9th Edition

cancéropôle

BOOKLET

ANNUAL SEMINAR

5TH & 6TH JULY 2022

Saint-Raphaël

PALAIS DES CONGRÈS

cancéropôle Provence-Alpes-Côte d'Azur

le propulseur régional des recherches et innovations anticancers

#WEARECANCEROPOLE

INSTITUT NATIONAL DU CANCER

RÉGION SUD PROVENCE ALPES CÔTE D'AZUR

ANNUAL SEMINAR

5TH & 6TH JULY, 2022 – PALAIS DES CONGRÈS, SAINT RAPHAËL

cancéropôle Provence-Alpes-Côte d'Azur

PROGRAM

JULY 5TH

09:20 WELCOME

09:45 OPENING CEREMONY & UPDATE FROM THE CANCEROPÔLE
C. Ducord, Director & X. Morelli, Scientific Committee President

10:10 SPEECH FROM FONDATION ARC
S. Daubeuf, Head of Education and Exploration Research

10:30 TEASING POSTER SESSION

11:00 HEMATOLOGY SESSION – EMA PROJECTS
- "Tackling acute lymphoblastic leukemia with a small molecule targeting dCK, a nucleotide kinase from the salvage pathway" - X. Morelli, CRCM, Marseille
- ATLAS Project - B. Nadel, CIML & Carnot Lymphoma Institute Director, Marseille

11:40 TEASING POSTER SESSION

12:00 TEASING PARTNERS

12:30 LUNCH BREAK

CHAIRPERSONS E. Saada & F. Maina

13:30 PLATFORM & POSTER SESSION / SPONSORS STANDS VISIT

14:20 TKI DIFFERENCIATION & MECHANISMS OF RESISTANCE IN BREAST CANCER
SYMPOSIUM SEAGEN – C. Vicier, IPC / AMU, Marseille

14:40 THE TALENTED RESEARCHERS POPULARIZE THE SCIENCE
SATT Sud-Est & Patient Associations Awards

15:40 NEWCOMERS IN THE REGION
- "Mechanisms of lung cancer pathogenesis driven by the oxidative stress-ubiquitin pathway" L. Lignitto, CRCM, Marseille
- "Repetitive elements as signals for developmental & regenerative hematopoiesis" E. Trompouki, IRCAN, Nice

16:20 SOLID TUMORS SESSION
- Feat. Publi: "Blockade of the pro-fibrotic reaction mediated by the miR-143/-145 cluster enhances the responses to targeted therapy in melanoma" S. Diazzi, C3M, Nice

16:40 PLACE OF ANTIBODY-DRUG CONJUGATE IN ONCOLOGY, MECHANISMS OF RESISTANCE & PERSPECTIVES - SYMPOSIUM DAIICHI SANKYO / ASTRAZENECA
A. Ducoulombier, CAL / UCA, Nice & A. De Nonneville, IPC / AMU, Marseille

17:20 AWARDS CEREMONY – THE TALENTED RESEARCHERS POPULARIZE THE SCIENCE
SATT Sud-Est & Patient Associations representatives

18:00 END OF THE FIRST DAY

JULY 6TH

09:00 WELCOME

CHAIRPERSONS S. Roulland & F. Hubert

09:15 SOLID TUMORS SESSION
- "Development and validation of a fast automatic screening system for melanoma detection based on machine learning algorithms" - J. Monnier, AP-HM / CRCM, Marseille
- Oral Com: "Diversity of preneoplastic behaviours: cellular and molecular traits in quiescent versus evolving lesions" - C. Sequera, IBDM, Marseille

09:55 HIGHLIGHTS OF THE YEAR IN ONCOLOGY & HEMATOLOGY - SYMPOSIUM BMS CELGENE
E. Saada, CAL / UCA, Nice, E. Tabouret, AP-HM / AMU, Marseille
T. Cluzeau, CHU de Nice / UCA & G. Brisou, IPC / AMU, Marseille

11:00 COFFEE BREAK / PLATFORM & POSTER SESSION

CHAIRPERSONS T. Cluzeau & C. Ginestier

11:45 "LES TRANSLATIONNELLES" ROUND TABLE
- "The Purinergic Landscape of Non-Small Cell Lung Cancer" V. Vouret-Craviari & J. Benzaquen, IRCAN, Nice

12:20 SOLID TUMORS SESSION
- Oral Com: "Restoring anti-sarcoma immune response through Vanin-1-mediated metabolic reprogramming" - R. Miallot, CIML, Marseille

12:40 ONCO-IMMUNOLOGY SESSION
- Oral Com: "The extracellular matrix of oral squamous cell carcinoma modulates the spatial distribution & the phenotypes of tumor-associated myeloid immune cell populations" L. Petti, IPMC, Nice

13:00 LUNCH BREAK

CHAIRPERSONS V. Braud & P.H. Gaillard

14:00 PLATFORM & POSTER SESSION / SPONSORS STANDS VISIT

14:30 DNA DAMAGE/REPAIR & CONSEQUENCES IN THE CLINIC - SYMPOSIUM ASTRAZENECA
M. Godinho Ferreira, IRCAN, Nice & R. Sabatier, IPC / AMU, Marseille

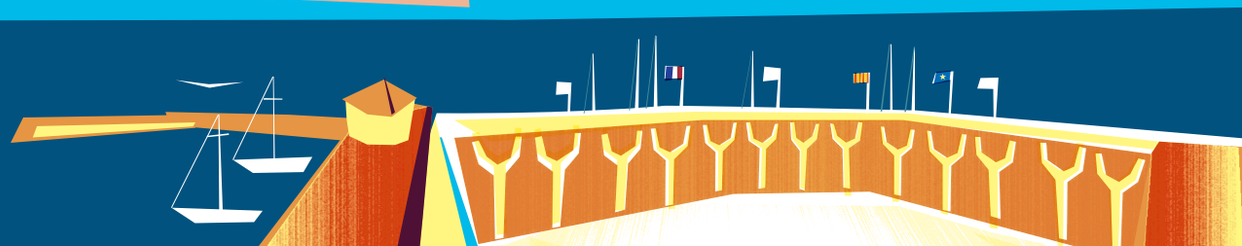
15:10 PRESENTATION FROM FRENCH NATIONAL CANCER INSTITUTE
A. Eychène, Head of Research & Innovation

15:30 NEWCOMER IN THE REGION
- "At the edge of abomination: how a glyco-pathway allows cancer to carve into surrounding tissues" - F. Bard, CRCM, Marseille - Intl. leaders in Oncology awarded by Fondation ARC

15:50 ONCO-IMMUNOLOGY & HEMATOLOGY SESSION
- "Do the ganglioside reshuffling at senescence can favor immune surveillance escape and tumorigenesis?" - J. Cherfils Vicini, IRCAN, Nice
- Feat. Publi: "Pharmacological reduction of mitochondrial iron triggers a non-canonical BAX/BAK dependent cell death" - S. Garciaz, IPC / CRCM, Marseille
- "Non-canonical EZH2 drives retinoic acid resistance of variant acute promyelocytic leukemias " M. Poplineau, CRCM, Marseille

16:50 CLOSING CEREMONY / ORAL COMMUNICATIONS & POSTERS AWARDS
N.Vey, Cancéropôle Vice-President & Scientific Committee members

17:30 END OF THE SEMINAR



SOMMAIRE

ANNUAL SEMINAR

JULY 5TH & 6TH 2022

LEXIQUE

C3M	Centre Méditerranéen de Médecine Moléculaire
CIML	Centre d'immunologie de Marseille-Luminy
CRCM	Centre de recherche en cancérologie de Marseille
CSM	Centre Scientifique de Monaco
IBDM	Institut de Biologie du Développement de Marseille
IBV	Institut de Biologie Valrose
ICN	Institut de Chimie de Nice
INP	Institut de Neurophysiopathologie
IPMC	Institut de Pharmacologie Moléculaire et Cellulaire
IRCAN	Institute for Research on Cancer and Aging
LMSC	Laboratoire Management Sport Cancer
TAGC	Theories & Approaches of Genomic Complexity

TUESDAY, JULY 5TH

Canceropôle Provence-Alpes-Côte d'Azur
Clara Ducord & Xavier Morelli

CANCEROPÔLE'S PROPELLERS

CALL FOR PROJECT

- Emerging projects, SSH-E-PH
- Prematuration, EmA
- Translationnal &clinical Research
- Equipment, Events, Mobility

SUPPORT ACTIONS

- New talents
- Go European
- Training
- Boosted Publications
- Transfer research Results

STRUCTURING ACTIONS

- CRISPR Screen
- 3D-Hub
- Bioinformatics
- Single Cell

NETWORKING

DISSEMINATION

- Annual Seminar
- Matching Days
- Lab tours

Fondation ARC: a partner for the cancer research community
Sandrine Daubeuf, Scientific Direction

The mission of Fondation ARC is to fight cancer through research. Building on a national and international expertise, its scientific policy is articulated around 3 strategic areas that meet the current needs and challenges of cancer research:

- **Increase knowledge about all cancers,** in all relevant scientific and medical fields, by supporting basic research that is essential to understand the disease;
- **Promote therapeutic innovation** by accelerating the development of clinical and translational research and by allowing access to these new solutions for all patients, children and adults;
- **Create the conditions for developing top-notch research in France** by relying on a long-term proactive policy based on training, identification and attraction of new talents.

At the crossroads of these areas, 3 priority topics are supported: oncopediatrics, aggressive cancers (such as pancreatic cancer), innovative treatments, and the study of the links between aging and cancer.
The Foundation's action covers the entire French territory and is carried out in complete independence. Guided by the general interest and scientific excellence, it identifies, selects, funds and supports promising research programs.
The Fondation ARC also wants to share with as many people as possible the advances in cancer research and the latest knowledge on the disease to provide everyone with the means to better prevent, manage and understand the disease.
The ARC Foundation is exclusively funded by the generosity of the public. Thanks to the support of its donors and testators it carries out its action in favor of research. It is approved by the control body « Don en confiance » since 1999.

HEMATOLOGY SESSION - EMA PROJECTS

Tackling acute lymphoblastic leukemia with a small molecule targeting dCK, a nucleotide kinase from the salvage pathway

Xavier Morelli, CRCM, Marseille

Enhanced proliferation of cancer cells drives to an insufficient capacity of the main De Novo Pathway (DNP) for deoxyribonucleotides biosynthesis. To meet the metabolic requirements, cancer cells engage the alternative Salvage Pathway (SP) to reach adequate nucleotide pools. The interrelation of these pathways enables the upregulation of SP upon DNP inhibition and increase the dependency of specific cancers on the SP for nucleotide production. Because deoxycytidine kinase (dCK) is the rate-limiting enzyme of the SP, it has recently emerged as a main target for anti-proliferative therapies towards cancers where the SP is essential. We present here the development of a dCK inhibitor applying an iterative multidisciplinary approach, DOTS, which relies on fragment-based drug design coupled to experimental evaluations. This strategy allows an acceleration of the hit-to-lead process by gradually implementing key chemical modifications that increase protein-ligand interactions and activity. Our lead compound, OR0642, is more than 1000 times more potent than its initial parent compound, masitinib, previously identified by us from a drug repositioning approach. OR0642 in combination with a physiologic inhibitor of the ribonucleotide reductase (key enzyme of the DNP) doubled the survival rate in a human T acute lymphoblastic leukemia mouse model, demonstrating the proof-of-concept of this “drug repositioning to drug design strategy”.

The ATLAS program: from genetic mutations to functional dynamics

Bertrand Nadel, CIML & Carnot Lymphoma Institute, Marseille

There are many ways to approach experimental design in the study of the living. At both extremes, the approach of exploiting technological advances, allowing the generation of unbiased (big) data, battles with an approach where the theorization of the concept remains dominant.

Do we need a large genomics program for oncology? Evidently, I do not have the answer. Nevertheless, as an example or testimony, I will try through this presentation to address the resolutely tortuous conceptual path, from genomics to functional dynamics through molecular epidemiology, which led our laboratory to set up a «large scale program» of functional genomics. Our primary motivation today is the same as at the beginning of our journey several years (decades) ago, namely to meet the urgent medical needs of responding to the treatments of patients with follicular lymphoma.

This major functional genomics program requires an investment that is not trivial at the scale of a research laboratory. It even requires a profound reorganization of skills, infrastructure, institutional and financial support. At the forefront, it has allowed to forge an unprecedented partnership collaboration. Through the EmA program, the Cancéropôle Provence-Alpes-Côte d’Azur was visionary and instrumental in building-up the successive steps of this innovating research program.
Beyond touching on the Atlas program on Follicular Lymphoma, of modest interest for most in the audience and anyway limited by industrial partnership confidentiality, my goal is that the discussions sparked by this testimony will be rich in mutual lessons.

"THE TALENTED RESEARCHERS POPULARIZE THE SCIENCE"

- Est-il plus avantageux d’utiliser une gaufre ou une crème caramel pour éviter les récidives de tumeurs cérébrales ? **Chiara Bastiancich, INP, Marseille**
- Tester in-vitro la toxicité des perturbateurs endocriniens avec la technologie « Organoïde » **Batistic Ludovic, C3M, Nice**
- La matrice, un bouclier thérapeutique. **Bouvet Océane, C3M, Nice**
- Tumeurs, réseaux sociaux et Fake news. **Chauvet Sophie, IBDM, Marseille**
- Les Endonucléases : Grey’s Anatomy…version moléculaire. **Dehé Pierre-Marie, CRCM, Marseille**
- Raccourcissement des télomères et vieillissement de l’intestin : un rôle central dans les cancers liés à l’âge ? **El Mai Mounir, IRCAN, Nice**
- Cibler le stress du Réticulum Endoplasmique, nouvelle stratégie thérapeutique pour les patients atteints de cancer du foie ? **Janona Marion, C3M, Nice**
- Révéler les secrets des médicaments pour développer de nouveaux traitements pour les enfants atteints de cancer. **Legrand Marion, CRCM, Marseille**
- Voyage au centre de la tumeur : les lymphocytes B sont sous les projecteur. **Playoust Eve, CIML, Marseille**
- Est-ce que votre métabolisme peut vous rendre allergique ? **Scorrano Giulia, CRCM, Marseille**

NEWCOMERS IN THE REGION

Mechanisms of lung cancer pathogenesis driven by the oxidative stress-ubiquitin pathway

Luca Lignitto, CRCM, Marseille

Cancer cells frequently boost antioxidants production to cope with high levels of oxidative stress, which build up as a consequence of their increased metabolic demand. To maintain oxidative homeostasis and sustain tumor growth, ~30% of Non-Small Cell Lung Cancers (NSCLCs) increase their antioxidant defense by selecting for mutations in the KEAP1/NRF2 complex which ultimately lead to NRF2 activation. The transcription factor NRF2 counteracts oxidative stress by upregulating several antioxidants pathways, including genes controlling glutathione and NADPH production as well as genes regulating heme homeostasis.
In this context, we recently uncovered a novel mechanism sustaining the progression of the KEAP1/NRF2-mutant tumors which is induced by alteration of the heme pathway. In particular, by combining biochemistry and mouse genetics approaches we demonstrated that heme regulates protein degradation via the Ubiquitin-Proteasome System (UPS), and that mutations of KEAP1/NRF2 in NSCLCs impinge on the

heme-UPS pathway ultimately promoting tumor progression.
Our research aims to achieve a deeper understanding of how heme regulates protein degradation via the UPS and determine the potential role of this pathway in the mechanisms of lung cancer pathogenesis. Our long-term goal is to identify new strategies and tools to develop precision therapeutics for lung cancer patients. In this presentation I will discuss the latest advances in our studies.

