The London Pancreas Workshop

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

Friday 30th April 2010
Charterhouse Square, London UK

Final programme

0930-1030: Diagnostics Chair: Prof Nick Lemoine & Dr Norbert Avril

Role of PET in pancreatic cancer diagnosis	Ms Paula Ghaneh, Liverpool
Role of novel biomarkers in pancreatic cancer diagnosis	Dr T Crnogorac-Jurcevic, London

1030-1100: Coffee Break

11.00-12.30hrs: Treatment options Chair: Prof Ian Hart & Mr Satya Bhattacharya

Surgery: state of current trials	Mr Hemant Kocher, London
Targets for prevention and treatment of pancreatic cancer	Prof Roland Schmid, Munich
Hedgehog inhibitors for pancreatic cancer	Dr David Tuveson, Cambridge

12.30-14.00hrs: Lunch

14.00-15.00hrs: New targets: Prof Marco Falasca & Dr Richard Grose

Pancreatic cancers: is hypoxia a determinant	Prof Ralf Segersvärd, Stockholm
Targeting pancreatic cancer stroma	Dr Fieke Froeling, London

15.00-15.30hrs: Tea

15.30-16.30hrs: Molecular and genetic insights Chair: Mr Hemant Kocher & Dr Thorsten Hagemann

Pancreatic endocrine tumours: molecular insights	Prof Aldo Scarpa, Verona
From signalling pathways to familial genes	Dr Gunnel Hallden

Organisers: Prof Nick Lemoine & Mr HM Kocher
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Role of urine biomarkers in pancreatic cancer diagnosis

Dr Tatjana Crnogorac-Jurcevic
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Centre for Molecular Oncology & Imaging, Barts and The London

Biological markers are measurable indicators of normal and pathological state and form a basis of much talked about 'translational research' and 'personalized medicine'. Biomarkers for early detection of pancreatic adenocarcinoma would be invaluable for timely diagnosis and increased survival of patients with this malignancy, for which current prognosis is bleak.

A large number of '-omics' technologies have been applied in pancreatic cancer research, however, no useful biomarkers for the definitive pre-operative diagnosis are available at present. We have recently shown using 2D-DIGE (two-dimensional difference in-gel electrophoresis) that urine is a valuable body fluid where signatures of pancreatic adenocarcinoma can be found (Weeks et al, Proteomics, Clinical applications, 2008), and we have continued to expand on this work.

The recently performed GeLC MS/MS experiments resulted in the detection of almost 1500 unique proteins in our urine samples, which formed a good source for the selection of candidate biomarkers that would differentiate chronic pancreatitis, pancreatic cancer and healthy specimens based on both statistics and biology. Preliminary validation of several such biomarkers using ELISA assays will be presented.

It is our hope that after extensive validation, we will have a useful biomarker panel that could be used for the non-invasive detection of pancreatic cancer.

Role of PET IN pancreatic cancer diagnosis

Paula Ghaneh
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Combined positron emission tomography and computed tomography (PET/CT) has been developed to add precise anatomic localization to functional data. PET and CT is acquired concurrently and co-registered, merging functional information from PET with the anatomical information from CT. Several studies have demonstrated that FDG PET/CT is more accurate than FDG-PET in solid tumours, including pancreatic tumours. In pancreatic cancer, a study by Heinrich et al found that FDG PET/CT had a sensitivity of 89% for the detection of pancreatic cancer, altered treatment planning in 16% of 59 patients and was cost saving. A recent study demonstrated that the sensitivity and specificity of FDG PET/CT was 88% and 89% respectively in patients being assessed for pancreatic cancer and changed the management of 6 (11%) patients. These patients were found to have extra-pancreatic disease which prevented them from undergoing pancreatic resection. Another study assessed two groups of patients; a diagnosis and staging group and a screening group for progressive or recurrent disease. The accuracy rate for FDG PET/CT for diagnosis and staging was 91.2% and 85.3% respectively. In the restaging group FDG PET/CT had a sensitivity of 90% [33]. The additional feature of PET/CT is semi-quantitative analysis of glucose uptake (FDG activity) in suspicious pancreatic lesions. Determination of FDG activity is obtained by calculating standardised uptake value (SUV) in a given region of interest. An SUV of >3.5 may indicate pancreatic malignancy; a recent study revealed SUV_{max} in malignant lesions of 6.5 +/-4.6 and 4.2+/-1.5 in benign lesions. A definite cut off value is difficult to define for pancreatic malignancies and therefore qualitative data should also be included such as FDG tracer uptake patterns in clinical studies. The use of contrast enhanced PET/CT may represent a complete diagnostic staging procedure without the need for separate MDCT. It has been assessed in two recent studies. One found that contrast enhanced FDG PET/CT was superior to FDG-PET (p=0.035) and there was a trend (p=0.07) for contrast enhanced FDG PET/CT to be superior to unenhanced PET/CT in assessing resectability. Another study assessed 46 patients with solid pancreatic lesions, the sensitivity and specificity of contrast enhanced PET/CT to detect malignancy was 89% and 74%. The use of other radiopharmaceuticals such as ^{18}F-fluorothymidine (FLT) may be a focus for future investigations. FLT PET assesses the proportion of cells undergoing active proliferation and this process occurs before a change in glucose metabolism. This may be useful in monitoring response to therapy. In a pilot study of five patients with pancreatic adenocarcinoma, who underwent FLT PET/CT, FDG PET/CT and contrast enhanced CT; FLT PET/CT demonstrated poor lesion detectability.

