1ST EDITION

YOUNG RESEARCHERS WORKSHOP

5TH / 6TH / 7TH OCTOBER 2023 | PORQUEROLLES ISLAND

cancéropôle Provence-Alpes-Côte d'Azur
le propulseur régional des recherches et innovations anticancers

RÉGION SUD PROVENCE ALPES CÔTE D'AZUR

INSTITUT NATIONAL DU CANCER

LA LIGUE CONTRE LE CANCER
VAR

1ST EDITION

WORKSHOP FOR YOUNG RESEARCHERS IN CANCER

5TH / 6TH / 7TH OCTOBER 2023 | PORQUEROLLES ISLAND

THURSDAY OCTOBER 5TH

13:00 WELCOME LUNCH

14:00 OPENING CEREMONY
Canceropôle's Director & Scientific Committee President

14:15 SESSION 1 "NEW THERAPIES & RESISTANCE"
(Drug Design, Cancer Stem Cells, Tumor Heterogeneity)

Keynote speaker: Emmanuelle Charafe-Jauffret - CRCM / IPC
"Targeting breast cancer heterogeneity"

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

- *"Triple-negative breast cancer metastasis involves complex epithelial - mesenchymal transition dynamics and requires vimentin"* Éloïse Grasset - CRCI²NA
- *"CTGF: A new therapeutic strategy in metastatic renal cell carcinoma?"* Manon Teisseire - IRCAN
- *"Targeting tumor exosomal communication"* Raphaël Leblanc - CRCM
- *"Integrin-alpha V beta 3 is a fundamental factor in medulloblastoma tumorigenicity and radioresistance: A new game for an old player"* Christopher Montemagno - Centre Scientifique de Monaco

16:00 BREAK

16:15 SESSION 2 "SIGNALIZATION – MOLECULAR MECANISMS"

Keynote Speaker: Jean-Ehrland Ricci - C3M / UCA
"Metabolic control of anti-tumor immunity"

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

- *"Translational landscape of MAP3K8/MEK signaling in ovarian cancers : impact on cell metabolism and chemosensitivity"* Martina Serafini - Institut Curie
- *"OTX2, a potential therapeutic target for group 3 medulloblastoma?"* Aurélie Farnet - iBV
- *"Targeting Stress Granule Formation as a Synthetic Lethality Strategy for Kras-Induced Pancreatic Cancer Initiation"* Patricia Santofimia Castaño - CRCM
- *"Switching adhesion, invasion, and molecular properties of hepatocellular carcinoma cells by targeting the secreted glycoprotein ADAMTSL5"* Aurélie Dobric - CRCM

18:00 END OF THE FIRST DAY

FRIDAY OCTOBER 6TH

09:00 SESSION 3 "MICROENVIRONMENT – IMMUNOTHERAPIES"

Keynote Speaker: Eric Vivier - Professor of Immunology, CIML, AP-HM / AMU - Scientific Director, Innate Pharma
"Harnessing innate immunity in cancer therapy"

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

- *"Dissecting tumor sensitivity to NK cell-mediated lysis"* Hakim Medjouel - CIML
- *"Variation in lipid species profiles among leukemic cells significantly impacts their sensitivity to the drug targeting of lipid metabolism and the prognosis of AML patients"* Caroline Lo Presti - CHU Grenoble Alpes
- *"Role of JAM-C-mediated adhesion in the maintenance of stemness of acute myeloid leukemia cells"* Céline Testut - CRCM

10:30 COFFEE BREAK, POSTER SESSION & FREE TIME FOR DISCUSSION

- *"Reprogramming anti-inflammatory macrophages through cathepsin B and caspases inhibition to improve cancer therapies"* Emeline Kerreneur - C3M
- *"Combined CAR-NK & CAR-gdT cells as a therapeutic tool post Allo-HSCT"* Nassim Salem - CRCM

11:30 SESSION 4 "SENESCENCE – INITIATION – DNA DAMAGE – GENOMIC INTEGRITY"

Keynote Speaker: Dmitry Bulavin - IRCAN
"In search of molecular Shangri-La:building disease tolerance & broad defense mechanisms by p16High immune cell subsets"

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

- *"Role of Neutrophil Extracellular Traps (NETs) in squamous cell carcinoma (SCC) initiation"* Alexandra Mousset - IRCAN
- *"EPIC-SCENITH: Single-cell readout of immunometabolism and epigenetics in cancer"* Paulina Garcia-Gonzalez - CIML
- *"Timing of lesion tolerance pathways in Saccharomyces cerevisiae"* Katarzyna Maslowska - CRCM
- *"P21 driven expression of Telomerase prevents Adipose Tissue Senescence"* Laura Braud - CRCM

13:15 LUNCH BREAK

14:30 TEASING PLATFORMS OF PROVENCE-ALPES-CÔTE D'AZUR

15:00 FREE TIME TO EXCHANGE WITH PLATFORMS COORDINATORS

16:30 SESSION 5 "IA & CANCER"

Keynote Speaker: Sébastien Benzekry - Inria, CRCM / IPC
"Integrative kinetics & machine learning modeling for prediction of outcome following immunotherapy in lung cancer"

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

- *"Electronic medical records processing pipeline for clinical data structuring and interactive statistical exploration"* Sara Contu - CAL
- *"Generative models for clinical datasets"* Paul Dufossé - Inria / CRCM

18:00 POSTER SESSION & AWARDS CEREMONY

SATURDAY OCTOBER 7TH

09:00 TRAININGS OR FREE TIME

- ***Training 1:*** Atelier prise de parole (in FRENCH)
- ***Training 2:*** "Collaboration Management": The keys to successful collaborations (in ENGLISH)

13:00 LUNCH & END OF THE WORKSHOP

canceropôle Provence-Alpes-Côte d'Azur – le propulseur régional des recherches et innovations anticancers

RÉGION SUD PROVENCE ALPES CÔTE D'AZUR

INSTITUT NATIONAL DU CANCER

LA LIGUE CONTRE LE CANCER VAR

FRENCH LEAGUE AGAINST CANCER, VAR COMMITTEE

The French League Against Cancer, is a close-knit community made up of 103 committees across France, including the French oversea territories. About a hundred volunteers and only two employees team up in the Var committee which is headquartered in Toulon with half a dozen of delegations spread throughout the administrative area. This committee shares the same goals as the 102 others, and benefits from national support for communication, financial, scientific or legal issues.

In fact, these objectives could be summarized in one word: to provide cancer patients and their families with all the help they need. Namely, today's patient is offered any kind of supportive care, counselling and the League is the only one charity providing direct financial assistance in times of need (300 to 400 cases per year). League volunteers are also involved in the hospitals as users representatives and in the process of patients empowerment. The promotion of screening mainly for breast, colon, rectum and HPV-induced cancers is aimed to increase the proportion of early stage-cancers in future patients and, therefore to improve the survival rates. Similarly, promoting prevention, in the best-case scenario can prevent the onset of cancer as has been demonstrated for tobacco-induced lung cancers or various types of HPV-induced cancers, and consequently, this approach allows our society to reduce the burden of cancer diseases. The role of screening is emphasized during dedicated months such as Pink October or Blue March for breast or colon cancers, respectively. The committee runs all these information campaigns with the support of our national organization. Screening and prevention information is also repeated all year round, everywhere as close as possible to the target population: companies, administrations, insurances companies, schools, universities, associations. Finally, today's and tomorrow's patients benefit from research, and our committee subsidizes accredited research teams in the south of France, as it does with the Canceropôle Sud. Let's remember the League charity is the leading funding association for cancer research in France.

As public contribution is limited to less than 2% of our budget, we can admit that all our resources come from the public generosity (up to 6000 donors and some companies). Knowing the operating budget is contained at 15%, including payroll, marketing and operating expenses, federation royalties etc.., roughly 2 thirds of the remaining resources are allocated to the research field while patients or their families receive the final third in the form of direct financial assistance. Screening and prevention information is freely given by the volunteers as well as a large part of supportive care and counselling.

Even the humblest intervention by a volunteer in a village market is fully appreciated as part of a wider effort to improve all aspects of cancer care.

THURSDAY, OCTOBER 5TH

SESSION 1 "NEW THERAPIES & RESISTANCE"

Keynote Speaker: **Emmanuelle Charafe-Jauffret** – CRCM / IPC, Marseille
"Targeting breast cancer heterogeneity"

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

"Triple-negative breast cancer metastasis involves complex epithelial-mesenchymal transition dynamics and requires vimentin"
Eloïse Grasset – Centre de recherche en cancérologie et immunologie intégré de Nantes-Angers

Triple-negative breast cancer (TNBC) is an aggressive subtype associated with early metastatic recurrence. TNBC tumors express molecular markers of the epithelial-mesenchymal transition (EMT), but its requirement during spontaneous TNBC metastasis in vivo remains incompletely understood. We demonstrated that TNBC tumors from a genetically engineered mouse model (GEMM), multiple patient-derived xenografts, and archival patient samples exhibited large populations in vivo of hybrid E/M cells that lead invasion ex vivo while expressing both epithelial and mesenchymal characteristics. The mesenchymal marker vimentin promoted invasion and repressed metastatic outgrowth. We next tested the requirement for five EMT transcription factors and observed distinct patterns of utilization during invasion and colony formation. These differences suggested a sequential activation of multiple EMT molecular programs during the metastatic cascade. Consistent with this model, our longitudinal single-cell RNA analysis detected three different EMT-related molecular patterns. We observed cancer cells progressing from epithelial to hybrid E/M and strongly mesenchymal patterns during invasion and from epithelial to a hybrid E/M pattern during colony formation. We next investigated the relative epithelial versus mesenchymal state of cancer cells in both GEMM and patient metastases. We observed a complex spectrum of epithelial, hybrid E/M, and mesenchymal cell states. Together, our results demonstrate an important and complex role for EMT programs during TNBC metastasis.

