The annual Controlling Cancer Summit is an international academic event with plenty of opportunity for networking and debate. In an informal setting, this meeting will bring you up to date with current research and thinking regarding screening, prevention and treatment in this ever-growing field. Presenting at this event, we will have a variety of clinicians, academics and members of the pharmaceutical industry; we encourage presentations from the wide spectrum of cancer research, development and healthcare professionals.

This event has [CPD accreditation](#).

This abstract book will be finalised two weeks before the event [www.lifescienceevents.com/Cancer2016](http://www.lifescienceevents.com/Cancer2016).
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Non-Natural Nucleosides as Therapeutic Agents Against Glioblastoma
Dr. Anthony J. Berdis, Ph.D., Chair, IACUC Committee, Associate Professor of Chemistry and Biology, Cleveland State University, Cleveland, OH, USA
Brain cancers are the deadliest form of all cancers, having very low 5-year survival rates. One agent used to treat brain cancer is temozolomide that causes cell death by damaging DNA. Unfortunately, this drug is only moderately effective as resistance frequently occurs due to mutagenesis. To combat this problem, we developed a nucleoside analog that is efficiently and selectively incorporated opposite DNA lesions generated by temozolomide. This nucleoside potentiates the effects of temozolomide by inhibiting the misreplication of DNA lesions created by temozolomide. Combining our nucleosides with temozolomide provides a new and more effective therapy to treat brain cancer.

Using chemical and biological data for targeted compound selection and biomarker discovery in cancer and beyond
Dr. Andreas Bender, University of Cambridge, Chemistry Department, Cambridge, UK
While a wealth of both chemical and biological information for both disease characterization and the selection of targeted treatments has become available, the question is often still how to make best use of it in practice. In this presentation, I will present approaches which can be used to characterize disease (which focuses mainly on the transcriptomic level in our current work), as well as to select targeted treatments for a particular setting. Furthermore, I will describe how chemical and biological information can be jointly used for the selection of treatments, and to gain further insight into their mode-of-action.

DNA repair gene polymorphisms as risk factors and chemotherapy response predictors for lung adenocarcinoma in Serbia
Miss Ivana Boljevic, Laboratory for Molecular Genetics, Institute for Oncology and Radiology of Serbia, Serbia
Different DNA repair systems maintain the integrity of the human genome. Failure to repair DNA damage leads to genomic instability and possibly cancer development. In addition to associations with cancer risk, DNA repair gene polymorphisms are candidates for affecting the efficacy of chemotherapy and survival time after cancer diagnosis. XRCC1 is a major protein involved in DNA base excision repair, while Rad51 is crucial for homologous recombination during double-strand break repair. We hypothesized that polymorphisms in these genes influence the susceptibility of individuals to lung adenocarcinoma as well as clinical outcomes among patients treated with platinum based chemotherapy in Serbian population.

Molecular factors associated with resistance to drugs targeting BRAF in malignant melanoma
Dr. Suzanne Egyházi Brage, Department of Oncology-Pathology, Cancer Center Karolinska, Karolinska University Hospital, Stockholm, Sweden
Treatment of metastatic melanoma with chemotherapy has been inefficient and has had little impact on clinical outcome. However, recently targeted therapies including BRAF inhibitors have been developed with significantly improved clinical responses in metastatic melanoma but relapses are common and it is thus clear that acquired resistance is a clinical problem. We have identified a number of resistance candidates and potential therapeutic targets and are currently investigating these further to evaluate if downregulation of them can overcome resistance to BRAF inhibitors. Identification of resistance mechanisms may hopefully provide possibilities to improve treatment protocols by combining two targeted drugs.
The stress protein TP53INP1 plays a tumor suppressive role by regulating metabolic homeostasis

Dr. Alice Carrier, Cancer Research Center of Marseille (CRCM), Marseille, France
The gene encoding the Tumor Protein 53-Induced Nuclear Protein 1 (TP53INP1) is a p53-target gene, which is over-expressed during stress events including inflammation. TP53INP1 contributes to stress responses by two different ways. First, in the nucleus, TP53INP1 regulates the transcriptional activity of p53 and p73 by direct interaction, and mediates the antioxidant activity of p53. Second, independently of p53, TP53INP1 contributes to autophagy and more particularly mitophagy. Control of cell redox status by TP53INP1 stems from its implication in mitochondrial quality control and regulation of energetic metabolism. TP53INP1 is thus a key stress protein with antioxidant-associated tumor suppressive function.

p53 regulates miRNA-AGO2 association to control miRNA-mediated post-transcriptional gene repression in cancer

Dr Leandro Castellano, Imperial College London, South Kensington Campus, London, United Kingdom
DNA damage activates p53 that, in turn, suppresses tumorigenesis. p53 transcriptionally modulates genes including microRNAs and regulates miRNA processing. We showed that following DNA damage, p53 interacts with AGO2 to induce or reduce AGO2’s association of a subset of miRNAs. We show that the DNA-damage-induced increase in binding of miRNAs to the RISC complex is functional. Additionally, we observe that miRNAs whose cellular abundance or differential association with AGO2 is regulated by p53 are involved in a network of regulatory feedback and feedforward circuits. p53-mediated regulation of AGO2-miRNA interaction represents a new mechanism of miRNA regulation in carcinogenesis.

Targeted nanomedicines in cancer therapy

Dr Christine Dufes, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK
The possibility of using genes or natural product extracts as medicines to treat cancer is limited by the lack of delivery systems able to selectively deliver these promising drugs to tumours. We demonstrated that the intravenous administration of a tumour-targeted dendriplex led to tumour disappearance of 90% of the tested A431 tumours over one month. In addition, the intravenous administration of green tea extract epigallocatechin gallate encapsulated in novel tumour-targeted vesicles resulted in complete disappearance of 40% of the tested tumour types.

Crosstalk between cell death modalities as anticancer target

Dr Marc Diederich, Department of Pharmacy, College of Pharmacy, Seoul National University, Korea
Cell death plays an essential role in the development of organs, homeostasis, and cancer. Apoptosis and programmed necrosis are two major types of cell death, characterized by different cell morphology and pathways. Accumulating evidence shows autophagy as a new alternative target to treat tumour resistance. Besides its well-known pro-survival role, autophagy can be a physiological cell death process linking apoptosis and programmed necrosis cell death pathways, by various molecular mediators. Here, we summarize the effects of pharmacologically active compounds as modulators of different types of cancer cell death depending on the cellular context. Indeed, current findings show that both natural and synthetic compounds regulate the interplay between apoptosis, autophagy and necroptosis stimulating common molecular mediators and sharing common organelles. In response to specific stimuli, the same death signal can cause cells to switch from one cell death modality to another depending on the cellular setting.

The discovery of important interconnections between the different cell death mediators and signalling pathways, regulated by pharmacologically active compounds, presents novel opportunities for the targeted treatment of cancer. The aim of this review is to highlight the potential role of these compounds for context-specific anticancer therapy.
Nucleosomics®- Revolutionising Cancer Diagnostics
Dr Mark Eccleston, Business Development Director, VolitionRx, United Kingdom
Cell free nucleosomes derived from dying cancer cells provide an opportunity for novel blood-based biomarker development. The profile of epigenetic features, including histone modifications and variants, DNA modifications and adducts between nucleosomes and non-histone proteins can be correlated with clinical disease and overcomes a major limitation of simple nucleosome quantification for diagnostic and prognostic use. This talk will focus on the development of the Nucleosomics technology platform with initial data from a 14 000 prospective FIT screened colorectal cancer cohort.

CYP3A variation, hormone levels, breast cancer risk and prognosis
Dr Olivia Fletcher, Genetic Epidemiology The Institute of Cancer Research, London, United Kingdom
Epidemiological studies provide strong evidence for a role of endogenous hormones in the etiology of breast cancer. We geno-typed single-nucleotide polymorphisms (SNPs), tagging genes involved in the synthesis and metabolism of estrogen in premenopausal women and tested for association with urinary estrone glucuronide (E1G) levels. We identified a SNP mapping to the CYP3A locus that was associated with lower E1G levels, earlier menarche and reduced breast cancer risk. Fine-mapping implicates a putative causal allele (CYP3A7*1C). Predicated on the assumption that genetically-determined effects on metabolism may impact on patient outcome, we tested this allele for association with breast cancer specific survival.

