ASSOCIATION FRANCAISE POUR LA RECHERCHE SUR LE CANCER DU PANCREAS

6ème Journée Scientifique de l'Association pour la Recherche sur le Cancer du Pancréas (AFRCP)

3 Novembre 2021

Hôpital Beaujon, Clichy

Bâtiment CHU, Amphithéâtre Baumann

Comité d'organisation:

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Dr. Richard Tomasini, CRCM, Marseille

Programme

9h30 – 10h15 Accueil des participants

10h15 Introduction du Président, Louis Buscail (CRCT, Toulouse).

10h30 – 11h10 N. Jonckheere (Modérateur)

Association of oxaliplatin-based chemotherapy and ATR inhibitor in pancreatic cancer
Marine Bruciamacchie, Inserm U1194, IRCM, Montpellier, France.

A new pancreatic adenocarcinoma-derived organoid model of acquired chemoresistance to FOLFIRINOX: first insight of the underlying mechanisms
Elsa Hadj Bachir, UMR9020 U1277, CANTHER, Lille, France.

Targeting cancer cells with basal-like, mesenchymal phenotype with oncolytic virus to inhibit the growth of pancreatic cancer
Pierre Cordelier, Cancer research center of Toulouse, Toulouse, France.

11h15 – 11h40 L. Buscail (Modérateur)

Deux lauréats 2019-2020 « Fonds d'amorçage en recherche » :

3D structural resolution and therapeutic targeting of the MUC4-ErbB2 oncogenic complex in the treatment of pancreatic cancer
Nicolas Stoup, UMR9020 U1277, CANTHER, Lille, France.

The CRISPR/CAS Technology for the detection of rare KRAS^{G12} mutant alleles
Samuel Amintas, INSERM U1035, Bordeaux, France.

11h45 – 12h30 L. Buscail (Modérateur)

Keynote: Submitting a paper to Gut… hearing back from Gut: (almost) all you want to know »

Francisco X REAL, CNIO, Madrid, Spain.

12h30 – 13h30 Déjeuner

13h30 – 14h10 Assemblée générale

14h10 – 14h55 S. Dabernat (Modératrice)

Keynote: KRAS in all of its states

Louis BUSCAIL, CRCT, Toulouse, France.

14h55 – 16h00 S. Dabernat (Modératrice)

PI3K signaling and tumoral metabolism in pancreatic cancer
Coralie Cayron, CRCT, INSERM U1037, Toulouse, France.

Targeting mitochondrial and redox metabolism to prevent relapse in pancreatic cancer
Nadine Abdel Hadi, CRCM, INSERM U1068, Marseille, France.

FAK kinase activity in cancer-associated fibroblasts impacts PDAC vascularization
Ismahane Belhabib CRCT, INSERM U1037, Toulouse, France.

TNFR2 blockade decreases immunosuppression in a mouse model of PDAC
Anaïs Debesset, Univ. Paris Est Créteil, INSERM, IMRB U955, Créteil, France.

Crosstalk between stromal compartment and macrophages lead to CD169+ macrophages in pancreatic ductal adenocarcinoma.
Kevin Thierry, CRCL, UMR INSERM 1052; Centre Léon Bérard, Lyon, France.

16h00 – 16h20 Pause-Café

16h20 – 17h25 A. Hennino (Modératrice)

Bioinformatical analysis of tumor cell with stroma crosstalk that impact aggressiveness of pancreatic ductal adenocarcinoma
Alexia Brunel, CRCT, INSERM U1037, Toulouse, France.

Dissecting and targeting tumour-stroma crosstalk mediated by extracellular vesicles in PDAC
Zainab Hussain, CRCM, INSERM U1068, Marseille, France.

RNAseq analyses from patient derived xenograft to decipher the stromal impact on the acquired chemoresistance to gemcitabine
Jérôme Raffenne, CRCT, INSERM U1037, Toulouse, France.

Orai1 channel regulates human activated pancreatic stellate cell proliferation and TGFβ1 secretion through the AKT signaling pathway
Silviya Radoslavova, Laboratory of Cellular and Molecular Physiology (Amiens) & INSERM U1003-PHYCEL-Cellular Physiology (Lille), France.

Tenascin-X is abolished during pancreatic carcinogenesis in profit to its pro-tumoral counterpart, Tenascin-C
Elise Lambert, LBTI, UMR CNRS 5305, Lyon Cedex 07, France.

Intramuscular islet auto transplantation following extended pancreatectomy for IPMN
Mikael Chetboun, Lille University Hospital, INSERM, EGID, Lille, France.

Keynotes

- **Submitting a paper to Gut… hearing back from Gut: (almost) all you want to know »**

  Francisco X REAL, CNIO, Madrid, Spain.

➢ KRAS in all of its states

Louis Buscail

Department of Gastroenterology and Toulouse Centre for Cancer Research - INSERM UMR 1037, University of Toulouse, Rangueil Hospital and Oncopole, Toulouse, France

In pancreatic carcinoma, the major genetic event remains the activating point mutation of the *KRAS* oncogene. The KRAS protein is thus permanently activated as well as downstream signalling pathways, consequently maintaining the cellular processes of proliferation, transformation, invasion and survival. Activation of KRAS is also responsible for many cellular functions such as production of lactate and reactive oxygen species, micropinocytosis, interactions between the cancer cells and the surrounding stroma and tumour microenvironment. For many years, the study of this major oncogene has made it possible to decipher and unravel pancreatic oncogenesis through relevant mouse models based on the targeted activation of *KRAS* G12D in the pancreas. Using these transgenic models, many processes have been studied and dissected, in particular the role of other genes or inflammation in pancreatic carcinogenesis, but also the important role of the tumour microenvironment. These models are also valuable for testing new molecules or therapeutic strategies.

