SOMMAIRE

Gilbert LENOIR

Vice-Président de la Fondation ARC

ÉDITORIAL

La Fondation ARC est convaincue du rôle central que vous, jeunes chercheurs, jouez dans la lutte contre le cancer par la recherche. Nous mettons un point d'honneur à vous soutenir, à nous assurer que vous êtes formés dans les meilleurs laboratoires, pour que vous intégriez le monde de la recherche, et *in fine* que vous montiez vos propres équipes de recherche. Chaque année, vous êtes plus d'une centaine à bénéficier de notre soutien pour mener à bien vos travaux de master, de thèse ou de post-doctorat. Aujourd'hui, il nous tient à cœur de mettre en lumière vos recherches et votre engagement. Vous aurez également l'opportunité de rencontrer les donateurs de la Fondation, grâce auxquels nous pouvons mener nos actions au quotidien, et qui n'ont qu'une hâte : partager les espoirs que suscitent vos travaux.

Nancy ABOU-ZEID

Directrice scientifique de la Fondation ARC

La Fondation ARC se mobilise pour garantir que la formation des futurs chercheurs et médecins soit complète. C'est pourquoi, en plus d'accompagner vos formations académiques, nous vous encourageons aussi à interagir et à échanger entre scientifiques. Ces Journées sont une belle occasion pour vous de rencontrer des chercheurs issus de divers horizons, de partager vos expériences, vos résultats, vos hypothèses et, peut-être, générer de nouvelles collaborations. Vous profiterez également du regard aiguisé d'un Jury de grande qualité, mobilisé pour évaluer vos travaux et pour vous aider à les mettre en perspective. En plus de vos compétences et de votre rigueur, la Fondation ARC souhaite valoriser aujourd'hui votre curiosité, votre ouverture d'esprit et votre imagination !

Karin TARTE

Présidente du Jury Hélène Starck 2022 & du Conseil scientifique de la Fondation ARC - Directrice de l'unité mixte de recherche MOBIDIC - « MicrOenvironnement and B-cell : Immunopathology cell Differentiation and Cancer »

En tant de Présidente du Conseil Scientifique de la Fondation ARC, je mesure l'importance donnée à la formation des jeunes chercheurs au sein de la Fondation, à tel point qu'elle constitue un axe stratégique majeur représentant près d'un tiers de nos soutiens. Cette année, j'ai également l'honneur de présider le Jury des Prix Hélène Starck avec, à mes côtés, plusieurs membres de nos instances scientifiques. Nous sommes tous en accord pour souligner la grande qualité des résumés reçus, qui reflète toute la diversité de vos approches et l'excellence des travaux que vous menez au quotidien. Nous sommes impatients de vous rencontrer et de nourrir de riches échanges scientifiques avec vous, jeunes chercheurs qui ferez les grandes découvertes de demain !

Jury 2022
Prix Hélène Starck et Prix Kerner

JURY HÉLÈNE STARCK 2022

- **Karin TARTE,** Présidente – CHU de Rennes
- **Jacques-Olivier BAY** – CHU de Clermont-Ferrand
- **Anne-Sophie CHRETIEN** – Centre de Recherche en Cancérologie de Marseille
- **Alexandre DAVID** – Institut de Génomique Fonctionnelle, Montpellier
- **Thomas FARGE** – CHU de Toulouse
- **Hinrich GRONEMEYER** – Institut de Génétique, Biologie Moléculaire et Cellulaire, Illkirch
- **Christophe LAMAZE** – Institut Curie, Paris
- **Jacqueline LEHMANN-CHE** – Institut de Recherche Saint-Louis, Paris
- **Karen LEROY** – Centre de recherche des Cordeliers, Paris
- **Laurence NIETO** – Centre de Recherches en Cancérologie de Toulouse
- **Julie PANNEQUIN** – Institut de Génomique Fonctionnelle, Montpellier
- **Jean-Ehrland RICCI** – Centre Méditerranéen de Médecine Moléculaire, Nice
- **Stéphanie TORRINO** – Institut de Pharmacologie Moléculaire et Cellulaire, Valbonne

JURY KERNER 2022

- **Charles BEHR** - E=M6
- **Ingrid BERNARD** - Top Santé
- **Charline DELAFONTAINE** - Pleine Vie
- **Thierry FEDRIGO** - L'Est Républicain
- **Pauline FRÉOUR** - Le Figaro
- **Jimmy MOHAMED** - France 5
- **Sylvie MONTARON** - Le Progrès
- **Lise LOUMÉ** - Sciences & Avenir la recherche
- **Emmanuelle REY** - La Dépêche
- **Vincent VALINDUCQ** - France 2

Programme
Lundi 21 novembre 2022

MATIN

8h30-9h • Accueil autour d'un café

9h-9h10 • Ouverture des journées par **Gilbert LENOIR,** Vice-Président de la Fondation ARC & **Karin TARTE,** Présidente du Jury Hélène Starck 2022

9h10-11h25 • Session 1 – Prix Hélène Starck Oral - Catégorie Doctorat

Amandine AMALRIC • Institut des Neurosciences - Montpellier
"Epitranscriptomics": a promising source of circulating biomarkers for personalized medicine

Pierric BIBER • Centre méditerranéen de médecine moléculaire - Nice
The mechanically-activated deubiquitinase USP9X controls melanoma invasiveness and drug response through YAP stabilization

Marine BRUCIAMACCHIE • Institut de recherche en cancérologie de Montpellier
Synergistic effect of FOLFIRINOX with an ATR inhibitor on pancreatic tumor cells and its microenvironment

Ghita CHABAB • Institut de recherche en cancérologie de Montpellier
Regulatory γδ T cells in solid cancer : characterization, role and ecosystem

Remy CHAR • Centre d'immunologie de Marseille-Luminy
Characterization of RUFY3 protein in Dendritic Cells and macrophages: Potential modulator of autophagy and immunity

Gonçalo FERNANDES • Institut Curie - Paris
Synthetic reconstruction of the hunchback promoter identifies the roles of Bicoid, Zelda and Hunchback in the dynamics of its transcription

Julie OLABE • Centre de recherche bio-clinique - Clermont-Ferrand
Role of the immune microenvironment in adrenal tumorigenesis

Monika VILIMOVA • Institut de biologie moléculaire et cellulaire - Strasbourg
Study of mechanisms regulating the biogenesis of microRNAs expressed by Kaposi's sarcoma-associated herpes virus

Yanan WANG • École polytechnique - Palaiseau
The WAVE shell complex, a novel molecular machine that regulates migration persistence

11h25-11h45 • Pause-café

11h45-13h • Session 2 – Prix Hélène Starck Oral - Catégorie Post-Doctorat

Christine BARUL • Institut de recherche Sante Environnement et Travail - Rennes
Role of occupational exposure to pesticides in cancer mortality: analysis of a cohort of banana plantation workers in the French West Indies

Julie GIRAUD • Centre Paul Papin Institut de Cancerologie de l'Ouest - Bordeaux
TREM1+ CD163+ myeloid cells are potent immunosuppressive cells and associate with poor survival in human liver cancer

Marion GUÉRIN • Institut Pasteur - Paris
The immune system and the anatomical site dictate the clonal composition of developing tumor

Élise MARTIN • Gustave Roussy - Villejuif
INTERWORK - Designing an intervention to help patients return to work after breast cancer

Clémence NGUYEN-VIGOUROUX • Gustave Roussy - Villejuif
Does the concept of plasticity apply to collective migration?

13h-14h15 • Cocktail déjeunatoire

APRÈS-MIDI

14h15 • Session 3 – Prix Hélène Starck Posters

16h45 • Pause-café

18h • Fin de la session posters

Programme

Mardi 22 novembre 2022

MATIN

8h30-9h • Accueil autour d'un café

9h-10h30 • Introduction de la journée par **Nancy ABOU-ZEID,** Directrice scientifique
« Les réseaux scientifiques et professionnels des accélérateurs de carrière »

Amandine BUGNICOURT • Co-fondatrice ADOC Talent Management
Vincent MIGNOTTE • Président de l'Association Bernard Gregory (ABG)
Annabelle SUISSE • Présidente de l'association des Doctorants et Jeunes Docteurs de l'Institut Curie (ABG)
Karin TARTE • Présidente du Jury Hélène Starck 2022 & du Conseil Scientifique de la Fondation ARC - Directrice de l'unité mixte de recherche MOBIDIC - «MicrOenvironnement and B-cell : Immunopathology cell Differentiation and Cancer»

10h30-10h50 • Accueil des donateurs & testateurs

10h30-10h50 • Pause café

10h50-12h30 • Ouverture du Prix Kerner par **François DUPRÉ**, Directeur général et **Chantal LE GOUIS**, Responsable marketing
Présentations en 180 secondes des candidats suivies d'échanges avec les donateurs et testateurs

Simon AHO • Centre de Recherche en Cancérologie de Lyon
Cibler les cellules souches cancéreuses pour traiter le cancer du sein basal-like

Carlo ARELLANO • Institut de Pharmacologie et de Biologie Structurale - Toulouse
Le dialogue cellulaire entre cancer du sein et graisse voisine : une nouvelle piste contre la résistance aux traitements

Christine BARUL • Institut de Recherche Santé Environnement au Travail - Rennes
Pesticide et santé : les travailleurs de la banane qui utilisent des mélanges de pesticides auraient un risque plus important de mourir de certains cancers

Ségolène LADAIGUE • Institut Curie - Paris
Le pouvoir des tumeurs sur puces : reconstituer l'écosystème d'une tumeur sur un timbre

Alessandro MAOIRAGHI • Institut de Psychiatrie et Neurosciences de Paris
Développer un outil pour estimer les risques et les bénéficies de l'ablation chirurgicale d'une tumeur cérébrale

Khaled TIGHANIMINE • Institut Necker Enfants Malades - Paris
L'accumulation des lipides entraîne l'induction de la sénescence et de l'inflammation

Maxime VASSAUX • Institut de Physique de Rennes
Prédire pour mieux guérir : comprendre comment les sarcomes osseux se développent, avec des ordinateurs

Monika VILIMOVA • Institut de Biologie Moléculaire et Cellulaire - Strasbourg
Couper le mal à la racine : nouvelle stratégie de lutte contre un oncovirus

12h30-14h • Déjeuner de rencontre entre les jeunes chercheurs, les donateurs & testateurs, les membres du Jury et les membres de la Fondation ARC

APRÈS-MIDI

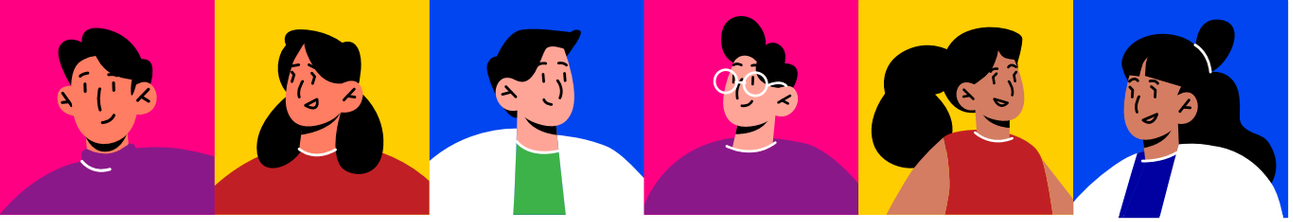
13h30-14h • Accueil institutionnel

14h-15h30 • Table Ronde Grand Public
« Patients, médecins, chercheurs : une alliance face aux cancers »

Corinne BALLEYGUIER • Radiologue, Gustave Roussy
Hélène PÉRÉ • Pharmacienne, Immunologiste et virologue, Hopital Européen Georges Pompidou
Raphaël ITZYKSON • Hématologue, Hôpital Saint-Louis
Guillemette JACOB • Fondatrice Seintinelles
Un(e) patient(e) • *Sous réserve*

15h30-16h30 • Cérémonie de remise des Prix Hélène Starck, Prix Kerner & Prix « Coup de coeur » des donateurs, par **Claude Tendil,** Président de la Fondation ARC, **Karin Tarte** Présidente du Jury Hélène Starck 2022 et le **représentant du Jury du Prix Kerner**

16h30–18h00 • Cocktail de clôture



ATELIER JEUNES CHERCHEURS

Les réseaux scientifiques et professionnels : des accélérateurs de carrière

Que ce soit pour développer ses projets de recherche, initier de nouvelles collaborations, prévoir la prochaine étape de son parcours académique, ou simplement pour trouver un emploi, ou dynamiser et faire évoluer sa carrière, disposer d'un bon réseau professionnel et scientifique est un atout précieux. Mais comment intégrer de nouvelles communautés ? Où trouver les évènements de networking ? Comment se mettre en avant, dépasser sa timidité ? Comment s'appuyer sur son réseau pour aller plus loin ? Afin de répondre à ces questions et à bien d'autres, nous avons réuni quatre personnalités investies au quotidien dans l'accompagnement des carrières des jeunes chercheurs. Lors de cet atelier, vous aurez le plaisir d'échanger avec l'audience et avec nos intervenants, et repartirez riches de nouvelles connexions !

INTERVENANTS

Amandine BUGNICOURT

Co-fondatrice Adoc Talent Management

Docteure en Sciences de la vie, Amandine Bugnicourt a co-fondé en 2008 la société Adoc Talent Management, pour favoriser l'irrigation du tissu socio-économique par les docteurs. Cette société s'est développée en France, au Benelux et au Canada autour de trois activités : le conseil RH en recrutement des docteurs pour des organisations tous secteurs, le coaching carrière et les formations pour les jeunes chercheurs, et enfin, la R&D et l'étude du devenir professionnel des docteurs. Convaincue des atouts des jeunes chercheurs, elle est aujourd'hui recruteuse, formatrice et coach carrière. Elle partagera avec les jeunes chercheurs l'évolution des secteurs et métiers ouverts aux docteurs, ainsi que des conseils pour bâtir sa carrière, notamment en développant et en mettant à profit son réseau.

Vincent MIGNOTTE

Président de l'Association Bernard Gregory (ABG)

Polytechnicien et docteur en biologie, Vincent Mignotte anime des équipes depuis 1992. Il est tout d'abord responsable d'une équipe de recherche en génétique moléculaire et hématologie au CNRS et Professeur de biologie à l'École Polytechnique et à l'École Nationale des Techniques Avancées. Dans une seconde partie de sa carrière, il se forme au coaching, puis crée une Délégation aux Cadres Supérieurs au sein de la DRH du CNRS. Pendant 6 ans, il se charge du recrutement, de l'accompagnement, de la mobilité et de la formation managériale des cadres supérieurs notamment. Il est ensuite Directeur adjoint pour l'innovation et les relations industrielles au CNRS. Enfin, depuis 2021, il dirige l'ABG où il accompagne les parcours des jeunes chercheurs et participe activement à l'animation de certaines formations.

Annabelle SUISSE

Présidente de l'Association des Doctorants et Jeunes Docteurs de l'Institut Curie (ADIC)

Annabelle Suisse a obtenu son doctorat en Biologie Cellulaire et Moléculaire à New York University en 2018 et est aujourd'hui chercheuse post-doctorante à l'Institut Curie. Elle a obtenu le premier Prix Hélène Stark de présentation orale scientifique de la Fondation ARC aux Journées Jeunes Chercheurs 2021 grâce à ses travaux sur la perte de chromosomes des cellules souches intestinales chez la Drosophile. Annabelle Suisse est également présidente de l'Association des Doctorants/Docteurs de l'Institut Curie (ADIC) et co-organise des petits-déjeuners & afterworks professionnels avec d'autres associations de jeunes chercheurs parisiens. Grâce à ces activités, elle promeut les rencontres entre jeunes chercheurs et la mise en réseau avec d'autres professionnels de la science.

Karin TARTE

Présidente du Jury Hélène Starck 2022 & du Conseil Scientifique de la Fondation ARC - Directrice de l'unité mixte de recherche MOBIDIC - « MicrOenvironnement and B-cell : Immunopathology cell Differentiation and Cancer »

Karin Tarte est professeur d'immunologie et dirige le service « Immunologie, thérapie cellulaire et hématopoïèse » du CHU de Rennes. Elle est aussi Directrice d'une unité mixte de recherche associant l'Inserm et l'université de Rennes 1. Professeure passionnée et chercheuse reconnue, elle est spécialiste des lymphomes B, et plus particulièrement du lymphome folliculaire. Convaincue de l'importance de soutenir la recherche et les jeunes chercheurs, elle assure cette année, la Présidence du Jury des Prix Hélène Starck. Enthousiaste, dynamique, et forte d'une grande expérience, Karin Tarte nourrira de riches échanges avec les jeunes chercheurs, notamment autour de l'importance des collaborations scientifiques pour la poursuite de leurs carrières.

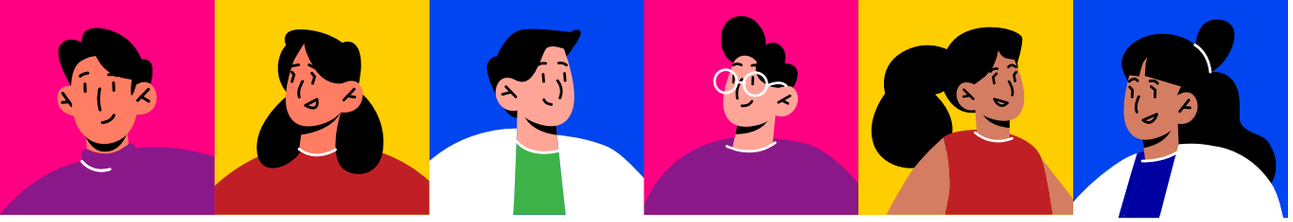


TABLE RONDE GRAND PUBLIC

Patients, médecins, chercheurs : une alliance face aux cancers

Il ne peut y avoir de recherche sur le cancer sans patients. Mais quel rôle jouent-ils et quelle place occupent-ils exactement ? De manière générale, comment s'articulent les interactions entre patients, médecins et chercheurs pour mieux faire face aux cancers ? La discussion sera menée autour de grands projets visant à améliorer le dépistage, le diagnostic et l'innovation thérapeutique, et donnera la parole aux différents acteurs de cette alliance. Les échanges porteront également sur la question de l'accès pour tout citoyen à cette démarche de recherche. Le débat sera ouvert à la participation du public.

INTERVENANTS

Raphaël ITZYKSON

Hématologue, Hôpital Saint-Louis

Raphaël Itzykson est Professeur d'Hématologie à l'Université Paris Cité et membre du département d'hématologie de l'Hôpital Saint-Louis (AP-HP.Nord), à Paris.

Membre actif de deux groupes coopérateurs français, l'Association Française de la Leucémie Aigüe (ALFA) et le Groupe Francophone des Myélodysplasies (GFM , Raphaël Itzykson s'intéresse particulièrement au développement de la médecine de précision pour traiter les leucémies aigües myéloïdes et à l'évaluation de nouveaux traitements de la leucémie myélomonocytaire chronique, une pathologie rare et sévère qui touche des personnes âgées.

Raphaël Itzykson mène, entre autres, un projet qui vise à comprendre comment la co-existence de plusieurs types de cellules leucémiques chez un patient pourrait expliquer l'émergence d'une résistance aux traitements.

Hélène PÉRÉ

Pharmacienne, immunologiste et virologue,
Hôpital Européen Georges Pompidou

Hélène Péré est docteur en Pharmacie et en biologie. Elle est maître de conférence et praticienne hospitalière dans l'Unité fonctionnelle de virologie à l'Hôpital Européen Georges Pompidou – Faculté de médecine Paris Descartes. Ses travaux portent principalement sur l'amélioration du diagnostic et de la prise en charge des patientes et des patients atteints de cancers liés à une infection par le Papillomavirus (HPV). L'un des axes de ses travaux consiste, par exemple, à identifier des signatures moléculaires propres à certaines infections à HPV, pour les mettre en relation avec la réponse à l'immunothérapie des patientes atteintes d'un cancer du col de l'utérus. Pour mener à bien ces travaux, Hélène Péré est pleinement impliquée dans la constitution de biobanques d'échantillons prélevés notamment au moment du diagnostic.

Corinne BALLEYGUIER

Radiologue, Gustave Roussy

Corinne Balleyguier est Professeure de radiologie à Gustave Roussy (Villejuif), où elle dirige le département d'imagerie médicale et du service d'imagerie diagnostique. Son implication dans la recherche se traduit par une participation à de nombreux projets qui l'ont menée, dans les deux dernières années, à cosigner une quarantaine d'articles scientifiques, notamment dans les domaines de l'imagerie innovante du sein, diagnostique et pronostique et les nouvelles techniques en mammographie comme l'angiomammographie, la tomosynthèse ou l'intelligence artificielle.

Depuis 2019, Corinne Balleyguier coordonne le volet français de l'étude internationale MyPeBS. Promue par Unicancer et financée par l'Union Européenne, cette étude vise à évaluer la possibilité d'adapter le dépistage des cancers du sein au niveau de risque de chaque femme.

Guillemette JACOB

Fondatrice Seintinelles

Guillemette JACOB est la co-fondatrice et la dirigeante de la communauté Seintinelles. Un communauté de 37 800 citoyens, anciens malades, malades, non malades et chercheurs, qui s'engagent, ensemble pour une recherche contre le cancer plus rapide et plus proche des attentes et des besoins des citoyens. Elle s'interroge donc au quotidien sur la place des citoyens dans la recherche, sur les outils et les méthodologies disponibles pour les engager, les impliquer, et sur les changements culturels à insuffler aussi bien chez les citoyens que chez les chercheurs et les médecins, pour que la collaboration soit fructueuse. Elle est diplômée de l'EM Lyon et travaille depuis 25 ans dans le marketing digital.

Avec la présente d'un(e) patient(e) • *Sous réserve*

26e Journées Jeunes Chercheurs en Cancérologie

Prix Hélène Starck Oral

Catégorie Doctorat

AMALRIC Amandine

Scientific supervisor : Sylvain LEHMANN
Institute : Institut des Neurosciences - Montpellier
Team : Protéinopathies

“Epitranscriptomics”: a promising source of circulating biomarkers for personalized medicine

Despite significant progress in targeted therapies, colorectal cancer (CRC) remains a major cause of mortality and morbidity worldwide. Identification of accurate biomarkers could improve diagnosis and promote personalized medicine. Recently, cancer-associated alteration of RNA marks has emerged as a promising source of diagnostic and prognostic biomarkers. Epitranscriptomics is an emerging field that encompasses more than 150 chemical modifications in all types of RNA. These modifications fine-tune gene expression and play a role in key cellular processes in both physiological and pathological contexts. Therefore, a growing number of studies have connected variations of specific modified nucleoside levels in biopsies with cancer onset and progression. Our goal is to exploit multiplex targeted mass spectrometry in order to establish RNA modification patterns that could be used for early CRC diagnosisand patient stratification.