"CTGF: A new therapeutic strategy in metastatic renal cell carcinoma ?"
Manon Teisseire – IRCAN, Nice

Exacerbated angiogenesis and an immunotolerant context characterize renal cancer (RCC) and uveal melanoma (UM), a rare disease with a different aetiology from cutaneous melanoma. Despite considerable efficacy of first-line treatments (anti-angiogenic
/immunotherapies (RCC), proton therapy (UM)), patients develop metastases. Currently, the combination of anti-angiogenic and immunotherapies delays the fatal problem of RCC and treatment of metastases from UM patients is not very efficient.
ELR+CXCL are pro-angiogenic/pro-inflammatory cytokines and exert their effects via the G-protein-coupled receptor CXCR2. High levels of ERL+CXCL cytokines in the tumor correlate with shorter survival of RCC and UM patients. Given the importance of this pathway in both tumors, we developed a pharmacological inhibitor of CXCR2 (RCT001), which we tested first for RCC aggressiveness and then for UM aggressiveness.
It decreased proliferation and induced death of RCC and UM cells; it inhibited angiogenesis (in vitro and in vivo), the production of ROS, and it reversed the polarisation of M2 macrophages (pro-tumor) into M1 macrophages (anti-tumor). It reduced the growth of experimental RCC and UM in immunodeficient mice, and it acted synergistically with immunotherapies (anti-PD1+/-anti-CTLA4). Therefore, RCT001 appears to be a breakthrough for the treatment of aggressive tumors in the therapeutic dead-end.
This work is supported by Canceropôle Provence-Alpes-Côte d'Azur, SATT Sud-Est and Roca Therapeutics (start-up, spin-off from Côte d'Azur University). Our ultimate goal is to launch our lead compound RCT001 in a phase.

“Targeting tumor exosomal communication”
Raphaël Leblanc – CRCM, Marseille

Cancer relapse is a main challenge in medicine. It is now clear that relapse is supported by tumor-stroma exchanges that rely on exosomes, nanovesicles transporting complex information between cells. Today, no therapeutic approach is available to block pro-cancerous exosome exchanges. My host laboratory identified syntenin, a scaffold protein upregulated in several cancers that, together with syndecans (SDC), controls the biogenesis, composition and uptake of a class of exosomes. I provided evidence that this pathway can be targeted by pharmacological inhibitors diminishing the loading of pro-tumoral factors. I now propose to investigate the pro-tumoral effects of syntenin-SDC exosomes in Acute myeloid Leukemia (AML). AML is a disease nested in the bone marrow for which 60% of patients relapse after treatment. Specifically, I aim to (i) investigate the role of syntenin-SDC in AML blast intrinsic resistance; (ii) clarify the importance of syntenin-SDC exosomes in bone-marrow remodeling and (iii) explore the pertinence of syntenin-SDC as a therapeutic target. I thereby hope to contribute to the prevention of chemoresistance/relapse in AML.

“Integrin-alpha V beta 3 is a fundamental factor in medulloblastoma tumorigenicity and radioresistance: A new game for an old player”
Christopher Montemagno – Centre Scientifique de Monaco

Medulloblastoma (MB) is one of the most frequent solid tumors in children, localized in the brain’s posterior fossa. Its standard of care comprises surgery followed by craniospinal irradiation and chemotherapy. Despite a long-term survival rate of 70%, wide disparities among patients have been observed. Relevant targets for naive and recurrent MB are urgently needed. Primary and recurrent MBs are characterized by aggressive invasion into surrounding brain tissue and radioresistance. Integrin-αvβ3 was a major driver of these features in glioblastoma. Nevertheless, such observations have not yet been reported in MB. Integrin-αvβ3 was found to be expressed in a subset of MB patients. We investigated the role of integrin-αvβ3 using MB-derived cell lines with β3-subunit depletion or overexpression both in vitro and in vivo. Radioresistant MB cell lines showed increased integrin-αvβ3 expression, which correlated with increased susceptibility to pharmacological integrin-αvβ3 inhibition with cilengitide, a competitive ligand mimetic. In addition, our data showed that the depletion of the β3-subunit increased sensitivity of MB cells to conventionnal radiotherapy. Finally, we conducted single-photon emission computed tomography (SPECT)/magnetic resonance imaging (MRI) studies on orthotopic models using a radiolabeled integrin-αvβ3 ligand (99mTc-RAFT-RGD). This approach offers the prospect of a novel predictive imaging modality in MB. Altogether, our data pave the way for SPECT/MRI-based selection of a subpopulation of MB patients eligible for αvβ3-directed therapies.

SESSION 2 "SIGNALIZATION – MOLECULAR MECANISMS"

Keynote Speaker: **Jean-Ehrland Ricci** – C3M / UCA, Nice

"Metabolic control of anti-tumor immunity"

While extremely diverse in origin, all cancer cells show profound metabolic changes. As researchers tackle these differences from numerous angles, it became obvious that metabolic adaptations were not limited to glucose metabolism (Warburg effect) but are more general and overall are intrinsically linked to whole body metabolism. Exposure of immune cells to conditions present in the tumor microenvironment (TME) triggers distinct stress-induced signaling pathways that may limit their anti-tumor potential. Stress is mediated in part by metabolite depletion/secretion in the TME and its detection and adaptation to stress is coordinated at the ER level by the unfolded protein response (UPR), a signalling pathway governed by three ER stress sensors, of which IRE1 is the most conserved.
I will discuss our latest research indicating how modulation of tumor metabolism may stimulate the sensitivity to chemotherapy and how it can influence anticancer immune responses.

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

"Translational landscape of MAP3K8/MEK signaling in ovarian cancers: impact on cell metabolism and chemosensitivity"
Martina Serafini – Institut Curie, Paris

High-Grade Serous Ovarian Cancers (HGSOC) represent more than 70% of all ovarian cancers. We previously found that MAP3K8 accumulates and leads to a constitutive activation of MEK/ERK in 50% HGSOC to favor tumor growth, despite the lack of KRAS/BRAF mutations. Most of the oncogenic pathways, including MAPK, promotes the translation of specific mRNA to sustain tumorigenesis. In HGSOC we also found that MAP3K8/MEK activation controls the translation of an interesting mRNA subset that could be involved in tumorigenesis and chemosensitivity. Among them, we focused on a specific protein that we showed having an impact on patient survival. The aim of this project is to decipher the causes and consequences of MAP3K8/MEK translational reprogramming in HGSOC. By combining analysis in HGSOC from patients and relevant cell models, we obtained strong data supporting that this protein is part of MAP3K8/MEK translational landscape and plays key functions in HGSOC tumors associated with oxidative phosphorylation (OXPHOS) metabolism and chemosensitivity. Indeed, we showed that HGSOC are metabolically heterogeneous. High-OXPHOS tumours exhibit features of chronic oxidative stress and are more chemosensitive. We found that the protein accumulates in High-OXPHOS patients, who show higher chemosensitivity in 2 independent HGSOC cohorts. To complete this project, we will decipher the molecular mechanism by which the protein of interest controls OXPHOS and increases chemosensitivity. With this study we hope to identify new targetable pathways for HGSOC that still represent a clinical challenge.phase.

"OTX2, a potential therapeutic target for group 3 medulloblastoma?"
Aurélie Farnet – iBV, Nice

OTX2 (orthodenticle homeobox 2) is a transcription factor involved in many developmental processes such as gastrulation and development of several organs. OTX2 is also involved in the development of medulloblastoma, a pediatric cancer of the cerebellum. Abnormal over-expressions and genomic amplifications of OTX2 have been found in the group 3 medulloblastoma (MB3) which is the most aggressive subtype with a lot of metastasis. Therapeutic resources are based on surgery completed by heavy treatments such as radiotherapy and chemotherapy which can leave profound neurological sequelae. It is therefore relevant to develop more efficient and less agressive treatments for this disease.

In our laboratory, we have demonstrated through in vitro experiments that OTX2 is involved in the tumorigenic capacity of MB3 by increasing cell proliferation and polyploidy. In vivo experiments in mouse have also shown that decreasing OTX2 in MB3 induces a significant reduction in tumour size and improved mice survival.

These observations suggest that a decrease of OTX2 in MB3 would help to control the tumoral growth and therefore constitute an interesting therapeutic target. Unfortunately, up to now, no chemical inhibitors of OTX2 have been described. In order to identify such molecules, we have carried out an analysis of 1200 pharmacological molecules by RTqPCR on MB3 cells, which has enabled us to obtain several interesting molecules that we wish to analyse in greater depth in order to know their mechanism of action and their impact on medulloblastoma cells.

"Targeting Stress Granule Formation as a Synthetic Lethality Strategy for Kras-Induced Pancreatic Cancer Initiation"

Patricia Santofimia Castaño – CRCM, Marseille

Stress granules (SGs) are membrane-less organelles formed by liquid-liquid phase separation (LLPS) that play a critical role in regulating RNA metabolism, and protein synthesis, in a wide range of stress responses. These granules are required to support pancreatic cancer (PDAC) transformation, cell survival, growth, and chemotherapy resistance.

