**ABSTRACT BOOK**

**Meritxell Rovira**
Universitat de Barcelona - IDIBELL, Barcelona.

**Shedding light on pancreas regeneration and PDAC cell of origin with single cell sequencing?**

*Pancreatic ducts form an intricate network of tubules that secrete bicarbonate and drive acinar secretions into the duodenum. This network is formed by centroacinar cells, terminal, intercalated, intracalated ducts, and the main pancreatic duct. Ductal heterogeneity at the single-cell level has been poorly characterized; therefore, our understanding of the role of ductal cells in pancreas regeneration and exocrine pathogenesis has been hampered by the limited knowledge and unexplained diversity within the ductal network.*

*In mouse, we used single cell RNA sequencing to comprehensively characterize ductal heterogeneity at single-cell resolution of the entire ductal epithelium from centroacinar cells to the main duct. Moreover, we used organoid cultures, injury models, and pancreatic tumor samples to interrogate the role of novel ductal populations in pancreas regenera tion and exocrine pathogenesis. We identified the coexistence of 15 ductal populations within the healthy pancreas and characterized their organoid formation capacity and endocrine differentiation potential. Moreover, we have characterized the location of these novel ductal populations in healthy pancreas, chronic pancreatitis, and tumor samples. The expression of Wnt-responsive, interferon-responsive, and epithelial-to-mesenchymal transition population markers increases in chronic pancreatitis and tumor samples.*

*In human, we have now mapped gene regulation in healthy pancreatic tissue including endocrine and exocrine epithelial cells as well as non-epithelial pancreatic cells. We have analyzed in depth ductal and mesenchymal heterogeneity using multiome (joint snRNA-seq and snATAC-seq) to characterize the cell type-specific gene regulatory programs of all epithelial pancreatic cell types in 8 healthy cadaveric donor pancreas We further characterize ductal cell heterogeneity and gene regulatory networks governing this heterogeneity. Moreover, most of the mesenchymal pancreatic cells are located nearby ductal cells, therefore we also characterized their heterogeneity as these cells might play a key role on fibrosis and exocrine pathogenesis. We have analyzed ligand-receptor interactions of mesenchymal cells and ductal cells and the signaling pathways involved in its communication. Comparison of mouse and human ductal heterogeneity highlighted species-specific differences between previously identified ductal populations. Moreover, correlation of the identified populations with pancreatic cancer subtypes suggests that Ly6D population correlates with basal A subtype while mucinous and chemokine secreting populations correlate with classical subtypes.*

*In light of our discovery of previously unidentified ductal populations, we unmask potential roles of specific ductal populations in pancreas regeneration and exocrine pathogenesis. Thus, we have developed novel lineage-tracing models to investigate ductal-specific populations in vivo.*

**Bruno Sainz**
Instituto de Investigaciones Biomédicas Sols-Morreale (IIBM), Madrid.

**Advances in understanding pancreatic cancer: from bench to preclinical models**

*Pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, has a median overall survival of only 6–12 months and a 5-year survival rate below 11–12%. PDAC is currently the fourth leading cause of cancer-related death worldwide but is projected to become the second by 2030. These dismal outcomes stem largely from the tumor’s intrinsic chemoresistance and metastatic potential, as well as the presence of a highly plastic subpopulation of “stem-like” cancer stem cells (CSCs). Over the past decade, significant progress has been made in understanding PDAC CSCs at the molecular, cellular, and metabolic levels. For instance, new biomarkers expressed by CSCs, such as autofluorescence, can stratify tumors into CSC-high and CSC-low groups with prognostic value. Using these markers to identify and isolate CSCs has proven valuable for patient subtyping and for developing personalized medicine platforms. Furthermore, specific CSC-dependent processes, including mitochondrial respiration, have been uncovered as pharmacologically targetable vulnerabilities - an Achilles’ heel of pancreatic CSCs. Herein, we will highlight these recent advances in PDAC CSC research and discuss their therapeutic and personalized medicine implications.*