A method using coupled liquid chromatography with tandem mass spectrometry (LC-MS/MS) has been developed and optimized to quantify RNA modifications from solid and liquid biopsies (plasma/serum). The innovation lies in the fact that we analyze 35 RNA modifications simultaneously in order to establish an «epitranscriptomic signature». A machine learning algorithm able us to stratify patients and to determine the predictive power of these biomarkers. As a proof-of-concept, we have analyzed blood samples from a cohort of 41 CRC patients at different stages of the disease (Adenoma and grades 0, I,II, III, IV) and 20 healthy donors as controls.

12 modifications were successfully detected in circulating RNA (cRNA) and 20 as free nucleosides (free-nuc). Interestingly, using “epitranscriptomic signature”, the prediction of the healthy / CRC status reaches an accuracy of 91.7% and 100% from cRNA and free-nuc data, respectively. This study shows that nucleoside quantification by multiplex targeted MS approaches could help early diagnosis of CRC . A bigger cohort will be soon analyzed to validate the use of our “epitranscriptomic signature” for early CRC detection as well as patient stratification (e.g. discriminate cancer grades or types, such as BRAF mutated).

BIBER Pierric

Scientific supervisor : Marcel DECKERT
Institute : Centre méditerranéen de médecine moléculaire - Nice
Team : Microenvironnement et cancer

The mechanically-activated deubiquitinase USP9X controls melanoma invasiveness and drug response through YAP stabilization

The Ubiquitin-Proteasome-System (UPS) uses ubiquitin to address for proteasomal degradation. Deubiquitinases (DUBs) remove ubiquitin from their targets to prevent their degradation and with the UPS, they are gatekeepers of protein homeostasis. DUBs can be hijacked to modulate oncogenic pathways, enhancing cell proliferation and/or invasion.

Cutaneous melanoma exhibits a high propensity to form metastasis that are highly resistant to targeted therapies. We have recently shown that extracellular matrix (ECM) stiffening and mechanotransduction play a major role in proliferation, migration and drug-resistance of melanoma cells through the mechanosensor YAP.

To identify DUBs involved in melanoma mechanotransduction, we used cell lines cultivated on collagen matrices with various stiffnesses combined with an activity-based ubiquitin probe for profiling DUB activity. Using this approach and quantitative proteomic, we identified USP9X as a DUB whose activity is increased by collagen stiffness. In silico analysis further revealed that YAP belongs to the USP9X interactome and showed a correlation between USP9X expression and YAP transcriptional signature in melanoma. We thus hypothesized that USP9X regulates YAP levels in melanoma cells through its DUB activity. Consistently, siRNA-mediated depletion and pharmacological inhibition of USP9X decreased YAP expression at protein but not mRNA levels. Conversely knockdown of the E3 ligase βTRCP increased YAP protein expression. A GST-TUBE pulldown approach revealed that combined USP9X and proteasome inhibition increased YAP poly-ubiquitination, indicating that USP9X deubiquitinates YAP to prevent its proteasomal degradation. In line with a role of USP9X in mechanotransduction upstream of YAP, USP9X targeting was found to impair stiffness-induced responses including YAP nuclear translocation and transcriptional activity, cell migration and invasion. Finally targeting USP9X enhances BRAF inhibitor efficacy, counteracts drug-induced collagen remodeling and delays tumor relapse in a syngeneic melanoma mice model.

Our results reveal an original role of USP9X in melanoma invasiveness and mechanoresistance through stiffness-dependent stabilization of the oncoprotein YAP. We therefore propose USP9X as a “mechano-DUB” in melanoma.

BRUCIAMACCHIE Marine

Scientific supervisor : Christel LARBOURET
Institute : Institut de recherche en cancérologie de Montpellier - Montpellier
Team : Drug resistance and new cancer treatments

Synergistic effect of FOLFIRINOX with an ATR inhibitor on pancreatic tumor cells and its microenvironment

Pancreatic Ductal Adenocarcinoma (PDAC) is an extremely aggressive disease. Recently, a new polychemotherapy oxaliplatin-based (FOLFIRINOX) has been approved. It has showed a significant increase of the overall survival in patients compared to gemcitabine, but associated with more toxicity and still limited efficiency. Most chemotherapies induce their toxicity by provoking DNA damages and replicative stress, leading to the activation of DNA repair pathways.

That is why our research project proposes to find a synergistic association of FOLFIRINOX with a specific inhibitor of DNA damage repair - Ataxia Telangiectasia and Rad3 related inhibitor (ATRi) – to increase the efficiency of the chemotherapy while reducing its toxicity. The resistance to chemotherapy can come from the stroma that represents up to 90% of the tumor mass, therefore the impact of the chemotherapies on the microenvironment can be a key to increase the efficiency of these treatments. In order to be as close as possible to the clinic, the impact of our combination is studied _in vitro_ in 3D co-culture models of tumor cells associated with microenvironment cells, more particularly cancer-associated fibroblasts (CAFs).

We demonstrated a synergistic effect of the association _in vitro_ (2D and 3D) independently of mutation status in several pancreatic models (ATCC and derived from PDX) and in co-culture with CAFs. We observed chemoresistance from the CAF and a protection of the tumor cells in co-culture. Higher DNA damage were observed in tumor cells treated with FOLFIRINOX combined with ATRi compared to FOLFIRINOX alone. These results were associated with a decrease of DNA damage repair pathways leading to apoptosis. _In vivo_, the association FOLFIRINOX with ATRi significantly inhibits the tumor growth compared to each treatment alone, in both immunodeficient and immunocompetent models. We also observed more immune infiltration in tumors treated with the association compared to the chemotherapy alone. The localization and the nature of infiltrating immune cells are now under investigation.

To conclude, our work shows that FOLFIRINOX associated with an ATRi is highly synergistic_ in vitro_ in our co-culture models and _in vivo_. This association could be a new therapeutic strategy in order to increase the survival of patients with PDAC for whom only a few solutions have been found until now and that is why this cancer represents a major challenge of public health today.

CHABAB Ghita

Scientific supervisor : Virginie LAFONT
Institute : Institut de recherche en cancérologie de Montpellier - Montpellier
Team : Immunité et cancer

Regulatory γδ T cells in solid cancer : characterization, role and ecosystem

γδ T cells contribute to the anti-tumor immunity within the tumor microenvironment (TME) in various cancers. Despite their well-described effector functions, recent studies correlated their presence in the TME with solid tumor progression suggesting that γδ T cells may display pro-tumor activities. My project aims to characterize those pro-tumoral or regulatory γδ T cells and decipher their role in cancer.

We demonstrated in vitro that inflammatory signals promote the development of a regulatory γδ T cell sub-population characterized by the expression of CD73 and displaying immunosuppressive functions through the production of immunosuppressive molecules such as IL-10, adenosine and the angiogenic and chemotactic factor IL-8. The challenge associated with the characterization of CD73+ γδ T cell resides in assessing their existence in vivo as well as their relevance in human cancers. We showed in human breast cancer that ~20% of γδ tumor infiltrating lymphocytes (TILs) expressed CD73 and displayed the same immunosuppressive functions as described in vitro, suggesting that they could promote tumor development via these mechanisms. In line with these observations, we showed that the presence of γδ TILs is associated with late tumor grades in breast cancer. We extended such observations to ovarian cancer and showed that the density of CD73+ γδ TILs negatively correlates with patient survival, suggesting that CD73+ γδ TILs density could be used as a prognosis factor. Using Imaging by Mass Cytometry, we are now investigating the cellular networks of regulatory γδ TILs (CD73+) and their effector counterpart (CD73-) in breast and ovarian tumors to better understand their role in cancer. Our data show different immediate ecosystems for CD73+ compared to CD73- γδ TILs, with more cancer-associated fibroblasts in contact with CD73+ γδ TILs, while CD73- γδ TILs interact more with activated αβ TILs reinforcing the idea that CD73+ and CD73- γδ T cells are functionally different.

Altogether, these data improve our knowledge on human γδ T cell immunobiology during cancer development, with the in-depth characterization of the new regulatory γδ T cell subset, their localization and their functions within the TME.

CHAR Remy

Scientific supervisor : Philippe PIERRE
Institute : Centre d'immunologie de Marseille-Luminy - Marseille
Team : PPlab

Characterization of RUFY3 protein in Dendritic Cells and macrophages: Potential modulator of autophagy and immunity

Autophagy is a central regulator of metabolism and inflammation, as well as an important proteolysis node for the treatment of antigeni peptides. This pathway is essential in the host's response to infection and interfaces with almost all aspects of innate and adaptive immunity. Dendritic cells (DC), which are powerful orchestrators of T cells response to antigenic presentation, require significant autophagic activity.

We focused on several poorly characterized genes involved in the regulation of endocytosis and autophagy in DC, among which rufy3. RUN and FYVE domain-containing protein (RUFY) participate in endosome dynamic and membrane trafficking by interacting with small G-Proteins and lipids by RUN and FYVE domains, respectively. RUFY3 is mainly expressed and studied in the brain but doesn't have FYVE domain.

However, no studies have been done in immunology. This is the reason why I tried to decipher the fundamental molecular mechanisms controlled by RUFY3 and unravel its importance for immunity. We first found that in Immune cells, RUFY3 is found as a unique

isoform with a functional FYVE domain. In addition, upon stimulation, the level of rufy3 mRNA and protein is significantly higher. Plus, this isoform is located in lysosomes and its deletion alters lysosome localization and autophagic flux. To prove the action of RUFY3 in endolysosomal pathway, we challenged macrophages rufy3-/- with S.enterica, known to use lysosome to replicate, and proved that RUFY3 is located in salmonella containing vacuole and it's required for bacterium replication. Also, we tested in vivo Acute Lung Inflammation model with E.coli and observed that CD11c-Cre-rufy3loxp/lox mice have higher inflammation and presents more clinical pain.

Actually, we found in multiple myelome patient that high _rufy3_ expression is associated with poor progonisis and particulary with bortezomib resistance. These results encourage us to continue and may suggest that RUFY3 have a specific function in immune cells. The effect of RUFY3 on trafficking and autophagy could help us to better understand the fundamental mechanisms involved in host-pathogen interaction. Plus, iRUFY3 could potentially act as an effector in multiple myeloma cancer.

FERNANDES Gonçalo

Scientific supervisor : Nathalie DOSTATNI
Institute : Institut Curie - Paris
Team : Epigenetic Plasticity and Polarity of the Embryo

Synthetic reconstruction of the hunchback promoter identifies the roles of Bicoid, Zelda and Hunchback in the dynamics of its transcription

As most tumor cells have generally lost their identity, a key question in the context of cancer, is to understand how cell identities are established and maintain during development. In many developmental systems, cell identity is determined by morphogen gradients providing concentration-dependent positional information along polarity axes. Although the critical role of these gradients is well recognized, it is unclear how they can provide reproducible expression patterns despite the stochastic nature of transcription. To address this question, I studied the response downstream of the Bicoid (Bcd) morphogen gradient in fruit fly embryos, focusing on its main and earliest target gene, _hunchback _(_hb_). I used the MS2-MCP system to fluorescently tag nascent mRNA and analyse transcription dynamics at an unprecedented spatiotemporal resolution in living embryos. Adapting this approach to synthetic MS2 reporters with various combination of DNA binding sites, my work highlighted the roles of Bcd and its partners, Hb and Zelda (Zld), in the transcription mechanism. Expression of a reporter with only nine Bcd binding sites reproduces the hb-MS2 reporter pattern, except for the very steep expression boundary and the speed to reach steady-state. This suggests that Bcd alone defines the positioning of the boundary but not its steepness nor the speed of its establishment. In addition, binding of Bcd's partners to the promoter speed-up the process by acting in different steps of the transcription mechanism: i) Hb synergizes with Bcd by reducing transcription burstiness and increasing the polymerase firing rate; ii) Zld lowers the Bcd concentration threshold required for Bcd-dependent expression.

In collaboration with physicists, a physical model of Bcd-dependent expression was developed providing a theoretical framework for the experimental data. This model showed that the very rapid establishment of the _hb _expression boundary can be solely explained by an equilibrium involving the binding of Bcd molecules to their NA-binding sites for positional information and requiring Zld and Hb for its temporal dynamics.

Finally, reducing the dose of Bcd by half and quantifying the corresponding shifts of Bcd-dependent reporter boundaries confirms that Bcd is the main source of positional information for _hb expression but argues that the decay length of the protein gradient is larger than the decay length of the transcriptionally active protein.

OLABE Julie

Scientific supervisor : Pierre VAL
Institute : Centre de recherche bio-clinique - Clermont-Ferrand
Team : Pathophysiologie moléculaire des tissus surrénaux et endocriniens

Role of the immune microenvironment in adrenal tumorigenesis

In contrast with most cancers, adrenocortical carcinomas (ACC) are more frequent in women than men, but the underlying mechanisms of this sexual dimorphism remain elusive. Homozygous deletion of the negative WNT pathway regulator ZNRF3 is the most frequent alteration in ACC patients. Our results show that Cre-mediated inactivation of Znrf3 in steroidogenic cells of the mouse adrenal cortex is associated with sexually dimorphic tumour progression. Indeed, although most knockout female mice develop metastatic carcinomas over an 18 month-time course, adrenal hyperplasia gradually regresses in male knockout mice. This male-specific regression is associated with induction of senescence and recruitment of macrophages, which differentiate as active phagocytes that clear-out senescent preneoplastic cells. Macrophage recruitment is also observed in female mice. However, it is delayed and dampened compared to males, which allows for tumour progression. Interestingly, testosterone treatment of female knockouts is sufficient to induce senescence, recruitment of phagocytic macrophages and regression of hyperplasia. We further show that although macrophages are present within adrenal tumours at 18 months, MERTKhigh active phagocytes are mostly found in indolent lesions in males but not in aggressive tumours in females. Consistent with our observations in mice, analysis of RNA sequencing data from the TCGA cohort of ACC shows that phagocytic macrophages are more prominent in men than women and associated with better prognosis. Altogether, these data establish that phagocytic macrophages prevent aggressive ACC development in male mice and suggest that they may play a key role in the unusual sexual dimorphism of ACC in patients.

VILIMOVA Monika

Scientific supervisor : Sébastien PFEFFER
Institute : Institut de biologie moléculaire et cellulaire - Strasbourg
Team : ARN non codants et infections virales

Study of mechanisms regulating the biogenesis of microRNAs expressed by Kaposi's sarcoma-associated herpesvirus

MicroRNAs (miRNAs) are important regulators of gene expression involved in all aspects of cell biology. The biogenesis of these molecules is tightly controlled by numerous regulatory mechanisms allowing to express precise amounts of functional molecules adapted to their physiological functions. Indeed, deregulation in miRNA expression has been associated to many pathologic conditions, including cancer. Several human viruses also encode viral miRNAs that help them to optimize infection conditions and modulate cell environment to favor viral replication. Among them, the oncogenic Kaposi's sarcoma-associated herpesvirus (KSHV) expresses twelve miRNAs to convert host cell processes, such as proliferation, cell cycle and immune response, to its own advantage and thereby maintain latent infection which is the main factor for KSHV-induced oncogenesis. As a consequence, KSHV miRNAs are directly involved in cell transformation. Moreover, inhibition of KSHV miRNAs would not only decrease the tumorigenic potential of the virus, but also enable to mitigate the infection itself. It is therefore crucial to understand the mechanisms driving and regulating the biogenesis of these molecules. Our study focuses on the regulation of a cluster of ten viral miRNAs which have the specific feature of being transcribed as a polycistron. Polycistronic transcription allows not only to produce all the miRNAs from one single precursor, but also favors development of peculiar post-transcriptional mechanisms that fine-tune the processing of individual miRNAs. The aim of our work is to understand these mechanisms in order to counteract the virus. We have recently discovered a regulatory mechanism operating at the level of the KSHV polycistronic miRNA transcript that enhances the processing of all the miRNAs expressed from the cluster. This is based on the presence of two of the miRNA precursors (pre-miRNAs) on the transcript serving as cis-regulatory elements. We have shown that

their activity is required for the entire cluster expression since their deletion leads to a global decrease of all the miRNAs. We have also developed an approach to inhibit the processing of one of them, pre-miR-K1, and thus impact the expression of the miRNA cluster as a whole. This method based on targeting pre-miR-K1 via antisense oligonucleotides was exploited in KSHV infected cells showing that this strategy could be further adapted for therapeutic purposes.

WANG Yanan

Scientific supervisor : Alexis GAUTREAU
Institute : École polytechnique - Palaiseau
Team : Cytogénèse et morphogénèse cellulaire

The WAVE shell complex, a novel molecular machine that regulates migration persistence

The RAC1-WAVE-Arp2/3 signaling pathway generates branched actin networks that power lamellipodium protrusion of migrating cells. Feedback is thought to control protrusion lifetime and migration persistence, but its molecular circuitry remains elusive. Using roteomics, we identified PPP2R1A among proteins differentially associated with the WAVE complex subunit ABI1 when RAC1 was activated and downstream generation of branched actin was blocked. PPP2R1A was found to associate at the lamellipodial edge with a novel form of WAVE complex, the WAVE Shell Complex (WSC), that contains NHSL1 instead of the Arp2/3 activating subunit WAVE as in the canonical WAVE Regulatory Complex (WRC). PPP2R1A was required for persistence in random and directed migration assays and for RAC1-dependent actin polymerization in cell extracts. PPP2R1A requirement was abolished by NHSL1 depletion. PPP2R1A mutations found in tumors impaired WSC binding and migration regulation, suggesting that this novel function of PPP2R1A is critical for its tumor suppressor activity.

26e Journées Jeunes Chercheurs en Cancérologie

Prix Hélène Starck Oral

Catégorie Post-Doctorat

BARUL Christine

Scientific supervisor : Luce DANIELE
Institute : Institut de Recherche Santé Environnement et Travail - Rennes
Team : Épidémiologie en Santé au Travail et Ergonomie (Ester)

Role of occupational exposure to pesticides in cancer mortality: analysis of a cohort of banana plantation workers in the French West Indies

Background:The increasing use of pesticides over the last decades and theirdissemination in the environment have raised major concerns amongpopulations and public authorities. Little is known about long-termhealth effects of pesticides exposure on agricultural workers,particularly in tropical environments, where climatic conditions leadto heavier use of these substances than in temperate areas.ObjectiveWe examined the role of multiple exposure to pesticides on cancermortality in banana workers.MethodsData come from a retrospective cohort study of banana workers in theFrench West Indies who were followed up for mortality from 1 January1973 to 31 December 2017. Pesticide exposure was assessed using abanana-specific crop-exposure matrix. A total of 8,007 subjects withcomplete exposure data were included in the study. The role ofpesticide exposure profiles (identified with classification methods)and pesticide mixtures were examined using Cox and quantileg-computation models. The role of each pesticide, after adjustment forother pesticides, was also investigated using hierarchical Bayesianmodels, which overcome the problem of strong correlations betweenexposures.ResultsTwo profiles of subjects were identified: light vs heavy users of acocktail of pesticides. Compared to light users, heavy male usersshowed an increased mortality by hematological malignancy (HR=2.19 95%IC 1.22-3.91) particularly by non-Hodgkin lymphoma (HR=1.83 95% IC1.01-3.34). In the quantile g-computation model, the simultaneous 25%increase in pesticide exposure levels was associated with an excess ofdeaths from hematological malignancy, particularly among farm owners.Preliminary analyzes of the different pesticides did not show anyassociation for this last location. ConclusionOur results suggest a deleterious role of exposure to a mixture ofpesticides at high levels in mortality from hematological malignancy,particularly in men and farm owners, without being able to implicate aspecific pesticide.

GIRAUD Julie

Scientific supervisor : Maya SALEH
Institute : Centre Paul Papin Institut de Cancerologie de l'Ouest - Bordeaux
Team : Immunology of Cancer and Inflammatory Diseases

TREM1+ CD163+ myeloid cells are potent immunosuppressive cells and associate with poor survival in human liver cancer

Hepatocellular carcinoma (HCC) is among the deadliest cancersworldwide. It is an inflammation-associated cancer arising from viraland non-viral etiologies. The clinical trials for the treatment ofadvanced HCC has recently shifted to the field of immunotherapy.However, despite significant therapeutic advance, ~75% of patients donot respond to immune checkpoint inhibitors (ICI) for unclear reasons.Recently, a meta-analysis showed a superior efficacy of administeringICI in virally infected patients compared to the metabolicsyndrome-associated non-alcoholic steatohepatitis affected patients.This suggests that the tumor microenvironment of HCC is an important-determinant of therapeutic success and highlight the need to furtherexplore human liver-specific immunity towards the identification oftheranostic immune biomarkers for patients' stratification and novelimmunotherapies. Expansion of suppressive myeloid cells is a hallmarkof chronic inflammation and cancer. Their heterogeneity in HCC is notfully resolved and might underlie immunotherapy resistance.In this study, we setup to discriminate and localize human-liver-specific innate immunity cells to improve the stratification andthe treatment of patients with HCC. We implemented single cell RNA-seqon purified CD45+panTCRαβ-CD19- cells freshly isolated from tumoraland juxta-tumoral tissues from patients with HCC of differentetiologies, and performed spatial transcriptomics. We validated ourresults by multiplex immunofluorescence, by functional analysesperformed on ex-vivo FACS-sorted cells co-cultures, on a mouse modelof HCC, and by computational analyses of published HCC data sets. Wereport a high-resolution atlas of innate immunity cells in HCC andunravel a strong myeloid bias in NK cell differentiation and aremarkable myeloid cell heterogeneity. In particular, among threephenotypically distinct subsets of myeloid-derived suppressor cells(MDSC), we show that TREM1+CD163+ MDSC are the most potentimmunosuppressive subset ex vivo and expand in models of liverinflammation and fibrosis in vivo. They highly produce TGFb and arespatially localized at liver fibrotic lesions. A specific genesignature defining TREM1+CD163+ MDSC correlate with poor patientsurvival in HCC and response to immune checkpoint blockade indifferent cancers. Collectively, our data support myeloidsubset-targeted immunotherapies to treat HCC.

GUÉRIN Marion

Scientific supervisor : Philippe BOUSSO
Institute : Institut Pasteur - Paris
Team : Dynamique des réponses immunes

The immune system and the anatomical site dictate the clonal composition of developing tumor

Tumor development stems from a complex evolutionary process notablylinked to genomic and/or chromosomal alterations and to selectiveprocesses for cell survival and proliferation. While immune systemalso exerts a selective pressure on tumor cells, the extent to whichimmune components shapes the genetic alterations and the diversity ofemerging tumors remains to be fully understood.Here, we demonstrate that the diversity and genomic landscape oftumors is strongly shaped by the immune system and by the anatomicalsite of tumor development. By tracking the genetic evolution of earlytransformed B cells in distinct hosts using whole exome sequencing, weestablished that the immune system has a drastic impact on tumorclonal diversity and mutations. In parallel, we developed a multicolorbarcoding strategy to visualize and quantify clonal heterogeneity invivo. We show that the anatomical site of tumor development alsoexerted a strong selective pressure on tumor subclones. Anatomicaldifferences in clonal selection were also evident during therapy in amodel of anti-CD19 CAR T cells. We propose that the immune system andthe anatomical site dictate the clonal dynamics of a developing tumor.