Signalling therapy for cancer: from target proteins to target signalling networks
Dr Alexey Goltsov, School of Science, Engineering & Technology, University of Abertay Dundee, Scotland, United Kingdom
We have developed a computational systems biology approach to support signalling therapy in cancer and demonstrate its application to drug therapy targeting upstream and downstream signalling in the RTK/AKT/PTEN/mTOR pathway in cancer cells. The method aims to translate on-target drug effects to the response of the different signalling network branches to kinase inhibition. Analysis of the network responsiveness outcomes to various drug therapies allows classifying different mechanisms of drug therapy escape and drug sensitivity loss of targeted pathways leading to drug resistance at oncomutations. We discuss the application of the dynamic signalling network analysis to the development of the different strategies to overcome and prevent drug resistance such as 1) searching for sensitive sub-network targets and retargeting cancer therapy to responsive pathway-targets; and 2) resensitizing specific drug escape sub-pathways by customizing co-targeted therapy.

Adoptive T cell Therapy for Cancer
Dr Gray Kueberuwa, Manchester Cancer Research Centre, The University of Manchester, Withington, Manchester, United Kingdom
Advances in immune therapy have seen success in adoptive cell therapy, particularly in the context of chimeric antigen receptor (CAR) T cells and tumour infiltrating lymphocytes (TILs). This talk will provide an overview of our research in these areas and implications for future directions

Dendritic cell derived exosomes for cancer therapy
Associate Professor Susanne Gabrielson, Karolinska Institutet, Dept. of Medicine, Translational Immunology Unit, Stockholm, Sweden
Peptide loaded exosomes are promising cancer treatment vehicles, however, low T cell responses in human clinical trials indicate a need to further understand exosome-induced immunity. We previously demonstrated that antigen-loaded exosomes carry whole protein antigens and require B cells for induction of antigen-specific T cells. I will discuss our latest data where we investigated the need for different immune related molecules on exosomes to induce T cell responses and tumor rejection in the B16 mouse melanoma model. Our data demonstrate ways to increase the feasibility of exosome-based therapeutic approaches in cancer.
**Targeting non death domain-containing TNFR family members for cancer therapy: direct, carcinoma cell-specific death by CD40 signalling**

Dr Nikolaos Georgopoulos, Department of Biological Sciences, School of Applied Sciences, University of Huddersfield, Huddersfield, United Kingdom

The role of TNFR family members in regulating cell fate has been under extensive research for decades. Due to their ability to induce cell death, death receptors represent a promising target for cancer therapy. Most studies have focused on death receptors, such as Fas and TRAIL-R, due to their strong pro-apoptotic potential in malignant cells, yet these can also be toxic to normal cells. However, cell death can be triggered via non death domain-containing TNFRs. We were the first to show that CD40 ligation by membrane ligand (mCD40L), but not soluble agonist, triggers extensive apoptosis in carcinoma cells, whilst sparing their normal counterparts, a unique property for a TNFR superfamily member. We have now identified the molecular nature of the tumour-specific CD40-signalling ‘black-box’ which allowed us to a) explain the differences in pro-apoptotic potential between soluble and membrane agonists, and b) design a novel combinatorial therapeutic approach that shows therapeutic efficacy.

**Chromosomal instability and the metabolic constraints on cancer growth**

Dr Stephen Gregory, The University of Adelaide, Adelaide, Australia

Advanced tumours frequently show defective regulation of chromosome segregation (CIN), which makes them a moving target for therapy. We use genetic approaches in Drosophila to identify inhibitors that can specifically kill these chromosomally unstable cells. Our data suggest that CIN cells are highly sensitive to any perturbation that increases glycolytic flux or mitochondrial membrane potential; such changes lead to the production of Reactive Oxygen Species (ROS), DNA damage and apoptosis. Our latest data on a tumour explant model will be presented, showing the metabolic constraints on CIN tumour growth and possible interventions.

**Recognition of LINE-1 derived DNA by the cGAS-STING pathway leads to inflammmation in Fanconi Anemia**

Dr Jessica Guerra, CNRS UPR1142, IGH Molecular Basis of Cancer Related Inflammation, Montpellier, France

Chronic inflammation favors tumorigenesis, negatively influencing patient prognosis. Yet, the underlying molecular mechanisms are poorly understood. We will present data showing that increased endogenous retroelement-associated reverse transcriptase activity contributes to induce a pro-inflammatory response in the Fanconi Anemia (FA) cancer susceptibility syndrome. Indeed, thereby generated nucleic acids are recognized through the cGAS-STING pathway and sustain the inflammation. Furthermore, reverse transcriptase inhibitor (RTi) treatment decreases pro-inflammatory cytokine production induced by chemotherapy regimen and in FA cells. We will discuss the involvement of endogenous reverse transcriptase activities in sustaining pervasive chronic inflammation, and the potential use RTi in preventing tumor-inducing inflammation.

**IV Iron in Anemia of Oncology, Inflammation, and other disorders of Iron deficiency**

Dr David Henry, Vice Chair, Department of Medicine, Clinical Professor of Medicine University of Pennsylvania, Pennsylvania Hospital, Philadelphia, PA, USA

Iron is poorly absorbed in cancer patients and in other patients with inflammatory disorders like autoimmune disease or inflammatory bowel disease due to elevated levels of hepcidin. In addition, iron deficiency anemia from GI, GU, or GYN causes may respond faster to IV than oral iron. This presentation will review causes and treatment of absolute iron deficiency, functional iron deficiency, and iron sequestration syndromes.

**Cognitive impairment in patients with glioblastoma: single institution experience**

Dr. Ana Misir Krpan, University Hospital Center Zagreb, Zagreb, Croatia

Maximal surgical resection, concurrent chemoradiotherapy and adjuvant chemotherapy are standards of care for glioblastoma. We prospectively tested 192 patients with glioblastoma treated in our institution
from 2011 to 2015. The aim of analysis was to access how cognitive impairment affects overall survival and what is the psychological profile of patients with glioblastoma. Patients were subjected to psychological tests before starting oncological treatment. In 30 patients we made up testing after one year to evaluate what is the effect of treatment on neurocognitive function.

**RAD18 is involved in the resistance of glioblastoma cancer stem cells to the therapy.**
Dr Chames Kermi, Genome Surveillance and Stability Laboratory, Institute of Human Genetics (IGH), Montpellier, France
Upon DNA damage, checkpoint signals are generated so to block cell division and activate repair pathways necessary to regenerate the normal state of the DNA. Mutations in checkpoint genes have been found in cancers at an aggressive stage, making this pathway as a cellular barrier to malignant transformation. Despite the presence of efficient repair mechanisms that deal with damage, DNA lesions can persist when cells initiate DNA synthesis. In order to complete DNA synthesis under DNA damaging conditions cells have evolved a DNA Damage Tolerance mechanism that involves recruitment of specialized DNA polymerases, called translesion DNA polymerases (TLS pols). These enzymes have the unique ability to replicate damaged DNA. TLS pols of the Y-family are recruited at arrested replication forks through interaction with the mono-ubiquitinated form of PCNA (PCNAmUb). This post-translational modification of PCNA is catalysed by the E3-type ubiquitin ligase Rad18.

**Immunotherapy for cancer dormancy**
Dr. Masoud H. Manjili, VCU School of Medicine, Richmond, United States
Tumor cell heterogeneity results in different types of response to conventional cancer therapies, ranging from apoptosis and elimination to growth inhibition and dormancy. Remaining dormant tumor cells could lead to distant recurrence of the disease. Distant metastases are the cause of about 90% of deaths due to breast cancer. We propose that dormant tumor cells that are generally resistant to additional chemotherapy and/or radiation therapy (RT) remain highly sensitive to immunotherapy. Therefore, administration of immunotherapy during tumor dormancy would be an effective strategy to prevent distant recurrence of cancer as advanced stage disease.

**The antitumor activity of cannabinoids in colorectal cancer**
Dr David Meiri, Technion-Israel Institute of Technology, Haifa, Israel
Colorectal cancer (CRC) is considered to be one of the most common forms of malignancy. During the past decade, significant strides have been made in our understanding of the biology of CRCs and the prognosis for CRC patients has been steadily improving. However, despite these recent advances, CRC often results in mortality, thus underscoring the importance of elucidating novel and fresh strategies for the treatment of CRC.

Recently, the therapeutic potential of phytocannabinoids, the unique active compounds of the plant Cannabis, has been rediscovered in the area of cancer research. More than 100 phytocannabinoids have been identified within the Cannabis plant. A few specific cannabinoids have been proposed as having therapeutic potential for various diseases, including cancer.

In this study we establish the antitumor consequences of different cannabinoids on CRCs. Our preliminary data indicate that cannabis extracts have the capacity to inhibit CRC cell growth. However, the magnitude of this inhibition is dependent upon the specific cannabis strain.