KRAS study has also a clinical interest: detection of *KRAS* mutations can be performed in a variety of biological samples including fresh and fixed tumour tissue or biopsy, fine-needle aspiration materials and cytology, total blood and plasma. The *KRAS*-mutation assay can be combined with endoscopic ultrasound-guided cytopathology in order to increase the sensitivity, the negative predictive value and accuracy of cytopathology alone for the positive diagnosis of pancreatic cancer and its differential diagnosis with chronic pancreatitis. In addition, the presence of *KRAS* mutation in tumour tissue, biopsy as well as in serum and plasma correlates with a worse prognosis of pancreatic cancer patients whether or not they undergo curative surgery. *KRAS* mutation assay could also provide important predictive information on tumour progression and recurrence. Finally, the presence or not of mutated *KRAS* can also have therapeutic implications, especially at gene level and during its post-translational maturation as well targeting interaction of KRAS protein with adaptor proteins or nucleotides and downstream oncogenic signal proteins.

- Buscail L et al. Role of oncogenic KRAS in the diagnosis, prognosis and treatment of pancreatic cancer. Nat Rev Gastroenterol Hepatol. 2020;17:153-168.
- Moore AR et al. RAS-targeted therapies: is the undruggable drugged? Nat Rev Drug Discov. 2020;19:533-552.

Communications orales

1 - Association of oxaliplatin-based chemotherapy and ATR inhibitor in pancreatic cancer

M. Bruciamacchie[1], N. Vie[1], V. Garambois[1], P-E. Colombo[2], C. Gongora[1], C. Larbouret[1]

[1] Inserm U1194, IRCM, Montpellier, France; [2] ICM, Surgery department, Montpellier, France.

Pancreatic Ductal Adenocarcinoma (PDAC) is an extremely aggressive disease with no efficient treatment. Recently, a new polychemotherapy oxaliplatin-based (FOLFIRINOX) has been approved but associated with toxicity and limited efficiency[1]. Most of the drugs induce their toxicity by provoking DNA damages and replication stress leading to the activation of DNA repair pathways[3]. Recently, a PARP inhibitor has been approved by the FDA for patients with BRCA mutated PDAC showing the potential of this type of therapy[2]. Therefore, in this project, we added an ATR inhibitor (ATRi) to FOLFIRINOX to increase responses and analyzed the effect of this combination on the tumor microenvironment [3,4,5].

Viability matrix in 2D & 3D co-culture of tumor cells with primary CAFs were carried out and DNA damage repair pathways, cell death and autophagy were analyzed. *In vivo*, immunodeficient mice xenografted with ATCC and Patient Derived Xenograft models were treated with FOLFIRINOX and ATRi to evaluate the effect on tumor progression.

A synergistic effect of the combination was demonstrated in pancreatic models in co-culture with CAFs independently of the DDR deficiency. A higher apoptosis and DNA damages were observed in tumor cells treated with the combination associated with a decrease of DNA repair pathways and an inhibition of the autophagy flux. A protective effect of the CAFs on tumor cells was observed and secretome of CAF analysed. In vivo, the combination inhibits significantly the tumor growth compared to each treatment alone.

A validation of this polychemotherapy in vivo using co-culture models in immunodeficient mice is crucial to confirm the therapeutic potential of this new treatment for PDAC.

1. Conroy et al., New Engl J Med 2011
2. Golan T et al, NEJM 2019
3. Perkhofer L, et al. Gut 2021
4. Dreyer SB et al., Gastroenterology 2020
5. Combès E et al., Cancer Research 2019

Keywords: pancreatic cancer, polychemotherapy, co-culture, Cancer-associated Fibroblast, DNA damage, cell death pathways

2 - A new pancreatic adenocarcinoma-derived organoid model of acquired chemoresistance to FOLFIRINOX: first insight of the underlying mechanisms

E. Hadj Bachir[1*], C. Poiraud[1,2*], S. Paget[1], N. Stoup[1], S. El Moghrabi[1], B. Duchêne[1], N. Jouy[3], A. Bongiovanni[3], M. Tardivel[3], L-B. Weiswald[4], M. Vandepeutte[1], C. Beugniez[1,2], F. Escande[5], E. Leteurtre[1,6], OrgaRES consortium[§], L. Poulain[4], C. Lagadec[1], P. Pigny[1], N. Jonckheere[1], F. Renaud[1,6], S. Truant[1,2], I. Van Seuningen[1*], A. Vincent[1*]

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* Both authors contributed equally to this work.
§ OrgaRES consortium: C. Mariette, G. Piessen, F. Corfiotti, C. Eveno, F-R. Pruvot, S. Truant, M. El Amrani, E. Leteurtre, F. Renaud, V. Gnemmi, L. Wicquart, F. Escande, J. Leclerc, S. Paget, A. Vincent, I. Van Seuningen.

Although improvements have been made in the management of pancreatic adenocarcinoma (PDAC) during the past 20 years, the prognosis of this disease remains poor with an overall 5-year survival under 10% (Vincent et al., 2011; Mizrahi et al., 2020). Treatment with FOLFIRINOX is nonetheless associated with an excellent initial tumor response and its use has allowed numerous patients to go through surgery while their tumor was initially considered unresectable (Murphy et al., 2018). These discrepancies between initial tumor response and very low long-term survival are the consequences of rapidly acquired chemoresistance and represent a major therapeutic frontier. Patient-Derived tumour Organoids (PDO) are relevant to evaluate tumor sensitivity to cancer therapies, including pancreatic cancers, and are useful to study the mechanisms of innate or acquired resistance (Baker et al., 2017; Boj et al., 2015).

