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The London Pancreas Workshop 2018

The London Pancreas Workshop 2018

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

Friday 4th May 2018

Charterhouse Square, London UK

Final Programme

0930-1030: Diagnostics for pancreatic cancer

Chairs: Prof Nick Lemoine & Dr Tatjana Crnogorac-Jurcevic, London

0930-0945 Using informatics for diagnostics — Claude Chelala, London

0945-1000 Early diagnostics in secondary care — Steve Pereira, London

1000-1015 Detecting pancreatic cancer in individuals with new-onset diabetes mellitus: why and how? — Eithne Costello-Goldring, Liverpool

1015-1030 Q&A

1030-1100: Tea/Coffee, The Shield

1100-1230: Clinical trials

Chairs: Mr Satyajit Bhattacharya, London and Prof Francisco X. Real, Madrid

1100-1115 NICE guidelines for pancreatic cancer — John Primrose, Southampton

1115-1130 PRECISION-PANC — Andrew Biankin, Glasgow

1130-1145 ESPAC5F: what next — Paula Ghaneh, Liverpool

1145-1200 PRICKLE — Bristi Basu, Cambridge

1200-1215 Adapted physical activity and alternative exercise modalities — Cindy Neuzillet, Paris

1215-1230 Q&A

1230-1400: Lunch, The Shield

1400-1500: Targeting pancreatic cancer: preclinical work

Chairs: Prof Kairbaan Hodivala-Dilke, London and Prof Nuria Malats, Madrid

1400-1415 Drug discovery efforts — Caroline Springer, Manchester

1415-1430 From Xenograft epigenomics to therapeutic opportunities — Remy Nicolle, Paris

1430-1445 Pharmacological targeting of stellate cells for therapeutic gain in pancreatic adenocarcinoma — Corrine Bousquet, Toulouse

1445-1500 Q&A

1500-1530: Tea/Coffee, The Shield

1530-1630: Paget Lecture

Chair: Prof Hemant Kocher, London

1530-1545 Introduction

1545-1630 Paget Lecture: Mapping the neoepitope landscape in human pancreatic cancer — Steven Leach, USA

Organisers: Prof Nick Lemoine & Prof Hemant Kocher

Contact: Miss Elizabeth Shrimpton; e.shrimpton@qmul.ac.uk; 020 7882 3573

Web: bci.qmul.ac.uk/seminars-a-events/london-pancreas-workshop

Barts Health NHS Trust

Invited Speakers'

Barts Cancer Institute
Queen Mary University of London

1.

Data integration for patient benefit

Dayem Ullah, Hemant Kocher, Claude Chelala

Barts Cancer Institute, United Kingdom

Resume: My research interests lie in the area of computational and integrative bioinformatics. Current research projects are focused in data analysis and integration, databases and software development.

Keywords: Pancreatic cancer, data integration;

Abstract: I will present the Pancreatic Expression database (PED), a rich platform for the sharing, mining, integration and analysis of pancreatic cancer data. Its modalities provide researchers with access to a centralised information gateway from which they can access a network of bioinformatic resources to query findings from publicly available, in-house and experimental data generated using samples supplied from the Pancreatic Cancer Research Fund Tissue Bank (PCRFTB). This in silico environment aims to help researchers use pancreatic cancer data to their full potential, irrespective of any bioinformatics barriers. PED was designed to allow data sharing, discoverability and re-usability. This platform is not a bioinformatics silo but rather a niche within the PCRFTB tissue banking ecosystem that offers an unparalleled opportunity to add informative layers of molecular data to existing patient data available from the Bank. Soon, this will create a biobanking ecosystem, one in which patient benefit is core.

References:

Marzec J*, Dayem Ullah AZ*, Gadaleta E, Pirrò S, Lemoine NRL, Kocher H, **Chelala C,** (2018). The Pancreatic Expression Database. **Nucleic Acids Res, in press**

Dayem Ullah, A.Z., R.J. Cutts, M. Ghetia, E. Gadaleta, S.A. Hahn, T. Crnogorac-Jurcevic, N.R. Lemoine, and **C. Chelala,** (2014).The pancreatic expression database: recent extensions and updates. **Nucleic Acids Res**, **42**(Database issue): p. D944-9. https://doi.org/10.1093/nar/gkt959

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Balarajah, V., A. Ambily, A.Z. Dayem Ullah, A. Imrali, T. Dowe, B. Al-Sarireh, M. Abu Hilal, B.R. Davidson, Z. Soonawalla, M. Metcalfe, J.A. Chin Aleong, **C. Chelala,** and H.M. Kocher, (2016).Pancreatic cancer tissue banks: where are we heading? **Future Oncol**, **12**(23): p. 2661-2663. https://doi.org/10.2217/fon-2016-0243

2.

Early diagnostics in secondary care

Stephen Pereira

University College London, United Kingdom

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, as well as the benign conditions primary sclerosing cholangitis and autoimmune pancreatitis.

Keywords: Pancreatic cancer; biomarkers

Abstract: Earlier diagnosis is critical to improving survival in pancreatic ductal adenocarcinoma (PDAC) by making intervention strategies successful. However, positive identification of early tumours is made more challenging by pre-malignant conditions from which cancers arise, but where the transformation rate is low, and many biomarker studies utilising retrospective cohorts in late-stage disease. Biomarker panels which identify early cancers and stratify precursor lesions that need treatment from those that do not would be expectedd to extend life and reduce unnecessary interventions. In recent years, a variety of novel biomarkers from body fluids, including blood, urine, saliva, breath, pancreatic juice and stool, have been reported. With advances in high throughput techniques and “omics” analyses, various circulating biomarkers, such as circulating tumour cells, metabolites, cell-free DNA (cfDNA), noncoding RNA, and exosomes, have been widely studied and show promising diagnostic value. Collaborative large-scale studies are required to test the clinical validity and applicability of potential biomarkers in ‘at-risk’ poulations.

References:

Cohen JD, et al. Detection and localization of surgically resectable cancers with a multi-analyte blood test. Science 2018; 359: 926-30.

Zhang X, et al. Circulating biomarkers for early diagnosis of pancreatic cancer: facts and hopes. Am J Cancer Res 2018; 8: 332-53.

Jimenez-Luna C, et al. Proteomic biomarkers in body fluids associated with pancreatic cancer. Oncotarget 2018; 9: 16573-87.

3.

Detecting pancreatic cancer in individuals with new-onset diabetes mellitus: why and how?

Lucy Oldfield [1], Rohith Rao [1], Tejpal Purewal [2], William Greenhalf [1], Christopher Halloran [1], Eithne Costello [1]

[1] Department of Molecular and Clinical Cancer Medicine, University of Liverpool, United Kingdom
[2] Department of Diabetes and Endocrinology, Royal Liverpool University Hospital, United Kingdom

Resume: An estimated 200,000 cases of type 2 diabetes mellitus (DM) are diagnosed in the UK each year. In 0.8-1% of cases have DM is secondary to pancreatic cancer (type 3c DM).

Distinguishing new-onset type 3c DM from type 2 DM will allow for earlier detection of PDAC.

