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 Chetaila, London

0930-0945 ADEPTS & EDRA
Stephen Pereira, UCL, London
0945-1000 UK: EDI: Detecting pancreatic cancer with DM
Ethene Costello-Goldring, Liverpool
1000-1015 UroPanc
Tatjana Crnogorcevic-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 Castelliano, 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
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Web: https://www.londonpancreasworkshop.org.uk/

Barts Health NHS
NHS Trust

Barts Cancer Institute
Queen Mary University of London
ADEPTS (Accelerated Diagnosis of neuroEndocrine and Pancreatic Tumours) and EDRA (Early Diagnosis Research Alliance)

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

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Resume: Professor of Hepatology & Gastroenterology at UCL and Honorary Consultant Gastroenterologist in PancreatoBiliary 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 Pancreatobiliary 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.

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 targeted 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 (NOD) 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.

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 3, Greta Brezgyte 4, Alexander Ney 5, Stephen P. Pereira 1, William Greenhalf 6, Patrick Wilson 7, Stephen Duffy 8, Oleg Blyuss 9, Melody Zhifang Ni 10

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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 of 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.

References:
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, Chinemei Iwuiji 4, Marion Harris 5, Daniel Crough 6, Morteza Aghmesheh 7, Adnan Nagrial 8, Nam Nguyen 9, Mehrdad Nikfarjam 9, Nicole Wilson 10, Daniel Kenny 11, David Turner 11, Harpreet S. Wason 12

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**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: 4.5 cm (range 2.6–7.1). Median follow-up: 16.1 months. 988 AEs were reported (PP); 148 were Grade ≥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 maximum 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.

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

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**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 Pancreatic Adenocarcinoma Signature Stratification 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 tissue biopsies can be safely obtained 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.
References

8. STAR PAC clinical trial
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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 reassessment 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/m2 orally, days 1–5 / 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 predictive of response. Re-purposing ATRA as a stromal-targeting agent with gemcitabine-nab-paclitaxel is safe and tolerable.

References

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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 miRNA targets repressed by miR-125b and miR-100, in PDAC. We are currently using CRISPR/CAS9 genome engineering to understand if any of these miRNAs 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

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Keywords: FAK, Il6, PD-L2, CD4 T-cell, pancreatic cancer

Abstract: Pancreatic cancer is one of the most lethal cancers with less than 1% 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.

References:

11. The roles of autophagy in pancreatic cancer

Kevin Ryan

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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.
Elevated microRNA expression could be diagnostic biomarker for PDAC

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Background: Pancreatic ductal adenocarcinoma (PDAC) is the most common type of PCa with 2-5% 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.

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16. DIFFERENTIAL ACTIVATION PATTERNS OF RECEPTOR TYROSINE KINASES: NOVEL POTENTIAL TARGETS IN THE PANCREATIC CANCER STEM CELL NICHE
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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 autoluciferase 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 recognize 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 Klince 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. Pancreatoduodenectomy (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 peri-ampullary 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

Ismail Sert1,2, Degercan Yesilyurt 1, Cem Karaalı 1, Mustafa Emroglu 1

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

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

Material method: Medical records of consecutive forty five patients underwent PD by the same general surgeon between Jan 2019 and May 2020 were retrospectively 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 descriptive measures were reported due to lack of control group in this study and main purpose of this study 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 relevant 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 feasible and has acceptable pancreatic fistula rates. This technique can be used by surgeons who get difficulties with the duct to mucosa anastomosis due to aforementioned causes.

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

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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.


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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 culture 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 mechanotransduction 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

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Introduction: With a 5-year survival rate of only 9%, Pancreatic Ductal Adenocarcinoma (PDAC) is the 7th leading cause of cancer related death worldwide. 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. 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 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 and can be used for long term therapeutic assessments. 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. 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. 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.

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
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