**Justo P. Castaño**Maimonides Biomedical Research Institute of Córdoba (IMIBIC) and University of Córdoba, Spain.

**Dysregulated splicing is a new key player in pancreatic cancer**

*The development of genetic and multiomic landscapes of pancreatic cancer have provided a precise molecular picture of the disease and helped to identify its key drivers, yet, unfortunately, they barely improved patient survival. RNA biology is emerging as a powerful source of information and translational tools in cancer. In particular, altered splicing is growingly regarded as a novel cancer hallmark that pervades all other hallmarks. In pancreatic cancer, there is ample evidence that the splicing machinery is profoundly dysregulated. As a consequence, disruption of individual core spliceosome components and splicing factors such as SF3B1, RBMX, PRPF8, RBFOX2, QKI or SRSF1 can impart malignant features that comprise from proinflammatory, to oncogenic, metastatic and chemoresistant properties. Biocomputational and functional studies aimed at deciphering the mechanistic underpinnings of these pathological defects are unveiling novel tumor vulnerabilities and therapeutic opportunities to tackle pancreatic cancer. Moreover, neoantigens derived from altered splicing are being harnessed as a new strategy to develop personalized pancreatic cancer vaccines. Thus, a better understanding of alternative splicing and the ever-expanding regulation of RNA biology in pancreatic cancer can yield promising tools to combat this deadly disease.*

**Francisco X Real**
Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid.

**Leveraging genetic mouse models for precision prevention of pancreatic cancer**

*Patients with pancreatic ductal adenocarcinoma (PDAC) have a dismal prognosis, even when the tumor is diagnosed at an early stage. In addition, screening strategies are challenging, even in high-risk individuals. Therefore, it is mandatory to develop - in parallel - preventive strategies. Our lab aims at unveiling the molecular mechanisms involved in the early steps of PDAC development. Building on the knowledge of genetic and non-genetic risk factors, we use the excellent available genetic mouse models to identify mechanisms that sensitize the pancreas to the effects of mutant Kras, the oncogene involved in PDAC initiation. Using a variety of strategies, we have shown that pre-inflammation contributes to early PDAC and that AP-1 is involved in this process. Endoplasmic reticulum stress cooperates with metabolic factors and inflammation to promote PDAC development, as well. Finally, we show that genetically-driven risk can be suppressed through pharmacological manipulation. This knowledge can be leveraged to develop strategies for precision prevention in subjects at risk. In summary, the war against pancreatic cancer requires a "land, sea, and air" approach.*

**Jen Morton**
CRUK Scotland Institute, UK.

**Microenvironmental mechanisms of treatment resistance in mouse models of PDAC**

*The dense fibrotic microenvironment that surrounds and supports the tumour cells is a characteristic feature of pancreatic cancer. Each component plays an important role in pancreatic cancer progression, but also therapeutic response or resistance. To study this, we use genetically engineered mouse models that recapitulate human tumours and adapt them to mirror subsets of the disease. These models provide a clinically relevant platform for us to trial novel tumour and microenvironment targeting therapies.*

*We have found that the responses to therapeutic intervention vary significantly between different models, in part, due to the complex nature of tumour-stromal interactions in different models. We have also found that therapeutic interventions can have significant effects on the stroma which may favour tumour growth and treatment resistance. Here I will discuss our findings using radiotherapy, immunotherapy, and targeted therapies (both tumour cell and microenvironment targeting), in relevant models.*

**Vasiliki Liaki**
Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid.

**“Combined Targeted Therapy Achieves Durable Pancreatic Tumor Regression and Prevents Tumor Resistance”**

*Pancreatic ductal adenocarcinoma (PDAC) has one of the lowest cancer survival rates.*

*Recent studies using RAS(ON) inhibitors as single agents have opened the door to more efficacious therapies. Here, we demonstrate that genetic ablation of three independent nodes involved in downstream (RAF1), upstream (EGFR) and orthogonal (STAT3) KRAS signaling pathways leads to complete and permanent disappearance of orthotopic PDACs induced by KRAS/TP53 mutations. Likewise, a combination of RAS(ON) (RMC-6236/daraxonrasib), EGFR family (afatinib) and STAT3 (SD36) selective inhibitors/degraders induced the effective regression of these orthotopic tumors with no evidence of tumor resistance for over 200 days post-treatment. This combination therapy also led to significant regression of genetically engineered mouse tumors as well as patient derived tumor xenografts (PDX) in the absence of tumor relapses. Finally, this combination therapy was well tolerated by the animals. These results should guide the development of clinical trials that could benefit PDAC patients.*

