FONDATION ARC
POUR LA RECHERCHE
SUR LE CANCER
Reconnue d'utilité publique

25èmes JOURNÉES JEUNES CHERCHEURS EN CANCÉROLOGIE

LIVRET SCIENTIFIQUE

18 et 19 Novembre 2021

#JJC2021

Éditorial

Gilbert LENOIR

Vice-Président de la Fondation ARC pour la recherche sur le cancer

La Fondation ARC mesure le rôle central que vous, jeunes chercheurs, jouez pour la réussite de notre mission, vaincre le cancer. Elle est convaincue de l'importance de vous soutenir et de s'assurer que vous êtes formés dans les meilleurs laboratoires. Dans un contexte bouleversé par la crise sanitaire mondiale, la Fondation a confirmé son engagement. Ainsi, l'année dernière, vous êtes plus d'une centaine à avoir bénéficié d'un soutien pour mener à bien vos travaux de master, de thèse ou de post-doctorat. Aujourd'hui nous avons occasion 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 : ils ont hâte de partager les espoirs que suscitent vos travaux.

Nancy ABOU-ZEID

Directrice Scientifique de la Fondation ARC

La Fondation ARC met tout en œuvre pour accompagner la formation des futurs chercheurs et médecins. Cette formation ne serait pas complète si nous ne vous encouragions pas à interagir et à échanger entre scientifiques. Ces Journées sont justement l'occasion pour vous de rencontrer des chercheurs issus d'horizons divers et de partager avec eux vos expériences et vos résultats, de confronter des concepts et des approches, et de générer peut-être de nouvelles hypothèses ou de nouvelles collaborations. Vous profiterez également du regard aiguisé d'un jury de grande qualité, mobilisé pour évaluer vos travaux et vous aider à les mettre en perspective. En plus de vos compétences et de votre rigueur, la Fondation souhaite valoriser curiosité, ouverture d'esprit et imagination !

Marie-Caroline DIEU-NOSJEAN

Présidente du Jury Hélène Starck 2021
Présidente de la Commission Nationale 1 de la Fondation ARC
Directrice de recherche au Centre d'Immunologie et des Maladies Infectieuses

En tant que membre des instances scientifiques de la Fondation ARC, je mesure l'importance stratégique que revêt la formation des jeunes chercheurs au sein de la Fondation ARC. En 2020, nous avons examiné près de 550 demandes de financement de jeunes chercheurs. Plus de 120 experts se sont ainsi mobilisés pour identifier les candidats les plus prometteurs et dont les travaux contribuent significativement à la recherche sur le cancer. L'exercice est complexe mais d'une incroyable richesse ! Cette année, j'ai également l'honneur de présider le jury des Prix Hélène Starck avec à mes côtés plusieurs membres de ces instances. La grande qualité des résumés reçus reflète une fois de plus toute la diversité de vos approches et l'excellence des travaux que vous menez. Nous sommes impatients de vous écouter.

JURYS DES PRIX
HÉLÈNE STARCK ET KERNER 2021

JURY HÉLÈNE STARCK 2021

Marie-Caroline DIEU-NOSJEAN, Présidente du Jury
Centre d'Immunologie et des Maladies Infectieuses, Paris

Johanna CHICHE, Centre Méditerranéen de Médecine Moléculaire, Nice
Bertrand DUBOIS, Centre de Recherche en Cancérologie de Lyon
Sandrine FAURE, Université de Montpellier
Jean-Noël FREUND, Université de Strasbourg
Caroline HOFFMANN, Institut Curie, Paris
Emmanuelle JAUFFRET, Centre de Recherche en Cancérologie de Marseille
Yohann LORIOT, Gustave Roussy, Villejuif
Hadia MOINDJIE, Gustave Roussy, Villejuif
Catherine MULLER-STAUMONT, Institut de Pharmacologie et de Biologie Structurale, Toulouse
Santos A. SUSIN, Centre de Recherche des Cordeliers, Paris
Lucas WALTZER, Génétique, Reproduction & Développement(GReD), Clermont-Ferrand
Michel WERNER, Institut Jacques Monod, Paris

JURY KERNER 2021

Florence COTTIN, La Provence
Héloïse DUFOUR, Présidente du Cercle FSER
Jean-Marc GALAN, Chercheur au CNRS & Médiateur Scientifique
Karelle GOUTORBE, Le Quotidien du Médecin
Jimmy MOHAMED, France 5 (Le Magazine de la Santé)
Sandrine MOUCHET, Rose Magazine
Éléonore PERES, Présidente et Rédactrice en chef de Papier-Mâché
Renaud POURPRE, Facilitateur de Science, Co-fondateur de Lonely Pipettes
Emmanuelle REY, La Dépêche du Midi Édition Toulouse
Aurélie SIPOS, Le Parisien
Anaïs THIÉBAUX, Le Journal des Femmes

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Programme

Jeudi 18 novembre

8h30 – 9h00 • **Accueil des participants**

9h00 – 9h10 • **Introduction de la journée** par **François DUPRÉ**, Directeur Général de la Fondation ARC et **Marie-Caroline DIEU-NOSJEAN**, Présidente du Jury Hélène Starck

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

- **Nicolas AUBERT,** Centre d'Immunologie et des Maladies Infectieuses, Paris
  Validation of novel immune checkpoints in vivo for cancer immunotherapy
- **Alexandre CASANOVA,** Institut pour l'Avancée des Biosciences, La Tronche
  SMYD2 drives breast cancer metastatic dissemination through BCAR3 methylation
- **Juan de Dios BARBA TENA,** Institut de Génétique Moléculaire, Montpellier
  Role of DNA polymerase α phosphorylation in homologous recombination
- **Camille LANDRAGIN,** Institut Curie, Paris
  Mapping early steps of Brca1-tumorigenesis: identification of p16-high cells with heterochromatin re-organization undergoing dedifferenciation and EMT
- **Pauline LANDWERLIN,** Institut de Génétique et Biologie Moléculaire, Illkirch
  Study of the human Cohesin SMC1/SMC3/RAD21/STAG1-2 complex and its implication in cancer
- **Margaux LECACHEUR,** Centre Méditerranéen de Médecine Moléculaire, Nice
  Role of mechanotransduction in melanoma cell plasticity and progression
- **Jacinthe MEKARY,** Institut de Génétique Moléculaire, Montpellier
  New theranostic ligands targeting two nutrient transporters that control serine or glutamine-dependent tumors
- **Mélanie ROUSSEAU,** Institut de Recherche en Cancérologie de Montpellier
  Role of E4F1 in melanocyte homeostasis and melanoma development

11h10 – 11h30 • **Pause café**

11h30 – 13h00 • **Session 2 - Prix Hélène Starck Oral** - Catégorie Post-Doctorat