Surgery for pancreatic cancer

Hemant M Kocher
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Pancreatic cancer is a lethal disease [1, 2]. Surgical removal of pancreatic cancer is possible in a minority of patients. Surgical resection is a complex procedure with high morbidity and mortality and therefore should be performed in high volume centres with the requisite expertise [3]. Surgical resection should be performed adequately. Recent meta-analysis comparing pancreaticoduodenectomy with extended pancreaticoduodenectomy, performed by us, suggest that the extended lymph node resection does not offer survival benefit and may be detrimental to patients in the short term (due to increase in peri-operative complications) [4]. A meta-analysis comparing pancreaticoduodenectomy with pylorus preserving pancreaticoduodenectomy (PPPD) suggested that the smaller operation (PPPD) may have beneficial short-term and long-term effect for the patients [5]. Surgery should not be carried out solely to palliate patients, as better outcome may be achieved by less invasive means (endoscopic, radiological) [6].

Reference:

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Targets for prevention and treatment of pancreatic cancer

Prof Roland Schmid, Munich
Technical University of Munich, Germany

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Developing Pancreatic Cancer Medicine

Dr David Tuveson, MD PhD,
CRUk/Li-Ka Shing Cambridge Research Institute,
Cambridge University, Addenbrooke's Hospital

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Pancreatic cancer – is hypoxia a determinant?

Ralf Segersvärd
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About 50-60% of locally advanced solid tumors exhibit hypoxic tissue areas that are independent of size, stage, histology or grade. Tumor hypoxia is a result of an imbalance between supply and consumption of oxygen due to limitations in diffusion and/or perfusion of the tumor. Tumor associated anemia or carboxyhemoglobin formation in heavy smokers may contribute. Studies using O2 needle electrodes and endogenous markes have demonstrated hypoxia in in primary tumor and metastases of pancreatic tumors.
Common phenotypic properties of cancer cells are readily observed. Aerobic glycolysis in human cancers indicates adaptation to hypoxia and acidosis as major component of the carcinogenic sequence. However, microenvironmental selection forces are usually not included in the conceptual genetic models of carcinogenesis. Hypoxia induced aerobic glycolysis is critical for the final stages of evolution of a invasive phenotype with proliferative advantages even in normoxic conditions.
Data suggest that cellular adaptations to hypoxia and acidosis are usually mediated by upregulation of hypoxia inducible factor-1α (HIF-1α) and it targets genes eg. vascular endothelial growth factor (VEGF) or macrophage migration inhibitory factor (MIF). HIF-1α expression is positively correlated to tumor size, angiogenesis, metastatic potential, and a negative clinical outcome indicating that hypoxia in pancreatic cancer is a determinant.

Targeting pancreatic cancer stroma

Fieke E M Froeling

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Pancreatic cancer is a devastating disease with a poor prognosis, partially due to its poor response to the currently available chemotherapeutic drugs. One of the characteristics of pancreatic cancer is the deposition of a fibrotic extracellular environment, also called a desmoplastic stroma. The main cell type responsible for this stroma is the pancreatic stellate cell (PSC), which in pancreatic cancer changes from a quiescent fat-storing phenotype to a myofibroblast-like cell secreting extracellular matrix (ECM) proteins. By targeting these PSCs with 1μM all-trans retinoic acid (ATRA), we have shown that PSCs were rendered quiescent (demonstrated by a shift to the G1 phase of the cell-cycle and a characteristic expression profile in immunostaining and western blotting). Subsequently, in an physio-mimetic 3D organotypic co-culture model [1,2], we demonstrate that quiescent PSCs have an indirect effect on cancer cell morphology, proliferation (decrease), cancer cell death (increase) and invasion (decrease). Gene-expression profiling of PSCs treated with ATRA identified effects on numerous key canonical pathways, which will be discussed in detail. In conclusion, targeting the desmoplastic stroma offers exciting opportunities for therapy for pancreatic cancer.

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Pancreatic endocrine tumours: molecular insights

Prof Aldo Scarpa,
University of Verona

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Combining a novel oncolytic adenovirus mutant (AdΔΔ) with gemcitabine for improved efficacy in pancreatic cancer models

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Replication-selective oncolytic adenoviruses are promising tumour targeting agents with proven safety in hundreds of patients. However, viral mutants with higher potency are needed. The most frequent alterations in pancreatic cancer are deletions of p16, CDKN2 or p53 and activating mutations of the Kras gene, generating cells that enter S-phase in the absence of growth factors. Adenoviruses inactivate the same cellular pathways and complementation mutants unable to bind pRb and induce S-phase (ΔCR2 mutants) can readily infect and kill cells harbouring these gene alterations. Consequently, pancreatic cancer is an ideal target for E1ACR2-deletion mutants such as our newly generated AdΔΔ virus.

AdΔΔ was highly efficacious in all tested pancreatic carcinoma cells both alone and in combination with several chemotherapeutics including the standard of care gemcitabine and 5-fluorouracil (5FU). We found that deletion of the anti-apoptotic E1B19K-gene in AdΔΔ synergistically enhanced cancer cell killing in combination with chemotherapeutics by enabling a more potent apoptotic response. The absence of E1B19K-expression also eliminated toxicity to normal cells. Potency of AdΔΔ was higher than the clinically evaluated *dl*1520 (Onyx-015) and *dl*922-947 (AdΔ24RGD) mutants. Studies are in progress to determine cellular mechanisms for the cancer-selective synergistic cell killing.

These data suggest that our novel oncolytic mutant AdΔΔ is a promising candidate for targeting of pancreatic tumours in combination with chemotherapeutics.