In this study, we first extrapolated physiological concentrations of the three drugs combined in the FOLFIRINOX regimen (5-fluorouracil, irinotecan/SN-38 and oxalipatin) using previous pharmacodynamics studies and bi-compartmental elimination models of oxaliplatin and SN-38. We then treated PaTa-1818x naive PDAC organoids with six cycles of 72h- FOLFIRINOX treatment followed by 96h interruption.

We reproductively obtained resistant organoids, FoxR, which are representative of the sequential steps of chemoresistance observed in patients in terms of growth arrest (proliferation blockade), residual disease (cell quiescence/dormancy) and relapse.

To our knowledge, this work introduces the first genuine PDO model of acquired resistance to the three drugs combined in the FOLFIRINOX, recapitulating as accurately as possible clinical aspects of pancreatic cancer chemoresistance. This model could pave the way for new therapeutic strategies.

Vincent, A. et al. (2011). Pancreatic cancer: An overview. Lancet *11*, 168–180.
Mizrahi, J.D. et al. (2020). Pancreatic cancer. Lancet *395*, 2008–2020.
Murphy, J.E. et al. (2018).Total Neoadujuvant therapy with FOLFIRINOX followed by individualized chemoradiotherapy for bordeline resectable pancreatic adenocarcinoma. JAMA Oncol. 963-969
Baker LA et al. Modeling pancreatic cancer with organoids. 2017;2(4):176–90.
Boj, S.F et al. (2015). Resource Organoid Models of Human and Mouse Ductal Pancreatic Cancer. Cell 160, 324–338.

3 - Targeting cancer cells with basal-like, mesenchymal phenotype with oncolytic virus to inhibit the growth of pancreatic cancer

P. Garcin [1], H. Lulka[1], M. Vienne[1], N. Dusetti[2], L. Buscail[1,3], N. Panté[4], and P. Cordelier[1,*]

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Pancreatic cancer (PDAC) is soon to become the second cause of death by cancer in the western world and remains one of the most aggressive of all cancers due to the lack of efficient treatment or diagnostic markers. Recently, molecular investigations revealed two main tumor phenotypes that stratify patients with PDAC. While gene expression classifications proved prognostic value, PDAC molecular subtyping is yet to inform precision medicine strategies. Oncolytic virotherapy is fastly emerging as credible anticancer agent for the treatment of numerous cancer entities. Oncolytic viruses have already shown great safety during clinical trials, including in PDAC. Among them, the fibrotropic minute virus of mice prototype (MVMp) shows promise, but its oncolytic potential has not been fully explored in PDAC models. We report here that MVMp specifically targets, replicates within and kills primary PDAC cells both from mouse or patient origin, with a mesenchymal, basal-like profile, when normal cells, or cells with classical phenotype were left unarmed. Molecular investigations indicate that RhoC is critical for MVMp infection of PDAC cells. Systemic delivery of MVMp in immunocompetent models significantly decreases the growth of experimental orthotopic tumors with basal-like, mesenchymal phenotype, and stimulates an antitumoral immune response. Collectively, we demonstrate herein for the first time that MVMp is specific and oncolytic in PDAC tumors with mesenchymal, basal-like profile, paving the way for precision medicine opportunities for the most aggressive form of PDAC tumors.

Garcin PO, Panté N. Cell migration is another player of the minute virus of mice infection. Virology. 2014 Nov;468-470:150-159. doi: 10.1016/j.virol.2014.08.001. Epub 2014 Aug 28. PMID: 25173091.

Grekova SP, Raykov Z, Zawatzky R, Rommelaere J, Koch U. Activation of a glioma-specific immune response by oncolytic parvovirus Minute Virus of Mice infection. Cancer Gene Ther. 2012 Jul;19(7):468-75.

4 - 3D structural resolution and therapeutic targeting of the MUC4-ErbB2 oncogenic complex in the treatment of pancreatic cancer

N. Stoup[1], M. Liberelle[2], J. Franck[3], R. Magniez[1], N. Renault[4], X. Thuru[1], N. Jonckheere[1], I. Fournier[3], N. Lebègue[2] and I. Van Seuningen[1]

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Pancreatic cancer is a deadly cancer for which no diagnosis or no efficient treatments exist. The incidence for this cancer is constantly increasing for years[1] (+247.7% globally between 1980 and 2012), whereas conventional therapies and/or targeted therapies often remain inefficient and/or fail[2]. So, this cancer has risen a serious problem of public health, for which new therapeutic targets are urgently needed. In this way, the MUC4 mucin is highly regarded as a potent target as it is neo-expressed in early neoplastic precursor lesions. In the laboratory, we have shown the pro-tumorigenic role of the MUC4-ErbB2 complex[3]. Moreover, we have identified the EGF domains of MUC4 as involved in this interaction with ErbB2 and in tumor progression[4]. Unfortunately, the 3D structure of the complex, necessary to develop therapeutic targeting, is still unknown.

In this project, using the Carbene Footprinting technology[5], an innovative biophysical approach based on surface mapping of binding sites in protein-protein interactions, we aim at solving the interface of interaction between MUC4 and ErbB2. For the first time, we have experimentally identified the amino acids on the EGF domains of MUC4 involved in the interaction with ErbB2. These data will allow us to better understand and solve the 3D structure of the complex and propose (i) efficient ligands targeting the EGF domains of MUC4 (ii) to reduce the tumor progression in pancreatic cancer. This strategy could provide new therapeutic options for this deadly cancer, aiming at increasing patient survival, quality of life and decrease treatment costs.