- **Mohamed ABOUELMAATY,** Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch - **Single-cell analyses unravel cell type–specific responses to a vitamin D analog in prostatic precancerous lesions**
- **Pierre BOURDELY,** Institut Cochin, Paris
  Delineating the activation of tissue-resident memory CD8+ T cells in lung adenocarcinoma
- **Gergo GOGL,** Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch
  Perturbation of host interaction networks by viral oncoproteins
- **Xavier GUILLORY,** Centre de Lutte Contre le Cancer Eugène Marquis, Rennes
  Development of novel blood brain barrier-permeable IRE1 inhibitors for adjuvant therapy in glioblastoma
- **Leticia LERNER,** Centre de Recherche des Cordeliers, Paris
  Metabolic specificities in chronic lymphocytic leukemia: Combination of metabolism and PARP inhibitors as a potential therapy against the drug-resistant forms of the disease
- **Annabelle SUISSE,** Institut Curie, Paris
  Consequences of monosomy: How stem cells can lose their female identity and start tumors

13h00 – 14h00 • **Déjeuner et délibération du jury Starck sur les oraux**

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16h00 – 16h30 • **Session Posters & Pause café**

Programme

Vendredi 19 novembre

8h30 – 9h00 • Accueil des participants

9h00 – 9h05 • Introduction de la journée par **Nancy ABOU-ZEID**, Directrice scientifique de la Fondation ARC

9h05 – 10h30 • Table Ronde Jeunes Chercheurs
« La parole libérée des chercheurs »

Héloise DUFOUR, Directrice du Cercle FSER
Jean-Marc GALAN, Chercheur au CNRS et Médiateur Scientifique
Éléonore PERES, Présidente et rédactrice en chef de Papier-Mâché
Renaud POURPRE, Facilitateur de Science & Co-fondateur de Lonely Pipettes

et les témoignages de

Rafael ARGÜELLO, Chargé de Recherche au Centre d'Immunologie de Marseille-Luminy
Florent PÉGLION, Post-doctorant à l'Institut Pasteur Paris

10h30 – 10h50 • Pause café

9h30 – 10h50 • Accueil des donateurs par **François DUPRÉ**, Directeur Général de la Fondation ARC

Prix Kerner : Présentation orale en 180 secondes des candidats

- **Anaïs ASSOUVIE,** Institut de Radiobiologie Cellulaire et Moléculaire, Paris
  Personnaliser les thérapies anticancéreuses : quand la génétique s'en mêle
- **Blandine BAUDON,** Institut Curie, Paris
  Exploiter le génome silencieux pour améliorer les protocoles d'immunothérapie
- **Charlotte DEGOUTTE,** Institut Necker, Paris
  Le meilleur traitement cible dans un cancer rare des jeunes
- **Théo DESIGAUX,** Unité Mixte de Recherche en Bio ingénierie Tissulaire, Bordeaux
  Cancer du sein : l'imprimer en 3D pour mieux l'étudier
- **Camille LANDRAGIN,** Institut Curie, Paris
  La cacophonie de l'épigénome impliquée dans le développement des tumeurs du sein
- **Marion LE GRAND,** Centre de Recherche en Cancérologie de Marseille
  Révéler les secrets des médicaments pour aider les enfants atteints de cancer
- **Luca SIMULA,** Institut Cochin, Paris
  Optimiser l'alimentation des cellules pour combattre le cancer
- **Isabelle TIHY DAMEI,** Gustave Roussy, Villejuif
  Immunothérapie : À la recherche d'un facteur prédictif
- **Yoann ZELMAT,** Faculté de Médecine de Purpan, Toulouse
  Le Big Data au service de la santé

12h30 – 14h00 • Déjeuner avec les donateurs, les chercheurs et les membres de la Fondation ARC

14h00 – 15h15 • Table Ronde Grand Public - « Jeunes chercheurs, des parcours engagés et multiples »

1 • Des maillons essentiels pour faire avancer la recherche

Johanna CHICHE, Centre Méditerranéen de Médecine Moléculaire, Nice
Margaux LECACHEUR, Centre Méditerranéen de Médecine Moléculaire, Nice
Benoît TESSOULIN, CHU Nantes

2 • Fuite des cerveaux, mythe ou réalité ?

Marion LE GRAND, Centre de Recherche en Cancérologie de Marseille
Camille LOBRY, Institut de Recherche Saint Louis Paris
Maya SALEH, ImmunoConcEpT Bordeaux
Jessica ZUCMAN-ROSSI, Centre de Recherche des Cordeliers, Paris

15h15 – 16h15 • Cérémonie de remise des prix Hélène Starck, prix Kerner et prix « Coup de coeur » des donateurs animée par **Gilbert LENOIR**, Vice-président de la Fondation ARC

16h15 • Cocktail

Table ronde jeunes chercheurs

LA PAROLE LIBÉRÉE DES CHERCHEURS

La communication sur les sujets scientifiques et sur le monde de la recherche est de plus en plus foisonnante et il est très facile de s'y perdre. Libérer la voix des chercheurs est une nécessité, comme en attestent les deux dernières années de crise sanitaire. Cependant, les messages sont multiples, parfois complexes et il existe autant de sujets que d'émetteurs, de destinataires ou de moyens de les diffuser. Dans ce contexte, finalement, « ce qui compte vraiment, c'est que votre message soit bien compris ». Autour de cette table ronde, nos invités vous donneront un aperçu du domaine de la médiation scientifique en France, la diversité de ses métiers et l'importance de s'y former. Ils exploreront avec vous la variété des dispositifs existants et l'explosion de la communication scientifique sur les réseaux sociaux avec les avantages et les inconvénients que cela représente. Ils partageront leurs expériences personnelles et les objectifs qu'ils se fixent pour rendre toujours plus accessibles leurs projets et leurs domaines.

INVITÉS

Héloise DUFOUR

Directrice du cercle FSER

Titulaire d'un doctorat en neurobiologie, Héloïse Dufour a travaillé plus de dix ans dans des laboratoires en France et à l'international sur les thèmes des neurosciences, du développement et de l'évolution. Après avoir longtemps conjugué ses pratiques de médiation scientifique avec son activité de recherche, elle choisit de se concentrer sur la diffusion de la culture scientifique. Elle dirige depuis sa création le Cercle FSER, qui agit sur deux axes principaux : diffuser la culture scientifique auprès des jeunes publics et favoriser l'engagement des chercheurs dans la médiation scientifique. Elle est également responsable du groupe de travail sur ce sujet au sein de EuroScitizen, réseau de recherche financé par l'UE, qu'elle a initié et vice-présidé jusqu'en 2021.

Jean-Marc GALAN

Chercheur au CNRS et Médiateur Scientifique

Après une carrière de recherche au CNRS en biologie cellulaire, Jean-Marc Galan se consacre à la médiation scientifique. Producteur et animateur de l'émission de radio Recherche en cours, il est également responsable du cycle de conférences pluridisciplinaires Treize minutes. Il enseigne la communication des sciences pour différents publics (doctorants, chercheurs, étudiants en journalisme scientifique) et coordonne le diplôme universitaire Médiation scientifique innovante. Il anime régulièrement des conférences & tables rondes sur des thématiques scientifiques en général et en particulier sur les problématiques qui ont trait aux relations science et société.