**Cancer resistance to photodynamic therapy**
Dr. Marek Murias, Poznan University of Medical Sciences, Poznan, Poland
Photodynamic therapy (PDT) is the one of the youngest methods of cancer treatment and still remains underutilized clinically. In PDT three essential components are used - photosensitizer (PS), light and oxygen. Together they may initiate a photochemical reaction that culminates in the generation of ROS
and/or free radicals. Antitumor effects of PDT derive from three interrelated mechanisms - direct cytotoxic effects on tumor cells (leading to cell death via several cell death pathways), damage to the tumor vasculature and induction of inflammatory reaction followed by immunological response. The relative contribution of these mechanisms depends to a large extent on the type and dose of PS, PDT protocol, tumor oxygen concentration and perhaps other still poorly recognized variables. Similarly cancer resistance to PDT is mediated by general mechanisms of drug resistance as well as antioxidative enzymes status, stress proteins and activation of prosurvival pathways. Moreover the structure of PS is often considered as a key factor related to its subcellular localization, uptake and efflux mediated by transmembrane transporters. Supported by Polish National Science Center, grant number: UMO-2014/15/B/NZ5/01488

The surface and shape of the breast cancer tumors and its relationship with lymph node metastases

Dr Marcel Segura Badia, Hospital del Mar. Autonomous University of Barcelona, Barcelona, Spain

In breast cancer, TNM staging is very important to perform accurate prognosis, choose the best treatment and make comparable studies. However, T only tell us about the maximum diameter, neglecting factors as the tumor shape and, therefore, its surface. This can give us more information about the probability to suffer nodal metastasis than the diameter, being that metastasis is more likely in surface tumor cells. In this study we try to ascertain which one of both methods (maximum diameter or tumor surface) give us more accurate and reliable information about breast cancer tumors.

Precious metals for cancer treatment - a novel approach

Dr. Isolda Romero-Canelón, University of Warwick, Coventry, United Kingdom

DNA methylation in epithelial-to-mesenchymal transition

Dr. Bozena Smolkova, Cancer Research Institute of Slovak Academy of Sciences, Bratislava, Slovakia

In a majority of cancers, including breast cancer, mortality is caused by metastases rather than primary tumours. Genesis of metastases is believed to be preceded by dissemination of tumour cells into the blood circulation or lymphatic channels, which is determined by their morphological and functional dedifferentiation from the epithelial to mesenchymal phenotype. This complex process, known as epithelial-to-mesenchymal transition (EMT), leads to an increased motility and loss of cell adhesion. The genome-wide loss of DNA methylation accompanied by gene specific hypermethylation is regarded as a common epigenetic event in malignancies and may play crucial roles in carcinogenesis, including regulation of EMT processes and subsequent metastatic spread. However EMT-related epigenetic alterations are still poorly understood.

Stem Cell based Therapies for Cancer: Mechanism and Translation into Clinics

Dr. Khalid Shah, Harvard Medical School, Massachusetts General Hospital, Boston, USA

Stem cell-based therapies are emerging as a promising strategy to tackle cancer. Using our recently established invasive, recurrent and resection models of primary brain tumors and breast and melanoma metastatic tumors in the brain that mimic clinical settings, we show that that engineered adult stem cells expressing novel bi-functional proteins or loaded with oncolytic viruses target both the primary and the invasive tumor deposits and have profound anti-tumor effects. These studies demonstrate the strength of employing engineered stem cells in preclinical-therapeutic tumor models and form the basis for their clinical translation.

OMICS biomarkers and their implication in cancer control

Mukesh Verma, National Cancer Institute, National Institutes of Health, Rockville, MD, USA

Precision medicine is an emerging science with the potential to improve early cancer diagnosis and enable the development of treatment based on an individual’s genetic background, family history, and other characteristics. Identifying patients who may benefit from personalized and precision therapy depends on identifying accurate assays for the biomarkers that are needed to determine optimal treatment. Compared to the rapid progress in technology development, the progress in treatment timing has been
Most clinicians rely on pathology reports that become available in due time, which often is too late to control or treat cancer. Molecular profiling (mostly omics profiling based on genomics, metabolomics, epigenomics, transcriptomics, and glycomics data) and molecular classification of cancer can be achieved in real time and may help to identify those cancer-associated biomarkers that are expressed much earlier than pathological symptoms and characteristics appear in histopathological analyses. Once these biomarkers are included in personalized medicine, it will enable treatment to be implemented earlier, which will produce better outcomes. Although the traditional approach to personalized medicine has been “reactive” in the future, it will be “Proactive.”

Research Questions discussed during presentation include:

- Identifying targets of therapy from profiling of genomics, epigenomics, metabolomics, and transcriptomics and integrate them in clinical practice
- Combining molecular pathology data with omics data to reduce false positive results
- Develop new algorithms based on molecular profiling and make novel risk prediction models
- Integrate microbiome data with omics data to help develop new screening and risk prediction tools
- Apply precision medicine to identify individuals/populations who will respond to treatment
- Develop cost-effective companion diagnostic texts based on omics profiling

Responsive lanthanide complexes for imaging of key cell cycle regulators and inhibition of tumor cells

Dr. Gary Ka-Leung Wong, Hong Kong Baptist University, Pokfulam, Hong Kong

Dr. Ka-Leung Wong (Gary) has his research field which mainly focuses on lanthanide chemistry for spectroscopy studies and molecular imaging. He completed a PhD degree in the University of Hong Kong in 2006, following two-year post-doctoral in the City University of Hong Kong and one-year Royal Society Post-doctoral fellowship with Professor David Parker in Durham. In September 2009, he returned to Hong Kong and joined the department of chemistry in Hong Kong Baptist University as a faculty member. He has published more than 80 papers with h-index 31 (Citations > 2300). He has been bestowed the ERES Junior award in 2015, an international triennial prize by the European Rare Earth Society and has selected international advisory board for Multidisciplinary Chemistry Journal in ChemPlusChem (Wiley Publisher).

DNA methylation in early detection and risk prediction of women specific cancers

Prof Martin Widschwendter, MD, UCL Chair in Women's Cancer, Head of Department, Women's Cancer, Consultant Gynaecological Oncology Surgeon, UCL EGA Institute for Women’s Health, University College London, UK

Cancer is at least in part an epigenetic disease. Age, environmental exposures (such as tobacco, alcohol, infectious agents, etc) and endogenous stimuli (such as circulating hormones) can trigger alterations in the epigenetic pattern. These alterations affect gene expression without changing the nucleotide sequence. Epigenetic changes are generally stable and propagate over cell divisions resulting in changes of the phenotype. DNA methylation is the most studied mechanism of epigenetic gene regulation and due to its biological and technical stability an excellent clinical target to develop tests for early detection and risk prediction.

DNA damage repair and p53 gene in platinum-drug resistance

Dr Jing Jie Yu, Mary Babb Randolph Cancer Center, West Virginia University, Morgantown, WV, United States

Tumor drug resistance remains a major obstacle in the treatment of cancers. p53, Chk2 and ERCC1 of the DNA damage/repair pathway were activated after cells were exposed to cisplatin or dicycloplatin. Overexpression of p53 in wt-p53 (but not p53-deficient) cells doubled Chk2 phosphorylation. p53 knockdown greatly reduced Chk2 phosphorylation, indicating that wild-type p53, in response to platinum-drugs, plays a role in the upstream regulation of the DNA-adduct repair pathway and mediates acquired
platinum resistance. We strongly suggest that it is important to include p53 mutational status in any p53-involved studies due to the functional differentiation of wt-p53 and p53-mutant.
Day 1:

Oral Presentation Abstracts

Oral presentations will be added after the submission deadline

HIGH CONCENTRATION OF MELATONIN POTENTIATES THE TOXICITY OF RADIO- AND CHEMOTHERAPY IN HEAD AND NECK CANCER CELLS IN CULTURE AND IN VIVO
Bl. Fernandez-Gil1; A. Guerra-Librero; YQ. Shen; S. Garcia-Lopez; J. Florido; M. Gonzalez-Diez; RK. Sayed; L.C. Lopez; D. Acuña-Castroviejo; I. Tovar; G. Escames

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Background: We recently reported the first effective treatment for the prevention and healing of oral mucositis induced by radio- or chemotherapy, consisting in a melatonin’s gel. With this therapy, which avoids the mucositis development, the life quality of cancer patients would improve significantly, and the radio- and/or chemotherapy could carry on without discontinuation. Here, we evaluated whether melatonin can synergize with radio- or cisplatin- (CDDP), therapies to enhance the cytotoxic effects of the treatment in human cancer cells.