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM.Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014 Jun 1;74(11):2913-21.
2. Garrido-Laguna I, Hidalgo M. Pancreatic cancer: from state-of-the-art treatments to promising novel therapies.Nat Rev ClinOncol. 2015 Jun;12(6):319-34.
3. Jonckheere N., Van Seuningen, I. The Membrane-Bound Mucins: How Large O-Glycoproteins Play Key Roles in Epithelial Cancers and Hold Promise as Biological Tools for Gene-Based and Immunotherapies. Crit RevOncog.2008; *14*(2-3): 177–196.
4. Stoup, N., Liberelle, M., Schulz, C., Vasseur, R., Magnez, R., Thuru, X., Melnyk, P., Renault, N., Jonckheere, N., Lebegue, N. Van Seuningen, I. The EGF domains of MUC4 oncomucin interact with ErbB2 and mediate tumorigenic activity of cancer cells represent new potential therapeutic targets. Cancer Res. 2021. Vol81 Issue13 SupplementS Meeting AbstractLB106!m:
5. Manzi L, Barrow AS, Scott D, Layfield R, Wright TG, Moses JE, Oldham NJ. Carbenefootprinting accurately maps binding sites in protein-ligand and protein-protein interactions. NatureComm. 2016; *16*(7) :13288.

5 - The CRISPR/CAS Technology for the detection of rare KRAS^{G12} mutant alleles

S. Amintas[1], L. Karembe[1], G. Cullot[2], D. Cappellen[1], B. Turcq[2], V. Prouzet-Mauléon[2], A. Bedel[1], F. Moreau-Gaudry[1] and S. Dabernat[1]

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The diagnosis of pancreatic ductal adenocarcinoma necessitates tumor biopsy by endoscopic ultrasound fine needle aspiration (EUS-FNA), which shows insufficient negative predictive value. As mutations in the *KRAS* oncogene are very common in PDAC, their detection from circulating tumor elements may prove powerful for PDAC formal diagnosis but this requires a level of sensitivity challenging the available molecular tools. We assessed the emerging CRISPR/Cas technology promising the high discrimination of single nucleotide polymorphisms.

Cas13a RNA guides hybridizing various positions of the *KRAS* target were designed to detect *KRAS*^{G12V}, *KRAS*^{G12C} and *KRAS*^{G12D} alleles. Mismatches around the single mutation of interest were tested to prevent hybridizing the wild-type allele. Mutant allele detection was tested on matrix containing known concentrations and compared to Q-PCR, allele-specific Q-PCR and ddPCR. The sensitivity of a 15nt deletion of the *EGFR* was compared to that of single mutation.

The position of RNA guide affected the ability of Cas13a to detect *KRAS* alleles and the possibility to discriminate between different alleles. We observed efficiency variations between mutations, possibly related secondary structures of the matrices and the nature of the mismatches between the guide and the matrix, which may also affect specificity. The detection of a 15 nt deletion mutation in the *EGFR* gene reached total specificity and increased the sensitivity by 50 times as compared to the gold standard ddPCR.

As other sensitive tools, CRISPR/Cas13a technology is challenged to detect mutant variants outnumbered by WT alleles. However, the use of highly discriminant guides outperforms the gold standard ddPCR for the detection of rare alleles. It is implemented with a simple workflow, without expensive equipment. Efforts are still needed to increase the specific detection of single mutations.

- Abudayyeh OO, Gootenberg JS, Essletzbichler P, Han S, Joung J, Belanto JJ, Verdine V, Cox DBT, Kellner MJ, Regev A, Lander ES, Voytas DF, Ting AY, Zhang F. RNA targeting with CRISPR-Cas13. Nature. 2017 Oct 12;550(7675):280-284. doi: 10.1038/nature24049. Epub 2017 Oct 4. PMID: 28976959; PMCID: PMC5706658.

- Gootenberg JS, Abudayyeh OO, Kellner MJ, Joung J, Collins JJ, Zhang F. Multiplexed and portable nucleic acid detection platform with Cas13, Cas12a, and Csm6. Science. 2018 Apr 27;360(6387):439-444. doi: 10.1126/science.aaq0179. Epub 2018 Feb 15. PMID: 29449508; PMCID: PMC5961727.

- Kellner MJ, Koob JG, Gootenberg JS, Abudayyeh OO, Zhang F. SHERLOCK: nucleic acid detection with CRISPR nucleases. Nat Protoc. 2019 Oct;14(10):2986-3012. doi: 10.1038/s41596-019-0210-2. Epub 2019 Sep 23. Erratum in: Nat Protoc. 2020 Mar;15(3):1311. PMID: 31548639; PMCID: PMC6956564.

6 - PI3K signaling and tumoral metabolism in pancreatic cancer

C. Cayron[1,2], B. Thibault[1,2], M. Di Luoffo[1,2], N. Therville[1,2], C. Guyon[1,2], J-E. Sarry[1] and J. Guillermet-Guibert[1,2]

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Pancreatic cancer (PDAC) patients have a low survival rate; chemotherapy does not cure. In 80% of the cases, KRAS mutation is present. PI3K pathway is a KRAS downstream target, that regulates glycolysis and insulin response [1]. Targeting PI3Kα and γ isoforms reduces PDAC tumor progression [2]. However, the importance of PI3K isoforms in tumoral metabolism regulation in PDAC is unknown. This knowledge is critical as the modulation of PDAC tumoral metabolism represents a promising therapeutic strategy.