Eléonore PERES

Présidente et rédactrice en chef de Papier-Mâché

Dans le cadre de sa thèse sur les propriétés leucémogènes de la protéine Tax du rétrovirus HTLV-1 au Laboratoire de Biologie et Modélisation de la Cellule à l'ENS de Lyon, Eléonore PERES a souhaité travailler au plus proche de l'humain, et a donc déployé son projet sur un modèle de souris humanisée. Titulaire d'un doctorat, elle a ensuite décidé de se réorienter dans la vulgarisation et la médiation scientifique. Elle a poursuivi sa formation par un M2 de communication scientifique à Grenoble qui lui a permis de travailler 6 mois dans l'émission La Méthode Scientifique de France Culture. Elle a également travaillé dans l'édition scolaire, tout en concrétisant une idée qu'elle avait depuis quelques années : un site où seraient accessibles gratuitement les publications scientifiques, mais vulgarisées pour que tout le monde puisse les comprendre, c'est ainsi qu'est né le site de Papier-Mâché. Elle est aujourd'hui rédactrice scientifique pour une association de défense de l'environnement.

Renaud POURPRE

Facilitateur de Science & Co-fondateur de Lonely Pipettes

Docteur en biologie, il se consacre au soutien de la recherche scientifique via la production et la diffusion des connaissances. Il crée du contenus audio/vidéo en étroite collaboration avec les scientifiques et coordonne des initiatives au profit du dialogue science-société. Il est ainsi directeur artistique du documentaire et spectacle immersif Cell Worlds, cofondateur du podcast The Lonely Pipette et porte-parole de l'Exploratoire, le 1er incubateur de la culture Open Science. Il croit aux bénéfices d'une culture scientifique ouverte qui casse les murs entre la science et les citoyen.nes. Il a donc œuvré dans l'événementiel scientifique tel que Pint of science, Le Collectif Conscience et la Fête de la science au sein du Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation. Enfin, pour démultiplier la diffusion du savoir, il a cofondé ComSciCon France, un workshop unique de formation à la communication scientifique.

TÉMOIGNAGES

Rafael ARGÜELLO

Chargé de Recherche au Centre d'Immunologie de Marseille-Luminy

Originaire d'Argentine, Rafael Argüello rejoint Marseille en 2013 pour effectuer un post-doctorat. Il est aujourd'hui chargé de recherche au Centre d'immunologie de Marseille-Luminy. Il était l'un des 5 chercheurs sélectionnés et coachés par l'humoriste engagé Karim Duval pour intégrer la série #Invivo de la Fondation ARC et expliquer face camera, avec humour, de façon décalée et passionnante, la nature très pointue de ses travaux de recherche.

Florent PEGLION

Post-doctorant à l'Institut Pasteur à Paris

Post-doctorant à l'Institut Pasteur, il a obtenu le 1er Prix Kerner de vulgarisation scientifique de la Fondation ARC attribué par un jury de journalistes aux Journées Jeunes Chercheurs 2020. Son article intitulé « Tumeurs Cérébrales : les nageoires de l'espoir » a permis d'expliquer ses travaux de recherche sous forme d'un article de presse attractif et compréhensible sans rien sacrifier au fond.

Table ronde grand public

JEUNES CHERCHEURS, DES PARCOURS ENGAGÉS ET MULTIPLES

La table-ronde proposée cette année aux donateurs et aux jeunes chercheurs sera l'occasion de faire découvrir la réalité complexe des parcours des jeunes chercheurs, de mieux comprendre les défis auxquels ils font face tout au long de leur carrière naissante mais surtout de mieux appréhender leur rôle dans la recherche en cancérologie. Comment la Fondation ARC et, plus généralement, les institutions de la recherche en France accompagnent-elles ces parcours ? Comment la mobilité internationale contribue-t-elle à la riche diversité des profils et des expertises ? Une attention particulière sera portée à cette mobilité, qui peut aussi devenir un problème pour la recherche française… Lorsque le retour des talents s'avère difficile. Jeunes chercheurs, chercheurs confirmés qui ont monté une équipe en France, directrices d'unités de recherche impliquées dans différentes instances stratégiques pour la recherche française ou nouvellement arrivée sur le territoire… Toutes et tous nos invité.e.s pourront témoigner de leur expérience et éclairer un sujet fondamental pour la recherche et son devenir.

DES MAILLONS ESSENTIELS POUR FAIRE AVANCER LA RECHERCHE

Johanna CHICHE

Centre Méditerranéen de Médecine Moléculaire, Nice

Johanna Chiche a bâti son parcours autour de deux disciplines complémentaires, la chimie et la biologie. Diplômée Ingénieur chimiste en 2005, elle obtient un doctorat de biologie cellulaire sous la direction de Jacques Pouyssegur en 2009. En 2011, elle rejoint l'équipe de Jean-Ehrland Ricci au Centre méditerranéen de médecine moléculaire, à Nice, pour y effectuer un post-doctorat. En 2013, le prix Hélène Starck de la Fondation ARC récompense son travail sur l'identification d'un nouvel acteur de la progression tumorale. En 2016, Johanna Chiche est recrutée en tant que chargé de recherche à l'Inserm dans la commission « Cancérologie et maladies génétiques ». Elle s'intéresse actuellement au métabolisme des cellules de certains lymphomes.

Margaux LECACHEUR

Centre Méditerranéen de Médecine Moléculaire, Nice

Margaux Lecacheur effectue sa thèse dans l'équipe du Dr Sophie Tartare-Deckert pour étudier le rôle de la rigidité matricielle dans la progression, la plasticité et la résistance thérapeutique du mélanome. Elle a réalisé son cursus universitaire à l'Université de Nice, en Sciences de la Vie et de la Santé. Elle a réalisé son premier stage de recherche, en Master 1, dans l'équipe du Dr Tartare-Deckert sur le rôle de la mécanotransduction dans la résistance thérapeutique du mélanome. Sa seconde expérience de recherche, en Master 2, s'est déroulée dans l'équipe du Dr Cédric Gaggioli, pour étudier le rôle de la rigidité matricielle dans l'invasion collective des carcinomes cutanés.

Benoît TESSOULIN

CHU Nantes

Benoît Tessoulin est hématologue clinicien au CHU de Nantes. Il a effectué son internat au CHU de Nantes et a complété sa formation au CHU de Lyon. Sa formation médicale a été enrichie d'une thèse de sciences en oncologie, puis d'un post-doctorat à Stanford dont il revient cette année. Praticien Hospitalier au CHU de Nantes, son activité clinique est axée sur la prise en charge des cancers du système immunitaire, lymphomes et des myélomes. Il est membre du Groupe LYSA d'études des Lymphomes, participant aux développements cliniques de nouvelles stratégies thérapeutiques et de surveillance, tout en poursuivant une activité de recherche fondamentale sur le microenvironnement tumoral.

FUITE DES CERVEAUX, MYTHE OU RÉALITÉ ?