Materials and Methods: The dose-dependent effects of melatonin were analyzed in head and neck cancer human cells (HNSCC) Cal-27 and SCC-9 in culture, treated with irradiation or with CDDP. Cells were maintained in DMEM medium, supplemented with 10% foetal bovine serum at 37°C in a humidified atmosphere of 5% CO2 and 95% air. Cells were treated with melatonin (100 µM, 500 µM, and 1500 µM) alone or in combination with irradiation (8 Gy) or 10 µM CDDP. To analyze the treatment efficacy, we performed clonogenic assays; apoptosis (flow cytometry); cell proliferation (MTT); mitochondrial respiration (SeaHorse); mtDNA content (RT-qPCR); mitochondrial mass (NAO); ROS production (DCFH-DA); nitrites (Griess); antioxidant enzymes (WB), and GSH/GSSG levels. We also studied the potential synergistic effects of the melatonin with the different treatments in vivo in nude mice using Cal-27 cells. Xenografts mice were treated with radio- or chemotherapy for 5 days and with melatonin for 10 days (300 mg/Kg). Immunohistochemical and MRI studies were done to evaluate the tumoural proliferation and metastasis. The results were analyzed with GraphPad Prism 6 Software.

Results: The results showed a relationship between increased mitochondrial function and ROS production by melatonin in Cal-27 and SCC-9 cells. Melatonin also enhanced the irradiation and cisplatin toxicity in vitro, and it also acts inhibiting the tumor growth in vivo.

Conclusion: High melatonin concentrations potentiate the cytotoxic effects of radio- and chemotherapy in head and neck human cancer.

Supported in part by grant nº SAF2009-14037 (Ministerio de economía y Competitividad y Fondos Feder, Spain)
ONCASTATIC EFFECTS OF MELATONIN: ROLE OF MITOCHONDRIAL FUNCTION
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Background: Cancer cells have mitochondrial and metabolic advantages that provide them resistance to different cancer treatments. These advantages consist in the so-called Warburg effect. At normal O2 concentration, cancer cells depend on glycolysis instead of oxidative phosphorylation to get the energy necessary to proliferate, to survive and to grow. Thus, a treatment against this mechanism would control cancer spread. Melatonin targets and improves mitochondrial function in normal cells. Melatonin has oncostatic effects, but its mechanism of action is not well known. Our objective was to analyse whether the mitochondria are involved in the oncostatic effects of melatonin.

Materials and Methods: The effects of high concentrations of melatonin (100 µM, 500 µM, and 1500 µM) were evaluated in Cal-27 cell line. Cells were cultured in DMEM supplemented with 10% fetal bovine serum at 37°C in a humidified atmosphere. Cells were treated with melatonin for 24h, 72h and 5 days. The following analysis were performed: proliferation (MTT), cell cycle assay, mitochondrial mass and mtDNA quantification, mitochondrial respiration, and glycolytic capacity (Seahorse), ROS production (DCFH-DA), activity of antioxidant enzymes, and glutation levels (spectrophotometry), and metabolomics study. Moreover, the in vivo oncostatic effect of melatonin was assessed in mice with HNSCC xenografts. Tumor-carrying mice were treated with 300 mg/kg melatonin for 21 days, and immunohistochemical and MRI studies to evaluate the tumoural proliferation and metastasis, were performed.

Results: The results showed that melatonin induced a shift to aerobic mitochondrial metabolism that increased the ROS production and produced a decrease in cancer cell proliferation. Melatonin also revealed an oncostatic effect in vivo.

Conclusion: Mitochondrial changes induced by melatonin lead to a metabolic shift in cancer cells producing cellular dead.

Supported in part by grant nº SAF2009-14037 (Ministerio de Competitividad y Fondos Feder)


MACROPHAGE-BASED TECHNOLOGY FOR CANCER TREATMENT: M3 SWITCH PHENOTYPE EFFECTIVELY RESTRICTS TUMOR GROWTH IN VITRO AND IN VIVO
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Macrophages play the key role in carcinogenesis. Depending on the microenvironment macrophages acquire or, in other words, reprogram themselves into either a pro-inflammatory, antitumor M1 phenotype or an anti-inflammatory, protumor M2 phenotype. Many tumors produce anti-inflammatory cytokines, which reprogram the antitumor M1 phenotype into the protumor M2 phenotype. We have hypothesized that the problem of protumor macrophage reprogramming could be solved using a special M3 switch phenotype. The M3 switch phenotype, in contrast to the M1 phenotype, should respond to anti-inflammatory cytokines by increasing production of proinflammatory cytokines to retain thereby its antitumor properties. The aim of the study was to verify this hypothesis. Results: 1. Activation of M1 reprograming pathways and inhibition of M2 reprograming pathways programs the M3 phenotype of macrophages, 2. M3 macrophages exerted an effective anti-tumor effect in vitro and in vivo and 3. The antitumor effect of M3 macrophages was due to an anti-proliferative rather than a cytotoxic effect, and
accompanied by pro-inflammatory reprogramming of tumor microenvironment. Conclusion: Development of new biotechnologies for restriction of tumor growth using in vitro reprogrammed M3 switch macrophages is very promising.

EFFICACY OF A NEW PHARMACEUTICAL FORMULATION OF MELATONIN IN PREVENTING RADIOTHERAPY-INDUCED MUCOSITIS

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Background: The complexity of mucositis pathogenesis is yet unclear, and this disease has not currently effective intervention for its prevention or treatment, except limiting the dose of radiotherapy and/or quimiotherapy. The objective of this study was then to analyze whether a new pharmaceutical formulation of melatonin is able to prevent radiation-induced toxicity in oral mucosa and intestine.

Materials and Methods: Male Wistar rats were subjected to irradiation, and their duodenum were obtained for subsequent determinations. The radiation was administered using a Ray-X YXLON Y.Tu 320-D03 irradiator, and the rats received a dose of 7.5 Gy/day for 5 days in their oral cavity. Rats were topically treated with 45 mg/day melatonin gel or vehicle during 21 days post-irradiation, by application in their mouths. Inflammatory reaction was determined measuring NF-κB, NLRP3, ASC, caspase-1, and proinflammatory cytokines expression. Apoptosis studies were also performed through the quantification of pro- and anti-apoptotic proteins. Finally, macro and microscopy damage was evaluated by histology and electron microscopy. Pharmaceutical preparation of melatonin in gel is currently under patent.

Results: A typical irradiation-induced oral and intestinal mucositis was macroscopically observed, which was absolutely prevented by melatonin gel treatment. Mitochondria were impaired after irradiation, losing their bioenergetic capacity and structure, whereas melatonin gel restored mitochondrial function, increasing the activity of the mitochondrial antioxidant enzymes. Irradiation resulted in oral mucosa and duodenal inflammatory damage with a significant increase in the expression of NF-κB and NLRP3. Irradiation also induced apoptosis, increasing the Bax/Bcl2 ratio. Melatonin gel application inhibited the expression of NF-κB, iNOS/i-mtNOS, NLRP3, caspase-1, and proinflammatory cytokines.

Conclusions: The administration of melatonin gel was highly effective against radiation-induced oral and intestinal toxicity. We obtained a patent in Europe and USA and these results have led to a clinical trial (Nº EudraCT: 2015-001534-13)

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TARGETING CANCER CELL PROTEIN SYNTHESIS WITH BETA-CARBOLINE DERIVATIVES TO COMBAT BRAIN CANCERS

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Cancer remains a leading cause of death in developing and developed countries and brain cancers are more incident, thus causing more deaths in the developed regions of the world. Chemotherapy remains indeed challenging because these cancers display intrinsic and/or acquired resistance mechanisms. Furthermore, brain tumor chemotherapy can be specially challenging due to low brain penetration of the drugs. Growing evidence indicates that protein synthesis is deregulated in cancers, including glioblastoma, and plays important roles in cancer onset and progression. Previous substituted beta-carbolines revealed to be potential protein synthesis inhibitors and pharmacological improvement led to the discovery of CM16 1. In this study, we showed that CM16 exerts cytostatic anti-cancer effects in vitro without cell cycle arrest at its IC50 concentration (mean IC50: 0.2 µM) and is more effective against cancerous than non-cancerous cell lines (~ 10 times). CM16 was tested by the National Cancer Institute on their 60-cell-line panel (mean GI50 of 0.2 µM) and its global growth inhibition profile was found to correlate with the ones of other protein synthesis inhibitors. In vitro metabolic labeling assays showed that protein synthesis was decreased when treated with CM16, in a time- and concentration-dependent manner. By contrast no effects on transcription were observed, at least until 24h treatment with 5 µM. Ribosomal subunit assembly and polysome profiling showed that exposure of cells to CM16 led to polysome disruption and increase in 80S complexes. The inhibition of protein synthesis by CM16 is likely to occur at the initiation phase as it induced eIF2α phosphorylation. In addition, the EIF1AX, EIF3E and EIF3H mRNA expression levels appeared different when comparing resistant to sensitive cellular models. Accordingly, the intracellular distribution of CM16 parallels to the endoplasmic reticulum staining. As CM16 was previously characterized by a high predicted blood brain barrier penetration1, these results suggest CM16 as a potential candidate to combat cancers including brain tumors and contribute to the understanding of protein synthesis inhibition in cancer therapy perspectives.