**Peter Bailey**
Botton-Champalimaud Pancreatic Cancer Centre, Lisbon, Portugal.

**Genetic and non-genetic mechanisms driving progression and resistance to therapy in PDAC.**

*Pancreatic ductal adenocarcinoma (PDAC) remains a lethal malignancy characterized by profound therapeutic resistance.  Genomically, PDAC is defined by canonical driver mutations in KRAS, TP53, CDKN2A, and SMAD4. Recent research highlights a critical role for extrachromosomal DNA (ecDNA) in PDAC tumor progression. By carrying amplified oncogenes like MYC, ecDNA promote intratumor heterogeneity and plasticity. Therapy resistance is also increasingly understood to be governed by non-genetic plasticity, which may alter gene expression without DNA sequence changes. Central to therapeutic failure is the emergence of drug-tolerant persister (DTP) cells—a subpopulation of cells that survive initial cytotoxic insults and which may form a reservoir for relapse. This talk will focus on the complex interplay of genetic and non-genetic mechanisms driving disease progression and resistance to therapy in PDAC.*

**Dieter Saur**
German Cancer Research Center and the Technical University of Munich, Germany.

**Tumor host interactions in pancreatic cancer**

*To address the inherent complexity of PDAC, we have systematically mapped the tumor ecosystem using large-scale single-cell analyses across both human samples and genetically engineered mouse models. This effort has yielded a comprehensive PDAC cell atlas comprising over one million cells, enabling the resolution of distinct tumor subtypes and their associated immune microenvironments. These subtypes range from T cell–rich to myeloid- or neutrophil-dominated TMEs, each exhibiting distinct immunological and stromal features. Crucially, these immune phenotypes are not passive byproducts but are actively shaped by tumor-intrinsic programs and respond dynamically to therapeutic pressures.*

*To functionally interrogate the role of immune context in shaping PDAC evolution and drug response, we have conducted in vivo CRISPR-based genetic screens in both immunocompetent and immunodeficient mouse models. These screens explored how cancer cells adapt to and remodel their microenvironments and how specific TME components either support or restrict tumor progression. Insights from this work are guiding the development of combination therapies that concurrently target cancer cell–intrinsic pathways, the TME, and the immune system. For instance, in one line of investigation, we found that combining a MEK inhibitor (trametinib) with a multikinase inhibitor (nintedanib) remodels the TME in highly context-specific ways. In classical PDAC subtypes, this combination led to increased infiltration by neutrophils and myeloid-derived suppressor cells (MDSCs), failing to improve responsiveness to checkpoint blockade. In contrast, in basal-like subtypes, the same treatment enhanced recruitment of CD8⁺ T cells and M1-like macrophages, effectively converting an immunologically “cold” tumor into a “hot” one, and thereby sensitizing it to PD-1/PD-L1–directed immunotherapies. These findings underscore that a one-size-fits-all approach fail in PDAC - effective therapy will likely require tailoring to subtype or rationally combining treatments to induce a more favorable immune context. They also illustrate the principle that manipulating signaling pathways in tumor cells can have a profound indirect impact on immune infiltration and drug response, by altering the array of factors cancer cells secrete into their microenvironment.*