Marion LE GRAND

Centre de Recherche en Cancérologie de Marseille

Marion Le Grand est pharmacienne et chercheuse en post-doctorat au Centre de recherche en cancérologie de Marseille. Sa curiosité pour la recherche médicale est née lors d'un stage au Centre de lutte contre le cancer de Rennes, lors de sa 5e année de pharmacie. Après une thèse de science, elle s'est rendue en Australie pour travailler dans un institut dédié à la lutte contre les cancers pédiatriques. L'énergie et la combativité des enfants malades qu'elle a pu rencontrer ont forgé sa vocation. Depuis son retour en France, ses projets de recherche se concentrent sur l'identification de nouvelles cibles thérapeutiques et le développement des traitements plus efficaces en oncopédiatrie.

Camille LOBRY

Institut de Recherche Saint-Louis, Paris

En 15 ans de carrière, Camille Lobry s'est frayé un chemin exemplaire dans la recherche en cancérologie. Convaincue de son potentiel, la Fondation ARC l'a soutenu dès 2007 pour la poursuite de sa thèse. Sa volonté le pousse ensuite à réaliser son post-doctorat aux États-Unis, où il fera une découverte décisive sur l'impact de l'environnement cellulaire dans la formation des cancers du sang. Dès son retour en France en 2014, la Fondation ARC lui a permis de monter sa propre équipe de recherche pour décrypter la formation de divers cancers du sang et identifier ainsi les cibles de nouveaux traitements à développer. Avec son équipe, il déposera un brevet pour développer des médicaments anticancéreux contre la leucémie aigüe myéloïde, cancer du sang fréquent chez les plus de 60 ans. Aujourd'hui, group leader à l'Institut de Recherche Saint-Louis, centre de renommée internationale en hématologie à Paris, il poursuit ses recherches pour identifier de nouvelles cibles thérapeutiques et encadre à son tour de jeunes chercheurs talentueux.

Maya SALEH

ImmunoConcEpT, Bordeaux

Maya Saleh a obtenu son PhD en biochimie à l'Université McGill au Canada en 2001. Après deux post-doctorats au Canada et aux États-Unis, elle a accédé au poste de Professeur en médecine au sein de l'Université McGill en 2005. Elle y est directrice du programme « Inflammation et cancer » de 2011 à 2019. En 2019, Maya Saleh est lauréate du programme Leader international en oncologie de la Fondation ARC. Grâce à la subvention obtenue, Maya Saleh a pu installer une nouvelle équipe au sein du laboratoire ImmunoConcEpT à Bordeaux, afin d'étudier le lien entre traitement par immunothérapie, immunité innée, réponse anti-tumorale et influence du microbiome sur ces interactions. C'est dans ce cadre que la lauréate vient d'accéder au poste de Professeur des Universités à Bordeaux (PU).

Jessica ZUCMAN-ROSSI

Centre de Recherche des Cordeliers, Paris

Jessica Zucman-Rossi est professeur de médecine à l'Université de Paris, au sein du département d'oncologie de l'Hôpital Européen Georges Pompidou (AP-HP). Elle est directrice du Centre de Recherche des Cordeliers et de l'équipe «Génomique Fonctionnelle des Tumeurs Solides». Son groupe est pionnier dans l'élucidation de la classification moléculaire des tumeurs hépatiques bénignes et malignes. Elle est actuellement présidente de l'International Liver Cancer Association (ILCA), rédactrice en chef du journal européen en libre accès de l'EASL «Journal of Hepatology Reports» et présidente du Comité d'orientation de la recherche de la Fondation ARC.

PRIX HÉLÈNE STARCK ORAL

CATÉGORIE DOCTORAT

AUBERT Nicolas
Scientific supervisor: MARODON Gilles - Immunology and Infectious Diseases Center, U1135, Immunoregulation and Therapy of Autoimmunity and Cancer Team, PARIS

Validation of novel immune checkpoints in vivo for cancer immunotherapy

Context & Objectives
Cancer immune escape is mainly dependent of three mechanisms: becoming invisible to the immune system, hijack regulatory cells or directly suppress antitumor immune response. In the last few years, the development of immune checkpoint inhibitors to counter these last mechanisms has been a major breakthrough in cancer therapy. However, not all patients are responsive. Thus, new strategies to enhance antitumor immune responses are needed. The main goal of the project is to validate new potential molecules, expressed by the tumor and that may negatively influence the antitumor immune response directly or via the promotion of regulatory cells. First, we choose to focus on HVEM which may be involved in inhibition of antitumor T-cells response through BTLA. For that, we used a murine monoclonal antibody to human HVEM in PBMC-humanized NSG mice grafted with human tumor cell lines, allowing us to study effect of HVEM blockade on both human T-cells and tumor cells. We first showed that HVEM and BTLA mRNA expression levels were associated with a worse progression-free interval in patients with prostate adenocarcinomas, indicating a detrimental role for the HVEM/BTLA immune checkpoint during prostate cancer progression. We then showed that administration of a monoclonal antibody to human HVEM resulted in a reduction in the growth of a prostate cancer cell. Using CRISPR/Cas9, we showed that the therapeutic effect of the mAb depended on HVEM expression by the tumor, with no effect on graft vs. host disease or activation of human T cells in the spleen. In contrast, the proliferation and number of tumor-infiltrating leukocytes increased following treatment, and depletion of CD8+ T cells partly alleviated treatment's efficacy. The expression of genes belonging to various T cell activation pathways was enriched in tumor-infiltrating leukocytes, whereas genes associated with immuno-suppressive pathways were decreased, possibly resulting in modifications of leukocyte adhesion and motility. Finally, we developed a simple in vivo assay in humanized mice to directly demonstrate that HVEM expressed by the tumor is an immune checkpoint for T cell-mediated tumor control. Our results show that targeting HVEM is a promising strategy for prostate cancer immunotherapy. Now, we are planning to use this model of CRISPR-engineered tumor in humanized mouse to investigate the influence of ICOSL and 41BBL expression by the tumor on the antitumor immune response.

Publications
Blockade of HVEM for Prostate Cancer Immunotherapy in Humanized Mice – Cancers. 2021. N Aubert*, S Brunel*, D Olive, G Marodon (* co-first)

CASANOVA Alexandre
Scientific supervisor: REYNOIRD Nicolas
Institute for Advanced Biosciences, UMR5309, LA TRONCHE

SMYD2 drives breast cancer metastatic dissemination through BCAR3 methylation

Context & Objectives
Improved therapy has greatly ameliorated breast cancer patient's survival, but malignant breast cancer refractory or becoming resistant to existing therapies remains a major issue due to metastatic spreading. Here, we show that the lysine methyltransferase SMYD2 drives breast cancer metastases, and that its repression in transgenic mouse models prevents metastases formation. We identify BCAR3 as a genuine substrate of SMYD2 in breast cancer cells, and show that loss of BCAR3 methylation impairs aggressive breast cancer cell migration and invasiveness. Mechanistically, we find that methylated BCAR3 interacts with the actin cytoskeleton regulators FMNLs proteins through a new reader domain. Notably, BCAR3 methylation recruits FMNLs to lamellipodia and is required for proper lamellipodia fitness. Breast cancer cells in which BCAR3 methylation is impeded fail to spread or to promote tumors in mouse. Finally, we demonstrate the therapeutic value of targeting SMYD2-BCAR3 lysine methylation signaling in breast cancer, by showing that SMYD2 genetic and pharmacologic inhibition alters lamellipodia strength, impairs breast cancer cells invasiveness, and limits metastatic dissemination.

