The Hellenic Medical Society UK

The Papanikolaou Prize 2018

The Finalists

Dr Myria Galazi

Title: ***ErbB activation and heterodimerisation is responsible for resistance upon PI3K-mTOR inhibition in metastatic prostate cancer.***

My hypothesis is that resistance to PI3K-AKT-mTOR targeting in metastatic prostate cancer involves ErbB activation and heterodimerisation. Current clinical trials are investigating the use of PI3K-AKT-mTOR inhibitors in metastatic castration-resistant prostate cancer (CRPC). 50-70% of metastatic CRPC patients have genomic aberrations of the PI3K pathway. Upregulation of HER3 was previously suggested to be an important resistance mechanism. Within the context of this project I have applied biophysical techniques to quantify protein-protein interactions i.e fluorescence lifetime imaging microscopy (FLIM), a gold-standard technique for measuring Forster resonance energy transfer (FRET). This was used to evaluate HER3 heterodimerisation in prostate cancer cells and mouse xenograft tissue, alongside biochemical methods to demonstrate changes in ErbB expression in response to PI3K-AKT-mTOR inhibition. In addition, I used this technology in cell line and patient-derived exosomes. My results demonstrate differential ErbB upregulation *in vitro* in response to PI3K-mTOR inhibition, depending on PTEN status. Concomitant upregulation of either AR or PSMA is also observed. In PTEN WT prostate cancer cells, the upregulation of PSMA is demonstrated to be HER2 dependent and can be inhibited by lapatinib. The clinical implications of my work propose the use of PI3K-AKT-mTOR inhibitors in the metastatic hormone-sensitive setting as well. In addition, tissue and/or exosomal ErbB heterodimerisation, together with the use of clinically available PSMA imaging probes, might prove additional biomarkers in resistance detection and subgroup classification (we show initial PSMA PET imaging analyses upon PI3K-mTOR inhibition *in vivo*).

Dr Yunan Gao. Gene Therapy, Centre of Neuroinflammation and Neurodegeneration, Division of Brain Sciences, Faculty of Medicine, Imperial College London

Title: Functional improvements following AAV gene replacement therapy in models of CDKL5 disorder

CDKL5 disorder is a severe neurodevelopmental disorder caused by mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5) gene. It predominantly affects females that typically present severe epileptic encephalopathy, intellectual disability, autistic features and motor dysfunction. Currently, there is no therapy except anti-epileptic drugs providing poor seizure management. To develop a gene replacement therapy, we initially characterised the CDKL5 isoforms in human brain, neuronal cell lines and primary astrocytes, in which hCDKL5_1 and to a lesser extent hCDKL5_2 isoforms were found ubiquitously expressed. We cloned their coding regions downstream of CBh promoter into ssAAV2 vector genome and produced hightitre rAAV vectors pseudotyped with AAV9, AAV-PHP.B and AAV-DJ capsids. Intrajugular delivery of AAV-PHP.B-GFP in WT mice transduced neurons and astrocytes throughout the brain more efficiently than AAV9; and transduced spinal cord, DRGs, kidney and retina. Cdkl5 KO mice were treated with AAV-PHP.B-hCDKL5_1 via intrajugular injection at age 28-30 days, tested behaviourally 1-2 months post-injection and analysed after 3 months. CDKL5-treated KO mice exhibited significant motor improvements compared to GFP-treated controls. Transgene brain expression was most prominent in CA1 hippocampal neurons and cerebellar Purkinje cells. Correction of PSD95 abnormality was found in cerebellar regions of high transgene expression. AAV-DJ vectors efficiently transduced CDKL5-mutant iPSC-derived neural progenitors and isogenic controls and subsequently differentiated into neurons. hCDKL5_1 expression in CDKL5-mutant neurons improved synaptic contacts whilst hCDKL5_2 ameliorated calcium signalling defect, implying distinct functions of these isoforms in neurons. This study provides the first evidence that AAV-mediated gene therapy can be effective in treating CDKL5 disorder.

Dr George Vassiliou, Reader in Haematological Malignancies at the University of Cambridge and Senior Fellow OF Cancer Research UK.