Abstract: At the time of diagnosis around two thirds of PDAC patients have diabetes mellitus (DM). For 50% of patients, DM is new-onset (diagnosed within the previous three years).

An estimated 200,000 cases of type 2 DM are diagnosed in the UK each year, in 10% of these cases DM is secondary to pancreatic disease (including PDAC), and is known as type 3c DM (although in the majority of cases type 3c DM is misdiagnosed as type 2 DM. PDAC-associated DM accounts for 8-10% of misdiagnosed type 3c DM cases, equivalent to 0.8-1% of all new diagnoses of type 2 DM.

Distinguishing new-onset type 3c DM from type 2 DM will allow for earlier detection of PDAC by facilitating the identification of a PDAC-enriched population suitable for screening. Methods to achieve this, along with potential candidate biomarkers will be discussed.

We previously performed a blood-based comprehensive mass spectrometry and Luminex based discovery program which identified potential diagnostic candidates for which an association with metabolic disease pathways was apparent in 45 of the 141 markers. Twenty-five of these were significantly enriched for an association with DM. Biomarker training and validation further selected a group of candidates, both DM-related and DM-unrelated, with potential to distinguish individuals with type 3c DM (PDAC- and chronic pancreatitis) from type 2 DM (long-standing and new-onset).

The potential of these markers to identify individuals with new-onset DM at the highest risk of a subsequent diagnosis of PDAC, enabling them to be clinically evaluated for PDAC will be discussed.

References:

Andersen DK, Korc M, Petersen GM, Eibl G, Li D, Rickels MR, et al. Diabetes, Pancreatogenic Diabetes, and Pancreatic Cancer. Diabetes. 2017;66(5):1103-10.

Jenkinson C, Elliott VL, Evans A, Oldfield L, Jenkins RE, O'Brien DP, et al. Decreased Serum Thrombospondin-1 Levels in Pancreatic Cancer Patients Up to 24 Months Prior to Clinical Diagnosis: Association with Diabetes Mellitus. Clin Cancer Res. 2016;22(7):1734-43.

Kleeff J, Costello E, Jackson R, Halloran C, Greenhalf W, Ghaneh P, et al. The impact of diabetes mellitus on survival following resection and adjuvant chemotherapy for pancreatic cancer. British journal of cancer. 2016;115(7):887-94.

4.

NICE Guidelines: Pancreatic cancer in adults: Diagnosis and management

Prof JN. Primrose

NICE, University of Southampton, United Kingdom

Resume: NICE has produced guidelines for the management of pancreas cancer in England. It is hoped this guidance will optimise care across England (and beyond) and also result in a quality of care that will enable the next generation of clinical trials.

Keywords: Pancreatic cancer, NICE, Multidiscipline teams, Endoscopic ultrasound, PET-CT

Abstract: Pancreatic cancer remains a disease with a very high mortality and it is noted that little improvement has been made is the last few decades. There is also evidence of variability in the standard of care across the UK. NICE has produced guidance for the management of diagnosed pancreatic cancer with the intention of standardising the quality of care based on the existing best evidence and also enabling future studies to be performed which may improve outcomes.

Key features of the guidance include 1. All patient being considered by a specialist MDT. 2. Routine use of CT-PET which may identify patients unsuitable for surgery as well as aiding the diagnosis. 3. Improving the provision of Endoscopic ultrasound such that tissue cores (suitable for genomics) can be obtained 4. Straight to surgery in fit patients. 5. Gem-Cap as standard if care adjuvant chemotherapy. 6. A stepwise approach to systemic chemotherapy reserving FOLFIRINOX for the most fit patients and gemcitabine combinations for the less fit.

References: https://www.nice.org.uk/guidance/ng85

5.

PRECISION-PANC

Andrew Biankin

University of Glasgow, United Kingdom

Abstract: Pancreatic Cancer (PC) has overtaken breast cancer to be the 3rd leading cause of cancer death in the USA. Genomic analyses of PC has revealed that beyond mutations in 4 well-known cancer genes (KRAS, TP53, CDKN2A and SMAD4), there are only a handful with a prevalence >10% amongst a sea of infrequently mutated genes. This diversity may explain the lack of progress, as actionable genomic events that are currently targeted occur in only a small number of unselected participants in clinical trials. The ability to select for responders to trials of therapeutics that target specific mechanisms is urgently needed, and must extend beyond the detection of mutations in coding genes.

We performed mRNA expression analysis (RNAseq), whole genome sequencing and methylome arrays, and further added Reverse Phase Protein Array (RPPA) and functional screen data for 48 Patient-derived cell lines. We show that patient-derived cell lines recapitulate the epithelium of pancreatic cancer and mimic previously-defined subtypes. The pure population of malignant cells eliminates stromal dilution revealing subtype specific differences in molecular mechanisms and therapeutic vulnerabilities. Therapeutic testing targeting some of these vulnerabilities supported subtype specific responsiveness, defining opportunities for molecular subtype directed therapy.

References:

Johns AL, et al. Lost in translation: returning germline genetic results in genome-scale cancer research. Genome Med. 2017 Apr 28;9(1):41.

Scarpa A, et al. Whole-genome landscape of pancreatic neuroendocrine tumours. Nature. 2017 Mar 2;543(7643):65-71.

Humphris JL, et al. Hypermutation In Pancreatic Cancer. Gastroenterology. 2017 Jan;152(1):68-74.e2.

Bailey P, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 2016 Mar 3;531(7592):47-52.

6.

ESPAC-5F and neoadjuvant therapy trials in pancreatic cancer

Paula Ghaneh

University of Liverpool, United Kingdom

Resume: Professor of Surgery, Director of Liverpool Cancer Trials Unit, research areas pancreatic cancer, clinical trials.

Keywords: Pancreatic cancer, neoadjuvant therapy.

Abstract: From the overall pancreatic cancer patient population, 20% of patients will present with resectable and borderline resectable disease. Standard treatment for patients with resectable pancreatic cancer is currently resection followed by six months adjuvant chemotherapy. The best survival rates for patients with resectable pancreatic cancer were demonstrated in the Phase III randomised adjuvant therapy ESPAC-4 trial. The majority of patients, however, do not achieve long term survival and 10-20% will develop early recurrence/distant metastatic disease within 6 months of surgery. There are several factors which contribute to this including; (i) level of micrometastatic disease; (ii) chemoresistance; and (iii) intrinsic susceptibility of the patient. The addition of neoadjuvant therapy can address some of these issues and potentially translate that into a survival benefit.

The European Study Group For Pancreatic Cancer - Trial 5F (ESPAC-5F), is a four-arm, prospective, multicentre, randomised feasibility trial of immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy for patients with borderline resectable pancreatic cancer and is currently recruiting. Future trials will focus on a more stratified approach to neoadjuvant therapy.

References:

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Ghaneh P, et al. The Impact of Positive Resection Margins on Survival and Recurrence Following Resection and Adjuvant Chemotherapy for Pancreatic Ductal Adenocarcinoma. Ann Surg. 2017 Oct 24.

