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The London Pancreas Workshop 2020

The London Pancreas Workshop 2020

A forum for state-of-the-art clinical and basic research in pancreatic cancer

Friday 11th September 2020 – Online

Programme

0930-1045: Diagnostics for pancreatic cancer

Chair: Prof Nick Lemoine & Prof Claude Chelala, London

0930-0945 ADEPTS & EDRA	Stephen Pereira, UCL, London
0945-1000 UK- EDI: Detecting pancreatic cancer with DM	Eithne Costello-Goldring, Liverpool
1000-1015 UroPanc	Tatjana Crnogorac-Jurcevic, QMUL, London
1015-1030 Co-morbidities and pancreatic cancer	Dayem Ullah, QMUL, London

1030-1115: Q&A and Breakout session

1115-1230: Clinical trials

Chair: Prof Juan Valle, Manchester and Dr Pippa Corrie, Cambridge

1115-1130 Precision-Panc	David Chang, Glasgow
1130-1145 PanCO	Paul Ross, GSTT, London
1145-1200 Clinical trials in the USA and Canada	Fieke Froeling, CSHL, USA
1200-1215 STARPAC	Hemant Kocher, London

1215-1300: Q&A and Breakout session

1300-1400: Abstract presentations

1400-1500: Targeting pancreatic cancer: preclinical work

Chair: Prof Richard Grose, London

1400-1415 MicroRNA-mRNA interactions controlled by TGF-beta	Leandro Castellano, Brighton
1415-1430 FAK promotes stromal PD-L2 expression associated with poor survival in pancreatic cancer	Alan Serrels, Edinburgh
1430-1445 The roles of autophagy in pancreatic cancer	Kevin Ryan, Glasgow

1445-1530: Q&A and Breakout session

1530-1630: Paget Lecture

Chair: Prof Hemant Kocher, London

1530-1545 Introduction

1545-1630 Paget Lecture: Prof Mariano Barbacid, CNIO, Spain

1630-1700: Q&A and Breakout session

Organisers: Prof Nick Lemoine & Prof Hemant Kocher

Contact: Elen McCabe; e.mccabe@qmul.ac.uk

Web: https://www.londonpancreasworkshop.org.uk/

Barts Health NHS
NHS Trust

Barts Cancer Institute
Queen Mary University of London

1.

ADEPTS (Accelerated Diagnosis of neuroEndocrine and Pancreatic TumourS) and EDRA (Early Diagnosis Research Alliance)

Stephen Pereira [1], Julia Hippisley-Cox [2], John Timms [3], Justin Hsuan [3], Kito Fusai [3], Norman Williams [3], Eithne Costello [4], Bill Greenhalf [4], Chiara Braconi [5], Melody Ni [6], Robert Van Der Meer [7], Chris Macdonald [8] on behalf of the Early Diagnosis Research Alliance

[1] University College London
[2] U. Oxford
[3] UCL
[4] U. Liverpool
[5] U. Glasgow
[6] Imperial
[7] U. Strathclyde
[8] Pancreatic Cancer, UK

Resume: Professor of Hepatology & Gastroenterology at UCL and Honorary Consultant Gastroenterologist in PancreaticoBiliary Medicine at University College Hospital and The Royal Free Hospital, with research interests in the pathogenesis, early diagnosis and novel endoscopic treatments of biliary tract and pancreatic cancer, and benign conditions including primary sclerosing cholangitis, autoimmune pancreatitis and cystic tumours of the pancreas.

Keywords: Pancreatic cancer; neuroendocrine tumours, biomarkers

Abstract: Pancreatic neuroendocrine tumours (PNETs) and pancreatic adenocarcinoma (PDAC) are often diagnosed at an incurable stage when already spread outside the pancreas. If we could detect these tumours at an earlier stage, we could treat them with surgery so that more people would survive these diseases. To deliver early diagnosis for people with these cancers the Early Diagnosis Research Alliance (EDRA) commenced in 2019 and encompasses four complementary work packages: 1) Improve early symptom identification in patients with PNETs and PDAC, using CALIBER (UCL Institute of Health Informatics) and QResearch (U Oxford) resources; 2) Support blood biomarker discovery and validation programmes to develop ultrasensitive combined biomarker panels for early PNETs and PDAC; 3) Develop a large multicentre prospective blood sample resource in patients with non-specific but concerning symptoms (assessed by CDSTs: cancer decision support tools) attending endoscopy, clinics and rapid diagnostic centres; 4) Perform a stakeholder analysis, assess barriers to adoption and health economic studies to support early detection of pancreatic cancers. The EDRA includes the Accelerated Diagnosis of neuroEndocrine and Pancreaticobiliary TumourS (ADEPTS) Study (IRAS Number: 234637, NIHR Portfolio no. 7343). This study is a component of work package 3 and acts as the ethical framework for the national EDRA.

2.

UK–EDI: Detecting Pancreatic Cancer with DM

Lucy Oldfield PhD [1], Rohith Gopala Rao MBChB [1], Claire Jenkinson PhD [1], Anthony Evans PhD [1], Tejpal Purewal MD [2], Eftychia E. Psarelli MSc [1], Usha Menon MD [1,3], John F. Timms PhD [4], Stephen P. Pereira PhD [5], Paula Ghaneh MD [1], William Greenhalf PhD [1], Christopher Halloran MD [1], Eithne Costello PhD [1,]*

[1] Department of Molecular and Clinical Cancer Medicine, University of Liverpool, UK
[2] Department of Diabetes and Endocrinology, Royal Liverpool University Hospital, UK
[3] Institute of Clinical Trials and Methodology, University College London, UK
[4] Women's Cancer, Institute for Women's Health, University College London, UK
[5] Institute for Liver and Digestive Health, University College London, UK

Keywords: pancreatic cancer, biomarker, new-onset diabetes mellitus, early detection, adiponectin, IL-1-Ra

Abstract: General population screening for pancreatic ductal adenocarcinoma (PDAC) is not feasible with current modalities. Screening in high-risk populations, however, is recommended. Individuals with new-onset type 2 diabetes mellitus (NOD) are the largest high-risk group for PDAC. The low incidence of PDAC in NOD means that strategies that enrich for PDAC amongst NOD subjects are required to enable screening. Diabetes mellitus (DM) secondary to pancreatic disease, known as type 3c DM (T3cDM), is frequently associated with PDAC, although it is commonly misdiagnosed as type 2 diabetes (T2DM).

Using mass spectrometry- and immunoassay-based methodologies in a multi-stage analysis of independent retrospective and prospective sample sets (n=443 samples), the blood levels of 264 proteins were considered, using Ingenuity Pathway Analysis, literature review and targeting training and validation, for ability to distinguish T2DM from T3cDM. In total 30 candidate biomarkers were evaluated yielding twelve blood proteins with statistically significant differences in levels between PDAC-DM and the more common, T2DM (both longstanding and NOD). Amongst the potential biomarkers with the best performance, the combination of adiponectin and interleukin-1 receptor antagonist (IL-1Ra) showed strong diagnostic potential, achieving an AUC of 0.91 (95% CI: 0.84-0.99) for the distinction of T3cDM from T2DM. Adiponectin and IL-1Ra warrant further consideration for use in screening for PDAC in individuals newly-diagnosed with T2DM.