Using transcriptomic databases of human pancreatic tumors, we searched for specific metabolic signatures associated with the level of expression of PI3Kα and PI3Kγ. We analyzed the metabolic flexibility after long-term treatment with PI3K inhibitors (Vehicle, BYL-719 (PI3Kα selective inhibitor), IPI-549 (PI3Kγ selective inhibitor) or the combination BYL-719 and IPI-549) in vitro (cell lines) or in vivo (xenograft of human tumor cells Capan-1 in female nude mice). Conversely, we analysed the same parameters in pancreatic cancer lines stably overexpressing PI3Ks. The metabolic parameters of tumor cells studied are: mitochondrial ROS, mitochondrial mass, mitochondrial membrane potential, viability and ATP production by pancreatic tumor cells in the presence of mitochondrial and / or glycolysis inhibitors. Finally, sensitivity to gemcitabine, the standard treatment for pancreatic cancer, was tested alone or in combination with metabolic pathway inhibitors (Phenformin, CPI-613 or 2-DG). In particular, we used CPI-613, a lipoic acid analogue, that blocks the activity of α-KG (α-ketoglutarate dehydrogenase) and PDH (pyruvate dehydrogenase).

Patients with high expression of PI3Kα and PI3Kγ (αHigh; γHigh) in the pancreatic tumor were associated with the basal subtype and a low probability of long-term survival; on the other hand, patients with low tumor expression of PI3Kα and PI3Kγ (αLow; γLow) exhibited characteristics of the classic pancreatic cancer subtype and had an encouraging probability of long-term survival. These tumors (αLow; γLow) expressed genes involved in glyco-oxidative metabolism while tumors (αHigh; γHigh) did not present an obvious metabolic signature. Tumors (αLow; γLow) were associated with the expression of genes involved in the assembly of cytosolic iron-sulfur aggregates and of genes involved in the assembly of mitochondrial complexes. Inhibition of PI3Kα and γ in vivo increased the level of tumor ROS (reactive oxygen species) without impacting the mitochondrial mass and the mitochondrial membrane potential. Tumor cells treated with the BYL-719 and IPI-549 combination were more sensitive to the combination Gemcitabine + metabolism modulators (CPI-613 or 2-DG) than the tumor cells treated with vehicle. Modulating the activity of PI3K changed metabolic dependencies (orientation towards a glyco-oxidative metabolism) and sensitized cells to its targeting. We are now exploring the underlying molecular mechanisms and validating whether the overexpression of PI3K mimics the effect of inhibitors.

Inhibition of PI3Ks may be a way to force pancreatic cancer tumor cells into a metabolism that makes them sensitive to combinations of chemotherapy drugs and metabolic inhibitors. These inhibitors act by increasing mitochondrial ROS leading to cell death of pancreatic cancer cells.

[1] Halbrook CJ, Lyssiotis CA. Employing Metabolism to Improve the Diagnosis and Treatment of Pancreatic Cancer. Cancer Cell 2017;31:5–19. https://doi.org/10.1016/j.ccell.2016.12.006.
[2] Cintas C, Douche T, Dantes Z, Mouton-Barbosa E, Bousquet M, Cayron C, et al. Phosphoproteomics identifies PI3K inhibitor-selective adaptive responses in pancreatic cancer cell therapy and resistance. Mol Cancer Ther 2021. (in press)

7 - Targeting mitochondrial and redox metabolism to prevent relapse in pancreatic cancer

N. Abdel Hadi[1], G. Reyes Castellanos[1], R. Masoud[1], T. Gicquel[1], E. Baudoin[2], N. Auphan Anezin[2], J. Iovanna[1] and A. Carrier[1]

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Mitochondrial metabolism is an emerging target in currently refractory cancers such as Pancreatic Ductal AdenoCarcinoma (PDAC) since mitochondria are implicated in chemoresistance [1]. We hypothesize that mitochondrial metabolism is reprogrammed in PDAC tumor during therapeutic treatment, supporting the relapse of PDAC patients. Our objectives are to: (1) Demonstrate this reprogrammation during chemotherapy, and (2) Target the involved pathways to prevent relapse.
We performed in vivo assays treating tumor-bearing mice with Gemcitabine alone or in combination with Perhexiline, a mitochondrial Fatty Acid Oxidation inhibitor. We used two mouse models: (1) heterotopic xenografts using human PDAC cells, and (2) syngeneic orthotopic allografts using murine PDAC cells. The tumors generated from these assays were analyzed at limit point ex vivo by flow cytometry to measure mitochondrial and redox characteristics. Total ATP level and molecular mechanisms underlying the reprogramming were determined.

In the first xenograft, Gemcitabine treatment induces complete tumor regression. In the second one, Gemcitabine treatment in combination with Perhexiline induces complete regression. In allograft model, all tumors regress during Gemcitabine treatment. But in both models, tumors relapse after stopping treatment. Ex vivo analysis of relapsing tumors shows a deregulation of mitochondrial and redox metabolism in both models, increase in energy capacity, and an overexpression of antioxidant genes.

Relapsed PDAC tumors result from the proliferation of persistent/residual cells [2] which survived during therapy-induced regression through the establishment of redox metabolic adaptations. Targeting redox metabolism is a candidate approach to sensitize residual cancer cells to cell death and prevent relapse in PDAC [3].

1. Masoud, R. et al. Targeting Mitochondrial Complex I Overcomes Chemoresistance in High OXPHOS Pancreatic Cancer. Cell Reports Medicine 1, 100143 (2020).

2. Shen, S., Vagner, S. & Robert, C. Persistent Cancer Cells: The Deadly Survivors. Cell 183, 860–874 (2020).

3. Abdel Hadi, N., Reyes-Castellanos, G. & Carrier, A. Targeting Redox Metabolism in Pancreatic Cancer. Int J Mol Sci 22, (2021).