Neoptolemos JP, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017 Mar 11;389(10073):1011-1024.

7.

Pancreatic Resectability in Cancers with Known Limited Extension (PRICKLE) – a single-arm phase 2a study of gemcitabine (Gem) plus Nab-paclitaxel (NabP) for borderline (un)resectable pancreatic ductal adenocarcinoma (BrPDAC)

Bristi Basu [1,2], Aarthi Gopinathan [3], Lisa Bax [2], Andrea Machin [2], Wendi Qian [2], Edmund Godfrey [2], Rebecca Brais [2], Siobhan Whitley [2], Ferdia Gallagher [1,2], Nicholas Carroll [2], Joanna Calder [2], Mary Mclean [3], Amanda Walker [2], Hemant Kocher [4], Mark Duxbury [5], John Scott [6], Richard Charnley [6], Colin Johnson [7], Siong-Seng Liau [2], Duncan Jodrell [1,3]

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[3] CRUK Cambridge Institute, United Kingdom
[4] Barts Cancer Institute, United Kingdom
[5] Glasgow Royal Infirmary, United Kingdom
[6] Newcastle Upon Tyne Hospitals NHS Foundation Trust, United Kingdom
[7] University of Southampton, United Kingdom

Resume: Dr Basu is an Academic Consultant Medical Oncologist in Experimental Cancer Therapeutics at University of Cambridge. She trained in medicine at Oxford University (Prosser Exhibitions) and in Medical Oncology at Cambridge. During this time, she completed a PhD in cancer cell biology and drug discovery as a CRUK Gordon Hamilton-Fairley fellow at the University of Cambridge. She translates preclinical findings on candidate agents into early phase clinical trials of novel therapeutic drugs as chief investigator, principal investigator and co-investigator in academic-led and industry-sponsored Phase I, II and III clinical trials, including first-in-human studies. She has a site-specific focus on hepatopancreaticobiliary tumours.

Keywords: Borderline resectable, pancreatic cancer, gemcitabine, Nab-paclitaxel

Abstract: A meta-analysis suggests PDAC pts initially staged as inoperable or borderline resectable by vascular involvement, may be downstaged by chemotherapy, enabling resection with outcomes comparable to those initially considered to be resectable. As Gem+NabP chemotherapy improves survival in metastatic PDAC, this single-arm phase 2a trial investigated resectability following 3-6 cycles of Gem+NabP for patients with BrPDAC. Pts with cytologically confirmed BrPDAC and adequate organ function were recruited to receive Gem (100mg/m2) + NabP (125 mg/m2) on days 1, 8, and 15 in every 4 week cycle followed by surgery if resectable. The primary endpoint was resectability rate (RR), as confirmed by an independent panel review of triple phase CT image. Secondary endpoints were response, institution determined operability (IDO) rate, margin status, and safety. Serial DCE-MRI, DW-MRI and endoscopic ultrasound (EUS) evaluations with tumour tissue biopsies were included as exploratory endpoints. A Simon two-stage approach (maximum 17 pts, first stage at n=9) was used to test H0 (null hypothesis) RR $\leq$5% vs H1 RR$\geq$25% with a 5% significance level and 80% power; H0 would be rejected if $\geq$3 pts were rendered resectable. 9 pts were enrolled (median age 64 range 59-77; 3 males), all of whom are evaluable for efficacy. All pts received $\geq$ 3 cycles of GEM + NabP, 1 stopped early due to progressive disease. Best response by RECIST 1.1 was PR (3); SD (6). The trial met its primary objective with 4/9 (44%) pts rendered resectable. Based on IDO, 5 pts went for surgery, and was abandoned in 1 pt with peritoneal metastasis. All 4 resected pts had R1 resection margin and tumour destruction grading was <10% necrosis (1 pt); 10%-90% necrosis (3 pts). No adverse post-operative complications were reported. **Gem+NabP regimen is well tolerated and shows efficacy in downstaging BrPDAC pts to permit resection. The BrPDAC setting presents an opportunity for correlative translational research.**

References:

Gillen et al PloS Med 2010 7:e1000267; von Hoff et al NEJM 2013 369: 1691-703

8.

Adapted physical activity and alternative exercise modalities

Cindy NEUZILLET

Henri Mondor University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris Est Créteil (UPEC), GERCOR, France

Resume: Exercise during cancer treatment is a promising strategy to reduce sarcopenia and improve quality of life. The GERCOR cooperative group develops multicentre clinical trials evaluating adapted physical activity and alternative modalities in patients with digestive cancers in France. The translational study programs involve biologists expert in cancer and muscle physiology.

Keywords: Physical activity, pancreatic cancer, exercise, sarcopenia, quality of life

Abstract: Adapted physical activity (APA) is an innovative non-pharmaceutical intervention in the field of supportive care and rehabilitation. In cancer patients, exercise is safe and may have beneficial effects on various symptoms, including fatigue, pain and treatment-related toxicities, thus improving their quality of life. In addition, APA may reduce mortality by exerting anti-tumour effects and counteracting sarcopenia and cachexia, which are important sources of morbidity and mortality in patients with gastrointestinal (GI) cancers.

The GERCOR group has been pioneer in France in the field of APA in GI cancer patients with the APACaP trial (NCT02184663), a multicenter randomized controlled trial evaluating a home-based exercise program in patients with advanced pancreatic cancer. More than 160 patients have been included to date in this study. Based on this experience, we obtained funding from the ARC Foundation and the French National Cancer Institute (INCa) for the randomized phase II APACaPOp-PRODIGE 56 study, evaluating two modalities of APA (home-based program, with or without group sessions at hospital) in patients operated on for pancreatic cancer; 252 patients will be enrolled (opening 05/2018). Ancillary studies on tumour, blood and imaging are planned to explore the molecular mechanisms of action of exercise and to identify predictive biomarkers of response to APA.

However, implementing voluntary exercise as a therapeutic intervention may be challenging in advanced cancer patients with altered performance status, in which tolerance to voluntary exercise may be poor. Therefore, we are also developing alternative physical-therapy strategies (neuromuscular electrostimulation) to reduce muscle wasting in these severely deconditioned patients.

References:

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2- Neuzillet C, Vergnault M, Bonnetain F, Hammel P. Rationale and design of the Adapted Physical Activity in advanced Pancreatic Cancer patients (APACaP) GERCOR (Groupe Coopérateur Multidisciplinaire en Oncologie) trial: study protocol for a randomized controlled trial. Trials 2015;16:454.

3- Ashcraft KA, Peace RM, Betof AS, Dewhirst MW, Jones LW. Efficacy and Mechanisms of Aerobic Exercise on Cancer Initiation, Progression, and Metastasis: A Critical Systematic Review of In Vivo Preclinical Data. Cancer Res 2016;76:4032-50.

9.