Day 2:

Oral Presentation Abstracts

**WNT SIGNALLING PATHWAY IS TARGETED IN MENINGIOMA**

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Meningiomas which originate from the arachnoidal cap cells of the leptomeninges account for approximately 30% of primary intracranial and intraspinl neoplasms. The molecular mechanisms, signaling pathways and candidate genes involved in their development still need elucidation. In the present study we investigated the involvement of Wnt signaling pathway in meningioma by analyzing its key molecules, beta-catenin, APC, DVL3, AXIN1 and E-cadherin. The chosen pathway is well known for its role in development and tumorigenesis. Genetic changes of tumor suppressor genes APC, E-cadherin (CDH1) and AXIN1 were analyzed by PCR/loss of heterozygosity (LOH). Multiplex PCR was used for DVL3 analysis. The expression and cellular localizations of proteins were investigated by immunohistochemistry. The results obtained on APC showed 47% of meningiomas with LOH of this gene. Immunostaining showed that samples with LOHs were accompanied with the absence of APC protein expression or presence of mutant APC proteins (Chi square =13.81, df = 2, P<0.001). Immunostaining showed that beta-catenin was upregulated and transferred to the nucleus in 71.2% of meningiomas. This high frequency is indicative of oncogenic activation of Wnt signaling. We also showed that nuclear localization of beta-catenin correlates to gross deletions of APC gene (Chi square =21,96, df = 2, P<0.0001). Downregulation or loss of E-cadherin expression was observed in 58% of samples and gross deletions (LOH) of this gene were found in 32% of meningiomas. Our findings demonstrated that there was significant association between the genetic changes of CDH1 and the nuclear localization of beta-catenin protein (Chi square =5,25, df =1, P<0,022). Loss of E-cadherin and beta-catenin’s translocation to the nucleus are two prominent features of epithelial to mesenchymal transition, a process involved in invasion and metastasis of tumors. LOH of AXIN1 gene was observed in 21.1% of meningiomas and AXIN1 expression levels were negative or very weak in 21.9% of meningiomas. All the other samples had AXIN1 localized in both the cytoplasm and nucleus with moderate expression in 34.4% and strong in 43.8%. DVL3 was amplified in 23,81% of analyzed samples. Microsatellite instability (MSI), the result of impaired cellular mismatch repair, was also detected, MSI for CDH1 gene in 11%, for DVL3 in 9,52% and for AXIN1 in 5.3% of investigated meningiomas. Our results suggest that Wnt signaling pathway plays important role in meningioma. The ongoing research is aiming to offer new molecular markers for meningioma based on the genetic pathways and molecules involved and help to develop new treatment modalities.
UPTAKE DYNAMICS OF NANOPARTICLE ENCAPSULATED THYMOQUINONE AND EFFECTIVE TARGETING OF BREAST CANCER CELLS

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The promising anticancer molecule Thymoquinone (TQ) suffers from limited bioavailability, therefore its encapsulation would help overcome low drug solubility, bioavailability as well as nonspecific targeting. We synthesized four different TQ nanoparticle (TQ-NP) formulations using flash nanoprecipitation, characterized their properties, uptake and delivery mechanisms, and assessed their anticancer potential in a panel of breast cancer cells. The size, morphology and stability of the NPs was characterized by dynamic light scattering and scanning electron microscopy and their anticancer effect was assessed by MTT. We subsequently formulated fluorescent TQ-NPs and evaluated their uptake and subcellular intake mechanism by both fluorometry and confocal microscopy. We were successful at formulating stable TQ-NPs that had an average diameter size between 45-130 nm. All TQ-NPs had high entrapment efficiency and loading content. In vitro testing showed that the TQ-NPs had enhanced antitumor activity in comparison to free TQ in both MCF-7 and MDA-MB-231 cells with no significant cytotoxicity of the blank NPs. The uptake of fluorescent TQ-NPs was found to be both time and concentration dependent. The endocytosis of TQ-NPs was found to be caveolin-mediated, based on experiments with inhibitors of endocytosis, which was also confirmed by examining the subcellular localization of TQ-NPs. The nanoparticle formulations colocalized with both caveolin and transferrin but not with lamp-1 and EEA-1 proteins. Altogether, our results describe a new approach for the enhancement of TQ anticancer activity and define the uptake dynamics of this specific formulation.
POOR KNOWLEDGE OF CERVICAL CANCER AND CERVICAL DYSPLASIA AMONG WOMEN IN ABAKALIKI, NIGERIA: THE NEED FOR HEALTH EDUCATION FOR CANCER PREVENTION.

by B.A.F, NGWU¹, E.C, AMADI², G.O NGWU³, G.O EZEIFEKA⁴, and, M.U, ORJI⁴,

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Abstract

The prevention of cervical cancer through cervical screening cytology (Pap smear) remains a major medical practice in cancer prevention and has reduced the incidence of cervical cancer in developed countries. Despite the extensive and routine use of Pap smear cytology in advanced countries, it is non-existence or rudimentary in most developing countries. In Nigeria, there has been reports from different regions of the country that there is poor knowledge of cervical cancer and cervical screening tests, and an abysmal low participation and uptake of cervical screening services by women. In this study we investigated the knowledge of cervical cancer, cervical dysplasia and uptake of cervical screening services among women in Abakaliki Nigeria using questionnaires and Pap smear cytology methods. The results showed that 360 women aged 20-63 years with mean age of 34 years participated in the study and knowledge about cervical cancer showed that only 101(28.1%) knew while 259(71.9%) did not know, while knowledge about cervical dysplasia showed that 65(18.1%) knew while 295(81.9%) did not know. Knowledge about cervical screening and pap smear cytology shows that only 132(36.7%) and 89(24.7%) knew about the cervical screening and pap smear cytology respectively; while knowledge about cervical screening centers showed that only 66(18.3%) had knowledge of the centers while 294(81.7%) did not know. The uptake and participation in cervical screening services for cervical dysplasia and cervical cancer showed that only 17(4.7%) and 28(7.8%) have participated in cervical screening for dysplasia and cancer respectively. We concluded that there is significant (Ps0.05) poor knowledge of cervical cancer and cervical dysplasia and poor up take of cervical screening services among women in Abakaliki and recommend urgent health education about cervical cancer and dysplasia for women in Abakaliki, Ebonyi State, Nigeria.

KEYWORDS: Prevention of Cervical Cancer; Cervical dysplasia; Up take of cervical screening services; Cancer screening centers; Health Education.

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MOLECULAR DETERMINANTS OF SENSITIVITY AND RESISTANCE TO FGFR INHIBITION IN FGFR2-AMPLIFIED GASTRIC CANCER.

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Despite improvements in diagnostics and chemotherapy regimen in gastric cancer, there is still an urgent need for novel biomarkers and second-line treatment interventions. High level FGFR2 amplification is found in ~5% gastric cancers, and responses in FGFR2-amplified gastric cancer have been observed in a phase II study of FGFR inhibitor AZD4547 (Smyth et al ASCO 2015). Here we studied patient-derived xenografts (PDX) to understand the mechanisms of sensitivity and resistance in FGFR2-amplified gastric cancer.

PDX models were generated from the baseline biopsies of two Caucasian patients with junctional FGFR2-amplified tumors who had durable responses to AZD4547 in the clinic. Both PDX recapitulated the histology of the original cancers, and whole exome sequencing demonstrated 85-90% agreement in mutations between the patient biopsies and the PDX tumors. Similar to the patients, both models were highly sensitive to AZD4547, with regression of ~60% seen after 10 days treatment, with subsequent stability on chronic dosing.

To understand the molecular mechanisms of sensitivity to AZD4547, we profiled PDX tumors and PDX-derived spheroid cultures with phospho-RTK antibody signaling arrays and by western blot. FGFR inhibition resulted in potent suppression of ERK and short-term suppression of PI3K-mTOR signaling. However, chronic exposure resulted in an increase in phospho-S6 after 72 hours of treatment. To examine adaptive response to AZD4547 we excised residual PDX tumors after 60 days treatment, demonstrating upregulated S6, ERBB3 and insulin receptor phosphorylation in tumors adapted to long-term FGFR inhibition, suggesting reactivation of mTOR signaling limits sensitivity of FGFR2-amplified tumors to AZD4547. Finally we investigated the mechanism of acquired resistance to the drug. Long-term treatment of PDX with AZD4547 gave rise to resistant PDX tumors, which were analysed by proteomic and genomic approaches, including RNA and DNA sequencing. Preliminary evidence suggests acquisition of genetic abnormalities in the resistant tumours, which are currently being investigated and will be presented at the summit.