In this study, we show that NUPR1 can produce droplets through LLPS, but not its mutants or under the treatment of its inhibitor (ZZW-115). We observed that LLPS induced by NUPR1 is essential for SGs formation since genetic or pharmacological inhibition of NUPR1 activity hampers SGs formation in pancreatic cancer cells. In addition, we found that KrasG12D mutation causes significant oncogenic stress which induces a strong overexpression of NUPR1, promoting the formation of SGs as a stress-dependent mechanism of cell survival. Consistently, forced KrasG12D expression in pancreatic cells elicits a solid sensitivity for NUPR1 inactivation by genetic or pharmacological means. Finally, inhibition of SGs formation with the NUPR1 inhibitor ZZW-115 in Pdx1-Cre;LSL-KrasG12D mice blocks the transformation process indicating that SGs formation is necessary for PDAC development.
In this work, we provide a preclinical proof of concept showing that SG formation is a targetable step in the KrasG12D signaling pathway, thus suggesting that inhibiting NUPR1-dependent SG formation can be utilized as a synthetic lethality therapeutic strategy for KrasG12D-dependent tumors.

"Switching adhesion, invasion, and molecular properties of hepatocellular carcinoma cells by targeting the secreted glycoprotein ADAMTSL5"

Aurélie Dobric – CRCM, Marseille

The molecular constitution of the tumour microenvironment drastically impacts cancer cell invasion, migration, and response to therapies. By performing -omics studies in mouse models and bioinformatics analysis of patient databases, we found an upregulation of the secreted glycoprotein ADAMTSL5 in hepatocellular carcinoma (HCC). We showed that ADAMTSL5 silencing in HCC cells: 1) reduces the levels of several oncogenic inputs including expression/phosphorylation of receptor tyrosine kinases; 2) depletes tumorigenic properties in vitro and in vivo; 3) confers sensitivity to drugs used for HCC treatment. How ADAMTSL5 sustains the aggressiveness of HCC cells remains elusive.
We found that ADAMTSL5 maintains HCC cells into a hybrid Epithelial-Mesenchymal state; its silencing leads to the acquisition of a fibroblastic-like morphology and identity (loss of E-Cadherin, β-Catenin, Epcam, Vimentin, CD61; gain of α-SMA, Collagen-1). Consistently, 2D and 3D culture systems revealed that ADAMTSL5 depletion increases cell adhesion, contractility, migration/invasion, and focal-adhesion formation/activity compared to controls. Furthermore, proteomic studies revealed changes in some canonical components of the cytoskeleton remodelling (Ezrin, Arp2/3 complex subunits, CapZa1), adhesion (cadherins, integrins), and extracellular matrix (collagens, fibronectin). Collectively, our results illustrate that ADAMTSL5 acts as a master regulator in cancer cells, preventing a switch of molecular and biological properties required for cancer cell aggressiveness.

FRIDAY, OCTOBER 6TH

SESSION 3 "MICROENVIRONMENT – IMMUNOTHERAPIES"

Keynote Speaker: **Eric Vivier** – CIML, AP-HM / AMU, Innate Pharma, Marseille

"Metabolic control of anti-tumor immunity"

New therapies that promote antitumor immunity have been recently developed. Most of these immunomodulatory approaches have focused on enhancing T-cell responses, either by targeting inhibitory pathways with immune checkpoint inhibitors, or by targeting activating pathways, as with chimeric antigen receptor T cells or bispecific antibodies. Although these therapies have led to unprecedented successes, only a minority of patients with cancer benefit from these treatments, highlighting the need to identify new cells and molecules that could be exploited in the next generation of immunotherapy. Given the crucial role of innate immune responses in immunity, harnessing these responses opens up new possibilities for long-lasting, multilayered tumor control. We will present innovative anti-tumor therapies based on the manipulation of Natural Killer cells in particular via Antibody-based NK cell Engager Therapeutics (ANKETs).

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

"Dissecting tumor sensitivity to NK cell-mediated lysis"
Hakim Medjouel – CIML, Marseille

Natural killer (NK) cells mediate killing of various cancer types, but tumor cells can develop resistance mechanisms to escape NK cell-mediated killing. Over the past two decades, several approaches have been developed to harness the ability of NK cells to control tumor growth.
Among the interesting possibilities is the combination of anti-tumor drugs with NK cell therapy to promote tumor cell recognition and enhance NK cell activation or to sensitize tumor cells to NK cell-mediated killing. We used a genome wide CRISPR-Cas9 screening system coupled with functional cytotoxicity assays to uncover proteins involved in tumor sensitivity and resistance to NK cell-mediated cytotoxicity. Our results show that apoptosis and IFN-γmediated signaling are the main pathways involved in tumor cell death triggered by NK cells.
Our data also revealed tumor gene candidates involved in the phenotype of tumor resistance to NK cell-mediated killing. From this, we will investigate what type of tumor cell death sensitizers can be used in combination with NK cell therapy to promote NK cell-mediated tumor killing.

"Variation in lipid species profiles among leukemic cells significantly impacts their sensitivity to the drug targeting of lipid metabolism and the prognosis of AML patients"
Caroline Lo Presti – CHU Grenoble Alpes

Several studies have linked bad prognoses of acute myeloid leukemia (AML) to the ability of leukemic cells to reprogram their metabolism and, in particular, their lipid metabolism. In this context, we performed "in-depth" characterization of fatty acids (FAs) and lipid species in leukemic cell lines and in plasma from AML patients. We firstly showed that leukemic cell lines harbored significant differences in their lipid profiles at steady state, and that under nutrient stress, they developed common mechanisms of protection that led to variation in the same lipid species; this highlights that the remodeling of lipid species is a major and shared mechanism of adaptation to stress in leukemic cells. We also showed that sensitivity to etomoxir, which blocks fatty acid oxidation (FAO), was dependent on the initial lipid profile of cell lines, suggesting that only a particular "lipidic phenotype" is sensitive to the drug targeting of FAO.We then showed that the lipid profiles of plasma samples from AML patients were significantly correlated with the prognosis of patients. In particular, we highlighted the impact of phosphocholine and phosphatidyl-choline metabolism on patients' survival. In conclusion, our data show that balance between lipid species is a phenotypic marker of the diversity of leukemic cells that significantly influences their proliferation and resistance to stress, and thereby, the prognosis of AML patients. NK cell therapy to promote NK cell-mediated tumor killing.

"Role of JAM-C-mediated adhesion in the maintenance of stemness of acute myeloid leukemia cells"
Céline Testut – CIML, Marseille

JAM-C is an adhesion molecule belonging to the immunoglobulin superfamily and expressed by hematopoietic stem cells (HSCs). JAM-C can interact with itself or with JAM-B, its high-affinity ligand, expressed by bone marrow stromal cells (Arcangeli et al, Blood, 2011). In Acute Myeloid Leukemia, JAM-C is expressed by leukemic stem cells (LSCs), and high frequencies of JAM-C+ LSCs are associated with poor prognosis (De grandis et al, Cancer Research, 2017). This study aims to explore whether JAM-C plays an active role in the production and maintenance of the LSC compartment in the early phases of the disease. To address this question, we generated mice that can be conditionally deleted for JAM-C expression in HSCs before induction of AML disease thanks to expression of MLL-AF9 fusion gene (Stavropoulou et al, Cancer Cell, 2016). We also generated several LSC-like cell lines expressing or not JAM-C in order to develop in vitro models amenable to functional assays. We have shown that deletion of JAM-C in leukemic mice modifies the leukemia-initiating cell compartment by altering gene expression in LSCs. We identified 53 overexpressed genes belonging to the pro-inflammatory signaling pathways AP-1 and TNF-a that had a prognostic value for human disease outcome. Using a reporter system for AP-1 activity, we further show that AP-1 activation is partially controlled by JAM-C expression and cell differentiation state. Ongoing experiments aim at identify the molecular mechanisms by which loss of JAM-C expression could lead to increased AP-1 and TNF-a pathway genes expression.

"Reprogramming anti-inflammatory macrophages through cathepsin B and caspases inhibition to improve cancer therapies"
Emeline Kerreneur – C3M, Nice

MDMs (monocyte-derived macrophages) are widely distributed innate immune cells that play an indispensable role in physiological processes, including host defense and anti-tumoral immunity. However, anti-inflammatory MDMs are also known to be deleterious in cancers. Indeed, Tumor- or Leukemia-Associated Macrophages (TAMs or LAMs) inhibit anti-tumoral responses and T cell-mediated cytotoxicity within the tumoral microenvironment, supporting tumoral growth and resistance to treatments. Therefore, understanding the mechanisms of MDMs generation/polarization might provide an opportunity for novel therapeutic strategies. In this context, we have developed a model to generate and polarize macrophages ex vivo. We highlighted an original and specific mechanism of caspase-8 (CASP8) activation during CSF-1-mediated macrophage differentiation that requires prior cathepsin B (CTSB) activation. This original and non-apoptotic activation of CASP8 leads to non-canonical activation of CASP3 and 7, which in turn cleave several cellular proteins. Using pharmacological and siRNA approaches, we proved that CTSB and non-apoptotic caspases are also required for IL-4-induced anti-inflammatory macrophage polarization contrary to pro-inflammatory macrophage polarization. Finally, we demonstrated that caspases inhibition can reprogram ex vivo anti-inflammatory macrophages towards a pro-inflammatory state. Altogether, our results highlighted the interest of targeting CTSB and non-apoptotic caspases to modulate the functions of anti-inflammatory MDMs, offering new therapeutic strategies in cancers.

