels, calcium-binding proteins and calcium activated proteins such as S100A6, CALM1, CAMTA1, ITPR1, ITPR3, RYR1 and RYR3. We also checked whether combinatorial treatment of 5-AZA or TSA with CDDP has an improved cytotoxic effect on neuroblastoma cells. In cytotoxicity tests the application of 5-AZA, TSA as well as 5-AZA and TSA did reduce cell viability of SH-SY5Y, IMR32, and NLF neuroblastoma cells. While concentrations of 50-200 µM of 5-AZA were needed to induce cell death, only 1 µM TSA was necessary to induce cytotoxicity of neuroblastoma cells, with 10 µM TSA concentration being highly cytotoxic. In live calcium imaging, 5-AZA and TSA exposure of neuroblastoma cells did increase calcium concentration in a time-dependent manner. Furthermore, pre-incubation of 48 h with 5-AZA and TSA reduced the elevation of [Ca^{2+}], caused by CDDP exposure. Combined treatment of 1 µM 5-AZA (72 h) and 1 µM 5-AZA (72 h) + 1 µM TSA (24 h) did change the mRNA expression of [Ca^{2+}]−-regulating proteins however, a differential effect depending on the neuroblastoma cell line used was observed. In SH-SY5Y cells, an increased mRNA expression of S100A6, COX2, CALM1, CAMTA1, RYR1, RYR3 was observed, while in IMR32 cells mRNA expression of ITPR1, ITPR3 was significantly up-regulated. In SH-SY5Y cells, up-regulation of CAMTA1, CALM1, ITPR3 was mainly related to histone modification while for up-regulation of S100A6, COX2, RYR1 and RYR3 both DNA demethylation and histone modification might play a role. In IMR32 cells, up-regulation of ITPR1 was mostly due to the histone modification while up-regulation of ITPR3 appeared to be related to DNA demethylation and histone modification. When the global methylation marker LINE1 was measured by pyrosequencing, a decreased global DNA methylation level of neuroblastoma cells treated with 5-AZA or 5-AZA + TSA was observed. In addition, in SH-SY5Y cells, the up-regulation of S100A6 mRNA was associated with decreased focal methylation of the S100A6-associated 5'-CpG island, while up-regulation of ITPR3 in IMR32 cells was associated with decreased focal methylation of the ITPR3 promoter region. Combinational treatment of neuroblastoma cells with epigenetic modulators and CDDP did increase the efficiency of anticancer treatment, i.e. combination of 100 µM 5-AZA + 1 µM CDDP showed higher cytotoxicity in neuroblastoma cell lines as compared to treatment with either 5-AZA or CDDP alone. Similar results were observed for the combination of 0.1 µM TSA and 1 µM CDDP.

Day 2:

Invited Speakers Abstracts

The Role of Intraoperative Radiation in Retroperitoneal Sarcoma
Richard Gray, Consultant, Section of Surgical Oncology, Mayo Clinic, US
The combination of external beam radiation, aggressive resection, and intra-operative electron radiation therapy (Surg-RT) on local recurrence for retroperitoneal sarcoma will be evaluated and compared to patients treated with surgery alone. Ongoing trials of intraoperative radiation for retroperitoneal sarcoma will be discussed. For patients treated with multimodality therapy, we have demonstrated the five-year local control rate to be 89%. These results demonstrate that combination therapy is an excellent strategy for retroperitoneal sarcoma.
EWAS and GWAS go together in cancer control

Mukesh Verma, Ph.D., Branch Chief, Methods and Technologies Branch, Program Director. Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences. National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD, USA

After completion of the human genome, genome-wide association studies (GWAS) were conducted to identify single nucleotide polymorphism (SNPs) associated with cancer initiation and progression. Most of the studies resulted in SNPs located outside the coding region and the odds ratios were too low to implement in clinical practice. While genome gives information about genome sequence and structure, human epigenome provides functional aspects of genome. Epigenome-Wide Association Studies (EWAS) provide an opportunity to identify genome wide epigenetic variants which are associated with cancer. Epigenetics defines mechanisms that involve mitotically heritable changes in DNA and chromatin that affect gene expression without altering the nucleotide sequence. Therefore, the functional importance of epigenetic changes lies in their ability to regulate gene expression. One of the current challenges is to understand the regulation of gene function, an activity that depends largely on epigenetic control. Four major steps in epigenetic regulation are promoter methylation, histone acetylation/deacetylation, noncoding mRNA expression, and chromatin conformational changes. Through their effects on chromatin structure, epigenetic changes can modulate transcriptional repression, X-chromosome inactivation, genomic imprinting, and suppression of the detrimental effects of repetitive and parasitic DNA sequences on genome integrity. However, there are problems and issues in implementing EWAS to establish association of epigenetic profiles with cancer. The current status of EWAS, challenges in the field and their potential solutions will be discussed. After completion of the ongoing human epigenome roadmap project and validation of key observation studies in nutrition epigenetics, strategies can be developed for disease control and treatment. Controlling cancer is a priority at the National Institutes of Health (NIH). An update from the Epigenomics Roadmap Program and the Cancer Genome Atlas (TCGA) will be presented.

Breast Cancer, Chemo-resistance and ErbB receptors

Professor Zhixiang Wang, PhD, Department of Medical Genetics, Signal Transduction Research Group, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

Targeted therapy with trastuzumab has become a mainstay for ErbB2-positive breast cancer without a clear understanding of the mechanism. We showed here that trastuzumab will only remove the excessive growth and survival signals induced by ErbB2 overexpression and other cancer drugs are needed to kill the breast cancer cells. Despite the progress in breast cancer treatment, chemoresistance is a major factor involved in a poor response and reduced overall survival in patients with advanced breast cancer. We showed here that multiple mechanisms including the expression of ABCB1 and the composition/localization of β-tubulin isotypes are involved in taxane resistance.

1st line chemotherapy in treatment of mCRC: FOLFIRI vs FOLFIRI+bevacizumab - single institution experience

Dr Zoran Rakusic, MD, PhD, Head of Clinical Ward, Department of Oncology, University of Zagreb, Croatia

Neoadjuvant chemotherapy is standard of care for mCRC. We retrospectively analysed 218 patients with mCRC who were treated in our institution from April 2007 to June 2014. The aim of study was to access PFS and evaluate toxicity of therapy. There were 135 male and 83 female patients. As first line of chemotherapy for metastatic disease 103 patients received FOLFIRI and 115 FOLFIRI + bevacizumab. Application of FOLFIRI ± bevacizumab in first-line therapy for mCRC is effective and well tolerated. Our data suggest that FOLFIRI+bevacizumab is significantly better combination than FOLFIRI in terms of PFS, with acceptable toxicity.

Second line treatments in advanced non-small cell lung cancer

Dr Mircea Dediu, MDPhD, Medical Oncology senior consultant, Chief of Medical Oncology Department, Institute of Oncology "Alexandru Trestioreanu" Bucharest, Bucharest, Romania

Second line treatments are among the major contributors in supporting the steady improvement of outcome in patients with advanced NSCLC. Nevertheless, the current guidelines recommend refining the initial treatment according to histology and EGFR mutational status, which moved some traditionally, used second line agents in first line setting. Subsequently, fewer agents remained available for second line. Expected benefit upon second line treatments is up to 2-3 months, therefore a rigorous balance between efficacy and quality of patients’ life should be considered. An overview on the current guidelines and some meaningful predictors for choosing the best option will be presented.
Experience of the European Institute of Oncology in the use of intra-operative radiotherapy with electrons (ELIOT)

Dr Simonetta Monti, Senior Assistant, Medico Assistente, Senology Division, Reparto di Senologia, Milano, Italy

There was therefore much interest in developing intra-operative RT which would complete the RT treatment in a single intra-operative session during surgery.

In 1999 the European Institute of Oncology (EIO) started a new method of irradiation called ELIOT (intra-operative RT with electrons) The aims of this talk are to present the results our ELIOT trial and assess which patients are suitable to ELIOT in the future.

Measuring Quality of Survival and Impact of Adverse Events on Quality of Life in Metastatic Disease

Dr Stacie Hudgens, Strategic Lead, Quantitative Science and Managing Partner, Clinical Outcomes Solutions, Tucson, Arizona, USA

The role for nutrional and lifestyle strategies after cancer

Professor Robert Thomas, Consultant Oncologist, Cranfield University, Bedford and Addenbrooke's Cambridge University, Hospitals, UK

With over 2 million cancer survivors in the UK the case for developing self help initiatives has never been stronger. This talk summarises the UK and international evidence which show that physical activity, nutrition and other lifestyle strategies can have major benefits for patients with cancer, their families and health providers.