MARTIN Élise

Scientific supervisor : Fabrice ANDRÉ
Institute : Gustave Roussy - Villejuif
Team : Breast Cancer Survivorship Group

INTERWORK - Designing an intervention to help patients return to work after breast cancer

Breast cancer (BC) is the most frequent cancer in women. BC detectionand care management have strongly improved during the past decades andnow in France, 86% of BC patients will live more than 5 years afterdiagnosis. At time of diagnosis, 32% of women are < 55 years old and20% are < 50 years old. Thus, a large part of the women diagnosed witha BC are still working, and the disease is likely to impact theirprofessional life. After diagnosis, there is usually a period of sickleave of several months motivated by the acute effects of BCtreatments and many patients will be at risk of not returning to workafter that period. Work trajectory may impact other aspects of thewoman's life, including her well-being, her material situation andher social life. Return to work (RTW) is often seen by cancersurvivors as an important part of their recovery.Return to work (RTW) after breast cancer (BC) can be a major challengefor patients. Multidisciplinary interventions seem to be effective butthe role of digital solutions is under-developed and therefore notevaluated. We explored the preferences, needs, and barriers regardingRTW interventions, including opinions about the use of digitalapproaches to deliver such interventions.We conducted a qualitative study based on interviews with 30 patientswith BC and 18 healthcare providers in four French regions. Emergentthemes were identified using thematic content analysis.Most providers declared that they did not proactively address RTW withpatients, mainly due to having other priorities and a lack ofknowledge. The following themes emerged: several development anddeployment barriers regarding RTW interventions exist,multidisciplinary interventions are preferred, and there is a need tomaintain contact between the patient and workplace during sick leave,including pathways and interlocutors that can facilitate RTW.Participants had mostly positive representations of using digitaltools to facilitate RTW; however, fear of loss of human contact andthe exacerbation of inequalities were identified as possible risksassociated with the development of digital-only interventions.Interventions blending the needs and preferences of patients with BCand the healthcare system are warranted. A personalized multimodalapproach with mixed digital and in-person features has surfaced as apossible solution to address the weaknesses of existing interventions.

NGUYEN-VIGOUROUX Clémence

Scientific supervisor : Fanny JAULIN
Institute : Gustave Roussy - Villejuif
Team : Invasion Collective

Does the concept of plasticity apply to collective migration ?

Migration is crucial for many physiological processes and deregulatedin numerous diseases, including cancer metastasis. Long considered asinitiated by a single cell, metastases also result from the collectivemigration of tumoral cohorts. To date, three modes of migration aredescribed: two modes of single cell migration based either on adhesionand traction (mesenchymal) or on propulsion and actomyosincontractility (amoeboid), and a collective mode relying on theadhesion and traction of the group. Yet, the study of patients'samples revealed tumoral cohorts invading the stroma and lymphaticvessels in the absence of adhesion to the environment. Our teamdiscovered a second mode of collective migration powered by propulsionand polarized contractility.Since only one mode of collective migration was described so far,whether cell groups, similarly to single cells, could be plastic andexploit both traction- and propulsion-based migration has never beenaddressed.Here, by observing in real time the migration of cancer cellcollectives in microfabricated devices, we demonstrate that collectivemigration plasticity exists. Mesenchymal cells migrate by adhering and remodeling the extracellularmatrix while amoeboid cells squeeze between narrow gaps withoutadhesion. We first showed that preventing adhesion either bypassivating microchannels walls with PEG or by inhibiting ß1integrins, induced a switch of cancer cell clusters from traction- topropulsion-based migration. Second, confinement was shown to increasesingle cell contractility, converting mesenchymal cells to amoeboidmigration, while reducing contractility switches amoeboid cells totraction-based migration. Inhibiting contractility converted cancercell clusters from propulsion- to traction-based collective migrationin microchannels. Last, our mice models of peritoneal carcinomatosissuggested that collective plasticity in neither an advantage nor adisadvantage for the seeding metastases. It might rather be commonfeature highjacked by tumor cell clusters to invade efficiently.Unveiling the determinants of collective plasticity will generate newtargets to inhibit cancer invasive behavior andimprove patient outcome.

26e Journées Jeunes Chercheurs en Cancérologie

Prix Hélène Starck Poster

Catégorie Master

ARELLANO Carlo

Scientific supervisor : Olivier NEYROLLES
Institute : Institut de pharmacologie et de biologie structurale - Toulouse
Team : Interactions des mycobactéries avec les cellules-hôte

Role of tumor-surrounding adipocytes in the aggressiveness of a metabolic subtype of triple negative breast cancer

Triple-negative breast cancers (TNBC), defined by the absence ofhormonal and HER2 receptors, are an heterogeneous group of cancers.TNBC have a poor prognosis due to their aggressiveness and highmetastatic potential. They represent a major therapeutic challengesince, in case of resistance to chemotherapy, survival is dramaticallyreduced. Understand the factors underlying the heterogeneity of thesetumors is essential. Recently, a metabolic classification of TNBC hasbeen proposed using a large cohort of patients, heterogeneity alsofound in TNBC cell lines (Gong et al, Cell Metabolism, 2021). The MPS2metabolic subtype that is of poorer prognosis exhibit a high abilityto uptake exogenous fatty acid (FA), suggesting that their interactionwith tumor-surrounding adipocytes, a lipid reservoir, might stimulatetheir aggressiveness and drug resistance. To study this cross-talk, weused a new 3D culture model of human primary mammary adipocytesrecently set up in our team. Interestingly, we show that, whencocultivated with adipocytes, the MPS2 sub-group accumulates higherlevels of FA than the two other sub-groups. As the cell linesrepresentative of different MPS can all induce FA secretion byadipocytes (a process called lipolysis) at similar levels, thisincrease of FA uptake by MPS2 cells can be due to an upregulation oflipid transporter, as suggested by a software providing the geneexpression of these proteins. In MPS2 sub-type, lipid accumulation isincreased by an inhibitor of the FA transport into mitochondriasuggesting that the captured FA are used for mitochondrial FAoxidation (FAO). We then investigated the effect of FA secreted byadipocytes on the drug sensitivity of the MPS sub-types. In contrastto the saturated FA palmitic acid, exposure of cancer cells to themonounsaturated FA oleic acid specifically protects the MPS2 cellsagainst doxorubicin-induced toxicity whereas the sensitivity topaclitaxel and mafosfamide was unchanged. Since doxorubicin can inducecell death by ferroptosis, our results suggest that the change in FAcontent, in addition to the reduced oxidative stress induced by FAO,might modulate ferroptosis in MPS2 cells. To conclude, our resultsshow that the interaction of MPS2 cells with tumor-surroundingadipocytes contribute to chemoresistance and explain their poorprognosis. Validation of this pathway in human tumors might offer newopportunities to treat these aggressive diseases.

ARQUE Basilia

Scientific supervisor : Audrey LUPO
Institute : Centre de recherche des Cordeliers - Paris
Team : Inflammation, complément et cancer

Small cell lung cancer molecular characterization and immune environment

Small cell lung carcinoma (SCLC) is a high-grade neuroendocrinecarcinoma with a very poor prognosis. Immunotherapy is now prescribedin association with chemotherapy in disseminated SCLC. The prognosticand predictive roles of the immune environment is currently indiscussion. Moreover, there is few reports that focused on theassociation between the molecular classification and the immuneenvironment.The aim of our study is to characterize the immune environment ofSCLC, to evaluate its association with clinical and biologicalparameters, including molecular classification, and to determine itsprognostic role in a cohort of patients with SCLC.We did a retrospective single-center study, including patients withSCLC operated for curative (N=26) or diagnostic intent (N=22) atCochin Hospital between 2008 and 2018. Clinical and histological data,including DLL3 and PD-L1 expression, were analyzed. Simpleximmunohistochemistry targeting ASCL1, NEUROD1 and YAP1 was performedto establish the molecular classification. We developed two 7-pleximmunohistochemistry to characterize the immune environment, focusingon T cells (CD8, CD4, Granzyme B, TIM3, TIGIT, PD1), B and plasmacells (CD20, CD27, CD3, MUM1, CD40 and CD40 ligand).We showed that the immune environment is very heterogeneous in SCLC,as in non-small cell lung cancer (NSCLC). The density of immunepopulations in early stage was significantly higher than in metastaticstage. The density of immune populations was significantly higher inlong-time survivors (survival greater than 2 years), compared withother patients. We did not find a significant association between theimmune environment and the molecular classification. In univariateanalysis, stage, immune cells PD-L1 expression, NEUROD1 expression,presence of tertiary lymphoid structure and CD4+ T cell density wereassociated with overall survival and only stage, NEUROD1 expressionand TLS were independent prognostic factors.We have shown that the immune environment of SCLC identifies long-timesurvivors and seemed not associated with the molecular classification.It would now be interesting to evaluate whether the immune environmentallows the identification of patients who respond to immunotherapy.

LOYAUX Romain

Scientific supervisor : Ivan SLOMA
Institute : Institut Mondor de Recherche Biomédicale - Créteil
Team : Oncogenèse des lymphomes et tumeurs de la Neurofibromatose 1

Clonal architecture of refractory angioimmunoblastic T-cell lymphoma (AITL) : an ancillary study of ORACLE trial

Angioimmunoblastic lymphoma (AITL) is the mostprevalent peripheral T-cell lymphoma in Europe, with a poor prognosisdue to frequent relapse. The molecular landscape of AITL shows twopredominant altered pathways: mutations in the TCR signaling pathway(_RHOAG17V_) and epigenetic modifiers such as _TET2_, _DNMT3A_, and_IDH2_. Few case reports suggest that AITL may be initiated by amutation acquired in an immature bone marrow (BM) progenitor. The study aims to determine the frequency of AITLderived from clonal hematopoiesis (CH) in an ancillary study of therandomized Phase 3 clinical trial, ORACLE (NCT03593018), evaluatingthe efficacy and safety of oral azacitidine (CC-486) compared tosingle-agent chemotherapy in patients with relapsed or refractoryAITL. To determine the clonal architecture of refractoryAITL, bone marrow progenitor cultures from 31 patients were performed.Overall, 517 single cell-derived colonies were genotyped by NGS.Meanwhile, total BM cells (bulk) from 29 patients were sequenced withthe same panel of 44 genes, and then compared to _cfDNA_ and lymphnode (LN). 471/517 (91%) colonies were successfully genotyped. CHdefined by at least one somatic mutation detected in the BM or myeloidcolonies was found in 29/31 (93.5%) patients. The proportion ofpatients carrying _DNMT3A_ mutations in the BM (75%) was significantlyhigher (Fisher's test = FET; _P = 0.003_) as compared with thefrequency in LN (33%). Conversely, _TET2_ mutations were more frequent(_P = 0.007_; FET) in the LN (89%) than in the BM (56%). Hotspotmutations _RHOAG17V_ and _IDH2R172G_ were never detected in myeloidcolonies. Three groups of patients were identified according to thedistribution of mutations found in the BM and the LN: 16/31 (52%)patients had AITL clonally derived from CH (CH-related AITL), 13 (42%)had CH unlinked to AITL (CH-unrelated AITL), and two patients (6%) hadno CH. CH-related AITL patients had an increased proportion of mutatedBM progenitors as compared with CH-unrelated AITL (51% ± 9, 20% ±7%, Mann-Whitney test, _P = 0.004_). These patients also carried muchmore _TET2_ mutations in the BM (15 vs. 2; _P < 0.0001_; FET).Biallelic_ TET2_ mutations (n=8/16 patients) and double mutant (_TET2+ DNMT3A_; n=9) colonies were exclusively identified in CH-relatedAITL patients. In conclusion, AITL was initiated in a hematopoieticstem cell in more than half of the patients tested. The prognosissignificance of this condition is currently evaluated in ORACLE Trial.

MATHIOT Laurent

Scientific supervisor : Christophe BLANQUART
Institute : Centre de recherche en cancérologie et immunologie Nantes-Angers - Nantes
Team : Team 1

Study of first line therapies on the molecular profile of non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is the leading cause of deathworldwide. Current first-line chemotherapy treatments will result inchanges in the transcriptome and miRNome of tumour cells. Ourobjective was to study the impact of these treatments on the molecularprofile of NSCLC cells. We performed three-dimensional culture models,from a patient-derived cell line, four treatments with first-linechemotherapy, carboplatin and pemetrexed. We extracted RNAs that weanalyzed by transcriptome and miRNome sequencing. We were able todemonstrate overexpression of CD274 encoding PD-L1, a target of immunecheckpoint inhibitors, and of NECTIN4, encoding the transmembraneprotein Nectin-4, which makes it a potential therapeutic target.Nectin-4 is also a ligand of TIGIT, a second immune checkpoint.Confocal imaging labeling of PD-L1 confirms the expression of theprotein. These results are being confirmed in other tumor lines. ThemiRNome found overexpression of miR-22-3p and underexpression ofmiR-15b-3p which appear as potential biomarkers. We finally realized arelapse model by expanding the previously treated cells, which can bestudied later. In conclusion, our study has identified a potential newtherapeutic target, Nectin-4, as well as two miRs of interest.

MOIRAGHI Alessandro

Scientific supervisor : Johan PALLUD
Institute : Institut de psychiatrie et neurosciences de Paris - Paris
Team : IMA-Brain

Développement d'un atlas cérébral de probabilité de résection des gliomes diffus supra-tentoriels de l'adulte

Diffuse supratentorial gliomas in adults are the most common primarycentral nervous system tumors and their incidence increased over time.The extent of surgical resection combined with the preservation of thepatient's neurological functions represent main prognostic factorsfrom a neurosurgical perspective. Among different techniques, the useof direct intraoperative functional mapping has allowed a significantreduction in permanent deficits while maximizing the extent of tumorresection. Each diffuse glioma operated on under awake monitoring atthe GHU Paris site Sainte-Anne - University of Paris, in PARIS,-between 2010 and 2022 will be segmented, annotated with clinical,neuro-cognitive, histomolecular, therapeutic and follow-up data, whichwill be collected. The first endpoint of this study will be to developa three-dimensional cerebral normalized atlas to predict theprobability of surgical resection without neuro-cognitive alterationof a diffuse cerebral glioma in adults using and integratedmethodology already validated by our research group. Such an atlaswould be useful during decision-making process for resection ofeloquent diffuse gliomas and at the same time to improve patient'sinformed consent preoperatively. The secondary endpoints of this studywill be: 1) to develop a «user friendly» methodological routineallowing this research methodology to be adapted to routine clinicalpractice; 2) to obtain a probabilistic three-dimensional cerebralatlas able to predict the risk of postoperative ischemia; 3) to obtaina three-dimensional cerebral atlas making it possible to predict,basing on preoperative MRI, the probability of neuro-cognitivedeficits; 4) obtain a three-dimensional cerebral atlas to predict forevery lesion the probability of a trans-cortical approach withoutfunctional lesions.

ROULLEAUX DUGAGE Matthieu

Scientific supervisor : Nathalie CHAPUT
Institute : Gustave Roussy - Villejuif
Team : Immunomonitoring en Oncologie

Human virome epitope-level antiviral antibody profiling identifies the cytomegalovirus (CMV) as the main driver of Senescent Immune Phenotype (SIP) in patients with advanced lung cancer

Immunosenescence is a progressive remodeling of immune functions witha multifactorial etiology including aging and chronic antigenicstressors (inflammation, infections, cancer). We showed that a highpretreatment SIP (CD28–CD57+KLRG1+CD8+ circulating T cells>39.5%,SIP+) was associated with resistance to ICB in patients with advancednon-small cell lung cancer (aNSCLC). Latent chronic infections andespecially CMV may be associated with premature immune aging andaffect blood T cell phenotypes (loss of CD28, overexpression of CD57). We aimed to assess the immunisation profile against human viruses andits association with SIP status.

Baseline SIP status was assessed by flow cytometry on fresh bloodsamples from ICB-treated and polychemotherapy-treated (PCT) aNSCLCpatients. Sera from patients were analysed with VirScan (CDI Labs,US), a high-throughput antiviral antibody (Ab) screening method(VirScan™) enabling simultaneous epitope-level antiviral antibodyprofiling of most viruses with human tropism via phage-display andimmunoprecipitation sequencing (PhIP-Seq). VirScan™ detectsantibodies against viral proteins corresponding to 206 species (1000strains, 100.000 viral epitopes) known to have human tropism.

132 aNSCLC patients (115 ICB-treated, 17 PCT-treated) were evaluablefor SIP and VirScan assay. The antiviral serological profile seemedsimilar between SIP+ and SIP- patients, except for CMV where the meanenrichment of anti-CMV antibodies was higher in SIP+. Of the 74antiviral Ab associated with a higher SIP, 70 (94.6%) recognizedCMV-peptides and CMV was the only virus globally associated with ahigher SIP. SIP+ patients were predominantly CMV+ compared to SIP-(93% vs 57%, p0.001), but 70.5% of CMV+ remained SIP-. In CMV+ patients, no difference was observed in the number of CMV epitodes targeted by antibodies (p=0.62) nor in their relative abundance between SIP+ and SIP- patients. Among all clinico-biological parameters studied in the CMV+ population, only median age was higher in SIP+ compared to SIP- patients (70 years vs 63 years, p=0.01).

Among 206 species, only anti-CMV Ab were associated with SIP+ status, which mainly concerned elderly patients. Fu rther work investigating the predictive value of CMV in the response to ICB in patients older than 60 years old is ongoing.

26e Journées Jeunes Chercheurs en Cancérologie

Prix Hélène Starck Poster

Catégorie Doctorat

ABDI GALAB Mahdia

Scientific supervisor : Estelle NICOLAS
Institute : Centre de biologie intégrative - Toulouse
Team : Chromatine et prolifération cellulaire

Role of the histone methyltransferase SETD2 in oncogene-induced senescence

Cellular senescence is an anticancer mechanism allowing a stableproliferation arrest of cells exposed to diverse stresses such as DNAdamage and oncogenic activation. In oncogene-induced senescence (OIS),the entry of cells into senescence is preceded by a strongproliferative burst, replicative stress and DNA damage and requiresthe activation of DNA damage checkpoints. In addition to growtharrest, a large-scale chromatin reorganization occurs in OIS with theformation of SAHFs (Senescence Associated Heterochromatin Foci). TheseSAHFs are dense foci of DNA composed of two non-overlapping layers ofheterochromatin marks and delimited by an active mark oftranscription, the lysine 36 trimethylation of histone H3 (H3K36me3).H3K36me3 is established during gene transcription by SETD2, atumour-suppressor protein, mutated in various types of cancer such asbreast cancer and renal cell carcinoma. Nevertheless, the involvementof SETD2 and H3K36me3 in senescence in particular in SAHF formationremains to be explored.Here, we show that the levels of SETD2 decrease during RAF1 OIS. Onehypothesis is that the decrease of SETD2 expression favors the entryof cells into senescence. To test this hypothesis, SETD2 expressionwas inhibited by RNAi or CRISPRi in proliferating cells. Strandspecific RNA-Seq analyses showed that SETD2 inhibition leads to thederegulation of 52 genes and to the up-regulation of several antisenseand read-through transcripts, which are due to transcription beyondthe termination site of genes and for which we previously showed theirup-regulation in RAF1 OIS. We also found that the depletion of SETD2resulted in an increase of DNA staining heterogeneity, an indicator ofDNA compaction in individual cells, which could reflect the formationof SAHFs. Moreover, SETD2 inhibition in proliferative cells or incells subjected to moderate oncogene activation resulted in increasedDNA damage. This was accompanied by an increased number of cellspassing S phase suggesting that SETD2 inhibition could favor aproliferative burst and replicative stress. These results suggest thatthe decrease in SETD2 expression during senescence could participateto the induction of senescence-specific read-through and antisenseRNAs, the formation of SAHFs and DNA damage response.

AHO Simon

Scientific supervisor : Véronique MAGUER-SATTA
Institute : Centre de Recherche en Cancérologie de Lyon - Lyon
Team : BMP, Ecosystem, Stemness and Dynamic in Cancer

Role of the BMP pathway in breast cancer stem cells formation and basal-like breast cancer initiation

Breast cancer is the leading cause of cancer death inwomen worldwide. It is a heterogeneous disease with a number ofmolecular subtypes. The basal-like subtype has the poorest prognosis.It is characterised by increased expression of basal differentiationmarkers and significant genetic instability, frequently due toalterations in homologous recombination DNA repair pathway. It is alsoenriched in cancer stem cells. These cells seem to be involved in theearly stages of carcinogenesis but also in resistance to cytotoxictreatments and relapse, hence the interest of targeting them forpatient outcome. Several signalling pathways influence their biology,notably the bone morphogenetic protein (BMP) pathway. Dysregulation ofthis pathway has been demonstrated in some luminal tumors but itsinvolvement in the emergence of basal-like tumors remains to beexplored.

Using primary samples and public databases, wesearched for BMP pathway abnormalities in basal-like tumors andBRCA1-mutated predisposed tissues. We also used the MCF10A humanimmature mammary epithelial cell line to model cancer stem cellsformation.RESULTS: We show that the expression of both BMPR1A receptor and BMP4ligand are deregulated in basal-like tumors and BRCA1-mutatedpredisposed tissues. These deregulations are linked withtranscriptional repression of BRCA1 and BRCA2 in MCF10A cells. Thisleads to a situation of simultaneous haploinsufficiency for these twogenes. The functional consequences include preferentialdifferentiation according to the basal phenotype and alterations inhomologous recombination in the form of over-recruitment of RAD51after DNA damage, inducing G0 accumulation without major associatedapoptosis events.

We suggest a role for the BMP4-BMPR1A axis in the earlystages of carcinogenesis of basal-like breast tumors, in promotingbasal differentiation and genetic instability.