Publications
Lysine Methyltransferases Signaling: Histones are Just the Tip of the Iceberg - Current Protein & Peptide Science. 2020. V Lukinović, A G. Casanova, G S. Roth, F Chuffart and N Reynoird

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Role of DNA polymerase α phosphorylation in homologous recombination

Context & Objectives

Chromosome instability is a hallmark of cancer but how and when during the cell cycle these DNA rearrangements take place is not fully understood. In conditions of strong replication stress during S phase, stalled or collapsed forks are recognized by the DNA Damage Response (DDR) checkpoint, repaired and reestablished to allow DNA replication to be completed before mitosis begins. However, it has been shown that upon low replication stress cancer cells can enter mitosis with unreplicated DNA and synthesize DNA in a process called Mitotic DNA synthesis (MiDAS). It is proposed that this process uses a recombination-dependent mechanism to finish DNA synthesis, at the expense of genome integrity. How MiDAS is initiated in mitosis and exploited by cancer cells is not fully understood.

Using baker's yeast as a model system, we recreated conditions where, by slowing DNA replication genetically, cells enter mitosis with under-replicated DNA and perform MiDAS without activating the DDR during S phase. DNA polymerase α (Polα) is responsible for the initiation of DNA synthesis on the leading strand and for every lagging strand Okazaki fragment. We discovered that Polα is hyper-phosphorylated by cyclin-dependent kinase (CDK) at mitotic entry on its Pol1 and Pol12 subunits, and that this phosphorylation is essential for the survival of late-replicating cells. Strikingly, non-phosphorylable Polα mutants have no phenotype in unperturbed cell cycles, but are lethal in cells that need to complete DNA synthesis in mitosis. We show that DNA Polα phosphorylation allows DDR activation in cells with under-replicated DNA, thus providing time to perform MiDAS. Our work identifies DNA Polα as a major player in the switch from normal to recombination-dependent DNA synthesis in mitosis.

Human DNA Polα is also hyper-phosphorylated in mitosis, suggesting a conserved role. Another line of research in the lab has shown that cancer cells replicate their DNA more slowly (unpublished) and may therefore use MiDAS for chromosome rearrangements and tumor progression. Thus advancing our knowledge on the role and regulation of DNA Polα phosphorylation may lead to new therapies against cancer.

PRIX HÉLÈNE STARCK ORAL
CATÉGORIE DOCTORAT

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Mapping early steps of Brca1-tumorigenesis: identification of p16-high cells with heterochromatin re-organization undergoing dedifferenciation and EMT

Context & Objectives

TNBC refers to a subgroup of aggressive breast cancers defined by the lack of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) accounting for 15–20% of all breast tumors. Along with transcriptional heterogeneity, TNBC is characterized by complex genomes, dictated by high genetic instability and complex patterns of copy number alterations and chromosomal rearrangements (Pareira et al. 2016). Defects in double-strand repair mechanisms - both through germline or somatic inactivation of repair genes - is a hallmark of basal-like breast cancers - subgroup associated with TNBC. In this genetically-unstable context, occurs a recurrent major shift in cell identity within the mammary epithelium: basal-like BRCA1 tumors are indeed suspected to originate from luminal progenitor cells (Perou et al. 2000, Molyneux et al. 2010). Such context-specificity of the BRCA1-induced tumorigenesis highlights the need for an integrative molecular history, combining genetic and non-genetic features, to understand tumor-initiating events and state-transitions. Here, we map the evolution of the epithelium compartment towards tumor formation in a Brca1 and Tp53 deficient context. We identify a population of cycling p16-high cells, emerging from the luminal progenitor compartment, undergoing epithelial-to-mesenchymal transition and losing luminal identity. Pseudo-temporal analyses position these cells as a transitory state between aberrant Brca1-deficient luminal progenitors and growing tumor cells. We further model this transition using mammary organoids from juxta-tumoral epithelium, naturally transforming ex vivo. During initial transformation, cells undergo an epigenomic crisis attested by the general re-organization of their heterochromatin. They simultaneously accumulate multiple H3K27me3 micro-foci - reminiscent of the formation of senescence-associated heterochromatin foci (SAHFs) (Zhang et al. 2007) - and lose their inactive X (Xi) – a hallmark of BRCA1-mutated cancers (Sirchia et al. 2005). In humans, we identify such SAHF-like structures across BRCA1 mutated tumors, which could be a scar from an initial transitory senescent-like state. We propose this transitory state as a target for early detection and interception of tumors in BRCA1-carriers.

LANDWERLIN Pauline
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Institute of Genetics and Molecular and Cellular Biology (IGBMC), U1258, ILLKIRCH

Study of the human Cohesin SMC1/SMC3/RAD21/STAG1-2 complex and its implication in cancer

Context & Objectives

The structure of chromatin and its modulation by epigenetic mechanisms govern the access to our genetic information, thus regulating nuclear processes with direct consequences on health and disease. It is therefore essential to characterize the structure/function relationships of epigenetic effectors to assist in the diagnosis and the development of new treatments against cancer. Cohesin is a major player of this regulation through its functions in sister chromatid cohesion, chromosome cohesion, DNA repair, transcription regulation and genome organization. Cohesin is mutated in many solid cancers (bladder cancer, glioblastoma, melanoma) and leukemia, and is considered as a significant therapeutic target. Cohesin is a complex of 4 proteins, SMC1A, SMC3, RAD21 and STAG1-2, which adopt a ring-shaped structure allowing the DNA entrapment. Cohesin has an ATPase activity which is at the core of its various functions. This activity is driven by specific domains of SMC1A and SMC3, called heads. These domains can interact together upon ATP binding. Despite the importance of human Cohesin in pathophysiology, our knowledge of the dynamics and functions of this complex and how these are influenced by its ATPase activity remains incomplete. I focus my work on the human Cohesin ATPase module by studying by biochemical, biophysical and structural approaches the SMC1A and SMC3 heads in their apo and ADP-bound states as well as upon their interaction in presence of ATP. I have shown that SMC1A and SMC3 heads can adopt different conformations depending on their nucleotide binding state. Moreover, my structures reveal novel and important insight into the dynamics of the ATPase module, including the flexibility of the SMC3 superhelix that interacts with the RAD21 N-terminal region. This flexibility has never been observed to date and locks SMC3 in an ATP hydrolysis inactive state. Our data show that heads interaction is insufficient to stimulate the Cohesin ATPase activity and that other structural changes driven by the binding of DNA and NIPBL (Cohesin loader) are essential for stimulation. I am pursuing the characterization of Cohesin by investigating the effect of its 4th subunit STAG1-2 on its ATPase activity. Collectively my results reveal novel mechanisms of the human Cohesin that enable us to better understand its physiological functions and that open new avenues to develop therapeutical strategies targeting this complex in multiple cancers.