Repetitive elements as signals for developmental and regenerative hematopoiesis

Eirini Trompouki, IRCAN, Nice

Repetitive elements like transposable elements (TEs) and other simpler repeats are dispersed throughout the genome and consist more than one third of it in multiple species. For many years this part of the genome was considered as “junk”, but it has lately become clear that many functions can be attributed to repetitive elements. Developmental processes and cellular states exhibiting high plasticity are often accompanied by expression of repetitive elements. Here we show that repetitive elements are transcribed during hematopoietic stem cell development and chemotherapy-induced regeneration. Repetitive element RNAs act as signals for innate immune receptors of the RIG-I-like receptor family. Activation of these receptors titrates the induction of sterile inflammatory signals that enhance hematopoietic stem cell development and chemotherapy-induced regeneration. Thus, RNA sensing of repetitive elements actively shapes cellular transitions.

SOLID TUMORS SESSION

Featured Publication: Blockade of the pro-fibrotic reaction mediated by the miR-143/-145 cluster enhances the responses to targeted therapy in melanoma

Serena Diazzi, C3M, Nice

Lineage dedifferentiation toward a mesenchymal-like state displaying myofibroblast and fibrotic features is a common mechanism of adaptive and acquired resistance to targeted therapy in melanoma. Here, we show that the anti-fibrotic drug nintedanib is active to normalize the fibrous ECM network, enhance the efficacy of MAPK-targeted therapy, and delay tumor relapse in a preclinical model of melanoma. Acquisition of this resistant phenotype and its reversion by nintedanib pointed to miR-143/-145 pro-fibrotic cluster as a driver of this mesenchymal-like phenotype. Upregulation of the miR-143/-145 cluster under BRAFi/MAPKi therapy was observed in melanoma cells in vitro and in vivo and was associated with an invasive/undifferentiated profile. The 2 mature miRNAs generated from this cluster, miR-143-3p and miR-145-5p, collaborated to mediate transition toward a drug-resistant undifferentiated mesenchymal-like state by targeting Fascin actin-bundling protein 1 (FSCN1), modulating the dynamic crosstalk between the actin cytoskeleton and the ECM through the regulation of focal adhesion dynamics and mechanotransduction pathways. Our study brings insights into a novel miRNA-mediated regulatory network that contributes to non-genetic adaptive drug resistance and provides proof of principle that preventing MAPKi-induced pro-fibrotic stromal response is a viable therapeutic opportunity for patients on targeted therapy.

Place of ADC in Oncology, Mechanisms of Resistance and Perspectives Symposium Daiichi Sankyo /AstraZeneca

Agnès Ducoulombier, CAL / UCA, Nice & **Alexandre De Nonneville**, IPC/ AMU, Marseille

ADCs are among the fastest growing drug classes in oncology, demonstrated impressive activity against refractory cancers. They comprise three main components: an antibody, a linker, and a payload. Each of them impacts on the clinical properties of ADCs, notably via bystander effect. ADC approach combines in a “Trojan horse” fashion the targeted delivery of the mAb with the tumor-killing potential of the payload. 11 ADCs are marketed worldwide for hematological /solid malignancies. 4 are already used in daily practice for solid tumors, 3 in breast cancer (BC): Sacituzumab Govitecan targeting TROP 2 for metastatic triple negative BC (ASCENT Trial), Trastuzumab Emtansine (TDM1) for early (KATHERINE study) and advanced (EMILIA study) HER2 metastatic BC, and Trastuzumab Deruxtecan (T-DXD) for refractory HER2 metastatic BC (DESTINY BREAST 03&01). Enfortumab Vedotin (Nectin-4 target) has demonstrated benefit in platine & immunotherapy refractory urothelial cancers (EV-301 study). The targeted delivery of cytotoxic payloads through ADCs has the potential to achieve antitumor activity in multiple cancer histologies. Nevertheless, their development still faces great challenges, as drug resistance. Current hypothetic mechanisms are antigen downregulation or loss, alteration of intracellular trafficking pathways/ lysosomal drug breakdown, and payload resistance, largely via efflux, by upregulation of ABC transporter proteins. Futures challenges include development of new generation of ADC and combinations with chemotherapy or target agents, immunotherapy, or anti-angiogenics.

Oral Communication: Diversity of preneoplastic behaviours: cellular and molecular traits in quiescent versus evolving lesions

Celia Sequera, IBDM, Marseille

Knowledge on cellular and molecular events at the early phases of the tumorigenic program remains elusive. This is linked to limited: early diagnosis, availability of early markers, accessibility to sensitive imaging systems for detection of small nodules, longitudinal follow up of early lesions in patients for ethical issues. Preneoplastic lesions in patients, as in animal models, have different behaviours. Whereas some preneoplastic lesions progress overtime (evolving lesions), others are stable (quiescent lesions), and in rare cases spontaneously regress. Uncovering molecular traits and cell type composition diversifying the fate of the preneoplastic lesions could provide essential knowledge in a perspective of cancer prevention and early treatment.

We are addressing this topic using preneoplastic lesions underlying the hepatocellular carcinoma (HCC) program as a paradigm. HCC is nowadays the 3rd cancer-related mortality worldwide, with limited biomarkers, particularly at early stages, and treatment options. We model initiation and evolution of HCC using a genetic setting, the Alb-R26Metmice, which spontaneously develop liver tumours recapitulating several human HCC features, including molecular heterogeneity and resistance to therapies. Furthermore, we developed a powerful imaging system to detect tumours and to longitudinally follow them in vivo, the Photon Counting micro-Computed Tomography (PC-CT). A cohort of Alb-R26Metmice was followed longitudinally with PC-CT to segregate preneoplastic lesions according to their behaviour (evolving vs. quiescent). Dissected lesions were dissociated to analyse: 1) tumour and immune cell type composition (spectral cytometry); 2) molecular characterisation of distinct cell types (single-cell-RNAseq).

“Les Translationnelles” Round Table
The purigenic landscape of non-small cell lung cancer

Valérie Vouret-Craviari & Jonathan Benzaquen, IRCAN, Nice

Lung cancer is the most prevalent cancer worldwide and despite the recent therapeutic advances, comprising targeted therapies and immune checkpoint inhibitors, disease progression occurs in nearly all advanced lung cancer and in up to 50% of early stages. We will discuss whether the purinergic checkpoints (CD39, CD73, P2RX7 and ADORs), described to mold the immune response in the tumor microenvironment, may represent new therapeutical targets to fight NSCLC progression by increasing antitumor immune responses.

Oral Communication: Restoring anti-sarcoma immune response through Vanin-1-mediated metabolic reprogramming

Richard Miallot, CIML, Marseille

Energetic production relies predominantly on glucose or fatty acid breakdown into mitochondrial acetyl-Coenzyme A fueling the TCA cycle. Pyruvate production by glycolysis can be diverted to lactate even under aerobic conditions in metabolically active tumor cells. This phenomenon, called the Warburg effect, is triggered by hypoxia and oncogene expression suggesting a context-dependent plasticity of energetic pathways. In addition, negative feedback regulation between glycolysis and oxidative phosphorylation occurs under high concentrations of glucose or ATP. Therefore, regulation of the Warburg effect may depend on both contextual signals and modifications of metabolic flux dynamics.
Taking the central role of CoA in this process, we investigated the role of the pantetheinase Vanin1, involved in CoA homeostasis, on tumor growth. Mechanistically, Vanin1 hydrolyzes pantetheine into pantothenate, the CoA biosynthetic precursor, and cysteamine. We showed that Vanin1 expression is associated with a better overall survival for soft tissue sarcoma (STS) patients and correlated with immune response signature. In mouse STS models, Vanin1 exerts an anti-Warburg effect linked to enhanced oxidative phosphorylation. Consequently, Vnn1-expressing sarcomas remain differentiated and grow slowly.
After characterizing the metabolic signature associated with Vanin1 expression on tumor cells, we characterize the effect of pharmaceutical delivery of pantetheinase activity substrates in vitro and in vivo. Taking the complexity of metabolic rewiring and cell-cell interaction, we aim to evaluate the shift in transcriptomic and metabolic levels in cancer cells and immune cells. Single resolution and multi-modal analysis integrates all informations obtains from single cell RNA sequencing, metabolomics studies and cell surface expression. Using prime editing, we evaluate the prognostic potential of a redox-sensitive protein, essential in mitochondria homeostasis and potential target of the Vanin1-dependent pathway. Identification of protein and cellular actors modulating pantethine efficiency is an essential step for the development of antitumor therapeutic combinations and immunotherapies improvement in solid tumors.

ONCO-IMMUNOLOGY SESSION

Oral Communication: The extracellular matrix of oral squamous cell carcinoma modulates the spatial distribtion and the phenotypes of tumor-associated myeloid immune cell populations

Luciana Petti, IPMC, Nice

Oral squamous cell carcinomas (OSCC) are cancers of the oral cavity and represents the sixth leading cancer worldwide. Only 50% of the OSCC patients survive up to 5 years after diagnosis due to disease relapse and loco-regional spread following treatment failure. Malignant cells escape immune surveillance by promoting the conversion of the physiological microenvironment into a pro-tumor state. These changes involve not only the direct recruitment and activation of immunosuppressive immune cell subsets, but also their in situ remodeling by the tumoral extracellular matrix (ECM). Recent studies showed that Tenascin-C (TNC) is one major ECM component upregulated in the stroma of OSCC lesions with immunosuppressive functions and a promoter of tumor malignancy (Spenlé, CIR2020). However, its role in the regulation of the immune phagocytic cells, main actors in the OSCC immune microenvironment, has not been thoroughly investigated.
This study aims to delineate the OSCC tumor immune microenvironment focusing on the in-depth characterization of macrophages and dendritic cell subsets and their phenotypic and functional regulation by the TNC ECM protein. We combined multiparametric analyses in human OSCC and in the 4-nitroquinoline-1-oxide (NQO)-induced OSCC model in TNC-sufficient and TNC-deficient background using spectral flow cytometry and imaging mass cytometry.
This study reveals the unique spatial distribution and the heterogeneity of macrophages and dendritic cells subsets in human and mouse OSCC models compared to non-tumoral tissues. The TNC protein not only modulates the positioning of macrophage and dendritic cell subsets but also their phenotype and functions. Our work contributes significantly to define the landscape of the immune and matrix microenvironment of HNSCC and may help to identify novel therapeutic strategies to improve current treatments.

DNA damage/repair & consequences in the clinic
Symposium AstraZeneca

Organismal consequences of telomeric DNA damage

Miguel Godinho Ferreira, IRCAN, Nice

DNA damage, such as the one elicited by classic chemotherapeutic agents, triggers a chain of events that culminates in the activation of p53, apoptosis or cell senescence. Consequently, sustained DNA damage leads to a reduction in the proliferative capacity that results in loss of tissue homeostasis. Likewise, as telomeres become critically short with age, they are sensed as irreparable DNA damage incurring in similar responses.
Recently, the cGAS-STING pathway was shown to be activated by short and dysfunctional telomeres. This pathway is part of the innate immune system, signaling inflammation upon viral infection and was shown to modulate cell senescence.
We study the consequences of DNA damage responses elicited by telomere shortening at the organism level in zebrafish. Like humans, zebrafish telomeres shorten to critical length during normal aging. Telomerase deficient zebrafish (tert-/-) die prematurely while recapitulating aging phenotypes, such as reduced fertility, cachexia, increased inflammation, and age-associated diseases.
We show that STING is responsible for the zebrafish telomerase mutant premature aging. We generated sting tert double mutant zebrafish and observed reduced senescence and interferon response when compared to tert single mutants. Consistently, sting tert double mutants showed higher levels of cell proliferation. At the organism level, we observed that inactivation of STING rescues infertility while improving the shorter lifespan of telomerase mutants. Thus, our data suggests that DNA damage triggered by telomere shortening activates the cGAS-STING pathway, resulting in a type I interferon inflammatory response and premature aging in tert mutants.

Presentation from Institut National du Cancer (INCa)

Alain Eychène, Head of Research & Innovation

The French National Cancer Institute (INCa) is the preeminent health and science agency in charge of cancer control in France, created under the Public Health Act of 9th August 2004. It reports to the ministries for Health and for Research.
The Institute is a public interest grouping (GIP) which brings together State representatives, charities, health insurance funds, research organisations and hospital federations. These stakeholders share a common goal of reducing the incidence of avoidable cancers and the number of cancer deaths, improving the quality of life of people with cancer during and after their illness, and reducing inequalities related to cancer.
The Institute provides an integrated approach encompassing all cancer-control dimensions (health, scientific, social and economic) and areas of intervention (prevention, screening, care and research) for the benefit of patients and their relatives.
To catalyse progress, the INCa acts as an interface with patients, their friends and families, the healthcare system users, general public, healthcare professionals, researchers, experts and decision-makers.

ONCO-IMMUNOLOGY & HEMATOLOGY SESSION

Do the ganglioside reshuffling at senescence can favor immune surveillance escape and tumorigenesis? Projet DISCOVERG

Julien Cherfils Vicini, IRCAN, Nice

Aging is at the origin of a significant number of diseases and cancers, for which the epistemological link is increasingly detailed. At the cellular level, the accumulation of senescent cells (SC) in tissues emerges as a key factor in aging and cancer. It is now well established that SC can be either eliminated by our immune system (pre-oncogenic SC for instance) but also can accumulate progressively during life and be tolerated in our tissues. We still do not know the molecular events regulating senescence immune clearance.

We show that SC, elicited by various stressors other than oncogenic activation, triggers immune escape toward natural killer (NK) cells. We reveal that SC reshuffle their glycocalyx composition, toward a marked increase in the ganglioside content, including the appearance of disialylated ganglioside GD3. The high level of GD3 leads to a strong immunosuppressive signal affecting NK cell-mediated immunosurveillance. In a mouse model of lung fibrosis, senescent cell-dependent NK cell immunosuppression is blunted by in vivo administration of anti-GD3 monoclonal antibodies leading to a clear anti-fibrotic effect. Finally, the presence of GD3+ SC is sufficient to blunt NK cell mediated anti-tumor immunosurveillance in vitro. These results demonstrate that GD3 upregulation in SC drives a switch from immune clearance toward immune tolerance. Therefore, we propose that GD3 level acts as a senescence-associated immune checkpoint (SIC) that determine senescent cell fate (Iltis et al., 2021, preprint BioRxiv DOI 10.1101/2021.04.23.440408; Patent ADN11450685PR).

Featured Publication: Pharmacologic Reduction of Mitochondrial Iron Triggers a Noncanonical BAX/BAK-Dependent Cell Death

Sylvain Garciaz, IPC /CRCM, Marseille

Cancer cell metabolism is increasingly recognized as providing an exciting therapeutic opportunity. However, a drug that directly couples targeting of a metabolic dependency with the induction of cell death in cancer cells has largely remained elusive. Here we report that the drug-like small-molecule ironomycin reduces the mitochondrial iron load, resulting in the potent disruption of mitochondrial metabolism. Ironomycin promotes the recruitment and activation of BAX/BAK, but the resulting mitochondrial outer membrane permeabilization (MOMP) does not lead to potent activation of the apoptotic caspases, nor is the ensuing cell death prevented by inhibiting the previously established pathways of programmed cell death. Consistent with the fact that ironomycin and BH3 mimetics induce MOMP through independent nonredundant pathways, we find that ironomycin exhibits marked in vitro and in vivo synergy with venetoclax and overcomes venetoclax resistance in primary patient samples.
Ironomycin couples targeting of cellular metabolism with cell death by reducing mitochondrial iron, resulting in the alteration of mitochondrial metabolism and the activation of BAX/BAK. Ironomycin induces MOMP through a different mechanism to BH3 mimetics, and consequently combination therapy has marked synergy in cancers such as acute myeloid leukemia

Non-canonical EZH2 drives retinoic acid resistance of variant acute promyelocytic leukemias

Mathilde Poplineau, CRCM, Marseille

Cancer cell heterogeneity is a major driver of therapy resistance. To characterize resistant cells and their vulnerabilities, we studied the PLZF-RARA variant of acute promyelocytic leukemia (APL), resistant to retinoic acid (RA), using single-cell multi-omics. We uncovered transcriptional and chromatin heterogeneity in leukemia cells. We identified a subset of cells resistant to RA with proliferation, DNA replication and repair signatures, that depend on a fine-tuned E2F transcriptional network targeting the epigenetic regulator Enhancer of Zeste Homolog 2 (EZH2). Epigenomic and functional analyses validated the driver role of EZH2 in RA resistance. Targeting pan-EZH2 activities (canonical/non-canonical) was necessary to eliminate leukemia relapse initiating cells, which underlies a dependency of resistant cells on an EZH2 non-canonical activity and the necessity to degrade EZH2 to overcome resistance.
Our study provides critical insights into the mechanisms of RA resistance that allow us to eliminate treatment-resistant leukemia cells by targeting EZH2, thus highlighting a potential targeted therapy approach. Beyond RA resistance and APL context, our study also demonstrates the power of single-cell multi-omics to identify, characterize and clear therapy-resistant cells.