Keywords: Pancreatic ductal adenocarcinoma, energetic metabolism, oxidative stress, mitochondria, therapeutic relapse.

8 - FAK kinase activity in cancer-associated fibroblasts impacts PDAC vascularization

I. Belhabib [1], S. Zaghdoudi [1], C. Bousquet [1] and C. Jean [1]

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Chemotherapy reaches the tumor through the vasculature, making the blood vessel quantity and quality a key regulator of the chemotherapy efficacy. Importantly, cancers such as pancreatic ductal adenocarcinoma (PDAC) are very poorly vascularized (collapsed and permeable vessels). PDAC, one of the most aggressive cancers is characterized by a strong desmoplastic reaction (accumulation of extracellular matrix (ECM) proteins due to the fibroblasts activation into cancer-associated fibroblasts (CAF) (Belhabib et al. Cancers 2021)), that participates to the generation of the aberrant and leaky vasculature. **We hypothesize that regulating the desmoplastic reaction could promote vessel "normalization" and subsequently enhance chemotherapy penetration within the tumor**.
We have recently identified that inhibiting the protein tyrosin kinase FAK (Focal adhesion kinase) in CAFs drastically decreases PDAC spontaneous metastases (Zaghdoudi et al. EMM 2020) supporting the idea of the implication of blood vessels. We postulate that the inactivation of FAK in CAFs may induce a crosstalk with vasculature cells (endothelial cells or pericytes) leading to the normalization of the vasculature.

In order to address that question, we developed two PDAC immunocompetent mouse model in which CAFs express an active or inactive FAK: 1- orthotopic and syngeneic mouse model of co-grafted FAK-WT or FAK-KD (kinase Dead) fibroblasts plus pancreatic tumor cells (KPC) and 2- immunocompetent inducible pancreatic fibroblast specific inactivation of FAK mice model.
By performing a Matrisome (mass spectrometry analysis leading to ECM protein quantification) on mice tumors from model 1, we show that FAK inactivation specifically in CAFs dramatically modifies the ECM composition: important decrease of "pro-tumoral ECM protein" level associated with a strong increase of basement membrane (BM) protein level. Immunohistochemical analysis of the BM protein localization reveals an accumulation of Collagen IV specifically around the blood vessels. As vessel BM regulates their stability and permeability, we evaluated the impact of fibroblastic FAK inactivation on vascular permeability by performing a « Miles Assay » *in vivo*. This test consists in the injection of a dye into the mice tail vein and analyzing its leak into different organs (an accumulation of the dye into an organ indicates that the vasculature is abnormally permeable). We show that fibroblastic FAK inactivation decreases vascular permeability in PDAC tumors and in lungs (metastasis organ) revealing a vessel « normalization ». The next step was to identify the involved mechanisms: we hypothesized that CAFs, dependently of their FAK activation status, could secrete soluble factors impacting BM protein production/secretion by endothelial cells or pericytes. Thus, pericytes or endothelial cells were incubated with conditioned medium produced by CAFs pretreated or not with FAK inhibitor (FAKi), and BM protein level were analyzed by immunofluorescence and western blot. Preliminary results support the idea that fibroblastic FAK activity is a key regulator of the establishment of a crosstalk between CAFs and vasculature cells involved in the pericyte-induced BM protein generation and deposition around vessels.

Altogether, we show that FAK inactivation in CAFs inhibits spontaneous metastasis (Zaghdoudi et al EMM 2020) and « normalizes » blood vessels through a mechanism involving a CAF/pericyte crosstalk and a pericyte-induced BM protein production. Our work supports the idea that a co-treatment composed of FAK inhibitor and chemotherapy should enhance chemotherapy delivery within the tumor (as the vasculature should be normalized), thus, being a treatment beneficial for PDAC patients.

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10 - Crosstalk between stromal compartment and macrophages lead to CD169^{+} macrophages in pancreatic ductal adenocarcinoma.

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Pancreatic ductal adenocarcinoma (PDAC) is associated with an abundant stromal reaction, which accounts for up to 80-90% of the tumor mass. Macrophages represent one of the major immune cell populations in tumor microenvironment and have been previously shown to display a M2 phenotype and an immunosuppressive role. We sought to determine the respective roles of the tumoral and stromal compartment in impacting macrophages phenotype and function. We used two different primary cell lines isolated from stromal and tumoral compartment respectively from mice with neoplasia and PDAC and co-cultured them with bone marrow derived macrophages. We report here that, in contrast to the tumoral compartment, the stromal compartment induces i) macrophages polarization towards a M2-like phenotype by expressing PD-L1, CD206 and, ii) a significant increased production of the immunosuppressive extracellular protein βig-h3 and iii) suppression of CD8^{+} T cell proliferation. Furthermore, upon stromal-macrophage crosstalk, we identified the induction of a newly described macrophage population CD169^{+}Tim4^{+} and the production of CXCL12 chemokine by the stromal compartment. This work may lead to the identification of a new immunosuppressive population playing a role in PDAC progression.

Keyword: Pancreatic cancer, macrophages, immune response

11 - Bioinformatical analysis of tumor cell with stroma crosstalk that impact aggressiveness of pancreatic ductal adenocarcinoma

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Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive cancers due mostly to its high metastatic and chemoresistance features. Hence, 5-year life expectancy is below 9% with a 6-month mean survival after diagnosis. PDAC is characterized by highly invasive pancreatic cancer cells, immerged in an exuberant stroma, which represents up to 80% of the tumor volume. Both tumor and stromal cells have to interact in order to survive in this harsh micro-environment.
Two major molecular (transcriptomic) subtypes of PDAC were clearly described through bio-informatical sequencing analysis of RNA extracted from patient tumor regions enriched with cancer epithelial cells: a dedifferentiated and more aggressive (associated with poor outcome) "basal" subtype, and a "classical" subtype presenting more general differentiation features and a better outcome. Molecular heterogeneity of the PDAC stroma was also studied through bio-informatical deconvolution analyses of bulk RNA sequences (extracted from tumor samples composed of both cancer epithelial and stromal cells); these analyses also stratified PDAC within two prognostic stromal subgroups, which however don't mirror the two identified epithelial (basal / classical) subgroups.