PRIX HÉLÈNE STARCK ORAL
CATÉGORIE DOCTORAT

LECACHEUR Margaux
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Role of mechanotransduction in melanoma cell plasticity and progression

Context & Objectives

Melanoma tumours are highly heterogeneous and display remarkable cell plasticity. Melanoma cells can switch between two distinct cell states, referred to as the melanocytic and mesenchymal-like invasive cell state. They are characterized, respectively, by their level expression of the melanocytic transcription factor MITF or the tyrosine kinase receptor AXL. Studies of the team focus on the role of tumour microenvironment and cues that drive melanoma phenotypic plasticity. Cancers develop within a complex and dynamic microenvironment composed of various non-malignant cells and extracellular matrix. The physical nature of the extracellular matrix greatly influences the progression and dissemination of various solid cancers, but its role in melanoma progression and heterogeneity is poorly described. We use melanoma cell lines and cells freshly isolated from melanoma patient biopsies representative of the melanocytic state or the mesenchymal-like state. To mimic changes in biomechanical signal of the melanoma microenvironment, we use in vitro models of collagen-coated polyacrylamide hydrogels with increasing stiffness. Our results demonstrate that seeding melanoma cells on high stiffness increases their proliferation, their migration and their invasive abilities. The stiffness induced increase of melanoma aggressive features is stronger on mesenchymal-like than melanocytic melanoma cells. We show that it occurs through the activation of the main mechanosensory YAP by the collagen receptors DDR1 and DDR2. These results show that the mesenchymal-like cell state displays a mechanosensitive phenotype that drives cell proliferation and invasion. This work demonstrates the unexpected role of the collagen receptors DDR in mechanotransduction and it will lead to a better understanding of melanoma heterogeneity through the dialogue between melanoma cells and their microenvironment.

MEKARY Jacinthe
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New theranostic ligands targeting two nutrient transporters that control serine or glutamine-dependent tumors

Context & Objectives

Tumor processes are governed by changes in cell metabolism and in particular by changes in the expression of nutrient transporters of the solute carrier family (SLC). Notably, SLC1A4/ASCT1 and SLC1A5/ASCT2, which are both neutral amino acid transporters, have been identified as key players in the serine-dependent liposarcomas, and the glutamine-dependent pancreatic adenomas, respectively. Both cancer types critically lag in treatment discovery, and tracking SLCs has been a difficult endeavor due to the lack of reliable antibodies that bind SLCs at the cell surface. Our group has identified cancer-associated SLCs as retrovirus receptors, and took advantage of this property to derive new soluble SLC ligands from retroviral envelope receptor-binding domains (RBDs). However, all RBDs generated thus far could not distinguish between the serine (SLC1A4) and the glutamine (SLC1A5) transporters. Using experiment-based modelization on 6 retrovirus envelopes that bind both SLC1A4 and SLC1A5, we generated a collection of RBD constructs and mutants that allowed us to: 1) identify a key residue responsible for binding to SLC1A4/ASCT1 and SLC1A5/ASCT2, 2) discard the role of a previously suspected highly conserved SDGGG motif in binding, 3) identify determinants that control binding specificity, located outside of the receptor-binding motif and the SDGGG motif, and 4) derive new soluble RBDs that specifically bind either SLC1A4/ASCT1 or SLC1A5/ASCT2. Using the new SLC1A4-specific RBD in immunohistochemical (IHC) profiling of patient tumors (CRB-ICM biobanks), we distinguish the marked staining of liposarcoma tumoral issues, with no or only a faint staining in the non-tumoral surrounding tissues. We are furthering IHC studies on other SLC1A4/ASCT1 or SLC1A5/ASCT2-dependent types of tumors, and, based on the specific inhibitory properties of our new RBDs on serine or glutamine transport in cell culture, we will next evaluate RBD nanoparticles as novel imaging and treatment agents using mouse xenograft models.

ROUSSEAU Mélanie
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Role of E4F1 in melanocyte homeostasis and melanoma development

Context & Objectives

Melanin, a pigment produced in melanocytes, is essential to protect the skin against UV induced DNA damages. Melanin synthesis is under the control of the master regulator of melanocyte homeostasis, MITF, which regulates the expression of the melanogenesis enzymes. Through many signaling pathways and transcription factors have been shown to regulate MITF, some cellular events leading to its deregulation remains to be identified. The multifunctional protein E4F1, an important regulator of the p53 tumor suppressor pathway, is a major player in skin homeostasis, controlling epidermal stem cell maintenance through its involvement in the regulation of the Bmi1-Arf-p53 pathway and the control of mitochondrial activity. Speculating that E4F1 might play a role in other skin cell types, we sought to determine E4f1 functions in melanocytes. Using genetically engineered mouse models enabling conditional inactivation of E4f1, I demonstrated that specific inactivation of E4f1 in melanocytes induces severe coat and skin pigmentation defects without impacting melanocyte survival nor differentiation. At the molecular level, I established that E4f1 depletion leads to the disruption of the Elongator complex, a complex involved in some tRNA modifications. The resulting translation defects induce an unfolded protein response that in turn repress MITF and melanogenesis enzymes transcriptional expression. Altogether, these data identified E4f1 as a new regulator of melanocyte homeostasis through the control of MITF and melanogenesis. Interestingly, MITF expression is frequently deregulated in melanoma, a type of cancer derived from melanocytes. A low expression of MITF has been associated with an aggressive tumor profile and resistance to targeted therapies. Thus, we now aim to further characterize the role of E4f1 in melanoma development, progression and drug resistance.

PRIX HÉLÈNE STARCK ORAL

CATÉGORIE POST-DOCTORAT

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Single-cell analyses unravel cell type–specific responses to a vitamin D analog in prostatic precancerous lesions

Context & Objectives
Epidemiological data have linked vitamin D deficiency to the onset and severity of various cancers, including prostate cancer, and although in vitro studies have demonstrated anticancer activities for vitamin D, clinical trials provided conflicting results. To determine the impact of vitamin D signaling on prostatic precancerous lesions, we treated genetically engineered Pten(i)pe-/- mice harboring prostatic intraepithelial neoplasia (PIN) with Gemini-72, a vitamin D analog with reported anticancer activities. We show that this analog induces apoptosis in senescent PINs, normalizes extracellular matrix remodeling by stromal fibroblasts, and reduces the prostatic infiltration of immunosuppressive myeloid-derived suppressor cells. Moreover, single-cell RNA-sequencing analysis demonstrates that while a subset of luminal cells expressing Krt8, Krt4, and Tacstd2 (termed luminal-C cells) is lost by such a treatment, antiapoptotic pathways are induced in persistent luminal-C cells. Therefore, our findings delineate the distinct responses of PINs and the microenvironment to Gemini-72, and shed light on mechanisms that limit treatment's efficacy.

Publications
Single-cell analyses unravel cell type–specific responses to a vitamin D analog in prostatic precancerous lesions. - Science Advances. 2021. M A. Abu el Maaty, E Grelet, C Keime, A-I Rerra, J Gantzer, C Emprou, J Terzic, R Lutzing, J-M Bornert, G Laverny, D Metzger.