BEAUMALE Eva

Scientific supervisor : Nicolas JOLY
Institute : Institut Jacques Monod - Paris
Team : Cycle Cellulaire et Développement

Characterization of functional roles of MEI-2 subunit in the regulation of Katanin microtubule-severing activity in C. elegans

Microtubules are dynamic polymers of cytoskeleton, essential fordiverse cellular events such as intracellular transport, cell divisionand cell migration. Among regulators of microtubule dynamics is thefamily of Microtubule-Severing Enzymes (MSE) consisting of ATPasesable to sever microtubules in order to modulate their number, lengthand network organization. A defect of activity can cause severe humanpathologies including neurodegenerative diseases and many cancer, asbreast, prostate, thyroid or lung cancers.MSE family comprises three members: Spastin, Fidgetin and Katanin.Their mechanism of action is well studied, but how their activity isregulated is not known. To answer this question, we are using C.elegan Katanin, whose activity is crucial for meiotic spindleassembly during female meiosis, as a model. Its activity howeveressential for meiosis has been described as toxic for mitosis duringembryonic development. In order to understand how Katanin activity isregulated during the meiosis-mitosis transition, we wanted todetermine how Katanin binds specifically its substrate and how thisinteraction contribute to modulate Katanin activity.Through combination of in vitro and in vivo approaches, I have identified two distinct Katanin microtubule-binding domains. Mutationsof these domains are modifying Katanin activity in a charge-dependentmanner. Moreover, I have determined that several tubulins arespecifically targeted by Katanin to interact with microtubules. Theseresults demonstrate a precise enzyme-subtract interaction required forKatanin activity during meiosis. By implementing, for the first time,a functional tool allowing us to follow Katanin localization in thewhole worm, we have highlighted, that even if Katanin levels aredrastically reduced during the meiosis-mitosis transition, Kataninremains present in mitosis, specifically on the mitotic spindle duringembryonic development. This unexpected result raises the question ofKatanin roles during mitosis.Our work will contribute to highlight different Katanin modes ofregulation allowing us, in the future and in therapeutic goal, tounderstand how an over-activity of MSE could be controlled in apathological context.

BERCIER Pierre

Scientific supervisor : Hugues DE THÉ
Institute : Collège de France - Paris
Team : Oncologie Cellulaire et Moléculaire

PML nuclear bodies and oxidative stress response

ProMyelocytic Leukemia (PML) protein organizes stress-sensitive,core-shell, membrane-less organelles called PML nuclear bodies(NBs). PML is involved in a number of physiological and pathologicalmechanisms, such as apoptosis, senescence, stem cell renewal ortumor-suppression . PML may elicit these functions by scaffolding thespherical shell of NBs and subsequently recruiting partner proteins,as well as their modifying enzymes in the inner core, acting ascellular hubs controlling their post-translational modifications, inparticular SUMOylation. PML NBs are disrupted in Acute PromyelocyticLeukemia (APL), driven by a chromosomal translocation yielding to theexpression of the PML/RARa fusion protein. Combination therapy basedon arsenic trioxide (ATO) and retinoic acid treatments drives APL cureby forcing NB reformation and subsequent activation of senescenceprogram in APL cells. Through direct binding, ATO targets the PML partof PML/RARA, but also PML expressed from the non-rearranged allele,promoting a rapid increase in PML NB formation, both in APL andnon-APL cells. Despite extensive research, the exact mechanism ofaction of arsenic on PML remains to be solved. Moreover, PML isnecessary for the therapeutic effects of the arsenic/interferoncombination in adult T cell leukemia driven by HTLV1 and inmyeloproliferative syndroms.As PML NB formation is likely the basis of their function, our lab isinterested in solving the exact mechanism of PML NB assembly,regarding its therapeutic role in cancer, in particular in response toarsenic, and demonstrate any link between control of PML dynamics andPML NBs activity. Here, combining high-resolution of a specific PMLdomain with in cellulo studies of PML dynamics at NBs, we unravel thata particular domain of PML controls the formation of PML NBs and theirdynamics through the formation of a trimer stabilized by hydrophobicinteractions between alpha helixes. We elucidate that arsenic inducesNB formation by directly binding to critical cysteine residues in thealpha helix, stabilizing the trimeric structure and immobilizing PMLinto NBs. Critically this domain is mandatory for the function of NBin vivo, controlling PML-induced partner SUMOylation.

BRUZEAU Charlotte

Scientific supervisor : Sandrine LE NOIR
Institute : CRIBL - Limoges
Team : B NATION

Influence of heavy chain locus regulatory elements on nuclear organization and genome integrity of B cell

According to a study conducted by Santé Publique France with theNational Cancer Institute, in 2018, 12% of newly diagnosed cancerswere hematological malignancies. The most frequent hematologicaldiseases emerge from the B lymphocyte (LB), a cell at the heart of theadaptive immune response due to its ability to produce antibodies(Ac). In order to produce highly specific antibodies, the B lymphocyteresorts to various gene alterations involving the introduction ofdouble-strand breaks or the introduction of point mutations within thelocus encoding the immunoglobulin heavy chains (IgH). Because of thesecharacteristics, the LB is constantly at risk of illegitimate eventssuch as oncogene mutations or translocations, making themconstitutively active and thus becoming initiators of lymphomagenesis.For example, in 30-40% of diffuse large B-cell lymphoma cases, theBcl6 oncogene is deregulated by translocation or mutation. Theunderstanding of the mechanisms inherent to the occurrence of suchevents is therefore a fundamental oncology issue. Our project consistsin determining the role of the IgH regulatory regions on the nuclearorganization of the LB and how this organization allows themaintenance of the LB genomic integrity. Our results show that inactivated LBs from models with altered IgH regulatory regions, themutation rate of the Bcl6 oncogene is increased, which correlates withits proximity to the IgH locus and an increase in its transcription.This suggests an important role of regulatory regions in LB genomicintegrity.

BUDZYK Manon

Scientific supervisor : Franck PEREZ
Institute : Institut Curie - Paris
Team : BASTO - Biologie des centrosomes et de l'instabilité génétique

Identification of suppressors of polyploid cell proliferation

Polyploid cells contain multiple copies of their entire genome. Wholegenome duplications (WGD) are associated with genetic instability andcontribute to cancer genome evolution. However, the molecularmechanisms linking polyploidy to genetic instability are still poorlyunderstood. We recently established that in the first interphasefollowing unscheduled WGD, cells fail to replicate their genome in anoptimal manner, leading to DNA damage. Further, when cells entermitosis, they fail to assemble bipolar spindles, which contribute togenerate abnormal karyotypes. We now want to identify pathwaysbecoming essential during polyploid cell proliferation. To do so, wedeveloped an _in vivo_ model of WGD, using _Drosophila_ neural stemcells. After polyploidy induction, these cells can continue toproliferate, reaching high levels of ploidy, while accumulating DNAdamage. To identify essential factors for polyploid cellproliferation, we screened for suppressors of polyploid cellproliferation. We identified Gen/GEN1, a member of the Rad2/XPGendonuclease family, resolving DNA intermediates during mitosis.Strikingly, depletion of Gen in polyploid cells slows down the cellcycle, while Gen overexpression results in accelerated cell cycles.Importantly, in diploid cells, alteration of GEN levels does not causemajor defects. These results suggest that polyploid cell proliferationrelies on proteins that are dispensable in diploid cells, but alsothat a nuclease that is exclusively active during mitosis has anunexpected influence on cell cycle timing. Finally, we show thatde-regulation of the levels of Gen impact DNA damage in polyploidcells, having broader implications in cancer. Indeed, throughbioinformatic analysis, we found that tumors with high levels oftetraploid cells seem to rely on increasing levels of GEN1 to survive.

CALVARY Lisa

Scientific supervisor : Krysztof JAGLA
Institute : Centre de recherche bioclinique – Clermont Ferrand
Team : Mirouse

Study of WAVE Regulatory Complex function in epithelial dynamics during development and tumoral initiation

During development, epithelial tissues undergo impressivemorphological changes. Some of them, like cell migration, are alsoinvolved during tumoral initiation or progression. Follicularepithelium is a powerful model to study epithelial dynamics as itelongates through its antero-posterior axis during its maturation.This elongation is correlated with a process called cell intercalationallowing neighboring cells exchanges observed in a lot ofdevelopmental processes requiring convergent extension. By performing a genetic screen of F-Actin regulators, I was able toidentify WAVE Regulatory Complex (WRC), involved in the generation ofbranched F-Actin, as required for proper early elongation. Furtheranalysis revealed that WRC was recruted at tri-cellular junctions,where it generates lamellipodia between adjacent follicular cells.Statistical analysis of cell junction length pointed out that WRC wasinvolved in junction lengthening and that its absence causes defect inthe resolution of cell intercalation. We also showed that therecruitment of WRC at this particular sub-cellular localization wasdependant of two proteins that co-localized with WRC, Sidekick (Sdk)and Fat2 and some preliminary datas seem to indicate that it can beactivated through the small GTPase Rac by the GEF Myoblast city (Mbc).Interestingly, WRC was already described as an invasion suppressorthat correlates with a decrease of tumors aggressiveness. Sdk and Mbcare also conserved in humans, with Mbc homolog being involved ininvasion properties and Sdk being frequently mutated in epithelialcancers. Nevertheless, functionnal links between these proteins in anormal, or in a pathological context have never been establishedbefore and this work support the hypothesis that they could act in thesame pathway to promote the generation of cell protrusions, and, in apathological situation, to enhance the aggresiveness of tumorcells.

COCHARD Audrey

Scientific supervisor : Zoher GUEROUI
Institute : Ecole Normale Supérieure - Paris
Team : Pôle chimie physique et biologique de la matière vivante

Engineering artificial condensates in cells to study the role of RNA and molecular motors in controlling their formation

Biomolecular condensates, like nucleoli and stress granules (SGs), areubiquitous functional subunits of intracellular organization. Phaseseparation has emerged as a common model to explain their formation. An increasing number of them are being described, exhibitingcompositions and functions depending on the cellular context, but alsoshedding light on links with neurodegenerative diseases and cancer.Indeed, many condensates have modified biophysical properties inresponse to cancer, and some can even help in cancer diagnosis. PMLbody absence is thus a marker of acute promyelocytic leukemia.Upregulation of SGs in cancer cells may allow for a sequestration ofvarious stressors and prevent apoptosis. In addition, manycancer-related proteins like the RNA-binding protein FUS (Fused insarcoma) form condensates and, if detected, could help to diagnosespecific cancers.Studying the biophysical properties of condensates can be valuable incancer diagnosis, as their size, dynamics and composition are oftenaltered in cancer cells. However, how cells, even healthy ones,regulate these properties remains unclear. Moreover, endogenouscondensates have a very complex composition, and a need forreconstitution study has emerged, but most of them are carried out invitro and fail to reconstitute the cellular environment.Therefore, my PhD aimed (1) at building artificial condensates incells and (2) at investigating the role of RNA and molecular motor incontrolling the biophysical properties of condensates. First,recruiting a target RNA in our artificial condensates allowed us tosuggest a mechanism for the regulation of condensates size and number,whereby RNA molecules adsorbed on condensate surface would modifytheir viscoelastic properties as well as prevent their growth andcoalescence by steric hindrance. Then, we functionalized condensateswith motor proteins and looked at the impact of their dynamics. Wefinally reconstituted an RNA transport system, which should be veryuseful for looking at the importance of subcellular localization.

DEMOUCHY Flora

Scientific supervisor : Grégoire MICHAUX
Institute : Institut de Génétique et Développement - Rennes
Team : Dynamique des épithélia

Intestinal hyperplasia is controlled by the PAR-4/LKB1 tumor suppressor in Caenorhabditis elegans

The polarity and tumor suppressor protein PAR-4/LKB1 is thought to bea major regulator of intestinal physiology. Its ectopic activation isindeed sufficient to induce apical microvilli formation in intestinalcancer cell lines. Moreover, mutations in the _lkb1_ gene areresponsible for the Peutz-Jeghers syndrome in which patients developbenign intestinal polyps. As this master kinase acts via varioussignaling pathways, it is crucial to better characterize its role inenterocytes _in vivo_.To do so, we used confocal and electron microscopy to observe theintestinal epithelium in _Caenorhabditis elegans_ _par-4_ mutantembryos. Surprisingly, PAR-4 is not strictly required for intestinalpolarity and microvilli formation. However,_ par-4_ mutant embryosdisplay extra enterocytes, which lead to striking defects in tissuearchitecture, notably to strong lumen deformations.Lineage experiments revealed that PAR-4 does not control the number ofenterocytes by regulating cell proliferation, but rather bycontrolling cell fate specification during embryogenesis. We tookadvantage of the well-described lineage of _C. elegans _embryos toidentify which cells abnormally adopt an intestinal fate. While inwild type embryos intestinal cells exclusively arise from the Eblastomere, in _par-4 _mutants additional enterocytes arise from the Cblastomere. Thus, PAR-4 prevents intestinal specification in the Clineage of wild type embryos. We are currently testing whether thisinvolves the regulation of specific transcription factors. We are alsoinvestigating the possible link between PAR-4 and two other kinases,PAR-1 and GSK-3, which also control intestinal cell number andspecification of the C lineage. Altogether, this work will allow us to characterize a novel signalingpathway by which PAR-4 regulates cell fate specification. This appearsto be essential to prevent intestinal hyperplasia in _C. elegans _andcould provide a new paradigm to analyze the origin of Peutz-Jegherssyndrome intestinal polyps.

DESIGAUX Théo

Scientific supervisor : Nicolas L'HEUREUX
Institute : Bioingénierie tissulaire -UMR1026 – Bordeaux
Team : ART Bioprint

Deciphering the dialogue between breast tumor cells and their ecosystem, following radio/chemotherapy, using bioprinting technologies

Breast cancer is the most common type of cancer in women, making it amajor public health issue. Depending on tumor subtype anddissemination, cancer therapy includes tumor resection, radiotherapyand various systemic treatments to avoid relapse. Recently, ourunderstanding of microenvironment effect on not only cancerdevelopment, but also metastasis and resistance to treatment havegreatly increased. Endothelial cells have been shown to secreteparacrine factors, including ceramide, in response to radio-inducedoxidative stress. While it stimulates endothelial cells apoptosis,these signals also inhibit cancer proliferation.However, even if reinforced by consistent in vivo results, there isstill a gap between these findings and human clinical relevance. Inthe last decade, biofabrication processes have emerged as a powerfultool to build in vitro tunable models using human cells andbiomaterials. Here, we discuss a 3D bioprinted breast cancer model that will be usedin future work to elucidate these mechanisms in complex humanmicroenvironments.We used MDA-MB231 or MCF7 cell line in combination with HumanUmbilical Vein Endothelial Cell (HUVEC) and primary fibroblasts,normal (NSF) or cancer associated (CAF) to mimic the tumor and itsmicroenvironment. By mixing these cells with a hydrogel composed ofCollagen-Methacrylate and Hyaluronic Acid Metacrylate, functionalizedwith laminin-derived peptides, we obtained a printable bio-ink. Wethen used extrusion bioprinting to deposit a cancerous core surroundedby stroma, thus building 3mm in diameter, and 500µm thick model.We first assessed the viability of cancer cells in this model andobserved high viabilities post-printing, suggesting the process isnot harmful to our cells. At D7 the viability is maintained in higherlayers of the model but decreases in depth of the model. Thisviability gradient,, indicates the appearance of a necrotic/hypoxiccore in our model. We then verified endothelial cell maturation in ourmodel, confirmed by the presence of capillary-like structures andexpression of CD31 and VE-Cadherin. Lastly we evaluated modelresponse's to treatment (paclitaxel and irraditation), demonstratingits relevance for tumor-stroma interaction study in the context oftreatment. We are now evaluating paracrine communication in the model, and areexpecting to integrate patient-derived cells in our model to increasetheir clinical relevance.

FRIEDRICH Chloé

Scientific supervisor : Michaela FONTENAY
Institute : Institut Cochin - Paris
Team : Hématopoïèse normale et pathologique

The role of the microenvironment in the pathophysiology of myelodysplastic syndromes

Myelodysplastic syndromes (MDS) are myeloid clonal disorders mainlyobserved in the elderly, which can evolve into acute myeloid leukemia(AML). MDS are characterized by genetic lesions affectinghematopoietic stem cells (HSC) and numerous studies have highlightedan important role of the bone marrow microenvironment (BMME) in thepathophysiology of the disease.Mesenchymal stromal cells (MSC), which constitute a key component ofBMME, have the ability to develop in vivo hematopoietic niches, calledhuman ossicles (hOss), that mimic human BMME in immune-deficient (ID)mice. Here, using MSCs from MDS and age-matched patients, we generatedhOss and studied their ability to host human hematopoiesis. Theobjective of this project is to better decipher the relationshipexisting between HSC and pathological BMME in the context of MDS.

Human MSCs were isolated from bone marrow (BM) of MDS patients andfemoral head (FH) of age-matched healthy patients. After an extensivein vitro characterization, normal and pathological MSC were used togenerate hOss in NSG mice. Notably, we studied in hOss and murin BM,the engraftment of long-term normal hematopoiesis following theintravenous injection of human cord blood (CB) CD34+ cells.ResultsSlight differences were observed in vitro between normal andpathological MSCs, especially with respect to the proliferation rate.

The results of RNA-Seq analysis identified candidate genesdysregulated in MDS-derived MSCs (HOXB6, HOXB7, HOXA2, HOXC10,EBP41L3, TBX15). Pathway analysis showed strong enrichment of TGFβ and senescence-related genes in MDS-derived MSCs.In NSG mice, MSCs from both origins were able to generate hOss, ofequivalent weight and size, and form an intact marrow cavity.Long-term hematopoiesis (% hCD45) was detected in all generated hOssand murin BM, without major differences in term of lineagedistribution. We were also able to detect human CD34+ cells in allgenerated hOss, with no major differences observed with respect to MSCorigin. CD34+ recovered from hOss were able to give rise to coloniesafter 7 weeks of culture, indicating the maintenance of their strainpotential.ConclusionAlthough MSCs from MDS and age-matched patients are different invitro, MSCs from both origins are capable of generating hOss, bothsupporting normal hematopoiesis. Based on this model, we now want tostudy at a transcriptional level the effect of MDS hOss on normalHSCs.

HUSTIN Lucie

Scientific supervisor : Leïla PERIE
Institute : Institut Curie – Paris
Team : Physico-Chimie Curie

GenCounter, a new method to count cell division in hematopoiesis

Hematopoiesis is a continuous process throughout life that give riseto tens of trillions of blood cells. The kinetic rates at which cellsdivide, differentiate and die are important regulators of bloodhomeostasis. However quantitative assessment of theses dynamicalprocesses remains a challenge and impairs our ability to treat theirpathological disruption such as leukemia. Among the quantitativeparameters related to hematopoietic dynamics, division rate has beenmeasured in hematopoietic stem cells (HSC) and mature blood cellsshowing that proliferation rates increase along differentiation.However, there are no current method to measure absolute number ofdivisions from a HSC to a mature blood cell. We have thereforedesigned a division counter, GenCounter, to quantify the number ofdivisions undertaken by a given cell population over months. We thenvalidated our GenCounter design on cell lines and went on to use iton hematopoietic cells. With this GenCounter, we hope toprovide the first time dynamic maps of cell population kinetics inhealth and disease and hopefully identify the key elements involvedin this process.

JULIA Edith

Scientific supervisor : Laurent GENESTIER
Institute : Centre International de Recherche en Infectiologie - Lyon
Team : UR Lymphoma Immunobiology

Chromatin Accessibility Profiling to Increase Diagnostic Accuracy and Refine Cell-of-Origin Classification of Mature T-Cell Lymphomas

Mature T-cell lymphomas and leukemias (MTCL) are heterogeneousdiseases with dismal prognosis. Differentiating between the numerousentities requires specialized pathology expertise and studies show upto 20% change in diagnosis after expert review of cases. Assay fortransposase accessible chromatin sequencing (ATAC-seq) is a simpletechnique to profile open chromatin regions (OCR) proven to be highlydiscriminant for cell-of-origin identification regardless of cellactivation status. We applied ATAC-seq to MTCL in order to explore theepigenetic landscape of these diverse entities, compared them tonormal T-cell subtypes and built a predictive model to help diagnosis.Ten-thousand FACS-sorted single cells from primary MTCL samples and50µm section of frozen tumoral tissue from the TENOMIC French T-cellLymphoma Consortium were processed according to the previouslypublished FAST-ATAC and OMNI-ATAC protocols respectively. Concurrentlywe applied FAST ATAC to different normal T- and NK-cell subsets sortedfrom healthy donor PBMC or lymph node suspensions. Sequencing datawere processed by an in-house pipeline to obtain matrix of insertionevents in peaks by sample.In total, 678 normal and tumoral samples were sequenced to provide acomprehensive landscape of chromatin accessibility in MTCL. Epigeneticprofiling by ATAC-seq of FACS-sorted tumoral samples resulted in acomplete segregation of the known MTCL entities. Most PTCL-NOS (13/17) clustered with a pre-defined MTCL subtype. All but one discordantdiagnosis between pathology and ATAC-seq (1/11) led to reviseddiagnosis after pathology review.Unsupervised clustering of normal NK- and T-cell subtypes (N=49) andsorted tumoral lymphoma cells (N=104) confirmed that AITL derive fromTFH cells. HSTL and LGL closely segregated with NK- and gamma-delta Tcells, in line with their known innate-like phenotype.Finally, using unsupervised deconvolution approaches, we were able todiscriminate different MTCL subtypes from 223 processed bulk frozensamples. A random forest model was then trained to predict diagnosisbased on chromatin-accessibility profiles and viral (HTLV1 and EBV)read counts to predict diagnosis. The model showed accurateprediction performance by cross-validation.

LALETIN Vladimir

Scientific supervisor : Jacques NUNES
Institute : Centre de Recherche en Cancérologie de Marseille - Marseille
Team : Immunité et cancer

Targeting intracellular inhibiting proteins DOK1 and DOK2 to improve CD8+ T cell immunotherapy

Targeting intracellular inhibiting proteins is a promising strategy toimprove CD8+ T cell anti-tumor efficacy. DOK1 and DOK2 are CD8+ Tcell inhibitory proteins that are targeted in this study in order toimprove the activation and cytotoxic capacities of these cells. Toevaluate the role of DOK-1 and DOK-2 depletion in physiology andeffector function of T CD8+ lymphocyte and in cancer progression, atransgenic T cell receptor mouse model specific to melanoma antigenhgp100 (pmel-1 TCR Tg) was established.Depletion of both Dok1 and Dok2 did not affect the development,proliferation, mortality, activation and cytotoxic function of naiveCD8+ T cells. However, after an in-vitro pre-stimulation Dok1/Dok2 DKO CD8+ T cells had higherpercentage of effector memory T cells and showed an increase in levelsof pAKT and pERK upon TCR stimulation. Despite this improved TCRsignaling, pre-stimulated Dok1/Dok2 DKO CD8+ T cells did not showany increase in their activation or cytotoxicity capacities againstmelanoma cell line expressing hgp100 in vitro.Altogether we demonstrate here a novel aspect of the negativeregulation by DOK1 and DOK2 proteins in CD8+ T cells. In conclusion,DOK1 and DOK2 have an inhibitory role following long term T cellstimulations.