New therapeutic approaches to pancreatic ductal adenocarcinoma

Caroline Springer

Cancer Research UK Manchester Institute, Drug Discovery Unit, United Kingdom

Resume: Professor Caroline Springer has been Director of the CRUK Manchester Institute Drug Discovery Unit since October 2017. Previously she led the multidisciplinary Gene and Oncogene Targeting team at the Institute of Cancer Research, comprising medicinal chemists, biochemists, computational chemists and pharmacologists. Her research focuses on the discovery of new cancer therapies.

Keywords: lysyl oxidase, PDAC, therapy

Abstract: Lysyl oxidase (LOX) is an enzyme that regulates cross-linking of structural proteins in the extracellular matrix and is important for metastasis in many cancers. In collaboration with Prof Owen Sansom, we have shown that LOX is upregulated in pancreatic ductal adenocarcinoma (PDAC) in humans and it plays a fundamental role in the metastasis of this cancer [Miller et al, 2015]. We have demonstrated that LOX is also important for primary growth in pancreatic cancer. LOX is upregulated in a

p53mut KRASmut mouse PDAC model (KPC) representative of human cancer, and the growth is dependent on LOX expression. Critically, LOX downregulation by shRNA or its inhibition by LOX antibodies, the relatively non-potent small molecule inhibitor β-aminopropionitrile (BAPN) and by our more potent LOX inhibitor CCT365623, significantly reduces invasion and metastasis in PDAC models [Miller et al, 2015][Saturno, 2014]. We have also set up PDAC models from patients and characterised their LOX expression. Several of our LOX inhibitors show efficacy in pancreatic cancer models including a PDX model. Thus, LOX is a validated therapeutic target, and our aim is to discover first-in-class orally bioavailable small molecule LOX inhibitors for the treatment of primary and metastatic cancers, with one particular focus on the challenging PDAC model.

References:

Bryan W Miller, Jennifer P Morton, Mark Pinese, Grazia Saturno, Nigel B Jamieson, Ewan McGhee, Paul Timpson, Joshua Leach, Lynn McGarry, Emma Shanks, Peter Bailey, David Chang, Karin Oien, Saadia Karim, Amy Au, Colin Steele, Christopher Ross Carter, Colin McKay, Kurt Anderson, Thomas R Jeffry Evans, Richard Marais, Caroline Springer, Andrew Biankin, Janine T Erler, and Owen J Sansom (2015) Targeting the LOX/hypoxia axis reverses many of the features that make pancreatic cancer deadly: inhibition of LOX abrogates metastasis and enhances drug efficacy. EMBO Mol Med. 2015 Aug; 7(8): 1063–1076.

Grazia Saturno, Filipa Lopes, Amaya Viros, Jennifer Morton, Owen Sansom, Caroline Springer and Richard Marais. (2014) Lysyl Oxidase a therapeutic target in pancreatic cancer. Cancer Research, Volume 76, Issue 14 Supplement, pp. LB-212

10.

From Xenograft epigenomics to therapeutic opportunities

Remy Nicolle [1], Yuna Blum [1], Laetitia Marisa [1], Gwen Lomberk [2], Aurélien de Reynies [1], Raul Urrutia [2], Nelson Dusetti [3], Juan Iovanna [3]

[1] Ligue contre le cancer, United Kingdom
[2] Medical college of Wisconsin, United Kingdom
[3] Centre de recherche en cancerologie de marseille (CRCM), United Kingdom

Resume: Research scientist at the cancer genomics programme “Carte d’Identité des tumeurs” of the ligue contre le cancer in Paris, France.

Designed, planned and conducted genomics projects on several cancers, in particular pancreatic adenocarcinoma. Emphasis on unravelling tumor heterogeneity and predicting treatment resistance.

PhD in cancer computational biology (Institut Curie, 2015).

Keywords: Genomics, Epigenetics, Tumor microenvironment, Patient-derived Xenografts

Abstract: Patient-derived xenografts are valuable pre-clinical models enabling concomitant high-throughput profiling and functional assays of the same tumor tissue. We obtained 29 pancreatic ductal adenocarcinoma (PDAC) xenografts from either resectable or non-resectable patients (surgery and endoscopic ultrasound-guided fine-needle aspirate, respectively). We first show that xenograft have remarkable specificity in distinguishing transformed human tumor cells from non-transformed murine stromal cells computationally.

Multiomics genome-wide molecular profiling revealed two subtypes, namely basal and classical, with distinct clinical outcomes and transcriptional patterns in both the tumor and stromal compartments. The exact tumor/stromal distinction identified subtype-specific signaling pathways involved in tumor-stromal cross-talk thereby uncovering novel therapeutic potential.

Furthermore, extensive epigenetic characterization of these tumors using chromatin immunoprecipitation-sequencing (ChIP-seq) on multiple histone modifications uncovered the epigenetic landscape of pancreatic adenocarcinoma. This revealed that the two subtypes of PDAC are deeply encoded in the chromatin states of these tumors. In this work, we describe the state of promoters, enhancers, super-enhancers, euchromatic, and heterochromatic regions for each subtype. Further analyses indicate that the distinct epigenomic landscapes are regulated by different membrane-to-nucleus pathways. Inactivation of one of these pathways, which targets the upstream regulator of basal-specific super-enhancers, reveals the existence of plasticity between subtypes. Thus, our study provides new insight into the epigenetic landscapes associated with the heterogeneity of PDAC, thereby increasing our mechanistic understanding of this disease, as well as offering potential new markers and therapeutic targets.

References:

Nicolle, R., Blum, Y., Marisa, L. et al. (2017). Pancreatic Adenocarcinoma Therapeutic Targets Revealed by Tumor-Stroma Cross-Talk Analyses in Patient-Derived Xenografts. Cell reports, 21(9), 2458-2470.

Bian, B. et al. (2017). Gene expression profiling of patient-derived pancreatic cancer xenografts predicts sensitivity to the BET bromodomain inhibitor JQ1: implications for individualized medicine efforts. EMBO molecular medicine, 9(4), 482-497.

Lomberk G., Blum Y., Nicolle R. et al. (2018). Distinct epigenetic landscapes underlie the pathobiology of pancreatic cancer subbtypes. Nature Communications, in press.

11.

Deciphering pancreatic Cancer-Associated Fibroblasts biology for therapeutic targeting of pancreatic adenocarcinoma

R. Samain [1], E. Decaup [1], S. Zaghoudi [1], J. Rochotte [1], S. Cassant-Sourdy [1], A.P. Perraud [2], M. Mathonnet [2], H. Schmid [3], Y. Martineau [1], S. Pyronnet [1], C. Jean [1], C. Bousquet [1]

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[2] University of Limoges, Faculty of Medicine, EA3842, Limoges, France
[3] Novartis Pharmaceuticals, Basel, Switzerland

Resume: Therapies aimed at targeting the stroma in addition to cancer cells are nowadays being tested in pancreatic cancer known to be refractory to polychemotherapies. Deciphering the biology of Cancer-Associated Fibroblast (CAF), the major cell component of pancreatic tumor stroma, may help to target key pathways driving CAF's chemoprotective and pro-metastatic features.