In conclusion, activation of mTOR signaling mediates adaptive response to AZD4547 in FGFR2-amplified gastric tumours and downstream genetic events are likely to facilitate acquired resistance to the drug.
INNOVATIVE APPROACHES IN METABOLOMICS FOR UNDERSTANDING DRUG RESISTANCE IN BREAST CANCER

Authors

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Breast cancer is one of the leading cause of death worldwide. Breast cancer is curable in the early stages but major clinical setback is drug resistance. Metabolomics is an emerging field that utilizes information of cellular biochemistry for the early detection, diagnosis and establishment of predictive biomarkers of breast cancer. This review highlights potential metabolomics applications to clinical pharmacology. The methodology is based on inclusion exclusion criteria. Literature survey, and questionnaire were included while clinical trial was excluded. This report provides a review of 12 articles out of few were excluded. According to the survey the average response rate of a cancer drug is the lowest at 21%, suggesting that 79% of patients with cancer are over-dosed. When specific therapies are chosen on the basis of a patient’s metabolomics profile, it will give rise to customized medicine and personalized tailored treatment. Using high-throughput information using metabolomics to clinical diagnosis and treatment can help accelerate the patient safety, quality of life and survival rate by identifying pathways involved in drug resistance. Metabolomics is future of anti-cancer pharmacology, following “the right drug for the right patient at the right time” can offer safety, quality and effectiveness of anti-cancer treatment.

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

BARRIERS TO BREAST CANCER SCREENING AMONG WOMEN IN JEDDAH, SAUDI ARABIA
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Introduction and Research Problem: In Saudi Arabia, breast cancer is the most common cancer among both sexes and all age groups. Breast cancer mortality rates have steadily been decreasing worldwide, with advances in screening programs being key to early detection and treatment. Literature points to very low screening rates in the Kingdom of Saudi Arabia. We aimed to understand what barriers may prevent Saudi women living in the city of Jeddah from early detection screening.

Materials and Methods: A cross-sectional study was conducted via inter-personal surveys, across various public locations in Jeddah, Saudi Arabia. With an estimated population of 491,678 Saudi females aged more than 20 years of age in the city of Jeddah, the sample required with a confidence interval of 95% and a 5% margin of error was 384 females.

Summary of Results: 421 women participated in the survey. They were aged twenty and above, clustered into six age groups. The most common barrier was “I didn’t know I’m supposed to screen for breast cancer”, with a frequency of 149 (35%); followed by difficulty with appointments (21%), and embarrassment (16%). Only 54 women (12.8%) reported regular check-up with a family or general physician.

Conclusion: Our findings highlight a wanting need for national breast cancer awareness campaigns. Lack of knowledge regarding screening protocols, especially among younger age groups, must be addressed by widespread national campaigns targeted at raising awareness towards screening options and availability. Orienting the public to the importance of primary healthcare and regular follow up, even when not ill, is crucial to promoting health awareness and early detection screening.

A SYSTEMS-LEVEL APPROACH TO CANCER CARE NAVIGATION AT A REGIONAL CANCER CARE CLINIC
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Background and Objectives: The Northern Cancer Control Strategy of British Columbia implemented and piloted a navigation model which centred around one cancer care navigator facilitating multidisciplinary workshops aimed towards creating a “seamless journey” for cancer patients at the University Hospital of Northern British Columbia in Prince George, BC. The objective of this pilot was to create a cost-effective method of cancer care navigation that was focused on systems-level solutions as opposed to one-on-one patient navigation, and that would be viable in northern BC.

Methods: An iterative model of continuous cancer care improvement was implemented using planning tools adapted from the process mapping methodology of the NHS Institute in the UK. A cancer care navigator acted as the primary facilitator for a series of workshops that enabled a multidisciplinary group of oncology stakeholders to describe the current and ideal breast cancer journeys for the hospital. Once the gaps in service were identified, the cancer care navigator worked with the cancer care team to prioritize problems and systematically solve each problem with smaller working groups.

Results: Over 70 participants were included throughout the initial 7 month process. Input was received from administrative professionals, oncology nurses, palliative care nurses, general surgeons, plastic surgeons, general practitioners, mammography technicians, social workers, radiology nurses, and patients. First, both “current” and “ideal” breast cancer journey maps were created. The top 3 prioritized
problems areas were subsequently identified and solved with input from the entire cancer care team. The top 3 problems included: 1) lack of coordination and extended wait times from diagnosis to surgery, 2) patient stress and anxiety surrounding breast pain and discharge symptoms, and 3) radiologists being unable to order further testing and/or biopsies because previous patient tests were unavailable, which led to an increase in diagnostic wait times.

Conclusion: A cancer care navigation model that is centred on one cancer care navigator who focuses on facilitating the creation of systems-level navigation solutions is a successful and potential alternative to one-on-one patient navigation.

DISRUPTION OF THE NFκB SIGNALING PATHWAY BY YM155 LEADS TO INDUCTION OF PROFOUND APOPTOSIS IN RENAL CELL CARCINOMA (RCC)

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Introduction: Constitutive activation of the NFκB signaling cascade has been associated with human cancers including RCC and may play a role in their resistance to the apoptotic stimulus. Deregulation of the apoptotic pathways facilitate the accumulation of gene mutations and play a critical role in promoting cell proliferation and viability in carcinogenesis. YM155 is a known inhibitor of the anti-apoptotic protein, survivin and it possesses potent anti-proliferative activity. The objective of this study is to investigate the role of NFκB signaling pathway in the induction of apoptosis by YM155 in RCC.

Materials and Methods: Paired isogenic human RCC cell lines: 786.0 EV and 786.0 VHL (VHL-mutant and VHL-wt), RCC786.0 and primary RCC cell lines (NCC010, NCC035, P.RCC) were used in this study. MTS cell proliferation assay was used to determine IC50 of YM155 on these cell lines. The binding activity of nuclear p65 was determined using a chemiluminescent-based NFκB p65 transcription factor kit. The transcription activity of NFκB was determined using a luciferase reporter assay. Flow cytometry and western immunoblotting was performed to determine the expression levels of molecules associated with the regulation of apoptosis.

Results: YM155 demonstrated potent growth inhibitory activity on seven RCC cell lines, with IC50 in the nanomolar range. YM155 reduced nuclear translocation of NFκB in a dose dependent manner and significantly inhibited the TNFα-induced transcriptional activity of NFκB. This led to the down-regulation of inhibitor of apoptosis (IAP) proteins such as survivin and induced apoptosis in RCC cells.

Conclusion: Our data suggests that the anti-survivin agent YM155 disrupts the NFκB signaling pathway at concentrations that are closely aligned to its growth inhibitory IC50. Inhibition of NFκB transcription factors and down-regulation of anti-apoptotic proteins by YM155 leads to profound growth inhibition of RCC cells, suggesting a potential candidate drug for clinical development.
QUANTUM THEORY OF CELL PROLIFERATION AND CARCINOGENESIS

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1. DNA of stem cells is an energy accumulator because of closed supercoiled structure and noncoding repeated nucleotide sequences.
2. Energy quants are transferred to DNA through chemical, physical, and biological carcinogens.
3. DNA of stem cells can divide (underthreshold dose) or be damaged (suprathreshold dose) depending on quantity of received energy.
4. DNA of stem cell accumulates energy up to threshold dose in case of impossibility of immediate cell division due to the changes in the local microenvironment.
5. Low doses of energy are accumulated in DNA of stem cell up to threshold value much longer than large ones.
6. DNA of stem cell begins replication on reaching threshold value regardless of local microenvironment.
7. DNA mutations can be the cause of the changes in the local microenvironment or appear due to energy transfer within the DNA.

EXTRACT OF RUBIA AKANE INHIBITS GASTRIC TUMOR GROWTH VIA ANTI-TUMOR PROLIFERATION AND TUMOR-ASSOCIATED MACROPHAGE REGULATION

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Lymph node metastasis occurs frequently and early in gastric cancer and its management is important in controlling tumor progression. Accumulating data suggested that tumor cells polarize macrophage differentiation toward tumor-associated macrophages (TAMs) which provide a favorable microenvironment to promote tumor development. Using the U937-derived TAM model, we identified that the ethanol extract of Rubia Akane (GC-248) diminished the expression of immune suppressive cytokines IL-10 and IL-1ra. Besides, in PBMC-derived TAM model, GC-248 inhibited monocyte differentiation as evidenced by lowering TGF-β and IL-1ra secretion. Viability assay and cell cycle analysis showed that GC-248 induced apoptosis and inhibited cell growth with IC50 at 3.84±0.60 μg/ml. In gastric cancer cell migration assay, GC-248 restrained the migratory activity of MKN-45 cell partially though inhibiting MMP-2 and MMP-9 expression. Western blot and real time PCR data revealed that GC-248 inhibited IL-4-STAT6 signaling by downregulating the phosphorylation of STAT6 and expression of PPAR, JMJD3, and IRF-4, since these factors played crucial roles in macrophage polarization toward TAM. In the orthotopic gastric cancer murine model, peritoneal injection of GC-248 dramatically retarded the tumor growth without the body weight change and aberrant behavior. The antitumor growth and immune modulation activity suggested that GC-248 is a potent herbal material for further drug development in gastric cancer therapy.
CLINICAL SIGNIFICANCE AND PROGNOSTIC VALUE OF SERUM TUMOR MARKERS FOR GASTRIC CANCER
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INTRODUCTION
Aim of this study was to determine preoperative and postoperative clinical importance of serum CEA, CA19-9, CA-125 and CA15-3 levels.

