PETRA Network

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

#WEARECANCEROPOLE

BOOKLET

MATCHING DAY

PrEclinical & TRAnslational Network for Research in Neuro-Oncology

Monday, January 15, 2024
Château de Valrose, Nice

Aix*Marseille université
Socialement engagée

INSTITUT NATIONAL DU CANCER

RÉGION SUD PROVENCE ALPES CÔTE D'AZUR

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PROGRAM

Morning Session
Platform Updates & Success Stories

10:00-10:20 > Welcome Coffee

10:20-10:30 > Opening Speech - Canceropôle's Team

10:30-11:00 > Update of the PETRA Network: Review of the first year!
Aurélie Tchoghandjian - PETRA"TECH", Marseille * Thierry Virolle - PETRA"TECH", Nice
Emeline Tabouret - PE"TRANSLA"

11:00-11:30 > Success Story #1 - Philipp Tsvetkov (INP) & PETRA"TECH"

11:30-12:00 > Success Story #2 - Marcel Blot-Chabaud * Ahmad Joshkon (C2VN) - PETRA"TECH" & PE"TRANSLA"

12:00-12:30 > Valorization Story - Gilles Pagès * Maeva Dufies (Roca Therapeutics)

12:30-13:30 > **Lunch Break**

Afternoon Session
Technical Updates & Upcoming Projects

13:45-14:05 > Technical Update #1 - Clément Peux - PETRA"TECH", Nice

14:05-14:35 > Short Talks Speech
Julie Lafont - E. Pasquier team, CRCM: "Using high-throughput screening to identify potent drug combinations against diffuse intrinsic pontine glioma"
Rosario Lavignolle-Heguy - R. Arguëllo team, CIML: "Epic-SCENITH: When Human Metabolism Meets Epigenetics"

14:35-14:55 > Fondation Flavien - Denis Maccario

14:55-15:25 > **Coffee Break**

15:25-15:45 > New Team joining the Network: Welcome!
Vincent Picco * Christopher Montemagno (Centre Scientifique de Monaco)

15:45-16:05 > Technical Update #2 - Aurélie Soubéran - PETRA"TECH", Marseille

16:05-16:20 > Discussion with the scientific coordinators of the PETRA Network for upcoming projects

16:20-16:30 > **Final Discussion**

Aix*Marseille université Socialement engagée

INSTITUT NATIONAL DU CANCER

RÉGION SUD PROVENCE ALPES CÔTE D'AZUR

Philipp Tsvetkov

INteractome Timone Platform (PINT), Institute of NeuroPhysiopathology (INP) - UMR 7051, Marseille

Title: **Validating new microtubules targeting agents that can cross blood brain barrier for glioblastoma treatment**

Abstract:

Objectives: This project aims to identify the most promising microtubule targeting agents (MTAs) from FDA-approved compounds, with a specific focus on those capable of crossing the blood-brain barrier (BBB). The ultimate goal is to reposition these compounds for effective treatment of brain tumors, particularly glioblastoma.

Novelty and Significance: MTAs have established their effectiveness as first-line therapies in cancer treatment. However, their application in treating glioblastoma has been limited due to their inability to penetrate the BBB. Our project stands out for its innovative approach: leveraging a newly developed screening assay, supported by Gefluc's "Emergence" 2019 initiative, to identify MTAs that target microtubule polymerization. This screening, applied to the Prestwick chemical library of 1520 FDA-approved compounds, has yielded several previously unrecognized MTAs. Notably, 14 of these have the potential to cross the BBB, presenting a groundbreaking opportunity for drug repositioning in brain tumor treatment.

Methodology: Our methodology encompasses a comprehensive evaluation of the antitumor potential of the 14 selected compounds. We will assess their effects on tubulin polymerization at the molecular level, as well as their influence on cell division and migration at the cellular level. The most effective compounds will then undergo validation on tumoroids using the PETRA platform. This rigorous process ensures the selection of the best candidates for further development in glioblastoma treatment.

Ahmad Joshkon & Marcel Blot-Chabaud (recorded presentation)
Aix-Marseille Univ, INSERM1263, INRAE1260, C2VN, Marseille

Title: **Soluble CD146, a novel biomarker and a target for preventing resistance to anti-angiogenic therapy in glioblastoma**

Abstract:

Glioblastoma multiforme (GBM) is a primary brain tumor with poor prognosis. The U.S. food and drug administration approved the use of the anti-VEGF antibody bevacizumab in recurrent GBM. However, resistance to this treatment is frequent and fails to enhance the overall survival of patients. We thus aimed to identify novel mechanism(s) responsible for bevacizumab-resistance in CD146-positive glioblastoma.

We found that an increase in sCD146 concentration in sera of GBM patients after the first cycle of bevacizumab treatment was significantly associated with poor progression free survival and shorter overall survival. Accordingly, in vitro treatment of CD146-positive glioblastoma cells with bevacizumab led to a high sCD146 secretion, inducing cell invasion. These effects were mediated through integrin αvβ3 and were blocked by mucizumab, a novel humanized anti-sCD146 antibody. In vivo, the combination of bevacizumab with mucizumab impeded CD146+ glioblastoma growth and reduced tumor cell dissemination to an extent significantly higher than that observed with bevacizumab alone.