POSTERS
FUNDAMENTAL RESEARCH

1 Exploiting the glioblastoma resection microenvironment as therapeutic target towards the development of local treatments to avoid long-term recurrences - INP

2 Targeting CISH enhances natural cytotoxicity receptor signaling and reduces NK cell exhaustion to improve solid tumor immunity - CRCM -

3 Role for the lysyl oxidase like 2 enzyme in stromal matrix remodeling and invasive properties of dedifferentiated melanoma cells - C3M -

4 Distinct types of cell death inducers to specifically remodel the immune landscape in TNBC mouse models - IBDM -

5 Reprogramming monocyte-derived macrophages through caspases and cathepsin B inhibition - C3M -

6 The serine/threonine kinase MINK1 regulates a phospho-dependent promigratory cascade in triple-negative breast cancer - CRCM

7 Sponge-associated fungus Stachybotrys chartarum MUT 3308 as a source of new anticancer compounds? - ICN -

8 Role of Galectine 1 in the control of leukemogenesis - CRCM -

9 PTK7 acts as a negative regulator of EPHA2 activation in colorectal cancer - CRCM

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28 PINK1-dependent mitophagy restrains tumor growth: link to the tumor immune response? - C3M

29 Immune cell populations in steady state prostate & prostate cancer - CIML -

30 SAM68: a guiding STAR during cell-extracellular matrix crosstalk - IBV -

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POSTER 1 - FR

Exploiting the glioblastoma resection microenvironment as therapeutic target towards the development of local treatments to avoid long-term recurrences

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Glioblastoma (GBM) is the most aggressive primary brain tumour. Following surgical debulking, the crosstalk between glial, immune and GBM cells at the tumor resection borders can impact the onset of recurrences. Here, we developed a tumor resection model in transgenic mice bearing GL261 tumors and established a chronic intracranial window post-surgery. We analyzed the recruitment and localization of immune cells coming to the resection site from the brain parenchyma or from the periphery, as well as blood vessels, cell morphologies and motilities by biphotonic imaging. Nuclear imaging was performed to evaluate neuroinflammation, neoangiogenesis, infiltrating tumor cells metabolism and BBB disruption following resection. The dynamics of the inflammatory landscape following surgery was characterized by blood sampling and post-mortem analysis on brain samples. We selected from the literature several molecules that could act both on residual GBM cells and on the TRe, and their combination has been tested on 2D and 3D cellular models. A nanomedicine-based formulation delivering the best performing drugs will be formulated and loaded into a biocompatible scaffold that can be injected in the tumor resection cavity.
This study expands the knowledge on the TRe by analyzing the impact of BBB disruption on immune cells recruitment and on the onset of tumor recurrences. Moreover, it describes the rational development of fit-for-purpose DDS for an application in the tumor resection cavity of GBM that will hopefully avoid tumor recurrences in the long-term.

POSTER 2 - FR

Targeting CISH enhances natural cytotoxicity receptor signaling and reduces NK cell exhaustion to improve solid tumor immunity

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The success and limitations of immunotherapies have pushed research toward the development of alternative approaches and the possibility to manipulate other cytotoxic immune cells such as natural killer (NK) cells. Here, we targeted an intracellular inhibiting protein ‘cytokine inducible SH2-containing protein’ (CISH) in NK cells to evaluate the impact on their functions and antitumor properties.To further understand CISH functions in NK cells, we developed a conditional Cish-deficient mouse model in NK cells (Cish fl/fl Ncr1Ki/+, «CishKO-NK»). We detected no developmental or homeostatic difference in NK cells. Global gene expression of Cish-KO NK cells revealed upregulation of pathways and genes associated with NK cell cycling and activation. We show that CISH does not only regulate interleukin-15 (IL-15) signaling pathways but also natural cytotoxicity receptors (NCR) pathways.Cish-KO NK cells display increased activation upon NCR stimulation. Cish-KO lowers activation NK thresholds and CishKO-NK mice are more resistant to tumor metastasis and to primary breast cancer growth. CISH deletion favors NK cell accumulation to the primary tumor, optimizes NK cell killing and decreases NK cell exhaustion.Finally, we targeted CISH in human NK-92 and primary NK cells, using a technology combining the CRISPR(i)-dCas9 tool with a new lentiviral pseudotype. We then tested human NK cells function, showing that CISH deletion also favors NCR signaling and antitumor functions in human NK cells.Our results validate CISH as an emerging therapeutic target to enhance NK cell immunotherapy.

POSTER 3 - FR

Role for the lysyl oxidase like 2 (LOXL2) enzyme in stromal matrix remodeling and invasive properties of dedifferentiated melanoma cells

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Despite novel therapies for skin melanoma, drug resistance remains a clinical challenge. Upon microenvironment and therapeutic pressures, melanoma cells can switch from a melanocytic state to dedifferentiated mesenchymal states. Such adaptive plasticity was described as a driver of resistance to targeted therapies (TT). This study relies on original observations that dedifferentiated cells produce an abundant extracellular matrix (ECM) enriched in LOXL2, a collagen crosslinking enzyme also known to drive the epithelial-to-mesenchymal (EMT) in breast cancer. Here, we hypothesized that LOXL2 production by melanoma cells and its presence within the stroma could influence cell plasticity towards a drug-tolerant dedifferentiated state.

We showed that LOXL2 is preferentially expressed by dedifferentiated cells and induced by TT or hypoxia, cues known to remodel and aggravate the tumor niche. On the contrary, LOXL2 induction by TT is reversed by PDGFR and AKT inhibitors. Using si/shRNA, we revealed that LOXL2 plays a role on cell morphology and promotes melanoma cell migration. Interestingly, we also show that targeting LOXL2 in melanoma-associated-fibroblasts impaired their ability to contract a collagen matrix and to assemble an organized ECM, impacting melanoma cell properties.

Together, these findings provide an original link between LOXL2, ECM remodeling and melanoma cell biology. This study improves our understanding of the biochemical and biomechanical cues from the tumor microenvironment that affect melanoma cell plasticity and adaptation to anti-melanoma therapies.

POSTER 4 - FR

Distinct types of cell death inducers to specifically remodel the immune landscape in TNBC mouse models

Olivier CASTELLANET[1], Paula MICHEA[2], Alix JAEGER[2], Jean-Paul BORG[2,3], Luc CAMOIN[2], Fabienne LAMBALLE[1], Flavio MAINA[1].

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Triple-negative breast cancer (TNBC) is a highly aggressive breast cancer subtype characterized by a remarkable molecular heterogeneity and resistance. We have recently reported the generation of a unique mouse model (MMTV-R26Met mice) in which subtly increased signaling levels lead to spontaneous, exclusive TNBC formation, recapitulating TNBC features. We exploit this model to decipher the immune landscape in the TNBC microenvironment and its remodeling in relation to the type of cell death triggered by anticancer drugs.Spectral cytometry analysis of the immune cell type composition within the MMTV-R26Met TNBC mice uncovered heterogeneity in the composition of immune cell types. We will integrate these data with those from human TNBC patients. Interestingly, we found specificities in how the immune landscape is remodeled according to the cell death mechanism triggered by anticancer drug combinations we recently identified, leading to either apoptosis or ferroptosis. In particular, preliminary results show different dynamics in immune cell type content and a specific enrichment in B-lymphocytes and dendritic cell subtypes in regressing tumors linked to apoptosis versus ferroptosis.We also present an overall interdisciplinary strategy we conceived to further explore these topics, integrating spectral cytometry data with studies based on tumoroids, single cell RNA-seq, proteomics, immunohistochemistry, and mathematical modeling. Outcomes will be translated into combinatorial treatments using agents targeting cancer cells with immunotherapies.

POSTER 5 - FR

Reprogramming monocyte-derived macrophages through caspases and cathepsin B inhibition

Paul CHAINTREUIL[1], Emeline KERRENEUR[1], Lucie LAPLANE[2,3], Sonia BOULAKIRBA[1], Marie-Laure ARCANGELI[1], Guillaume ROBERT[1], Nathalie DROIN[2,4], Eric SOLARY[2,4], Patrick AUBERGER[1], Arnaud JACQUEL[1]

1 C3M

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MDMs (monocyte-derived macrophages) play a crucial function in a wide variety of physiologic and pathologic settings, including cancers. Understanding the mechanisms of MDMs generation/polarization might provide an opportunity for the design of novel therapeutic strategies. In this context, we highlighted an original and highly specific mechanism of caspase activation involved in CSF-1-mediated macrophage differentiation, giving them non-apoptotic functions. Indeed, we showed a differentiation-specific mode of caspase-8 (CASP8) activation in CSF-1-treated monocytes that requires prior cathepsin B (CTSB) activation. This original activation of CASP8 leads to non-canonical cleavage of CASP3 and 7, which in turn cleave several cellular proteins, including p47 PHOX, at sites different from those cleaved during apoptotic condition. We took advantage of these original and specific cleavage sites to develop fluorescent synthetic substrates that allow us to measure non-apoptotic caspases activated in anti-inflammatory MDMs. Using pharmacological (Emricasan, CA-074) and siRNA approaches, we finally showed that maintenance of CASP8 and CTSB activation is also important for IL-4/IL-13-induced macrophage polarization conversely to pro-inflammatory macrophage polarization during which CASP8 activation is inhibited. These observations highlighted the interest of targeting caspases and cathepsin B to modulate the functions of anti-inflammatory MDMs, thus offering new therapeutic strategies in diseases, in which MDMs contribute to pathogenesis.

POSTER 6 - FR

The serine/threonine kinase MINK1 regulates a phospho-dependent promigratory cascade in triple-negative breast cancer

Avais DAULAT, Wagneer MÔNICA, Audebert STÉPHANE, Malgorzata KOWALCZEWSKA, Jeremy ARIEY-BONNET, Pascal FINETTI, François BERTUCCI, Luc CAMOIN, Jean-Paul BORG

CRCM

The developmental Wnt/planar cell polarity (PCP) pathway is the most recently described branch of the Wnt signaling pathways. Upregulation of Wnt/PCP components is observed in many cancers and is associated with cancer development at early and late stages. We recently showed that PRICKLE1are overexpressed in triple negative breast cancer (TNBC) and associated with poor prognosis. PRICKLE1 is a cytoplasmic protein phosphorylated by MINK1. Knockdown experiments have demonstrated that MINK1 and PRICKLE1 contribute to TNBC cell motility and spreading in vitro and in vivo. However, the identity of MINK1 substrates and the role of MINK1 enzymatic activity in this process have not yet been addressed issues. We carried out a phosphoproteomic strategy and identified novel MINK1 substrates including LL5β. LL5β is a membrane scaffold molecule that anchors microtubules (MTs) at the cell cortex through its association with the plus-end MT proteins CLASPs to trigger focal adhesion disassembly. LL5β is a prominent member of the MINK1-PRICKLE1 protein complex and is directly phosphorylated by MINK1 that promotes its interaction with CLASP. Using a kinase inhibitor, we demonstrate that the enzymatic activity of MINK1 is involved in the protein complex assembly and localization, and cell migration. Analysis of gene expression data show that the concomitant up-regulation of PRICKLE1 and LL5β mRNA levels encoding MINK1 substrates is associated with a poor metastasis-free survival for TNBC patients. Altogether, our results suggest that MINK1 may represent a potential target in TNBC.

POSTER 7 - FR

Sponge-associated fungus Stachybotrys chartarum MUT 3308 as a source of new anticancer compounds?

Marie DAYRAS[1], Estelle SFECCI[1], Elena BOVIO[2], Maeva DUFIES[3,4], Olivia RASTOIN[3,4], Thierry LACOUR[5], Gilles PAGES[3,4], Giovanna Cristina VARESE[6], Mohamed MEHIRI[1]

CRCM

Colorectal cancer (CRC) remains a major public health issue. Identification of biomarkers predicting which patient presents a high risk of recurrence and the discovery of novel targets for therapy are urgently needed. The cell surface receptor PTK7 is a poorly described evolutionary conserved member of the receptor tyrosine kinase superfamily that was first identified in human colon carcinoma and melanoma. Accumulated data highlighted the implication of PTK7 in diverse cancer-related signaling pathways. Anti-PTK7 approaches are currently in development at pre-clinical and clinical stages.

The project is studying PTK7 functions and associated pathways identified by proximity biotinylation coupled to mass spectrometry in CRC live cells. Among the PTK7-associated molecules identified, we showed that PTK7 interacts with the receptor tyrosine kinase EphrinA2 (EPHA2) whose expression correlates with poor prognosis in CRC. We highlighted that PTK7 acts as a negative regulator of EPHA2 activation. Indeed, the knock-down of PTK7 leads to an over-expression of phosphorylated EPHA2 on the tyrosine residue Y588 following its ligand EFNA-1 stimulation. This regulation confers EPHA2 protection from lysosomal degradation. We are defining the roles of PTK7 and small GTPases Rab proteins in the endocytic trafficking of EPHA2. Our study is also shedding light on the capacity of EPHA2 to signal in endosomes when its co-receptor PTK7 is depleted.

POSTER 8 - FR

Role of Galectine 1 (Gal1) in the control of leukemogenesis.

Marjorie DELAHAYE[1,2,3,4], Jeoffrey PELLETIER[1,2,3,4], Cyril BROCCARDO[3,5,6], Michel AURRAND-LIONS[1,2,3,4], Stéphane MANCINI[3,7,8]

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B Acute Lymphoblastic Leukemia (B-ALL) affects B cells during their development in the bone marrow (BM) and results from differentiation arrest and exacerbated proliferation of B cells. Studies show the influence of BM microenvironment on B cell differentiation.Our laboratory showed that Gal1, secreted by stromal cells, can interact with the pre-BCR inducing their proliferation and differentiation. The BM microenvironment is also involved in leukemic cell development. The laboratory studies on the impact of Gal1 secreted by stromal cells on the leukemogenesis. We use mice carrying the chimeric Pax5-Elastin (P5E) gene found in human B-ALL. These mice develop spontaneously BIII-ALL (pre-BCR+). P5E mice were crossed with Gal1-/- mice. Curiously, P5EGal1-/- mice develop BIII-ALL but also BIV-ALL (BCR+).The analysis of 6-week-old mice - devoid of secondary mutations - showed that the proliferation of pre-leukemic cells was affected in absence of Gal1. Also, while pre-leukemic cells accumulate at the pro-B/pre-B cell transition in P5E mice, a block at the pre-B/immature B transition could be observed in part of the P5EGal1-/- mice. A scRNAseq will allow us to determine the molecular mechanisms induce by Gal1 in pre-leukemic B cells. Finally, our preliminary results show pre-leukemic clusters essentially located close to the endosteum, in contact with Gal1+ stromal cells. In contrast, pre-leukemic clusters were located in a distinct niche away from the endosteum in P5EGal1-/- mice. In conclusion our results suggest that Gal1+ stromal cells dictate the leukemic fate of pre-B.