How lifestyle can reduce treatment risks and side effect including:

• Cancer related fatigue, hot flushes, weight gain and psychological well being
• Radiotherapy late effects - reproductive and urinary symptoms
• Osteoporosis, arthritis and bone health

How lifestyle can have a direct anti-cancer effect

• To help prevent prostate cancer
• Slowing growth of some tumours.
• Reduce the chance of relapse after treatment

This talk also summarises the results of the world's largest double blind RCT of a polyphenol rich food supplement The Pomi-T study

Targeted alpha therapy for cancer & the use of radioisotopes

Graeme Melville, Macquarie University, Sydney, Australia

Dr Graeme Melville was a senior nuclear researcher at St George Hospital in Sydney, Australia. In the past he was a professional tennis player, NASA astrophysics researcher (Magellan Project), university lecturer and government science policy advisor. Dr Melville has worked in a senior position with the Department of Defence and published many papers in astrophysics and nuclear physics as well as being Editor-in-Chief of an international journal. He was the recipient of the 2005 'Physics in Industry Day' award and 2007 'Research Futures Forum' prize. He is currently the Chairman of the Australian Institute of Physics (NSW) and has published two books. His current research involves producing Ac-225 for 'Targeted Alpha Therapy' (TAT) - a new kind of cancer treatment.

Oral Presentation Abstracts

DETECTION OF ANTICANCER RESPONSE BY MOLECULAR IMAGING TECHNIQUES

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Abstract

Introduction: Phospholipid metabolism is crucial for cell proliferation, division and growth as phospholipids are the major constituents of cell membranes and several intracellular signaling pathways. Key enzymes in phospholipid metabolism (for example, choline kinase) are up-regulated by signaling pathways in cancer cells. Therefore, noninvasive imaging techniques have been applied to detect alterations in phospholipid metabolites and also high energy phosphates (ATP) induced by drug treatment. However intracellular signaling pathways exhibit cross talk and branching. Here breast cancer cells responding to inhibitors of key enzymes of the PI3K/Akt/mTOR pathway have been subject to $^{31}$P-NMR spectroscopy (which measure metabolites of phospholipids including the phosphomonoesters (PME): phosphocholine (PC), phosphoethanolamine (PE), and the phosphodiesters (PDE): glycerophosphorylcholine (GPC) and glycerophosphorylethanolamine (GPE) and choline uptake assays to determine (a) the utility of $^{31}$P-NMR spectroscopy in monitoring response to these drugs and (b) the
**RESULTS AND DISCUSSION**

**Methods:** Cells were treated with drugs targeting components of the PI3K/Akt/mTOR pathway (LY294002 (LY), MK2206 (MK) and rapamycin (Rap) respectively) The IC$_{50}$ of the above anticancer drugs was detected by cytotoxicity assays (MTT) alone or in combination with the EGFR-targeting antibody cetuximab. $^{31}$P-NMR were carried out on extracts of cell after drug treatment for 24h. Uptake of [Methyl-$^3$H]-choline by treated cells was measured and its intracellular distribution determined.

**Results:** The findings showed dose dependent inhibition with both LY and MK treatments in which was increased by combination with cetuximab (p<0.05). Rapamycin achieved a maximum of 50% growth inhibition in the nM range (IC$_{50}$ 20nM requiring doses in the uM range to achieve full growth inhibition. All 3 treatments increased GPC and GPE content whilst LY and MK treatments decreased PC. (Interestingly, a UDP sugar peak was higher in LY-treated cells) $^3$H-choline uptake was decreased in LY and MK but not Rap-treated samples compared with control samples.

**Conclusion:** Inhibition of tumour cell growth by inhibitors of several components of the PI3K/Akt/mTOR pathway induced agent-specific changes in phospholipid metabolite content. Choline utilization was less varied across the range of agents used (generally decreased) but inhibition of mTOR with rapamycin resulted in almost no change in choline utilization despite significant effects on phospholipid metabolism by inhibition of elements further upstream in this pathway.

**IDENTIFICATION OF POTENTIAL BINDING PARTNERS FOR THE N-TERMINAL DOMAIN OF OCCLUDIN**

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**INTRODUCTION**

90% of all human cancers originate from the epithelium. Cell polarity and tight junctions (TJs) are necessary for intact epithelia (3). Loss of tight junction integrity is consistent with a display of mesenchymal phenotype which is characteristic of metastatic progression (1).

Occludin, the first identified transmembrane protein identified to localize at tight junctions, has been implicated in regulating tight junction function and cellular polarity (2). The N-terminal region of occludin has been shown to be an important factor in tight junction maintenance but the mechanism is not yet known.

**EXPERIMENTAL METHODS**

All materials were purchased from The Sigma-Aldrich Chemical Co. or Fisher Scientific Ltd unless otherwise stated. PCR (polymerase chain reaction) enzymes, PCR primers and reagents and competent cells were obtained from New England Biolabs. The plasmid containing rat occludin cDNA was obtained from Bert VH Hof, from VU University Medical Center, Amsterdam. Samples and buffers were prepared using 18.2 Ω Milli-Q water. PCR was carried out to amplify the occludin DNA. The required region of occludin was amplified using appropriate primers.

The plasmid (1 µL) was transformed in DH5α competent cells according to the manufacturer’s instructions and then cultured on kanamycin agar plates overnight at 37°C. Purified colonies were transformed into Rosetta 2 (DE3) competent cells and expressed in LB media containing kanamycin and chloramphenicol, using 1 mM IPTG. The expressed his-tagged peptide was attached to magnetic nickel beads and used as a bait to capture potential binding partners in the Pa4 and Pa4Raf1 cells.

**RESULTS AND DISCUSSION**

The N-terminal region (66 amino acids) of occludin was cloned and coupled to a hexa-histidine sequence (His tag). This chimera was expressed in E. coli, purified by size exclusion chromatography, and used as a bait to pull down potential binding partners for this region of occludin present in two cell lines: Pa4 and Pa4-Raf1. Pa4 is an immortalized cell line derived from rat salivary gland. Introduction of a constitutively active form of Raf1 (Pa4-Raf1) was used to establish a cell line that proliferated uncontrollably and lost the ability to form TJ structures and polarize. Immunoprecipitation results were separated by SDS-PAGE and silver stained; selected bands were sent to St. Andrews University for identification by mass spectrometry. It is interesting to note that many of the potential binding partners we have identified are involved in apoptosis and/or metastasis.

Importantly, N-terminal region of occludin has series of serine and tyrosine residues that are predicted to be phosphorylated by a wide range of kinases. In this regard, Ser8, Ser45, Tyr12, Tyr22, Tyr29 and the poly-proline (Pro-Leu-Ser-Pro-Pro-Pro-Tyr-Arg-Pro) region of the N-terminal bait peptide will be mutated...
in order to identify their specific functions. Serine will be mutated to aspartic acid, tyrosine to glutamic acid, and proline to alanine.

After a successful mutation, the subsequent peptide would be attached to magnetic nickel beads and used to pull down potential binding partners. Results obtained from the mutated peptides would be compared to the parent peptide. To date, Tyr12 has been successfully mutated and is presently at the expression stage.

CONCLUSION
The N-terminal region of occludin binds to several regulatory proteins. We aim to seek for ways by which manipulating these proteins will transform a cancerous cell to a normal cell.

REFERENCES

EPIGALLOCATECHIN-3-GALLATE INHIBITS NICOTINE-INDUCED MIGRATION AND INVASION VIA SUPPRESSION OF ANGIOGENESIS AND EPITHELIAL-MESENCHYMAL TRANSITION IN NON-SMALL CELL LUNG CANCER CELLS
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Abstract. Epigallocatechin-3-gallate (EGCG), the most abundant polyphenol in green tea extract, has been found to have anti-cancer activities in various types of cancers. However, the underlying mechanisms are not completely clear. In the present study, we observed the effects of EGCG on migration, invasion, angiogenesis, and epithelial-mesenchymal transition (EMT) induced by nicotine in A549 non-small cell lung cancer (NSCLC) cells, and preliminarily explored the underlying molecular mechanisms. Our results showed that different concentrations of EGCG significantly inhibited nicotine-induced migration and invasion. Moreover, EGCG reversed the up-regulation of HIF-1α, VEGF, COX-2, p-Akt, p-ERK, and Vimentin protein levels and the down-regulation of P53 and β-catenin protein levels mediated by nicotine in A549 cells, but had no significant effect on their mRNA levels. Furthermore, EGCG dramatically inhibited HIF-1α-dependent angiogenesis induced by nicotine both in vitro and in vivo, and suppressed HIF-1α and VEGF protein expression induced by nicotine in A549 xenografts of nude mice. Taken together, these results indicated that EGCG inhibited nicotine-induced angiogenesis and EMT, leading to migration and invasion in A549 cells. Our results suggest that EGCG can be developed into a potential agent for the prevention and treatment of smoking-associated NSCLC. [This work was supported by the grants from National Natural Science Foundation of China (81372511 and 81073103), Science and Technology of Guangdong Province (2013B031100002), and Zhanjiang Municipal Governmental Specific Financial Fund Allocated for Competitive Scientific & Technological Projects (2012C0303-56)].

