The London Pancreas Workshop

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

Friday 2nd May 2014; Charterhouse Square, London UK

First draft programme

0930-1030: Diagnostics:

Chair: Prof Nick Lemoine & Dr Steve Pereira

0930-0950 Biomarkers to select adjuvant chemotherapy	Will Greenhalf, Liverpool
0950-1010 Circulating tumour cells	Andy Rhim, Michigan
1010-1030 Pancreas cancer risk: inflammatory-related factors	Nuria Malats, Madrid

1030-1100: Coffee Break

1100-1220: Treatment options:

Chair: Dr Tim Meyer and Mr Satyajit Bhattacharya

1100-1120 Bio-banking for pancreatic cancer	Aldo Scarpa, Verona
1120-1140 Neo-adjuvant therapy for pancreatic cancer	Rienk Offringa, Heidelberg
1140-1200 Innovative trials in pancreatic cancer	Pippa Corrie, Cambridge
1200-1220 New targets for therapy in pancreatic cancer	John Marshall, London

1220-1230 Q&A

1230-1330hrs: Lunch

1330-1500: Targeting pancreatic cancer: preclinical work

Chair: Prof Christopher Heeschen & Prof Duncan Jodrell

1330-1350 Targeting Hedgehog pathway in pancreatic cancer	Tony Magee, London
1350-1410 Targeting FGF signalling in pancreatic cancer	Richard Grose, London
1410-1430 Targeted mouse models for preclinical therapy trials	Jens Siveke, Munich
1430-1450 Targeting angiogenesis in pancreatic cancer	Kairbaan Hodivala-Dilke, London

1450-1500 Q&A

1500-1530: Tea

1530-1630: Paget Lecture

Chair: Mr Hemant Kocher

1530-1545 Introduction

1545-1630 Paget Lecture: TBC

Organisers: Prof Nick Lemoine & Mr HM Kocher

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Barts Health NHS Trust

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Biomarkers to select adjuvant chemotherapy
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Background: Clinical trials have identified small survival benefits conferred on populations of patients by specific chemotherapeutics. This is the result of significant benefit to some patients that outweigh a lack of benefit or even harm to other patients. Stratifying treatment so that the patient subgroups obtain the optimal therapy will obviously improve survival further. In addition it may be possible to monitor patients during treatment and change the chemotherapeutic as and when the cancer adapts to one drug while potentially gaining sensitivity to another. Biomarkers are needed to allow this stratification. Discussion topics: 1. Use of immunohistochemistry in the adjuvant setting with specific reference to evidence supporting hENT1 expression as a biomarker for gemcitabine efficacy. 2. Genomic analysis for stratifying patients with particular reference to SNPs in enzymes involved in drug metabolism. 3. Use of circulating tumour cells to stratify treatment with reference to next generation deep sequencing. 4. Technical problems associated with sample collection, antibodies, sequencing and PCR error.
1 Greenhalf W, Ghaneh P, Neoptolemos JP et al: Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the espac-3 trial. Journal of the National Cancer Institute 2014;106:djt347. 2 Costello E, Greenhalf W, Neoptolemos JP: New biomarkers and targets in pancreatic cancer and their application to treatment. Nat Rev Gastroenterol Hepatol 2012;9:435-444. 3 Greenhalf W, Thomas A: Combination therapy for the treatment of pancreatic cancer. Anticancer Agents Med Chem 2011;11:418-426

Using Circulating Pancreas Cells as Biomarkers for Early Pancreatic Cancer

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We have previously shown that blood stream seeding of pancreas epithelial derived cells occurs early during the natural history of pancreatic cancer. Using a lineage labeled genetically engineered mouse models of pancreatic ductal adenocarcinoma (PDAC), we identified and isolated circulating pancreas epithelial cells (CPCs) within the circulation (1). CPCs were detected prior to the formation of large tumors, at the earliest stages if invasive carcinoma. To determine if a similar phenomenon occurred in patients, we utilized microfluidic geometrically enhanced differential immunocapture (GEDI); GEDI had been validated to capture circulating tumor cells from patients with biopsy-proven prostate, breast, and lung cancer. In a recently published pilot clinical trial (2), we detected CPCs from 0 of 19 disease-free controls and 8 of 11 patients with PDAC. However, we detected significant numbers of Pdx-1+ and cytokeratin+ CPCs from patients (7 of 21) with precancerous cystic lesions of the pancreas that were deemed benign by Sendai criteria. Subsequent analysis revealed that a portion of CPCs indeed contained mutations in Kras. Current studies that will test if quantitative and genomic analysis of CPCs may be predictive of PDAC risk will be discussed.

1. Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, et al. **EMT and dissemination precede pancreatic tumor formation.** *Cell*. 2012;148:349–361

2. Rhim AD, Thege FI, Santana SM, Lannin TB, Saha TN, Tsai S, et al. **Detection of circulating pancreas epithelial cells in patients with pancreatic cystic lesions.** *Gastroenterology*. 2014;146:647-51.

Pancreatic Cancer: risk factors

Núria Malats

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Chronic inflammation, both local and systemic, is a major pathophysiological mechanism involved in pancreatic ductal adenocarcinoma (PDAC) development. Chronic pancreatitis (CP) is an established risk factor for PDAC; other systemic inflammatory factors (i.e. allergies, asthma, BMI, Type 2 diabetes, periodontitis, vit D levels, and *ABO* and *NR5A2* variants, among others) also impact on PDAC risk pointing to a highly correlated multifactor aetiology. The causal mechanisms behind these associations are unknown. Recent studies have highlighted the importance of microbiome abundance and diversity on the development and progression of a wide variety of chronic diseases, including cancer. Additional evidence supports the complexity of such associations, clouded by the interaction of the microbiome with host genetic and non-genetic factors. There is already some suggestive evidence of an association between the oral microbiome and pancreatic diseases. An integrative approach is fundamental to understand not only the variation in microbiome profiles associated with PDAC, but also to understand how these interact with other factors to ultimately affect the development of the disease. An improved understanding of the mechanisms behind immune response and PDAC may lead to novel preventive, diagnostic, and therapeutic strategies.

* EU Pancreas - BM1204 COST Action
www.eupancreas.com<http://www.eupancreas.com>

Biobanking for Pancreatic Cancer
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Aldo Scarpa is the Director of the ARC-NET Research Centre for Applied Research on Cancer and Chair of the Department of Pathology and Diagnostics at the University and Hospital Trust of Verona. Prof. Scarpa's recent achievements include the design, financing, and development of a research centre for the identification and clinical validation of diagnostic/prognostic markers and therapeutic targets in oncology (ARC-NET). He is also responsible for the Italian initiative within the International Cancer Genome Consortium (ICGC) sequencing rare pancreatic tumours and collaborates with Australia on pancreatic ductal carcinoma.
http://www.icgc.org/icgc/cgp/68/427/1221

T-cell Therapy of Pancreatic Cancer
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In contrast to the general belief that pancreatic ductal adenocarcinoma is a poorly immunogenic tumor, we found cumulative evidence for an adaptive immune response in this aggressive cancer type. Immunohistochemistry reveals prominent T-cell infiltrates in the majority (~ 70%) of tumor biopsies, and these tumor-infiltrating lymphocytes (TILs) can be isolated and expanded ex vivo with similar efficiency as those isolated from melanoma. Furthermore, comparison of the T-cell receptor repertoire between TIL and PBMC isolates from patients points at the selective expansion of T-cell subsets in the tumors. Finally, in ~ 50% of tumor specimen, T-cell infiltration is accompanied by the presence of tertiary lymphoid structures that comprise areas rich in CD3+ T-cells and CD208+ dendritic cells as well as areas rich in B-cells and follicular dendritic cells. Based on these findings, our current efforts aim at: • Evaluating neoadjuvant treatment with agonist immunostimulatory antibodies as a means to mobilize this pre-existing immune response in patients with primary resectable disease* • Analysis of the anti-tumor reactivity and antigen-specificity of TCR-species that are prominently enriched in the tumor as compared to PBMC. • Exploration of TIL therapy for treatment of recurrent disease.
** Clinical trial in context of FP7 EU IACT program; Immunostimulatory Antibodies for Cancer Treatment;* http://ec.europa.eu/research/health/medical-research/cancer/fp7-projects/iact_en.html