POSTER 9 - FR

PTK7 acts as a negative regulator of EPHA2 activation in colorectal cancer

Charlotte DESSAUX, Constantin SEMENCHENKO, Laëtitia GANIER, Luc CAMOIN, Stéphane AUDEBERT, Avais DAULAT, Jean-Paul BORG.

CRCM

Colorectal cancer (CRC) remains a major public health issue. Identification of biomarkers predicting which patient presents a high risk of recurrence and the discovery of novel targets for therapy are urgently needed. The cell surface receptor PTK7 is a poorly described evolutionary conserved member of the receptor tyrosine kinase superfamily that was first identified in human colon carcinoma and melanoma. Accumulated data highlighted the implication of PTK7 in diverse cancer-related signaling pathways. Anti-PTK7 approaches are currently in development at pre-clinical and clinical stages.

The project is studying PTK7 functions and associated pathways identified by proximity biotinylation coupled to mass spectrometry in CRC live cells. Among the PTK7-associated molecules identified, we showed that PTK7 interacts with the receptor tyrosine kinase EphrinA2 (EPHA2) whose expression correlates with poor prognosis in CRC. We highlighted that PTK7 acts as a negative regulator of EPHA2 activation. Indeed, the knock-down of PTK7 leads to an over-expression of phosphorylated EPHA2 on the tyrosine residue Y588 following its ligand EFNA-1 stimulation. This regulation confers EPHA2 protection from lysosomal degradation. We are defining the roles of PTK7 and small GTPases Rab proteins in the endocytic trafficking of EPHA2. Our study is also shedding light on the capacity of EPHA2 to signal in endosomes when its co-receptor PTK7 is depleted.

POSTER 10 - FR

Modulation of cell adhesion and migration properties in cancer cells by the secreted glycoprotein ADAMTSL5.

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During tumour progression, cancer cells must undergo a complex microenvironment and adapt their invasion strategies.We highlighted a new secreted protein upregulated in HCC patients, not yet related to cancer: ADAMTSL5. Cancer patients' data display an overexpression of ADAMTSL5 in several bad prognosis cancers such as pancreatic (92%) or colorectal cancer (89%). Yet, how ADAMTSL5 function remains to be elucidated.By comparing the proteomic landscape of mouse HCC cells following ADAMTSL5 silencing vs controls, we identified changes in the expression of components involved in cell cytoskeleton remodelling and adhesion such as cadherins, integrins and actin-binding proteins (Ezrin, CapZa1). These molecular changes correlate with a drastic shift in cell morphology: ADAMTSL5 silencing leads to a transition from epithelial to fibroblast-like feature and is accompanied by an increase in cell adhesion, cell invasion and cell migration properties.To explore how ADAMTSL5 regulate those properties, we exposed control and ADAMTSL5-silenced cells to exogeneous ADAMTSL5 using a recombinant protein. Longitudinal analysis showed a partial reversion of fibroblast-like phenotype in ADAMTSL5 silenced cells incubated with the rec. ADAMTSL5 which could be explained by its internalization as supported by specific immunostainings (cell membrane and cytoplasmic localization).Strikingly, specific rescue of expression and phosphorylation levels of RTKs otherwise downregulated in ADAMTSL5 silenced cells was observed.These results suggest ADAMTSL5 as a decisive actor of cell invasion behaviour.

POSTER 11 - FR

CD98hc as potential therapeutic target in KRAS-driven lung cancer

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2 Homéostasie épithéliale et tumorigenèse

Lung adenocarcinoma, the major form of lung cancer, is the deadliest cancer worldwide and exhibits pronounced inter- and intra-tumor heterogeneity cofounding precision medicine. KRAS is the most frequently mutated gene in lung adenocarcinoma. Its mutation correlates with tumor heterogeneity and leads to a poor prognosis.Lung adenocarcinoma results from the transformation of several progenitor cells that accumulate genetic abnormalities. Stem cell maintenance is regulated through stem/progenitor cells and their niche dialog and a deregulation of these interactions leads to tumorigenesis. When mutated, KRAS leads to cellular reprogramming of the cell toward a 'stem' phenotype resulting in tumorigenesis. Thus, a better understanding of how genetic alterations and perturbed microenvironments impact progenitor-mediated tumorigenesis and treatment response is of the utmost importance to develop new therapeutic opportunities. Our results highlight that KRAS-driven tumorigenesis can proceed through both CD98hc-dependent and independent pathways depending on tumor cell-of-origin. CD98hc functions as amino acid transporter and co-receptor for integrins. CD98hc is involved in wound healing and its expression correlates with poor prognosis in lung cancer. The overall goal of my project is to understand the role of CD98hc in KRAS-driven lung cancer depending on tumor cell of origin.

POSTER 12 - FR

Integrating biochemical signals and mechanical cues of the extracellular matrix in pancreatic cancer cell metabolism

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Pancreatic ductal adenocarcinoma (PDAC) is a highly fatal cancer with increasing occurrence due to lack of early symptoms. This results to late diagnosis when the disease has already spread to other sites. A hallmark of PDAC is the deposition of a dense and rigid stromal compartment surrounding the tumor core. This CAF (cancer-associated fibroblast)-derived stroma differs from normal stroma by the elevated amounts of extracellular matrix (ECM) components, and the increased stiffness. These changes raise the interstitial pressure causing vasculature to collapse and impede the diffusion of nutrients and oxygen in the tumor niche. Cancer cells, however, maintain their growth and proliferative capacity by adapting their metabolic activity through the uptake of metabolites via macropinocytosis, and the utilization of signals relayed by the stroma.Most studies so far have focused on identifying metabolic adaptations driven by individual ECM components. Thus, the interactions between the physicochemical properties of the unabridged ECM and tumor cell energetics remain uncharted territory. To that end, by using a transcriptomic and metabolomic approach in an in vitro setting, we set out to discern the ensemble of the metabolic alterations that take place in pancreatic tumor cells when they grow in physiologically relevant bio-scaffolds in terms of composition and rigidity. The identification of pathways that link the ECM with tumor cell metabolism will pave the way for the discovery of novel targets for combinatorial therapeutic approaches.

POSTER 13 - FR

Comprehensive analysis of hypoxia-regulated long non-coding RNAs in lung adenocarcinoma cells using a single-cell CRISPR-interference-based transcriptional screening

Caroline LACOUX[1], Marin TRUCCHI[1], Julien FASSY[1], Iris MANOSALVA-PENA[2], Marine GAUTIER[1], Virginie MAGNONE[3], Kévin LEBRIGAND[3], Salvatore SPICUGLIA[2], Georges VASSAUX[1], Roger REZZONICO[1], Bernard MARI[1]

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Current treatments for lung adenocarcinomas (LUAD) have poor response rates and there is an urgent need to propose new strategies to prevent these escape routes. Variability in LUAD drug response is multifactorial including intrinsic altered pathways or extrinsic factors such as hypoxia. Recent advances in cancer genomics have highlighted aberrant expression of ncRNAs as a major determinant of early treatment resistance. We aim here at gaining new insights into the functions of lncRNAs on the hypoxic response of LUAD cells.We have developed a single-cell CRISPR-interference-based (CRISPRi) transcriptome screening on our best lncRNA candidates based on the CROP-Seq approach (Daltinger et al. Nat Methods 2017). A mini-CROP-seq library including validated gRNAs targeting 8 lncRNA candidates and several key regulators of the hypoxic response (HIF1A, HIF2A) has been amplified and transduced in A549 LUAD cells cultured in normoxia or hypoxia. The cells from the 2 conditions were then pooled, labelled with barcoded antibodies and analyzed by single-cell RNA-Seq in a single run, directly linking guide RNA expression to transcriptome responses in individual cells. We describe here the precise workflow and the validation of the method on key regulators of the hypoxic response. Moreover, our data indicate that several lncRNAs may be involved in the regulation of cell survival, cell adhesion and/or hypoxic response.In conclusion, this method should improve the knowledge on lncRNA-associated functions and provide new potential targets associated with drug resistance in lung cancer

POSTER 14 - FR

Marine origin new anticancer drugs: isolation, structural determination and synthesis

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The marine environment is a huge source to many species which, due to environmental conditions, produce several specific molecules, often different from the terrestrial environment, designated by the term specialized metabolites. Those different metabolites can be valued in the therapeutic field, in particular as anti-cancer drugs.1
In this context, the study of the Mediterranean marine spongeCrambe crambe has made it possible to highlight numerous guanidine alkaloids such as crambescins. The work currently being carried out concerns the isolation and elucidation structure of these derivatives in order to evaluate them within the framework of a new therapeutic approach against cancer.
Additionally, a new lipid compound, peroxyacarnoïc acid E was isolated from the sponge Clathria rugosa. This latter, exhibits cytotoxic properties against several tumor cell lines via a mechanism of action singular. Indeed, the latter induces cell death of the programmed necrosis type.2 Current work in the laboratory concern the synthesis of peroxyacarnoïc acid E in quantity.
Finally, we were interested in the metabolites of a Mediterranean sea squirt, Polysyncraton sp. The work revealed the presence of new lipid metabolites, Bolascidins A-D. These last were found to be non-cytotoxic at high concentrations. Synthesis of these metabolites is ongoing in our laboratory to determine their stereochemistry and evaluate them as vectoring agents.

[1] Abdelhameed R. F. A., et al, Marine Drugs, 2020, 18 (5), 1-13.
[2] Yang, W. S. et al, Trends Cell Biol., 2016, 26 (3), 165-176.

POSTER 15 - FR

Mechanisms of resistance to ferroptotic cell death: the impact of bioenergetic pathways

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2 Institute for Research on Cancer and Aging (IRCAN)

Ferroptosis is a newly described ROS-dependent type of regulated cell death. The major event leading to ferroptosis is oxidation of the lipids in the plasma membrane, resulting in the disruption of its integrity, cell bubbling and death. Under physiological conditions, ferroptosis is prevented by two antioxidant pathways involving: 1) glutathione peroxidase 4 (GPx4), which uses reducing power of glutathione (GSH), and 2) ubiquinol (coenzyme Q10) which is regenerated by ferroptosis suppressor protein 1 (FSP1).Although, the potential of ferroptosis as a powerful anticancer strategy has been widely recognized, still very little is known regarding the resistance mechanisms of some cancer cells to this type of cell death. To investigate this issue, we used colon adenocarcinoma cell line - LS174T that, according to our data, showed surprising resistance to ferroptosis induced either by genetic invalidation of FSP1 protein alone or in combination with inhibition of GPx4 by RSL3. Interestingly, the sensitivity to inhibition of both anti-ferroptotic axes was revealed in glycolysis-null cells (cells with genetically deleted both isoforms of lactate dehydrogenase, LDHA and LDHB). These «Warburg effect-incompetent» cells showed typical features of ferroptosis including lipid hydroperoxide accumulation, bubbling and ferrostatin-preventable cell death.In conclusion, our data indicate that anti-ferroptotic pathways of some cancer cells operate in the overall physiological context of cancer cells and in some instances their inhibition should be coupled with other metabolic modulators.

POSTER 16 - FR

Specificities and functionalities in MYC and MET cooperation in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the most common liver cancer and few therapeutic options are available. The transcription factor MYC and the receptor tyrosine kinase MET are associated with HCC pathology as both are frequently overactivated in patients. However, their concomitant alteration in HCC has not been explored, nor functionally documented. By analysing available database, we identified a subgroup of HCC patients with high MYC and MET levels, characterized by poor prognosis. We explored functionality of MYC and MET co-occurrence in vivo by forcing MYC expression in the R26stopMet genetic setting through hydrodynamic tail vein injection. We observed that MYC and MET upregulation in hepatocytes is sufficient to induce liver tumorigenesis, even in the absence of pre-existing injuries associated with a chronic disease state. Histological, immunohistochemical, and RT-qPCR studies revealed that ectopic MYC expression in MET tumours increased Mki67 expression, coherent with MYC action on cell proliferation, and switched their molecular features as exemplified by loss of Afp, Spp1, Gpc3, Epcam , and gain of Hgma1 expression. The cooperativity of MYC and MET is also exemplified by the vulnerability of human HCC cells we tested to agents targeting both signals. Mechanistically, simultaneous MYC and MET blockage converts cytostatic effects (observed with individual targeting) into cytotoxic effects, as shown by reduced proliferation and induced apoptosis. Results document functional and molecular cooperativity of MYC and MET to induce and to sustain liver tumorigenesis.

POSTER 17 - FR

Study of the role of the metalloprotease MT1-MMP for the PTK7 function in colorectal cancer.

Louis GUIRAUD[1,2]

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2 Polarité cellulaire, signalisation et cancer

Colorectal cancer (CRC) represents the 2th most deadly cancer in the world. There is therefore a real necessity to identify new biomarkers to promote the development of more efficient therapies. The Wnt/β-catenin signaling pathway, which is over activated in CRC, represent a huge point of dysregulation during CRC development. PTK7 (Protein tyrosine Kinase 7), a transmembrane receptor required during embryo development and involved in Wnt/β-catenin and PCP pathways, has been identified both as a poor diagnosis marker and therapeutic target in CRC. PTK7 is cleaved by the metalloprotease MT1-MMP on the Leucine 622 of its extracellular domain, promoting its shedding and constituting a prerequisite for two additional cleavages mediated by ADAM17 and ⍰-secretase, respectively on the Glutamate 689 and Glycine 721 of its extra- and intracellular domains. In CRC SW480 cells, PTK7-intracellular domain (PTK7-ICD) may be degraded by the proteasome or translocated into the nucleus to promote cellular migration and proliferation. In Xenopus cells, Wnt5a stimulation could promote PTK7 cleavage, this event would mediate PTK7-ICD nuclear translocation and papc expression. In this project, we demonstrated that MT1-MMP activity was associated with PTK7 cleavage and nuclear translocation in CRC HCT116 cells, suggesting an other function of this protein in CRC tumorigenesis.

POSTER 18 - FR

Hypoxia, Mitochondria, VDAC1-ΔC and Primary Cilium in Prostate Cancer

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C3M

The interaction between mitochondria and endolysosomes, in hypoxia and depending on HIF-1, leads to the truncation of mitochondrial voltage-dependent anion channel (VDAC1) to VDAC1-ΔC. We linked the primary cilia (PC) forming process to VDAC1-ΔC and cancer aggressiveness. This small sensory antenna plays an important role in tumor development.In clear cell renal cell carcinoma, we characterized a PC signature, IFT20 and Gli1. Presence of PC, IFT20+/Gli1+, is associated with more aggressive cancer and worse prognosis.We characterized a small group of IFT20+/Gli1+ prostate cancer (PCa) patients in pathology with no PC. Is this subgroup more aggressive? Our aim is to restore PC in PCa cells.Prostate epithelial cell lines and PCa cell lines were used in 2D and 3D culture. Gefitinib and clofibrate were used to restore PC in different O2 concentrations: normoxia (Nx) 21%- and hypoxia (Hx) 1%- O2.In 2D model with P69 normal cells, gefitinib increased percentage of PC in Nx and Hx, and clofibrate in Hx. However, VDAC1-ΔC was not inhibited. In DU145 cancer cells, absence of PC remained unchanged, but VDAC1-ΔC was inhibited by gefitinib.In 3D model, an increase of PC was observed after treatments. PC restoration modulated acini (RWPE1) and tumor-like (WPE1-NB26) structures, and their sizes were expanded.
PC restoration is not linked to absence of VDAC-ΔC in P69 and DU145, but to less cell proliferation. IFT20/Gli1 signature is in progress. RNA-seq will compare between WPE1-NB26 Nx ctl/ Nx G10 vs DU145 Nx ctl/ Nx G10 to detect new «candidates» involved in restoration of PC.