METHODS: 217 patients were diagnosed with gastric cancer between January 2009 and December 2011, in General Surgery Department, School of Medicine, Ege University. 134 of these patients had been operated and 83 patients were considered inoperable. Patients were evaluated retrospectively. Clinicopathological features of the patients, survival and serum CEA, CA19-9, CA-125 and CA15-3 levels were evaluated.

RESULTS: For all tumor markers, only elevated CA 125 level was statistically significant to show operability (P = 0.122). CA 125 level is more important than others for demonstrating survival (p = 0.000). None of the markers measured preoperatively was significant to assume postoperative recurrence, lymph node metastasis and perineural invasion of the tumor (p>0.05). Preoperative CA19-9 and CA15-3 levels viewed statistically significance for showing vascular invasion (p = 0.042, p = 0.016 respectively) and only CA19-9 was significant for showing lymph node invasion (p=0.042). For tumor markers measured postoperative 1, 3, 6, 12, and 24 th months; only CA19-9 and CA125 values at 24th month were statistically significant for demonstrating recurrence.

CONCLUSION: Serum CA125, CA19-9 and CA15-3 levels measured both preoperatively and postoperatively were thought to be significant for demonstrating survival, recurrence, vascular invasion, lymphatic invasion, and inoperability criteria

PHOSPHORYLATION OF HSP90 BY CDC7-DBF4 PROMOTES HR REPAIR AND CELL SURVIVAL IN ORAL CANCER
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Cdc7-Dbf4 kinase regulates DNA replication and S phase checkpoint signaling in eukaryotes. However, its role in S phase checkpoint and DNA repair is elusive. Our previous data showed that overexpressed Cdc7 inhibits genotoxin-induced apoptosis to increase the survival of oral squamous cell carcinoma (OSCC) and ATM/ATR phosphorylate Dbf4 in response to DNA damages, but the kinase activity of Cdc7 is still remained. Therefore, we hypothesis that Cdc7-Dbf4 may act as a downstream effector of ATR to regulate the S-phase checkpoints and inhibit DNA repair. HSP90 is upregulated in various cancers and binds with HCLK2 to form a chaperone complex to stabilize all phosphatidylinositol 3-kinase-related kinases (PIKKs) including ATM and ATR. We demonstrated that Cdc7-Dbf4 interacts with HCLK2-HSP90 complex and phosphorylates HSP90 at serine 164 under DNA damage response. PHA-767491, the inhibitor of Cdc7 kinase, disrupts the interaction of Cdc7-Dbf4 with HSP90-HCLK2 complex and prevents the HCLK2-HSP90 chaperone function, suggesting that Cdc7 kinase upregulates the interaction and stability of HCLK2-HSP90 complex. Furthermore, the HSP90 serine 164 mutant affects the stability and function of ATM, ATR, HCLK2, and Mre11-Rad50-NBS1. These results suggest that Cdc7-Dbf4 promotes S-phase checkpoint signaling and HR DNA repair by phosphorylating HSP90 serine 164, providing a rationale why overexpressed Cdc7-Dbf4 promotes cancer cells survival and a new insight for cancer therapy.
EVALUATION OF IMMUNE CHECKPOINT MARKERS AND IMMUNE FUNCTION OF TUMOR INFILTRATED LYMPHOCYTES IN TUMOR MICROENVIRONMENT

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Immunotherapy strategies that target checkpoint pathways have proved promising in recent years. In particular, blocking the immunosuppressive programmed death-1 (PD-1) pathway, either by targeting PD-1 or its ligand, PD-L1, has shown durable efficacy in patients with different cancer types, including melanoma and lung cancers. Numerous studies have demonstrated that PD-L1 in the tumor microenvironment and pre-existing CD8 (+) immune cells may predict response to the PD-1 pathway blockade. While various methods have been employed to measure biomarker expression, spatially mapped information at the single-cell level is crucial to understanding cellular organization and cell-to-cell interactions in complex tissue.

In this study, we analyzed the tumor microenvironment of twenty archived formalin-fixed paraffin-embedded (FFPE) non-small cell lung carcinoma (NSCLC) specimens for single-cell gene expression of immune checkpoint maker, PD-L1. To better understand gene expression and localization patterns of PD-L1, we applied the RNAscope® in-situ hybridization (ISH) assay to (1) identify and map PD-L1 gene expression profile in single-cells in tissue, (2) identify tumor-to-tumor heterogeneity of PD-L1 gene expression among different specimens, and (3) determine co-localization patterns of PD-L1 in relation to different markers in each tumor section. The co-localization of different checkpoint and immune markers, including PD-1, PD-L2, LAG3, CD8A and IFNγ, were measured by RNAscope® duplex analysis.

In this report, we present the use of RNAscope® based in-situ hybridization assay as a method to study the complex dynamics of immune checkpoint and functional markers in tumor microenvironment. Presently, we show single-cell gene expression profiles of PD-L1 from archived FFPE tissues of 20 NSCLC cases. Based on simultaneous detection of two different marker combinations, we observe spatial distribution of cells expressing CD8 and other checkpoint markers in relation to PD-L1 (+) cells. Similarly, the duplex analysis displays IFNγ (+) CD8 (+) cells with specific localization in both tumor and stromal regions. In addition to detecting and localizing immune and tumor cell markers in their complex microenvironment, this method can potentially reveal a complex landscape of interacting receptors, ligands, and soluble factors, such as cytokines and chemokines. Furthermore, the method presented here may contribute to identifying candidates for combination treatment regimens, especially for identifying ideal targets for multiple checkpoint blockade pathways.

THE ROLE OF AXL IN IRS-MEDIATED AEROBIC GLYCOLYSIS
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AXL is well known to be involved in the later stages of tumor progression such as migration/invasion, metastasis and/or drug resistance. Recently, AXL has also been reported to mediate the high-glucose-induced endothelial dysfunction and the adverse effects of high glucose in vascular smooth muscle cells. These effects not only are closely related with type 2 DM but may also engage AXL in cancer cells Warburg effect (increased glucose influx by GLUT, enhanced glycolysis and suppressed TCA cycle even in the presence of ample oxygen, a situation better described as aerobic glycolysis). Importantly, type-II diabetes (a known risk factor for pancreatic cancer) may contribute to the Warburg effect by fueling cancer cells with endless glucose in the course of cancer progression. Since our data demonstrated that AXL binds C1-TEN (a PTEN homolog), and the kinase activity of Axl did influence C1-TEN and regulates IRS-1 (Insulin
Receptor Substrate 1), and IRS-1 activates the glucose influx transporter GLUT in response to high glucose in previous studies. In this research, we investigated the novel roles of AXL in cancers Warburg effect and proved how AXL influences the cancer progression with C1-TEN/IRS-1 pathway.

Key words: AXL, IRS-1, Warburg effect, Aerobic Glycolysis

DYSREGULATION OF LYSOPHOSPHATIDIC ACID (LPA) SIGNALLING STIMULATES CELL MIGRATION AND INVASION IN ORAL SQUAMOUS CELL CARCINOMA

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Background: Early death from oral squamous cell carcinoma (OSCC) occurs as a result of local invasion and regional lymph node metastases. Elucidating the mechanisms that regulate invasion and metastasis of OSCC cells could lead to the development of more effective targeted therapies. Lysophosphatidic acid (LPA) is a lipid signalling molecule that activates a family of G protein-coupled receptors (LPAR1-6) to regulate a wide range of biological processes. Dysregulation of LPA signalling has been implicated in carcinogenesis and can occur as a result of altered receptor profiles on tumour cells. The role of LPA in the pathogenesis of OSCC, however, has not been investigated.