LIAN Yen-Ling

Scientific supervisor : Franck PEREZ
Institute : Institut Curie - Paris
Team : Biologie Cellulaire et Cancer

Synchronization of transport of Golgi glycosylation enzymes enabled a quantitative analysis of Golgi-to-ER retrograde transport

Bidirectional transport of proteins between the endoplasmicreticulum (ER) and the Golgi apparatus is essential to ensure properlocalization of enzymes in these intracellular compartments enablingthem to achieve their function. However, tools are missing toquantitatively analyze transport mechanisms between ER and Golgi,especially for retrograde Golgi-to-ER transport. Here we show thatsynchronization of Golgi-to-ER retrograde transport is enabled bycombining the Retention Using Selective Hooks (RUSH) assay andartificial ligands of Streptavidin (ALiS). Using “dynamic” or“immobile” ER hooks, KDEL- mediated ER retrieval and ER recyclingof Golgi glycosylation enzymes was quantitatively analyzed and showeddifferences in their kinetics. In addition, we tested the role of theknown regulators of retrograde transport, COG3 and Rab6, in theseGolgi-to-ER transport routes. Finally, we demonstrated that we can getrid of working with overexpressed Golgi glycosylation enzymes andgenerated genome-edited cells leading to synchronization of thebidirectional transport of endogenous Golgi glycosylation enzymes.

MONROSE Mélusine

Scientific supervisor : David VOLLE
Institute : Centre de Recherche Bio-clinique – Clermont Ferrand
Team : Environnement, spermatogenèse, pathophysiologie et hérédité

Étude des rôles du récepteur nucléaire des xénobiotiques CAR (Constitutive Androstane Receptor) dans la tumorigenèse testiculaire

The incidence of testicular cancer has been progressively increasing,suggesting that exposures to xenobiotics might be in part responsible.Indeed, scientific evidence indicate that environmental exposures-during the perinatal period contribute to the emergence of chronicdiseases such as testicular cancer. The nuclear receptor CAR(Constitutive Androstane Receptor) has been described as a keymediator of xenobiotics. Our team has recently shown that CAR isexpressed within the germ cell line in the mouse and in the humanfoetal testis, but its roles in the impacts of xenobiotics ontesticular physiology have not been fully studied so far. However, CARcontributes to some cancerous processes such as the suppression ofapoptosis in hepatocytes, what is associated with liver tumorigenesisin mice. Regarding the potential links between xenobiotics andcancers, we hypothesized that CAR could play key roles in testiculargerm cell tumours processes or chemoresistance.Our unpublished data support this hypothesis since we have identifiedthe accumulation of CAR protein in type 2 human seminoma, and theexpression of CAR in a human seminoma cell line. Moreover, our datasuggest that CAR is involved in the homeostasis of gonocytes, whichare thought to be the germ cells at the origin of the germ cell tumourformation. Indeed, we showed that the neonatal inhibition of CARsignalling in mice alters the gonocyte to spermatogonia transition,leading to the accumulation of ectopic germ cells within theseminiferous tubules. We demonstrated that these alterations areassociated with deregulations of FOXO1 signalling and the expressionof some of its target genes (CDH1 and GADD45β), which are oftenassociated with tumorigenesis according to the tissue. We also showedthat CAR inhibition leads to the decrease of apoptosis and to theincrease of cell migration in the mouse spermatogonial cell line.We also showed that the inhibition of CAR signalling in thespermatogonial cell line leads to deregulations in the expression ofgenes coding key epigenetic actors such as DNA methyltransferases, andto alteration of histone modifications. Yet, it is well known thatmodifications of epigenetic marks are frequently observed in cancers,leading to alterations of cell homeostasis, and taking part of thepro-tumour properties. These data open new perspectives on theunderstanding of the aetiology of testicular cancer in a context ofenvironmental exposures.

MONTEMURRO Marianne

Scientific supervisor : Magali SUZANNE
Institute : Centre de Biologie Intégrative - Toulouse
Team : Molecular Cellular and Developmental Biology

Identification of Apoptosis and Junctional Tension as Pro-tumoral Factors in Drosophila

Cancer is a largely widespread pathology that corresponds to anoverproliferation of cells that could finally invade others tissues.Tumors develop through three increasingly aggressive steps: (1)hyperplasia, corresponding to cells overproliferation without anymodification of epithelial properties; (2) neoplasia, during whichcells can acquire a more mesenchymal phenotype, and finally (3)metastasis, when cells leave the primary tumor, migrate and formsecondary tumors. Tumor development can be influenced by mutations (or combination ofmutations) but also by external factors, such as extracellular matrixrigidity. However, a comprehensive understanding of the factorsdriving tumor evolution is still lacking. My project aims to useDrosophila to identify unexpected factors that could influence tumordevelopment, and more specifically the hyperplasia/neoplasiatransition, a critical step in tumor aggressiveness. After an in-depthcharacterization of tumor progression at cellular level at successivetimepoints, I selected two complementary genetic contexts for furtheranalysis: a strictly hyperplasic tumor (“Yorkie overexpression”context) and an initially hyperplasic tumor that eventually evolves inneoplasia (“Avalanche loss-of-function” context). Strikingly, I identified two new and unexpected factors involved intumor progression and aggressiveness: apoptosis and tissue tension.Indeed, while tumor aggressiveness coincides with a high level ofapoptotic cells, abolishing apoptosis in Avalanche tumors stronglydecreases the hyperplasia/neoplasia shift. In addition, introducingcell death in Yorkie tumors induces partial junctions’ dismantling,most probably the first step of the hyperplasia/neoplasia transition.Hence, in those two different contexts, modulation of apoptosissurprisingly favors the hyperplasia/neoplasia transition. Moreover, Ifound that tumor aggressiveness is associated with high tissue tensionand that increasing junctional tension (by modulating a Myosin IIregulator or by redirecting Myosin II-GFP using a specific adherensjunction trap) is sufficient to induce a hyperplasia/neoplasiatransition in a tumor context normally strictly hyperplasic(Yorkie’s context). Overalll my work shows that in fly, adherensjunctions mechancs acts in synergy with cell death to trigger theepithelial-to-mesenchymal transition associated with tumouraggressiveness.

PICANT Valentin

Scientific supervisor : Christophe CAUX
Institute : Centre de Recherche en Cancérologie de Lyon - Lyon
Team : Caux - CISTAR

Characterization of the role of interleukin-33 in Natural Killer cells activation during anti-tumor immunosurveillance

Natural Killer (NK) cells are key players in cancer immunosurveillanceby directly killing tumor cells and supporting effective antitumorimmune responses. However, they get progressively dysfunctional indeveloping tumors. A promising strategy consists in the identificationof soluble factors or surface receptors that drive the activation andanti-tumor function of NK cells. The stress-induced alarminInterleukin-33 (IL-33) activates NK in infectious models while itsrole in tumor contexts remains unclear. Based on the team's previousresults, we hypothesized that the IL-33/IL-33R axis is a novel pathwayfor NK activation during tumor immunosurveillance and we investigatedthe activating potential of the IL-33 cytokine on healthy donors andcancer patients NK cells.First, we highlighted the importance of the dendritic cells (DC)/NKcrosstalk in the IL-33R induction, with a major role of activatedDC-derived cytokines, such as IL-12 and IL-15. Moreover, we observedthat IL-12 and IL-15 induce IL-33R expression on different NK cellsubpopulations, increasing their cytotoxicity, cytokine secretion,and proliferation in response to IL-33. RNAseq analysis reinforcedthat IL-33 effect is context- and NK cell subset-specific. In apathological context, NK cells isolated from various tumor types werestill able to get activated in response to IL-33 combined to IL-12and/or IL-15 _ex vivo_. Using _in vivo_ tumor models, we reported thatIL-33 synergizes with DC-activating TLR agonists to limit tumordevelopment in therapeutic settings. Finally, we observed a highertumor growth rate and a decreased antitumoral effects of DC-activatingTLR agonists in IL33KO mice compared to wild type mice, bothhighlighting a role for IL-33 in cancer immune surveillance.Thus, our work identifies IL-33 as a context- and subset-dependent NKcell activator that might be used to reverse intratumor NK celldysfunctionality, paving the way to a refinement of immunotherapiestargeting innate cells.

PIRIS Patricia

Scientific supervisor : Jean-Paul BORG
Institute : Centre de Recherche en Cancérologie de Marseille - Marseille
Team : iSCB

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

The present work is based on the theranostic properties ofAlkoxyamines (R1–ONR2R3), molecules that can undergo homolysis togenerate an alkyl radical that triggers cancer cell death and anitroxide that enhance the MRI signal. We synthesized a library of 105new Alkoxymines. The most efficient, _i.e_ Alk4, was selected for itsability to inhibit both the survival and migration of medulloblastoma(MB) and glioblastoma (GBM) cells. Alk4 accumulates in tumor cellcytosol after 2h of treatment and released alkyl radicals, whichtriggered the generation of ROS, fragmentation of the mitochondrialnetwork and finally apoptosis.To control the homolytic process, Alk4 was then bioconjugated to apeptide selectively recognized by the matrix metalloproteinases(MMPs), which are overexpressed in the microenvironment. Thebioconjugated Alk4-MMPp successfully inhibited proliferation andinvasion of GBM and MB 3D spheroids, while Alk4 bioconjugated to achymotrypsin-targeted peptide remained inactive. To furthercharacterize Alk4-MMPp benefits we developed an innovative organotypicmodel based on the graft of stably fluorescent GBM or MB spheroids in_ex vivo_ mouse brain or cerebellum slices. The daily monitoring ofresponse to treatment confirmed that Alk4-MMPp significantly impairedtumor progression, while no significant damage to the healthy tissuewas observed. Our work paves the way to the controlled use ofAlkoxyamines in MB and GBM, the most frequent intracranial tumors inchildren and adults respectively.

POTEAU Marion

Scientific supervisor : Olivier GAVET
Institute : Gustave Roussy - Villejuif
Team : Genome integrity, immune response and cancer - Cell Division and genetic stability

CyclinA2 overexpression: consequences on genetic integrity and cell outcome

CyclinA2 is a master cell cycle regulator required for both DNAreplication during S phase and timely commitment to mitosis. CyclinA2has been found to be overexpressed in various human cancers associatedwith a poor prognosis. Yet, the potential contribution of itsoverexpression in tumorigenesis remains to be characterized. Here, weaimed to decipher the consequences of CyclinA2 overexpression (OE) onthe regulation of the cell cycle and on the maintenance of the geneticintegrity. For this purpose, generated human stable cell linesconditionally overexpressing CyclinA2 WT (wild-type) or an inactiveform, in both p53 proficient or deficient contexts. We found thatCyclinA2 WT OE promotes a premature entry into S phase accompanied bya decrease in the density of active replication forks and fork speedprogression, as determined by DNA molecular combing assays, leading toreplication stress and over-activation of ATR/Chk1-dependent DNAreplication checkpoint. As a consequence, we found increasedunder-replicated regions at mitosis and chromosome breaks, favouringincorrect chromosome segregation and the appearance of micronuclei inthe progeny. In a p53-deficient background, this progressively leadsto the accumulation of aneuploid cells.Together, our results support that CyclinA2 OE, specifically in a p53deficient context, contributes to the establishment of a geneticinstability, a typical feature of pre-neoplastic lesions.

REYNAUD Amandine

Scientific supervisor : Antoine DUCLOS
Institute : Centre Léon Berard – Lyon
Team : RESHAPE

Supportive care needs of former child, adolescent and young adult cancer patients, and of their parents: Evaluation during long-term follow-up

Each year, there are 2100 new cases of cancer in children andadolescents/young adults in France. Due to a significant improvementin the effectiveness of therapies, the combined survival rate after 5years is 80-85%. This is leading to the emergence of new problems,requiring an adaptation of the long-term care. Many studies highlightthat 60 to 65% of pediatric oncology patients will present medicaland/or psychosocial complications in the 20 years following theironcological treatment, with a cumulative incidence of a seriousadverse event of 40% 30 years after the cancer diagnosis. It istherefore necessary to identify the risk factors by determining theexpectations and the supportive care needs of patients and theircaregivers in the long-term follow-up in order to intervene early andthus reduce the incidence of these later complications.Despite a growing need and existing recommendations, patients do notseem very committed to the different structures offered in France. Itis possible that some patient needs are currently not sufficientlyknown and met, or not early enough. Only 30 to 50% of former patientsattend a long-term follow-up medical consultation. We hypothesize thatthis lack of commitment is multifactorial (e.g. unmet supportive careneeds, geographical distance from home, lack of information about theimportance of long-term follow-up and follow-up structures nearby) andthat a precise study of the needs expressed by former patients andtheir family should lead to an improved attendance at theseconsultations. “Supportive care needs (SCN)” refer to issues that may or maynot be ultimately resolved. Thus, a SCN may be labeled “unmet”when the supportive care required to deal with the particular problemis not received. These “unmet” supportive care needs shouldprovide additional information about the gaps in the support given byhealth professionals. This information could then be used toprioritize the missing resources. As a result, the concept of “unmetSCN” is of interest to institutional decision-makers, clinicians andresearchers.A better understanding of the supportive care needs of these patientsand their families is therefore essential to improve their quality oflife, prevent or detect the sequela of therapies and reduce the riskof mordibity/mortality during the long-term care.

SAOUT Judikael

Scientific supervisor : Michael SAMSON
Institute : Institut de Recherche Santé, Environnement et Travail - Rennes
Team : Physiologie et physiopathologie du tractus urogénitale

Study of intra-tumor heterogeneity and impacts of anti-cancer drugs in clear cell renal cell carcinoma using single-cell transcriptomics approaches

Intra-tumor heterogeneity (ITH) in clear cell renal cell carcinoma andother malignancies is partly responsible for tumor progression,relapse and tumor escape. One of the challenges of cancer researchtoday is to uncover and characterize this ITH in order to takeadvantage of it in the treatment of patients. Single-cell RNAsequencing (scRNA-seq) has become the method of choice to decipher ITHby simultaneously profiling the individual transcriptome of thousandsof cells from a dissociated tumor. In this project, the firstobjective is to use single-cell RNA-seq in ccRCC in order to build asingle-cell malignancy atlas and better risk-stratify ccRCC patients.In this respect, we uncovered various degrees of inter- andintra-tumor heterogeneitis in malignant cells across multiple tumorsand were able to link particularly aggressive malignant clones tosurvival in a massive cohort using deconvolution approaches,which provides new avenues for personalized medicine et patientmanagment. A second objective was to study the impacts of anti-cancerdrugs on ITH in ccRCC 3D culture models. Ongoing work already providesa proof of concept for the implementation of a multiplexed screeningstrategy, and evidences that cellular subpopulations appear to bedifferentially impacted by antiangiogenic therapies.

SCHIRMEISEN Kamila

Scientific supervisor : Sarah LAMBERT
Institute : Institut Curie – Orsay
Team : Recombinaison de l'ADN, réplication et stabilité du génome

SUMO-dependent nuclear positioning safeguards replication fork integrity and competence

Resolving replication stress, which is a major source of genomeinstability and fuels cancer development, occurs within acompartmentalized nucleus with distinct DNA repair capacities.Replication fork (RF), when its progression is impaired, may shift tothe nuclear periphery for anchorage to nuclear pore complexes (NPCs),where specific types of homologous recombination (HR) pathways takeplace. This nuclear positioning is regulated by small ubiquitin-likemodifier (SUMO) metabolism. Distortion of SUMO equilibrium has beenreported in a variety of human diseases including cancer. For example,SUMO protease SENP1 is overexpressed in many cancer types, includingthyroid adenocarcinoma, breast cancer and prostate cancer. However,how deregulated SUMO metabolism influences the maintenance of genomeintegrity at replication stress sites is poorly investigated. Usingreplication fork barrier (RFB) in fission yeast _Schizosaccharomycespombe_, I have found that monoSUMOylation and the E3 SUMO ligase Pli1(hsPIAS1) catalytic activity are necessary to protect arrested RF fromexcessive nascent strand degradation when RF failed to relocate to thenuclear periphery. I have also established two functions of thenuclear basket, the nuclear part of NPCs: a Nup60-mediated function inpromoting replication fork restart via Ulp1, as described for the Ycomplex, and a Alm1-mediated function in anchoring arrested forks toNPCs. Furthermore, I have observed that the lack of anchorage to NPCcorrelated with the formation of unprotected forks (the degradation ofnascent strand becomes excessive) when Ulp1 is delocalized from thenuclear periphery. Interestingly, I found that the artificiallytethering of arrested forks to NPCs was sufficient to restore forkprotection. Together with additional data, I hypothesize that aspatially segregated SUMO metabolism between the nucleoplasm and thenuclear periphery is a key determinant of replication fork integrityand competence.

SEBA Mohammed

Scientific supervisor : Frédéric BOCCARD
Institute : Institut de Biologie Intégrative de la Cellule – Gif-sur-Yvette
Team : Conformation et ségrégation du chromosome bactérien

The role of MukBEF, in Escherichia coli chromosome conformation

The structuring of DNA into chromosomes is still poorly understood.Indeed, while many molecular players have been identified frombacteria to humans, their involvement in the organization andsegregation of chromosomes, or the regulation of gene expression,remains to be understood. Among these essential players, the SMC(structural maintenance chromosome) complexes are universally presentin living beings. The study of these SMCs, involved in the genesis ofmany cancers (for review: Nature Reviews Cancer 2020 504–515T.Waldman), can be facilitated by using bacterial systems which have asimpler chromosomal environment (1 single chromosome) and whosedeletion of these genes is not lethal. MukBEF is a bacterialcondensine of Escherichia coli responsible for chromosome segregation,and conformation; in its absence, the bacteria are no longer capableof rapid growth, but can nevertheless survive and multiply at 22°C,generating numerous cells without DNA. Using chromosome conformationtechniques, we showed that MukBEF promotes long-range DNA contact(about 1Mb) all along the chromosome except in the particular Terdomain (VS Lioy et al., 2018). The organization of the Ter domainrelies on the presence of a 13 bp motif (matS) repeated 28 times inthe 800kb long domain bound by MatP. We previously showed that thematS/matP system inhibits MukBEF activity. Here we characterized theloading preferences of MukBEF and the determinants of the inhibitionby MatP. To do so, we followed the activity of MukBEF after inductionand we modified the distribution of the matS on the chromosome.Our results show that MukBEF is loaded in a nonspecific way on thechromosome. The inhibition of MukBEF by MatP/matS system isaccompanied by a loss of interaction of MukBEF with the chromosome,-suggesting a mechanism of MukBEF unloading by MatP.

THOMAS Morgane

Scientific supervisor : Eric PINAUD
Institute : CRIBL - Limoges
Team : B-NATION

MAR binding protein functions in nuclear organization and genome integrity of B cells

B cells undergo genetic remodeling of their Immunoglobulin (Ig) genes,such as Class Switch Recombination (CSR), which determine Ig functionand Somatic Hypermutation (SHM), which increase Ig-antigen affinity,upon antigen stimulation. As CSR and SHM lead respectively to DNAdouble strand ad single strand beaks, these mechanisms must to beunder precise control. Alteration in CSR and SHM can conduce toillegitimate recombination or mutation that can cause tumordevelopment. For a meticulous control of such events, the IgH locuscontains different cis-regulatory regions such as the intronic regionEμ. This regulator brings together a Core-Eμ enhancer region and twoMatrix Attachment Regions (MARsEμ). Our team discovered that MARsEμregions are involved in SHM since their deletion in the mouse leads toa decrease of SHM frequency. The mechanism linking MARsEμ to SHM isunclear, but we suspect some MARs binding protein (MARs BP) to beinvolved ; such as ARID3A (A-T Rich Interaction Domain) & SATB1(Special A-T rich Binding protein 1). Since these two MARs BP areinvolved in multiple tumor development, it should be interesting tostudy their effect on genetic remodeling mechanisms in B-lineagecells. Our preliminary data show that SATB1 could repress SHM. Indeed,its deletion induces an increase of SHM frequency. Our data alsosuggest a function for ARID3A but in contrast to SATB1, ARID3A mightenhance SHM and plasma cell differentiation. Understanding the exactimplication of MAR BP is in these processes could help to specifytheir function in cancer development, especially in B-celllymphoproliferations.

TIGHANIMINE Khaled

Scientific supervisor : Mario PENDE
Institute : Institut Necker Enfants Malades - Paris
Team : Cell growth control by nutrients

Multi-omics approach across different senescence models reveals common senescence metabolic signature and possible interventions on senescence-related disorders

Senescence is an irreversible cell cycle arrest that can be triggeredby different stress, including oncogenes, DNA replication and telomereerosion, DNA damage. This makes senescence one important tumorsuppressor mechanism. In addition, senescent cells display a widesecretory phenotype of inflammatory molecules, calledSenescence-Associated Secretory Phenotype (SASP), that can promotetumorigenesis in a paracrine fashion and play deleterious role inaging. Accordingly, this secretion activity maintains senescent cellsmetabolically active. To elucidate the metabolic adaptations ofsenescent cells, we identified by MC/MS analysis a metabolic signaturethat is common to all senescence models. We called itSenescence-Associated Metabolic Shift (SAMS). Strikingly, all thesemarkers were repressed when senescence was delayed by pharmacologicaltreatments, such as the mTOR inhibitor rapamycin and the HIFhydroxylase inhibitor Dimethyloxalylglycine (DMOG). Of note, werevealed that two metabolic pathways at the intersection oftriglyceride accumulation and phospholipid synthesis were affected insenescent cells. We were able to confirm lipid alterations insenescent cells by lipidomic analysis. We elucidated the moleculARcauses underlying the lipid signature of senescent cells.Interestingly, p53 seems to coordinate both transcriptional andpost-translational modifications of enzymes involved in lipidmetabolism. Overall, our data reveal the pathways at the intersectionof triglyceride accumulation and phospholipid synthesis that play acausal role in senescence establishment and inflammation and give newinsights for therapeutic strategies for senescence-mediated tumorsuppression.