By performing bioinformatical analysis on transcriptomic data (RNAseq) from PDX (Patient Derived Xenograft), a hybrid tumor model from which human-derived tumor cell sequences are distinguishable from murine-derived stromal cell sequences, we searched for different stromal behaviours linked to the aggressiveness of the tumor, to be then validated in published PDAC patient databases.

According to NMF (Non-negative matrix factorization) and GSEA (Gene Set Enrichment) analyses, we identified two components allowing us to classify the samples according to a stromal gradient. Interestingly, these components are characterised by distinct functional signatures of aggressiveness and they are highly prognostic (correlated with survival). In addition, these components stratify patients independently on the described molecular tumor (basal / classical) classification. The results obtained (functional signatures as well as the impact on survival) were then validated on other PDAC published databases. Moreover, ligand-receptor bioinformatics analyses identified novel players of the TGFB superfamily in the most aggressive component.

Further analyses (bioinformatical and experimental) will now enable us to identify specific stromal therapeutic targets to be functionally tested using already available patient-derived cell models, including patient-derived tumor cell organoids and cancer-associated fibroblasts. Therapeutic targeting of the stroma must take into account its functional heterogeneity, and the functional validation of the newly identified players should define a promising axis for targeting the most aggressive PDAC.

Keywords : Stroma, Heterogeneity, Crosstalk, Aggressiveness, PDAC

12 - Dissecting and targeting tumour-stroma crosstalk mediated by extracellular vesicles in PDAC

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Pancreatic ductal adenocarcinoma (PDAC) represents one of the most malignant cancers worldwide with a low survival rate1. The tumour-microenvironment (TME), consisting of heterogeneous cell populations including cancer-associated fibroblasts (CAFs) and tumour-associated macrophages (TAMs), actively contributes to tumour progression, immune evasion and chemoresistance2. TME cells are in constant communication with tumour cells which may perpetuate pro-tumoural signals through extracellular vesicles (EVs), nanometer to micrometer-sized vesicles transmitting various signals between cells. This study investigates the impact of tumour cell (TC)-EVs on TME cells, CAFs and monocytes, one of the precursors of TAMs, hypothesizing that tumour cells, via EVs, maintain and modify pro-tumoural CAF populations, and recruit monocytes to produce immunosuppressive TAMs.

EVs were extracted from PANC-1 medium and incubated with primary human CAFs and healthy donor-derived monocytes, and resulting phenotypes were studied. Proteomics analyses were performed on monocytes and CAF-derived extracellular matrix (C-ECM) following TC-EVs treatment.

TC-EVs modify C-ECM fibre organization, enhancing migration and invasion of TCs on these ECM. EVs-treated CAFs decrease most cytokine production but increase IL-12/-13, and MIP-1-delta. TC-EVs differentiate monocytes into M2-like macrophages, with increased adhesion, phagocytosis, survival, granularity, expression of M2 markers, and decreased expression of MHC-II. Proteomics reveal Wnt/B-catenin and BMP signaling pathways dysregulation in both EVs-C-ECM and EVs-monocytes.

TC-EVs modify TME cells to produce a pro-tumoural environment, through modulation of C-ECMs and differentiation of immunosuppressive TAMs. Subsequent crosstalk between these TME populations, under the influence of TC-EVs, its' mechanisms and potential targets are currently under investigation in order to limit its impact on tumour development.

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13 - RNAseq Analyses from Patient derived xenograft to decipher the stromal impact on the acquired chemoresistance to gemcitabine

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The pancreatic ductal adenocarcinoma (PDAC) is refractory to chemotherapies. Stroma remodeling is observed in neaoadjuvant-treated resected patients suggesting an altered Stromal-Tumoral communication promoting chemoresistance. Our aim is to characterize this chemo-induced stroma remodeling and assessed its role in the treatment escape with the use of a patient derived xenograft model (PDX).

Height PDXs were treated with Gemcitabine (GEM) and defined as Responsive (Resp) if stabilized tumoral growth was observed at sampling, or Nonresponsive (Nresp) if exponential growth upon GEM treatment was observed (similar to Untreated PDXs). PDXs (UT=30, Resp=15, NResp=25) were characterized by bioinformatics after RNA-sequencing and a Stromal-GEM-Sensitive-signature was built after independent component analysis (ICA).

PDXs were Resp to GEM in the first line of treatment (Fn), then Nresp (regrafting, Fn+1) after a first ~10 week lasting phase of Response to GEM followed by treatment escape. The same Two-phase kinetic of GEM response was observe in Fn+2 PDX. Unsupervised analyzes showed that "Resp" can explain the RNAseq samples variability in Tumoral and Stromal compartments compare to NResp and UT samples close to each others. By ICA (Ncomponent=8), we selected the component number 6 (IC6) as the most correlated with our PDX GEM responsiveness ($p<1.10\text{-}10$). It is associated with an "Inactivated Stroma" ($p<0,001$) and "Immune Stroma" ($p<0,001$) classification (GSEA analysis, projection to Puleo's dataset with tumor patients' RNAseq). No correlation was seen with Classical/Basal-like classification. IC6 correlated with the GEM prediction score developed by Nicolle *et al*. Based on the tumoral compartment.