Keywords: Tumor microenvironment, Cancer-Associated Fibroblasts, metastasis, signaling pathways

Abstract: Pancreatic ductal adenocarcinoma (PDAC) presents an exuberant stroma (80% of the tumor mass). In this stroma, Cancer-Associated Fibroblasts (CAFs) are the most abundant cells. CAFs secrete large quantities of extracellular matrix and soluble proteins that promote cancer cell aggressivity. We discovered two pharmacological approaches to inhibit CAF chemoprotective and pro-metastatic effects.

First, we targeted protein synthesis, which is specifically high in CAFs as compared to normal pancreatic stellate cells, through activation of the G protein coupled somatostatin receptor sst1. We showed synergistic anti-tumoral and anti-metastatic effects when associating the sst1 agonist (SOM230, Novartis) to chemotherapy (gemcitabine), in the KPC (Pdx-1-Cre ; LSL-KrasG12D/+ ; LSL-Trp53R172H/+) mouse PDAC model, involving reduction of both tumor cell aggressiveness and ECM deposit, in correlation with decreased tumor recruitment of M2 macrophages and reduced tumor and plasmatic CSF-1 concentrations.

Second, we explored the benefit of Focal-Adhesion Kinase (FAK) therapeutic targeting in CAFs, since fibrosis and pancreatic tumor stiffening mainly involving CAF production of ECM may require FAK activity. Our data show that FAK activity is increased in CAFs as compared to normal pancreatic stellate cells, in correlation with a worse prognostic in PDAC patients (n=120). FAK inhibition within CAFs results in a drastic decrease of tumor cell metastasis in vivo as well as of ECM protein expression and deposition in vitro.

These results support the idea that protein synthesis and FAK activity within CAFs are key and druggable players in PDAC metastatic progression.

References:

Duluc C, et al. Pharmacological targeting of the protein synthesis mTOR/4E-BP1 pathway in cancer-associated fibroblasts abrogates pancreatic tumour chemoresistance. EMBO Mol Med. 2015 7:735-53.

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Chalabi-Dchar M, et al. Loss of Somatostatin Receptor Subtype 2 Promotes Growth of KRAS-Induced Pancreatic Tumors in Mice by Activating PI3K Signaling and Overexpression of CXCL16. Gastroenterology. 2015 148:1452-65.

12.

Paget Lecture: Mapping the Immune Landscape in Pancreatic Cancer

Steven D. Leach

Dartmouth College – Norris Cotton Cancer Center, United Kingdom

Resume:
Professor of Molecular and Systems Biology
Preston T. and Virginia R. Kelsey Distinguished Chair in Cancer
Director, Dartmouth Norris Cotton Cancer Center

Keywords: Pancreatic immunology neoepitope T-cell microbial

Abstract: Pancreatic ductal adenocarcinoma is a lethal cancer with fewer than 7% of patients surviving past 5 years. T-cell immunity has been linked to the exceptional outcome of the few long-term survivors, yet the relevant antigens remain unknown. Here we use genetic, immunohistochemical and transcriptional immunoprofiling, computational biophysics, and functional assays to identify T-cell antigens in long-term survivors of pancreatic cancer. Using whole-exome sequencing and in silico neoantigen prediction, we found that tumours with both the highest neoantigen number and the most abundant CD8+ T-cell infiltrates, but neither alone, stratified patients with the longest survival. Investigating the specific neoantigen qualities promoting T-cell activation in long-term survivors, we discovered that these individuals were enriched in neoantigen qualities defined by a fitness model, and neoantigens in the tumour antigen MUC16 (also known as CA125). A neoantigen quality fitness model conferring greater immunogenicity to neoantigens with differential presentation and homology to infectious disease-derived peptides identified long-term survivors in two independent datasets, whereas a neoantigen quantity model ascribing greater immunogenicity to increasing neoantigen number alone did not. We detected intratumoural and lasting circulating T-cell reactivity to both high-quality and MUC16 neoantigens in long-term survivors of pancreatic cancer, including clones with specificity to both high-quality neoantigens and predicted cross-reactive microbial epitopes, consistent with neoantigen molecular mimicry. Notably, we observed selective loss of high-quality and MUC16 neoantigenic clones on metastatic progression, suggesting neoantigen immunoediting. Our results identify neoantigens with unique qualities as T-cell targets in pancreatic ductal adenocarcinoma. More broadly, we identify neoantigen quality as a biomarker for immunogenic tumours that may guide the application of immunotherapies.

References: Balachandran et al, Nature. 2017 Nov 23;551(7681):512-516.

13.

MRI-based machine learning for detection of orthotopic pancreatic cancer in KPC mice

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Abstract: Genetically engineered mouse models allow the study of the development, progression and therapy response of pancreatic cancer in the context of an intact immune system. KPC model mice are born with a healthy pancreas but spontaneously develop orthotopic PanIN lesions as they age. Non-invasive imaging is essential to monitor tumour growth, but ultrasound can be challenging and user dependent. We have used MR imaging combined with a 3D computational mouse atlas to automatically detect pancreatic tumour in mice.

MR images were analysed automatically using spatial, textural and statistical methods and regions of interest were classified as either healthy pancreas or tumour. Results were compared with manual segmentation by a team of imaging experts with an accuracy of 97% when determining if a tumour is present.

This analysis pipeline allows for faster, more accurate and reproducible analysis and has yielded promising preliminary results, being able to identify tumours within mice more rapidly compared to manual analysis. Such early and accurate identification of tumours is critical for optimised evaluation of potential treatments which reduces variability, experiment duration and numbers of required animals.

*Voted as a Top 5 Abstract.

14.

αvβ6 targeted CAR-T cells in immunocompetent orthotopic murine PDAC

N. Brown, M. Nikolaidi, L. Cutmore, D. Cornish, D. Raj, C. Heeschen, J. Marshall

Barts Cancer Institute, Queen Mary University of London, United Kingdom

Abstract: αvβ6 is an integrin that is highly expressed in >90% of human pancreatic ductal adenocarcinoma (PDAC) with minimal expression in healthy tissues. Chimeric antigen receptor (CAR) T-cells targeting αvβ6 have demonstrated efficacy in intraperitoneal PDAC xenografts in immunodeficient mice. However, this model does not represent the immunosuppressive tumour microenvironment that is a hallmark of PDAC and a significant barrier to immunotherapies. In this study we aim to evaluate murine CAR-T cells targeting αvβ6 in immunocompetent C57BL/6 mice with orthotopically implanted PDAC.

We have generated an αvβ6 targeted CAR containing a CD28 costimulatory domain and deactivated 1st and 3rd CD3ζ immune-receptor tyrosine based activation motifs and cloned this into the MSGV backbone. CAR-T cells have been generated via gammaretroviral mediated transduction of T-cells isolated from C57BL/6 mice. Cultures derived from primary tumours isolated from KrasG12D p53R172H Pdx1Cre transgenic mice have been screened for αvβ6 expression, with enrichment of the most highly expressing line (CHX2018) with FACS.

We will present updated data including in-vitro cytotoxicity data of αvβ6 targeted CAR-T cells with CHX2018 and describe future experimental plans for in vivo and combination studies.

15.