Innovative trials in pancreatic cancer

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In the UK, over 7,000 patients annually are diagnosed with pancreatic ductal adenocarcinoma (PDAC). The close match between incidence and mortality rates suggest that current treatment options for PDAC are currently of limited benefit. In the last 3 years, 2 multi-centre phase III trials have established 2 new chemotherapy regimens[1,2] with improved outcome compared with standard gemcitabine, the standard of care for almost 20 years. However, the associated survival benefits are very modest, while the potential for treatment-related toxicity is high. Meanwhile, numerous other phase III trials involving many thousands of patients with advanced PDAC have not delivered any significant benefits whatsoever. A greater understanding of PDAC biology suggests that genetic markers exist (eg. *SMAD4* gene inactivation[3]) which might identify subgroups of patients whose tumours behave differently and therefore might benefit from different treatment strategies. More imaginative studies need to be designed to exploit phenotypic and genotypic differences in PDAC. For example, optimal management of early and advanced PDAC pose different challenges and treatment goals differ. Measurement of primary PDAC is notoriously difficult and endpoints other than conventional RECIST warrant exploration. Collection of patient samples - tumour tissue, blood and other material relevant to the study hypothesis - are an essential component of PDAC clinical trials, in order to maximise learning opportunities. Through tailored trial design, positive signals should more reliably translate to phase III trial success and secure much needed improvements in outcomes for patients diagnosed with this inherently chemo- and radio-resistant cancer.

Key references:

Conroy T, Desseigne F, Ychou, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817-1825.

Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691-703.

Blackford A, Serrano OK, Wolfgang C, et al. SMAD4 gene mutations are associated with poor prognosis in pancreatic cancer. Clin Cancer Res 2009;15:4674-4688

The integrin αvβ6 is a promising target for the therapy of PDAC: Toward Phase I trials.

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Abstract: The integrin αvβ6 is expressed on the tumour cell surface in >90% of pancreatic ductal carcinomas (PDACs) and high levels of expression of the β6 gene correlates with reduced overall survival from PDAC (HR=1.74, Logrank $p=6x10^{-4}$). Using a panel of human PDAC cell lines and αvβ6-blocking antibodies we find that in PDAC cells αvβ6 mediates cell migration, invasion, proliferation and survival. Antibody blockade of αvβ6 in vitro of Panc0403 induced a G2/M phase block (compared with control, 6.5% to 16%) whereas in CfPac1 cells there was a significant increase in apoptosis (compared with control, the sub-G1 fraction increased from 8.5% to 46%). Thus αvβ6 may be an effective therapeutic target for treating PDAC. To test this we grew xenografts of CfPAc1 co-implanted with the human pancreatic stellate cell line PS-1. Histologically the subcutaneous implanted tumours were indistinguishable from orthotopic implanted tumours and showed increased desmoplasia and reduced angiogenesis compared with tumours derived from CfPac1 cells injected alone. Therapy with αvβ6-blocking antibody (264RAD, ip, 10mg/kg), gemcitabine (ip, 100mg/kg), diluent or both antibody and gemcitabine was given to mice bearing $100mm^3$ CfPac1/PS1 sc tumours for 6 weeks. While all three therapeutic arms were significantly effective, the greatest therapeutic effect was seen with the 264RAD/Gem combination followed by Gem and then 264RAD alone. In fact combination therapy eliminated tumours in some mice and reduced the volume of all xenografts below $12mm^3$. Immunohistochemistry showed in 264RAD-treated mice that there was reduced proliferation (Ki67) and growth signaling (pErk) but increased apoptosis (activated Caspase3) in tumour tissue. These data suggest that antibody targeting of αvβ6 in humans could have a major therapeutic effect and should be considered as part of future treatment regimens for PDAC.