"Combined CAR-NK and CAR-gdT cells as a therapeutic tool post Allo-HSCT"
Nassim Salem – CRCM, Marseille

Allogeneic hematopoietic stem cell transplantation (Allo-CSH) is the main curative treatments for Acute Myeloid Leukemia Graft VS Leukemia (GVL) effect triggers the lysis of the remaining leukemic blasts. Post-allograft T cell-based immunomodulation strategies can be implemented to improve the anti-leukemic effect of Allo-CSH. However, the enhancement of the GVL effect is often followed by higher incidence of GVHD. It was reported that other immune effectors can mediate a GVL effect without GVHD. In particular, NK cells and gdT lymphocytes (gdT) are appealing. We propose here an expansion process, to generate a clinically compatible cell therapy product composed of both NK and gdT cells.The validation is made on phenotypic and functional aspects, in vitro and in vivo. We genetically engineered these cells to establish a combined CAR-NK and CAR-gdT product The process allows to achieve a 1000-fold expansion for NK cells and T within 14 days. Both NK cells and gdT acquired a hyperactivated phenotype, which led to major degranulation and cytokine production toward leukemic blasts, and a significant cytotoxicity. In vivo, we showed a tumor regression, less circulating blasts, and a prolonged survival. Simultaneously, the genetic editing led to a combined aCD19 CAR-NK and CAR-gdT product with enhanced degranulation abilities against CD19+ targets. These results pave the way for a customizable cytotoxic platform, in term of molecular target as well as immune cell. Their efficacy toward leukemic blasts with a known reduced GVHD make it relevant in the post-Allo-CSH context.

SESSION 4 "SENESCENCE – INITIATION – DNA DAMAGE – GENOMIC INTEGRITY"

Keynote Speaker: **Dmitry Bulavin** – IRCAN, Nice

"In search of molecular Shangri-La: building disease tolerance and broad defense mechanisms by p16High immune cell subsets"

Our organism has evolved to limit the negative impact of pathogens and tissue damaging agents on homeostasis. This defense mechanism relies on the concerted action of both innate and adaptive immunity but also is coupled to an important but poorly understood defense strategy that limits the extent of tissue damage known as disease tolerance. Here we found that different immune subsets that exhibit strong p16 activation are robustly induced with age in mice, exert important regulatory functions and contribute to disease tolerance. We identified that p16High immune cells often express regulatory markers of Treg (Foxp3, PD1 and PD-L1) in T cells and IL10 in macrophages. In turn, induction of p16High immune cells played a key role in establishing an early and broad tolerance in response to multiple lethal conditions following severe inflammation and tissue damage, including LPS-induced sepsis, early lethal SARS-CoV-2 infection and ionizing irradiation. Mechanistically, we showed that TLR7 and its FDA- approved agonist, the BNT162b2 mRNA COVID-19 vaccine, are potent inducers of p16High immune subsets in vivo. Importantly, we showed that standard vaccination with BNT162b2 in humans is sufficient to induce p16High immune cell subsets in peripheral blood while they are significantly reduced in severe COVID-19 patients. Our data support the broad benefits of TLR7-dependent induction of regulatory p16High immune subsets in response to mRNA vaccines to counteract severe cases of acute inflammation and tissue damage as a strategy for inducible disease tolerance.

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

"Role of Neutrophil Extracellular Traps (NETs) in squamous cell carcinoma (SCC) initiation"

Alexandra Mousset – IRCAN, Nice

Inflammation is known to predispose to cancer development. Neutrophils play a key role in the body's immune response to injury as they are among the first cells to arrive at the inflammatory site. While the role of neutrophils in cancer has recently attracted attention, it is still unclear whether neutrophils play an active role in cancer initiation. To study the role of neutrophils in cancer initiation, I used a mouse model of cutaneous Squamous Cell Carcinoma (cSCC) which relies on the application of a dose of the carcinogen 7,12-Dimethylbenz[a]anthracene (DMBA), followed by multiple doses of the cancer promoter Phorbol-12-myristate-13-acetate (TPA). I show that neutrophils are recruited to the skin of mice treated with these chemicals. Moreover, these neutrophils release Neutrophil Extracellular Traps (NETs), which are DNA scaffolds associated with cytotoxic enzymes and proteases released into the extracellular space. Interestingly, I show that targeting both neutrophils and NETs in vivo counteract cancer initiation. The accumulation of DNA damage is linked to the occurrence of mutations that can contribute to cancer initiation. In this context, I show that NETs amplify DMBA-induced DNA damage in keratinocytes. Specifically, I show that Myeloperoxidase (MPO), a NET-associated enzyme, amplify DMBA-induced DNA damage through the production of HOCl. Accordingly, targeting the MPO/HOCl axis decreases DMBA-induced DNA damage and counteracts cSCC initiation. Altogether, this project identifies the key role of neutrophils and NETs in cancer initiation.

"EPIC-SCENITH: Single-cell readout of immunometabolism and epigenetics in cancer"

Paulina Garcia-Gonzalez – CIML, Marseille

Metabolic plasticity is shared between the immune system and cancer. Like tumor cells, immune cells undergo metabolic reprogramming to adapt and respond to changes in their environment. This can be consequence of changes in epigenetic regulation, due to variations in the availability of metabolic co-factors of enzymes involved in epigenetic modification. Moreover, mutations of metabolic enzymes are found in many tumors, which can also affect the anti-tumoral response. We developed a method to simultaneously assess epigenetics and metabolism of cells ex-vivo, at single-cell level and from small amounts of sample. By combining SCENITH to measure functional metabolism, with intracellular/nuclear staining of epigenetic marks and spectral flow cytometry, we analyzed phenotype, metabolic profile (glycolytic vs respiratory) and histone modification marks (H3K4me3, H3K27me3 and H3K27Ac) of blasts as well as lymphocytes, monocytes, natural killer cells and polymorphonuclear cells, amongst others, in whole blood samples from healthy individuals and acute myeloid leukemia (AML) patients before and 48hr after treatment.

With this, we observed an acute effect in response to chemotherapy in cell frequency and metabolic state, and even at an epigenetic level in some cell types. In short, we established a novel strategy to simultaneously analyze histone modifications and immune cell metabolism with single-cell resolution. Further exploration sequencing will allow us to pinpoint targets of epigenetic regulation for therapeutic purposes and identify predictive biomarkers of patient response.

"Timing of lesion tolerance pathways in Saccharomyces cerevisiae"
Katarzyna Maslowska – CRCM, Marseille

DNA of a living cell is constantly challenged by damaging agents. Two mechanisms exist to tolerate DNA lesions encountered during replication: error-prone Translesion Synthesis (TLS) and error-free Damage Avoidance (DA). Balance between them is crucial as it defines the level of mutagenesis during lesion bypass. To study how this balance is maintained, I have developed a novel high-resolution assay which allows to simultaneously monitor TLS and DA events at the level of a single lesion in the yeast genome.
Previous studies have resulted in conflicting views about when and where the damage bypass takes effect: at the fork, or postreplicatively. Using my assay, I was able to observe a significant increase in TLS level across lesions bypassed predominantly by Rev1/ Pol ζ in the absence of PCNA polyubiquitylation, evidencing a competition between DA and TLS. However, I did not observe a similar increase in TLS at the CPD lesion. This suggests that while for most lesions the competition between DA and TLS occurs behind the fork during a gap filling reaction, certain lesions are efficiently bypassed at the fork without competition with DA.
Using my system, I set out to elucidate the mechanism responsible for the differences in lesion bypass timing for different lesions, focusing on the mechanism of Pol η recruitment and the role of Rad5 protein at the intersection of TLS and DA.

"P21 driven expression of Telomerase prevents Adipose Tissue Senescence"
Laura Braud – CRCM, Marseille

Accumulation of senescent cells within the white adipose tissue (WAT) has been described as key factor in the development of obesity-associated metabolic disorders. Telomere shortening has been recognized as one of the factors leading to cellular senescence, mainly by activating the p21-p53 pathway. More specifically, telomere attrition in adipocyte progenitors predisposes to metabolic disease (Gao et al., 2020). While clearance of p21high cells has been reported to improve WAT inflammation and insulin-sensitivity in obese mice (Wang et al, 2021), it is not known whether counteracting telomere shortening would have the same beneficial effects. We generated two mouse models called p21+/Tert and p21+/TertCi that expresses either the telomerase reverse transcriptase (Tert) or a catalytically inactive Tert (TertCi) under p21 (Cdkn1a) promoter. In this study, we demonstrate that accumulation of p21 expressing cells in high-fat diet is counteracted by p21-driven expression of telomerase in both p21+/Tert and p21+/TertCi obese mice. This is accompanied by a better insulin-sensitivity and glucose tolerance. However, this protective effect is greater in p21+/Tert mice compared to p21+/TertCi. Our results suggest that both Tert and TertCi induce the mobilization of stem cells within the WAT, however only Tert promotes their long-term differentiation through maintenance of telomere length. This process contributes to the WAT hyperplasia with increased number of adipocytes which has been shown to contribute to a protective effect on obesity-associated metabolic disorders. These findings reveal unique insights, by which active telomerase could improve metabolic disorders, and provide a mechanistic link between ageing, obesity and diabetes.