BODY SURFACE AREA-BASED VERSUS CONCENTRATION-BASED DOSIMETRY OF INTRAPERITONEAL CHEMOTHERAPY IN PERITONEAL CARCINOMATOSIS’ TREATMENT
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Peritoneal Carcinomatosis (PC) is a common manifestation of digestive and gynaecologic malignancies, associated with a poor prognosis (Kitayama 2014). Despite continuing advances in systemic chemotherapy, no long-term survival and poor quality of life for patients with PC in their terminal stages of disease are reported. Alternatively, a new treatment modality focussing on the local handling of the disease, combining Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Peroperative Chemotherapy (HIPEC) shows encouraging clinical results in several Phase II and III trials (Verwaal, Bruin et al. 2008, Franko, Shi et al. 2012). One of the problems preventing a wider application of intraperitoneal (IP) chemotherapy for PC patients is the astonishing variety in the dosimetry available worldwide. Most groups calculate the IP doses in HIPEC based on calculated Body Surface Area (BSA) (mg/m²) in analogy to systemic chemotherapy regimens (Leinwand, Bates et al. 2013). These regimens take BSA as a measure for the effective contact area. However, an imperfect correlation exists between actual peritoneal surface area and calculated BSA (Rubin, Clawson et al. 1988). Sex differences, but also altered pathophysiological characteristics or frequent complications in patients (ascites) are responsible for differences in peritoneal surface areas, which in turn affect absorption characteristics (Mas-Fuster, Ramon-Lopez et al. 2013). This
HUMAN PAPILLOMAVIRUSES MAY NOT PLAY A ROLE IN THE DEVELOPMENT OF HEAD AND NECK SQUAMOUS CELL CARCINOMA AMONG FILIPINOS

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There is considerable geographic heterogeneity of human papillomavirus (HPV) involvement in head and neck squamous cell carcinoma (HNSCC). This study analyses for the first time the situation in the Philippines. One hundred seventy nine (179) formalin-fixed paraffin-embedded (FFPE) and 22 fresh frozen tissues from 163 rural Filipino cases with histologically-confirmed squamous cell carcinoma of the oropharynx (n=15, 9.2%), the oral cavity (n=88, 54.0%), and of the larynx/hypopharynx (n=60, 36.8%) diagnosed in 2003-2013 were analyzed for HPV DNA by BSGP5+/6+-PCR/MPG and realtime qPCR. HPV16 E6*I mRNA was further analyzed in the HPV DNA-positive [n=2, both non-oropharyngeal squamous cell carcinoma (OPSCC)], all FFPE OPSCC (n=9 DNA valid, n=4 DNA invalid) and additional randomly selected non-OPSCC (n=5 DNA valid, n=8 DNA invalid) samples by reverse transcription-qPCR. The HPV DNA-negative, all FFPE OPSCC and randomly selected non-OPSCC (n=9 DNA valid, n=15 DNA invalid) samples were evaluated for p16INK4a and pRb expressions by immunohistochemistry. Serum samples from 22 cases and 20 controls were also analyzed for HPV antibodies by multiplex serology. Only 82 cases had DNA valid samples, of whom 2 (2.4%) were HPV DNA-positive (HPV11, HPV33). All RNA extracts, while Ubiquitin C RNA positive, were HPV16 E6*I transcripts negative. Of 39 tumor tissues two (5%) showed p16INK4a up-regulation and 3 others (8%) showed pRb down-regulation. None of the serum samples showed HPV antibody patterns with strong anti-E6 or positivity for at least 2 early proteins characteristic for patients with HPV-induced OPSCC. These results indicate that involvement of HPV in HNSCC development among Filipinos if at all existent is very rare. Hence, HPV vaccination may not have any impact on HNSCC prevention among this population.

Keywords: HPV-associated HNSCC, Philippines, PCR, E6*I p16, pRb, serologic markers

PROTEOMIC INSTABILITY OF CANCER: THE HSF1-MEDIATED PROTEOTOXIC STRESS RESPONSE CRITICALLY REPRESSIONS TUMOR-SUPPRESSIVE AMYLOIDOGENESIS

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Cancer cells constantly suffer intrinsic proteotoxic stress due to aggravated protein turnover, misfolding, and damage that is inevitably associated with malignant transformation. To survive and prosper, cancer cells hijack a cellular defensive mechanism that has evolved to counter proteotoxic stress: the heat shock factor 1 (HSF1)-mediated proteotoxic stress response (PSR). As a consequence, cancer cells depend on the PSR to maintain their malignant phenotypes, thus developing an addiction to it. However, the molecular mechanisms underlying constitutive activation of HSF1 and the PSR in cancer remain largely unclear. Signaling through RAS/MAP kinase pathway is central to biology. ERK has long been perceived as the only mediator of cell-environment interactions, the MEK-HSF1 regulation impacts malignancy. In tumor cells, MEK blockade inactivates HSF1 and thereby provokes proteomic chaos, presented as protein destabilization, aggregation, and, strikingly, amyloidogenesis. Unlike their non-transformed counterparts, tumor cells are particularly susceptible to proteomic perturbation and amyloid induction. Amyloidogenesis is tumor-suppressive, reducing in vivo melanoma growth and contributing to the potent anti-neoplastic effects of proteotoxic stressors. Our findings unveil a key biological function of the oncogenic RAS-MEK signaling in guarding proteostasis and suppressing amyloidogenesis. Thus, proteomic instability is an
MEASURING THE PREVALENCE, SEVERITY AND QUALITY OF LIFE PREDICTORS OF CONCURRENT SYMPTOMS IN CANCER PATIENTS IN JORDAN

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Abstract
Background
In Jordan, little is known about cancer-related symptoms prevalence, severity, and its impacts patients' quality of life.

Objectives
To estimate cancer-related symptoms prevalence, severity, and predictors of quality of life of cancer patients in Jordan

Methods
A descriptive cross-sectional survey design was used. The sample consisted of 498 Jordanian cancer patients.

Results
There were slightly more males (51.6%) and a mean of age of 44.3 (SD 15.3) years. In addition, 25.9% of the patients had breast cancer and 20.7% had haematological tumours. The mean of the number of symptoms reported by patients was 11 (SD 3.3). The most prevalent symptoms were fatigue (92.5%), feeling drowsy (87.1%), lack of appetite (86.3%), being distressed (86.1%), and pain (85.5%). Further, Jordanian cancer patients had low mean total scores for quality of life at a level of 18.5 (SD 4.9).

Conclusion
Jordanian cancer patients are suffering from a high prevalence of concurrent symptoms and poor quality of life. This needs the attention of healthcare providers to harmonise the efforts to reduce their suffering. A comprehensive palliative care programme is recommended, led by a representative from the Ministry of Health, to integrate palliative care within the current healthcare system in Jordan. Such programmes are expected to focus on training and educating healthcare providers in the provision of palliative care, and make the service accessible and available all over the country, both for in-patients and community-based care.
Conclusions
Jordanian cancer patients are suffering from a high prevalence of concurrent symptoms and poor quality of life. This needs the attention of healthcare providers to harmonise the efforts to reduce their suffering. A comprehensive palliative care programme is required, led by a representative from the Ministry of Health, to integrate palliative care within the current healthcare system in Jordan. Such programmes are expected to focus on training and educating healthcare providers in the provision of palliative care, and make the service accessible and available all over the country, both for in-patients and community-based care.

IMMUNE ACTIVATION BY ONCOTHERMIA
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Introduction – Oncothermia [1] is a specialized hyperthermia treatment for solid tumors. It has long history from the laboratory use to the human therapies [2]. Its specialties are focused on the cellular selection of the malignant cells [3] using sophisticated mechanisms of the effect of the electric field on the cellular membrane [4]. However, the local effect of the heat-treatment is limited to the actually treated tumor, but the far away situated metastases are out of the effect of the certain treatment. This general problem of the local therapies limits their applications. These shortages of the facilities are a huge challenge in advanced cases, when the metastatic spread becomes a real life-threatening event. Our objective is to present the immunactivation process of oncothermia which targets the bystander and abscopal effects induced by local treatment.