WILLIART Alice

Scientific supervisor : Mathieu PIEL
Institute : Institut Curie - Paris
Team : Biologie systémique de la polarité et de la division

Consequences of mechanical deformations of the nucleus

In the body, cells are often subjected to mechanical constraints andcan undergo large deformations. This can occur when cells move throughdense tissues or capillaries, or often during tumour development. Whenthe cell deforms, its nucleus, as its largest and stiffest organelle,is also subjected to deformation, up until loss of nuclear envelopeintegrity and rupture. Using a 2D confinement device, we can in vitroimpose a range of controlled heights to the cells, alter theirmechanical state and that of tehir nucleus, and study the consequencesof deformations.The mechanical deformation of the nucleus is associated with changesin the state of the nuclear envelope. Non-adhered, non-confined cellshave nuclei which display large folds that gradually open uponconfinement. This is associated with a decrease of NE fluctuations,which we interpret as an increase in NE tension (Lomakin et al.,2020).We show in three different cell lines that the nucleus follows tworegimes depending on the deformation magnitude. Under mildconfinement, the nucleus deforms at constant volume. At the same time,the amplitude of NE fluctuations decreases until reaching a plateau ata certain threshold height. This is associated with NE unfolding.Below this threshold, the nuclear volume decreases by up to 50%. Wepropose that the first regime defines a “safe” deformation range,with a constant volume and hence a preserved chromatin density. Belowa threshold, an altered regime begins, in which nuclear volume andthus physiology starts to be affected, with different cell linesswitching to the perturbation regime at different levels ofdeformation.The volume of the nucleus has been shown to be related to the cellvolume, in many different organisms, for reasons which are stilldebated. Our results suggest that it also depends on mechanicalconstraints. We are currently collaborating with physicists whodeveloped a theoretical model basedon mechanical and osmotic equilibrium to predict the volume of thenucleus and the state of the nuclear envelope depending on theosmolarity of the external medium and the deformation of the cell. Themodel predicts a key role for the mechanical contribution of the NEand its capability toextend, underlining the potential role of mechanical constraints incllular and nuclear responses.

ZIDI Nour

Scientific supervisor : Lionel LARUE
Institute : Institut Curie - Orsay
Team : Développement normal et pathologie des mélanocytes

Role of recently identified targets of β-catenin in the cellular functions of the melanocyte lineage

The Wnt/β-catenin signaling pathway plays a key role during embryonicdevelopment, homeostasis and cancer. The role of β-catenin inmelanocyte lineage establishment and homeostasis has been elucidated,but its role in melanoma remains poorly defined. In particular, itsfunction in cell invasion is controversial.Especially, we generated a signature of β-catenin activation toemerge proteins of interest including known β-catenin target genes(AXIN2, APCDD1, NKD1, SP5, NOTUM, ZNRF3, CCND1 and PPARD) and newgenes (SLC1A5, SLC7A11, SLC24A4 and MICAL2). Our signature gene mostcorrelated with invasive cells is MICAL2. MICAL2 oxidizes actinfilaments, destabilizes them, and modifies the migratory power ofcells. In melanoma cell lines, reduction or induction reduces orincreases the level of MICAL2, respectively. Decreasing the level ofMICAL2 reduces migration, invasion and cell growth. Finally, asignificantly unfavorable evolution for the patient is associated witha strong expression of MICAL2 and its invasive power. In conclusion, the identification of a transcriptional signature ofβ-catenin activation in melanoma is an important step towardsunderstanding the role of β-catenin during melanomagenesis. MICAL2which is pharmacologically targetable is an example.

ZOUIOUICH Mehdi

Scientific supervisor : Catherine TOMASETTO
Institute : Institut de Génétique et de Biologie Moléculaire et Cellulaire - Illkirch
Team : Biologie moléculaire et cellulaire des cancers du sein

Role of MOSPD2-mediated membrane contact sites in cancer

Lipid droplets (LDs) are dynamic storage organelles, which play a keyrole in the deregulation of cancer cell metabolism. Our laboratoryrecently identified a major player in the formation of contactsbetween the endoplasmic reticulum (ER) and other cellular organelles,a protein named MOSPD2 (MOtile Sperm Domain-containing protein 2).Interestingly, data from the literature implicate MOSPD2 in breastcancer tumour progression.I have recently identified a unique function of MOSPD2 which is toform contacts between the ER and the LDs. My thesis project aims toidentify the role of MOSPD2 in the deregulation of lipid metabolismvia LDs and its impact on the migration properties of cancer cells. Myhypothesis is that MOSPD2 enables the formation of contact sitesbetween the ER and LDs and could transport lipids to promote LDbiogenesis. So far, I have shown that MOSPD2 promotes the formation ofER-LDs contacts by interacting directly with the surface of LDs andthat loss of MOSPD2 expression leads to a decrease in LD size andnumber. The fourth year of the thesis will clarify the molecularmechanism of action of MOSPD2 in ER-LD contacts and study themechanism involving MOSPD2 in tumour cell migration.

26e Journées Jeunes Chercheurs en Cancérologie

Prix Hélène Starck Poster

Catégorie Post-Doctorat

DURAND Simon

Scientific supervisor : Julie CARAMEL
Institute : Centre de Recherche en Cancérologie de Lyon - Lyon
Team : Cancer cell plasticity in melanoma

The epigenetic regulators RBBP5 and TRIM24sustain phenotype plasticity of melanoma cells

Metastatic melanoma is a highly aggressive type of skincancer, the treatment of which has been recently revolutionized withthe advent of targeted therapy (BRAF/MEK inhibitors) and immunotherapy(anti-PD1). However, about fifty percent of patients still developresistance. Therapy failure is partly due to an exacerbated cancercell plasticity characterized by a phenotype switch between aproliferative/differentiated and an invasive/stem-like state. Epigenetic alterations have been proposed to account for the rapidadaptation of melanoma cells to treatment.We performed in silico analysis on multiple melanoma datasets tohighlight epigenetic regulators frequently mutated with an alteredexpression. We then investigated the role of two candidates, namely,RBBP5 and TRIM24, in melanoma phenotype switching and oncogenesis.RBBP5 is a core subunit of the Histone Lysine Methyltransferase 2complex (KMT2, or MLL) family while TRIM24 is a transcriptionco-regulator recognizing histone marks. These two epigeneticregulators have never been studied in the context of melanomaplasticity.

RBBP5 and TRIM24 expression were knocked-down separately by ashRNA approach in patient-derived melanoma short-term cultures. Molecular analyses (RNA sequencing, quantitative PCR, immunoblotting,flow cytometry) as well as functional assays (IC50 with BRAFinhibitors, incucyte and migration assay, protein degradation usingPROTACs) were performed.

RNA-sequencing analyses highlight an enrichment of neuralcrest-like, invasive and EMT signatures in the RBBP5 knocked-downcells. RBBP5 knock-down notably induces a loss of expression ofmelanocytic markers (MITF, SOX10) in favor of neural-crest markers(NGFR, AXL). Furthermore, functional analyses show that RBBP5knocked-down cells display increased migratory capacities andresistance to BRAF inhibitor. On the opposite, the downregulation ofTRIM24 induced cell differentiation with increased expression ofmelanocytic markers associated with both a higher sensitivity to BRAFiand a decreased migratory capacity. Together, these studies suggest that epigenetic regulators controlmelanoma cell plasticity, with RBBP5 and TRIM24 controlling anopposite path of differentiation. This work paves the way for thedevelopment of new therapeutic strategies targeting phenotypeplasticity to sensitize melanoma cells to treatment.

FABBRI Lucilla

Scientific supervisor : Stephan VAGNER
Institute : Institut Curie - Orsay
Team : RNA Biology, signalling and cancer

Investigating the role of mRNA translation in cancer cell mutability

The control of mRNA translation plays a key role in cancer cellplasticity, a main driver of resistance to anticancer therapies. Theability of cancer cells to reversibly transition into drug-tolerantphenotypes through non-genetic mechanisms is an important contributorof therapeutic failure. These drug-tolerant persister cells constitutea reservoir for the development of genetic acquired resistant cellsand drive relapse.Our previous results identified an mRNA translation remodeling as themechanism exploited by BRAF-mutated melanoma persister cells totransiently survive targeted therapy. Some m6A-modified mRNAs,essential for persister cell survival, maintained efficienttranslation despite a global reduction of protein synthesis. Inparticular, while mRNAs encoding proteins involved in accurate DNArepair were translationally downregulated, the translation of the mRNAencoding 53BP1, a key mediator of the error-prone non-homologous end-joining (NHEJ) repair pathway, was found to be selectivelyupregulated.By focusing on 53BP1, we show that its translational upregulation isassociated with the persistence state of different melanoma andcolorectal cancer cells upon targeted therapy as well as with anincrease of DNA damage. This correlates with a bias towards NHEJ andan increase of 53BP1-dependent mutagenesis in persister cells. To haveinsights into the link with its translational upregulation, we havefirstly interrogated the role of the 5'UTR. Using dedicated reporterplasmids, we show that the 53BP1 5'UTR is sufficient to drive thetranslation upregulation of 53BP1 in persister cells. We are currentlyinvestigating the molecular mechanisms underlying the translationalupregulation of the 53BP1 mRNA in persister cells that may offer apromising therapeutic opportunity to counteract the insurgence ofgenetic resistance.Our studies point towards proposing that 53BP1 and, specifically, thetranslation regulation of its mRNA, would be a mediator of thetransition from drug-tolerant persistence into permanent geneticresistance by favoring NHEJ and persister cells mutability. Inaddition, in melanoma biopsies, we show that 53BP1, together withother translational co-regulated proteins found in persister cells,may constitute a predictive marker of response to targeted therapy.This potentially highlights the importance of the control of mRNAtranslation in a clinical setting.

MAROTTE Lucine

Scientific supervisor : Bernard MALISSEN
Institute : Centre d'immunologie de Marseille-Luminy - Marseille
Team : Biologie intégrative des lymphocytes T et des cellules dendritiques

Optimizing the potency of adoptively transferred tumor-specific human T cells via system-levels analysis of their immune checkpoint signalosomes

Adoptive cell transfer (ACT) therapies are constantly evolving,seeking to combine increased specificity of injected cells withoptimized functional properties. Along that line, genomic editingtechniques of immune checkpoints (IC) intend to increase theanti-tumor efficacy of injected T cells. Accordingly, the team of Dr.Labarriere (INCIT, Nantes, France) in which I did my thesis, haddesigned a method for selection and amplification of melanoma-specificCD8+ T cells from patient blood which had been used in a clinicaltrial (MELSORT, NCT02424916). Then, we have produced tumor-specifichuman effector memory CD8+ T cells unable to express inhibitoryreceptors PD-1 and TIGIT, alone or in combination using CRISPR/Cas9system. PD-1KO clones obtained were characterized in terms ofphenotype, function and transcriptome, and TIGITKO T cell clones arecurrently being characterized. The study of PD-1KO T cell clonesallowed us to highlight changes in TCR activation and TIGIT expressioncompared to their WT counterparts. Therefore, prior to the use of suchT cell clones in therapy, additional information must absolutely beprovided, notably on the consequences of inactivation of one or moreICs on TCR signaling and T cell effector functions.We are currently attempting to answer these questions using expertisedeveloped in the Dr. Malissen's team. More specifically we usedCRISPR/Cas9-based mechanism insertion, of a One-STreP tag at theextremity of key proteins involved activation and TCR signaling tocharacterize the interactomes of the targeted proteins by AffinityPurification and Mass Spectrometry. We therefore began to characterizeTIGIT interactome signaling in human effector memory CD8+ T cells andwill compare it to the TCR interactome of different types of T cellclones lacking PD-1 and/or TIGIT. This study – which bypass the useof mouse models - aims to provide a rational basis for improving theefficacy and resistance to exhaustion of the adoptively transferredtumor-specific T-cells. Although the project focuses on TIGIT andPD-1, the simultaneous inhibition of which is currently used in cancerimmunotherapies, it will provide an integrative approach that can begenerically used to decipher the function and functional cross-talk ofthe ever-growing list of ICs in therapeutic T cells.

MONTEAGUDO SÁNCHEZ Ana

Scientific supervisor : Max GREENBERG
Institute : Institut Jacques Monod - Paris
Team : Chromatin Dynamics in Mammalian Development

Investigating the impact of DNA methylation on chromatin topology and gene regulation during epigenetic reprogramming

DNA methylation is an epigenetic mark typically associated withtranscriptional silencing. During the early stages of mammaliandevelopment, most of the parental epigenetic information, includingDNA methylation, is erased. Subsequently, during implantation, denovo DNA methylation occurs via action of the DNMT3A and DNMT3Benzymes. This period is accompanied by profound changes in thechromatin and transcription landscapes as theembryo prepares forlineage commitment. These changes are accompanied by alterations tothe 3D structure of the genome, which can both facilitate andinsulate cis-regulatory interactions. I aim to investigate how de novo DNA methylation affects chromatinarchitecture during this transition via altered CTCF binding. CTCF,a DNA-binding protein that helps generate DNA loop structures, isDNA methylation-sensitive at a subset of its targets. Importantly,embryonic dynamics are recapitulated in vitro using WTand Dnmt triple knockout (tKO) mouse embryonic stem cell lines,the latter being completely devoid of DNA methylation. To identifyDNA methylation sensitive CTCF binding sites we compared the CTCFbinding profiles in WT and tKO cells and found ~300 DNA methylationsensitive sites. I am currently performing genome-wide chromosomeconformation assays in WT and tKO to determine whether DNAmethylation at CTCF binding sites impacts promoter-enhancerinteractions. Integrated analysis of RNA-seq data will determinewhether impaired enhancer-promoter looping results in aberrant geneexpression. For those affected genes, site-directed epigenomeediting tools will be targeted to candidate CTCF sites in WTcells to directly characterize the impact of themethyl-mark on CTCF binding, expression and chromosomeconformation. This research will allow us to discover a non-canonical role of DNAmethylation-mediated gene regulation that could be critical forproper developmental progression. We also believe we will identifytranscripts regulated by DNA methylation-sensitive CTCF binding sitescritical for development and for cancer biology, where DNAmethylation and genome organization are broadly misregulated.

NAJAFI Javad

Scientific supervisor : Nicolas MINC
Institute : Institut Jacques Monod - Paris
Team : Cellular Spatial Organization

Hydrodynamics of bulk cytoplasm and division positioning

Many studies of cytoplasm mechanics have focused on small componentsat the scale of proteins and macromolecular complexes. However, thecytoplasm also baths large organelles like nuclei, microtubule astersor mitotic spindles that often take significant portions of cells andneed to move across the cytoplasm to regulate cell division orpolarization. Here, we address how cytoplasm fluid mechanics impactthe motion and positioning of large organelles in cells. Weimplemented magnetic tweezers to move with calibrated forces, spindlesor passive large oil droplets in the cytoplasm of living cells. Wefound that for objects larger than the micron size, thecytoplasm behaves as a Jeffreys' material, viscoelastic at shorttime-scales and fluidizing at longer times. However, as componentssize approached that of cells, cytoplasm viscoelastic resistanceincreased in a non-monotonic manner. Flow analysis and simulationssuggest that this size-dependent viscoelasticity emerges fromhydrodynamic interactions between the moving object and the staticcell surface. This effect also yields to position-dependentviscoelasticity with objects initially closer to the cell surfacebeing harder to displace. These findings suggest that the cytoplasmhydrodynamically couples large organelles to the cell surface torestrain their motion, with important implications for cell shapesensing, cellular organization and division.

TRAN NGUYEN Viet Khoa

Scientific supervisor : Pedro BALLESTER
Institute : Centre de Recherche en Cancérologie de Marseille - Marseille
Team : Apprentissage Automatique pour l'Oncologie de Précision et la Conception de Médicaments

Machine-learning scoring functions for structure-based virtual screening applied to cancer targets

This project considers the available biological activities, chemicalligand structures and protein structures for a considered cancertarget. The most suitable algorithms to generate the most predictivecomputational models for virtual screening on that target aredetermined. These models will be constructed using machine learning,which represents a form of artificial intelligence that can amelioratevirtual screening performance by exploiting the fast growing amount ofdata for most targets. A user-friendly and publicly-available protocolimplementing this cutting-edge methodology will be made available, sothat other researchers can also apply it to their targets. In thescope of this project, the protocol will be followed to build modelsspecific to BET (Bromodomain and Extra-Terminal domain) proteins. Thisis a protein family that includes four members, namely BRD2, BRD3,BRD4 and BRDT. A BET protein has two bromodomains (BD1 and BD2), eachwith over 80% sequence identity across the family members. The goal isto design potent small-molecule binders of the BD1 domain of each BETprotein in order to inhibit its interaction with chromatin. A currentchallenge in this area is selectivity: none of the current inhibitorsin the clinic has at least 10-fold selectivity over the other membersof the BET family for the BD1 domains. This is important, asBET-selective inhibitors would be less toxic than pan-BET inhibitors.An exciting opportunity to make progress in this area is buildingBET-specific machine learning scoring functions exploiting therelatively large volume of data that has been accumulating for thesetargets. Since generic machine learning scoring (using data from alltargets) have already shown significant improvements over classicalscoring functions, tailoring them to be BET-specific is expected tolead to even better results on each BET target. This project willenable the direct discovery of potent, selective and diverse BETinhibitors among the 750 million purchasable compounds in the ZINCdatabase.

26e Journées Jeunes Chercheurs en Cancérologie

Posters Hors concours

GABER Mohammed

Scientific supervisor : Pierre VIDI (France) - Katherine Cook (USA)
Institute : Institut de Cancérologie de l'Ouest (France) / Wake Forest University (Etats-unis) - Angers / Winston-Salem
Team : InGeno & Cook's lab

The Microbiome Mediates Carcinogenic Alterations of the Mammary Gland in the Context of Obesity

Obesity increases the relative risk for breast cancer incidence. Multiple molecular mechanisms linked to obesity drive breast cancer progression. However, if and how obesity contributes to breast cancer initiation is poorly understood. Obesity shifts the microbiome in ways that may increase breast cancer risk. Microbial-associated molecular pattern (MAMP)-proteins and metabolites could directly affect breast epithelial cell signaling. In this study, we focused on lipopolysaccharide (LPS), a toll-like receptor 4 (TLR4)-agonist. LPS levels are known to increase in obesity. We hypothesize that chronic low-grade inflammation caused by LPS contributes to breast cancer initiation. To test this hypothesis, we first quantified levels of LPS, along with a panel of adipokines/cytokines, in serum samples from women with different body mass indices (BMI). Donors with high LPS had significantly higher BMI, leptin, and leptin:adiponectin ratio, confirming a link between systemic LPS and metabolic markers of obesity. LPS levels also correlated with pro-inflammatory cytokines such as IL-8. Other biomarkers of breast cancer risk include DNA damage. Analyses of normal breast tissue sections from the same donors revealed higher densities of DNA double-strand breaks (estimated based on 53BP1 foci counts) in women with high serum LPS. Experiments with 3D culture of breast acini showed that LPS increases DNA break frequencies and oxidative stress levels in the mammary epithelium. We also found with this 3D culture system that LPS disrupts epithelial polarity, a hallmark of breast tissue homeostasis. Preliminary data show that LPS activates the nuclear factor-kappa B (NFκB) pathway by binding to the TLR4 receptor, leading to an increased expression of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α). Interestingly, TLR4 blockade prevented the loss of apical polarity and DNA damage induced by LPS. The outcomes of our study underscore the importance of considering the microbiome in the prevention of breast cancer.

HASHEMKHANI Mashid

Scientific supervisor : Florence GAZEAU
Institute : MSC-Med (Laboratoire Matière et Systèmes Complexes) - Paris
Team : Biofluidique

Luminescence nanothermometry for the control and understanding of heat-induced process in biological applications

Temperature is one of the most common physical quantities and contributes greatly to mechanical resistance, chemical reactivity, and biological processes. The pitfalls of temperature readouts are mostly represented by the currently achievable spatial resolution which is too low for nanotechnology and nanoscience requirements. To address key issues, such as intracellular temperature fluctuations and in vivo thermal transients, a technique able to go below 1 µm urgently needed, as the traditional contact-based sensors and near infrared thermometers are not suitable for measurements at that tight spatial range. To overcome these limitations, a non-contact thermometry approach granted with high temporal and spatial resolution called nanothermpmetry has been recently achieved, and also providing real-time high relative thermal sensitivity values.

The goal is to develop a reliable, reproducible, and cost-effective nanothermometry method for applications involving hyperthermia. The objective is to measure the local temperature close to nanoparticles (NPs) heated by a laser. We synthetized nontoxic Ag2S luminescent NPs, to work in in situ and operando environmental conditions (biological compartment, chemical reactor…), and second to allow a non-contact measurement of temperature compatible with hyperthermia application. The temperature-dependent luminescence of NPs was measured using a system to measure the emission ratio and/or decay profiles versus temperature which is applicable for both cells and solution. The effective delivery of that major advance in thermal bioimaging will be implemented through two impactful biomedical showcases: highly spatially-modulated intracellular hyperthermia and detection and tracking of cancer in vitro and in vivo.

In the long-term, we foresee our technology having a broad impact on non-invasive clinical imaging and theranostics. For instance, the accurate measurement of temperature gradients´ sources will be an invaluable tool for real-time control of thermal therapies, thus making them harmless for the patient.

IMERZOUKENE Ghiles

Scientific supervisor : Jacques LE SEYEC & Marie-Thérèse DIMANCHE BOITREL
Institute : IRSET - Rennes
Team : Infection, immunité, facteurs environnementaux et foie

Role of the pseudokinase MLKL in the development of NASH-HCC

The rising incidence of hepatocellular carcinoma (HCC) is driven by the growing epidemic of fatty liver disease. During non-alcoholic steatohepatitis (NASH), a self-perpetuating cycle of cell death and inflammation promotes chronicity leading to cancer. Necroptosis is a form of programmed cell death executed by the mixed lineage kinase domain like pseudokinase (MLKL). After its oligomerization to form pores at the plasma membrane, the necroptotic cell releases damage-associated molecular patterns (DAMPs) fueling the inflammation. Although MLKL has been associated with certain cancers, its involvement in HCC occurring in the context of NASH remains to be defined. To test this hypothesis, male mice genetically modified to specifically prevent MLKL expression in liver parenchymal cells (MlklLPC-KO), in parallel with their wild-type littermate controls (Mlklfl/fl), were subjected to an experimental protocol reproducing the pathogenesis observed in humans. Thus, pups, exposed to streptozotocin to induce hypoinsulinemia, were fed as adults with a high-fat high-sugar diet (HFHSD) for 4, 8 or 12 weeks. Clinical monitoring of mice showed that the lack of MLKL in liver parenchymal cells did not affect the onset of liver damage, steatosis and fibrosis. However, MlklLPC-KO mice displayed a slower evolution of their splenomegaly and also of the appearance of intrahepatic nodular lesions. Furthermore, the number and size of visible nodules and tumors on the surface of the livers from MlklLPC-KO mice were lower. Likewise, their livers had a lower density of glutamine synthetase-positive tumors. In conclusion, our data suggest that MLKL, potentially by activating necroptosis, contributes to carcinogenesis during NASH, revealing a probable pro-tumoral function of this pseudokinase.