VAR2CSA-based CAR-T cells for the treatment of pancreatic ductal adenocarcinoma

L. Cutmore, D. Cornish, N. Brown, M. Nikolaidi, D. Raj, C. Heeschen, J. Marshall

Barts Cancer Institute, Queen Mary University of London, United Kingdom

Abstract: Chimeric antigen (CAR) receptor T cells represent a novel treatment modality, but efficacy is limited in solid tumours primarily due to the immunosuppressive tumour microenvironment and on-target toxicity, highlighting a need to target tumour-restricted antigens. Chondroitin sulphate A (CSA) is a distinct oncofoetal glycosaminoglycan (ofGAG) expressed on >95% of cancer cells, including PDAC. VAR2CSA is a malarial protein that binds to CSA with high affinity with minimal binding to healthy tissue. In this study we examined the utility of VAR2CSA as the antigen-binding domain in a 2nd generation CAR T cell to target CSA expressed on PDAC cells. We have generated a VAR2CSA CAR containing a 4-1BB co-stimulatory

and CD3ζ activating domain, and have successfully transduced primary human T cells using a lentiviral vector. We have demonstrated that VAR2-CSA CAR-T cells display enhanced cytotoxic killing of resected and circulating tumour cell derived PDAC cultures in vitro, compared with untransduced T cells. VAR2CSA CAR-T cells also showed higher secretion of IFNɣ than an untransduced control. Having established the efficacy of our human model in vitro we shall develop a murine VAR2CSA CAR-T cells to examine targeting PDAC in an immunocompetent model.

16.

Ataxia Telangiectasia Mutated and its value as a predictive biomarker of response to AZD6738 therapy in pancreatic cancer

Charles R. Dunlop [1], Yann Wallez [1], Sandra Bernaldo de Quirós Fernández [1], Alan Lau [2], Frances M. Richards [1], Duncan I. Jodrell [1]

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Abstract: Therapeutic targeting of the DNA damage response may improve the poor survival outcomes of pancreatic ductal adenocarcinoma (PDAC). Many common genetic alterations in PDAC augment replication stress, which activates Ataxia-Telangiectasia And Rad3-Related-Protein (ATR). We have previously demonstrated the efficacy of ATR inhibitors in PDAC, particularly when combined with gemcitabine. In some cancers, loss of Ataxia-Telangiectasia-Mutated (ATM) increases sensitivity to ATRi. Thus, we sought to evaluate the utility of ATM as a predictive biomarker of response in PDAC.

In a panel of ten cell lines, the two with inactivating homozygous mutations in ATM were the most sensitive to the ATR inhibitor, AZD6738. However PDAC cells harbouring heterozygous ATM mutations showed similar sensitivity to wild-type lines. The ATM inhibitor, AZD0156, partially sensitised MIA PaCa-2 and PANC-1 cells. In contrast, ATM depletion using siRNA failed to shift AZD6738 sensitivity, either as monotherapy or in combination with gemcitabine. The combination induced significant ATM autophosphorylation on Ser1981 in siCTR cells but not in siATM cells. Interestingly, the combination still activated many of ATM's targets (Chk-2, KAP-1) in siATM cells, perhaps indicating the contribution of compensatory pathways.

Despite ATM depletion failing to alter ATRi/gemcitabine sensitivity, siATM cells were more sensitive to irradiation (IR). Moreover, AZD6738 potentiated the effect of IR, and did so more effectively in siATM cells. Thus, "low ATM" in PDAC could be a useful biomarker for AZD6738 + radiotherapy treatment but not for AZD6738 + gemcitabine. This work has implications for the enrolment criteria for clinical trials of AZD6738 + gemcitabine in PDAC.

17.

The interplay between Met and autophagy in PDAC

Alejandro Noval [1], Katherine Fletcher [2], Oliver Florey [2], Stephanie Kermorgant [1]

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Abstract: The lack of improvement in survival of pancreatic ductal adenocarcinoma (PDAC) patients in the last 30 years makes imperative the investigation for new therapeutic targets. The RTK Met is overexpressed in PDAC samples, correlating with a poor prognosis. Met downstream signalling leads to tumour progression, metastasis, and plays a role in resistance to gemcitabine in PDAC cells. Autophagy, a catabolic process responsible for cell homeostasis, plays a role in PDAC cells survival. Autophagy is associated with the double-membrane autophagosome marker LC3, but the recent discovery of non-canonical autophagy (NCA) resulting in single-membrane LC3 compartments, makes necessary a further characterisation of LC3 structures. We have recently reported that Met colocalises with LC3 in autophagy related endomembranes (AREs), from where it sustains signalling to promote cell survival. We observed that upon HGF stimulation, Met internalises in PDAC cells and localises in AREs. Interestingly, after short stimulation times, Met rather colocalises with Rubicon, involved in NCA. Furthermore, using MEFs genetically modified to impair canonical or NCA, our results indicate that Met localises and signals from NCA vesicles and protects cells from anoikis. To characterize Met containing AREs, we are performing correlative light and electron microscopy (CLEM) experiments. So far, our results suggests that AREs from a NCA are a novel Met signalling platform.

18.

Self-assembling biomimetic hydrogels as a novel 3D in vitro platform for pancreatic cancer research

David Osuna de la Peña [1,2], Sara Trabulo [1], Estele Collin [3], Daniela Loessner [2], Álvaro Mata [3], Christopher Heeschen [1]

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Abstract: The ex vivo modelling of pancreatic ductal adenocarcinoma (PDAC) using patient-derived cells is one of the most promising tools for the prediction of clinical outcomes. However, current Matrigel-based organoid and organotypic cultures are still limited in their ability to recapitulate PDAC desmoplasia and chemoresistance. To further advance 3D modelling of PDAC, we use self-assembling peptide amphiphiles (PAs) to recreate the tumour microenvironment. Primary PDAC and stromal cells (CAF and macrophages) are embedded in PA hydrogels and basic components of the extracellular matrix (ECM). Matrisome analysis demonstrated consistent deposition of ECM proteins, strongly correlating with the ECM of their corresponding primary tumours. The use of PA hydrogels as a drug-testing platform is currently validated using gemcitabine, nab-paclitaxel, triptolide/minnelide and their respective combinations. First analyses suggest that the in vitro treatment response was highly reminiscent of the respective in vivo drug response. Implantation of cell-laden PA gels into immunocompromised mice revealed increased tumourigenicity and aggressiveness compared to Matrigel-based implants. Our data imply that the intrinsic biomimetic nature of self-assembling PA hydrogels results in improved 3D modelling of PDAC and their potential use as a drug-testing platform.

19.