Method – Oncothermia is a capacitive impedance coupled electromagnetic heating method, using 13.56 MHz radiofrequency (RF) amplitude modulated with time-fractal (1/f) pattern [5]. It is widely applied in medical practices as local curative or palliative method, mainly in complementary therapies [6]. One of its main specialties is the nanoscopic heating [7], which allows the massive energy-absorption in plasma-membrane of malignant cells, action directly on the rafts of transmembrane proteins [8].

Results – The method causes massive apoptosis following the outer signal pathway [9]. The large number of apoptotic bodies together with an early (4h) cytoplasmic to cell membrane exposure of Calreticulin and later (48-216h) the release of HMGB1 protein and membrane expression of HSP70 and HSP90 heat-shock proteins [10] are essentially forming a damage associated molecular pattern in vivo model systems, which is a solid basis of the immunogenic cell-death. This immune-activation process is shown to form abscopal effect with concomitant application of (anyway ineffective) immune-stimulators.

Conclusion – Oncothermia is able to produce abscopal effect in in vivo model systems and the abscopal effect has been shown in some human cases too.

BREAKING TUMOUR TOLERANCE BY SUCCESSFULLY SYNCHRONISING ANTI-TUMOUR IMMUNE RESPONSES WITH TIMED DELIVERY OF THERAPIES
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Clear evidence has emerged that tumour immune tolerance/suppression is caused by the normal homeostatic mechanisms of the immune system under the chronic antigen load from the growing tumour. However, in a small subset of patients this immune tolerance can be therapeutically broken.

Agents such as IL-2 and the CTLA-4/PD-1 Mabs clearly can disturb this homeostatic tumour-specific immune suppression to deliver complete responses in a subset of patients by releasing this pre-existing immune response from regulation. This means that downstream immune regulation is the principal problem, rather than antigen recognition/presentation as previously believed.

Immune homeostasis relies not only on antigen input, but also on highly coordinated time-dependent transient cytokine/receptor/cellular interactions controlled by synchronized expression thresholds. Each step in this immunological cascade is open to interference by standard therapeutic modalities such as cytotoxic chemotherapy, radiotherapy, cytokine agents, checkpoint blockade and certain efficacious vaccines.

Manipulating this system for consistent therapeutic benefit is hampered by the fact that pro-inflammatory effector/responsiveness circuits predominantly use the same receptors/cytokines as regulatory/inhibitory circuits. Moreover, the response 'read-out' is rapid exponential expansion of either effector or regulatory cells - to respectively produce 'activation' or 'inhibition' of in-vivo immune responses. The paradox of how either immunological responsiveness or tolerance is achieved with essentially the same cytokine signals and receptors remains unresolved.

Understanding this opposing dual role or 'bimodality' of the immune system in the time domain is the key to maximizing the probability of therapeutic success and deliver a complete response in the majority of patients.

We present a brief history of chemo-immunotherapy together with our data to explain why preclinical data has not been consistently clinically translated. We provide further evidence that the random timing of therapy can accidentally produce sporadic complete responses in a minority of patients via chemotherapy, radiotherapy, checkpoint immunotherapies and other treatments.

We further explain how this knowledge can be refined to maximize the probability of treatment success via monitoring and timing of chemo-immunotherapy.

References


XRCC1 GENE POLYMORPHISMS AND SUSCEPTIBILITY TO LUNG ADENOCARCINOMA IN SERBIA
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Background: Polymorphisms in genes involved in DNA repair are associated with variations in the repair efficiency which might predispose individuals to development of various cancers. The X-ray repair cross-complementing group 1 protein (XRCC1) plays important roles in the DNA base excision repair (BER) pathway, which may influence the development of lung cancer, one of the major causes of cancer mortality in the world. The codon 399 polymorphism of XRCC1 protein resides within the domain which is thought to mediate several protein-protein interactions. Amino acid substitutions in this domain are reported to disrupt the functionality of XRCC1 and possibly result in carcinogenesis. This study aimed to evaluate the potential association of the XRCC1 Arg399Gln genetic polymorphism with lung adenocarcinoma in Serbian population.
Methods: A case-control study including 62 late-stage lung adenocarcinoma patients (stage IIB or IV, performance status 0, 1 or 2) and 63 healthy age-matched control subjects was performed. The patient group consisted of 34 males (55%) and 28 females (45%), and the control group of 33 males (52%) and 30 females (48%), all of Caucasian descent. Age range in the control group was 23-63 and patient age range was 38-68 years. XRCC1 genotyping was done by Polymerase chain reaction (PCR) followed by Restriction length polymorphism (RFLP). Descriptive analyses included genotype and allelic frequencies; the odds ratio (OR) and 95 % confidence interval (CI) were calculated as an estimate of relative risk. Deviations of the genotype frequencies from those expected under Hardy-Weinberg equilibrium were assessed using the χ2 test. Significance was considered for p < 0.05.

Results: The distribution of Arg399Gln genotypes in patients and controls did not deviate from the Hardy-Weinberg equilibrium. The distribution of the XRCC1 variants in patients vs. controls was 48.4 % vs. 28.6 % for ArgArg, 48.4 % vs. 60.3 % for ArgGln and 3.2 % vs. 11.1 % for GlnGln. The frequencies of alleles in patients vs. controls were 0.73 vs. 0.59 for Arg, and 0.27 vs. 0.41 for Gln. We found that XRCC1 Arg allele is associated with lung adenocarcinoma risk [χ² = 5.31; OR (95% CI) = 1.86 (1.09 - 3.16) for Arg vs. Gln]. The XRCC1Arg allele exerts its effect in recessive model [ArgArg vs. ArgGln plus GlnGln] [χ² = 5.19; OR (95% CI) = 2.34 (1.12 - 4.91)].

Conclusions: A significant corelation between the ArgArg XRCC1 genotype and lung adenocarcinoma occurrence in Serbia was found. As this study is limited by a relatively small sample size, we are currently performing a larger case-control study including analysis of gene-gene interactions with genes coding for other proteins (Rad51, p53). Finding a potential correlation between XRCC1 gene polymorphisms and lung adenocarcinoma could contribute to earlier detection of this disease and better understanding of its biology.

Keywords: XRCC1, polymorphism, lung adenocarcinoma

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TARGETING MMP-9 INHIBITS VASCULAR INVASION IN HEPATOCELLULAR CARCINOMA
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Metalloproteinase-9 (MMP-9) is highly expressed in hepatocellular carcinoma (HCC) and is hypothesized to be a contributing factor in metastatic processes. The current study aims to evaluate the hepatoprotective and antitumor efficacy of doxycycline, as an MMP9 inhibitor, in an in vivo model of HCC. HCC was induced experimentally by Thioacetamide (200mg/kg) in rats that were treated with doxycycline (5mg/kg for 16 weeks). Tumor severity was evaluated by measuring AFP levels, histopathologically by investigating liver sections stained with Hematoxylin/Eosin and assessing the survival rate. Liver homogenates were used for the measurements of MMP-9, Fascin and hepatic heparan sulfate proteoglycan levels (HSPGs). Oxidative stress markers (MDA and Glutathione) as well as Fibroblast growth factor -2 gene expression were also among the assessed indicators. HCC in human and animal samples showed significant elevation in the levels of MMP-9 (231.7%, 90%), Fascin (33.17%, 140%), as well as FGF-2 gene expression (342% in animal samples; all respectively), associated with a significant decrease in hepatic HSPG level (23.3%, 35%) in both samples. Treatment of rats with doxycycline increased the animal survival rate (90%) and decreased serum AFP level (43.4%). Moreover, doxycycline ameliorated the extent of fibrosis and the induced massive hepatic tissue breakdown. It also restored the integrity of hepatic HSPGs and showed a magnificent inhibitory effect of tumor invasion cascade by significantly reducing the activities of MMP-9 (42%) and Fascin (50%), as well as reducing the gene expression of FGF-2 (85.7%). Furthermore, the antioxidant impact of doxycycline was evidenced by the significant elevation in glutathione level (47.6%) and depressing MDA level (53.8%).To this end, doxycycline, as an MMP9 inhibitor, proved promising hepatoprotective and antitumor activity and opens, thereby, a new horizon against vascular migration ability of the tumor cells.

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Background: Cervical cancer screening research in the Somali immigrant population in the United States (U.S.) has primarily focused on perceptions towards and barriers to uptake of screening services.

Purpose: This study aims to compare completion rates of a home based HPV screening test and the standard clinic based Pap test within 3 months of study entry.

Methods: Somali immigrant women who had not undergone cervical cancer screening within the past three years were randomly assigned to either a home based HPV test group (intervention) or a clinic based Pap test group (control). Univariate and multivariate logistic regression models were conducted to explore factors associated with test completion.