RUGGIU Mathilde

Scientific supervisor : Philippe BOUSSO
Institute : Institut Pasteur - Paris
Team : Équipe Dynamique des Réponses Immunes

PD-1 blockade promotes the priming of tumor-specific CD8+ T Cells in the tumor draining lymph node

PD-1 blockade is a powerful immune check-point inhibitor used in many oncologic and haematologic malignancies. PD-1 blockade induces re-invigoration of exhausted T cells but there is some indirect evidences that it could have extratumoral activity. Our aim is to investigate PD-1 blockade action in tumor draining lymph node. We demonstrated that PD-1 blockade promotes tumor specific T cell mobilization, activation and proliferation in tumor draining lymph node.

Here, we identified that PD-1 blockade induced endogenous tumor-specific CD8 T cells accumulation in tumor draining lymph node. We highlighted a global lymph node swelling with mobilization of all immune cell types that we demonstrated to be dependent of type I interferon. Moreover, in draining lymph node, PD-1 blockade improved quality of tumor-specific CD8 T cell activation: activation markers expression, capacity of cytokine secretion, notably pluri-functionality, and long CD8 T cells / dendritic cells interactions visualized by intra-vital imaging. Then, we demonstrated that PD-1 blockade enhanced tumor-specific CD8 T cells proliferation in draining lymph node that was associated with a reshape of T cells cytokine/chemokine landscape.

Our findings reveal that in addition to its activity in tumor micro-environment, PD-1 blockade has a direct action in tumor draining lymph node that enhances tumor-specific CD8 T cell priming.

WATZKY Manon

Scientific supervisor : Benoit MIOTTO
Institute : Institut Cochin - Paris
Team : Epigénétique, réplication de l'ADN et cancer

Dissecting the functions of Hexokinase 2 in cancer: from cell metabolism to the regulation of oncogenicity and stemness features

Elevated glucose uptake and aberrant expression of several glycolytic enzymes have been described as hallmarks of cancer. These alterations are often correlated with cancer aggressiveness, chemotherapy resistance and metastasis occurrence. Numerous studies have shown that overexpression of Hexokinase 2 (HK2), that fuels cells with metabolites required for proliferation and dissemination, is key in these processes. For instance, its deletion impairs tumour growth in mice models and its depletion in human cells blocks cell proliferation. HK2 is a promising target for cancer therapy but inhibitors of its catalytic activity have not been proven efficient and safe in trials. There is thus a need to better describe HK2 function(s) and its downstream targets in cancer cells to find new ways to block its action. Our project addresses this issue.

We demonstrated that stable HK2 overexpression in poorly tumorigenic bone cancer cells is sufficient to increase tumorigenic features. HK2 overexpressing cells acquired the ability to form colonies and to proliferate in an anchorage-independent manner and grow bigger tumours masses when engrafted in zebrafish embryos. Interestingly, we identified that a subset of HK2 overexpressing cells shows features of cancer stem cells including the ability to form 3D spheroids enriched for OCT4 pluripotency factor expression. By flow cytometry, we showed that HK2 overexpression led to the emergence of a rare subpopulation relying on the drug efflux transporter ABCG2. We further confirmed that HK2 regulates this subpopulation in another bone cancer model. In addition to these cellular assays, we carried out proteomics analysis and identified proteins interacting with HK2 and regulated by HK2. HK2 negatively impacts on mechanical signalling and positively regulates the abundance of nuclear proteins and pathways important for tumorigenesis and stemness. We notably identified as new targets of HK2 the membrane protein CAV1 as well as the DNA replication regulator RIF1, two proteins important in cancer. Finally, we observed that HK2 shuttles between the cytoplasm and the nucleus and that this process involves a phosphorylation site of the protein.

In sum, our work reports a new link between HK2 and the regulation of cancer stemness and unsuspected targets of HK2 that might be important for its functions, opening the door to new ways to target HK2's action in cancer cells.

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Prix Kerner

AHO Simon Centre de Recherche en Cancérologie de Lyon

1 Cibler les cellules souches cancéreuses pour traiter le cancer du sein basal-like

Oncologue et doctorant au Centre de Recherche en Cancérologie de Lyon, Simon Aho étudie le cancer basal-like. Ce cancer du sein agressif abrite de redoutables cellules souches cancéreuses à l'origine de son développement. Le jeune chercheur nous en dit plus sur ces cellules intensivement étudiées dans son unité comme cibles potentielles de traitements novateurs.

Pourquoi étudier ce type de cancer ?

En France, on estime qu'1 femme sur 8 développera un cancer du sein. Néanmoins, il existe de nombreux sous-types de gravité variable. Le cancer dit basal-like compte pour environ 15% des cas et ses caractéristiques biologiques offrent peu de possibilités de traitement. Il faut donc mieux le comprendre pour mieux le soigner. Malheureusement, son origine reste méconnue. Mais une piste se dégage : les cellules souches.

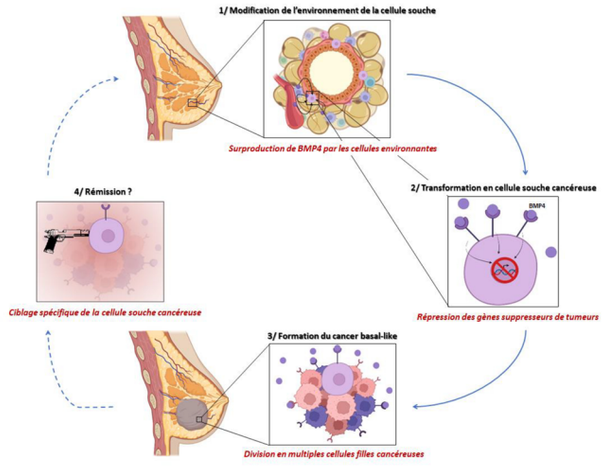
Quel est le rôle de ces cellules et quel rapport avec le développement du cancer ?

Le sein est un organe fait de nombreuses cellules différentes. Par exemple, les cellules productrices de lait, les cellules graisseuses, etc... Ces cellules sont programmées pour mourir avant qu'un vieillissement trop important n'altère leur fonction. Lorsque l'une d'entre elles disparait, il faut néanmoins la remplacer pour maintenir la cohésion de l'organe. C'est le rôle des cellules souches. Elles peuvent se diviser en cellules filles capables de se substituer aux cellules manquantes en acquérant les mêmes caractéristiques.

Le problème, c'est que les cellules souches peuvent parfois devenir cancéreuses. Elles se divisent alors en de multiples cellules filles cancéreuses différentes qui vont former la tumeur. Les cellules souches cancéreuses sont donc essentielles au développement et au maintien du cancer.

Donc vous voulez les éliminer ?

Exactement ! Malheureusement, elles sont peu sensibles aux traitements actuels qui ne sont pas des traitements les ciblant spécifiquement. L'idée est donc d'identifier les mécanismes par lesquels une cellule souche normale va se transformer en cellule souche cancéreuse et se maintenir sous cette forme dans la tumeur. Ainsi, nous espérons proposer des traitements innovants ciblant ces mécanismes.



La formation du cancer du sein basal-like implique l'émergence de cellules souches cancéreuses. Pour traiter plus efficacement la tumeur, Simon Aho et son équipe proposent de les cibler directement.

Qu'avez-vous découvert jusqu'à présent ?

Dans un premier temps, on a observé au microscope de nombreuses tumeurs basal-like de patientes. Dans ces tumeurs, on a mis en évidence une quantité anormale d'une molécule appelée BMP4. Cette molécule est produite par les cellules voisines des cellules souches. En quantité normale elle assure leur viabilité. En quantité trop importante ? On ne sait pas ! Mais nos observations suggèrent un rôle dans leur transformation en cellules souches cancéreuses.

Comment le prouver ?

Et bien nous avons au labo des cellules souches mammaires normales, dans des boîtes où sont réunies toutes les conditions nécessaires à leur survie. Dans ces boîtes j'ajoute des quantités importantes de BMP4 et je regarde l'impact sur les cellules souches à différents temps d'exposition. J'ai déjà montré qu'une exposition de seulement quelques jours conduit à l'inactivation de gènes dits suppresseurs de tumeurs. Leur rôle est de réparer dans la cellule les anomalies qui conduisent à l'apparition du cancer. Ils sont comme un frein au développement tumoral. BMP4 lève donc ce frein, ce qui va accélérer l'émergence de cellules souches cancéreuses et favoriser la formation et le maintien du cancer.

Quelles perspectives ce travail ouvre-t-il ?

Nous avons aussi identifié le récepteur par lequel passe les effets délétères de BMP4. Celui-ci est particulièrement abondant dans les tumeurs basal-like, ce qui pourrait en faire une cible thérapeutique très intéressante à l'avenir ! La route sera longue jusqu'à cette étape mais l'espoir est bien présent.

ARELLANO Carlo Institut de Pharmacologie et de Biologie Structurale - Toulouse

2 Le dialogue cellulaire entre cancer du sein et graisse voisine : une nouvelle piste contre la résistance aux traitements

À l'Institut de Pharmacologie et Biologie Structurale de Toulouse, Carlo Arellano est interne en chirurgie gynécologique s'intéresse à l'interaction entre cellules cancéreuses du sein avec la graisse avoisinante. Cette interaction pourrait être un évènement clé permettant aux tumeurs de résister aux traitements.

Bonjour M. Arellano, quel est l'objectif de vos travaux de recherche ?

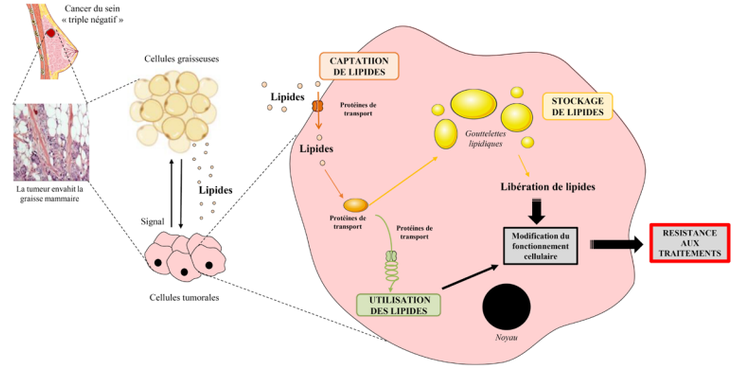
Les cancers du sein dits « triples négatifs » sont souvent très agressifs, concernent souvent la femme jeune et lorsque les patientes répondent mal à la chimiothérapie le risque de rechute est très important. Actuellement on ne sait pas à l'avance quelles patientes vont répondre ou non au traitement. Mon objectif est de démontrer que ce sont les cellules cancéreuses capables d'utiliser les lipides des cellules graisseuses voisines qui seront plus agressives et résistantes aux traitements.

Mais pourquoi travaillez-vous sur cette problématique ?

Une étude récente a montré que ces cancers peuvent se diviser en sous-groupes dépendants de différentes sources d'énergie comme les sucres ou les lipides. Cette étude a également montré que le sous-groupe le plus agressif dépend des lipides de façon plus importante. Si nous montrons que les tumeurs de ce sous-groupe utilisent les lipides des cellules graisseuses et que cette utilisation les rend résistantes aux traitements, nous pourrions alors bloquer le dialogue avec les cellules graisseuses pour améliorer l'effet du traitement.

Quelles méthodes de recherche utilisez- vous ?

Nous utilisons des cellules graisseuses provenant de chirurgies de cancer du sein. Grâce au système de culture mis au point par mon équipe, nous pouvons préserver les cellules graisseuses pendant au moins 5 jours, contrairement aux vieux systèmes de culture où elles ne pouvaient survivre plus d'un jour. Pour comprendre ce système de culture, imaginez-vous une cellule graisseuse enveloppée par une couverture de fibres dans la partie haute d'un lit superposé et une cellule tumorale dans la partie basse du lit, les deux cellules sont séparées d'une fine membrane permettant les échanges dans les deux sens. Ainsi grâce à ce système nous pouvons étudier les changements de comportement des cellules tumorales en présence de cellules graisseuses humaines.



Lorsque le cancer envahit la graisse du sein, un dialogue entre cellules tumorales et adipocytes va s'installer. Ces derniers sous l'influence tumorale, vont libérer des lipides qui seront captés par la cellule cancéreuse, stockés et utilisés dans divers mécanismes pour promouvoir la résistance aux traitements.

Quelles sont les conclusions de vos travaux jusqu'ici ?

Toutes les cellules du cancer du sein dit « triple négatif » sont capables d'induire la libération de lipides par les cellules graisseuses, mais seul le sous-groupe le plus agressif peut les capter massivement. Cela semble être dû à une quantité augmentée de protéines qui captent et intègrent les lipides dans les cellules tumorales. Ces lipides seront stockés dans des gouttelettes et utilisées préférentiellement par la cellule dans divers mécanismes aboutissant à une plus grande résistance aux traitements.

Qu'est-ce que vous espérez accomplir dans l'avenir ?

Nous voulons identifier les protéines responsables de l'augmentation de la captation des lipides, et les mécanismes cellulaires qui mènent à la résistance à la chimiothérapie spécifiquement dans les tumeurs les plus agressives. Si nous caractérisons les protéines en cause, nous pourrons les étudier dans les tumeurs humaines pour identifier les patientes à risque de mauvaise réponse au traitement. De la même manière, nous pourrons développer de nouveaux médicaments qui bloquent la captation et l'utilisation des lipides pour restituer l'effet des thérapies et diminuer le risque de rechute.

BARUL Christine Institut de Recherche Santé Environnement au Travail – Rennes

3 Pesticide et santé : les travailleurs de la banane qui utilisent des mélanges de pesticides auraient un risque plus important de mourir de certains cancers.

Depuis Pointe-à-Pitre en Guadeloupe, la chercheuse en épidémiologie Christine Barul cherche à comprendre si chez les travailleurs de la banane, l'exposition aux pesticides – pas seulement un en particulier, mais un mélange peut plus tard provoquer la mort en raison d'un cancer.

Bonjour Madame Barul, dans ce contexte de pandémie mondiale, nous avons beaucoup entendu parler d'épidémiologie. Quel est le lien avec les recherches que vous menez sur le cancer ?

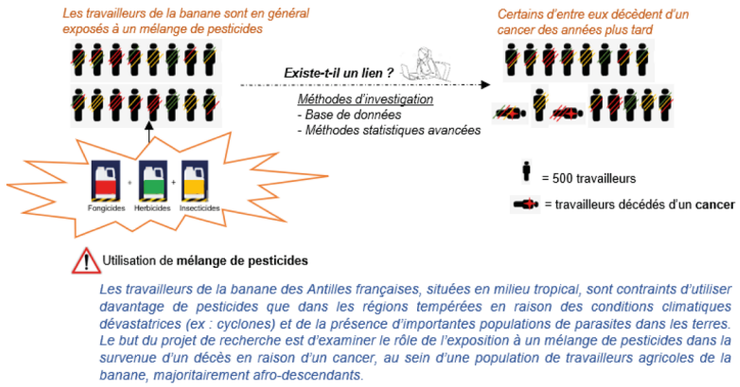
Bonjour, effectivement, quand on entend « épidémiologie », on pense immédiatement à « épidémie ». Mais l'épidémiologie porte également sur l'étude des maladies chroniques incluant les maladies cardio-vasculaires et le cancer. On sait maintenant que plus de 70% de ces maladies seraient dues à des facteurs environnementaux. Certains « coupables » sont bien identifiés, incluant l'amiante et le diesel qui sont responsables de cancers respiratoires. D'autres sont en « garde à vue » car on les suspecte fortement de jouer un rôle dans l'apparition d'un cancer. C'est le cas des pesticides, substances sur lesquelles je mène mes recherches.

Comment menez-vous votre enquête ?

On sait maintenant qu'on a tout a gagner à considérer les pesticides comme agissant en bande organisée plutôt que de façon isolée. On parle alors d'effet mélange. Avec des méthodes de statistiques avancées, je mène une sorte d'interrogatoire en confrontant les données d'exposition aux pesticides et celles des décès par cancer survenant plus tard. L'idée est de déterminer s'il y a un lien entre l'utilisation de mélange de pesticides et le fait de mourir en raison d'un cancer chez les travailleurs de la banane. Mes résultats préliminaires montrent un lien entre l'utilisation à des niveaux élevés de mélange de pesticides et la mort par cancer des globules rouges.

Pourquoi avez-vous décidé de vous intéresser aux travailleurs de la banane des Antilles françaises ?

Il existe très peu de connaissances sur les effets des pesticides sur la santé. Les connaissances que l'on a proviennent majoritairement d'investigations de leur effet « en solitaire » et d'études conduites dans des zones tempérées. Mener mes recherches sur ces travailleurs, c'est d'abord une opportunité de fournir des résultats sur des populations afro-descendantes en manque de données scientifiques, notamment sur le cancer. De plus, en milieu tropical, les conditions climatiques (ex : cyclones) et les nombreuses populations de parasites dans le sol conduisent à une utilisation de pesticides plus importante qu'ailleurs. Nous avons ce type d'environnement en France, particulièrement aux Antilles françaises.



Les travailleurs de la banane des Antilles françaises, situées en milieu tropical, sont contraints d'utiliser davantage de pesticides que dans les régions tempérées en raison des conditions climatiques dévastatrices (ex : cyclones) et de la présence d'importantes populations de parasites dans les terres. Le but du projet de recherche est d'examiner le rôle de l'exposition à un mélange de pesticides dans la survenue d'un décès en raison d'un cancer, au sein d'une population de travailleurs agricoles de la banane, majoritairement afro-descendants.

Vos résultats sont-ils transposables à un agriculteur qui cultive de la pomme de terre dans le Nord de la France ?

Si cet agriculteur utilise des pesticides dans ses champs de pommes de terre, mes résultats de recherche vont directement le concerner car il est sûrement exposé à un mélange de ces substances au quotidien. Il y a également d'autres travailleurs qui sont concernés notamment le personnel affecté à l'entretien des espaces verts ou des chaussées qui seront directement concernés par ces nouvelles connaissances.

Quel impact votre projet peut-il avoir pour les patients ?

Le cancer de la prostate et celui des globules rouges sont les seuls qui sont aujourd'hui reconnus comme maladie professionnelle en lien avec l'exposition aux pesticides en France. Mais qu'en est-il des autres cancers ? Mon rôle est un peu comme celui d'un juge d'instruction qui diligente une enquête pour en savoir plus dans le cadre d'une affaire. L'idée est de fournir des éléments de preuves scientifiques qui vont éclairer la communauté scientifique ainsi que les décideurs en charge de la reconnaissance d'un cancer en tant que maladie professionnelle. C'est un enjeu de reconnaissance important pour les agriculteurs et leurs proches.

LADAIGUE Ségolène Institut Curie - Paris

4 Le pouvoir des tumeurs sur puces : reconstituer l'écosystème d'une tumeur sur un timbre

À l'institut Curie dans le berceau de la cancérologie, Ségolène Ladaigue, chercheuse post-doctorante, participe à la création d'un système de cancer du poumon sur puce vascularisée. Le but ? Miniaturiser un écosystème tumoral cliniquement pertinent pour étudier les mécanismes de résistance aux traitements.

Dr Ladaigue, les tumeurs sur puces qu'est-ce que c'est ?

Les tumeurs sur puces sont des outils permettant de miniaturiser et de reconstituer fidèlement en trois dimensions une tumeur et son écosystème. Les tumeurs sont complexes et sont formées de différents types de cellules. On y retrouve les cellules cancéreuses bien sûr, mais aussi les cellules immunitaires, les cellules de soutien appelées fibroblastes et les vaisseaux sanguins composés de cellules vasculaires.

Il existe des moyens similaires d'étudier les tumeurs, en quoi votre approche est-elle originale ?

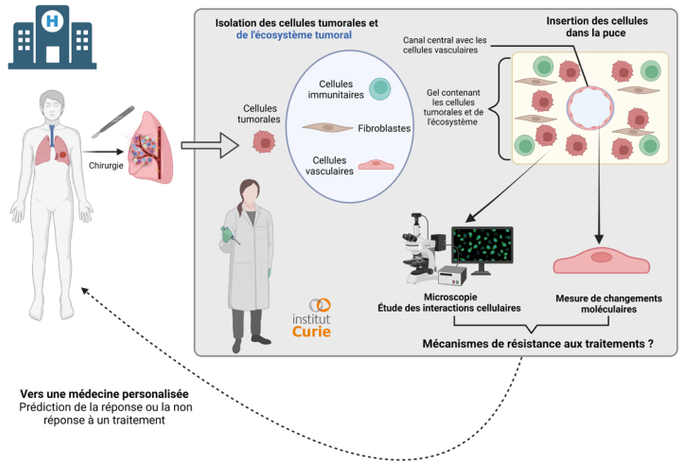
C'est vrai, ce genre de dispositif existe depuis une dizaine d'années. Néanmoins, notre approche est originale car nous isolons nos cellules à partir de pièces opératoires de patients opérés pour un cancer du poumon. En effet, la grande majorité des publications dans le domaine utilisent des lignées cellulaires qui ne représentent pas tout à fait la réalité clinique et biologique.

Dans cet écosystème, est-ce que vous vous intéressez à des cellules particulières ?

Mes cellules de prédilection sont les cellules vasculaires. Pourquoi ? Car elles sont essentielles à la tumeur. En l'absence de vaisseaux sanguins la tumeur a du mal à grandir car elle ne reçoit pas les nutriments nécessaires. Plus récemment, il a été suggéré que les cellules vasculaires pourraient modifier le comportement des cellules immunitaires essentielles pour lutter contre la tumeur.

À quoi ressemble votre tumeur sur puce ?

La puce fait à peu près la taille d'un timbre, on peut y introduire un gel contenant les cellules tumorales et celles de l'écosystème. La particularité c'est qu'au centre de ce gel j'insère une aiguille qui permet de former un canal central. Cette aiguille est ensuite retirée pour ajouter les cellules vasculaires qui tapissent le canal.



Du patient au laboratoire de recherche : création des tumeurs sur puces vascularisées.

Est-ce que c'est techniquement difficile à faire ?

Alors oui, déjà il y a des contraintes organisationnelles car nous collaborons avec l'hôpital et les expériences ne fonctionnent pas toujours. On ne peut pas acheter la puce toute faite, je réalise chaque étape de A à Z : de la production du support à l'isolation des cellules. Parfois ce sont des détails qui nous empêchent d'aller au bout de notre expérience, vous n'imaginez pas comment une simple bulle peut être ennuyeuse (*rires*).

Quel type d'expériences réalisez-vous ? Et quels sont vos derniers résultats ?

L'étude du comportement des cellules les unes par rapport aux autres est possible par microscopie. On peut notamment visualiser et quantifier la mort de cellules tumorales induite par les cellules immunitaires. On peut aussi étudier des changements moléculaires dans une population cellulaire donnée en fonction de nos conditions expérimentales. Nos résultats préliminaires indiquent que la présence de cellules cancéreuses ou de l'écosystème, induit des changements moléculaires chez les cellules vasculaires. Ces changements pourraient contribuer à inactiver les « bonnes » cellules immunitaires aidant à tuer les cellules cancéreuses.