POSTER 19 - FR

Tau protein as new therapeutic target for glioblastoma: focus on new thiazoloflavonoid derivatives.r

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The microtubule-associated protein Tau is expressed in many cancers, including glioblastoma(GBM). It was shown that Tau is crucial for GBM progression, 3D cell organization and migration. Here, we explored the antitumor potential of targeting Tau in GBM with new thiazoloflavonoid(TZF). The Tau oligomers inhibition and Tau-induced microtubule(MT) assembly activity of 20 TZFs was evaluated. The biological activity of compounds was determined on GBM cells through i)cell viability, ii)cell migration, and iii)spheroid growth. Inhibition of Tau oligomers formation was total for compounds 5-7, and partial for 1 and 4. However, no compound disrupted Tau-induced MT assembly. Moreover, viability of cells treated with 1 and 4 was reduced and correlated with Tau expression. Surprisingly, active compounds had no significant effect on cell cycle, suggesting anti-proliferative rather than cytotoxic effect. In addition, 1 and 4 reduced the migration of Tau-expressing cells exclusively. This was associated with a strong remodeling of MT. For 3D spheroid growth, only 4 exhibited up to 2-fold reduction in growth of Tau-expressing cells spheroids. To determine the structure-activity relationship of 4, 8 derivatives were examined with cell viability experiments. Preliminary results indicate that 4 is the compound with the highest anti-proliferative activity in Tau expressing cells. Our data show that some TZFs act on cellular processes by remodeling the cytoskeleton. In conclusion, we have determined hit 4 as a potential new drug for GBM, with a specificity towards Tau protein expressing cells.

POSTER 20 - FR

Dissecting and targeting tumor-stroma crosstalk via extracellular vesicles in PDAC

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A rapidly-evolving and incurable disease, pancreatic ductal adenocarcinoma (PDAC) is one of the most malignant cancers worldwide with increasing incidence and a 5-year survival rate of less than 8%. The tumor microenvironment (TME), consisting of heterogeneous cell populations such as cancer associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs), is an active contributor to tumor progression, immune evasion and resistance to treatments. TME cells are in constant communication with tumor cells which may perpetuate pro-tumoral signals via extracellular vesicles (EVs). This study investigates the impact of tumor cell (TC)-EVs on TME cells' phenotypes, CAFs, and monocytes (precursors of TAMs). It is hypothesized that tumor cells, via EVs, maintain and modify pro-tumoral CAF populations and recruit monocytes to produce immunosuppressive TAMs. It was found that TC-EVs promote production of a remodeled CAF-derived extracellular matrices (C-ECM). TCs demonstrate enhanced migration/invasion on TC-EVs-treated C-ECMs. TC-EVs increase the secretion of immune cell recruiting cytokines by CAFs. By TC-EVs, monocytes are differentiated into immunosuppressive macrophages, with increased adhesive, phagocytic, survival capacity, and decreased T-cell activation. Proteomics reveals the implication of Wnt/B-catenin signaling pathway dysregulation in both EV-treated CAF-ECM and monocytes. Subsequent crosstalk between these two TME populations under the influence of TC-EVs and its potential targets and biomarkers are currently under investigation.

POSTER 21 - FR

Role of the protein tyrosine kinase 7 (PTK7) in dendritic cells functions

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PTK7 is a co-receptor of Wnt pathway, involved during embryonic development and in adult tissue homeostasis. It is overexpressed in many cancers, which are associated with poor prognosis. Recently, PTK7 expression was observed in dendritic cells (DCs) but the role of PTK7 in DC functions remain completely unknown. DC play a central role in initiating the cancer-immunity cycle, they are the essential for the anti-tumor immune response. Here, we investigate for the first time the expression and role of PTK7 in DCs to further understand its implication in cancer. In WT mice, we showed that PTK7 was expressed in 40% of Langherans cells (LCs) from skin and by 70% of migratory LCs from cutaneous lymph nodes (cLN). In tumor micro-environment, PTK7 was observed on certains myeloid cells including DCs substets. Using DC-T cell co-culture assays, we found that PTK7+ bone marrow derived cDC2 (BM-DC2) had a poor capacity to induce proliferative effector CD8+ T cells compared to PTK7- BMDCs. With Skin contact sensitization model, we observed that at day 4 after painting (peaking day of migratory LCs) we found twice more PTK7+ LCs in FITC+ LCs than in FITC+ LCs. This result suggest that PTK7+ LCs would have a higher promigratory capacity than PTK7+ LCs. Our study shows for the first time that PTK7 isexpressed in myeloid cells, specially in a subset of DC where it may play a promigratory role as well as an immunosuppressive role in CD8+ T cell response. We are now studying the consequences of the loss of PTK7 in DCs functions using a CD11C-Cre X PTK7-Lox mouse model.

POSTER 22 - FR

Macrophages awaken dormant cancer cells via matrix modifications and EGFR activation

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Although tumor cells are characterized with high proliferative activity, some cancer cells within the tumor mass can acquire a non-proliferative status. Due to microenvironmental stimuli, these dormant cells can awake and resume proliferation, which can eventually lead to patient relapse. It has been described that cancer cells co-evolve with a reactive stroma containing extracellular matrix (ECM) components and cancer-promoting cellular elements such as tumor-associated macrophages. Although macrophages can support cancer development via various mechanisms, their involvement in dormancy escape has never been addressed.We demonstrate that macrophages awaken dormant D2.0R cells, via the secretion of paracrine factors. We found that inhibition of matrix metalloproteases (MMP) within the macrophage-conditioned media (CM) can abolish its cancer cell awakening potency, suggesting that macrophages awaken dormant cells via matrix modifications. In line with this, we found that macrophage CM-primed ECM is sufficient to resume proliferation of dormant cells. Mechanistically, this process requires EGFR activity, as in the presence EGFR tyrosine kinase inhibitors, D2.0R cells maintained quiescence. However, the EGFR-targeting monoclonal antibody did not block the awakening. Therefore, we postulate that MMP secretion by macrophages triggers ECM remodelling that promotes EGFR activation in a ligand-independent manner. Understanding mechanisms that regulate dormancy or the switch to a proliferative state is critical for discovering novel targets to prevent disease recurrence.

POSTER 23 - FR

Inhibition of hypusination reprograms Prostate Cancer cell metabolism and decreases aggressiveness

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Prostate cancer (PCa) is a public health problem, despite great advances it is still difficult to treat advanced stages. Cancer cells adapt their metabolism to resist various stresses and treatments and to provide the metabolites, energy and co-factors required for their proliferation and progression. Our team is interested in innovating therapeutic approaches targeting cancer cell metabolism. Here, we focus on the polyamine/hypusination pathway which is associated with poor prognosis in PCa. Hypusination is a unique post-translational modification of the eukaryotic translation initiation factor 5A (EIF5A). This reaction is dependent on spermidine (a polyamine) and it is regulated by two enzymes, the deoxyhypusine synthetase (DHPS) and the deoxyhypusine hydroxylase (DOHH). Hypusination is involved in several cellular processes such as autophagy, metabolism, senescence, and differentiation, however, the mechanism by which it is implicated in tumor growth and metastasis is still unclear. To elucidate its role in PCa, we inhibited the enzymes that catalyzes this reaction and investigated the effects on cell growth and metabolism. We have shown that inhibition of hypusination decreases cell growth, cell migration and mitochondrial respiration three biological processes implicated in PCa aggressiveness and metastasis. In addition, our metabolomic and proteomic analysis revealed a significant downregulation of mitochondrial metabolism. Our results highlight a potential therapeutic opportunity for PCa that target hypusination and could be used for clinical applications.

POSTER 24- FR

Analysis of the interaction between UFMylated MRE11 and VCP to understand AML sensitivity to VCP inhibition

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The Ubiquitin-fold modifier 1 (UFM1), an ubiquitin-like, is implicated in hematopoiesis, transcriptional regulation, cellular signalling pathways, endoplasmic reticulum (ER) stress, neurodevelopmental disorders and cancer. More recently, UFMylation (i.e covalent modification by UFM1) was also shown to play a role in the DNA damage response and the maintenance of genome stability. We showed that the DNA repair protein MRE11, belonging to the MRN complex, is UFMylated and that MRE11 UFMylation is essential for telomere length maintenance and to prevent anemia.The Valosin-containing protein VCP (p97) is involved in various biological processes. A study showed that VCP interacts with the MRN complex on chromatin. Chemical inhibition of VCP blocks the disassembly of the MRN complex from DNA damage sites, impaired homologous recombination and increased radiosensitivity. Recently, another report identified the nuclear form of VCP as a promising therapeutic target in acute myeloid leukemia (AML) and proposed that the efficiency of VCP inhibition relies on a compromised DNA repair and DNA damage response.Taken together, these results suggest that MRN clearance by VCP may be important for the proliferation of AML. Moreover, our preliminary data indicates a decreased interaction of VCP and MRE11 in an UFM1-defective background, suggesting a functional link between MRE11 UFMylation and VCP-dependent MRN regulation. My project aims to analyze the interplay between UFMylated MRE11 and VCP and to evaluate its relevance in the context of the acute sensitivity of AML to VCP inhibition.

POSTER 25 - FR

Targeting prostate cancer cells metabolism with CRO15 a new biguanide derivative

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4 Northwestern University, Chicago, USA

Prostate cancer is a major public health problem, and resistance to treatment for the advanced stages remains challenging. Our team is interested in therapeutic approaches targeting cancer cells metabolism. We showed that Metformin, a widely used anti-diabetic drug, decreases prostate cancer cell proliferation, tumor growth and inhibits the complex 1 of the mitochondrial respiratory chain. However, the biological effects of metformin in experimental models require high concentration (millimolar range) and a poor efficacy was observed in the clinical trials published so far. In collaboration with Stéphane Rocchi's team we have studied the effects of CRO15 a new compound derived from biguanides in prostate cancer cells. CRO15 decreased prostate cancer cell proliferation in a dose dependent manner from 5µM and reduced the viability of the most aggressive prostate cancer cells (PC3). These effects were confirmed in hypoxia (1% O2) using different concentrations of glucose. Interestingly, we also showed that CRO15 strongly inhibits prostate cancer cell migration. Using the Seahorse and steady state metabolomics, we observed a significant decrease in Oxygen consumption and Krebs cycle intermediates, suggesting that similarly to metformin, CRO15 inhibits mitochondrial metabolism. Finally, at the molecular level, we demonstrated that CRO15 strongly inhibits mTORC1 a kinase frequently activated in prostate cancer. In conclusion, our results reveal that CRO15 may be a new potential therapeutic option that target cancer cell metabolism in prostate.

POSTER 26 - FR

Metabolic rewiring in response to chemotherapy in pancreatic ductal adenocarcinoma

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Pancreatic ductal adenocarcinoma (PDAC), with an increasing incidence and a 5-year survival rate of only 11%, will become the second leading cause of cancer-related deaths by 2030. Only 20% of PDAC patients are eligible for curative tumor-resection. Two standard chemotherapeutic options exist for the remaining 80% of patients presenting an advanced PDAC: FOLFIRINOX (5-FU, Irinotecan, Oxaliplatine; FOX) and gemcitabine.It is acknowledged that non-TCs cells (stromal/tumor microenvironment (TME), mainly Cancer-Associated-Fibroblasts (CAFs)), that account for up to 80% of PDAC, alter PDAC tumor cells' (TCs) drug responses with consequences on therapy efficiency. Due to this dense stroma, PDAC is poorly vascularized and therefore has suboptimal oxygen and nutrients supply. Depending on the nature and availability of ready-to-use nutrients, non-TCs also impact and drive the TCs' metabolic routes and thereby favor tumor cell survival and proliferation. But whether and how cross-talk between stromal and TCs, in response to chemotherapeutic treatment, drives the metabolic reprogramming leading to acquisition of chemoresistance (chemoR) is an un-answered question. As FOX-treated PDAC patients still have a limited overall survival together with tremendous side effects impacting their clinical management, understanding the tumor metabolic changes associated with chemosensitivity (chemoS) and chemoR in the context of a dense TME warrants to elaborate a therapeutic strategy relying on the synergistic effect of inhibiting tumor-specific metabolism with traditional chemotherapy.

POSTER 27 - FR

Association between P-bodies, IGF2BP1 and drug resistance in Small Cell Lung Cancer

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Small Cell Lung Cancer (SCLC) is a very aggressive cancer with a 5-year survival rate of less than 7% mostly because 80% of patients are diagnosed at advanced stages. After an initial response to chemotherapies, tumor recurrences are often fatal within 6 months to 1 year of treatment because no second line of treatment is available. Therefore, it is important to discover both early biomarkers of resistance and new treatment strategies for SCLC.
An initial bioinformatics study allowed us to point that genes encoding for Processing bodies (P-bodies) scaffold proteins that are highly expressed in lung cancer, especially in SCLC. Interestingly, preliminary work showed that resistant cells express a higher number of P-bodies compared to the sensitive cells. P-bodies, small cytoplasmic membraneless granules composed of proteins and RNAs, are highly dynamic structures in cells that play important roles in various cellular processes, particularly in resistance to stress. Here, our results suggest that post-transcriptional regulation of P-bodies may also be involved in drug resistance. Thanks to RNAseq studies, we identified Insulin Growth Factor 2 mRNA Binding Protein 1 (IGF2BP1) as a potential biomarker of drug resistance that is associated with P-bodies, which was confirmed by western blot studies. We are now investigating the association between P-bodies, drug resistance and IGF2BP1 in SCLC through models of invalidation and complementation.
Altogether, changes of number and components of P-bodies could be useful as both biomarkers and targets for novel therapeutic strategies.

POSTER 28 - FR

PINK1-dependent mitophagy restrains tumor growth: link to the tumor immune response?

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The role of damaged mitochondria elimination in lung cancer cells has been studied in vitro, but how mitophagy impacts lung tumor development in vivo remains sparce. Low level of PINK1 was associated to poor prognosis and was correlated to immune infiltration. In the present study, we demonstrated in vitro the ability of the murine lung cancer cell line LLC-1 to remove damaged mitochondria by mitophagy following mitochondrial damages. This process relies on PINK1 activity, but not PARKIN which is not expressed in those cells. Using immunocompetent mice, we identified that disruption of PINK1-dependent mitophagy, alongside of ATG7 loss as a complete autophagy/mitophagy inhibition, significantly increased LLC-1 tumor growth in vivo. PINK1-deficient tumors accumulated aberrant mitochondria and reduced inflammatory cytokines production, correlating with reduction of neutrophil infiltration. Those preliminary data suggest that PINK1-dependent PARKIN-independent mitophagy in lung cancer cells contributes to the control of lung tumor growth. We hypothesize that it may be based, at least in part, on the induction of an effective anti-cancer immune surveillance.