**Nuria Malats**
Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid.

**Metabolic Crossroads: Exploring the Diabetes–Obesity–Pancreatic Cancer Axis**

*Pancreatic ductal adenocarcinoma (PDAC) etiology is multifactorial. While type-2 diabetes mellitus is a well-established risk factor for PDAC, it remains uncertain whether it is a consequence or a cause of pancreatic cancer. It has even been suggested that both scenarios likely point to the existence of two subtypes of diabetes with different roles in pancreatic carcinogenesis: new-onset (NODM) and long-lasting diabetes (LSDM). Whether the tumor causes NODM or LSDM triggers carcinogenesis in the pancreas remained an unresolved dilemma. We characterized the causal relationship between diabetes mellitus subtypes and pancreatic cancer risk in detail using Mendelian randomization and mediation approaches. Our findings did not support a causal effect of LSDM on PDAC but suggest that PDAC causes NODM. We also examined the complex relationship between obesity, diabetes, and the risk of pancreatic cancer. We are currently investigating the roles of the fecal microbiome, serum metabolome, and germline DNA methylome in PDAC risk, specifically in relation to the two subtypes of diabetes mellitus. Additionally, we are applying spatial in situ single-cell RNA sequencing to identify differential expression profiles between LSDM and NODM.*

**Nelson Dusetti**Cancer Research Center of Marseille (CRCM) and Institut Paoli-Calmettes (IPC), France.

**Exploring the molecular routes of resistance in pancreatic cancer**

*Pancreatic ductal adenocarcinoma outcomes are constrained by profound inter- and intra-tumoral heterogeneity and the rapid emergence of chemoresistance. We developed Pancreas-View, a transcriptomics-based tool that integrates features from neoplastic, stromal, and immune compartments. It was trained on patient-derived models (primary cultures, organoids, PDXs) and calibrated in clinical cohorts to generate regimen-specific sensitivity scores (for gemcitabine- and 5-FU/oxaliplatin/irinotecan-based backbones) as well as an MDR (multidrug-resistant) class. In retrospective multicohort validation, including a PRODIGE resected series (n≈350) and independent metastatic cohorts, Pancreas-View stratified treatment benefit and showed improved survival when treatment was concordant with biomarker prediction. The MDR subgroup, although resistant to all standard regimens, exhibited consistent molecular features that defined a coherent biological entity. To resolve clonal drivers from routine bulk RNA-seq, we developed PANCprofiler, a reference-guided deconvolution algorithm that quantifies malignant cell-state spectra and detects the expansion of resistant subclones without requiring single-cell assays.*

*Together, these tools provide actionable patient stratification and mechanistic insights to guide therapy selection, inform rational combination strategies, and enable the identification of novel therapeutic targets for multidrug-resistant tumors. Ongoing multicenter prospective trials (PACsign-01, GemSign-01, NeoPREDICT) are evaluating Pancreas-View-guided treatment assignment and MDR-directed interventions.*

**Silvestre Vicent**
Centre for Applied Medical Research (CIMA, University of Navarra).

**Combination strategies to potentiate the effect of KRAS inhibitors**

*The systematic study of the underlying mechanisms ignited by oncogenic KRAS may lead to the identification of potential targets, in particular by integrating molecular data across tumors, and serve as the basis for developing novel therapeutic strategies. We recently uncovered the extracellular matrix protein LAMC2 as a functionally relevant target in pancreatic cancer. Exploration of the LAMC2 network unveiled druggable elements which provided the foundation for drug combination approaches with inhibitors of the KRAS pathway. These findings have been supported by pharmacological and CRISPR screen data positioning AXL as a potential mechanism of resistance to KRAS pathway inhibitors, including direct KRAS inhibitors. We have tested this hypothesis by concurrently inhibiting AXL and KRAS in in vitro (2D and 3D) and in vivo (immunocompetent and immunodeficient) pancreatic cancer models, showed that the anticancer effect is deeper than single treatments, and lastly identified mechanistic insights behind the antitumor efficacy of this drug combination.*

**Laura Soucek**
Vall d’Hebron Institute of Oncology (VHIO), Barcelona.

**The long journey to inhibit an “undruggable” target in pancreatic cancer and beyond**

*MYC is a most wanted target in cancer therapy long considered “undruggable”. Against this preconceived notion, Dr. Soucek’s laboratory designed and validated Omomyc, the most characterised direct MYC inhibitor to date, which demonstrated potent therapeutic impact in various mouse models of cancer. An Omomyc-based mini-protein therapeutic developed by Peptomyc S.L. – OMO-103 – has recently successfully completed a Phase 1 clinical study, demonstrating safety and encouraging signs of clinical activity, including in pancreatic cancer patients. OMO-103 is now being tested in a Phase Ib clinical trial in metastatic pancreatic adenocarcinoma patients in combination with standard of care chemotherapy.*