Relevant to this, in the United Kingdom, Cancer Research UK are funding the UK Early Detection Initiative (UK-EDI) to recruit 2,500 individuals aged >50 years who were diagnosed with new-onset diabetes mellitus (N0D) in the previous six months (UK-NOD). The UK-NOD cohort is designed to recruit from both primary and secondary care centres, and to collect questionnaire and clinical data, alongside longitudinal biosamples over three years. Data and biospecimens will be made available for research on early detection of PDAC, including validation of existing biomarkers that have shown promise for early detection as well as supporting new discovery programs.

3.

EARLY DETECTION OF PANCREATIC ADENOCARCINOMA IN 'AT-RISK' POPULATIONS USING A BIOMARKER PANEL IN URINE (UROPANC)

Tatjana Crnogorac-Jurcevic [1], Silvana Debernardi [2], Daria Jach [2], Greta Brezgyte [2], Alexander Ney [3], Stephen P. Pereira [3], William Greenhalf [4], Patrick Wilson [5], Stephen Duffy [6], Oleg Blyuss [7], Melody Zhifang Ni [8]

[1] Centre for Cancer Biomarkers and Biotherapeutics, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom
[2] Centre for Cancer Biomarkers and Biotherapeutics, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom
[3] Institute for Liver and Digestive Health, University College London, London, United Kingdom
[4] Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, United Kingdom
[5] Gastrointestinal and Liver Services, The Royal London Hospital, London, United Kingdom
[6] Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom
[7] School of Physics, Astronomy and Mathematics, University of Hertfordshire, Hatfield, United Kingdom
[8] Faculty of Medicine, Department of Surgery & Cancer, Imperial College London, London, United Kingdom

Resume: Tatjana Crnogorac-Jurcevic is a Professor of Molecular Pathology and Biomarkers at Barts Cancer Institute, Queen Mary University of London. She obtained the MBBS degree and completed an MD thesis at the Medical Faculty, University of Zagreb in Croatia, and her PhD at the Imperial College School of Medicine in London. Her postdoctoral training

includes molecular biology at CNRS in Toulouse, France and molecular oncology at CRUK laboratory at Hammersmith Hospital, London. She joined Barts Cancer Institute in November 2004, where she heads Pancreatic Biomarker group. Her research focuses on molecular pathology of pancreatic ductal adenocarcinoma with the aim to develop biomarkers for early, non-invasive detection of this malignancy in urine.

Keywords: pancreatic cancer, urine, biomarkers

Abstract: We have previously described the urinary biomarker panel comprising LYVE1, REG1B and TFF1 that showed promise for earlier detection of pancreatic ductal adenocarcinoma (PDAC) (1). We have also developed a logistic regression algorithm based on these three biomarkers, urine creatinine and age, PancRISK, that enables stratification of patients into the ones that have' normal' or 'elevated' risk of developing PDAC (2). The biomarker panel and the affiliated PancRISK score were recently successfully validated on app 600 retrospective urine samples. We also assessed the daily variation and stability of our three biomarkers and explored the complementarity of the panel with CA19-9 (unpublished data), currently the most commonly used biomarker for PDAC (3).

A prospective clinical study, UroPanc (http://www.pcrf.org.uk/pages/uropanc-clinical-study.html), which is currently under way will evaluate this urinary panel, without or in combination with CA19-9 in the urine samples collected from patients at risk at developing PDAC. We will test the ability of the PancRISK score to triage which patients need further clinical workup, thus enabling risk stratification and precision surveillance for pancreatic cancer.

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4.

COVID-19 in patients with hepatobiliary and pancreatic diseases in East London: a single-centre cohort study

Abu Dayem Ullah [1], Hemant Kocher [2], Claude Chelala [3]

[1] UKRI/Rutherford Research Fellow, Barts Cancer Institute, QMUL
[2] Professor of Liver and Pancreas Surgery, Barts Cancer Institute, QMUL
[3] Professor of Bioinformatics, Barts Cancer Institute, QMUL

Resume: Dr Ullah is a current recipient of UKRI/Rutherford Research Fellowship to study epidemiology of pancreatic cancer in East London using longitudinal electronic health records data. He has also developed data and bioinformatics platform for several cancer-specific (national and local) tissue banks including Pancreatic Cancer Research Fund Tissue Bank.

Keywords: COVID-19, hepatobiliary and pancreatic disease, demographic, comorbidity, lifestyle, medication, complication

Abstract: The impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on patients with pre-existing hepatobiliary and pancreatic (HPB) conditions is not clearly understood. The study aimed to analyse the course of COVID-19 in patients with these conditions, living in a diverse multi-ethnic community of East London in the UK. The study used linked secondary and primary care electronic health records from the Barts Health NHS Trust and East London General Practices to extract clinical history of study cohort - patients diagnosed or reported with HPB diseases in hospitals under the Trust since 2008. In this HPB cohort, the significant risk factors for acquiring SARS-CoV-2 infection seems to be being men, Black ethnic background, presence of additional medical conditions, substance use and history of smoking. Use of antihypertensive and stomach acid regulating medications as well as vitamin D intake were also associated with increased risk of infection. The study also indicated that patients with kidney condition in particular should be carefully managed for any recurrent episode of renal complication to prevent fatality.

5.

Precision medicine for pancreatic cancer in national health care system: The initial Precision-Panc experience

David K. Chang, Susie Cooke, Stephan B. Dreyer, Jon Stobo, Fraser Duthie, Nigel B. Jamieson, Judith Dixon, Christine Wilshire, Nicola Williams, Colin J. McKay, Juan Valle, Andrew V. Biankinthe Precision-Panc Consortium

[1] Wolfson Wohl Cancer Research Centre, Institute of Cancer Sciences, University of Glasgow, Garscube Estate, Switchback Road, Glasgow, G61 1QH, UK
[2] West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, 16 Alexandra Parade, Glasgow G31 2ES, UK
[3] University of Manchester, Division of Cancer Sciences / The Christie NHS Foundation Trust, Wilmslow Road, Manchester, M20 4BX, UK
[4] Institute of Cancer Sciences, Garscube Estate, Glasgow, G61 1BD, UK
[5] CRUK Clinical Trials Unit, Institute of Cancer Sciences, University of Glasgow, Glasgow, UK
[6] Laboratory Genetics, NHS Greater Glasgow and Clyde, Queen Elizabeth University Hospital Campus, Govan Road, Glasgow, G51 4TF

Resume: Dr David Chang is a Reader in Surgery at University of Glasgow. His research focus on the development and implementation of novel therapeutic strategies for pancreatic cancer particularly around DNA-damage response deficiency, by utilising molecular biomarkers of therapeutic response. Dr Chang undertook his pancreatic surgical fellowship, PhD, and post-doctoral training in Australia. He was recruited to University of Glasgow in 2013, as part of an initiative to implement precision medicine in Scotland and the UK. He co-leads Precision-Panc, a Cancer Research UK precision medicine programme to deliver personalised cancer care for pancreatic cancer, and is the overall translational lead. Dr Chang is also involved in the Precision Promise, a Pancreatic Cancer Action Network (USA) precision medicine initiative. He also contributes to ICGC-ARGO, aiming to shape the future of the next generation cancer genomic projects to ultimately realise the goals and promises of precision medicine. Clinically Dr Chang is a Consultant Pancreatic Surgeon at the West of Scotland Pancreatic Unit in Glasgow Royal Infirmary, a tertiary pancreatic referral centre for the West of Scotland. As a surgeon scientist, he aims to shorten the distance between the bench and the clinic to ensure meaningful and seamless translation.