SESSION 5 “IA & CANCER”

Keynote Speaker: **Sébastien Benzekry** – Inria, CRCM / IPC, Marseille

“Integrative kinetics and machine learning modeling for prediction of outcome following immunotherapy in lung cancer”

I will present recent results from COMPO (COMPutational pharmacology and clinical Oncology) ai- ming at combining mechanistic modeling and machine learning ("mechanistic learning") to integrate longitudinal, multi-modal and high-dimensional data into predictive models of outcome following im- munotherapy in non-small cell lung cancer (NSCLC). This will be based on two studies. The first leverages clinical trial data (N = 1,500 patients) to help 1) predict individual outcome and 2) assist drug development by predicting outcome of late-phase trials (e.g., phase 3) from early data (e.g., phase 2). The second is an integrative analysis of multi-modal deep-level biomarkers (multiplex immunohistochemistry, immune-monitoring, vasculo-monitoring, hematology and biochemistry) collected during the RHU PIONeeR.

ORAL COMMUNICATIONS OF YOUNG RESEARCHERS

“Electronic medical records processing pipeline for clinical data structuring and interactive statistical exploration”

Sara Contu – CAL, Nice

Electronic medical records (EMRs) are a valuable source of clinical information but are often free-text documents from which accurate information is retrieved through laborious manual review. Data are then analyzed and interpreted by statistical experts who carry out their analysis upon request to respond to specific clinical questions. We developed a EMRs processing pipeline to extract, structure and complement clinical data, and provide physicians and researchers with an interactive and intuitive tool for statistical exploration. The pipeline predicts the primary cancer from EMRs, retrieves reports of patients' treatment and applies deep learning models and keyword extraction rules to extract clinical information (entities). Entities are converted by postprocessing rules into structured data, and complemented by demographic and follow-up data and death status. The dataset is available in a web app to perform descriptive, graphical and inferential statistical analyses. The pipeline determined the primary cancer of 113K patients. It structured 47 variables from consultation, biopsy, pathology and surgery reports of 24K breast cancer patients and 85 from consultation, anesthesia, surgery, echography and pathology reports of 13K thyroid cancer patients. Two physicians tested the web app. A preliminary evaluation showed that the pipeline can effectively predict the primary cancer, extract data from EMRs, and allow people with no programming knowledge to perform statistical explorations. The pipeline optimizes resources and time for data structuring and analysis.neutrophils and NETs in cancer initiation.

“Generative models for clinical datasets”

Paul Dufossé – Inria / CRCM, Marseille

Generative models are a powerful tool for modeling various type of data, including tabular data.
They are for, e.g., privacy concerns, data augmentation, and for inference and learning tasks. In this communication, I will review the state-of-the-art of generative models for tabular data based on neural networks and their applications to learn from clinical patient data. I will illustrate their use in the context of improving time-to-event models from several cancer clinical datasets.There will be two parts::
- First, I will present an introduction to the topic, from supervised learning and neural networks to variational auto-encoders (VAEs) and generative adversarial networks (GANs), and provide pointers to the literature.
- Second, I will present our work on applying GANs and VAEs to tabular data with survival outcome. Evaluation was performed on several publicly available cancer datasets, as well as an original one from the PIONeeR study - discovering biomarkers predictive of the efficacy of immunotherapy treatments in non-small cell lung cancers. Our goal was to improve the performance of discriminative models as a downstream task. I will also show how these models can be extended to become conditional (CTGAN), allowing to sample specific sub-populations from the data.

I will conclude with emphasizing other practical interests of such models, e.g., data anonymization.

POSTERS

#01 Impact of Organoid-derived Extracellular Vesicles on CAFs and Matrix: Correlation with therapeutic resistance in PDAC
C. Rovera — CRCM

#02 Deciphering the link between Glucocorticoid Receptor and Processing-body formation
V. Nicolini — IRCAN

#03 SIRPα conformational landscape and its impact on CD47 interaction
S. Barelier — CRCM

#04 Integrin-avB3 is a fundamental player of medulloblastoma tumorigenicity and radioresistance: A new game for an old player
W. Echavidre — CSM

#05 Characterizing the Role of Radiotherapy in Breast Cancer Recurrence
S. Sarlak — IRCAN

#06 Development of a novel and safe NUPR1 inhibitor with efficient anticancer activity for pancreatic cancer treatment
P. Santofimia-Castaño — CRCM

#07 Using predictive single-cell dynamics to profile tumor cells sensitivity to immune effectors
B. Bian — IPMC

#08 Role of Senescence Immune Checkpoints (SIC) in age-related diseases and cancer
A. Moskalevska — IRCAN

#09 Regulation of homologous recombination (HR) in cis and trans
A. Jguirim — CRCM

#10 The extracellular matrix influences pancreatic cancer cell sensitivity to chemotherapy by modulation of purine metabolism
G. Efthymiou — CRCM

#11 Exploiting SNDS data with AI techniques for cancerology research
R. Urena — SESSTIM

#12 Phagocytoses assay to assess the activity of pre-therapeutic small molecules in a cellular medium
M. Storder — CRCM

#13 MUC1 roles on properties of lung cancer cells and cisplatin chemoresistance
M. Goujon — CHU Lille

POSTER #01

"IMPACT OF ORGANOID-DERIVED EXTRACELLULAR VESICLES ON CAFS AND MATRIX: CORRELATION WITH THERAPEUTIC RESISTANCE IN PDAC"

Pancreatic ductal adenocarcinoma (PDAC) is one of the most deadliest cancer because of late diagnosis and lack of efficient treatments against the metastatic disease.

By secreting factors that can circulate in their immediate environment or reach distal tissues, tumor cells modify and educate neighboring as well as distant cells, creating a supportive microenvironment. There are growing evidence that Extracellular Vesicles (EVs) play a key role in this process, by inducing signaling pathways or carrying.

In particular, Pancreatic ductal adenocarcinoma (PDAC) is characterized by a rich stoma that forms a protective cocoon against both immune cells and chemotherapeutic molecules. This stroma is mainly composed of Cancer-Associated Fibroblasts (CAF) and the extracellular matrix they produce, and play key roles in tumor proliferation, metabolism reprogramming, invasion and chemoresistance.

Since tumor cells and CAF are very heterogeneous populations, we need to better understand the role of their intercellular dialogue which drive a pro-tumoral microenvironment. The lab has developed cultured organoids from resected human PDAC tumors that keep and maintain the transcriptomic and phenotypic heterogeneity observed in patients (Collab. Nelson Dusetti's Group).`

We already characterized the proteic composition of EVs (vesiculome) of 15 different organoids by mass spectrometry (Collab. MaP Platform). Our preliminary results suggest that the vesiculome can be correllated with the presence of locally advanced / metastatic tumors in patients, with different signatures related to extracellular matrix. The aim of this project is to characterize the vesiculome of a total of 60 organoids and the composition of the respective EV-treated CAF Matrix (matrisome). I will be able to relate the composition of vesiculomes with the changes that occurs in CAF extracellular matrix and clinical history of patients. By performing functional experiments to test chemoresistance of tumor cells and how the phenotype and activity of immune cells is affected on these EV-modified CAF matrices, I will be able to decipher which are the main molecular factors involved in the specification of a chemoprotective supportive microenvironment.

This work may lead to highlight new biomarkers and therapeutic targets to prevent PDAC progression and give new tools to clinicians to refer patients to the best treatment they need.

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(2) Marseille Protéomique – Plateforme Ibisa - Centre de Recherche en Cancérologie de Marseille, CRCM - Inserm UMR1068, CNRS UMR7258, Aix Marseille Université U105
(3) Group Nelson Dusetti – Team PacaOmics - INSERM U1068 : Pancreatic cancer - Cancer Research Centre of Marseille, Aix-Marseille University

POSTER #02

"DECIPHERING THE LINK BETWEEN GLUCOCORTICOID RECEPTOR AND PROCESSING-BODY FORMATION"

Processing bodies (Pbodies) are small cytoplasmic membranless organelles important in various cellular processes by controlling RNA translation. They are composed of mRNA and RNA binding proteins, but their formation is still poorly understood.

Thus, we conducted a drug screening to identify targets able to enhance Pbody formation. We uncovered that glucocorticoids (GC) were able to increase Pbody number and decrease Pbody size in non small cell lung cancer (A549 cells) after 48 hours of treatment. By combining microscopy and biochemistry experiments, we surprisingly found that Pbody regulation was associated with the decreased expression of the glucocorticoid receptor (GR) in response to its ligand. Consistent with this finding, we also showed that a genetic deletion of GR by CRISPR Cas9 blocked the modification of the Pbodies, demonstrating that the formation of Pbodies is dependent of GR induced transcription by GC.

Overall, our results illustrate that it exists a link between the GR and the Pbody regulation. Since the GR has two main different isoforms: α that is known to bind to GC and the β isoform lost this ability, we now want to decipher what is the impact of the different GR isoforms on Pbody regulation.