Title: Prediction of acute myeloid leukaemia risk in healthy individuals

The incidence of acute myeloid leukaemia (AML) increases with age and mortality exceeds 90% when diagnosed after age 65. Most cases arise without any detectable early symptoms and patients usually present with the acute complications of bone marrow failure. The onset of such de novo AML cases is typically preceded by the accumulation of somatic mutations in preleukaemic haematopoietic stem and progenitor cells (HSPCs) that undergo clonal expansion. However, recurrent AML mutations also accumulate in HSPCs during ageing of healthy individuals who do not develop AML, a phenomenon referred to as age-related clonal haematopoiesis (ARCH). Here we use deep sequencing to analyse genes that are recurrently mutated in AML to distinguish between individuals who have a high risk of developing AML and those with benign ARCH. We analysed peripheral blood cells from 95 individuals that were obtained on average 6.3 years before AML diagnosis (pre-AML group), together with 414 unselected age- and gendermatched individuals (control group). Pre-AML cases were distinct from controls and had more mutations per sample, higher variant allele frequencies, indicating greater clonal expansion, and showed enrichment of mutations in specific genes. Genetic parameters were used to derive a model that accurately predicted AML-free survival; this model was validated in an independent cohort of 29 pre-AML cases and 262 controls. Because AML is rare, we also developed an AML predictive model using a large electronic health record database that identified individuals at greater risk. Collectively our findings provide proof-of-concept that it is possible to discriminate ARCH from pre-AML many years before malignant transformation. This could in future enable earlier detection and monitoring, and may help to inform intervention.

Dr Georgios Sotiropoulos, Barts Thorax Centre, Londo, UK and National and Kapodistrian University of Athens, Greece

Title: Chemerin as a novel biomarker in resectable lung cancer

Objectives: Chemerin is an emerging adipocytokine involved inflammation, chemotaxis, thrombosis, fibrinolysis and metabolism. Our aims were to explore circulating chemerin in resectable non-small cell lung cancer (NSCLC),to study its diagnostic potential, to assess its associations with clinicopathological features of NSCLC.

Materials and Methods: In a large case-control study, serum chemerin, insulin resistance and lipid parameters, classic adipocytokines, inflammatory, coagulation, fibrinolysis and tumor biomarkers were determined in 110 consecutive patients with resectable NSCLC and 110 healthy controls matched on age gender and date of blood draw

Results: NSCLC cases exhibited significantly elevated circulating chemerin compared to controls ($p < 0.001$). In NSCLC cases, chemerin was positively associated with Homeostasis model assessment score of insulin resistance (HOMA-IR), fibrinogen, plasminogen activity, tumor and inflammatory biomarkers, adiponectin, number of infiltrated lymph nodes and NSCLC stage. In control participants, circulating chemerin was positively correlated with somatometric, metabolic, lipid, hemostatic and inflammatory biomarkers, and leptin. Serum chemerin was independently associated with NSCLC, above and beyond NSCLC risk. In cases, hemostatic parameters (platelet count and plasminogen activity), HOMA-IR, CYFRA 21-1, creatinine and plant food consumption emerged as independent predictors of circulating chemerin ($p < 0.05$). Serum chemerin greater than 220 μg/L (cut-off point) yielded a sensitivity and a specificity of 63% and 91.8% respectively with a modest discriminative ability (AUC=0.72, 95% C.I. 0.64-0.79) for the diagnosis of NSCLC.

Conclusion: Chemerin may represent a potentially useful biomarker in NSCLC integrating tumor-promoting networks, inflammatory and hemostatic mechanisms, and cancer-related metabolic pathways.