Results: Using an intention to treat analysis, participants in the HPV test group were 6.8 times more likely to complete the test compared to those in the Pap test group (Odds Ratio (OR)=6.82; 95% Confidence Interval (CI): 2.24-20.71) p = 0.0002). In addition, women who reported having friends/family members to talk with about cancer screening were approximately 3 times more likely to complete screening than those who did not (OR: 3.14; [95% CI: 0.72-13.67], p=0.127) and participants who reported residing in the U.S. longer were more likely to complete a screening test (OR) = 1.23 [95% CI: 1.05-1.44], p=0.011).

Conclusions: The use of a self-sampling HPV kit has the potential to increase cervical cancer screening in this community. Future research should explore the potential of using the home based HPV test kits as an initial approach to cervical cancer screening in underserved communities in the U.S.

Poster Presentation Abstracts
Poster abstracts will be finalised weeks before the event

ICI CATALYZED SYNTHESIS OF 3,6-DISUBSTITUTED-1,2,4,5-TETRAZINES UNDER MICROWAVE IRRADIATION: NEW TOOL TO IMAGING SCIENCE & CANCER THERAPY
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ABSTRACT

Heterocyclic chemistry is been playing major role in synthetic organic chemistry and heterocycles are the important constituents of most cancer drug candidates. It is evident from the literature that more than 50 percent of cancer drugs and other bio-molecules are heterocycles. Among other hetero atoms nitrogen is unique which stands first and most contributor and backbone of heterocycles and many other potent bio-molecules. Tetrazines are electro-active heterocycles and 3,6-disubstituted-1,2,4,5-tetrazines have drawn attention of chemists and biologists for their wide spectrum of biological applications and anti-tumor activity being the major point to highlight. Tetrazines have also been emerged as tool for labeling cells using fluorescent small molecule probes and to label bio-markers on cells with magneto-fluorescent nanoparticles. The rapid cycloaddition of tetrazines is utilized in cellular microscopy, clinical point-of-care diagnostics, and in vivo imaging. Recently, tetrazines have been coupled with methyl-cyclopropene dienophiles and these conjugated systems have been studied for imaging and labeling applications. Researchers have also utilized fluorogenic tetrazine imaging probes via coupling chemistry to track the distribution of lipid analogs in live mammalian cells.

While scientists are striving to develop novel bio-orthogonal reactions as tools for addressing problems in biological imaging, the inverse electron demand cycloaddition between 1,2,4,5-tetrazines and strained dienophiles such as norbornene, cyclooctyne, and trans-cyclooctene has emerged as a valuable bio-orthogonal coupling tool. Since the coupling of tetrazines with suitable dienophiles is very rapid, it is quite advantageous to click chemistry and researchers are engaged in exploring tetrazines in imaging technique via click chemistry approach. The labeling of live cells with tetrazine-fluorophores proceeds in minutes with nanomolar concentration. Since the tetrazines can act both as anti-cancer drugs and labeling tool, an elegant methodology is developed to synthesize substituted-1,2,4,5-tetrazines utilizing Iodine monochloride as catalyst under microwave irradiation. The method affords excellent yields of the pure
products in 5-10 minutes and involves easy work-up procedure. This is of great importance in tetrazine chemistry and will uncover additional bio-medical applications especially in cancer therapy.

**IN VITRO ANTIPROLIFERATIVE EFFECT OF RUBUS FAIRHOLMIANUS GARD. ON HUMAN COLORECTAL CANCER CELLS**

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Cancer is a dreaded disease characterized by uncontrolled growth and spread of abnormal cells. The high mortality rate amongst cancer patients is an indication of limited efficiency of current therapies. Cancers that start in the cells lining inside of the colon and rectum are colorectal cancers (CRC). CRC is the third most predominant cancer worldwide and is the fourth most common cause of cancer mortality. It is significant that over 60% of currently used anticancer agents are from natural sources. Plants and plant derived products exert chemopreventive effects on various cancer cell lines by inducing cell death. Berries are rich in bioactive phytochemicals with anticancer properties due to scavenging free radicals, regulation of gene expression, cellular signalling and induction of apoptosis. *Rubus* species have been used in folk medicine. On the basis of previous pharmacological properties, we have selected *R. fairholmianus* to investigate the *in vitro* anticancer potential and track the possible cell death mechanisms, to put forward a scope to develop an effective drug.

The effects of root acetone extract of *R. fairholmianus* (RFRA) on the proliferation of human colorectal cancer (Caco-2 cells) have been investigated in this study. The extract led to a dose dependent decrease in viability, proliferation and increased cytotoxicity using trypan blue exclusion, Adenosine 5′-triphosphate (ATP) and lactate dehydrogenase (LDH) assay. The morphological features of the treated cells were supportive for the antiproliferative activity. The Annexin V/Propidium iodide staining indicate that *R. fairholmianus* induced toxic effects in Caco-2 cells and the percentages of early and late apoptotic population significantly increased when compared with control cells. Also we studied the apoptosis inducing ability of the extract by analysing caspase 3/7 activity and the induction of cell death via the effector caspases was confirmed; the activity increased in treated cells compared with control. Moreover, the morphological alterations in the Caco-2 cells exposed to RFRA extract were suggestive for the apoptotic activities. The outcome of this study recommends the substantial antiproliferative activity of *R. fairholmianus* may be due to the caspase dependent apoptosis and the compounds of this extract may have promising use as a cancer chemotherapeutic agent.

**ISOLATION OF A NOVEL MARINE DERIVED POLYSACCHARIDE (NMP) WITH ANTICANCER ACTIVITY**

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**Background**

Despite the successes made in the treatment of leukaemia more needs to be done to increase the survival rate from its current level of about 80%. New treatments aimed at the inhibition of leukaemia cell growth will be crucial, however they should also aim to minimise damage to normal tissue and if possible help treat patients whose cancer cells have built up resistance to conventional chemotherapy drugs. Polysaccharides have great potential as therapeutic drugs their solubility is a great advantage as it gives them excellent bioavailability and decreases the risk of side effects from off target interactions. We report here the isolation of a novel polysaccharide from shellfish, which shows potent anticancer activity against two leukaemia cell lines.

**Methods**

Extraction and isolation of the polysaccharide was carried out using the method described by Kim et al., 1996 with slight modifications made to optimise the percentage yield. The growth inhibitory activity assay was performed using the standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide (MTT) colorimetric assay.

**Result**

The novel polysaccharide isolated from shell fish shows a very high significant (p<0.01) dose dependent growth inhibitory effect on leukemia cell lines that is comparable, on a mass basis, to that observed for the standard anticancer drug (cisplatin). Interestingly, commercial available members of this polysaccharides family did not inhibit the growth of these cell lines but instead supported the cell’s growth. The growth inhibition appears to show some selectivity to leukemic cells as high doses of the polysaccharide failed to inhibit the breast cancer cells.

**Conclusion**
We have demonstrated in this study that a novel natural sugar like polysaccharide extracted from shellfish has growth inhibitory activity and shows some selectivity for leukaemia cells. The polysaccharide may form basis of a new class of therapeutic treatments for leukaemia and work is continuing on further structural characterisation and elucidation of the mechanism of action.

CHARACTERISTICS OF METASTATIC BREAST CANCER PATIENTS IN ROMANIA: RESULTS OF A MEDICAL CHART REVIEW STUDY (EMER)

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Objectives
In Romania breast cancer is the most common malignancy in women, with around 9000 new cases per year. However, due to the lack of a national cancer registry, only limited data is available regarding the stage distribution at diagnosis or the current survival data. This study is aimed to describe the clinical characteristics of newly diagnosed patients with metastatic breast cancer (MBC) in our country, some relevant data regarding the patient outcome as well as the use of local healthcare resources.

Methods
EMER (Epidemiology and management of Metastatic Breast Cancer in Romania: A Retrospective cohort study, NCT01711502) was a multi-center, non-interventional, medical chart review study including patients with newly diagnosed MBC, either de novo or having progressed from a non-metastatic stage. Retrospective data collection was carried out from the study index event, e.g. the diagnosis of metastatic breast cancer, for a period of 18 months

Results
125 patients were evaluated, that were diagnosed between October 2010 and March 2011. The mean patients' age at diagnosis was 57 years. While 38 (30.4%) were de novo MBC, 87 (69.6%) patients had relapsed after an initial curative treatment. Postmenopausal women account for the majority patient population (89%). ECOG performance status 1 was recorded for 42% of patients. The distribution of patients according to the biologic characteristics is as follows: 17.6% ER+/PR+/HER2+, 20.8% ER+/HER2+, 42.4% ER+/HER2- and 8.8% triple negative. Distribution of the metastatic sites was as following: bone (60%), liver (29%) and lung (28%). The incidence rate of disease progression per patient-year was 0.545 (95% confidence interval [CI]: 0.439-0.669). The analysis of the time to metastatic disease in the group of patients with progression from an initial curative treatment (n=87) showed a mean value of 3.36 years with a median value of 2 years. The analysis of progression free survival indicated a median time to event of 456 days (95% CI: 368- 565). Time to progression indicated a median time to event of 469 days (95% CI: 399-632). The mortality rate was of 0.159 per patient-year for death of any cause, and 0.131 per patient year for death due to MBC. In terms of healthcare resource use, hospitalizations were the most frequently reported, both as continuous (76.8% of patients) and 1-day hospitalizations (75.2% of patients). The average number of hospital admissions per patient was 6.9, with an average number of total days spent during hospitalization of 36.0.