POSTER 29 - FR

Immune cell populations in steady state prostate & prostate cancer

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Prostate cancer is the second leading cause of cancer death among men of western societies, yet the involvement of the immune cell implication in tumor development has been addressed recently and immunotherapy trials were unsuccessful. The aim of this project is to establish a detailed map of the immune compartment in steady state prostate and in a prostate cancer mouse model based on tamoxifen-induced PTEN gene ablation in adult animals mimicking human prostate cancer. Lymphoid and myeloid cells are studied to decipher their heterogeneity but also to uncover their functions and their expression of immunotherapy targets. The strict temporal control of PTEN ablation in PTEN(i)pe-/- mouse model is a powerful tool to characterize the molecular and cellular events underlying prostate cancer development, to study the fate of immune cells in the microenvironment and to test therapeutic strategies.
Therefore, we aim to:i. Map the immune cells phenotypically, histologically & functionally in steady state murine prostate tissue at different timepoints of the mouse growth.ii. Map the immune cells phenotypically, histologically & functionally at the different developmental stages of prostate cancer in PTEN(i)pe-/- mice and compare them with the steady state prostateiii. Finally, we will seek for immunotherapy targets and monitor the tumor development and the immune infiltrates in response to immunotherapy.Thus, this study will lead to a better understanding of the immune infiltrates during prostate cancer development and should allow to improve immunotherapeutic approaches.

POSTER 30 - FR

SAM68: a guiding STAR during cell-extracellular matrix crosstalk

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iBV

Interactions of cells with their extracellular matrix (ECM) is fundamental for the regulation of key cellular processes such as survival, migration, proliferation and differentiation. These interactions rely on the ability of cells to physically interact with their substrate via membrane receptors that convert biochemical and physical signals from the ECM into intracellular molecular signals to regulate cytoskeletal organization, gene expression and cell behaviors.

Over the years, accumulating data has revealed that protein complexes at cell-substrate interfaces, called adhesomes, constitute hubs for mechanotransduction and play important roles in the transduction of ECM signals and regulation of transcriptional responses. Advanced high-throughput screens have revealed the presence within adhesomes of a new molecular class of proteins with RNA-binding activity whose functions at adhesion sites remain poorly understood. Here, we explored the role in endothelial cells of one such RNA binding protein (RBP), SAM68 (Src associated in mitosis, of 68 kDa), that belongs to the STAR (signal transduction and activation of RNA metabolism) family RBP. We demonstrate the involvement of SAM68 in multiple cell adhesion-dependent processes, from the regulation of focal adhesion maturation to the modulation of ECM gene expression that conditions the endothelial basement membrane and promotes capillary morphogenesis. Overall, our study on the adhesion-modulating activity of SAM68 highlights a promising role for RBP as crucial modulators of endothelial cell adaptation to their environment.

POSTER 31 - FR

Role of Fas receptor-induced extracellular vesicles in colon cancer: towards the use of these vesicles for the diagnosis and treatment of colon cancer

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Development of cancer is favored by an imbalance between cell renewal and cell death, with proliferation being favored and cell death inhibited. However, recent studies show that cell apoptosis has the capacity to endow dying cells the capacity to promote proliferation of neighboring cells by secreting in the tumor environment various signals including extracellular vesicles (EV). Indeed, secretion of EV plays a key role in tumorigenesis by modulating immune response against the tumor or by promoting tumor growth and dissemination.Our recent data demonstrate that the death receptor Fas interacts with Syntenin-1 (Synt-1), a component involved in the biogenesis of a type of EV called Exosomes. We show that Fas activation by its ligand (FasL) generates a strong secretion of Exosomes and that their biogenesis requires caspase activation. We demonstrate that Synt-1 overexpression increases the production of Fas-dependent Exosomes whereas invalidation of its expression do not impact their biogenesis. We show that Fas activation triggers the endocytosis of Fas receptor that strongly accumulates in CD63-enriched compartments, known to correspond to multi-vesicular bodies (MVB) and lysosomes. This Fas accumulation in MVB correlates with maximal caspase-8 activation.Our data suggest that the intracellular endocytotic trafficking of Fas to the MVB promotes cell death signaling and is a prerequisite to the biogenesis of Fas-dependent Exosomes.Our aims are now to determine the composition of these Fas-dependent Exosomes and determine their pro- or anti-tumoral function.

POSTER 32 - FR

Glioblastoma tumoroids: overview and challenges

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With the increasing role of the microenvironment on tumor growth, appropriate pre-clinical models are needed to develop promising therapeutic strategies and to promote bench to bedside transfer. Tumoroids aim to reconstitute a tumor in a dish for a long-term culture. In the 1990's a brain tumoroid model was first developed but abandoned in favor of simpler models such as cell lines until 2016 when the development of this model again emerged to get closer to the real tumor. The current challenge of this model, in the context of glioblastoma, is to preserve the heterogeneity of the cell composition, in particular the cancer stem cells and the microenvironment.In the GlioME lab, we are successfully developing tumoroids of glioblastoma based on the culture of small human tumor pieces to preserve the organization and the cellular composition of the tumor (vessels, immune cells, tumor stem cells). To monitor the stability of the model over time, we compare the cellular composition of cultured tumoroids to the parental tumor by immunohistochemistry and flow cytometry. In parallel, we are standardizing our approach to perform drug screening and to move towards a personalized medicine.

POSTER 33 – FR

What are the signaling pathways downstream of JAM-C that maintain the stemness of LSCs?

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Acute Myeloid Leukemia (AML) is a disease with a poor prognosis and an accumulation of genetic alterations occurring in hematopoietic stem or progenitor cells (HSPC) leads to abnormal proliferation and blockage of differentiation of sick hematopoietic cells that are replenished by leukemic stem cells (LSC). In the laboratory, it has been shown that the adhesion molecule JAM-C is expressed by LSC and interacts with JAM-B expressed by bone marrow stromal cells. Accordingly, high frequencies of JAM-C-expressing leukemic cells have been associated with poor AML prognosis. Increased proportions of JAM-C-expressing cells were found in relapsing samples suggesting that JAM-C may play an active role in the maintenance of LSC in chemo-protective microenvironment. However, the link between JAM-C expression and adhesion of LSC to bone marrow microenvironment remained to be defined. To answer this question, we set-up several leukemic model cell lines expressing JAM-C or not in order to study the biochemical modalities of JAM-C signaling. We found that the intracellular domain of JAM-C (ICD) is cleaved, similar to Notch signaling. Cleavage of JAM-C is modulated by cell/cell interactions and by cell adhesion to ligands present in the bone marrow microenvironment. Accordingly, JAM-B, the high affinity ligand of JAM-C, supported LSC adhesion and reduced JAM-C cleavage. Altogether, our data suggest that cleavage of JAM-C may switch LSC from extrinsic stromal dependent chemo-resistance to cell-autonomous signaling.

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35 Overcoming Resistance to Anti-nectin-4 Antibody-Drug Conjugate - CRCM -

36 Characterizing the Follicular Lymphoma Precursor Cell and its supporting microenvironment governing disease progression and recurrence - CIML -

37 High-Plex Spatial Imaging to decipher Tissue Microenvironment Complexity: Skin disease model - AMKBIOTECH

38 Identification of Atypical Circulating Tumor Cells with Prognostic Value in Metastatic Breast Cancer Patients - CRCM

39 Pancreatic ductal adenocarcinoma ubiquitination profiling reveals specific prognostic and theranostic markers - CRCM

40 Reshaping immune lung populations to inhibit pulmonary fibrosis and cancer by activation of purinergic receptor P2RX7 - IRCAN -

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43 Neutrophil extracellular traps formed during chemotherapy confers treatment resistance via TGFβ activation - IRCAN -

44 Unraveling the polypharmacology of beta-blockers in neuroblastoma using chemo-proteomics approaches - CRCM -

45 Development of CXCR1/2 inhibitor for the treatment of metastatic uveal melanoma IRCAN

46 Targeting of the ELR+CXCL/CXCR1-2 pathway is a promising strategy for the treatment of pediatric medulloblastomas - IRCAN -

47 Conditional generation of free radicals by selective activation of alkoxyamines : towards a more effective and less toxic targeting of brain tumors - CRCM -

48 Integrative analysis of the diversity, location, BCR repertoire and antigen specificity of tumor-infiltrating B cells in lung cancer - "CIML INNATE PHARMA" -

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POSTER 34 - TR/CR

Cholesterol pathway influences tumor phenotype and disease-free survival in colon cancer patients

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CRCM

Metastatic colorectal cancer (CRC) is a leading cause of death worldwide. Epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET) are two important biological programs required during metastatic progression. However, most approaches that tried to target key molecules responsible for EMT or MET have failed so far. To identify new «alternative» pathways associated with EMT / MET programs we used a controlled but dynamic approach based on a spheroids and an exhaustive inducer of EMT. Spheroids from the colon tumor cell line HT29 were collected before, during and after treatment with this EMT-inducer. For each condition, we performed pan-transcriptomic analyses. The originality of our strategy resides in the selection of genes that were inversely regulated during EMT and MET induction. The selected genes were obviously related to the EMT pathway, but also to cholesterol, revealing a link between these biological processes. This link was confirmed with the use of statins, well-known inhibitors of cholesterol's synthesis. It showed that the cholesterol pathway delayed MET process. To assess the clinical relevance of this finding, we built individual metagenes, which, when applied to a transcriptomic database from primary colorectal tumors, showed that the EMT and the cholesterol homeostasis pathways were independent prognosis markers for survival. This prognostic value was increased when both were combined into a multi-metagene model. Altogether, our data suggest that interplay between these two pathways might drive tumor's aggressiveness.

POSTER 35 - TR/CR

Overcoming Resistance to Anti-nectin-4 Antibody-Drug Conjugate

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1 CRCM

2 Plateforme ICEP (CRCM)

3 Institut Paoli-Calmettes

Metastatic colorectal cancer (CRC) is a leading cause of death worldwide. Epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET) are two important biological programs required during metastatic progression. However, most approaches that tried to target key molecules responsible for EMT or MET have failed so far. To identify new «alternative» pathways associated with EMT / MET programs we used a controlled but dynamic approach based on a spheroids and an exhaustive inducer of EMT. Spheroids from the colon tumor cell line HT29 were collected before, during and after treatment with this EMT-inducer. For each condition, we performed pan-transcriptomic analyses. The originality of our strategy resides in the selection of genes that were inversely regulated during EMT and MET induction. The selected genes were obviously related to the EMT pathway, but also to cholesterol, revealing a link between these biological processes. This link was confirmed with the use of statins, well-known inhibitors of cholesterol's synthesis. It showed that the cholesterol pathway delayed MET process. To assess the clinical relevance of this finding, we built individual metagenes, which, when applied to a transcriptomic database from primary colorectal tumors, showed that the EMT and the cholesterol homeostasis pathways were independent prognosis markers for survival. This prognostic value was increased when both were combined into a multi-metagene model. Altogether, our data suggest that interplay between these two pathways might drive tumor's aggressiveness.

POSTER 36 - TR/CR

Characterizing the Follicular Lymphoma Precursor Cell and its supporting microenvironment governing disease progression and recurrence

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1 CIML

2 MOBIDIC MicrOenvironment and B-cell: Immunopathology cell DIfferentiation and Cancer

Follicular Lymphoma (FL) is a disseminated B-cell neoplasia characterized by a slow progression. Despite a favorable response to first-line regimens, FL is considered incurable as most patients undergo relapse periods suggesting that therapy does not fully eradicate residual tumor cells. Current lymphomagenesis model suggests that relapses seed from rare Cancer Precursor Cells (CPC), which likely remain tolerant to therapy due to homing in a propitious niche such as the Bone Marrow (BM) and/or adopting a specific functional B cell state. Yet, the rarity of CPC and the use of bulk analyses have hampered their identification. A better characterization of CPC remains a major unmet need to prevent relapses. We harness a unique collection of longitudinal patient's BM from a clinical trial evaluating anti-CD20 therapy at diagnosis and 1-year post-treatment. We apply single-cell analysis combining gene expression and BCR repertoire to study FL cell heterogeneity within the BM microenvironment. Transcriptomic analysis revealed a major inter-patient tumor cells heterogeneity while non-malignant B cell clusters were mixed across patients. Among tumor cells, we found functional cell states shared between patients including a GC-like cluster, a cluster expressing both memory and activation markers and a quiescent memory-like cluster. We tracked clonally-related persistent tumor cells overexpressing genes associated with cell-matrix adhesion and apoptosis negative regulation. Our study enabled a first functional CPC characterization that we will explore to identify therapeutic targets.

POSTER 37 - TR/CR

High-Plex Spatial Imaging to decipher Tissue Microenvironment Complexity: Skin disease model

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Unraveling tissue contexture is emerging as a key step to understand tumor development and mechanisms of treatment resistance. Addressing a tissue as a heterogeneous complex system allows the analysis of its cellular and acellular component phenotypes, functions and interactions. Such a comprehensive and integrative analysis drives to a global scheme that depict the tissue homeostasis breakdown. Imaging Mass Cytometry (IMC) is a High-Plex tissue imaging system which allows an in situ exploration at a single cell level. Several works already described the use of this technology to analyze formalin-fixed paraffin-embedded tumor samples, but very rare studies addressed its use with fixed frozen (FF) tissues, the fastest and most convenient way for long-term preservation of experimental tissue samples and biopsies.We describe here the design of a 26-marker IMC panel for the staining of FF human skin sections of melanoma, psoriasis and vitiligo lesions and peri-lesion tissues. This panel targets structural skin components and resident and infiltrating immune cells. We also provide an optimized staining workflow.This panel allowed us to decipher the nature of immune cells, especially resident memory T cells and their functional status in different pathological conditions. Our workflow for IMC panel validation and analysis is suitable to FF samples, and scale up for cohort analysis. Addition of clinical data will implement a new analysis level, allowing patient clustering, to identify mechanisms of resistance to current therapies, or find new biomarkers or therapeutic targets.

POSTER 38 - TR/CR

Identification of Atypical Circulating Tumor Cells with Prognostic Value in Metastatic Breast Cancer Patients

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1 CRCM

2 Institut Paoli-Calmettes

Circulating tumor cells (CTCs) have a strong potential as a quasi-non-invasive tool to set up precision medicine strategy for cancer patients. Using a second-generation «filtration-based» technology to isolate CTCs, we performed a large and simultaneous analysis of all atypical circulating tumor cells (aCTCs) isolated from the blood of metastatic breast cancer (mBC) patients. We correlated their presence with clinicopathological and survival data. We included 91 mBC patients from the PERMED-01 study. The median number of aCTCs was 8.3 per mL of blood. Three subsets of aCTCs, absent from controls, were observed in patients: single (s-aCTCs), circulating tumor micro-emboli (CTM), and giant-aCTCs (g-aCTCs). The presence of g-aCTCs was associated with shorter progression free survival and overall survival. This study highlights the heterogeneity of aCTCs in mBC patients both at the cytomorphological and molecular levels. In addition, it suggests the usefulness of the g-aCTC subset as a prognostic factor and a potential stratification tool to treat late-stage mBC patients and improve their chance to benefit from early clinical trials. In the future, we want to use single-cell RNA sequencing approach to further clarify the inference of each cell subsets. For this, we will use the Parsortix™ Cell Separation System (ANGLE plc, UK) to enrich viable CTCs in a range compatible with further downstream extensive molecular applications. With this approach, we are expecting to shed light on mechanisms activated by the tumor to encourage tumor cells broad dissemination.

POSTER 39 - TR/CR

Pancreatic ductal adenocarcinoma ubiquitination profiling reveals specific prognostic and theranostic markers

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CRCM

Pancreatic ductal adenocarcinoma (PDAC), which accounts for 95% of pancreatic cancers, is one of the deadliest forms of cancer. While numerous PDAC multi-omics studies have been published last decade, from genomic and epigenomic to transcriptomic and proteomic, little is known about the post-translational modifications (PTMs) of proteins (the modifome) and their alterations associated with this disease. Among PTMs, ubiquitination is the broadest and most versatile, regulating the stability of proteins, via the proteasome, but also their activity, their interactions and their intracellular location, in a timely dependent manner. In this work, we used recently developed proteomic tools to establish the ubiquitin dependent modifome (ubiquitinome) of 60 PDACs tumors and investigated its possible association with tumor phenotype, patient survival and drug resistance. The computational and statistical analysis of the data allowed the identification of top four ubiquitination markers that can predict patient overall survival and 38 ubiquitination markers that correlated with the PDAC molecular gradient, a transcriptomic phenotyping of tumors. In addition, we identified 17 ubiquitin marks correlating with response to gemcitabine, seven with 5-FU, six with oxaliplatin and 13 with irinotecan. Finally, we validated the ubiquitination of PSMD2 as a drug response marker, by PLA (proximity ligation assay) directly on paraffin embedded tissues, demonstrating also the possible application of this new kind of biomarkers in clinical setting.