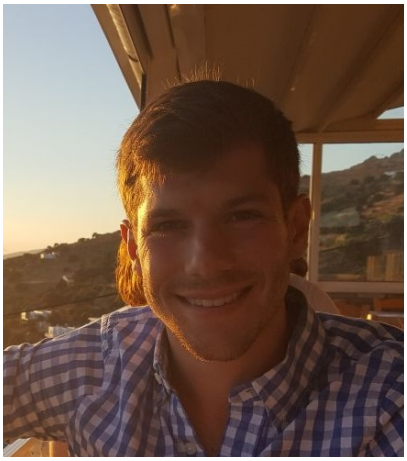
The winner of the Student Scholarship

Dimitrios Karponis BSc (Hons), 5th Year Medical Student, Imperial College London School of Medicine (ICSM) and Institute of Biomaterials and Bioengineering, Tokyo, Japan,

Title: Evaluation of a pneumatic surgical robot with dynamic force feedback

Robot-assisted surgery is limited by the lack of haptic feedback and increased operating times. Force scaling adjusts feedback transmitted to the operator through the use of scaling factors. Herein, we investigate how force scaling affects forces exerted in robotic surgery during simple and complex tasks, using a pneumatic surgical robot, IBIS VI. Secondary objectives were to test the effects of force scaling on operating time, depth of needle insertion and user satisfaction. Two novice males performed simple (modified block transfer) and complex (needle insertion) tasks under four scaling factors: 0.0, 0.5, 1.0 and 2.0. Single-blind experiments were repeated five times, with alternating scaling factors in random order. Increasing the scaling factor from 0.0 to 2.0 reduces forces in block transfer ($p = 0.04$). All feedback conditions reduce forces in needle insertion compared to baseline (0.5: $p < 0.001$, 1.0: $p = 0.001$, 2.0: $p = 0.001$). Time to complete block transfer is shorter for scaling factor 0.5 ($p = 0.02$), but not for 1.0 ($p = 0.05$) or 2.0 ($p = 0.48$), compared to baseline. Depth of needle insertion decreases consistently with incremental scaling factors ($p < 0.001$). Further reductions are observed upon augmenting feedback (0.5-2.0: $p = 0.02$). User satisfaction in block transfer is highest for intermediate scaling factors (0.0-1.0: $p = 0.01$), but no change is observed in needle insertion ($p = 0.99$). Increments in scaling factor reduce forces exerted, particularly in tasks requiring precision. Depth of needle insertion follows a similar pattern, but operating time and user satisfaction are improved by intermediate scaling factors. In summary, dynamic adjustment of force feedback can improve operative outcomes and advance surgical automation.

The Contestants



Epaminondas Markos Valsamis MB BChir, MA(Cantab), MRCS, PGCert Med Ed, Brighton and Sussex University Hospitals NHS Trust

Title: Predictors of mortality in elderly patients with fractures of the odontoid process: can we use established hip fracture scoring systems?

Fractures of the odontoid process (OP) in the elderly are associated with mortality rates akin to hip fractures. Currently there are no scoring systems specific to these fractures, which may identify higher risk patients. Established hip fracture scoring systems may be beneficial as predictors of mortality in these patients. We conducted a retrospective review of patients presenting with OP fracture at two institutions. Data collected included demographics, medical history, residence, mobility status, admission blood tests, abbreviated mental test score, presence of other injuries and neurological deficit. All patients were treated with rigid cervical orthoses. Multivariate analysis was performed to identify predictors of mortality at 30 days and 1 year. Ninety patients (mean age 83) were identified. Mortality was 16.8% at 30 days and 36% at 1 year. Through logistic regression analysis statistically significant independent predictors of 30-day mortality included the presence of neurological deficit (p=0.0010), the Nottingham Hip Fracture Score (NHFS) (p=0.0089), presence of other injuries (p=0.0141) and the presence of other spinal injuries (p=0.0361). Independent predictors for 1-year mortality included the presence of other injuries (p=0.0040) and the NHFS score (p=0.0044). ROC curve analysis demonstrated an optimal cut off value of NHFS of 5 as a predictor of mortality (AUC= 0.694 for 30 days and 0.686 for 1 year mortality). In conclusion, the NHFS may be used to identify high-risk patients with fractures of the OP. This may help to guide multi-disciplinary management and inform patients.