PRIX HÉLÈNE STARCK ORAL
CATÉGORIE POST-DOCTORAT

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Delineating the activation of tissue-resident memory CD8+ T cells in lung adenocarcinoma

Background
CD8+ T cells play a pivotal role in providing effective antigen-specific immunity against tumors. Activated CD8+ T cells can be classified as effectors (Teff), effector memory (TEM), lymph node-associated memory (TCM) and tissue resident memory (TRM). Lung adenocarcinoma infiltration by TRM is associated with favorable clinical outcome and improved responses to immunotherapy. The dendritic cells (DCs) are a heterogeneous population of phagocytes migrating from tumor to draining mediastinal lymph nodes (MedLN) where they prime naïve T cells.

Aims
Here, we aimed at identifying the DC population priming TRM in a murine model of Kras-dependent lung adenocarcinoma (KP; KrasG12D, p53-/-).

Results
We show that KP tumor induces a strong infiltration of CD103+CD69+ CD8+ TRM concomitant with an increased infiltration of phagocytes, DCs and macrophages, and DC migration in the MedLN. TRM infiltration in tumor is lost in DC-deficient FLT3L-/-, but not CCR2-/-, monocyte deficient mice. KP tumor induces the differentiation and infiltration of DC1s and CD103+Mgl2+ DC2 subset in the lung. This process is controlled by the release of GM-CSF by tumors. DC1 and CD103+Mgl2+ DC2s uptake and cross present tumor antigens by MHC I after migrating to lymph nodes. Impairment of DC1 in XCR1-DTA mice and CD103+Mgl2+ DC2s differentiation in IRF4-deficient mice and prevents the accrual of TRM in KP tumors.

In summary, both DC1s and DC2s seem to be needed for a full in vivo TRM differentiation. Current experiments aim at elucidating the cooperation of DC population in TRM activation.

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Perturbation of host interaction networks by viral oncoproteins

Context & Objectives
Human cells have ~500,000 already identified interactions and likely much more that is still awaiting experimental investigation. Specific interaction networks, organized around classes of peptide recognition domain families are extremely rich parts of interactomes. These extensive and interconnected domain-motif networks are often prone to perturbations under pathological conditions. For example, proteins with functional PDZ-binding motifs are often found in viruses, including human papillomavirus (HPV), human T-lymphotropic virus (HTLV), hepatitis b virus (HBV), West Nile virus (WNV), and coronaviruses, such as SARS-CoV2. These viral proteins, with the help of their binding motifs target various host PDZ-containing proteins thereby provoking various molecular events. For example, if they are expressed at sufficient concentrations, they may out-compete the binding of other host PBM proteins to their common PDZ-targets. Viral proteins may also alter their binding partners directly, via enzymatic reactions, or indirectly, by scaffolding them to other proteins. Eventually, these events can collectively lead to a general perturbation in the host. Here, we present an unprecedented affinity survey of the human interactome that focuses on the sub-network that is mostly exposed to viral perturbation by HPV-E6 and HTLV1-TAX1 oncoproteins. We experimentally measured 65,000 interactions involving 266 human PDZ domains (practically the complete «PDZome»), 424 human PDZ-Binding Motifs (~10% of the human «PBMome») and 24 viral motifs. Independent mass-spectometry-based experiments and database surveys demonstrated the strong agreement of the results of our quantitative fragment-based assay with interactomic data of full-length proteins. We evidence extensive hot spots for viral interference and our results shed light on the complexity of viral hijacking mechanisms.

Publications
Hierarchized phosphotarget binding by the seven human 14-3-3 isoforms - Nature Communications. 2021. G Gogl, K V Tugaeva, P Eberling, C Kostmann, G Trave, N N Sluchanko.

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Dual specificity PDZ-and 14-3-3-binding motifs: a structural and interactomics study – Structure. 2020. G Gogl, P Jane, C Caillet-Saguy, C Kostmann, G Bich, A Cousido-Siah, L Nyitray, R Vincentelli, N Wolff, Y Nomine, N N Sluchanko, G Trave

PRIX HÉLÈNE STARCK ORAL
CATÉGORIE POST-DOCTORAT

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Development of novel blood brain barrier-permeable IRE1 inhibitors for adjuvant therapy in glioblastoma

Context & Objectives
Inositol Requiring Enzyme 1 (IRE1), an Endoplasmic Reticulum (ER)-resident type I transmembrane protein, exerts a dual catalytic activity including kinase and endoribonuclease (RNase). IRE1 transduces ER stress and contributes to the Unfolded Protein Response (UPR). IRE1 signals through the non-canonical splicing of XBP1 mRNA and/or through regulated IRE1-dependent decay (RIDD) of RNA. It is involved in several diseases such as immune, metabolic and degenerative disorders as well as cancer. Tumour cells experience ER stress due to adverse environmental cues such as hypoxia or nutrient shortage as well as high metabolic/protein folding demand. To cope with those stresses, cancer cells utilize IRE1 signalling as an adaptive mechanism and it has been proven to play an instrumental role in several cancers, including GBM.
Together, this makes of IRE1 inhibition an attractive therapeutic option in oncology as monotherapy or as adjuvant therapy alongside established treatments. Several preclinical studies have successfully showcased it as such in multiple myeloma, prostate cancer, acute myeloid leukaemia and triple negative breast cancer (TNBC). We recently demonstrated through local intracerebral inhibition that IRE1 is a highly relevant therapeutic target for adjuvant treatment in glioblastoma, the most frequent and malignant form of primary brain tumors. However, known modulators of IRE1 activity cannot cross the blood-brain barrier (BBB) and are therefore incompatible with concomitant systemic administration as adjuvant. In this context, we developed a structure driven drug discovery pipeline to identify novel inhibitors able to cross the BBB. This study led to the discovery of Z4P, a BBB-permeable and kinase site-bound ligand showing inhibitory activities in GBM cell models, sensitization of tumor cells to Temozolomide (TMZ), and more strikingly prevents tumor relapse in mice when used in combination with TMZ. Although a highly promising entry point, several key aspects of Z4P need to be addressed for further development, in particular, the structure-activity relationships (SAR); potency; kinase selectivity; ADMET and PK/PD profiles. This hit-to-lead process represent the goal of this medicinal chemistry project.