POSTER 40 - TR/CR

Reshaping immune lung populations to inhibit pulmonary fibrosis and cancer by activation of purinergic receptor P2RX7

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4 Laboratoire de Pathologie Clinique et Expérimentale (LPCE)

Lung cancer is the most prevalent cancer worldwide with high mortality rate despite recent advances in therapies. Not only is fibrosis a major hallmark of lung cancer, it is also a risk factor for its development. However, treatment and outcome of lung cancer patients with IPF is different than those without IPF despite their common genetic, molecular, cellular and immune properties.To address this, we proposed that boosting the activation of P2RX7 with a positive modulator (HEI3090) would be a novel strategy. P2RX7 is a purinergic receptor activated by high extracellular ATP levels found in inflamed and tumor sites. It has anti-tumor and immunomodulatory properties by its ability to induce cell death and the release of IL-1β and IL-18. We showed that HEI3090 inhibits lung tumor growth by triggering an anti-tumor immune response that relies on IL-18.Given that lung fibrosis is partly driven by inflammation with a dysregulated Th1/Th17 ratios and given the ability of HEI3090 to favor a Th1 immune response, we wondered if HEI3090 was able to inhibit fibrosis. We show that activation of P2RX7 with HEI3090 inhibits lung fibrosis in a bleomycin mouse model. HEI3090 targets the P2RX7/NLRP3 axis in immune cells, decreases lung inflammation and favors an anti-fibrotic immune signature.Overall, we show that reshaping lung immune phenotype by activation of P2RX7 is a promising strategy in lung fibrosis. We highlight a new therapeutic strategy for patients with IPF that would ameliorate treatment and outcome of patients with both lung cancer and fibrosis.

POSTER 41 - TR/CR

The needs of adolescents and young adults with cancer

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In France, each year approximately 2,300 adolescents and young adults (AJAs), from 15 to 24 years old are diagnosed with cancer. This population, between childhood and adulthood, finds itself in a in-between therapeutic path. Either paediatrics or adult path aren't necessarily adapted to their needs as patients. In order to improve the daily life of AYA's cancers in France, it is necessary to understand the nature of their needs as well as the presence of unmet needs that can negatively influence their quality of life. This work will introduce a detailed methodology to help identifying their needs and allows care stakeholders to interact with the competent services to meet their needs.We are proposing a systemic analysis of the needs of AJAs patients and as well as the study of their perception by the stakeholders of the patient's hospital environment. We had first proceeded with a quantitative study by a construction and validation of a questionnaire sent to 397 patients aged 18 to 25 at the time of the diagnosis. In a second step, to understand the perception of their trajectory in the therapeutic pathways, we will question through semi-structured interviews, a sample of AJA's patients in treatment or in remission on the one hand, and experts and actors of the care pathway, on the other hand to access the «practitioner» vision of the needs of their patients

POSTER 42 - TR/CR

Developing a new method to measure DNA repair efficiency and predict response of breast tumor to chemotherapy

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CRCM

Breast cancer represents 26% of cancer in women worldwide. Chemotherapies based on DNA damaging agents are frontline in breast cancer. One of the main limitations of breast cancer treatment is the development of resistance. Unfortunately, there are very few methods to predict cancer response to treatment and the diagnosis is usually done when the tumor keeps growing despite treatment. It has been shown that DNA damage response (DDR) participates in cancer resistance to chemotherapy. Indeed, if enhance, DDR will remove efficiently the treatment-induced lesions allowing tumor development.

In this context, the development of new tools that assess DDR could predict cancer response to treatment. Currents methods to measure DNA repair efficiency are based on the evaluation of the consequences of deficient repair such as an increased level of chromosome breaks. However, these are labor-intensive and costly methods, so there are currently only a few hospitals running such a diagnosis routinely, making the process of diagnosis difficult and delayed at the national level.

In this study, we have developed a new method to measure DNA damage repair, based on a new trackable DNA damaging agent. Our new method is directly detectable in cells, allowing a fast quantification of lesions accumulation by FACS or microscopy.

We have selected two different breast cell lines, one sensitive to chemotherapy and one resistant to chemotherapy. Using these cell lines, we will demonstrate the potential of our method to quickly predict response to chemotherapy.

POSTER 43 - TR/CR

Neutrophil extracellular traps formed during chemotherapy confers treatment resistance via TGFβ activation

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Metastasis is the major cause of cancer death and although most patients with metastases are treated with chemotherapy, the development of therapy resistance is common. The tumor microenvironment can confer chemoresistance, yet little is still known about how specific host cells influence therapy outcome. We show that chemotherapy induced neutrophil recruitment and Neutrophil Extracellular Trap (NET) formation which reduced therapy response in a mouse model of breast cancer lung metastasis. We found that chemotherapy-treated cancer cells released adenosine triphosphate causing other cancer cells to secrete IL-1β, which in turn triggered neutrophils to form NETs. Two NET-associated proteins where required for NETs' ability to induce chemoresistance: first, integrin-αvβ1 in NETs trapped latent TGFβ. Then, matrix metalloproteinase 9 cleaved and activated the trapped latent TGFβ. The NET-mediated TGFβ activation caused cancer cell to undergo epithelial to mesenchymal transition and correlated with chemoresistance. Critically, pharmacologically targeting of IL-1β, NETs, integrin-αvβ1, MMP9, and TGFβ all dramatically improved chemotherapy response in our mice model. Our work establishes a novel paradigm for how NETs regulate activities of neighboring cells by trapping and activating cytokines. Additionally, our data suggest that chemotherapy resistance in the metastatic setting can be reduced or prevented by targeting the previously unrecognized IL-1β-NET-TGFβ axis.

POSTER 44 - TR/CR

Unraveling the polypharmacology of beta-blockers in neuroblastoma using chemo-proteomics approaches

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Our lab has previously shown that β-blockers can increase the efficacy of chemotherapy in neuroblastoma (NB), one of the deadliest forms of childhood cancer. The mechanism(s) involved in their chemo-sensitizing activity remains however unknown. Here we developed an integrative method that combines unsupervised and candidate approaches to highlight the polypharmacology of drug repurposed in cancer treatment.

Using two complementary chemo-proteomics strategies, our first goal was to uncover the interactome of β-blockers. We performed «cellular thermal shift assay» coupled with quantitative mass spectrometry (MS-CETSA). It is a biophysical test based on the principle of ligand-induced thermal stabilization of target proteins, allowing us to test the impact of our drugs, in cellulo. In parallel, we exploited the biocompatible chemical reactions called click chemistry. By developing a pull-down experiment coupled with quantitative MS (click-proteomics), we were able to identify the interacting partners of β-blockers in NB cells. Since we found an enrichment in proteins involved in metabolism within our two complementary chemo-proteomics approaches, we then performed 13C glucose and 13C glutamine tracer experiments by quantitative MS. Our results showed an alteration of the nucleotides synthesis pathways following the combinatory treatment.Overall, by integrating MS-CETSA, click-proteomics and metabolomics data, our results show that β-blockers increase the efficacy of chemotherapy agents in NB by interfering with cancer cell metabolism, independently of β-adrenergic receptors.

POSTER 45 - TR/CR

Development of CXCR1/2 inhibitor for the treatment of metastatic uveal melanoma

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Uveal melanoma (UM) is the most common intraocular malignancy in adult population. Despite successful treatment of the primary tumor, more than 50% of patients develop metastases. At this stage, 80% of patients die within 1 year as there is currently no effective treatment for metastatic UM. It is therefore urgent to find new therapies.We observed that the ELR+CXCL cytokines stimulate angiogenesis and inflammation in UM. They exert their effects via the G-protein coupled receptors, CXCR1 and CXCR2. These receptors are physiologically expressed by endothelial and immune cells and aberrantly expressed by tumor cells.We have shown, in 2 cohorts of UM patients, that the presence of ERL+CXCL in the primary tumor correlates with the development of metastases and shorter patient survival.We developed a CXCR1/2 inhibitor (RCT001), which selectively neutralizes several mechanisms responsible for the aggressiveness of this cancer.We demonstrated that RCT001: i) decreased proliferation and induced UM cell death, ii) inhibited angiogenesis, iii) reverted M2 (pro-tumor) macrophages polarization in favor in M1 macrophages (anti-tumor) in primary human macrophages, iv) decreased the UM tumor growth in mice and v) synergized with immunotherapies.However, the mechanism of action of this inhibitor is not fully elucidated and several actions of RCT001 could be mediated by other targets. My work is to identify and determine the role of these secondary targets.Our final objective is to introduce our lead compound RCT001 in a phase 1/2A clinical trial to treat UM patients with metastatic UM.

POSTER 46 - TR/CR

Targeting of the ELR+CXCL/CXCR1-2 pathway is a promising strategy for the treatment of pediatric medulloblastomas

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Medulloblastoma (MB) is the most common and aggressive pediatric brain tumor. Despite an aggressive multimodal treatment, leading to important side-effects, 30% of patients develop resistance and relapse associated with metastasis. Recurrences cannot be controlled by conventional or targeted treatments. The reasons are a strong heterogeneity of the disease and strong propensity to develop resistance to reference treatments. So, more effective and less toxic therapies are needed at diagnosis or after relapse. Here, we showed the efficacy of a new inhibitor (C29) of ELR+CXCL/CXCR1-2 pathway, for the treatment of MB.
Methods: The correlation between ELR+CXCL/CXCR1-2 expression and patients' survival was established. The efficacy of C29 in vitro was evaluated on its ability to inhibit proliferation, migration in Boyden chamber and 3D spheroids invasion, of MB cells (DAOY, ONS-76, (Sonic hedgehog subgroup), HD-MB03 (Group 3)) either sensitive or resistant to radiotherapy. C29 efficacy was tested on the growth of experimental MB obtained by grafting MB spheroids on organotypic mice cerebellum slices.
Results: The levels of ELR+CXCL/CXCR1-2 correlated to a shorter survival. C29 inhibited proliferation, clone formation, CXCL8/CXCR1-2-dependent migration, invasion, and formation of pseudo-vessels by sensitive and radiation resistant cells. C29 reduced the growth experimental MB in ex vivo organotypic mice model and crossed the Blood Brain Barrier.
Conclusion: Targeting CXCR1-2 represents a promising strategy for the treatment of pediatric MB, in the first line or following relapses.

POSTER 47 - TR/CR

Conditional generation of free radicals by selective activation of alkoxyamines : towards a more effective and less toxic targeting of brain tumors

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The present work is based on the theranostic properties of Alkoxyamines (R1-ONR2R3), molecules that can undergo homolysis to generate an alkyl radical that triggers cancer cell death and a nitroxide that enhances the MRI signal. We synthesized a library of 105 new Alkoxyamines. The most efficient molecule, i.e., Alk4, was selected for its ability to inhibit both the survival and migration of medulloblastoma (MB) and glioblastoma (GBM) cells. Alk4 accumulates in tumor cell cytosol after 2h of treatment and released alkyl radicals, which triggered the generation of ROS, fragmentation of the mitochondrial network and finally apoptosis.
To control the homolytic process, Alk4 was then bioconjugated to a peptide selectively recognized by the matrix metalloproteinases (MMPs), which are overexpressed in the tumor microenvironment. The bioconjugate Alk4-MMPp successfully inhibited proliferation and invasion of GBM and MB 3D spheroids, while Alk4 bioconjugated to a chymotrypsin-targeted peptide remained inactive. To further characterize Alk4-MMPp benefits, we developed an innovative organotypic model based on the graft of stably fluorescent GBM or MB spheroids in ex vivo mice brain or cerebellum slices. The daily monitoring of response to treatment confirmed that Alk4-MMPp significantly impaired tumor progression, while no significant damage to the healthy tissue was observed.Our work paves the way for the controlled use of Alkoxyamines in MB and GBM, the most frequent intracranial tumors in children and adults respectively.

POSTER 48 - TR/CR

Integrative analysis of the diversity, location, BCR repertoire and antigen specificity of tumor-infiltrating B cells in lung cancer

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1 CIML

2 Innate Pharma

Tumor-infiltrating B lymphocytes (TIL-B) are associated with favorable outcome in lung cancer. TIL-B cells are grouped in tertiary lymphoid structures (TLS) that occasionally contain germinal centers (GC), yet it is unclear whether intra-tumoral PC are exported from GC-containing TLS and are the product of affinity maturation towards tumor antigens. We analyzed human lung cancer samples with single-cell and bulk RNA-seq and BCR-seq, multiplex immunofluorescence imaging and spatial transcriptomics. We also cloned recombinant monoclonal antibodies (mAbs) from subsets of TIL-B cells. We identified 6 subsets of TIL-B cells. PC and Memory (Mem) B cells were much more frequent than GC B cells. BCR repertoire analysis and clonotype tracking suggested poor PC output from GC B cells, but frequent PC differentiation from in situ reactivation of Mem B cells. Spatial analyses revealed that naïve, Mem and GC B cells resided mostly in TLS, whereas PC were in the stroma, at distance from TLS. We tracked TIL-B clonotypes among single blood plasmablasts, suggesting that TIL-PC may transit through the blood to or from the tumor site. Human proteome array analysis of 52 TIL-B mAbs revealed frequent reactivity to intra-cellular human antigens. Reverting TIL-B mAbs to their unmutated germline precursors abolished antigen binding, suggesting self-antigen binding capacity was acquired through affinity maturation. Our results suggest that most TIL-PC do not differentiate from in situ GC B cells, but are rather the product of reactivation of Mem B cells with previous history of affinity maturation.

POSTER 49 - TR/CR

Development of a new treatment for neovascular glaucoma of uveal melanoma patients

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Uveal Melanoma (UM) is a rare ocular disease with a different etiology compared tocutaneous melanoma. The reference treatment for UM is proton therapy. However,30% of patients treated develop a neovascular glaucoma (NVG) leading toenucleation. NVG is characterized by an overexpression of VEGF that leads touncontrolled neovascularization. Currently it is treated by intravitrealinjections of anti-VEGF agents, however, some patients are resistant to it.We have demonstrated that ELR+CXCL (CXCL1,2,3,5,6,7,8) cytokines and their CXCR1/2receptors play a key role in the resistance to anti-VEGF therapies. Thesecytokines are pro-angiogenic/pro-inflammatory and are overabundant in theaqueous humor of UM patients post-proton therapy (ancillary study associated-with «PROTECT» clinical trial conducted by the University Hospital of Nice (unpublishedresults)).Our innovation is based on competitive inhibitors of CXCR1 and CXCR2. Their inhibition willselectively neutralize multiple mechanisms responsible for NVG associated toUM: i) exacerbated/resistantangiogenesis independent of VEGF ii)detrimental chronic inflammation iii) autocrineloops of ELR+CXCL and CXCR1/2 expression by epithelial cells after treatment byproton therapyiv) Productionof reactive oxygen species and oxidative stressOur objective is to realize the research anddevelopment (hit to lead development) necessary to select RCT002, ourcandidate, to treat and/or prevent NVG. Administered topically, RCT002 could beproposed as a monotherapy or in combination with anti-VEGFs.