Keywords: Pancreatic cancer, platform trials, therapeutic development, next generation sequencing

Abstract: A major challenge inherent to lower incidence cancer types (ranking 5th and lower) is that to make significant advances a network approach is required to co-ordinate research, generate greater clinical capacity and recruit sufficient patients. This is particularly the case for pancreatic cancer which although being the tenth in incidence, is the third, and soon to be the second leading cause of cancer death. Our increasing appreciation for the molecular diversity of cancer further exemplifies the need for a networked platform approach. To address this, we established Precision-Panc in the UK. Precision-Panc is a synergistic and dynamic therapeutic development platform aligning "discovery", "pre-clinical" and "clinical" therapeutic development to form a continuous loop of discovery, learning, refinement, and implementation through efficient forward and backward translation. In this presentation, the initial experience of Precision-Panc will be presented, including the rationale and the design of the

genomic assays. The early progress of initial suites of clinical trials will also be presented.

6.

PanCO: Updated Results of an Open-Label, Single-Arm Pilot Study of OncoSil P-32 Microparticles in Combination with Standard-of-Care (SoC) Gemcitabine + Nab-Paclitaxel or FOLFIRINOX Chemotherapy in Unresectable Locally Advanced Pancreatic Cancer (uLAPC)

Paul Ross [1], Alain Hendlisz [2], Thankamma Ajithkumar [3], Chinenye Iwuji [4], Marion Harris [5], Daniel Croagh [5], Morteza Aghmesheh [6], Adnan Nagrial [7], Nam Nguyen [8], Mehrdad Nikfarjam [9], Nicole Wilson [10], Daniel Kenny [10], David Turner [11], Harpreet S. Wasan [12]

[1] Guy's & St Thomas' NHS Foundation Trust, London, UK
[2] Institut Jules Bordet Universite Libre de Bruxelles, Brussels, Belgium
[3] Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[4] University Hospitals of Leicester NHS Trust, Leicester, UK
[5] Monash Health, Melbourne, Australia
[6] Southern Medical Day Care Centre, Wollongong, Australia
[7] Westmead Hospital, Sydney, Australia
[8] Royal Adelaide Hospital, Adelaide, Australia
[9] Austin Health, Melbourne, Australia
[10] OncoSil Medical Ltd., Sydney, Australia
[11] Adjuvantyx Ltd, Sevenoaks, UK
[12] Imperial College Healthcare NHS Trust, London, UK

Background: uLAPC has a poor prognosis. Phosphorus-32 (P-32) microparticles is a brachytherapy device implanting a predetermined dose of beta-radiation-emitting P-32 into uLAPC via endoscopic-ultrasound (EUS) guidance. Updated results of a pilot study of P-32 microparticles combined with SoC chemotherapy in uLAPC are presented.

Methods: Patients received gemcitabine+nab-paclitaxel or FOLFIRINOX chemotherapy. P-32 microparticles (OncoSil™; OncoSil Medical) implantation was planned at weeks 4-5. P-32 activity was calculated from patients' tumour volume (TV) to deliver 100Gy absorbed dose. Primary endpoint was safety/tolerability (CTCAEv4.0). Response was assessed using RECIST 1.1.

Results: 50 patients were enrolled (Intention-to-Treat [ITT] population); 42 were implanted with OncoSil™ (Per-Protocol [PP] population); 40 received gemcitabine+nab-paclitaxel, 10 FOLFIRINOX (PP: 34/8, respectively). Median age: 65 years; median longest lesion diameter: 4.5cm (range 2.6-7.1). Median follow-up: 16.1 months. 988 AEs were reported (PP); 148 were Grade $\geq$3 involving 81% of patients. No serious device- or radiation-related toxicities were reported. PP Local Disease Control Rate at Week 16 was 90.5% (95%CI: 77.4-97.3%; $p<0.0001$); Overall Response Rate (ORR) was 31%. Median maximal TV change was -52%. Total lesion glycolysis by FDG-PET showed a median reduction of -65% ($p=0.0010$) at week 12. Median maximum reduction in CA19-9 (baseline >35U/mL) was -80.8% ($p<0.0001$). Ten patients (23.8%) underwent surgical resection; 8 had R0 margins. Median Overall Survival PP: 16.0 months (95% CI: 11.1-non-calculable); ITT: 15.5 months (95%CI: 11.3-non-calculable).

Conclusion(s):

EUS-guided P-32 implantation is feasible, with an acceptable safety profile in combination with first-line SoC chemotherapy for uLAPC. Encouraging clinical outcomes were observed, particularly tumour response, surgical resection and survival.

7.

Organoid Personalized Therapeutics and the Pancreatic Adenocarcinoma Signature Stratification for treatment (PASS) – 01 trial

Fieke E.M. Froeling [1,2], Dennis Plenker [1], Grainne O'Kane [3,4], Andrew J. Aguirre [5], Brian M. Wolpin [5], Daniel A. Laheru [6], M Wasif Saif [7], Kenneth H. Yu [8], Sandra Fischer [4], Steven Gallinger [3,4], Jennifer J. Knox [3,4], Elizabeth M. Jaffee [6,9], David A. Tuveson [1]

[1] Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA
[2] Edinburgh Cancer Centre, NHS Lothian, Edinburgh, Scotland, UK
[3] Ontario Institute for Cancer Research, Toronto, Ontario, Canada
[4] Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada
[5] Dana-Farber Cancer Institute, Broad Institute, Boston, Massachusetts, USA
[6] Department of Medical Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[7] Northwell Health Cancer Institute, Feinstein Institutes of Research and Zucker School of Medicine, Lake Success, New York, USA
[8] Memorial Sloan Kettering Cancer Center, New York, NY, USA
[9] The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, Maryland, USA

Keywords: pancreatic cancer, patient-derived organoids, transcriptomic signatures, PASS-01

Background: Patients with advanced pancreatic ductal adenocarcinoma (PDAC) continue to have a dire prognosis and only a minority of patients is fit enough to receive second-line treatment. Using patient-derived organoids (PDOs), we have identified transcriptomic signatures of chemotherapy sensitivity that may be able to stratify patients such that they receive maximal benefit from the currently approved, first-line chemotherapy regimens [1-3]. We will now test this hypothesis in the **P**ancreatic **A**denocarcinoma **S**ignature **S**tratification for treatment (PASS) – 01 trial, which is a multi-institutional randomized phase II trial between FOLFIRINOX (mFFX) and gemcitabine/nab-paclitaxel (GA).