We thus propose sCD146 to be both an early predicting biomarker and a potential target to prevent bevacizumab resistance in patients with glioblastoma.

Gilles Pagès & Maeva Dufies

University Cote d'Azur; Institute for research on cancer and aging of Nice UMR CNRS 7284/U INSERM 1081, Nice

Title: **Roca Therapeutics: A Chronicle of Translational Research Program to Startup Creation, Unveiling an Odyssey in Innovative Therapy Development for Patients in Therapeutic Impasse**

Abstract:

The inception of Roca Therapeutics originated from a laboratory study revealing the pivotal role of the ERK pathways in driving VEGF expression (Milanini et al JBC 1998). Building upon Sparmann and Bar Sagi's groundbreaking publication in Cancer Cell (2004), which highlighted that constitutively active Ras stimulates not only VEGF but also interleukin 8 (CXCL8) expression, our hypothesis emerged. We posited that CXCL8 contributes to resistance mechanisms against therapies targeting VEGF or its receptors (VEGFRs).

Our focus was on renal cancers, where anti-angiogenic therapies targeting VEGF/VEGFRs had been the standard of care for 15 years. Over this period, we unraveled various resistance mechanisms to anti-angiogenics, with the ELR+CXCL cytokine family, particularly CXCL7, emerging as a major driver. Our translational program demonstrated that ELR+CXCL and their receptors CXCR1 and CXCR2 served as therapeutic targets not only for renal cancers but also for head and neck tumors, breast tumors, pancreatic tumors, colon cancers, uveal melanoma and pediatric medulloblastoma.

In collaboration with the Institute of Chemistry in Nice, we developed CXCR1/2 inhibitors, forming the foundation for the establishment of Roca Therapeutics in 2021. Roca Therapeutics aspires to translate these inhibitors into clinical applications, combating resistance mechanisms not only in oncology but also in ophthalmology. Similar resistance mechanisms, involving the ELR+CXCL/CXCR1/2 axis, play a crucial role in both cancer and ophthalmology. The journey of Roca Therapeutics encompasses this transformative path, aiming to make a significant impact in the clinic. process ensures the selection of the best candidates for further development in glioblastoma treatment.

Denis Maccario

Père de 3 enfants dont une étoile, Fondation Flavien, Principauté de Monaco

Titre: **«Tu ne seras jugé que par tes actes > #MEPENDAX»**

Abstract:

Le combat face à la maladie avec son enfant VS après envol, le combat continue.

Julie Lafont
CRCM, Aix-Marseille University, CNRS, Inserm, Public Assistance - Hospitals of Marseille

Title: **Using high-throughput screening to identify potent drug combinations in patient-derived diffuse midline glioma model**

Abstract:

The power of high-throughput drug screening comes from the ability to test a large number of molecules on multiple models in a very short time. Our approach is based on the use of a custom-made library of 110 drugs divided into four main groups (i.e. chemotherapies, epidrugs, targeted therapies and repositionable agents) with at least two compounds of the same therapeutic family. It is then possible to identify the most efficient compounds for a given type of tumor models. This sensitivity to a particular therapeutic class enables rationally deducing and identifying the molecular vulnerabilities of a given cell model, depending on the target(s) of the hit compounds. This weakness can then be exploited to better understand tumor pathophysiology and also develop innovative therapies. In the current study, we applied our methodology to a fatal type of pediatric brain tumor called Diffuse Intrinsic Pontine Glioma (DIPG). Approximately 80 % of DIPG have a recurrent somatic mutation on histone 3 (i.e., H3K27M), resulting in a major epigenetic dysregulation. Recently, a compound called ONC-201 has demonstrated therapeutic benefit for patients with H3K27M mutated tumors and is currently being evaluated in several clinical trials. The objective of this project is to quickly identify new therapeutic vulnerabilities that can targeted to increase the efficacy of ONC-201 and its derivatives ONC-206 and ONC-212. To achieve this, we performed a high-throughput drug screening using our 110-drug library in combination with ONC-201 or its derivatives in 8 different patient-derived primary models of diffuse midline glioma with distinct molecular features. Amongst the 330 tested pairwise combinations, the association of ONC compounds with two types of metabolic inhibitors were identified as most potent drug combinations, highlighting potential therapeutic vulnerabilities. Using a matrix of 6x5 different drug concentrations, we then proceeded to validating the potency of the top drug combination in 5 different cellular models. By calculating the Bliss score, we were able to define the association as being highly synergistic. Thus, using high-throughput drug screening we uncovered therapeutic vulnerabilities that could be leveraged by combining ONC compounds with metabolic inhibitors, which could open novel therapeutic avenues for DIPG patients.