POSTER 50 - TR/CR

AI-empowered quantitative characterization of geometrical attributes of ExtraCellular Matrix (ECM) components in tumor tissue

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Immune infiltration in the tumor microenvironment (stroma) and metastatic spread of tumor cells is impacted by structural organization of proteins, such as fibronectin and collagen, that make up the extracellular matrix (ECM), anon-cellular component of the stroma. Our previous work on ECM topology, based on confocal images of fibrillar fibronectin (FN) networks assembled by cultured fibroblasts, has provided a framework for quantitative and spatial description of ECM features associated with normal and tumor-like states.

Aims: The present project aims to quantitatively characterize the ECM architecture and spatial distribution in human tumor tissue, with respect to the presence of immune and tumor cells, using multiplex multispectral immunofluorescence imaging.

Methods: Tumor samples were obtained from patients with head and neck cancer enrolled in the TOPNIVO ORL09 multicenter immunotherapy trial (n=305) promoted by Unicancer. Multispectral IF images (n≈3200) of ECM components and immune cells obtained using the Vectra Polaris slide scanner and InForm spectral unmixing software (Akoya Biosciences). Automatic image quantification was performed using the HALO® trainable feature-recognition software.

Existing image analysis softwares are not adapted for quantifying non-cellular, structural components of tumor tissue. The development, in progress, of an automatic analysis tool for integrative profiling the ECM and immune cell landscape in tumor tissue should improve tissue phenotyping and the prediction of patient responsiveness to immunotherapy.

POSTER 51 - TR/CR

CAR-NK and CAR-gd T cells promote the killing of leukemic blasts

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1 Institut Paoli Calmettes

2 AMU

3 CRCM

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. It was initially shown that T cells had a major role in the GVL effect. Unfortunately, allogeneic T cells also lyse healthy tissues of the recipient, as part of an alloreactivity syndrome: Graft VS Host Disease (GVHD). Also, while mortality related to the procedure decreased in recent decades, relapse of AML after Allo-CSH still occurs in 30% of patients. Post-allograft immunomodulation strategies can be implemented to improve the anti-leukemic efficiency of Allo-CSH. However, the enhancement of the GVL effect is often followed by an increased incidence of GVHD, as these are based on T immunomodulation. Recently, it was reported that other immune effectors can mediate a GVL effect without GVHD. In particular, NK cells and Tγδ lymphocytes (Tγδ) appear to be interesting. Also, their slightly different activation patterns suggest complementary or even synergistic abilities. To demonstrate the feasibility and efficacy of a cellular product composed of NK and Tγδ, we validated a combined expansion process from peripheral blood. The validation was made on both the phenotype and functional aspects. In parallel, we were able to genetically engineer these cells to establish a functional combined CAR-NK and CAR-Tγδ model. To summarize, these results pave the way for a customizable genetic edition platform, in term of molecular target as well as immune cell.

POSTER 52 - TR/CR

Characterizing the Role of Radiotherapy in Breast Cancer Recurrence and Lymphedema

Saharnaz SARLAK[1,2], Frédéric LUCIANO[1,3], Gilles PAGÈS[1,3,4]

1 IRCAN

2 CNRS

3 Inserm

4 Centre Scientifique de Monaco

Breast cancer is the leading cause of cancer mortality among women worldwide (1). Despite of the improvement of the therapeutic strategies, numerous patients are either prone to relapse or suffer from treatment-related side effects (2).One of these side effects is related to arm lymphedema, the impairment in draining of the lymphatic fluid which leads to their accumulation in tissue (3)(4). An increased risk of arm lymphedema was reported after radiotherapy (RT)(2).Consequently, optimizing the irradiation strategies could help breast cancer patients and survivors to reduce side effects of RT and a better quality of life.Here we investigated the effect of RT on lymphangiogenesis and lymphedema. In parallel, we compared two types of irradiations; Proton (P) and Photon (X) to understand which type of irradiation prevents deleterious lymphangiogenesis while conserving a maximal therapeutic index.To these aims, we studied the efficiency of P and X irradiations on endothelial and breast tumor cells.We observed an induction of vascular endothelial growth factor C (VEGFC), a major pro-lymphangiogenic factor (6), post P and X Irradiation in endothelial and tumor cells which suggests that RT triggers exacerbated lymphangiogenesis.Moreover, we observed that VEGFC KO tumor cells are more sensitive to RT than parental cell line. These interesting results suggest that accompanying anti-VEGFC medication alongside the RT can result in a more effective combination for breast cancer patients and avoid the incidence of lymphedema as a side effect of RT.

POSTER 53 - TR/CR

Genome-wide CRISPR screens reveal novel oncogenic dependencies in B cell lymphomas

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INSERM / U1104 / CIML / Lab SR/BN

Despite its indolent nature, follicular lymphoma (FL), a germinal center (GC)-derived B-cell blood cancer, remains a clinical burden, as most patients relapse or transform into a form of cancer with poor prognosis. We currently lack an integrated understanding of the molecular mechanisms supporting FL cell proliferation/survival and of the heterogeneity of response to therapy. Among cutting-edge technologies that emerged in recent years, genome-wide loss-of-function CRISPR-Cas9 screens have become powerful tools to reveal mechanisms of cell survival and death. Here, we performed CRISPR screens on 10 human transformed FL cell lines. We used Model-based Analysis of Genome-wide CRISPR-Cas9 KO (Mageck), an algorithm that provides differential abundance of sgRNAs between the initial and final population 3 weeks later and allows to score genes important for cell survival, that may represent potent therapeutic targets. We were able to reveal common oncogenic dependencies shared by most lymphoid cell lines (>90%) involving the anti-apoptotic pathway (MCL1) or GC B cell transcription factors (BCL6). By comparing the 10 lines according to their genetic landscape, we identified context-specific dependencies linked to genetic aberrations (EZH2). Finally, we revealed specific dependencies in some lines, e.g. the BCR signaling pathway involving SYK/PI3K/AKT. This integrative study generated a large dataset of gene essentiality in FL cells that we are currently validating and that may provide novel targets for therapies.

POSTER 54 - TR/CR

Targeting CTGF : A new therapeutic strategy in metastatic renal cell carcinoma ?

Manon TEISSEIRE, Julien PAROLA, Maëva TOTOBESOLA, Frédéric LUCIANO, Gilles PAGES, Sandy GIULIANO

University Cote d'Azur (UCA) ; Institute for research on cancer and aging of Nice (IRCAN), CNRS UMR 7284, INSERM U1081, Normal and pathological angiogenesis ; Centre Antoine Lacassagne, France

Sunitinib, an oral tyrosine kinase inhibitor, is one of the first line treatment for metastatic renal cell carcinoma (mRCC). Sunitinib prolongs progression-free-survival (PFS) in patients with mRCC. Unfortunately, in most cases, patients relapse after one year of treatment. The anti-angiogenic role of sunitinib on endothelial cells is well described, but its role on tumor cells is poorly understood. We aim to investigate mechanisms of resistance induced by sunitinib on tumor cells.Previous results described sunitinib as a lysosomotropic agent which disrupts autophagy pathway (Giuliano et al., Autophagy, 2015). In the literature, autophagy inhibition creates a pro-inflammatory environment. Proteomic analysis of sunitinib treated and resistant cells to this treatment confirmed an increase in pro-inflammatory proteins and secreted factors in mRCC (Giuliano et al., Theranostics, 2019). Among them, we identified Connective Tissue Growth Factor (CTGF). CTGF is a signaling factor which can promote cancer initiation, progression and metastasis.We demonstrated an increase of CTGF mRNA levels and secreted form in mRCC sunitinib treated and resistant cells. We also demonstrated that CTGF invalidation by siRNA i) induces a cell cycle arrest and decreases proliferation, ii) induces cell death at 96h after transfection, iii) reduces migration and iii) decreases invasion of mRCC cells. Moreover, CTGF recombinant protein increases mRCC cell migration.Our preliminary results indicate that CTGF may play a key role in aggressiveness of mRCC cells and need to be further investigated.

POSTERS
PLATFORM / STRUCTURING ACTION

POSTER 55 - PL/SA

3D-Hub-S: A 3D multicellular tumor spheroid platform for anti-cancer drugs screening

Audrey LAFON[1], Enora LECORGNE[1], Kitti JENOVAI[2], Isabelle BOURGET[2], Cédric GAGGIOLI[1,2]

1 Université Côte d'Azur, Inserm U1081, CNRS UMR 7284, IRCAN, plateforme 3D-Hub, 28 Avenue de Valombrose, 06107 Nice

2 Université Côte d'Azur, Inserm U1081, CNRS UMR 7284, IRCAN, Tumor Stroma Interactions, 28 Avenue de Valombrose, 06107 Nice

Sunitinib, an oral tyrosine kinase inhibitor, is one of the first line treatment for metastaCancer is the leading cause of death worldwide highlighting the urgent need to develop innovative methods in order to identify new generation anti-cancer treatments. Three-dimensional (3D) cell culture has recently emerged since such systems recapitulates more closely the complexity of solid tumor. Indeed, 3D cell culture models can recreate a complex tumor microenvironment including diffusion of oxygen, nutrients, waste and drugs where cellular interactions can be recapitulated. In this context, we developed the 3D-Hub-S platform, specialized in 3D multicellular tumor spheroids (MCTS) embedded into an extracellular matrix, enabling low or medium throughput screenings of anti-cancer drugs targeting cell proliferation, invasion and chemoresistance. Drug efficiency is evaluated by measuring the integrated density of the spheroid core and tumor cells invasion within the matrix using transmitted light microscopy acquisitions. Moreover, image-based analysis is confirmed by mitochondrial activity quantification through bioluminescence assay. Our platform is opened to researchers, clinicians and companies working in cancer research. The platform offers an access to our expertise in spheroids screenings and identification of new anti-cancer strategies. 3D-Hub-S is a Canceropole PACA and IRCAN institute (Nice)-based facility supported by INSERM, CNRS, Université Côte d'Azur and IBiSA labelled, which ultimately aims at providing personalized medicine solutions for oncologists.

POSTER 56 - PL/SA

3D-Hub-O: Organoids Production Platform

Manon SAUBIN[1,2]

1 CRCM

2 Inserm U1068

3D-Hub-O: Organoids Production PlatformVéronique Chevrier1, Manon Saubin1 and Géraldine Guasch11 Aix-Marseille University, CNRS, INSERM, Institut Paoli-Calmettes, CRCM, Epithelial Stem Cells and Cancer Team, Marseille, France.

Organoids are multicellular three-dimensional structures that reproduce in vitro the microanatomy of an organ and at least one function of the organ. It must mimic the basic functions of the corresponding organ. In vitro 3D culture of adult stem cells has revolutionized cell culture by bringing this innovative study model more faithful to the biology of the original tissue making the organoids a highly valuable tool to study organ homeostasis and tumorigenesis.

The 3D-Hub-O platform aims to advice, train and support research teams in the Southern Region in their 3D model study projects to modeling of tissue physiology and disease from specific patient cells or murine model cells. The platform proposes the development of organoid models mainly from adult stem cell and specifically dedicated to cancer research for bio-banking, for molecular screening to identify new cancer drugs and analysis of response to treatment for developing personalized and regenerative medicine.

In conclusion, the 3D-Hub-O platform will enable research combining developmental biology with cancer biology by promoting the development of preclinical models and their use in the discovery of new anti-cancer approaches.

POSTER 57 - PL/SA

Crispr screen action, an initiative of the Canceropôle PACA

Nori SADOUNI[1], Julien FASSY[2], Sara SCARAMUZZINO[3], Els VERHOEYEN[4], Bernard MARI[2], Sandrine ROULLAND[3], Salvatore SPICUGLIA[1]

1 Université Aix-Marseille, Inserm, TAGC, UMR1090, Marseille, France

2 Université Côte d'Azur, CNRS, IPMC, FHU-OncoAge, Valbonne, France

3 Aix Marseille Univ, CNRS, INSERM, CIML, Marseille, France

4 Université Côte d'Azur, INSERM, C3M, Nice, France

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 non-coding 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. As an example, we describe here a comparaison between loss-of-function and repression screens performed in the Jurkat T-ALL cell line.

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1DAY MEETING

CRISPR Screening in Cancer Discovery

SCREENACTION CRISPR

CRISPR'it

September 26th, 2022
Le Pharo, Marseille

PRELIMINARY PROGRAM

MORNING SESSION

09:30-09:45
> Welcome Coffee

09:45-10:00
> Opening Speech

10:00-10:50
> "In vivo genetic screening for cancer research"
R. Rad - IMO, Munich, Germany

> Short talk (to be selected)

10:50-11:40
> "Identification of epigenetic regulators by CRISPR-Cas9 screening in mammalian cells"
M. Weber - BSC/ESBS, Illkirch

> Short talk (to be selected)

11:40-12:30
> "Functional epigenomics screens reveal lineage-specific cancer dependencies"
G. Galli - NIBR, Basel, Switzerland

> Short talk (to be selected)

12:30-14:00
> Lunch Break & Poster Session

AFTERNOON SESSION

14:00-14:50
> "Prioritizing cancer therapeutic targets via CRISPR screens and multiomics data integration"
F. Iorio - Human Technopole, Milan, Italy

> Short talk (to be selected)

14:50-15:20
> Round Table "Single cell / CRISPR CAS Screen"
S. Roulland - CIML, Marseille, B. Mari - IPMC, Sophia Antipolis & M. Wassef - Institut Curie, Paris

15:20-15:50
> Round Table "*In Vivo*"
L. Menger - IGR, Paris & A. Boré - Institut Curie, Paris

15:50-16:20
> Coffee Break & Poster Session

16:20-17:10
> "Systematic immunotherapeutic targets discovery for Advanced T cell Therapy"
L. Menger - IGR, Paris

> Short talk (to be selected)

17:10-17:40
> "CRISPR screens to identify human genes regulating viral infections"
C. Goujon - IRIM, Montpellier

ORGANIZING COMMITTEE & CHAIRPERSONS

Aurélien Boré, Institut Curie, Paris - **Raphaël Margueron**, Institut Curie, Paris - **Bernard Mari**, IPMC, Sophia-Antipolis
Sandrine Roulland, CIML, Marseille - **Salvatore Spicuglia**, TAGC, Marseille - **Els Verhoeyen**, C3M, Nice
Michel Wassef, Institut Curie, Paris - **Vanessa Zepponi**, Cancerôpole Provence-Alpes-Côte d'Azur

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Training, information, expertise, these are the missions of our society which have been provided for more than a hundred years.

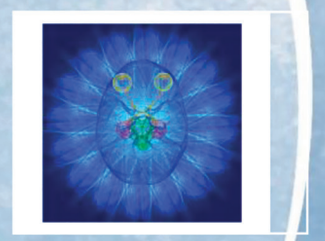
It publishes the **Bulletin du Cancer**, the only French-language oncology journal indexed in international databases, which has reached its 109th volume this year and is open to the entire Francophonie.

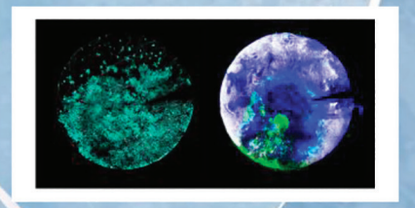
Every year, the French Cancer Society organizes a **high-level international scientific day, the Louise-Harel Day**, named after its founder, by inviting French and foreign researchers to discuss current topics.

The French Cancer Society also organizes an **annual training cycle at the interface between biology and the clinic** and aimed at fostering the mutual understanding of clinicians and researchers.

It publishes a collection of books on therapeutic innovation in oncology and has trained generations of oncology clinicians in clinical research.

In the areas of expertise of its members, it ensures **active participation in expert committees** set up by the public authorities, in particular within the framework of the National Cancer Institute.





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