We were able to build a Stromal-Gemcitabine-Response-Signature. GEM treatment did not promote a switch to the Basal-like subtype, but a stromal modulation. Future combination of our signature with tumoral signatures (Molecular gradient/GEM prediction, Nicolle R. et al) may improve the prediction of patient response to GEM.

14 - Orai1 channel regulates human activated pancreatic stellate cell proliferation and $TGF_{\beta 1}$ secretion through the AKT signaling pathway

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Pancreatic ductal adenocarcinoma is defined by an extensive desmoplastic stroma, mainly orchestrated by the activated pancreatic stellate cells (aPSCs). aPSCs are characterized among others, by high proliferative potential and abundant transforming growth factor $_{\beta 1}$ ($TGF_{\beta 1}$) secretion (Ferdek and Jakubowska, 2017). Furthermore, over the past years, the role of the calcium-permeable channels in PSC's pathophysiology has attracted great interest in pancreatic cancer research (Radoslavova et al., 2020). We, hence, aimed to investigate the role of the Orai1 calcium channel in these two PSC activation processes. Using the siRNA electroporation approach, we invalided Orai1 expression in human aPSC lines and assessed the channel functionality by calcium imaging. We, thereafter, evaluated the effect of Orai1 silencing on aPSC proliferation by MTT colorimetric assay and on $TGF_{\beta 1}$ secretion by Elisa assay. We supported our results by assessing the associated-signaling pathway using the western blot technique. We demonstrated, for the first time, the functional expression of the Orai1 channel in human aPSCs and its implication in the store-operated calcium entry (SOCE). Orai1 silencing led to a decrease of aPSC proliferation, $TGF_{\beta 1}$ secretion, and AKT activation. Interestingly, $TGF_{\beta 1}$ treatment induced a higher SOCE response by increasing Orai1 mRNAs and proteins, and promoted both AKT phosphorylation and cell proliferation, abolished by Orai1 silencing. Together, our results highlight the role of Orai1-mediated calcium entry in human aPSC activation, by controlling cell proliferation and $TGF_{\beta 1}$ secretion, through the AKT signaling pathway. Moreover, we showed a $TGF_{\beta 1}$-induced autocrine positive feedback loop by promoting the Orai1/AKT-dependent proliferation via the stimulation of Orai1 expression and function.

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15 - Tenascin-X is abolished during pancreatic carcinogenesis in profit to its pro-tumoral counterpart, Tenascin-C

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Throughout Pancreatic Ductal AdenoCarcinoma (PDAC) progression, a dense extracellular matrix is deposited around neoplastic cells and accompanies tumor development and aggressiveness. This stroma could include targets for innovative therapies to improve patient survival.

Through *in silico* analyses of Gene Expression Omnibus database and immunohistochemical labelling on human Tissue MicroArray and on sections of [LSL-*Kras*^{G12D}; *Ink4a/Arf*$^{lox/lox}$; *Pdx1*-Cre] (KIC) mouse model, we investigated the expression of two members of the Tenascin matricellular protein family during pancreatic carcinogenesis: (1) Tenascin-X (TNX) that we previously described as commonly lost in numerous solid tumors and (2) Tenascin-C (TNC), which is generally up-regulated during cancer and associated with poor prognosis.

We thus demonstrated *TNXB* gene expression and TNX protein level are drastically decreased in pancreatic tumor samples, and this loss tends to be correlated with higher grade tumors and reduced survival. On the contrary, TNC is significantly upregulated. Subsequently, we correlated *TNXB* and *TNC* dysregulations in human PDAC samples to antagonistic modulations of various biological processes and notably proliferation. This Gene Ontology analysis was then confirmed *in vivo* by Ki67-positive cell immunodetection on human and mouse samples.

Altogether, our results show TNX is lost during pancreatic carcinogenesis and suggest an anti-proliferative role of TNX as opposed to its pro-tumoral counterpart, TNC. Further experiments are required to determine the mechanism by which these Tenascin members could exert opposing effects on tumor cell proliferation and to consider using TNX or one of its fragments as a new therapeutic tool for pancreatic cancer and/or solid tumour treatment.

16 - Intramuscular islet auto transplantation following extended pancreatectomy for IPMN

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Pancreatic islet autotransplantation is emerging as a therapeutic option to limit the metabolic burden of extensive pancreatectomy. Human islets are usually infused into the portal vein with risks of bleeding and/or portal thrombosis, which may compromise the outcome of the graft (2).

Intramuscular autotransplantation may offer a minimally invasive alternative (3). We report here a case of intramuscular islet autotransplantation following extended pancreaticoduodenectomy (PD) for IPMN.

A 64-year-old female patient with a family history of pancreatic ductal adenocarcinoma presented with IPMN lesions, combining a 35-mm central cystic tumor and smaller secondary ductal lesions of the pancreatic body. The PD procedure, extended to the body of the pancreas, left only a 4 cm left pancreatic remnant. The head of the pancreas was sent for extemporaneous histological examination which confirmed the diagnosis of IPMN with low-grade dysplasia. The body of the pancreas was preserved in UW solution and shipped to the cell therapy platform located at 1050 km for islet isolation at D0 and transplanted at D3, into the brachioradialis muscle (49422 islet equivalents). At 3 months, fasting blood glucose (1.01 g/L) and HBA1c (5.6%) were within normal values in the absence of any antidiabetic treatment.

The function of ectopic islets, as well as their contribution to overall insulin secretion, was documented by bilateral assessment of the acute insulin response to arginine (AIRarg), without or with vascular exclusion of the left forearm ectopic islet transplant site.

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