Key references:

1: Allen MD, Thomas GJ, Clark S, Dawoud MM, Vallath S, Payne SJ, Gomm JJ, Dreger SA, Dickinson S, Edwards DR, Pennington CJ, Sestak I, Cuzick J, Marshall JF, Hart IR, Jones JL. Altered Microenvironment Promotes Progression of Preinvasive Breast Cancer: Myoepithelial Expression of αvβ6 Integrin in DCIS Identifies High-risk Patients and Predicts Recurrence. Clin Cancer Res. 2014 Jan 15;20(2):344-57.

2: Kogelberg H, Miranda E, Burnet J, Ellison D, Tolner B, Foster J, Picón C, Thomas GJ, Meyer T, Marshall JF, Mather SJ, Chester K. Generation and characterization of a diabody targeting the αvβ6 integrin. PLoS One. 2013 Sep 4;8(9):e73260.

3: Eberlein C, Kendrew J, McDaid K, Alfred A, Kang JS, Jacobs VN, Ross SJ, Rooney C, Smith NR, Rinkenberger J, Cao A, Churchman A, Marshall JF, Weir HM, Bedian V, Blakey DC, Foltz IN, Barry ST. A human monoclonal antibody 264RAD targeting αvβ6 integrin reduces tumour growth and metastasis, and modulates key biomarkers in vivo. Oncogene. 2013 Sep 12;32(37):4406-16.

Lipidation of Hedgehog proteins: function, enzymology and therapeutic potential in pancreatic cancer

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Hedgehog (Hh) proteins (Shh, Dhh and Ihh) are secreted intercellular signalling molecules important in mammalian development and also in the aetiology of many human cancers, hence the Hh signalling pathway is a popular target for development of anti-cancer therapies (1). Hhs are unique in being dually lipidated with a N-terminal amide-linked palmitate and a C-terminal cholesterol, added during its transit through the secretory pathway. These modifications are crucial for assembly into macromolecular complexes for cell-to-cell transport and also for biological function; non-lipidated Hhs are dramatically less potent than the fully lipidated protein.
Hedgehog acyltransferase (Hhat) is the enzyme responsible for palmitoylation of the N-terminal cysteine of Hh proteins, and belongs to the membrane bound O-acyltransferase (MBOAT) protein family. Knockdown experiments in pancreatic ductal adenocarcinoma and non-small cell lung cancer cells demonstrate that Hhat is crucial for Shh palmitoylation, assembly into macromolecular complexes and function as assessed by Hh pathway activation, cell growth and invasion, and para/juxtacrine signalling (2). Our results underline the potential of this enzyme as a target for chemotherapy in diverse human cancers including PDAC.
Our work has been greatly facilitated by development of bioorthogonal chemical labels for the palmitate and cholesterol moieties (3). Recent results using these to study novel inhibitors will be presented. Hhat is predicted to have 8-12 transmembrane domains but the true number is not known. We have made recent progress in analysis of the membrane topology of Hhat which will allow us better to understand how it functions, and aid in inhibitor screening.

Key references (3):

1. Dlugosz AA, Talpaz M. Following the hedgehog to new cancer therapies. N Engl J Med 2009; 361: 1202-5.
2. Konitsiotis AK, Chang SC, Jovanovic B, Masumoto N, Ciepla P, Palmer CP et al. Attenuation of Hedgehog acyltransferase-catalyzed Sonic hedgehog palmitoylation causes reduced proliferation and invasiveness of human carcinoma cells. *PLoSONE in press*.
3. Heal WP, Jovanovic B, Bessin S, Wright MH, Magee AI and Tate EW. Bioorthogonal chemical tagging of protein cholesterylation in living cells. Chem Comm 2011; 47: 4081-3.

