We focus on the molecular pathophysiology of pancreatic ductal adenocarcinoma (PDAC) and urothelial bladder carcinoma (UBC), adopting a disease-oriented approach. We use patient samples, cultured cells, and genetically modified mice, giving a similar weight to the 3 model systems. Observations made at either of these levels are then extended through additional work. To translate the findings, we bring this knowledge to a ‘population’ level – leveraging on information and samples from large patient cohorts – in close collaboration with Núria Malats’ Group.

In PDAC, a main hypothesis is that cell differentiation is a potent tumour suppressor mechanism acting early on in carcinogenesis. We use the excellent genetic mouse models available because these processes cannot be readily studied in humans. In mice, PDAC can originate in pancreatic progenitors and in adult acinar and ductal cells. Understanding the contribution of early molecular events is crucial to design better strategies for prevention and early tumour detection.

In UBC, we focus on identifying new genes, using them for improved tumour taxonomy, characterising the mechanisms of action, and applying this knowledge for improved prediction of outcome and therapy.

“Our Group was the initiator of the International Bladder Cancer Molecular Taxonomy Group, which, in 2019, released the Second Consensus Classification.”
Pancreas cancer molecular pathophysiology

The genetic/genomic changes associated with PDAC have been extensively described over the last few years by the genome consortia, and there is increasing interest in defining the contribution of precursor lesions and the molecular changes that precede tumour development. Our lab has pioneered the notion that cell differentiation is the first tumour suppressor process in the pancreas. Focusing on acinar cells, we have identified several novel players - and mechanisms - including GATA6, GATA4, NR5A2, HNF3A, and NFTC. Dysregulation of these transcription factors is associated with a scenario of pre-inflammation or inflammation and with predisposition to PDAC development using mutant K-Ras-driven genetic mouse models. These studies provide the basis for the pharmacological – or genetic – manipulation of acinar differentiation as a tumour preventative strategy.

We have found that while loss of either GATA6 or GATA4 favour PDAC development/progression in mice, these proteins play distinct roles in acinar differentiation and inflammation, and they contribute differentially to tumour initiation. We are now focusing on understanding their specific functions and deciphering their transcriptional programmes using a combination of mouse models and genomic approaches (i.e. RNA-Seq and ChIP-Seq). In collaboration with J. Ferrer (CRG, Barcelona), we have developed conditional knockout mouse models of Hnf1a that are providing new evidence of the tumour suppressor role of this gene in PDAC initiation. Using a dual recombine system, we are exploring whether HNF1 and its partner NR5A2, play similar roles in tumour maintenance. Our overarching goal is to establish the rules governing the transcriptional control of acinar differentiation and its contribution to preneoplasia and cancer.

STAG2 is a cohesin complex component. Increasing evidence shows that it acts as a tumour suppressor through rather unique mechanisms, largely unrelated to the canonical role of cohesin in chromosome segregation. Using normal cultured urothelial cells, we have found that the genomic effects of STAG2 loss are largely dependent on the differentiation state of the cells. These findings support the strong association of STAG2 inactivation with a luminal/urothelial phenotype and pave the way for the discovery of new mechanisms leading to UBC.

Our recent effort to develop organoids from normal urothelial cells has culminated in the first single cell RNA-Seq analysis of these cells, which provided novel evidence on the role of the NOTCH pathway in urothelial differentiation, and uncovered new genes associated with this process (FIGURE 1). The organoid cultures provide key clues to understanding urothelial stem cell biology and the control of cell proliferation and regeneration in homeostasis and upon damage.

Our translational studies focus on the prediction of response to cisplatin-based chemotherapy and to immune checkpoint blockade (ICB). In collaboration with an extended group of Spanish uro-oncologists and Núria Malats, we are assessing the value of immune signatures to stratify patients to receive neoadjuvant therapy (cisplatin-based chemotherapy vs ICB) in a randomised clinical trial.