TGF-ß induces miR-100 and miR-125b but blocks let-7a to promote pancreatic cancer

Silvia Ottaviani [1], Adam E. Frampton [1], Sladjana Zagorac [1], Justin Stebbing [1], Nick R. Lemoine [2], Christopher Heeschen [2], Leandro Castellano [1,3]

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Abstract: The TGF-ß pathway plays critical roles during tumourigenesis of pancreatic ductal adenocarcinoma (PDAC) by promoting epithelial-to-mesenchymal transition (EMT), metastasis and stemness. However, the role of microRNAs (miRNAs) in this response remains largely undefined. Here, we show that TGF-ß up-regulates MIR100HG, a long non-coding RNA (lncRNA) and host transcript for miR-100, miR-125b and let-7a, via SMAD2/3 transcription factors. Interestingly, we find that whilst the oncogenic miR-

100 and miR-125b are up-regulated by TGF-ß the level of anti-tumourigenic let-7a remains unchanged as TGF-ß also up-regulates LIN28B, a well-known inhibitor of let-7 maturation. Silencing of miR-100 or miR-125b impairs EMT, motility, sphere formation and tumourigenesis but only inhibition of miR-125b reduces metastasis in vivo. Importantly, inhibition of miR-125b, and to a lesser extent inhibition of miR-100, impairs TGF-ß-mediated tumourigenesis suggesting that miR-125b is the most important effector in this response. Clinically, we show that miR-100 and miR-125b are up-regulated in PDAC patient samples (n=100), and their specific tumoral expression strongly correlates with reduced overall survival and disease-free survival. Finally, using AGO2-RIP-seq and RNA-seq, we found that miR-100 and miR-125b targets significantly overlap and mainly inhibit p53 and cell to cell junctions' pathways. Together, our data reveal that TGF-ß induces miR-100 and miR-125b but blocks let-7a through up-regulation of MIR100HG and LIN28B to promote PDAC progression. We therefore propose that the inhibition of miR-125b and/or miR-100 in patients could be considered as a new therapeutic approach for treating PDAC.

20.

Molecular mechanisms that govern pancreatic cancer stem cell formation and maintenance in pancreatic ductal adenocarcinomas

Siim Pauklin

University of Oxford, Botnar Research Centre, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, United Kingdom

Abstract: Pancreatic ductal adenocarcinoma is a common type of pancreatic cancer and one of the most lethal malignancies in human due to its highly metastatic characteristics and the poor responsiveness to currently used cancer therapeutics. In recent years, solid evidence has accumulated on a dedifferentiation process of cellular identity during tumorigenesis, and the acquisition of a stem cell-like state of a subpopulation of cells in cancers. These cells are called cancer stem cells, and they are exceptionally important because their developmental plasticity allows them to metastasize and give rise to the whole tumour in the organism. What molecular mechanisms control pancreatic cancer stem cells during pancreatic ductal adenocarcinoma development is currently poorly understood. My proposed research will utilize state-of-the-art cell culture methods with genome-wide techniques, proteomics, in vitro mechanistic studies and in vivo tumorigenesis experiments. The general objective of my research is to identify and characterize novel signal transduction/transcription pathways in pancreatic cancer stem cells. I am particularly interested in identifying novel factors that mediate TGFβ/Nodal-Smad2/3 signalling, whose deregulation is among the hallmarks of pancreatic ductal adenocarcinoma. TGFβ/Nodal-Smad2/3 pathway has a central function in maintaining the stem cell identity of human pluripotent stem cells as well as pancreatic cancer stem cells during tumorigenesis. Collectively, this research will provide key insight to the signalling pathways and molecular mechanisms essential for the formation and maintenance of pancreatic cancer stem cells, helping to better understand the tumorigenic process, and to uncover novel ways for diagnosing and treating this lethal cancer.

21.

Switchable CAR-T cells mediate long-term remission of PDAC

D. Raj, J. Marshall, T.S. Young, A. Aicher, C. Heeschen

Queen Mary University of London, United Kingdom

Abstract: The efficacy of chimeric antigen receptor-T (CAR-T) cells for solid tumors is challenged by a lack of tumor-specific antigens to avoid on-target, off-tumor effects. CAR-T cell targeting of HER2 has shown efficacy in preclinical tumour models, but low levels of HER2 expression in the lung may cause dangerous toxicity in patients.

We therefore previously developed a switchable CAR-T cell platform targeting HER2, whereby dose titration of a HER2-specific recombinant Fab-based "switch" allows control over CAR-T cell response. In this present study we used conventional and switchable CAR-T cells to target HER2, which is expressed at low levels in many human PDAC tumors. We used primary PDAC cultures from stage IV PDAC patients to generate mouse models mimicking the most aggressive features of PDAC. We found both conventional and switchable CAR-T approaches induced a striking remission in localized and metastatic tumors, with comparable efficacy. Unlike conventional HER2 CAR T cells, the activity of switchable CAR-T cells was tunable in vivo by switch administration.

Our results therefore suggest that the switchable CAR-T system, besides being more amenable to titration than conventional CAR-T cells, has comparable efficacy, and may therefore be translatable into a safe and effective therapeutic strategy in human patients.

*Voted as a Top 5 Abstract.

22.

Anti-tumor effect of an oligosaccharide API in a Genetically Engineered Mouse- Derived Allograft (GEDA)

Shalini V. Rao [1,2], Tonje Strømmen Steigedal [2], Aarthi Gopinathan [1], Sabina P. Strand [2], Duncan I. Jodrell [1], Kurt I. Draget [2,], Catherine Taylor Nordgård [2,*], Frances M. Richards [1,*]*

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Abstract: The use of oligosaccharides as active pharmaceutical ingredients lags behind that of other biological molecules such as proteins and nucleic acids. However, growing understanding of the complex biological functions of saccharide structures has increased interest in exploring the pharmaceutical applications of both oligosaccharides and glycoconjugates.

RiXOVA (G-Blocks), a new drug candidate, consists of highly defined and specialized short oligomers comprising α-L-guluronate residues derived from alginates extracted from brown seaweed. G-blocks are nontoxic and well tolerated at i.v./i.p. doses >100mg/kg body weight in mice. Previous studies have demonstrated G-blocks to alter matrices of biological macromolecules including mucins, giving rise to the hypothesis that they may have similar effects on the dense desmoplastic tissue within tumours. Here, we report the anti-tumour effects of RiXOVA in a Genetically Engineered Mouse-Derived Allograft (GEDA) of Pancreatic Ductal Adenocarcinoma.

KPC (LSL-KrasG12D; LSL-Trp53R172H; Pdx1-cre) mouse tumour fragments (2 donors) were subcutaneously implanted in the flank of recipient LSL-Trp53R172H; Pdx1-cre (PC), immunocompetent mice. RiXOVA was non-immunogenic and inhibited tumour growth when administered repeatedly (I.P dosing) to these mice. Tumour growth at endpoint (compared to start of dosing) was 260% +/- 160 with RiXOVA (25 mg/kg TIW), compared to 540% +/- 210 for Vehicle ($p = 0.001$) and 130 % +/- 57 with RiXOVA + gemcitabine (100 mg/kg BIW $p < 0.001$). Tissue from these tumours is currently under histological examination. RiXOVA also inhibited CAPAN-2 xenograft growth.

Whilst these results are in a preliminary stage they indicate G-block oligomers may represent a novel treatment modality in PDAC.

*Voted as a Top 5 Abstract.

* equal contributions (GEDA model FR, project inception and treatment modality CTN/KID)

23.