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(1) IRCAN
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(3) C3M
(4) PCBIS
(5) FHU OncoAge
(6) CHU de Nice
(7) iBV

POSTER #03

“SIRPA CONFORMATIONAL LANDSCAPE AND ITS IMPACT ON CD47 INTERACTION”

The CD47-SIRPα protein-protein interaction is a major immune checkpoint that regulates the activity of myeloid cells and contributes to tumor resistance against immuno-therapies. Overexpression of CD47 as a 'Don't eat me signal' on tumor cells allows them to evade immune surveillance and confers a proliferative advantage. It was shown that blocking CD47-SIRPα interaction facilitates tumor elimination, a promising therapeutic avenue currently explored with antibodies such as Magrolimab.

The structural basis for CD47 - SIRPα interaction are known, however SIRPα is highly flexible and has access to a diverse conformational landscape. Why is there such flexibility in a protein that has - so far - only one known interacting partner?

Our goal is to:
- Characterize the full range of potential SIRPα structural conformations ;
- Predict and design mutants that stabilize the open and closed conformations and characterize their interaction with CD47 ;
- Look for cryptic pockets that could be targeted to lock SIRPα in a non-CD47 binding conformation.

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POSTER #04

“INTEGRIN-AVB3 IS A FUNDAMENTAL PLAYER OF MEDULLOBLASTOMA TUMORIGENICITY AND RADIORESISTANCE: A NEW GAME FOR AN OLD PLAYER”

The standard of care of medulloblastoma (MB) consists of maximal resection surgery, followed by craniospinal irradiation and chemotherapy. Despite this combination allows long-term survival rate of 70%, wide disparities among patients were observed. Recent advances in the molecular understanding of MB have defined 4 prognosis molecular subgroups (WNT, SHH, group 3 and 4). Nonetheless, the translation of these observations is just starting to emerge. The discovery of relevant targets for naive and recurrent MB is an urgent need. Integrin-αvβ3 is a major driver of angiogenesis, invasion and radioresistance in glioblastoma. Nonetheless, such observations have not yet been reported in MB. The objective of this study is to investigate the relevance of integrin-αvβ3 in MB using genetic-depletion, pharmacological approach (using cilengitide, a RGD-derived competitive inhibitor) and radioresistant MB. The role of integrin-αvβ3 in MB features (proliferation, invasion) was investigated in vitro and in vivo, in orthotopic xenograft models using MB derived cell-lines depleted for β3-subunit (CRISPR/Cas9) or treated with cilengitide. Integrin-αvβ3 was found to be a relevant target for a subpopulation of MB. SPECT/MRI studies carried out on orthotopic models and using a radiolabeled-RGD (99mTc-RAFT-RGD) targeting integrin-αvβ3 supported our study and offer the prospect of a novel predictive imaging modality in MB. Together, our data paved the way for integrin-αvβ3-directed therapies for a subpopulation of MB patients who could be selected through SPECT/MRI studies.

***William ECHAVIDRE*[1]*, Jérôme DURIVAULT*[1]*, Benjamin SERRANO*[2]*, Alexis BROISAT*[3]*, Vincent PICCO*[1]*, Christopher MONTEMAGNO*[1]

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(3) Université de Grenoble Alpes, INSERM (LRB)

POSTER #05

“CHARACTERIZING THE ROLE OF RADIOTHERAPY IN BREAST CANCER RECURRENCE”

Breast cancer (BC) is the leading cause of cancer mortality among women worldwide. Despite of the improvement of the therapeutic strategies including surgery, systemic therapy and irradiation, numerous patients are either prone to relapse or suffer from treatment-related side effects.

Radiotherapy (RT) by ionizing radiation is an effective modality for the treatment of many tumors, including BC. Although widely used, there are fraction of patients who develop local or distant relapse of the tumour post-RT. Therefore, optimizing irradiation strategies could potentially improve treatment responses and reduce the side effects.

One of the main routes of cancer cell spread is through the lymphatic system that can be affected during cancer either via the reshaping of the tumor microenvironment or by different types of therapies.

Here we investigated the effect of RT on lymphangiogenesis in BC. In parallel, we compared two types of irradiations; Proton (P) and Photon (X) on BC and tumor microenvironment cells.

The findings revealed that both P and X irradiations induced the expression of vascular endothelial growth factor C (VEGFC), a major pro-lymphangiogenic factor, in BC and tumor microenvironment cells which suggests that RT triggers exacerbated lymphangiogenesis.

Furthermore, the study demonstrated that BC cells lacking VEGFC (VEGFC knockout cells) were more sensitive to RT compared to the parental cell line. These results suggest that combining RT with anti-VEGFC medication can lead to a more effective treatment approach for BC patients.

Saharnaz SARLAK, *Delphine MAROTTE, Jessy SIRERA, Frederic LUCIANO, Gilles PAGES*

IRCAN

POSTER #06

"DEVELOPMENT OF A NOVEL AND SAFE NUPR1 INHIBITOR WITH EFFICIENT ANTICANCER ACTIVITY FOR PANCREATIC CANCER TREATMENT"

Pancreatic cancer is a deadly disease with the highest mortality rate because there are no efficacious treatments. We previously developed a promising drug candidate, ZZW-115, a trifluoperazine-derivate, for the treatment of pancreatic cancer. ZZW-115 binds and inhibits the nuclear protein 1 (NUPR1), a stress-related protein essential for pancreatic cancer development and progression. However, the clinical translation of ZZW-115 appeared limited because it could bind to the potassium channel hERG, thus causing the potential risk of cardiotoxicity when administered to patients. As such, there is an urgent need to identify a novel and safe NUPR1 inhibitor.

Among the 28 NUPR1 binding compounds identified in our screening AJO14 was retained because its low IC50 on several PDAC-derived cells and its absence of binding to the hERG channel. In addition, we found that AJO14 showed an excellent dose-dependent tumor reduction activity on xenografted mice. Mechanistically, we demonstrated that AJO14 induced cell death mainly through apoptosis and necrosis, accompanied by a mitochondrial catastrophe followed by a strong metabolism failure with a decrease in ATP production. This process seems to be mediated by hyperPARylation since it could be reversed by Olaparib. Finally, we tried to improve the compound using an AI-based approach and among the 55 candidates proposed and tested 6 showed a significant gain of efficiency and have been retained for further studies.

Collectively, AJO14-derived compounds are new potent NUPR1 inhibitors to treat pancreatic cancer without cardiotoxicity.

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POSTER #07

“USING PREDICTIVE SINGLE-CELL DYNAMICS TO PROFILE TUMOR CELLS SENSITIVITY TO IMMUNE EFFECTORS”

Immune evasion is a major hallmark of cancer cells limiting treatment efficacy. The main goal of therapeutic immuno-oncology has been to block tumor cell inhibition of immune cells, and less is known of the actual tumor cell killing efficacy by the immune cells once activated. Cytotoxic lymphocyte (CTL) and Natural Killer (NK) cells induce specific killing of cancer cells by releasing immune effectors (e.g., Granzymes/Perforin, TRAIL, and FAS Ligand). Our goal is to profile the molecular state of cancer cells allowing their evasion to immune. effectors in order to identify targets of adjuvant therapy that will increase the therapeutic index of immune checkpoint inhibitors (ICI) and CAR-NK cells treatments. Our single-cell pipeline called FATE-SEQ couples three experimental approaches: 1/ Timelapse video-microscopy and cell response trajectory analyses of a FRET sensor, 2/ Single-cells micro-dissection followed by 3/ sc-RNA-seq profiling to obtain the molecular profiles of resistance to immune effectors. In this study, we use NK cell lines to produce large amount of purified cytolytic granules content. Our preliminary results in HeLa, PANC01 and DLD-1 tumor cell lines, showed that immune effectors could induce the activation of a FRET sensor used to predict the cells responses prior to molecular profiling. In perspective, laser-capture micro-dissection of predicted resistant versus sensitive cells will be performed to isolate single-cells for transcriptomics and proteomics comparative analyses.

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POSTER #08

“ROLE OF SENESCENCE IMMUNE CHECKPOINTS (SIC) IN AGE-RELATED DISEASES AND CANCER”

Aging is characterized by a gradual decline of physiological functions causing age-related diseases and increasing vulnerability against cancer. At a cellular level, aging is associated with a progressive accumulation of senescent cells. Senescent cells are involved in tissue homeostasis on one hand but, on another hand, their accumulation can lead to pathological aging processes. The events regulating the elimination of senescent cells by the immune system are still poorly known. Understanding how they accumulate in tissues would allow simultaneously to better understand the etiology of age-related diseases and to improve the design of therapies against age- related diseases and cancer. We suggest that senescent cells developed specific immune checkpoints (Senescence Immune Checkpoints or SIC) to escape the immune system by progressively increasing immunosuppression, altering the immune composition of the senescence micro-environment, accelerating the aging process. Therefore, by analogy with immune checkpoint blockade in cancer, blocking these SIC might be a new immunotherapeutic strategy to prevent and treat age-related diseases. We evaluated the therapeutic potential of a SIC-targeting antibody in a murine model of senescence- associated disease, idiopathic lung fibrosis as well as in an aging murine model.

Iryna MOSKALEVSKA, *Iryna MOSKALEVSKA, Eric GILSON, Julien CHERFILS*

IRCAN

POSTER #09

“REGULATION OF HOMOLOGOUS RECOMBINATION (HR) IN CIS AND TRANS”

DNA double-strand breaks (DSBs) are dangerous DNA lesions that need to be repaired to prevent cell death. Homologous recombination (HR) is a major DSB repair pathway which can accommodate both types of DSBs by two different sub-pathways, Two-ended recombination and One-ended recombination, called also Break induced replication (BIR) which is highly mutagenic. On one side, to study the balance between these two sub-pathways, we performed a reporter system, by which we can look for genes (Trans-acting factors) that could affect this balance through the whole genome. On the other side, two other reporter systems will be constructed to measure the BIR and two-ended recombination efficiency in different regions of the genome to look if there are some genomic structures (Cis-acting factors) that could affect the homologous recombination repair efficiency.