Vincent Picco - Christopher Montemagno
Département de Biologie Médicale, Centre Scientifique de Monaco, Principauté de Monaco

Titre: **Présentation de l'équipe Cellules Souches et Tumeurs du Cerveau du Centre Scientifique de Monaco**

Abstract:

Les cancers pédiatriques (CP) du système nerveux central (SNC) représentent une palette de maladies meurtrières. Les données moléculaires pan-cancéreuses suggèrent que, contrairement aux cancers adultes où l'accumulation de nombreuses mutations est généralement responsable de la tumorigenèse, les CP du SNC sont dus à des défauts développementaux qui provoquent le blocage de certaines cellules dans un état embryonnaire prolifératif, résultant en l'apparition de tumeurs à des âges parfois extrêmement précoces. Malgré ces divergences majeures, le traitement des CP repose sur la chirurgie d'exérèse, la radiothérapie et l'utilisation de chimiothérapies adultes repositionnées, avec toutes les conséquences néfastes qu'impliquent ces modalités thérapeutiques dans un contexte pédiatrique. Les propriétés embryonnaires/souches des cellules tumorales des cancers pédiatriques ainsi que leur plasticité phénotypique suggèrent que des vulnérabilités spécifiques à ce type de cancers pourraient être mobilisées dans le but d'améliorer la prise en charge de ces pathologies, notamment par radiothérapie, voire de développer des thérapies spécifiques à ces cancers. Dans ce but, notre équipe s'intéresse à la plasticité de l'identité des cellules de tumeurs embryonnaires du cerveau et à son lien avec le métabolisme et la réponse à la radiothérapie de ces tumeurs.

Rosario Lavignolle-Heguy

CIML, Marseille

Title: **Epic-SCENITH: When Human Metabolism Meets Epigenetics**

Abstract:

Background: Immune cells infiltrating the tumour can have either pro- or anti-inflammatory profiles. This switch in function is associated with cellular metabolism as well as epigenetic remodelling. Additionally, enzymes responsible for epigenetic modifications depend on metabolites such as NAD, SAH and Acetyl-CoA, whose availability changes in the tumour microenvironment. Glioblastoma tumours are characterized by oedema, angiogenic and necrotic regions, containing different metabolites and thus potentially impacting on the function of immune cells in them.

Objectives: The interplay between Epigenetics and Metabolism could be a key factor of anti-tumour immunity, however few tools allow to study them simultaneously. To solve this, we are developing a method called Epic-SCENITH, combining functional metabolic readouts with epigenetic measurements.

Methods: A 30-colours spectral cytometry panel was used to assess immune populations infiltrating glioblastoma tumours, as well as their total level of H3K4me3, H3K27me3 and H3K27ac histone modifications. For the development of Epic-SCENITH, an in-vitro model of metabolic heterogeneity was first set by treating THP-1 cells with low doses of 2-deoxyglucose to block glycolysis. Cells were then sorted according to their metabolic profile (SCENITH), and the CUT&RUN technique was performed, for future assessment of epigenetically activated or repressed genes in these cells.

Results: Immune cells infiltrating glioblastoma tumours were successfully identified, as well as their total level of H3K4me3, H3K27me3 and H3K27ac. Upon treatment with 2-deoxyglucose, THP-1 cells became metabolically heterogeneous. Half of them remained highly dependent on glycolysis, whereas the other half became mitochondrial dependent. Additionally, mitochondrial dependent cells showed a lower H3K27ac than glycolytic cells.

Conclusion: We established a model that mimics metabolic heterogeneity in-vitro and allowed us to identify a link between the metabolic profile and histone acetylation. The following step will consist of pinpointing and sequencing epigenetically modified genes. This method will then be applied to immune cells infiltrating human glioblastoma samples to evaluate how Metabolism and Epigenetics contribute to tumour progression.

Aurélie Soubéran

Platform PETRA»TECH», Aix-Marseille Univ, CNRS, INP, Inst Neurophysiopathol, GlioME Team, Marseille

Title: **PETRA»TECH» Marseille - In vitro models offer**

Abstract:

The GlioME team has been working for several years on the cellular and molecular characterization of gliomas, and has acquired expertise in setting up cellular models. It was on these foundations that the PETRA network and the PETRA'TECH' Marseille platform emerged. Thanks to long-lasting collaboration with the La Timone hospital, we are developing a series of in vitro models for preclinical research in neuro-oncology.

We offer 3 models that have been fully characterized: organotypic slices with tumor spheroid grafted a onto a mouse brain slice in order to study the invasion and migration properties of tumor cells; explant models that are pieces of tumor cultured on a matrix to assess cellular heterogeneity and cell migration, including videomicroscopy; and we succeeded in developing a protocol to derive tumoroids from glioblastomas and brain metastases. The special features of this model are that no matrix is required to ensure cell survival and growth, ant that cell diversity is maintained for up to 4 weeks in culture.

These models provide answers to a wide range of biological questions and are also suitable for testing new therapeutic molecules in neuro-oncology.