Methods: The overall aim of PASS-01 is to evaluate biomarkers and gene signatures that may predict response to mFFX and GA. The primary objective is to determine the progression free survival (PFS) benefit of mFFX compared to GA. Using 1:1 randomization, 131 evaluable patients with untreated metastatic PDAC will be recruited to provide 80% power to detect a 2-month improvement in PFS with mFFX (one-sided alpha 0.2). Secondary and exploratory objectives include determine the objective response rate, duration of response and overall survival associated with mFFX or GA, whether the chemotherapy sensitivity signature predictions correlate with responders, if PDO transcriptomic profiles parallel those obtained from patient samples, whether GATA6 expression can serve as a biomarker of response [4], the use of serial cell free circulating tumor DNA and circulating tumour cell analysis to identify emerging or de novo resistance and evaluate biomarkers of immune-oncologic sensitivity. The main inclusion and exclusion criteria are similar to major efficacy trials, with the mandatory requirement that a minimum of 4 x 18G good quality tumour core biopsies can be safely obtainable under CT or US guidance. At progression, as per RECIST 1.1 criteria, chemotherapy sensitivity signatures (RNA) and/or PDO pharmacotyping and WGS data will be used where possible to guide second-line therapy in an effort to continually provide the most active therapeutic regimens to each patient. The trial is anticipated to open Q4 2020.

Conclusions: PASS-01 will provide candidate biomarkers and gene signatures that predict response to mFFX and GA, which will be further investigated in a subsequent adaptive, stratified trial.

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8.

STARPAC clinical trial

Hemant M. Kocher [1,2,3,4,], Bristi Basu [5], Fieke EM. Froeling [6], Debashis Sarker [7], Sarah Slater [3], Dominic Carlin [8], Nandita M. deSouza [8], Katja N. De Paepe [8], Michelle R. Goulart [1], Christine Hughes [1], Ahmet Imrali [4], Rhiannon Roberts [4], Maria Pawula [9], Richard Houghton [9], Cheryl Lawrence [2], Yathushan Yogeswaran [2], Kelly Mousa [2], Carike Coetzee [2], Peter Sasieni [10], Aaron Prendergast [2], David J. Propper [2,3,11]*

[1] Centre for Tumour Biology, Barts Cancer Institute- a CRUK Centre of Excellence, Queen Mary University London, London, UK
[2] Centre for Experimental Cancer Medicine, Barts Cancer Institute- a CRUK Centre of Excellence, Queen Mary University of London, London, UK
[3] Barts and the London HPB Centre, The Royal London Hospital, Barts Health NHS Trust, Whitechapel, London, UK
[4] Barts Pancreas Tissue Bank, Barts Cancer Institute- a CRUK Centre of Excellence, Queen Mary University London, London, UK
[5] Department of Oncology, University of Cambridge and Cambridge University Hospitals NHS Foundation Trust - Addenbrooke's Hospital, Cambridge, UK
[6] Department of Surgery and Cancer, Imperial College London – Hammersmith Hospital, London, UK
[7] School of Cancer and Pharmaceutical Sciences, King's College London, Guy's Hospital Campus, London, UK
[8] Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK
[9] PK/Bioanalytics Core Facility, Cancer Research UK Cambridge Institute, University of Cambridge, Li Ka Shing Centre, Robinson Way, Cambridge, UK
[10] Cancer Prevention Trials Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK
[11] Centre for Cancer and Inflammation, Barts Cancer Institute- a CRUK Centre of Excellence, Queen Mary University London, London, UK

Resume: I am a surgeon-scientist. My clinical research interests include tissue banking, clinical trials, innovative surgical techniques, epidemiology, meta-analysis and patient care pathways. My translational research interests include pancreatic cancer stroma and tumour-stroma cross-talk including cell signalling, adhesion, metastasis, invasion leading to innovative therapies and novel biomarkers.

Keywords: Stroma, biomarkers, MTD, OBD, phase 1

Abstract: We have previously shown in murine and other laboratory models that by targeting pancreatic stellate cells with all-trans-retinoic-acid (ATRA) we can render them quiescent and in turn suppress pancreatic ductal adenocarcinoma (PDAC) growth. This led to a phase Ib, dose escalation and expansion, clinical trial for patients with advanced, unresectable PDAC (n=27). ATRA as a stromal-targeting agent was re-purposed in combination with gemcitabine-nab-paclitaxel chemotherapy using a two-step adaptive continual re-assessment method trial design. We determined the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D, primary outcome) as the approved dose of gemcitabine-nab-paclitaxel along-with ATRA (45 mg/m^2 orally, days 1-15 / cycle). ATRA pharmacokinetics were unchanged due to chemotherapy. Median overall survival for RP2D treated evaluable population was a promising 11.7 months (95%CI 8.6-15.7m, n=15). Pharmacodynamic studies including changes in diffusion-weighted (DW)-MRI measured apparent diffusion coefficient after one cycle, and, modulation of cycle-specific serum pentraxin 3 levels indicated stromal modulation. Baseline stromal-specific retinoid transport protein (FABP5, CRABP2) expression may be predicitve of response. Re-purposing ATRA as a stromal-targeting agent with gemcitabine-nab-paclitaxel is safe and tolerable.

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9.

MicroRNA-mRNA interactions controlled by TGF-b

Silvia Ottaviani [1], Adam F. Frampton [1], Monika Chugh [2], Paola Dama [2], Thomas Stiff [2], Qi Liu [2], Salih Bayraktar [2], Jonathan Krell [1], Luca Magnani [1], Sladjana Zagorac [1], Sara Trabulo [3], Nicholas R. Lemoine [4], Justin Stebbing [1], Leandro Castellano [1,2,]*

[1] Department of Surgery and Cancer, Division of Cancer, Imperial College London, Imperial Centre for Translational and Experimental Medicine (ICTEM), London, W12 0NN, UK
[2] University of Sussex, School of life Sciences, John Maynard Smith Building, Falmer, Brighton, BN1 9QG, UK
[3] Molecular Pathology Programme, Spanish National Cancer Research Centre (CNIO), Madrid, 28029, Madrid, Spain
[4] Barts Cancer Institute, Cancer Research UK Centre of Excellence, Queen Mary University of London, London, EC1M 6BQ, UK

E-mail address: lc562@sussex.ac.uk

Abstract: TGF-b signalling has a dual and opposite role during formation and progression of Pancreatic adenocarcinoma (PDAC) and other cancers. During the initial phases of PDAC formation, TGF-b signalling blocks cell proliferation of normal, pancreatic cells to maintain a typical quiescent status. Accordingly, loss of function of members of the TGF-b pathway, at this stage, are important events for the initiation and progression of PDAC. However, when PDAC becomes metastatic, TGF-b signalling further augments the metastatic process. We have identified two

miRNAs, called miR-100 and miR-125b, that are induced by TGF-b in PDAC and are important effectors of the oncogenic TGF-b response. We also developed an experimental and bioinformatic pipeline, that we called RNA Immuno-Precipitation followed by Unbiased Sequence Enrichment (RIP-USE), that was able to detect all the mRNA targets repressed by miR-125b and miR-100, in PDAC. We are currently using CRISPR/CAS9 genome engineering to understand if any of these mRNAs repressed by miR-100 and miR-125b is important for the TGF-b induced tumourigenesis in PDAC. Discovering of such targets can provide new avenues to treat metastatic PDAC.

10.