Dr. Maria Pantelidou, Academic Clinical Fellow and Specialist Registrar, Department of Radiology, Cambridge University Hospitals

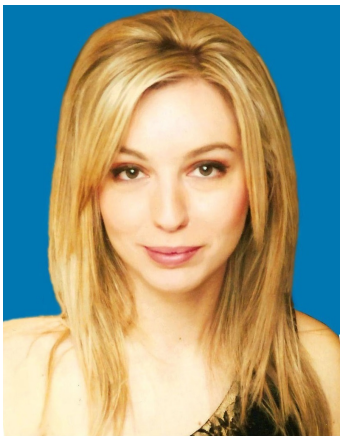
Title: Robotic-assisted partial nephrectomy versus percutaneous radiofrequency ablation for the treatment of small renal cell carcinoma

Purpose: A single center comparison of Radio-frequency ablation (RFA) with Robotic assisted Partial Nephrectomy (RPN) for the treatment of T1 renal cell carcinoma (RCC) in terms of oncological and functional outcomes.

Material and Methods: RPN was performed using the DaVinci robot and RFA under CT-guided radiofrequency electrodes. Data collected included baseline demographics, P.A.D.U.A score and tumor size. Peri-operative complications and oncological outcomes were compared.

Results: In total, 126 cases were audited. Baseline demographics were well-matched but comorbid conditions were more pronounced in RFA. Tumour size was greater in the RPN group (2.88cm vs. 2.11, p= 0.0003) but PADUA score showed no significant difference (7.38 RPN vs. 7.27 RFA). More single kidneys were treated with RFA (15/63 vs. 1/63, p=0.0002). There were no conversions to open surgery and no blood transfusions. Follow-up was longer in RFA due to a recent commencement of RPN (4 vs. 0.5 years, p=<0.0001). Length of stay was significantly shorter in the RFA group (1 vs. 3 days, p= <0.0001). More minor complications were recorded in RPN (10/63 vs. 4/63, p=0.15) but local recurrence was more frequent in RFA (6/63 vs. 1/63, p=0.11). Disease-free survival (DFS) was not significantly different in the two groups (HR ratio=0.91, p=0.92). Tumour size had a significant effect on DFS (HR= 1.7; 95% Cl: 1.1-2.6; p= 0.02).

Conclusion: Both RPN and RFA offer excellent oncological outcomes for the treatment of T1 RCC with low peri-operative morbidity. RFA was associated with less perioperative complications, whereas RPN had a lower local recurrence rate. RFA should be offered alongside RPN for selected cases.



Maria-Angeliki Gkini, MD, MSc, PhD, Specialist Registrar in Dermatology Barts Health NHS Trust

Title: Are dermatologists at risk of major complaints and being stalked?

Patients with delusional infestation (DI) usually seek help from dermatologists and deny firmly referral to psychiatrists. Psychiatrists and related healthcare staff are at risk of complaints, abuse and being stalked, but so are other specialties. In a survey of cosmetic surgeons in Australasia, 20% reported having been harassed by patients. No relevant data are available for dermatologists.

Objectives of our study were to assess the number of dermatologists who treat patients with DI and their approach and to evaluate the volume and nature of complaints, abuse and/or stalking for which dermatologists are the target from this group of patients.

A 10-item questionnaire was sent to dermatologists [members of Psychodermatology UK (n=152) and European Academy of Dermatology and Psychiatry (n=161)] through a Surveymonkey .

44 dermatologists responded. 50% of them referred patients with DI to psychiatry, while 75% admitted feeling stressed when dealing with this category of patients. In total, 48% of physicians, who regularly see patients with DI, had received complaints, were verbally abused or were threatened with defamation. Nobody reported physical abuse or stalking. Internet abuse (trolling) was becoming more of a risk.

This study is the first to evaluate the prevalence and nature of complaints among dermatologists, who manage patients with psycho-cutaneous disease. Our data indicate that managing such patients could invoke significant risks to dermatologists' personal and professional wellbeing. A multidisciplinary approach through a psychodermatology clinic should be encourage for both the patient and the clinician.

Dr Konstantinos C. Fragkos, Clinical Fellow in Gastroenterology, GI Services, University College London Hospitals NHS Foundation Trust, London

Title: Home Parenteral Nutrition in Advanced Cancer

Background: Home parenteral nutrition (HPN) in advanced cancer patients remains controversial in the UK. We explored many aspects of this treatment with original research of primary and secondary data.