Regulation of tumour progression and metastasis by Endothelial-FAK upon chemotherapy treatment

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Abstract: Poor prognosis in pancreatic cancer patients has been associated in part to acquiring resistance to chemotherapies. It has been suggested that the tumour responsiveness to some anti cancer treatments is not only modulated by malignant cells but can also be highly influenced by the tumor microenvironment. In particular, angiocrine factors secreted by tumour endothelial cells have been shown to play key roles in modulating chemotherapeutic response of malignant cells and influencing subsequent disease progression. We have previously published that deletion of endothelial FAK (EC-FAK) in established tumours, has no apparent effect on the blood vessel function, but induces chemosensitisation of malignant cells in response to DNA damaging therapies in an angiocrine manner. Here we use pancreatic orthotopic models to study the role of EC-FAK in pancreatic ductal adenocarcinoma (PDAC) upon gemcitabine treatment. EC-FAK loss in established pancreatic tumours does not show any effect in primary tumour growth regardless of treatment. Tumour angiogenesis is not altered in EC-FAK KO gemcitabine treated mice but shows increased tumour necrosis. Interestingly, although metastatic incidence to the liver is the same, EC-FAK deleted mice treated with gemcitabine have decreased liver metastatic burden and metastatic nodule area. These data suggest a potential angiocrine effect of EC-FAK regulating pancreatic cancer cell survival in both primary tumour and secondary sites.

*Voted as a Top 5 Abstract.

24.

Genomic profiling in pancreatic cancer reveals spatial genetic heterogeneity but spatial transcriptomic homogeneity

Shivan Sivakumar [1], Anas Rana [2], Chandan Seth [1], Ines de Santiago [3], Zahir Soonawalla [1], Robert Morgan [1], Aniko Rendek [1], Michael Silva [1], Srikanth Reddy [1], Stephanie Jones [1], Jerome Nicod [1], Casmir Turnquist [1], Ruchi Tandon [1], Eric O'Neill [1], Simon Lord [1], Michael Dustin [1], Jenny Taylor [1], Mark Middleton [1], Christopher Yau [2]

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Abstract: Pancreatic cancer has a five-year survival of 4%. Tumours are described to be genetically heterogeneous and information on carcinogenesis and evolution can be gained from this. The transcriptome provides useful information about the pathways activated in a tumour and information about the microenvironment, stromal and immune content. We performed a five patient multi-regional study of primary pancreatic cancer where four regions were obtained and concurrently genetically (one region whole genome and the other three whole exome) and transcriptomically sequenced. Our data showed that there was a substantial mutational burden, with three of five tumours displaying genome wide copy number changes. There was considerable nucleotide level variation in different regions of the same tumour. Transcriptomic data showed that tumour samples from each patient strongly clustered together with little overlap. Within the limitations imposed by sample size this qualitatively suggests that the dominant mode of transcriptomic heterogeneity is driven by inter-patient rather than intra-tumoral expression differences. Hierarchical clustering based on pancreatic cancer and immune gene sets gave groups that again predominantly divided by patient suggesting that transcriptional programming of pathways associated with these gene sets was largely homogenous on a per patient basis. Our analysis indicates that although intra-tumoral somatic variant and copy-number heterogeneity exists in each patient, as previously reported, in our data does not appear to drive significant transcriptional changes across the different regions sampled. This finding has many important ramifications for the interpretation of intra-tumoral heterogeneity and its impact on our understanding of cancer development and also clinical decision-making.

*Voted as a Top 5 Abstract.

25.

Investigation of the role of YAP (Yes-associated Protein) during the progression of pancreatic ductal adenocarcinoma

Asmita Thapa, Eric O'Neill

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Abstract: Pancreatic cancer, 90% of which comprises of pancreatic ductal adenocarcinoma (PDAC), is considered one of the most fatal cancer types with a very low survival rate of 5-year in less than 4% of patients. Early diagnosis in patients has proven to be difficult with challenges for effective treatment strategies, making PDAC a leading cause of cancer death. KRAS mutations occur during early stage of pancreatic lesions and act as a critical event in both initiating and maintaining PDAC development. Previous work showed the role of YAP to play an important role in facilitating progression of the neoplastic precursor lesions to invasive cancer in KRAS mutated pancreas. YAP, a transcriptional co-activator, is a nuclear effector of the Hippo pathway which is best known for regulating organ size and cell proliferation. However, it is still unclear how the hippo pathway is lost and YAP is activated in PDAC. Here we show, via immunohistochemical (IHC) analyses, heterogeneity in nuclear YAP expression among pancreatic lesions in Kras-mutant (KrasLSL.G12D+/-; Pdx-Cre) mice. Interestingly, nuclear localisation of YAP associates with activation levels of ERK, the output signal of RAS pathway responsible for growth promotion. In agreement, in vitro results also demonstrate correlation of RAS and MAPK activation with YAP levels. Moreover, we have identified a number of upstream hippo pathway components lost during PDAC development that may contribute to YAP activation in mouse models of pancreatic cancer.

A progression model has been used to define for the development of tumour in pancreas and is divided into different stages of low and high-grade pancreatic intraepithelial neoplasia (PanIN) lesions. However, more recently, studies have shown that the cell of origin play a critical role in causing PDAC to undergo varying multi-stage processes before turning invasive, by affecting developmental phenotype of the disease. We correlate for the presence of nuclear YAP in pancreatic lesions that are both positive and negative for acidic mucins. The correlation with acidic mucins, which are typical feature of low-grade PanIN lesions, will enable in providing better understanding of YAP's role in the development of PDAC that originated from acinar or ductal cells. This, in turn, can be useful in predicting prognosis of PDAC patients.

Our aim is understand the complex interplay between Hippo and MAPK signalling pathway and to identify whether YAP is a crucial event for KRAS mutated lesions, with different cellular origin, to progress into aggressive form in pancreas.

26.

Development of FGFR targeted therapies in pancreatic cancer

Abigail Wilson

Hemant Kocher and Richard Grose, BCI, United Kingdom

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer related death, with a 5 year survival rate of less than 5%. PDAC tumours consist of a desmoplastic stroma, which can prevent chemotherapy treatment from being effective. Pancreatic stellate cells (PSCs) form a key part of this stroma, which become activated in response

to tumour development. Activated PSCs can induce tumour cell proliferation and invasion, leading to metastatic spread. Nuclear fibroblast growth factor receptor 1 (FGFR1) has been found in PSCs at the invasive edge of tumours. Inhibition of FGFR1 prevents nuclear translocation of the receptor and decreases invasion in 3D organotypic models. Further investigation of the nuclear action of FGFR1 shows that it co-localises with SC35, suggesting it has a role in transcriptional regulation. Therefore, chromatin immunoprecipitation (ChIP) is being used to elucidate the functional role of FGFR1 within the nucleus. This will also provide potential therapeutic hits for targeting PSCs in patients. Alongside this work, combination therapy regimes including FGFR1 inhibitors are being investigated in PDAC models to see if this could lead to improved therapeutic responses in patients.

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