Nuclear FGFR signalling as a driving force in pancreatic cancer
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Fibroblast growth factor (FGF) signalling provides a critical pathway mediating epithelial-mesenchymal crosstalk during organogenesis, and this axis is implicated in the growth of a wide range of cancers. Over-expression of FGFs and their receptors is a characteristic of pancreatic cancer and correlates with poor prognosis. We have studied the importance of FGF signalling during pancreatic stellate – cancer cell crosstalk both in clinical samples and in cell culture models. In particular, we have focussed on the significance of nuclear FGF/FGFRs. FGFR1 and its ligand FGF2 both localise to the nucleus in activated PSCs but not cancer cells, specifically at the invasive front of PDAC, and inhibiting FGF signalling in 2D and 3D cultures has particularly significant effects on PSCs, compared with cancer cells. Targeting FGFR signalling in 3D co-cultures showed that invasion of PSCs, and the cancer cells that track them, was critically dependent on FGFR kinase activity, suggesting that FGFR inhibition may represent a novel therapeutic approach for preventing pancreatic cancer cell invasion. Since immunofluorescence studies showed that nuclear FGFR1 localises to areas of active gene expression, we have begun investigating the mechanistic aspects of nuclear localisation, focusing on the mechanism of nuclear import and on identifying putative target genes. Dissecting the functional relevance of this nuclear localisation is fundamental to our understanding of the growing field of nuclear receptor tyrosine kinases, and may offer additional targeting possibilities for future treatment.
Key references Coleman SJ, Chioni AM, Ghallab M, Anderson RK, Lemoine NR, Kocher HM et al. Nuclear translocation of FGFR1 and FGF2 in pancreatic stellate cells facilitates pancreatic cancer cell invasion. EMBO Molecular Medicine. DOI: 10.1002/emmm.201302698. Turner N, Grose R. Fibroblast growth factor signalling: from development to cancer. Nature Reviews Cancer. 2010. 10(2): 116-29.

Targeted mouse models for preclinical therapy trials
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Pancreatic ductal adenocarcinoma (PDAC) remains a clinically most challenging and arguably the deadliest of all cancers. Recent advances in genetic characterization and preclinical modeling, powerful novel technologies for genetic and epigenetic analysis and novel therapeutic approaches all raise some hope to eventually overcome the grim resistance of this malignancy. Despite tremendous efforts, preclinical drug testing lacks predictive value for clinical success. However, recent developments in mouse modeling including patient-derived xenografts (PdX) and genetically engineered mouse models (GEMM) recapitulate many aspects of human PDAC. Latest advances include combination of genetic recombination systems and RNAI-mediated gene regulation. Recent studies using GEMM have shed light on the complex tissue- and context-specific signaling cascades in human cancers. Besides targeting of genes and signaling pathways of tumor cells, recent approaches have focused on targeting the stroma and immune system as well as combinations thereof. Thorough characterization of any therapeutic approach eventually requires sophisticated imaging modalities for assessment of tumor responses and resistance. We will provide examples of preclinical studies highlighting potentially promising approaches but also examples of early resistance. Such preclinical diagnostic and therapeutic trials, if performed in a well-controlled and standardized manner, will hopefully lead to the identification of novel approaches and their successful translation into clinical oncology.
Key references (3): Pancreatology format.

Stromal manipulation and Pancreatic cancer treatment

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Angiogenesis is the formation of new blood vessels from pre-existing ones. This process is thought to be essential for tumour growth and spread. Elucidating the molecular basis of tumour angiogenesis and how it regulates tumour growth and spread is therefore considered to be critical. Enhanced tumour blood vessel density is thought to correlate with poor outcome and thus attempts to reduce tumour blood vessel numbers and function, anti-angiogenic therapies, are a major focus of current cancer research. However, pancreatic ductal adenocarcinoma has a very low angiogenic index whilst having an extremely poor prognosis. Unpicking this paradox may lie the key to improved treatment of this cancer. Our laboratory has focused on understanding the roles of adhesion related molecules in tumour angiogenesis and we have come to realize that these molecules can provide both positive and negative regulatory functions. We have taken and *in vivo* approach to explaining how manipulation of the vasculature would affect pancreatic cancer treatment.

1: Kostourou V, Lechertier T, Reynolds LE, Lees DM, Baker M, Jones DT, Tavora B, Ramjaun AR, Birdsey GM, Robinson SD, Parsons M, Randi AM, Hart IR, Hodivala-Dilke. K. FAK-heterozygous mice display enhanced tumour angiogenesis. Nature Communication. 2013;4:2020.