**Teresa Macarulla**
Vall d’ Hebron University Hospital, Vall d’ Hebron Institute of Oncology (VHIO), Barcelona.

**State of the art and new therapeutic options in advance pancreatic cancer**

*Pancreatic cancer (PDAC) presented dismal prognosis, with an estimated 5 years overall survival less than 15%. Chemotherapy is still the standard therapy for this disease, but the median overall survival achieved with this treatment is less than one year. There is an urgent need to find new treatment options in PDAC to improve the prognosis of patients with PDAC. 90% of PDAC presented mutation in KRAS, KRAS inhibitors are a potential practice changing therapy for PDAC patients. 10% of patients don´t have KRAS mutation, and in this population is more frequent to find potential targetable alterations such as nrg1 or RET fusions. Zenocutuzumab and selpercatinib demonstrated promising activity in PDAC patients with nrg1 fusion and RET fusion respectively. Zolbetuximab is an antibody against claudin 18.2, that is overexpressed in 35-40% of PDAC patients. A phase 2 clinical trial in first line setting tested the combination of gemcitabine and nab-paclitaxel (GN) +/-zolbetuximab. Results will be presented soon.*

*Other potential targets in early stage of development are PRMT5 inhibitors in patients with MTAP loss. This drugs have been tested as a monotherapy strategy or in combination with chemotherapy. Immunotherapy failed to demonstrate activity in PDAC due to the immune suppressive microenvironment in PDAC. Some strategies try to activate the immune microenvironment in this disease, like CD40 agonists, the combination of adenovirus plus chemotherapy or the combination of classical immunotherapy plus chemotherapy plus TTFields.*

*Globally 7% of PDAC patients presented a germline mutation in BRCA 1 or 2. Polo trial demonstrated that Olaparib, a PARP inhibitor, prolongs the progression free survival, compared with placebo after a period of treatment with platinum based chemotherapy. Currently new PARP inhibitors, and new combinations of PARP inhibitors with immunotherapy are trying to improve the results of the polo trial in this specific group of patients. The hope with these new therapeutic strategies is to improve survival rates for patients with pancreatic cancer in the next decade.*

**Ignacio Garrido-Laguna**Huntsman Cancer Institute - Cancer Hospital South; University of Utah School of Medicine, USA.

**Targeting KRAS beyond G12C**

*RAS mutations are present in more than 90% of patients with pancreatic ductal adenocarcinoma (PDAC). However, KRAS was considered undruggable for 40 years. A breakthrough to develop direct RAS inhibitors was the discovery of a new pocket in KRAS G12C with a highly reactive cysteine residue. This led to the identification of compounds that covalently bind to G12C and lock it in its non-active GDP bound state. Two of these compounds (Sotorasib and adagrasib) attained approval by the FDA in KRAS G12C non-small cell lung cancer and colorectal cancer. I will start discussing some of the lessons learnt from the development of G12C inhibitors. Then I will review early clinical data in PDAC with tricomplex inhibitors including RMC-6236, a multi-RAS(ON) inhibitor and RMC-9805, an allele-specific KRAS G12D(ON) inhibitor. I will review GFH-375, the first KRAS G12D(ON) non-tricomplex inhibitor to report activity in PDAC as well as  ASP3082, the first-in-class PROTAC targeting KRAS G12D. During this talk I will also introduce some of the ongoing first-in-human trials evaluating novel PanKras inhibitors as well as allele specific inhibitors (G12V, G12D) that are expected to report clinical data in next months. The talk will conclude with an overview of KRAS-targeted vaccine strategies currently in development, highlighting how immunotherapy may complement direct KRAS inhibition. Together, these advances reflect a rapidly expanding clinical trial landscape that will deeply impact how we treat patients with PDAC very soon.*