FAK promotes stromal PD-L2 expression associated with poor survival in pancreatic cancer

Catherine Davidson [1], David Taggart [1], Andrew H. Sims [2], David W. Lonergan [1], Marta Canel [1], Alan Serrels [1,2,]*

[1] Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, Edinburgh Bioquarter, UK
[2] Cancer Research UK Edinburgh Centre, MRC Institute of Genetics & Molecular Medicine, University of Edinburgh, UK

Keywords: FAK, IL6, PD-L2, CD4 T-cell, pancreatic cancer

Abstract: Pancreatic cancer is one of the most lethal cancers with less than 8% of patients surviving for greater than 5 years following diagnosis. With only small incremental improvements in treatment options over the last 40 years there is a continued need to better define the cellular and molecular pathways that contribute to therapy response and patient prognosis. We have identified that the immune checkpoint ligand, Programmed Death Ligand 2 (PD-L2), is associated with poor prognosis, tumour grade, clinical stage and molecular subtype in patients with Pancreatic Ductal Adenocarcinoma (PDAC). PD-L2 is predominantly expressed in the tumour stroma and using an orthotopic murine model of PDAC we identify cancer cell intrinsic Focal Adhesion Kinase (FAK) signalling as a key regulator of PD-L2 stromal expression. FAK inhibitors are currently undergoing clinical testing in combination with anti-PD-1 immune checkpoint inhibitors in patients with advanced pancreatic cancer. Our data supports the continued exploration of FAK as a potential therapeutic target for the treatment of pancreatic cancer through modulation of the immune-suppressive PDAC TME.

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11.

The roles of autophagy in pancreatic cancer

Kevin Ryan

Cancer Research UK Beatson Institute

Keywords: autophagy, pancreatic ductal adenocarcinoma, tumour promotion, tumour suppression, metabolism

Abstract: Macroautophagy (hereafter simply autophagy) is a cellular membrane-trafficking process that carries cargoes to lysosomes for degradation. The process is active in all cells and is highly adaptable. In response to a variety of stimuli, the rates and cargoes of autophagy can be tailored to bring about specific effects. Being as autophagy degrades misfolded proteins and damaged organelles, autophagy helps to maintain cellular integrity and as a result protects against various forms of disease including infection, neurodegenerative diseases and cancer. In the case of cancer, however, it seems that autophagy has different functions at different stages. Several lines of evidence indicate that autophagy is tumour suppressive in preventing cancer and in the early stages of cancer, but then more oncogenic in more established tumours. This indeed appears to be the case in pancreatic ductal adenocarcinoma (PDAC) although this also seems to depend on the genetic lesions that are associated with the development of the disease. One caveat of all current conclusions is that they are drawn from different models at different stages that do not necessarily mirror the human disease. To try to address this issue, we have developed a model of PDAC in which loss of autophagy is addressed in tumours that are initiated in adult tissue by lesions that are known to be frequently associated with disease. Using this model we have been able to analyse the role of autophagy all the way from disease initiation to metastatic disease in a single mouse model. Our findings using this model will be discussed.

12.

TARGETING KRAS SIGNALING IN PANCREATIC CANCER.

Mariano Barbacid

Molecular Oncology Program, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid Spain

Resume: Complete regression of advanced pancreatic ductal adenocarcinomas in genetically engineered mice upon combined inhibition of EGFR and RAF1 signaling pathways.

Keywords: KRAS oncogenes, p53, GEM tumor models, RAF1, EGFR

Abstract: The last two decades have witnessed significant advances in our understanding of the molecular events responsible for the initiation and progression of pancreatic ductal adenocarcinoma (PDAC) (1). Yet, progress in the treatment of this deadly disease has been disappointing. Therapeutic strategies still rely on cytotoxic compounds (2). Molecular studies using tumors from cancer patients as well as from genetically engineered mouse (GEM) tumor models have indicated that most PDACs are initiated by activation of KRAS oncogenes (1). Although most KRAS oncogenes remain undruggable, they signal through two pathways, the MAPK and the PI3K, primarily made up of druggable kinases. Yet, none of the selective inhibitors developed so far against these kinases have proven to be effective in clinical trials. In order to understand the reason for these failures, we have embarked in a series of genetic studies using sophisticated GEM tumor models to evaluate the therapeutic potential of each of these kinases. Whereas ablation of some of these kinases has no effect on tumor progression, other induce unacceptable toxicities. However, recent studies have revealed that combined ablation of EGFR and RAF1 results in complete regression of a significant percentage of advanced PDAC tumors driven by K-*Ras/Trp53* mutations (3). Moreover, this therapeutic strategy is well tolerated. Response to this targeted therapy correlates with transcriptional profiles that resemble those previously observed in human PDACs. In addition, inhibition of EGFR and RAF1 expression effectively blocked tumor progression in nine out of ten independent patient-derived xenograft (PDX) models carrying KRAS and TRP53 mutations (3). EGFR inhibitors have already been approved to treat PDAC tumors in combination with gemcitabine (4). Thus, our results should stimulate the identification of selective RAF1 inhibitors that preserve MAPK activity. Availability of such inhibitors will make it possible to translate these observations to a clinical scenario.

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Invited Delegates Abstracts

13.

Targeting FGFR signalling to disrupt cellular cross-talk in pancreatic cancer

A.S. Coetzee, E.P. Carter, C.I. Milton, J.A. Heward, F. Uluyur, J. Miao, F.K. Mardakheh, Y. Wang, H.M. Kocher, R.P. Grose

Pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis with a 5 year survival rate of less than 5%. PDAC tumours consist of a dense desmoplastic stroma, which limits the effectiveness of chemotherapy. Pancreatic stellate cells (PSCs), which form a key part of this stroma, become activated in response to tumour development. Activated PSCs enter a cross-talk with cancer cells to induce tumour cell proliferation and invasion, leading to metastatic spread. Nuclear fibroblast growth factor receptor 1 (nFGFR1) has been found in PSCs at the invasive edge of PDAC tumours. Inhibition of FGFR1 prevents its nuclear translocation in PSCs, which results in decreased invasion in 3D *in vitro* PDAC models. Nuclear translocation of FGFR1 in PSCs appears to be a vital mechanism that triggers the transcription of key proteins involved in PDAC invasion.

We have used a powerful combination of chromatin immunoprecipitation (ChIP-seq) and mass spectrometry to determine the transcriptional targets of nFGFR1 and subsequent protein flux in PSCs. These techniques have allowed us to dissect the functional consequences of FGFR1 knockdown or inhibition in the PSCs. Candidate drivers of invasion are being validated in state-of-the-art 3D *in vitro* PDAC models. We have extended these functional studies to combination therapy with the clinical agent gemcitabine (targeting cancer cells) and all-trans retinoic acid (ATRA, modulating PSCs), providing translational relevance for our findings. This novel therapeutic strategy is being validated using *in vivo* co-culture xenograft models with specific reference to FGFR1. Effectively disrupting the cross-talk between the tumour and stroma, either alone or in combination with other therapies, could translate to improved therapeutic responses in PDAC patients in the clinic.

*Voted as Top 5 Abstract

14.