Methods: The effects of exogenous LPA on OSCC cells behaviour were examined using a number of in vitro functional assays, namely proliferation, colony dispersal, transwell migration and three-dimensional organotypic invasion assays. Quantitative real-time PCR was performed to determine the expression of LPAR in OSCC tissues. The LPAR1/3 receptor antagonist, Ki16425, was used to investigate the role of LPAR1 and LPAR3 on cell migration.

Results: Exogenous LPA had little effect on cell proliferation, but greatly stimulated cell motility in colony dispersal assays; cell colonies dispersed into single, highly migratory cells with elongated morphology and lamellipodia. LPA also enhanced the migration and invasion of OSCC cells. Quantification of LPAR expression in OSCC samples revealed that LPAR3 mRNA levels were significantly higher in malignant tissues compared to normal oral mucosa. We further showed that cell migration was significantly inhibited by Ki16425, demonstrating the involvement of LPAR1 and/or LPAR3 in this phenomenon.

Conclusion: The results of this study show that dysregulation of LPA signalling contributes to the aggressive phenotype in OSCC and identifies this pathway as potential therapeutic target for this disease.
IMPACT OF ABERRANT DNA METHYLATION OR PROTEIN EXPRESSION OF CXCL12, ADAM23 and SOCS1 GENES ON METASTATIC RISK OF PRIMARY BREAST CANCER


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Although metastasis is widely regarded as an inefficient process, most cancer patients die from metastases rather than from their primary tumours. Once a migratory cell(s) has detached from the tumour, it may intravasate into venous capillaries or blood vessels or lymphatic system. Circulating tumour cells are independent prognostic factors in the primary and metastatic breast cancer and play crucial role in haematogenous dissemination.

In the tumour tissues of 203 primary breast cancer patients we quantified DNA methylation changes in nine genes (APC, ADAM23, CXCL12, CDH1, RASSF1, SYK, TIMP3, BRMS1, SOCS1) that have a putative role in regulation of cell growth and metastatic potential. We analyzed the effect of DNA methylation on protein expression and its association with disease progression. Expression of these proteins in tumour tissues were also evaluated to identify their influence on the presence of circulating tumour cells in peripheral blood of patients. The quantitative DNA methylation analyses were performed using pyrosequencing. Expression level of selected proteins was evaluated by immunohistochemical analysis in formalin fixed paraffin embedded tumour and normal breast tissues.

The highest methylation levels were found in the primary tumour samples in the RASSF1A, APC, CXCL12, and ADAM23 genes. No associations were observed between the methylation levels and the related protein expression. The risk for lymph node metastases development was associated with CXCL12 hypermethylation. Ki-67 proliferation was influenced by ADAM23 hypermethylation. The presence of circulating tumour cells in the peripheral blood of patients was significantly associated with positive CXCL12 protein expression and lack of SOCS1 protein expression in tumour tissues.

Results of our study suggest that the quantification of CXCL12 and ADAM23 methylation could be useful for the prediction of advanced stages of breast cancer. Association between aberrant expression of the CXCL12 and SOCS1 proteins and CTC supports the hypothesis that aberrant signalling cross-talk between cytokine and chemokine responses could play role in haematogenous dissemination of tumour cells in breast cancer.

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THE EFFECTS OF THE IKKβ-SPECIFIC INHIBITOR PS1145 ON TUMOR FORMATION IN NASOPHARYNGEAL CARCINOMA

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Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma which arises from the epithelium of the nasopharynx and is characterized by the inflammatory tumor microenvironment with intensive lymphocyte infiltration. Inflammation is generally believed to play a critical role in cancer development, as cancer development is a consequence of chronic inflammation; this is consistently associated with activation of nuclear factor kappa-B (NF-κB) and its downstream pathways. Cumulative evidence has indicated the intimate relationship of NF-κB and NPC carcinogenesis. A number of studies have demonstrated the frequent over-expression or activation of NF-κB in NPC cell lines and tissues. Our previous study indicates that the canonical NF-κB pathway is essential to tumor development as well as angiogenesis in NPC, suggesting that the NF-κB pathway including its upstream modulators and downstream effectors is a potential therapeutic target for NPC. Inhibition of upstream IKK kinases represents one of the pharmacological strategies to target NF-κB. The small molecular PS1145 is a specific IKKβ inhibitor derived from a β-carboline natural product. It can inhibit the IκB phosphorylation and degradation and the subsequent activation of NF-κB. In this study, we aim to determine whether PS1145 has the potential to be used as an anti-cancer drug to suppress NPC primary tumors. Our results showed that significant inhibitory effects were observed in the three tumorigenic NPC cell lines (HONE1, HK1, C666) in response to PS1145, but not in the immortalized normal nasopharyngeal epithelial cell line (NP460). In addition, administration of PS1145 to nude mice inoculated with NPC cell lines was performed and the results show that a low concentration of 3 mg/kg PS1145 could significantly suppress the subcutaneous tumor formation in both C666 and HONE1 cell lines. The effects of PS1145 on C666 in vivo and in vitro tumor growth are more obvious than in other NPC cell lines; this may be due to its highest total and active p65 protein levels. With respect to the body weights of the animal, there was no significant change in the presence of this IKKβ inhibitor during the whole experimental periods for the two independent experiments. As can be seen, PS1145 appears to be safe for animal experiments and its effects are tumor-specific.

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HIGH FREQUENCY OF HLA CLASS I ANTIGEN PROCESSING MACHINERY (APM) COMPONENT UP-REGULATION IN PRIMARY HEPATOCELLULAR CARCINOMA TUMORS

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Malignant transformation of cells is associated with down-regulation of HLA class I APM components in most of the tumors. These defects are clinically relevant, since they are frequently associated with the clinical course of the disease. Only in a few tumors malignancy is associated with the up-regulation of HLA class I antigens. Among them is hepatocellular carcinoma (HCC). The frequency of HLA class I APM component up-regulation and its clinical significance in HCC are not known. These topics were investigated in the present study, since the resulting information may contribute to assess the therapeutic efficacy of T cell-based immunotherapy for the treatment of HCC. Twenty-one surgically resected primary HCC tumors and autologous adjacent non-malignant tissues were stained with a unique panel of monoclonal antibodies which recognize HLA class I APM components. The staining patterns of the malignant tumors were compared to those of the autologous non-malignant tissues. To assess the functional significance of changes in HLA class I APM component expression in HCC tumors, the results of immunohistochemical staining were correlated with the extent of CD8+ cytotoxic T-lymphocyte infiltrate, quantified with a computer-aided image analysis system. In all the HCC tumors, malignant hepatocytes expressed high levels of HLA class I APM components. In contrast these molecules were not detected in normal hepatocytes, although they displayed a low expression in some apparently normal hepatocytes adjacent to the HCC tumor. The HLA class I APM component up-regulation in HCC was associated with the extent of CD8+ T cell infiltrate, although this association did not reach the level of statistical significance. Our results corroborate the information in the literature about the lack of HLA class I antigen expression in hepatocytes. Furthermore our study shows for the first time that APM components are also not detectable in normal hepatocytes. Lastly our study shows that HLA class I APM component up-regulation is very frequent in HCC. Its association with T-cell infiltrate, although not statistically significant, is compatible with the possibility that HCC cells are recognized by CD8+ T lymphocytes. If so, HCC should represent an attractive target to apply T cell-based immunotherapy.

ROLE OF ADAM17 IN TUMOR INVASION AND METASTASIS OF A MELANOMA CELL LINE IN MURINE AND ZEBRAFISH MODELS


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Background: Identification of proteins involved in tumor growth and metastasis is a crucial step in designing new potential therapeutic strategies. One of such molecules is ADAM17, a membrane metalloproteinase, which regulates various processes such as cell proliferation, adhesion and the immune response via ectodomain shedding of numerous proteins: cytokines, growth factors and receptors. Overexpression of ADAM17 is observed in many types of neoplasms and is correlated with poor patient prognosis.
Methods: To further understand the role played by ADAM17 in melanoma, we have silenced ADAM17 expression in mouse skin melanoma cells (B16F10) using a lentiviral vector encoding ADAM17 shRNA. Then, we evaluated the influence of diminished ADAM17 expression on tumor growth and metastatic potential in zebrafish and murine models. Transplantation of cancer cells into zebrafish embryos enables observing tumor vasculature remodeling and cancer cell invasion. In murine model, tumor growth and metastatic potential of the cells were monitored after intradermal injection, as well as the ability of injected intravenously cells to create lesions in the lungs.

Results: In both models, silencing of ADAM17 expression in tumor cells inhibits their invasive and metastatic potential as well as tumor induced angiogenesis. In mouse model the tumor growth was also significantly diminished, and the number of lesions in lungs was significantly lower in intravenous cell injection model.

Conclusion: These results collectively suggest that ADAM17 may play a role in tumor growth and metastasis, making the molecule a promising target for anticancer therapy.