Conclusions
This study provides real-world evidence data on MBC management in Romania. The results suggest that once diagnosed, the disease was progressing to metastatic disease within 2 years. The study indicates that MBC is associated with a high burden of disease in terms of utilization of healthcare resources.

CANCER PAIN: THE EXPERIENCE OF A NATIONALLY REPRESENTATIVE STUDY OF OLDER ADULTS

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This study specifically responds to the United States’ Institute of Medicine’s 2013 report calling for creation of "a comprehensive population health-level strategy for pain prevention, treatment, management, and research,"1 by addressing a gap in the literature about the trajectory of cancer pain in older adults with respect to epidemiology of such pain and outcomes of cancer pain including healthcare disparities. We utilized the Health and Retirement Study (HRS), which is a United States nationally representative sample of older adults. This longitudinal study collects data every two years starting in 1990. For this project we utilized data from the 2010 and 2012 waves and regression analysis to examine how cancer pain over time negatively impacts overall health and changes in quality of life (QOL) and does so to a greater degree than non-cancer pain. Further, we explored bivariate relationship differences for disparities in gender, race, and education.
socioeconomic status (SES). In this older population we found there was a significant difference in high school education with Whites being more educated than Blacks. The average age of the study population is 71 years and educational access for the minority population in the 1960s was limited which could explain the educational gap. Other SES factors were similar between racial and gender populations. The presence of comorbidities was significantly associated with both cancer and pain. Life satisfaction was higher in both Whites and men at trend level. We found that cancer was not a predictor of life satisfaction and only when pain was present, concurrent with cancer or alone, life satisfaction significantly decreased. This was also observed when the population was separated by gender and race. Evidence suggests that cancer (C+) is protective of life satisfaction. People with cancer and no pain (C+P-) have a similar and somewhat higher level of life satisfaction than people without cancer and pain (C-P-). HRS respondents with pain have the lowest life satisfaction suggesting that pain is a heavy predictor of poor QOL. This study provides new knowledge about populations who may suffer disproportionately from cancer and pain (e.g. older adults, minorities, and low income people) and furthers goals to improve population health and eliminate healthcare disparities.

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VOLUME AND SURFACE TUMOR ARE PREDICTORS OF LYMPH NODES METASTASIS IN EARLY BREAST CARCINOMA
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**Aim:** Analyze significant tumor characteristics associated with lymph node metastases in early breast cancer patients with clinically N0 at the time surgical operation.

**Methods:** We studied prospective and consecutive database patients with breast carcinoma, that they were susceptible to perform sentinel node biopsy (SNB) according to the guidelines of the Spanish Medical Societys from 31 January 2001 to 31 December 2007 at a tertiary university center. The variables included were: sex, age, the 3 tumor diameters, volume and surface of the tumor, relationship volume/surface, laterality, predominant type of tumor, maximum and minimum nuclear activity, internal mammary sentinel nodes, tumor grade, hormone receptors, p53 and , C-erb2. A multivariate logistic regression analysis was performed.

**Results:** We included 665 consecutive patients. It was excluded 45 patients: 38 for loss of follow-up and 7 for their outlier values of size. Finally, we analyzed 620 patients. In the multivariate study, tumor surface was higher risk factors to associated axillary lymph nodes metastasis in clinically N0 patients. Every 100 mm² surface tumor increase, at equal volume, had an increased risk for lymph nodes metastasis at the time of the intervention of 44% (OR 1.44; (1.23-1.69) p < 0.01). However, volume tumor was associated a decrease risk for lymph nodes metastasis. Every 100 mm³ volume tumor increase, to equal surface, had a decreased risk of having lymph nodes metastasis at the time of the intervention of 7% (OR 0.93 (0.90-0.97) p < 0.01). It highlighted that increments of maximum diameter of the tumor did not show increased risk by a same surface.

**Conclusions:**
1) Tumor surface is associated with increase of risk of axillary lymph nodes metastasis in clinically N0 patients.
2) Tumor volume is inversely associated with risk axillary lymph nodes metastasis in clinically N0 patients.
3) Increments of maximum diameter of the tumor did not show increased risk by a same surface.
Aim: Analyze characteristics that predict other metastatic axillary nodes in breast carcinoma patients with positive sentinel node.

Methods: We studied prospective and consecutive database patients with breast carcinoma, that they were susceptible to perform sentinel node biopsy (SNB) from from 31 January 2001 to 31 December 2007, at a tertiary university center. The study variables included sex, age, diameter, volume, surface, volume/surface, laterality, histologic type and grade tumor, palpable or not, and migration of the axillary sentinel node (SN), SN activity, internal mammary SN, hormone receptors, C-erb2 and p53. We performed a multivariate logistic regression analysis.

Results: We included 665 patients. It excluded 45 patients: 38 for loss of follow-up and 7 for their outlier values of size. Finally, we analyzed 620 patients. In the multivariate study, tumor surface (OR 1.06; (1.01 - 1.11) p < 0.03) and age (OR of 1.03 (1.00 - 1.06) p < 0.03) were risk factors to associated axillary lymph nodes metastasis in positive SNB patients. Tumor surface increase risk 6% for each 100 mm2. Moreover age increase axillary metastasis risk 3% each year.

Conclusions:
1) Tumor surface is a risk factors of axillary lymph nodes metastasis, increasing risk 6% for each 100 mm2.
2) Age is risk factors of axillary lymph nodes metastasis, increasing risk 3% each year.

Day 3:

Invited Speakers Abstracts

From cancer genotype to phenotype by proteomics
Associate Professor Janne Lehtio, Karolinska Institutet, SciLifeLab, Stockholm, Sweden
How the numerous cancer genome aberrations influence the cancer proteome at the systems level is poorly understood. To study this we have developed a mass spectrometry-based method (HiRIEF LC-MS/MS) that enables in-depth proteome analysis and unbiased genome-wide discovery of protein-coding loci in tissues1. We have used this in-depth proteomics method previously to study endocrine-therapy resistant breast cancer2 and here we will present comprehensive analysis of the breast cancer proteome. The HiRIEF LC-MS/MS generated proteogenomics data was used to compare normal breast, luminal A, luminal B and basal like breast cancer proteomes. Surprisingly, we detected a large number of novel protein coding regions that were previously annotated as pseudogenic loci with several of the novel proteins appearing to be tumor specific. Our results show that mass spectrometry data obtained via HiRIEF LC-MS enables gene prediction-independent proteogenomics of higher eukaryotes and allows for the characterization of novel protein coding loci.

Involvement of key components of wnt signalling in human astrocytic brain tumours
Professor. Dr. sc. Nives Pečina-Šlaus, Department of Biology, Laboratory for Neurooncology, Croatian Institute for Brain Research, Medical School University of Zagreb, Zagreb, Croatia
Wnt signaling pathway is one of the basic cellular pathways whose misregulation plays important roles in tumorigenesis. Molecular landscapes of human astrocytic brain tumors, the most common primary central nervous system neoplasms, still need elucidation. Key players of wnt signaling: beta-catenin (CTNNB1), TCF1 and LEF1, adenomatous polyposis coli (APC), axin (AXIN1) and disheveled-1 (DVL1) were investigated in the set of human astrocytic brain tumors. Our results suggest that molecular changes of wnt signaling play important roles in astrocytic tumor etiology. The findings would help to better understand human astrocytic brain tumor genetic profile and may provide biomarkers for diagnostics and therapeutic decision-making.
Use of ESAs to treat cancer chemorx induced anemia, with or without IV iron
Dr David Henry, Vice Chair, Department of Medicine, Clinical Professor of Medicine University of Pennsylvania, USA,
Cancer chemorx induced anemia (CIA) is common. Some 2/3 of patients respond to ESAs with increased Hb, decreased transfusion, and better QOL. Pathophysiology of CIA and potentially better responses with IV Iron will be presented

ErbB-targeted CAR T-cell immunotherapy of cancer: a strategy to maximize the window of therapeutic opportunity.
Dr John Maher, Senior Lecturer in Immunology, NIHR Biomedical Research Centre at Guy’s and St Thomas’ NHS Foundation, Trust and King’s College London, Research Oncology, Division of Cancer Studies, Guy’s Hospital campus, St Thomas St, London, United Kingdom
The most effective targeted immunotherapies developed against solid tumours to date recognize ErbB family members. We have developed a chimeric antigen receptor (CAR) named T1E28z that targets the extended ErbB network. Engineered T-cells are expanded and enriched using a co-expressed IL4-responsive chimeric cytokine receptor. Efficacy of the resultant "T4 immunotherapy" has been demonstrated in tumour models of head & neck, breast and ovarian cancer in vivo, without significant accompanying toxicity. With excessive dosing however, human T4+ T-cells elicit macrophage-dependent cytokine release syndrome. To de-risk this approach in man, phase 1 testing will be performed in patients with head & neck cancer, commencing in June 2015. Intra-tumoral delivery will be used to minimize risk of toxicity.