Elevated microRNA expression could be diagnostic biomarker for PDAC

Maria Mortoglou [1], Damla Arisan [2], Tiago Ferreira [1], Adele McCormick [1], Pinar Uysal-Onganer [1]

[1] Cancer Research Group, School of Life Sciences, University of Westminster, London W1W 6UW, UK
[2] Institute of Biotechnology, Gebze Technical University, Gebze, 41400 Kocaeli, Turkey

Background: Pancreatic ductal adenocarcinoma (PDAC) is the most common type of PCa with 2-9% 5-year survival rate. PDAC is the most lethal malignancy worldwide and hence the molecular mechanisms, which are linked to the aggressive features, should be further examined to develop better diagnostic, prognostic and therapeutic agents. microRNAs (miRs) are small non-coding RNAs (18–24 nucleotides), that can control cell growth, proliferation, apoptosis, differentiation, metastasis and angiogenesis. Furthermore, several studies have suggested that miRs could be utilized for the discrimination between PDAC and non-malignant lesions and thus the evaluation of them as novel diagnostic biomarkers is crucial for PDAC. Aim of this study is to examine miRs and their role in PDAC progression and metastasis. **Methodology:** miR expression levels of paired normal and malignant pancreatic tissue samples from ten PDAC patients were analyzed by using their RNA-sequencing data. Then, their cellular and molecular functions as well as the associated molecular signaling pathways with the target genes were identified. The most significant miRs were selected based on their fold changes (FC) and p-value ($p<0.05$). Data analysis was performed by using SPSS software and specifically paired t-tests between normal and malignant patient tissue samples. Moreover, expression levels of the most significantly altered miRs were further analysed by using Panc-1, CAPAN-2, MiaPaca-2 and Panc10.05 PDAC cell lines. **Results:** 31 upregulated and 13 downregulated miRs were reported, approximately 3000 target genes were detected to be modulated by abnormally expressed miRs, while the bioinformatic analysis disseminated that the dysregulated miRNAs were correlated to numerous signaling pathways such as EGF-Jak-STAT, KRAS/NRAS and PI3K. The PDAC cell line-based analysis confirmed the aberrant miR expression. **Conclusions:** Taking the data together, we suggest that specific miR signature profiles could prove useful for PDAC in order to determine patient diagnosis and prognosis. miRs modulate expression of other miRs and/or genes, which are interrelated with metastasis in human neoplasms. In addition, both form mutual feedback circuits, thereby increasing the connectivity and complexity of the regulatory network. Targeting this network will facilitate not only the development and advancement of miR-based clinical applications, but also will illuminate the gap between genotypic and phenotypic features of PDAC. Conclusively, the findings of this research could be the cornerstone of a pioneer precision medicine era of research.

15.

Molecular and Metabolic subtypes for Pancreatic Ductal Adenocarcinoma Classification

Pilar Espiau-Romera [1], Patricia Sancho [1]

[1] IIS Aragon, Hospital Universitario Miguel Servet, Zaragoza, 50009, Spain

Pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, is an extremely lethal disease due to late diagnosis, aggressiveness and lack of effective therapies. Considering its intrinsic heterogeneity, patient stratification models based on transcriptomic and genomic signatures, with partially overlapping subgroups, have been established. Besides molecular alterations, PDAC tumours show a strong desmoplastic response, resulting in profound metabolic reprogramming involving increased glucose and amino acid consumption and lipid scavenging and biosynthesis. Interestingly, recent works have also revealed the existence of metabolic subtypes with differential prognosis within PDAC, which correlated to defined molecular subclasses in patients: lipogenic subtype correlated with a classical/progenitor signature, while glycolytic tumours associated with the highly aggressive basal/squamous profile. Our bioinformatic analyses have demonstrated that the representative genes of each metabolic subtype are up-regulated in PDAC samples and predict patient survival. This suggests a relationship between the genetic signature, metabolic profile, and aggressiveness of the tumour. Considering all this, definition of metabolic subtypes constitutes a clear opportunity for patient stratification considering tumour functional behaviour independently of their mutational background.

*Voted as Top 5 Abstract

16.

DIFFERENTIAL ACTIVATION PATTERNS OF RECEPTOR TYROSINE KINASES: NOVEL POTENTIAL TARGETS IN THE PANCREATIC CANCER STEM CELL NICHE

Beatriz Parejo-Alonso [1], Patricia Sancho [1]

[1] IIS Aragon, Hospital Universitario Miguel Servet, Zaragoza, 50009, Spain

Pancreatic Ductal Adenocarcinoma (PDAC) is the most common form of pancreatic cancer and an extremely aggressive disease. This aggressiveness is partially on account of PDAC intrinsic heterogeneity with distinct tumour cells hierarchically organized. The so-called cancer stem cells (CSCs) are at the apex of this hierarchy and give rise to tumour bulk differentiated cells (non-CSCs). On the other hand, CSCs harbour tumour-initiating properties and govern metastases onset, resistance to chemotherapy and tumour relapse after treatment. Since these cells represent the main source for treatment failure, patients' long-term survival could eventually be improved by combining chemotherapy with therapies targeting CSCs. Receptor tyrosine kinases (RTKs) are commonly overexpressed and/or hyperactivated in the majority of human cancers, making them excellent candidates for targeted therapy. In order to identify signalling pathways differentially activated in the most aggressive PDAC subpopulations, a series of proteome profiler human phospho-RTK arrays in PDAC patient-derived xenografts were conducted. The widely described CSC markers CD133 and autofluorescence were used to study CSCs *versus* non-CSCs, and metformin-resistant PDAC PDXs as a model for resistance to therapy. We identified several RTKs hyperphosphorylated in different CSC subpopulations, as well as in metformin-resistant cells. These preliminary data provide fundamental information for further drug screening targeting the most aggressive subpopulations in PDAC in order to find an effective treatment for these patients.

*Voted as Top 5 Abstract

17.

Can we screen for pancreatic cancer? Identifying a sub-population of patients at high risk of subsequent diagnosis using machine learning techniques applied to primary care data

Ananya Malhotra, Bernard Rachet, Audrey Bonaventure, Stephen P. Pereira, Laura M. Woods

Abstract:

Objective: To assess whether it is possible to identify a sub-population at higher risk of developing pancreatic cancer using machine learning.

Design: We conducted a retrospective case-control study on individually linked electronic health records collected from primary care linked to cancer registrations. Our cases comprised of 1,139 patients, aged 15-99 years, diagnosed with pancreatic cancer between January 1, 2005 and July 31, 2008. Each case was individually age- sex- and diagnosis time-matched to four non-pancreatic (cancer) controls. Disease, symptoms and prescription codes for the 24 months prior to diagnosis were used to identify the occurrence of 57 individual symptoms. Using a machine learning approach, we trained a logistic regression model on 75% of the data to recognise a combination of atypical symptoms experienced by patients who later develop pancreatic cancer.

Results: Using patients' medical history recorded between 20-24 months before diagnosis we were able to identify 41.3% of the population up to 60 years who were at high-risk of developing pancreatic cancer with 72.5% sensitivity, 59% specificity and 66% AUC. Amongst patients above age 60, 43.2% were similarly identified at higher risk up to 17 months before diagnosis, with 66% sensitivity, 57% specificity and 61% AUC.

Conclusion

A sub-population of patients later diagnosed with pancreatic cancer is detectable up to 20 months before diagnosis, but the specificity is relatively low which would result in a large number of false positive tests. The use of cancer patient controls would have contributed to this, so further work is required to using population-based controls. Nevertheless, the model has the potential to be used alongside a pre-screening (biomarker) test to increase earlier diagnosis. This would result in a greater number of patients surviving this devastating disease.

18.