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3: Reynolds AR, Hart IR, Watson AR, Welti JC, Silva RG, Robinson SD, Da Violante G, Gourlaouen M, Salih M, Jones MC, Jones DT, Saunders G, Kostourou V, Perron-Sierra F, Norman JC, Tucker GC, Hodivala-Dilke KM. Stimulation of tumor growth and angiogenesis by low concentrations of RGD-mimetic integrin inhibitors. Nature Medicine. 2009 Apr;15(4):392-400.

Paget Lecture: Introduction

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Barts had long tradition of distinguished physicians and surgeons working at its institute. This lecture commemorates Stephen Paget. His distinguished father Sir James Paget, lent his name to diseases of the bone and nipple. Both father and son introduced a number of surgical techniques at Barts. Stephen Paget, in the 1890s, was intrigued by the predilection of certain organs harbouring most of the metastasis in breast cancer patients. He coined the seed and soil hypothesis which was based on the concept that the soil in certain organs was more receptive to the metastatic cancer cell. This hypothesis was lent experimental basis by Ian Hart, in the 1980s. Ian Hart, ex-lead for Centre for Tumour Biology at Barts Cancer Institute. This has been cited as the first milestone in Cancer biology. He has retired recently sowing the seeds at the Institute, where many of the investigators are elaborating further on tumour-stroma interaction.

Matthias Hebrok will give this Paget Lecture dissecting the tumour-stroma interaction in pancreas.

1. Paget S. The distribution of secondary growths in cancer of the breast. *Lancet* **1**, 571–573 (1889).

2. Hart IR, Fidler IJ. Role of organ selectivity in the determination of metastatic patterns of the B16 melanoma. *Cancer Res.* **40**, 2281–2287 (1980).

3. http://www.nature.com/milestones/milecancer/full/milecancer01.html

4. Froeling FE, Feig C, Chelala C, Dobson R, Mein CE, Tuveson DA, Clevers H, Hart IR, Kocher HM. Retinoic acid-induced pancreatic stellate cell quiescence reduces paracrine Wnt-β-catenin signaling to slow tumor progression. Gastroenterology. 2011 Oct;141(4):1486-97.

Analyzing pancreas development with the goal to generate functional ß-cells from stem cells and prevent neoplastic transformation

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The pancreas is a heterogenous organ with all of the functional cells, including enzyme-producing acinar and hormone-generating endocrine cells are derived from the definitive endoderm. However, the endodermal cells require critical signals from surrounding mesenchyme for full differentiation and identification of such signals might be critical to direct differentiation of human stem cell populations towards Insulin-producing ß-cells. While functional studies delineating the exact function of pancreatic mesenchyme in the adult pancreas are missing, the fact that mesenchymal cells reside both in the endocrine and exocrine pancreas and that they change their appearance during diabetes and pancreatic cancer supports the notion that they continue to play important roles after development, both with regard to maintenance of normal function and in the context of pancreatic diseases.
Here, I will describe efforts to determine the role of the mesenchyme during pancreas development and present experimental strategies to identify mesenchymal factors that guide the differentiation of human embryonic stem cells towards ß-cells. In addition, I will discuss the plasticity of cells within exocrine pancreas and how distinct signals are required to induce neoplastic transformation of duct and acinar cells resulting in diverse subsets of pancreatic adenocarcinoma.

1. Landsman L, Nijagal A, Whitchurch TJ, Vanderlaan RL, Zimmer WE, MacKenzie TC, et al.: Pancreatic mesenchyme regulates epithelial organogenesis throughout development. PLoS Biol 2011 Sep;9:e1001143.

2. Guo T, Landsman L, Li N, Hebrok M: Factors Expressed by Murine Embryonic Pancreatic Mesenchyme Enhance Generation of Insulin-Producing Cells From hESCs. Diabetes 2013; 62(5):1581-92.

3. Figura von G, Fukuda A, Roy N, Liku ME, Morris Iv JP, Kim GE, et al.: The chromatin regulator Brg1 suppresses formation of intraductal papillary mucinous neoplasm and pancreatic ductal adenocarcinoma. Nat Cell Biol 2014 Feb 23; DOI: 10.1038/ncb2916