Latest developments in non-melanoma skin cancer
Professor Patricia Tak Hing Tai, University of Saskatchewan, Regina, Saskatchewan, Canada
Over the past decade, there are many new developments on non-melanoma skin cancer prevention, diagnosis, staging, and treatment. Tanning beds should not be used in individuals under 18 years of age. Preliminary studies on vitamin A and aspirin showed that they can reduce skin cancer risk. For staging of Merkel cell carcinoma, sentinel node imaging is increasingly being utilized. Adjuvant radiotherapy effectively minimizes local recurrence and improved overall survival. The role of chemotherapy is still controversial for Merkel cell carcinoma. Vismodegib has been shown to induce response in 47% of locally advanced and 33% of metastatic basal cancer carcinoma.

Vitamin D binding protein-based immunotherapy leads to reversal of the neoplastic phenotype and suppression of oncogene expression.
Dr Heinz Reinwald, Dr Reinwald Academy, Italy
Vitamin D binding protein-derived macrophage activating factor is a powerful tool in the immunotherapy of cancer that has proven effective in a variety of cancers. We recently developed an array of novel molecules that mimic its physiological assembly. These novel molecules based on the hydrophobic interaction with the cancer cell membrane, were made lethal to cancer cells. Here we demonstrate that immunotherapy based on these molecules and in conjunction with glucose deprivation, supplementation of proimmunogenic fermented milk products, amino acids and vitamins of the D type reverts the neoplastic phenotype and suppresses oncogene expression.

Oral Presentation Abstracts
Oral presentations will be added after the submission deadline

RADIATION-INDUCIBLE ONCOLYTIC ADENOVIRUS SELECTIVELY MEDIATES SULFATASE-1 GENE EXPRESSION AND MUTUALLY REINFORCES ANTITUMOR ACTIVITY OF I131-METUXIMAB IN HEPATOCELLULAR CARCINOMA
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ABSTRACT
Gene therapy and antibody approaches are crucial auxiliary strategies for hepatocellular carcinoma (HCC) treatment. Previously, we established a survivin promoter-regulated oncolytic adenovirus that has inhibitory effect on HCC growth. The human sulfatase-1 (hSulf-1) gene can suppress the growth factor signaling pathways, then inhibit the proliferation of cancer cells and enhance cellular sensitivity to radiotherapy and chemotherapy. $^{131}$-metuximab ($^{131}$-mab) is a monoclonal anti-HCC antibody that conjugated to $^{131}$I and specifically recognizes the HAb18G/CD147 antigen on HCC cells. To integrate the
oncolytic adenovirus-based gene therapy and the 1131-mab-based radioimmunotherapy, this study combined the CarG element of early growth response-1 (Egr-1) gene with the survivin promoter to construct a radiation-inducible enhanced promoter, which was used to recombine a radiation-inducible oncolytic adenovirus as hSulf-1 gene vector. When 1131-mab was incorporated into the treatment regimen, not only could the antibody produce radioimmunotherapeutic effect, but the 1131 radiation was able to further boost adenoviral proliferation. We demonstrated that the CarG-enhanced survivin promoter markedly improved the proliferative activity of the oncolytic adenovirus in HCC cells, thereby augmenting hSulf-1 expression and inducing cancer cell apoptosis. This novel strategy that involved multiple, synergistic mechanisms, including oncolytic therapy, gene therapy and radioimmunotherapy, was demonstrated to exert an excellent anti-cancer outcome.

**Keywords:** oncolytic adenovirus, radiation-inducible promoter, human sulfatase-1, radioimmunotherapy, hepatocellular carcinoma

THE ROLE OF P38 MAPK IN TETRAARSENIC HEXOXIDE-INDUCED CELL DEATH IN SW620 HUMAN COLON CANCER CELLS

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Running title: Anticancer effects of Tetraarsenic hexoxide

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ABSTRACT

Arsenic hexoxide (As4O6) has been used as a folk remedy for the treatment of cancer since the late 1980’s in Korea, and evidence suggests that As4O6-induced cell death pathway was different from that of As2O3. Here, we investigated the anticancer effects of As4O6 on SW620 human colon cancer cells. As4O6 induced cell death in a dose-dependent manner. Western blot revealed that As4O6 did not induce caspase activation even though As4O6 induced significant cleavage of PARP, suggesting the cell death was caspase-independent. Interestingly, As4O6 suppressed XIAP and Bcl-2, and increased Beclin 1 with promoting the conversion of LC3-I to LC3-II in dose-dependent manner. In addition, As4O6 augmented p38 MAPK, and the cell death was inhibited by the inhibitor of p38 MAPK, but not by p-Akt inhibitor, suggesting p38 MAPK was associated with As4O6-induced cell death. This study provides the evidence that As4O6 induced cell death at least in part through augmenting p38 MAPK in human colon cancer.

**Keywords:** Arsenic hexoxide, colon cancer, cell death, p38 MAPK

IDENTIFICATION OF TUMOUR PROGRESSION GENES IN A MOUSE MODEL FOR NON-SMALL-CELL-LUNG-CANCER

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The 5 year survival rate of patients with Non-Small-Cell-Lung-Cancer (NSCLC) is only 16%. As most patients are diagnosed at an advanced stage, little is known about early stages and mechanisms underlying the progression to metastatic disease. There are few targeted therapies available and targeting KRas driven lung cancer is especially challenging. KRas is one of the most frequently mutated oncogenes in lung adenocarcinomas at ~25% of cases and is notably associated with resistance to EGFR inhibitors. In order to study tumour progression in vivo we chose a Cre/loxP inducible system in which Cre expressing Adenovirus is delivered to the lung by intranasal inhalation. In this model, Cre-mediated induction of a conditional KRasG12D allele gives rise to benign papillary adenomas (BPAs) that rarely progress to adenocarcinoma. Combined activation with conditional Myc overexpression however increases both the growth rate of the BPAs and their frequency of progression to Adenocarcinoma. Importantly, this model faithfully recapitulates the morphology of a subset of the human disease. We used Erk phosphorylation
status to distinguish between benign (p-Erk negative) and more advanced (p-Erk positive) tumour regions, and laser capture microdissection to harvest regions of interest. RNA was isolated from those regions and analyzed by RNA-Seq. GenoGo pathway analysis revealed that the ERBB and WNT pathways are significantly upregulated in the p-Erk positive regions. In order to validate the importance of these pathways, we treated cells derived from the same KRas<sup>61D</sup> and Myc-driven mouse tumours with the pan-ERBB-family inhibitor Neratinib and the WNT-inhibitor LGK974. Single treatment with either inhibitor suppressed cell migration and invasion into Matrigel, whereas combined treatment had a stronger effect on both characteristics. A panel of human NSCLC lines, including several bearing activating mutations in KRas, were similarly sensitive to at least one inhibitor or to the combination of both.

With KRas being downstream of ERBB family receptors and EGFR- and KRas-mutations being mutually exclusive in NSCLC, the reliance on ERBB family signalling in KRas mutant cells was not expected. Our results suggest that broad-specificity inhibitors of these proteins may be effective against a broader spectrum of NSCLC than hitherto anticipated. Our results moreover indicate significant cooperation between the Ras and Wnt pathways that likewise may be exploited for therapy.