Can Preoperative Skeletal Muscle Area and Prognostic Nutrition Index Be Predictive For Postoperative Mortality and Morbidity In Patients With Periampullary Region Tumors?

Gizem Kilinc [1], Ismail Sert [1], Korhan Tuncer [1], Orkun Sarioglu [2], Degercan Yesilyurt [1], Cem Karaali [1], Mustafa Emiroglu [1]

[1] University of Health Sciences Izmir Tepecik Training and Research Hospital, Department of General Surgery
[2] University of Health Sciences Izmir Tepecik Training and Research Hospital, Department of Radiology

Abstract

Background: Periampullary region tumors include the tumors arising from pancreatic head, ampulla of Vater, duodenum and distal common bile duct. Pancreaticoduodenectomy (PD) is considered as the curative resection method for the periampullary region tumors. The skeletal muscle area (SMA) is one of the parameters that shows sarcopenia and prognostic nutrition index (PNI) is a parameter that shows patients' nutritional status. Both of them is considered as a predictive parameter for mortality and morbidity in patients that have various type of cancer. In this study we aimed to identify the correlations of preoperative SMA and PNI values with postoperative mortality and morbidity in patients with periampullary region tumors.

Methods: A total of eighty nine patients that underwent PD for periampullary region malignant tumors between January 2010 and January 2020 were retrospectively analyzed. Patients were divided into two groups according to cut off values of SMA and PNI. Differences between these two groups were compared. Also association between patients' comorbidities, ASA scores, serum albumin levels and mortality and morbidity were analyzed. Datas were statistically analyzed by using IBM SPSS Statistics 25.0 package program and $p < 0.05$ value was considered statistically significant .

Results: The mean age was 65.94 (range, 38-86) and 54(60.6 %) of the patients were male. In patients with low PNI group mortality and clavien dindo complication score were found significantly higher ($p=0.010$, $p=0.011$) (OR for mortality 0.220, 95% CI 0.065-0.740). SMA was found not associated with postoperative complications in both sex. Factors affecting morbidity were hypertension and diabetes mellitus. ($p=0.035$ and $p=0.045$). Serum albumin level and COPD were the factors that affect the mortality ($p=0.011$ and $p=0.040$)

Conclusion: Although patients have lower SMA cut off value, SMA is not found associated with postoperative mortality and morbidity. HT and DM are risk factors for morbidity and COPD and serum albumin level are associated with high mortality rates. Also, PNI can be considered as a predictive parameter for postoperative mortality in patients that underwent PD for periampullary region tumors.

19.

Duct-to-mucosa Pancreaticojejunostomy with Less Serosal Stitches: A Different Approach to Well-known Problem

İsmail Sert [1,2], Degercan Yesılyurt [1], Cem Karaalı [1], Mustafa Emıroglu [1]

[1] Tepecik Training and Research Hospital, Depertment of General Surgery, Izmir, Turkey
[2] Tepecik Training and Research Hospital, Depertment of HPB Surgery and Transplantation, Izmir, Turkey

Keywords: Postoperative pancreatic fistula, surgical technique, duct to mucosa pancreatiocjejunostomy, less serosal stiches,

Purpose: Clinically relevant Postoperatie Pancreatic Fistula(POPF) is still the most troublesome complication of the pancreatcioduodenectomy(PD). One of the modifiable risk factors for POPF is surgical technique. Here we describe a new approach to overcome this unresolved problem and challanging situations.

Material method: Medical records of consecutive fourty five patients underwent PD by the same general surgeon between Jan 2019 and May 2020 were rectospectively reviewed. Pylorus preserved PD and Duct-to-mucosa PJ with less serosal suture technique is used for all patients. Grade B and C fistulas are accepted as clinically relevant POPF. Only discriptive measures were reported due to lack of control group in this study and main purpose of this sudy is escribe a surgical technique.

Results: Seventeen of the patients were female and median age was 66 years. Number of patients with pancreatic duct size <3 mm was five. Rate of soft pancreas texture was 33%. And the number of the patients underwent vascular or additional organ resection were 6 (13.3%) and 8 (17.7%) ,respectively. Median operation time was 360 minutes.

Clinically releavent POPF was seen in 6 patients (grade B: 4 and grade C: 2) .The most postoperative complication was surgical site infection (40%). There was no POPF related mortality.

Conclusion: Present study suggest that two layer duct to mucosa PD with Less serosal stitches technique is feasiable and has acceptable pancreatic fisula rates. This technique can be used by surgeons who get difficculties with the duct to mucosa anostomosis due to afforementioned causes.

20.

Human and Murine CAR T cells for targeting integrin Alpha V Beta 6 in Pancreatic Ductal Adenocarcinoma

Lauren Cutmore, Nicolas Brown, John F. Marshall

Barts Cancer Institute, Queen Mary University of London

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer. The 5 year survival rate is under 4% and prognosis has not improved in the last 40 years, illustrating the need for new treatments. Chimeric antigen receptor (CAR) T cells have had revolutionary effects in hematological malignancies but show limited success in the treatment of solid tumours. This is primarily due to the immunosuppressive tumour microenvironment and on-target, off tumour toxicity. This highlights the need to identify and target tumour-restricted antigens as well as develop a more realistic immunocompetent mouse model to test the CAR T cells in-vivo.

We have designed and generated a second generation CAR constructs targeting integrin Alpha V Beta 6, and have successfully transduced primary human T cells with the construct using a lentiviral vector. We have seen encouraging anti-tumour cytotoxicity in-vitro and will proceed to test the CAR T cell in-vivo.

We have also generated a second generation murine CAR construct to target integrin Alpha V Beta 6 to be tested in an immunocompetent mouse model which will better recapitulate the immunosuppressive tumour microenvironment present in PDAC tumours This will facilitate testing of combination therapy, as well as lead to better translation into the clinic.

We hope these novel CAR T cells will provide a new treatment option for PDAC patients and the immunocompetent model will allow improved bench to bedside translation.

21.

Engineering the 3D Tumour microenvironment *in vitro* for Drug Discovery using Self-Assembling Peptide Hydrogels

A. Del Rio Hernandez [1], D. Lachowski [1], A. Miller [2,3]

[1] Department of Bioengineering, Imperial College London, South Kensington Campus, London, SW7 2AZ
[2] Manchester Institute of Biotechnology, University of Manchester, Manchester, UK
[3] Manchester BIOGEL, Alderley Park, Alderley Edge, Cheshire, UK

The communication of cells with their environment is vital to understand the intracellular processes, and this research area has been very dynamic in cell and cancer biology. Nowadays, available matrices to study those interactions have tuneable mechanical properties. However, the extracellular matrix (ECM) in tissues of different organs and cellular settings has very different chemical properties, such as ionic strength, charge, pH and ECM ligands. Here we will demonstrate how peptide hydrogel substrates (PeptiGels®, *Manchester BIOGEL*) offers both the mechanical and biochemical tuneability necessary to recreate cancer tissues.