Results: 1. Systematic review: Eighteen studies met inclusion criteria. Overall survival was 3.8±1.4 months. Variation in clinical practice exists between countries. A cultural change and education of professionals is required to ensure early access to HPN for appropriate patients. 2. Retrospective cohort (107 patients, UK largest): Main indications were bowel obstruction (74.3%) and high output ostomies (14.3%). Cancer cachexia was present in 87.1% of patients. Performance status, prognostic scoring and HPN requirements predicted survival in Cox regression. Most patients passed away in their homes or hospice (77.9%). 3. Nomograms: Based on the Cox regression, patients who score over 150 units in the 3-month and over 100 units in the 12-month nomograms, had less than 20% survival probability, respectively. Internal validation confirmed nomogram results. 4. Readmissions: Hospital readmissions reduce quality of life in this cohort. Whilst the median number of readmissions was three, the median percentage of readmission days to overall survival was 19%. Readmission reasons were mainly oncology-related (over 70%) versus HPN-related. 5. Standard bags: The use of standard (instead of bespoke) HPN bags may offer time and costs savings in this sensitive cohort of patients. Comparisons of the discharge HPN scripts with 29 standard bags were conducted. Standard bags could not be safely applied to this cohort, however, may be applicable to a sub-set based on calories and electrolytes requirements.

Dr Savvas Vlachos, The Department of Intensive Care Medicine, Guys and St Thomas Hospital, London, UK

Title: The Utility of ICU Readmission as a Quality Indicator and the Effect of Selection

Objectives: Intensive care readmission rates are used to signal quality, yet it is unclear whether they represent poor quality in the transition of care from the ICU to the ward, patient factors, or differences in survival of the initial admission. This study aims to measure the selection effect of surviving the initial ICU admission on readmission rates.

Design: Retrospective cohort study of adult patients admitted to ICUs participating in the Case Mix Program database from the Intensive Care National Audit Research Centre. The study includes 262 ICUs in the United Kingdom. The study includes 682,975 patients admitted to ICUs between 2010 and 2014.

Measurements and Main Results: The study includes 682,975 patients admitted to ICUs in the United Kingdom. There were 591,710 patients discharged alive, of which 9,093 (1.53%) were readmitted within the first 2 days of ICU discharge. Post-ICU admission hospital mortality and ICU readmission were poorly correlated ($r = 0.130$). The addition of a selection model resulted in a weaker correlation ($r = 0.082$).

Conclusions: ICU readmission performed poorly as a performance metric. The selection process by which only patients who survive their index admission are eligible for readmission has a significant effect on ICU readmission rankings, particularly the higher ranked ICUs. Failure to consider this selection bias gives misleading signals about ICU performance and leads to faulty design of incentive schemes.

Dr Andreas Panagiotopoulos, Institute of Orthopaedics and Musculoskeletal Science, University College London and the Royal National Orthopaedic Hospital, Stanmore, London, UK

Title: Damage Patterns at the Head-Stem Taper Junction Helps Understand the Mechanisms of Material Loss.

BACKGROUND:

Total hip replacement is a very common operation in the NHS. Material loss at the taper junction of metal-on-metal total hip arthroplasties has been implicated in their early failure. The mechanisms of material loss are not fully understood; analysis of the patterns of damage at the taper can help us better understand why material loss occurs at this junction.

METHODS:

We mapped the patterns of material loss in a series of 155 metal-on-metal total hip arthroplasties received at our center by scanning the taper surface using a roundness-measuring machine. We examined these material loss maps to develop a 5-tier classification system based on visual differences between different patterns. We correlated these patterns to surgical, implant, and patient factors known to be important for head-stem taper damage.

RESULTS:

We found that 63 implants had "minimal damage" at the taper (material loss <1 mm3), and the remaining 92 implants could be categorized by 4 distinct patterns of taper material loss. We found that (1) head diameter and (2) time to revision were key significant variables separating the groups.

CONCLUSION:

These material loss maps allow us to suggest different mechanisms that dominate the cause of the material loss in each pattern: (1) corrosion, (2) mechanically assisted corrosion, or (3) intraoperative damage or poor size tolerances leading to toggling of trunnion in taper.