Pour terminer, quel serait l'impact de vos travaux ?

Ces tumeurs sur puces forment des outils cliniquement pertinents par leur architecture et par la présence de cellules de patients. Elles pourraient permettre de découvrir des mécanismes de résistance aux traitements induits par l'écosystème tumoral et identifier des cibles thérapeutiques. À l'avenir nous souhaiterions prédire la réponse ou la non-réponse d'un patient à un traitement pour faire de la médecine personnalisée, la route est encore longue vers ce chemin.

MOIRAGHI Alessandro Institut de Psychiatrie et Neurosciences de Paris

5 Développer un outil pour estimer les risques et les bénéfices de l'ablation chirurgicale d'une tumeur cérébrale

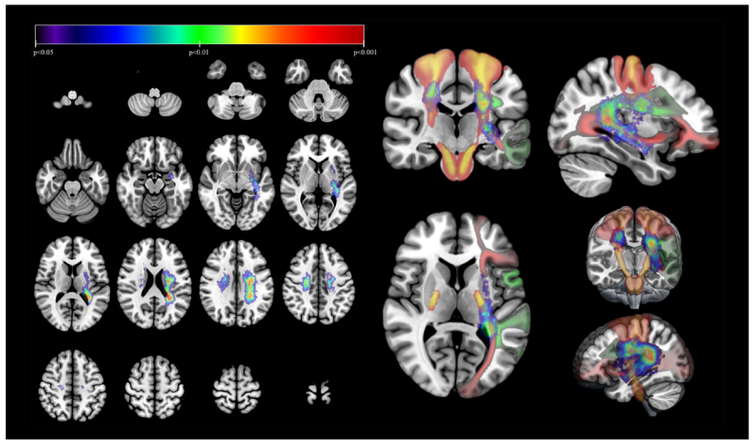
Au GHU Paris on travaille pour développer un atlas de tumeurs du cerveau, pour arriver à établir le taux d'ablation chirurgicale et les risques liés à ce geste.

Bonjour Dr Moiraghi, quel est l'objectif de votre projet ?

Bonjour, j'étudie les gliomes diffus, qui sont les tumeurs du cerveau le plus souvent situées dans des régions du cerveau hautement fonctionnelles, où la résection chirurgicale peut être dangereuse et créer des handicaps au patient (un peu comme dans un AVC).

À ce jour, l'état de l'art est d'opérer ces patients en chirurgie avec le patient éveillé, ce qui permet de tester ses fonctions neurologiques pendant le geste. Tout se base sur l'expérience du chirurgien et sa capacité de faire la balance entre la volonté de retirer le plus de tumeur possible et la nécessité de préserver les fonctions du patient.

Nous n'avons pas d'outils capables de prédire de façon claire, et avant l'opération, la probabilité d'obtenir une résection complète, ou d'identifier les zones plus à risque d'être endommagées.



À gauche les images de l'atlas cérébral avec une représentation en code-couleur de la probabilité de résidu tumoral postopératoire (probabilité élevée en bleu, très élevée en vert, presque certain en rouge). À droite la même image avec reconstruction dans les trois dimensions et superposition de structures fonctionnelles (faisceaux nerveux qui contrôlent la motricité en orange et le langage en vert et en rouge).

Mais alors quel serait le bénéfice pour le chirurgien ?

Aujourd'hui nous n'avons pas un référentiel clair qui puisse aider le chirurgien dans le processus décisionnel. Avec cet atlas on pourrait mieux prédire, seulement en regardant l'IRM du patient et les caractéristiques de la tumeur, les probabilités de retirer complètement la tumeur, sans causer des lésions irréversibles au patient.

L'objectif est d'anticiper avec une meilleure précision les cas dans lesquels retirer la tumeur en totalité n'est pas envisageable à cause des risques trop élevés. Cet outil est conçu pour aider le chirurgien et le patient dans un processus décisionnel difficile et avec une référence basée sur des analyses détaillées.

Comment avez-vous développé cet outil ?

Pour créer l'atlas nous avons analysé chaque gliome diffus opéré en chirurgie éveillée dans notre service. Nous avons annoté des données cliniques des patients et les données des différents composantes tumorales sur l'IRM de chaque patient.

Grace à des logiciels qui permettent le traitement des images radiologiques, on a normalisé les IRM de tous les patients sur un cerveau standard : c'est-à-dire recalées sur une référence commune, qui est la moyenne entre les petites différences anatomiques existantes entre chaque patient.

Sur cette référence commune, grâce à des logiciels qui permettent de superposer les tumeurs de chaque patient, nous avons pu analyser les fréquences avec lesquelles une résection complète ou non, et l'apparition d'un déficit ou non, se sont produites et à quel endroit exact du cerveau.

Quelle est l'évolution en termes de perspectives futures de votre projet ?

Notre objectif est l'application clinique dans le processus décisionnel. Le patient aussi pourra mieux comprendre les enjeux liés à l'acte chirurgical et discuter en conscience la prise en charge avec son chirurgien. Pour arriver à ce résultat, nous travaillons sur l'automatisation du processus d'analyse d'image, en essayant de le rendre plus rapide et simple, pour qu'il devienne une routine aussi dans la clinique et pas seulement pour la recherche.

Grace à ce développement technique, nous pourrions agrandir la base de données qui forme l'atlas, avec des données de suivi à distance de la chirurgie, et inclure des patients d'autres centres de référence en Europe. Avec une base de référence très large, l'atlas aura une capacité de prédire les risques encore plus précise et fiable.

TIGHANIMINE Khaled Institut Necker Enfants Malades - Paris

6 L'accumulation des lipides entraîne l'induction de la sénescence et de l'inflammation.

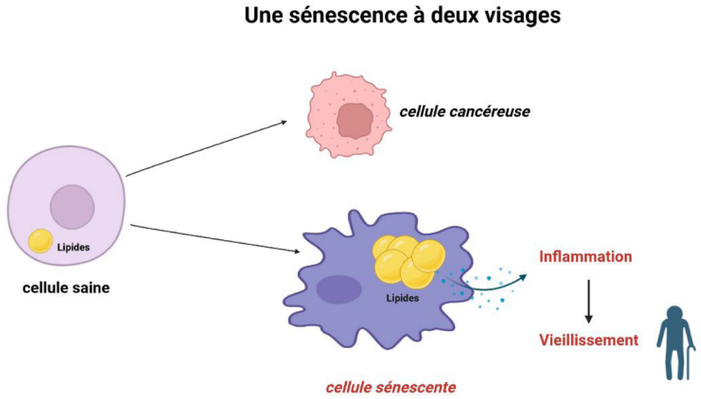
À l'Institut Necker à Paris, on s'intéresse à l'induction de la sénescence qui est un mécanisme naturel de suppression de tumeurs. Cependant, la sénescence participe aussi à l'inflammation dans l'organisme. L'objectif de Khaled est de trouver un moyen d'induire la sénescence chez les cellules pré-tumorales tout en réduisant l'inflammation qui en résulte.

Bonjour Mr Tighanimine, qu'est-ce que la sénescence ?

Bonjour. Je fais souvent l'analogie entre la sénescence et l'histoire de « Dr Jekyll et Mr Hyde ». La sénescence, c'est le destin d'une cellule qui va s'empêcher elle-même de devenir cancéreuse. C'est-à-dire que quand une cellule sent qu'elle va devenir tumorale, elle se met en état « sénescent », ce qui fait qu'elle ne prolifère plus mais ne meurt pas non plus. C'est son côté Dr Jekyll. À la suite de ça, elle va sécréter plein de molécules inflammatoires pour prévenir le système immunitaire. Celui-ci va donc se mobiliser pour la tuer. Or, plus un organisme vieillit, plus le système immunitaire est défaillant. Ce qui fait que l'élimination des cellules sénescentes est de moins en moins performante avec l'âge. On s'aperçoit donc qu'il y a une accumulation de cellules sénescentes chez les personnes âgées. Ces cellules vont s'accumuler dans les organes et les tissus et induire une inflammation persistante. À la longue, cette inflammation fait apparaître les maladies liées au vieillissement. Les cellules sénescentes deviennent donc délétères. C'est leur côté Mr Hyde.

Quelle a été votre approche pour étudier cette sénescence ?

Dans mon équipe à Necker, on est spécialisés dans le métabolisme des nutriments à l'intérieur des cellules. Par exemple, une cellule normale va ingérer une molécule de glucose et l'utiliser pour une tâche donnée. Dans les cellules sénescentes, j'ai remarqué que le destin des nutriments ingérés changeait radicalement. Ces cellules vont se mettre à fabriquer un grand nombre de lipides et les stocker dans des « poches » dédiées à ça. Ce qui est intéressant, c'est que j'ai réussi à démontrer que « booster » artificiellement la synthèse des lipides poussait des cellules pré-tumorales à devenir sénescentes. Ça, c'est le côté Dr Jekyll de ces lipides. Malheureusement, ce stock de lipides joue un rôle fondamental dans l'inflammation. C'est leur côté Mr Hyde.



Lorsque soumise à un stress, une cellule peut devenir cancéreuse ou à l'inverse devenir sénescente. L'accumulation des lipides (en jaune) joue un rôle fondamental dans le destin qu'aura cette cellule. Cependant, ces lipides participent activement à l'inflammation des cellules sénescentes, et donc à l'apparition des maladies liées au vieillissement.

Comment avez-vous fait pour étudier l'accumulation de ces lipides ?

Une des techniques que j'ai utilisées s'appelle la spectrométrie de masse. C'est un outil qui permet de caractériser la nature des molécules qu'on a dans un échantillon. Par exemple, ça permet de discriminer les protéines, les lipides, les glucides, etc. Grâce à ça, j'ai pu connaître la nature des lipides qui s'accumulent pendant la sénescence. Ensuite, j'ai utilisé de la microscopie pour localiser ces lipides à l'intérieur des cellules sénescentes.

Quel intérêt peuvent avoir vos résultats à l'avenir ?

Actuellement, je travaille sur une molécule qui va peut-être nous permettre de résoudre la question de l'ambivalence de la sénescence. C'est une molécule qui permet de réduire la synthèse des lipides suffisamment pour réduire l'inflammation, mais pas trop non plus pour permettre aux cellules pré-tumorales de devenir sénescentes. C'est donc une molécule avec un potentiel anti-cancéreux aussi bien qu'anti-vieillissement. On débutera des essais sur des souris et des vers de terre dans les prochains mois.

VASSAUX Maxime Institut de Physique de Rennes

7 Prédire pour mieux guérir : comprendre comment les sarcomes osseux se développent, avec des ordinateurs

En utilisant les lois de la physique, des chercheurs rennais tentent de comprendre comment des cellules cancéreuses sont capables de proliférer en détournant les mécanismes de construction de l'os.

À quel type de cancer vous intéressez-vous dans le cadre de vos travaux de recherche ?

Je cherche à modéliser la formation d'un ostéosarcome, une tumeur maligne qui apparaît dans l'os, notamment l'os en croissance. Il s'agit d'un donc d'une tumeur un peu spéciale du fait qu'elle touche principalement les adolescents.

Quelle question vous posez-vous au sujet de l'ostéosarcome ?

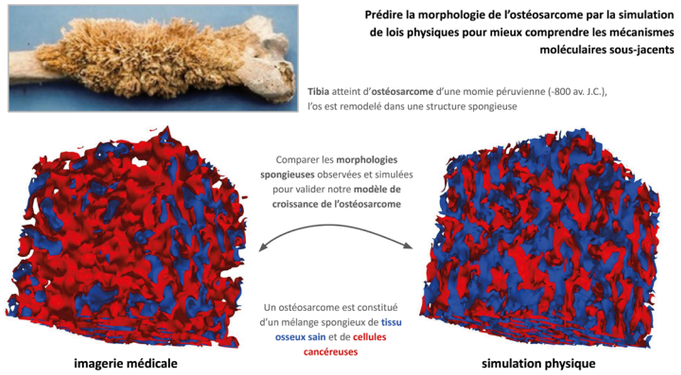
Je cherche à comprendre la morphologie de l'ostéosarcome et par quels mécanismes physiques des cellules cancéreuses transforment un os sain en un tissu dont la forme évoque une éponge. Une chose bien connue de l'ostéosarcome est qu'il se développe en perturbant le remodelage osseux.

Les cell... Un instant, qu'est-ce que le remodelage osseux ?

Ah, c'est vrai, l'os n'en a pas l'air, mais il se forme et se résorbe en permanence. Les constituants de l'os, le collagène, la partie souple et l'apatite, la partie rigide, sont assemblés, désassemblés et réassemblés en continu. Un peu comme sur un chantier de construction, l'os serait un bâtiment en béton armé, le collagène faisant office de béton et l'apatite d'acier. Un premier type de cellules, les ostéoblastes, oeuvrent à couler le béton renforcé par des armatures en acier. Mais il s'agit d'un chantier un peu particulier. Un second type cellulaire, les ostéoclastes, démantèle le béton lorsqu'il n'est pas utile ou légèrement endommagé. Les constituants du béton sont alors réemployés par le premier groupe d'ouvriers cellulaires.

Et donc les cellules seraient capables de perturber ce remodelage ?

Exactement, l'ostéosarcome résulte d'une communication perturbée entre les cellules ouvrières. Il en résulte une structure spongieuse, friable, et non plus compacte, résistante. Plus étonnant encore, les cellules cancéreuses semblent capables d'interférer à distance avec le chantier qui se trouve près des cartilages de croissance. Le messager prends probablement la forme d'une molécule, mais nous n'en connaissons pas encore les caractéristiques physiques qui permettraient de l'intercepter. C'est là que mon travail de recherche commence.



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En quoi consiste ce travail de recherche ?

Avec Franck Artzner et Arnaud Bardouil, nous avons émis l'hypothèse que l'interaction entre les cellules cancéreuses et les cellules osseuses peut être modélisée par un système dit de réaction-diffusion. Les paramètres de ce modèle physique sont liés à la taille de la molécule messager, et son affinité avec les cellules ouvrières. Je suis alors capable de simuler l'évolution de la structure du tissu pour un large spectre de molécules, aux caractéristiques différentes. Si par chance, j'arrive à trouver un jeu de paramètres qui permet de reproduire la structure spongieuse, j'obtiens alors des informations précieuses sur le messager.

Mais comment savoir si ce messager existe réellement ?

Pour cela, nous comparons les résultats avec des observations expérimentales. Des biologistes de l'INSERM nous fournissent des images en 3D de tissus osseux de souris remodelés en présence de cellules cancéreuses. Si les deux structures spongieuses se ressemblent, alors nous considérons que notre hypothèse est valide, et que nous tenons là des informations pertinentes sur notre messager.

Je comprends mieux votre démarche de physicien. Et d'ailleurs, à quel stade en est votre recherche ?

Un de nos premiers résultats a été de soutenir l'hypothèse du modèle de réaction-diffusion, et donc de montrer qu'il y a bien un messager moléculaire émis par les cellules cancéreuses qui perturbe le remodelage osseux. Il semblerait que pour observer un remodelage spongieux de la structure de l'os caractéristique de l'ostéosarcome, un messager rapide soit nécessaire. La molécule en question doit donc être de petite taille ou posséder une forte affinité avec les cellules ouvrières. Ces informations préliminaires restent relatives, mais à terme nous espérons pouvoir dessiner le portrait robot précis de notre messager, afin d'élaborer des pistes pour le déstabiliser.

VILIMOVA Monika Institut de Biologie Moléculaire et Cellulaire - Strasbourg

8 Couper le mal à la racine : nouvelle stratégie de lutte contre un oncovirus

Micro-organismes emblématiques des dernières années, les virus peuvent engendrer des maladies diverses et variées telles que la grippe ou le SIDA pour ne citer que celles-ci. Mais saviez-vous que certains pouvaient causer également des cancers ? En réalité, on estime que jusqu'à 15% de tous les cancers sont dus à des infections virales. Au cours de sa thèse effectuée au sein de l'Institut de Biologie Moléculaire et Cellulaire (IBMC) à Strasbourg, Monika Vilimova a consacré ses études à l'un de ces redoutables parasites, le KSHV. Elle nous présente aujourd'hui ses travaux qui visent à inspirer le développement de futures thérapies.

Pourquoi est-il important de s'intéresser à ce virus en particulier ?

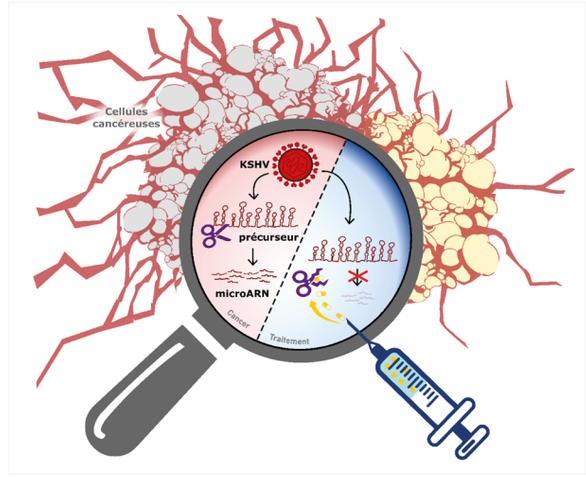
Le KSHV est un oncovirus, donc un virus qui provoque le développement de cancers. De plus, les cancers induits par le KSHV ne sont pas traitables avec les thérapies actuelles, en partie parce que nous ne savons pas cibler le virus lui-même. Il est donc urgent de chercher des pistes thérapeutiques originales et innovantes. Pour cela, nous avons besoin de connaître en détail le fonctionnement du virus et de comprendre comment il entraîne le développement cancéreux.

Plus précisément, quel aspect du virus étudiez-vous ?

Je m'intéresse en particulier à l'une des tactiques mises en place par le KSHV afin de survivre dans nos cellules. Cette tactique consiste à produire une grande quantité de petites molécules appelées microARN. Ces microARN interfèrent avec le fonctionnement normal de nombreux mécanismes cellulaires ou les détournent à l'avantage du virus. Par exemple, certains d'entre eux permettent au KSHV d'échapper à notre système immunitaire. D'autres poussent nos cellules à se multiplier de manière anarchique. De façon générale, les microARN permettent au KSHV non seulement de persister, mais aussi de favoriser la formation des cancers.

Quel est l'objectif de votre recherche ?

Je cherche une méthode efficace afin de priver le virus de ses microARN. En réalité, nous ne sommes pas le seul laboratoire qui s'intéresse aux microARN du KSHV et l'idée de les éliminer dans un but thérapeutique n'est pas toute nouvelle. Certains ont déjà développé des molécules qui pourraient cibler tel ou tel microARN unique. Cependant, le KSHV produit plus d'une dizaine de microARN différents et pour qu'un traitement puisse empêcher tous leurs effets néfastes, il faudrait un véritable cocktail de traitements différents. Ce type de thérapie est compliqué à mettre en place... Dans notre laboratoire, nous avons opté pour une autre approche. Nous avons décidé de ne pas cibler les microARN matures, mais de prendre le problème à la racine, c'est-à-dire d'agir en amont de leur production.



Les microARN du KSHV participent directement à la formation des cancers. Une méthode visant à empêcher leur production pourrait faire partie de futures thérapies.

Quelle a été votre démarche ?

Tout d'abord, il fallait bien comprendre comment les microARN étaient produits. On savait déjà qu'au départ, tous les microARN proviennent d'une seule longue molécule qu'on appelle un précurseur. Ce dernier est progressivement découpé en petits morceaux qui deviennent des microARN matures. Pour en savoir plus, j'ai cultivé des cellules cancéreuses infectées avec le KSHV et j'ai minutieusement suivi le découpage du précurseur par des protéines qu'on pourrait imaginer comme des ciseaux moléculaires. Le but était d'identifier un point faible de ce mécanisme qu'on pourrait ensuite cibler avec un traitement. Ainsi, j'ai découvert une étape clé qui déclenche tout le processus de découpage ce qui m'a permis de développer une méthode pour le bloquer. Après avoir testé cette méthode sur des cellules cancéreuses en culture, j'ai pu constater qu'il était possible d'empêcher la production de tous les microARN en utilisant une seule molécule thérapeutique. Dans le futur, cette stratégie pourrait être adaptée dans de nouveaux traitements.

Liste des participants 2022

39 • **ABDI GALAB Mahdia** • Centre de biologie intégrative - Toulouse
40/82 • **AHO Simon** • Centre de Recherche en Cancérologie de Lyon
14 • **AMALRIC Amandine** • Institut des Neurosciences - Montpellier
31/83 • **ARELLANO Carlo** • Institut de Pharmacologie et de Biologie Structurale - Toulouse
33 • **ARQUE Basilia** • Centre de recherche des Cordeliers – Paris
24/84 • **BARUL Christine** • Institut de Recherche Santé Environnement au Travail - Rennes
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49 • **FRIEDRICH Chloé** • Institut Cochin - Paris
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78 • **IMERZOUKENE Ghiles** • IRSET - Rennes
51 • **JULIA Edith** • Centre International de Recherche en Infectiologie - Lyon
85 • **LADAIGUE Ségolène** • Institut Curie - Paris
52 • **LALETIN Vladimir** • Centre de Recherche en Cancérologie de Marseille
53 • **LIAN Yen-Ling** • Institut Curie - Paris
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54 • **MONROSE Mélusine** • Centre de recherche bio-clinique - Clermont-Ferrand
72 • **MONTEAGUDO SÁNCHEZ Ana** • Institut Jacques Monod - Paris
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58 • **POTEAU Marion** • Gustave Roussy - Villejuif
59 • **REYNAUD Amandine** • Centre Léon Berard - Lyon
37 • **ROULLEAUX DUGAGE Matthieu** • Gustave Roussy - Villejuif
79 • **RUGGIU Mathilde** • Institut Pasteur - Paris
60 • **SAOUT Judikael** • Institut de Recherche Santé Environnement et Travail - Rennes
61 • **SCHIRMEISEN Kamila** • Institut Curie - Orsay
62 • **SEBA Mohammed** • Institut de Biologie Intégrative de la Cellule - Gif-sur-Yvette
63 • **THOMAS Morgane** • CRIBL - Limoges
64/87 • **TIGHANIMINE Khaled** • Institut Necker Enfants Malades - Paris
74 • **TRAN NGUYEN Viet Khoa** • Centre de Recherche en Cancérologie de Marseille
88 • **VASSAUX Maxime** • Institut de Physique de Rennes
21/89 • **VILIMOVA Monika** • Institut de Biologie Moléculaire et Cellulaire - Strasbourg
22 • **WANG Yanan** • Ecole polytechnique - Palaiseau
80 • **WATZKY Manon** • Institut Cochin - Paris
65 • **WILLIART Alice** • Institut Curie - Paris
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