Most solid carcinomas, such as pancreatic ductal adenocarcinoma (PDAC), are characterised by the formation of a large amount of connective or fibrous tissue around the tumour that hampers drug delivery, controls the growth and spread of tumours and regulates their resistance to chemotherapy. This acidic, fibrous tissue affects the behaviour of cancer cells from their ability to proliferate and survive. We have explored the response of Pancreatic Adenocarcinoma Suit-2 cell line cultured on soft (healthy tissue mimicking) and stiff (tumour mimicking) peptide hydrogels with low (6.0) and normal (7.4) pH using immunofluorescent staining. We have demonstrated that cells in the hydrogels with different stiffness and pH identified differences in the cell biology pathway; stiff and acidic (tumour mimicking peptide gels) induce a biomechanical response in the cells resulting in an increased proliferation (Ki67). We have gone onto explore independently the influence of both mechanical and chemical environment on cell activation, survival and growth and are now investigating details of mechanostransduction on signalling pathways.

22.

ON THE DEVELOPMENT OF A BIOINSPIRED, BIOMIMETIC PANCREATIC CANCER MODEL: ENGINEERING A HYBRID SCAFFOLD ASSISTED *IN VITRO* MULTICELLULAR MODEL OF PANCREATIC CANCER

Priyanka Gupta [1], Pedro A. Pérez-Mancera [2], Hemant Kocher [3], Andrew Nisbet [4], Giuseppe Schettino [5,6], Eirini G. Velliou [1]

[1] Bioprocess and Biochemical Engineering Group (BioProChem), Department of Chemical and Process Engineering, University of Surrey, Guildford, United Kingdom
[2] Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, United Kingdom
[3] Centre for Tumour Biology and Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom
[4] Department of Medical Physics and Biomedical Engineering, University College London, London, United Kingdom
[5] Department of Physics, University of Surrey, Guildford, United Kingdom

[6] Medical Radiation Science Group, The National Physical Laboratory, Teddington, United Kingdom

Introduction: With a 5-year survival rate of only 9%, Pancreatic Ductal Adenocarcinoma (PDAC) is the 7th leading cause of cancer related death worldwide[1]. The aggressive nature and high mortality rate of PDAC are attributed to its late diagnosis, heterogeneity in the tumour and the tumour microenvironment and its resistance to currently available treatment methods[2]. An in-depth study of PDAC biology and its resistance to current therapeutic methods requires the development *of biomimetic, niche mimicking in vitro tumour models*. Current research focuses on the development of 3D *in vitro* tumour models to replace 2D culture systems and animal models in order to tide over limitations associated with such systems. 3D *in vitro* models are considered to have better *in vivo* niche mimicking capabilities in comparison to 2D culture systems while mitigating the cost and reproducibility problems associated with animal models. Our lab had previously developed a poly urethane (PU) based 3D a pancreatic cancer model using pancreatic cancer cells wherein we were able to show long term maintenance of the *in vitro* model (> 2 months), feasibility of extracellular matrix (ECM) mimicry through scaffold coating *via* passive absorption, formation of dense cellular masses, secretion of ECM proteins, formation of realistic hypoxic gradients[3,4] and could be used for long term therapeutic assessments[5]. However, as in all tissues, the PDAC tumour microenvironment (TME) is heterogeneous in cellular nature consisting, additionally to cancer cells, of different cell types, e.g., stellate cells and endothelial cells, all contributing to the tumour formation, metastasis as well as its response and resistance to treatment. Thus, recent studies have focused on generating multicellular pancreatic cancer models, which are primarily spheroid based[6,7]. Spheroids are useful 3D models due to their ease of development, ability to allow for fast analysis and studies. However, it is difficult to maintain spheroid cultures for long time without requiring resuspension, the latter inevitably affecting the formed cell-cell and cell-ECM interactions. Additionally, it is also difficult to recapitulate the spatial organisation of the different cell types seen within *in vivo* tumours. The current work reports further advancement to our mono-culture model via the development of a PU scaffold assisted, zonal, multicellular, 3D pancreatic tumour model using pancreatic cancer, stellate and microvascular endothelial cells. We report here the need for specific cellular compartments with tailored ECM composition for the different cells.

Methods: PU scaffolds were prepared using the Thermal Induced Phase Separation (TIPS) method. Absorption based surface modification of the scaffolds enabled coating with ECM proteins (collagen and fibronectin) for enhancement of ECM mimicry[4]. A zonal structure with (i) endothelial and stellate cells on the outer side of the scaffold coated with collagen I and (ii) pancreatic cancer cells in the inner scaffold coated with fibronectin was designed. Various *in situ* assays for monitoring the cell viability, spatial organisation, ECM production were carried out at specific time points throughout the culture period.

Results: We report here for the first time a 3D PU scaffold-based triculture system involving pancreatic cancer, stellate and endothelial cells. Our scaffold enables to engineer a robust biomimetic *in vitro* model for PDAC. Coating of various ECM proteins enhanced cell growth rate within the culture system. Our zonal multicellular PDAC *in vitro* model shows extensive desmoplastic reaction and cellular migration, mimicking key *in vivo* characteristics of pancreatic cancer[8].

Conclusion: Our data show, for the first time, the feasibility of PU scaffolds to support a zonal multicellular pancreatic tumour niche growth along with the possibility of recapitulating desmoplasia. Our developed model is a low cost high throughput tool that can be used for personalized studies and treatment screening of pancreatic cancer.

*Voted as Top 5 Abstract

23.

Role of mitochondrial dynamics in pancreatic cancer stem cells

S. Courtois[2], B. De Luxán-Delgado[1], L. Penin-Peyta[1], A. Royo-García[2], B. Parejo-Alonso[2], P. Sancho[1,2]

[1] Centre for Stem Cells in Cancer & Ageing (Barts Cancer Institute), London, UK
[2] Instituto de Investigación Sanitaria de Aragón (IIS Aragón), Zaragoza, Spain

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest tumors nowadays, partly due to the intrinsic aggressiveness and chemoresistance of resident subpopulations of cancer cells, the Cancer Stem Cells (CSCs). These cells bear stemness-related properties and are responsible for tumor relapse and metastasis, representing a crucial target for long-term successful chemotherapeutic intervention. We have previously shown that CSCs are particularly dependent on mitochondrial metabolism and can be eliminated through targeting of this process. The regulation of mitochondrial dynamics is achieved through the balance between fusion (dependent on *MFN2*) and fission (regulated by *DNM1L*) processes and represent the most basic pathway to control the number and activity of mitochondria. In human PDAC tissues, the genes related to mitochondrial dynamics are overexpressed. Importantly, the expression of *DNM1L* positively correlates with a stemness signature, suggesting a relationship between both processes. In primary cultures from PDAC-derived xenografts (PDXs), we observed by transmission electron microscopy that CSCs ($CD133^+$ cells) bear smaller mitochondria than non-CSCs cells ($CD133^-$ cells), and have a higher DNM1L/MFN2 expression ratio, indicative of higher activation of mitochondrial fission in these cells. Interestingly, treatment with the mitochondrial fission mDivi-1 decreased proliferation and induced dose-dependent apoptosis in primary cultures from different PDXs. Furthermore, the compound greatly reduced $CD133^+$ content and inhibited stemness-related functions, such as self-renewal and clonogenicity. In summary, mitochondrial fission is an essential process for pancreatic CSCs and represents an attractive target for the design of novel combinatory treatments aimed at eliminating cells with high tumorigenic potential.

*Voted as Top 5 Abstract

Author Index

(Numbers refer to abstract number)

* Corresponding author.