Aya JGUIRIM

CRCM

POSTER #10

“THE EXTRACELLULAR MATRIX INFLUENCES PANCREATIC CANCER CELL SENSITIVITY TO CHEMOTHERAPY BY MODULATION OF PURINE METABOLISM”

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy with an increasing incidence and a mortality rate projected to almost double by 2040. This dismal prospective arises from the absence of early symptoms, resulting in late diagnosis, and the failure of current therapies due in part to the presence of extreme desmoplasia around the tumor. This thick and dense extracellular matrix (ECM) functions as a physical barrier causing oxygen and nutrient deprivation, but also limiting the delivery of chemotherapeutic drugs. As a result, cancer cells adapt their metabolism to maintain their proliferative capacity and such adaptation may also contribute to chemoresistance.

Recent reports suggest that apart from the biophysical protective properties of the desmoplasia in PDAC, ECM-relayed signaling may play a role in chemoresistance. In this study, we set out to understand how the biochemical properties of the ECM shape the metabolic landscape of PDAC cells and how this ECM-mediated metabolic adaptation may modulate chemosensitivity.

By using a multi-omics approach in a tissue-mimicking 2D in vitro setting, we show that a CAF-derived desmoplasia-mimicking bio-scaffold tunes purine metabolism in PDAC cells and influences sensitivity to chemotherapy by means of DNA repair. Our results couple the ECM with PDAC cell metabolic plasticity and suggest a link between purine metabolism and drug resistance. Identification of the key players in this crosstalk will pave the way for the discovery of novel targets for combinatorial therapeutic strategies.

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POSTER #11

“EXPLOITING SNDS DATA WITH AI TECHNIQUES FOR CANCEROLOGY RESEARCH”

The utilization of Artificial Intelligence (AI) methods like Machine Learning and Deep Learning to improve the detection, diagnosis, and prediction of cancer progression is becoming increasingly common. Conversely, the use of SNDS data, encompassing comprehensive medical consumption details for each individual in France, emerges as a pivotal information repository regarding the quality of life and disease propagation subsequent to a cancer diagnosis.

The aim of this contribution is to showcase how this data can be used to gain a deeper understanding of how cancer patients fare after treatment. By doing so, we aim to highlight the potential advantages and new perspectives that analyzing SNDS data can bring to our understanding of the journey cancer patients undertake. By combining AI techniques with this large dataset of real-world information, we strive to develop a more nuanced grasp of the elements that influence patient outcomes, the effectiveness of treatments, and the overall well-being of patients beyond their initial diagnosis.

Raquel URENA[1], *Mamoudou KOUME*[1], *Lorène SEGUIN*[2], *Louis TASSY*[2], *Anne Déborah BOUHNIK*[3]

(1) Sesstim, Aix Marseille Université
(2) Institut Paoli Calmettes
(3) Sesstim, Inserm

POSTER #12

“PHAGOCYTOSES ASSAY TO ASSESS THE ACTIVITY OF PRE-THERAPEUTIC SMALL MOLECULES IN A CELLULAR MEDIUM”

CD47 is an immune checkpoint receptor that regulates the immune response via the inhibitory counter-receptor SIRPα present on myeloid cells. Tumor cells with high CD47 expression bypass the immune surveillance. Blocking the CD47-SIRPα interaction of these tumor cells therefore overcomes immunosuppression by enhancing myeloid cell activation. Antibodies targeting CD47 have demonstrated early clinical activity as immunotherapies but cause toxicity in patients. To avoid this toxicity, the iSCB team at the CRCM is developing small molecule inhibitors by targeting SIRPα. The objective of this project is to evaluate the activity of the small molecules in biological models of immunotherapy by creating a robust and quantitative assay. We therefore optimized a phagocytosis assay to quantitatively compare the activity of the different inhibitors. The test consists of coculturing fluorescently labelled monocytes (THP1) and tumor cells (Raji) in presence of phagocytosis activators and CD47-SIRPα inhibitors. Using flow cytometry, phagocytosis is determined thanks to the proportion of cells emitting both fluorescences. Using compounds known to induce phagocytosis, we validated this assay and quantified their activity. Our next steps include the application of the assay to evaluate our small molecule inhibitors, other tumor types and other macrophage phenotypes. We also plan to miniaturize the assay to a format compatible with our automated high-throughput screening platform to discover novel immunotherapy targets and small molecule immunomodulators

Martin STORDER[1/2/3/4/5], *Audrey RESTOUIN*[1/2/3/4/5], *Rémy CASTELLANO*[1/2/3/4/5], *Yves COLLETTE*[1/2/3/4/5], *Xavier MORELLI*[1/2/3/4/5], *Thomas MILLER*[1/2/3/4/5]

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POSTER #13

“MUC1 ROLES ON PROPERTIES OF LUNG CANCER CELLS AND CISPLATIN CHEMORESISTANCE”

Lung cancer remains the leading cause of cancer death worldwide. Represented at 85% by the non-small cell subtype (NSCLC), lung cancer is often diagnosed at locally advanced stages. When surgery is not possible, treatment is mainly based on systemic therapies, such as platinum-based chemotherapy (cisplatin), in combination with other treatments : immunotherapies or targeted therapies. Nevertheless, a large number of patients has a primary or secondary resistance to these drugs.
In this context, we focus our attention on MUC1, a membrane bound mucin over-expressed in NSCLC. The project aims to better understand MUC1 roles on lung cancer cells properties, chemoresitance to cisplatin and immunosupression.

In our project, 2 human NSCLC lines are used: H1975 invalidated for MUC1 and PC9 stably overexpressing MUC1.

Our results show that MUC1 expression (i) is associated with increased cell survival, proliferation, migration and invasion (ii) leads to cisplatin chemoresistance, (iii) increases the expression of ABC family efflux pumps, (iv) protecting against DNA damages, a proliferation stop and apoptosis, (v) increases the expression of stem cell markers and finally (vi) can induce an immunosuppressive microenvironment. In our patient cohort, MUC1 over-expression correlates with a high PD-L1 score.

In conclusion, in NSCLC, our results show that MUC1 (i) is an actor of tumor progression, (ii) can induce an immunosuppressive microenvironment, (iii) is implicated in cisplatin chemoresistance. These results show that MUC1 is a key player in tumor progression and chemoresistance.

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PLATFORMS & STRUCTURING ACTIONS

- **PETRA** *“Réseau PrEclinique et TRAnslationnel de recherche en neuro-oncologie” : Une nouvelle action structurante dans la Région Sud*
- **EXTRACELLULAR VESICLES CEEVEC** *- Action régionale structurante du Canceropôle Provence-Alpes-Côte d’Azur*
- **MET'CONNECT**
- **CRISPR SCREEN ACTION,** *AN INITIATIVE OF THE CANCEROPÔLE PACA*
- **3D-Hub-O :** *Organoids Production Platform*
- **ST-omics :** *The Spatial Transcriptomics Structuring Action*

PETRA « RÉSEAU PRECLINIQUE ET TRANSLATIONNEL DE RECHERCHE EN NEURO-ONCOLOGIE » : UNE NOUVELLE ACTION STRUCTURANTE DANS LA RÉGION SUD

Le projet PETRA vise à structurer la Neuro-Oncologie au niveau régional. Ce réseau souhaite être un centre de référence en Neuro-Oncologie pour la Région Sud dans trois domaines principaux : le traitement des tumeurs cérébrales primitives adultes et pédiatriques, les métastases cérébrales qui sont en augmentation constante, et la problématique émergente de la
neurotoxicité due aux traitements oncologiques.

Le réseau PETRA regroupe plusieurs laboratoires et organismes œuvrant dans le domaine de la Neuro-Oncologie à Marseille et à Nice : équipes de recherche fondamentale, cliniciens, centres de ressources biologiques et associations de patients.

Il s'organise autour de 3 plateformes ouvertes aux équipes académiques, cliniques et aux compagnies privées de la Région Sud, mais aussi au niveau national et international :

— PETRA"TECH" : une plateforme technique implantée sur 2 sites, à Marseille pour l'étude du microenvironnement tumoral, et à Nice pour l'étude des cellules souches cancéreuses, avec une offre de modèles précliniques humains en 3D et de modèles animaux,

— PE"TRANSLA" : une plateforme de recherche translationnelle facilitant l'accès aux ressources biologiques annotées et accompagnant les équipes vers les essais cliniques,

— PETR"ADVICE" : une plateforme de conseil, d'orientation et de formation pour la conception des plans expérimentaux ou l'accès à des technologies/expertises spécifiques.

Ses actions devraient faciliter le transfert des découvertes en oncologie systémique vers la neuro-oncologie et accélérer l'accès des patients aux innovations thérapeutiques.

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EXTRACELLULAR VESICLES CEEVEC – ACTION RÉGIONALE STRUCTURANTE DU CANCEROPÔLE PACA

Since the early 2000s, Extracellular Vesicles (EVs) generated increasing interest due to their potential to revolutionize healthcare, both as diagnostic and therapeutic tools. EVs are lipid-bilayer organelles released by all cells and carrying bioactive molecules (proteins, lipids, metabolites, nucleic acids) that influence target cell behavior.