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THERAPEUTIC EFFICACY OF NOVEL CASEIN KINASE II INHIBITORS IN A PRECLINICAL MODEL OF HIGH-RISK LEUKEMIA

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High-risk B-cell acute lymphoblastic leukemia (B-ALL) is a considerable therapeutic challenge in oncology. Development of new technologies including next generation sequencing (NGS) and high-resolution cytogenetic techniques provided novel insights into the pathogenesis of this disease. However, current treatment is toxic, with significant side effects, and still often results in a poor outcome. Thus, novel therapy for high-risk B-ALL is essential to improve survival and reduce side effects. The development of precision medicine – an approach that targets the specific pathway(s) essential for the survival and/or proliferation of malignant cells provides hope for novel treatments for this disease. Casein Kinase II (CK2) is an enzyme that is overexpressed in multiple types of malignant diseases in humans. In leukemia, several biological models, along with epidemiological data have provided strong evidence that CK2 functions as an oncogene in high-risk B-ALL. Our published research shows that CK2 directly phosphorylates and inhibits the activity of the IKZF1 (Ikaros) tumor suppressor protein in leukemia. Ikaros is a DNA-binding protein that regulates the transcription of a large set of genes that control cellular proliferation. Loss of Ikaros function is associated with the development of high-risk B-ALL and poor prognosis. We tested the hypothesis that inhibition of CK2 by specific inhibitors will restore Ikaros function as tumor suppressor and produce a therapeutic effect in high-risk B-ALL. Treatment of B-ALL cell lines and primary high-risk B-ALL cells with novel CK2 inhibitors enhanced Ikaros DNA-binding affinity and its function as a transcriptional regulator of genes that control cell cycle progression. CK2 inhibition in primary high-risk B-ALL exhibits a powerful anti-proliferative effect, and is associated with global epigenetic alterations. We tested the efficacy of CK2 inhibitors in primary xenograft models derived from patients with high-risk B-ALL. Inhibition of CK2 resulted in a strong therapeutic effect in these preclinical models of high-risk B-ALL including a dramatic reduction of leukemia in bone marrow and spleen of treated mice as compared to controls. Gene expression analysis of treated leukemia cells demonstrated restored Ikaros tumor suppressor activity as a transcriptional regulator of its target genes. In conclusion, the presented data provide evidence that CK2 inhibitors have a potent in vivo therapeutic effect against high-risk B-ALL and identified one of the mechanisms of their action. Results support the use of CK2 inhibitors in Phase I clinical trial for high-risk leukemia.

INHIBITION OF MULTIDRUG RESISTANCE PROTEIN I (MRP1) IMPROVES CHEMOTHERAPY DRUG RESPONSE IN PRIMARY AND RECURRENT GIOBLASTOMA MULTIFORME

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Glioblastoma multiforme (GBM) is a highly aggressive grade IV brain cancer with an extremely poor prognostic outcome despite intensive treatment regimes. GBM represent ~17% of all primary brain tumours diagnosed worldwide; and 60-75% of astrocytomas, increasing in frequency with age (1). The average five year survival is less than 3%, leading to the fact that GBM is the most lethal form of brain, or central nervous system (CNS), tumour. Despite surgical resection of GBM tumours, recurrence at distal
Increased expression of the multidrug resistance protein 1 (MRP1) in high grade glioma, and its role in blood brain barrier active transport, renders this member of the ABC transporter family, a potential target for improving drug responses in this highly aggressive brain cancer. In this study we show that small molecule inhibitors of MRP1 had a significant effect on GBM cell drug responses to Temozolomide (150µM), Vincristine (100nM) and Etoposide (2µM). Pre-treatment with Reversan led to a significantly improved response in terms of Temozolomide, Vincristine and Etoposide-induced cell death, in both primary and recurrent GBM cell lines. The presence of MK571 led to an enhanced effect of Vincristine and Etoposide in reducing cell viability over a 72 hour period. MRP1 and MRP4 inhibition by MK571 did not have any effect on Temozolomide drug response in these cells. To ensure that the observed findings were MRP1 specific, an MRP1-targeting siRNA was used in three glioblastoma cell lines. Specific MRP1 inhibition led to a significant increase in Vincristine and Etoposide-induced cell death in all three cell lines assessed; (*p<0.05, ***p<0.001) relative to single chemotherapy-induced cell death. Notably, specific MRP1 inhibition did not have any effect on Temozolomide-induced cell death. The findings of this study have significant implications in terms of providing researchers an opportunity to improve currently used chemotherapeutics for the initial treatment of primary GBM, and improved treatment for recurrent GBM patients.

Poster Presentation Abstracts
Poster abstracts will be finalised weeks before the event

SHOULD GENERAL PRACTITIONERS BE INVOLVED IN THE MANAGEMENT OF MEN WITH ADVANCED PROSTATE CANCER?
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Background: We have shown that 2.7% of men registered in general practice and aged 40 years or older have a diagnosis of prostate cancer. Approximately 20% of these are being treated with androgen deprivation therapy (ADT). Currently New Zealand has no clear guidelines for the management of advanced prostate cancer.

Methods: We identified patients registered with prostate cancer on the New Zealand Cancer Registry in the Midland Cancer Network Region in 2009-2012. We reviewed these patients’ clinical records to identify all cases with evidence of metastatic prostate cancer. We investigated the pattern of treatment (ADT, radiotherapy and chemotherapy), and identified the specialist department who initiated prescribing ADT. A sample of patients was followed up with qualitative interviews about their management.

Results: Of the 2127 men diagnosed with prostate cancer, 234 were diagnosed with metastatic prostate cancer. After the metastatic diagnosis, 194 (82.9%) patients received ADT, 104 (44.4%) had radiotherapy, five had chemotherapy. Of the 194 men treated with ADT there was irregular biomarker monitoring with 46 (23.7%) men recorded as having no monitoring PSA tests and only 30 were recorded as having a testosterone test over the entire follow-up period.

Twelve patients were interviewed. Men identified issues regarding palliative and end of life care, access to counselling and support with financial hardship. The interviews illustrated an absence of clear information and anxiety over low transparency in future planning.

Conclusion: Our study showed clear differences in the management of men with advanced prostate cancer, including variable use of ADT, little use of chemotherapy, an absence of clear information for patients and a lack of practical support. We believe that there is a need for clear guidelines as to the management of men with advanced prostate cancer and better access to information for men and their relatives.
families. We believe general practitioners could play an important role in helping men negotiate quality care from their specialist and support services.

**MANAGEMENT OF GLIOBLASTOMAS USING CYTOKINE-INDUCED KILLER CELLS AND CONCOMITANT CHEMORADIOPEPAY WITH TEMOZOLOMIDE**

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Although significant advances have been made in surgical techniques, chemotherapy, and radiotherapy for glioma patients, glioblastoma (GBM) continues to have a dismal prognosis. Therefore, novel therapeutic approaches should be required to manage GBMs. Cytokine-induced killer (CIK) cell Immunotherapy is an attractive therapeutic option for GBMs because of its potential to selectively target residual tumor cells, while sparing normal brain.

We tried CIK cell immunotherapy combined with standard concomitant chemoradiotherapy with temozolomide (CCRT) following surgical resection in 2 GBM patients. The first patient was a 42-year-old female, who has been well-responded without local recurrence at 6 months after multimodal therapy. However, the second patient had a poor response to immunotherapy and CCRT.

There are many types of adoptive immunotherapy using dendritic cells or T cells for management of GBMs. Even though, its efficacy remains unclear, adoptive transfer of CIK cells with additional CCRT may be another option for therapeutic challenge of GBM. We also need a large sized-clinical trial to verify its therapeutic efficacy in GBM patients.

**FATAL TRANSTENTORIAL HERNIATION BY HEMORRHAGIC BRAIN METASTASIS OF THE HEPATOCELLULAR CARCINOMA: A CASE REPORT**

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Despite a high incidence of extrahepatic metastases by hepatocellular carcinoma (HCC), brain metastases were rare and only 1.2% of all the metastatic brain tumor were from HCC. We report a case with metastatic brain tumor, which occurred to subdural hemorrhage (SDH) due to brain metastasis of the hepatocellular carcinoma.

A 51-year-old male patient presented with sudden altered level of consciousness. He suffered from HCC since 2010 and transarterial chemoembolization was performed three times for HCC. The brain CT scans revealed SDH in the right fronto-temporal area and 6.0 x 3.5 cm sized intracerebral hemorrhage (ICH) in the right parieto-occipital lobe. He undertook an emergency decompressive craniectomy and evacuation of the acute SDH and ICH. During evacuation of ICH, the yellowish and hard mass was seen in the hemorrhage. Pathological examination displayed the findings of metastatic brain tumor from HCC. Postoperatively, the patient was kept with an artificial ventilator, and expired at 8th days after surgery.

We report a rare case of fatal transtentorial herniation by spontaneous subdural hemorrhage with intracerebral hemorrhage originating from a metastatic hepatocellular carcinoma. Metastatic brain tumors should be considered in the differential diagnosis as a cause of spontaneous SDH with ICH, and followed-up thoroughly.