To help structuration of education, research and innovation in the field of EVs in PACA, we created the CEEVEC (Centre d'Expertises et d'Expérimentations sur les Vésicules Extracellulaires en Cancérologie) that recently received financial support from the Cancéropôle PACA. This support will be used as a first impulse to (i) animate an "EVs-Cancer" network in PACA, stimulating and coordinating academic knowledge, efforts and interests around EVs in oncology, (ii) create a platform providing access to state-of-the-art technologies for the characterization of EVs as well as their bio-production for exploratory therapeutic purposes, (iii) support the training and education of scientists in the field of EVs and (iv) facilitate cross-fertilizing efforts with industry.

Twenty-two teams, distributed in 11 research centers (6 in Marseille and 5 in Nice) teamed-up to support the emergence of CEEVEC.

These teams conduct both flagship and emerging projects, and establish industrial partnership, patent/licences in the field of EVs. Moreover, 6 expert platform poles (3 in Marseille and 3 in Nice) joined the venture providing top-notch privilege access to proteomic, lipidomic, cytometry and high-resolution microscopy infrastructures and know-how.

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(2) AMU
(3) Inserm
(4) CNRS
(5) IPC
(6) iBV
(7) Université Côte d'Azur
(8) IPMC
(9) Centre de Recherche Cardiovasculaire et Nutrition (C2VN)

MET'CONNECT

Scientific Field: Met'Connect focuses on the study of tumor cell metabolism with the goal to solve technical and conceptual blockages that may delay the development of projects led by scientists who are not expert in the field of tumor metabolism.

Objectives :
1) To structure and strengthen scientific andtechnical skills on cancer cell metabolism in PACA.
2) To provide experimental solutions to questions about the metabolism of tumor cells.
3) To improve scientific knowledge and dissemination of results.
4) To develop a bioinformatics approach for the metabolic profiling of tumor samples based on omics data.

Concept :
Met'Connect includes (1) a support ranging from assistance in the design and realization of experiments, (2) a bioinformatics service specialized in the analysis of metabolic pathways, (3) the use of equipment available in Nice and Marseille and (4) the organization of thematic scientific events.

Expected results :
A better understanding of how cancer cells adapt to their environment by modifying their metabolism highlights vulnerabilities and allows to discover original therapeutic approaches. One of the applications of our action is, for example, the screening of drugs that can potentially target metabolism, but also the development of new techniques. We will advise researchers on complementary experiments (metabolomics or fluxomics).

Impact :
Through a single access portal, Met'Connect will offer a unique service for bioinformatics analysis, technical advice, access to equipment, the performance of experiments, networks of collaborators and scientific events.

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CRISPR SCREEN ACTION, AN INITIATIVE OF THE CANCEROPÔLE PROVENCE-ALPES-CÔTE D'AZUR

The CRISPR Screen action aims to build a regional infrastructure and a task-force working collaboratively with the PACA cancer research community on the innovative CRISPR/Cas9 technology. The objective of the action is to develop, improve and spread CRISPR/Cas9 functional genomics screening approaches that leverage different versions of the Cas9 enzymes to better understand gene function and identify biologically-relevant targets in various cancer subtypes. The CRISPR screen action staff work closely with Canceropôle PACA investigators throughout the planning and execution of each research project from assay development, to preliminary data analysis. Data from CRISPR/Cas9 screens in different tumors subtypes should allow us to better catalog the functional importance of protein-coding genes, non-coding RNAs as well as regulatory regions that are so far little explored, shed light on genetic vulnerabilities in tumor cells and the possibility of exploiting them as therapeutic targets, better understand the mechanisms of resistance to targeted therapies opening innovative avenues for translational research. We will present different examples of CRISPR-based screens with various readouts including "low complexity" phenotypic-based screens and "high-complexity" phenotype by coupling each individual CRISPR perturbation to single cell RNA-seq.

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ST-OMICS: THE SPATIAL TRANSCRIPTOMICS STRUCTURING ACTION

Single-cell sequencing technologies have brought unprecedented resolution to our understanding of complex tissues, including tumors. Yet, because single-cell sequencing technologies require single cell or single nuclei suspensions as input, the resulting datasets lack crucial information regarding in situ localization of specific cells in the tissue. Recently, several methods have emerged that enable high-throughput analysis of gene expression in tissues with spatial resolution; those methods are collectively called "spatial transcriptomics" (ST).

The Spatial Transcriptomics Structuring Action (ST-omics) has the ambition to (1) contribute to the regional deployment of state-of the-art ST equipment, (2) set up a working group composed of histo-genomics engineers and data analysts bringing expertise at all steps of ST data production, analysis, and validation (3) advance knowledge of tumor cell diversity and immune infiltration patterns for two major cancer types, (4) develop methods for adaptive immune receptor repertoire (AIRR) spatial analysis, and (5) provide trainings and analysis/ exploration solutions to enable the local cancer community to benefit from a fast learning curve in this field.

Here, we will present the ST-omics ongoing actions and their expected results for the Canceropôle PACA community in the short, mid and long terms. We will update the community on the recent progress we have made on single-cell ST data analysis for (1) quality control of cell segmentation, (2) filtering of low quality cells, (3) normalization of gene expression counts, and (4) integration of several datasets. We will discuss results obtained on different commercial single-cell ST platforms.

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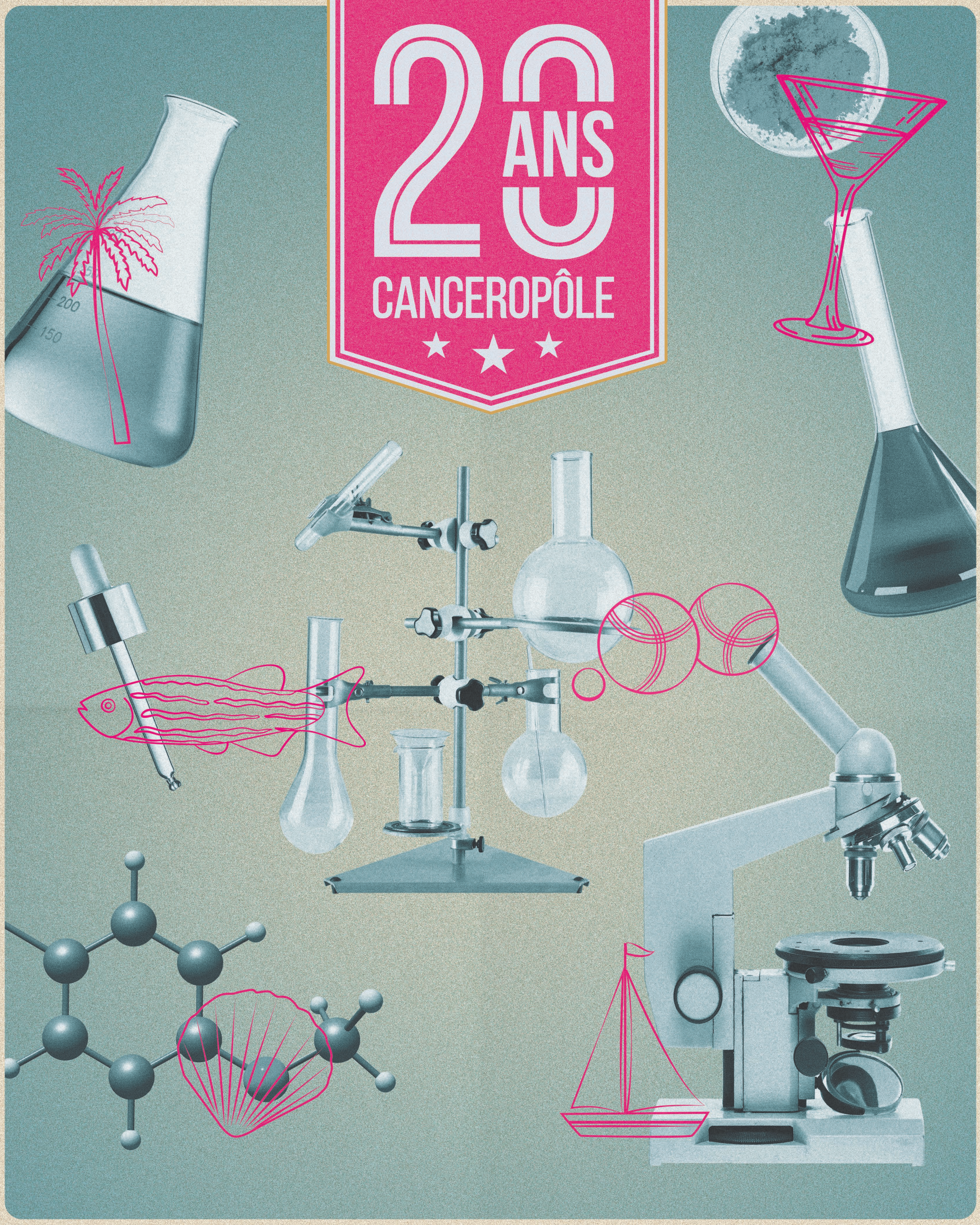
20 ANS CANCEROPÔLE



RÉGION SUD PROVENCE ALPES CÔTE D'AZUR

canceropôle Provence-Alpes-Côte d'Azur
le propulseur régional des recherches et innovations anticancers

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