Publications
Pharmacological Targeting of IRE1 in Cancer - Trends in Cancer. 2021. D.P Raymundo, D Doultsinos, X Guillory, A Carlesso, L.A Eriksson, A Chevet

Structural and molecular bases to IRE1 activity modulation - Biochemical Journal. 2021. T Langlais, D.P Raymundo, S.J Mahdizadeh, N Gouault, F Carreaux, E Chevet, L.A Eriksson, X Guillory

LERNER Leticia
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Metabolic specificities in chronic lymphotic leukemia: Combination of metabolism and PARP inhibitors as a potential therapy against the drug-resistant forms of the disease

Context & Objectives

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in Western countries, characterized by an accumulation of monoclonal CD5+ B lymphocytes. The genetic alterations are remarkably heterogeneous and CLL cells harbor chromosomal abnormalities, mutations and epigenetic modifications. The majority of CLL patients carry at least one of four common chromosomal alterations: del(13q), del(11q), del(17p) and trisomy 12. Del(17p) is associated with loss of TP53, while del(11q) is associated with loss of ATM; both are linked to adverse clinical outcomes. Although apparent remissions have been obtained with recent treatments, CLL remains an incurable disease with inevitable relapses and the appearance of drug-resistant clones. Therefore, it is crucial to develop alternative approaches to kill the malignant CLL B lymphocytes. Studies of cancer cell metabolism have demonstrated that altered cell metabolism is a critical component of the tumor phenotype. ATM deficiency in CLL patients has been linked to defective repair of DNA double-strand breaks (DSBs) by Homologous Recombination (HR) and, consequently, to Poly(ADP-Ribose) Polymerase inhibition (PARPi) sensitivity, in a similar mechanism of synthetic lethality described for the HR-deficient solid tumors. Seahorse experiments with PARPi show an immediate effect on the CLL mitochondrial respiration and metabolism, leading to a sharp decrease in the mitochondrial respiration and a concomitant increase of the glycolytic capacity, which points to a link between PARP and metabolism control in CLL. High-resolution oximetry experiments corroborate these results, and show this OCR decrease is detectable even in permeabilized cells. Upregulation of key genes implicated in glycolysis after PARPi detected by RT-PCR, as well as detection of increased levels of lactate by mass spectrometry, corroborate our hypothesis that PARPi leads to a metabolic reprogramming in CLL cells. Accordingly, the combination of PARPi and glycolysis inhibitors leads to a synergistic effect on cytotoxicity in both CLL cell lines and patient-derived primary cells, including those carrying deleterious genetic alterations, such as del(11)q and del(17)p. The same effect was not detected in normal B lymphocytes. These results provide a better understanding of the biology of the CLL B cells, and may lead to the opening of new therapies against drug-resistant CLL forms.

PRIX HÉLÈNE STARCK ORAL
CATÉGORIE POST-DOCTORAT

SUISSE Annabelle
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Consequences of monosomy: How stem cells can lose their female identity and start tumors

Context & Objectives

Aneuploidy, the loss or gain of chromosomes, is the most prevalent genetic hallmark of cancer. However, in a normal context, it is difficult to assess its frequency and its impact as aneuploid cells are often eliminated. It is not known whether chromosome gain or loss happens in healthy stem cells, whether this changes during aging, or how stem cells cope with it. Here, we use the Drosophila intestinal stem cell model to explore these questions. Our previous data from whole genome sequencing analysis in aged female Drosophila midguts have revealed a loss of an entire X chromosome (monosomy), suggesting that stem cells in healthy tissue can undergo aneuploidy. We have developed a genetic system to study this further, based on the loss-of-heterozygosity (LOH) of an X-linked tumor suppressor gene, whereby loss of the wild-type X chromosome results in neoplastic growth. Using a specific marker, we confirmed that loss of an X chromosome occurs frequently (1 in 800 stem cells).
How do these cells survive and compensate for the sudden loss of an entire chromosome? We believe that part of the answer lies with buffering by the dosage compensation (DC) pathway, which in male cells deposits H4K16ac on the single X and increases its transcription. We show that DC becomes activated in female monosomic cells at the most upstream level, indicating for the first time that a X chromosome counting mechanism still exists in adult cells. We are now testing whether DC is required in monosomic cells for neoplasia formation and effectively buffers the loss of one X. Our data suggest that another factor promoting the survival and fitness of aneuploid cells could be loss tumor suppressor activity. Indeed, X chromosome monosomy is more frequent when a tumor suppressor is inactivated than in a wild-type context. This suggests that the inactivation of tumor suppressor genes could foster an environment where aneuploid cells can survive and thrive.
Together, our work shows that monosomy happens frequently in healthy stem cells, is an important mechanism of LOH and can be viable, making it a driving force of tumorigenesis.

PRIX HÉLÈNE STARCK POSTERS

CATÉGORIE MASTER

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Multimodal MRI radiomics signature for early differentiation of pseudo-progression in patient treated with immunotherapy and stereotactic radiotherapy for recurrent glioblastoma in STERIMGLI trial

Context & Objectives
Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults. Local relapse is constant and no consensus is reached yet for an effective salvage treatment for patients with recurrent GBM. STERIMGLI trial evaluates the efficacy of combined stereotactic radiotherapy + Durvalumab. Images observations with immunotherapy depict morphological pseudoprogression (PP). Interestingly, patients in phase I who presented a PP had a prolonged local control. Up to date, no early imaging biomarkers are able to predict which patients will present a PP and potentially respond to the combined treatment. The study aims at identifying early predictive imaging biomarkers to characterize PP from true progression (TP).

Methods
26 patients from STERIMGLI phase I/IIa with longitudinal multi-parametric MRI follow-up (morphological MRI, diffusion (ADC) and perfusion (rCBV) maps) were included. BraTS Toolkit was used for automatic segmentation of tumor subregions: enhanced tumor (ET) and flair edema (ED). Segmentations were reviewed by a radiation oncologist and neuroradiologist, and MRIs classified as PP or TP. First order radiomic features were extracted with PyRadiomics:
- For ED label: in FLAIR, ADC and rCBV maps.
- For ET label: in T1, T1c, ADC and rCBV maps.

Extracted features were compared at baseline, first event and variation (Δ) between baseline and first event, in TP and PP groups, for tumor (ET, ED) and contralateral symmetrical healthy tissue.

Results
On baseline FLAIR, kurtosis in ED predicts PP (K< 2.52) and TP outcome (K> 2.52). Sensitivity and specificity were 76% and 89% in our study group. In ET label, Δvolume (p=0.0055), Δentropy on 3 modalities T1 (p=0.0142), T1c (p= 0.0253) and ADC map (p= 0.001) showed significant differences between TP and PP groups, whereas no difference was observed in healthy tissue. A combined score of those 4 features, dividing patients in low risk of TP group and high risk group, discriminates between TP and PP with 87% sensitivity and 88% specificity. Odd ratio is 19.50 [2.2 ; 173.5].

Conclusion
Radiomics analysis was able to identify a predictive feature of PP on baseline FLAIR MRI and a diagnostic combined score was able to discriminate between TP and PP, from variation between first significant volume increase and baseline MRI, in patients treated with combined stereotactic radiotherapy + Durvalumab for recurrent GBM. Validation on a larger and the rest of the cohort is required.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE MASTER

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Evaluation of the risk of Heart Failure following exposure to a Protein Kinase Inhibitor (PKI) drug from SNDS data and identification of the molecular targets potentially involved

Aims
Protein Kinase inhibitors (PKI) have revolutionized the prognosis of several cancer diseases, justifying the acceleration of their clinical evaluation before their marketing authorization. Pharmacoepidemiology is a key element to supplement these data with follow-up in «real-life» conditions. Pharmacovigilance signals of heart failure (HF) following exposure to PKI have been detected in recent years. Our objective was to identify the PKI most frequently associated with the development of HF.

Methods
Using the French National Healthcare System Database, all patients newly exposed to a PKI between January 2011 and June 2014 were followed 18 months. Incidence Rate Ratio (IRR) were measured and adjusted Hazard Ratio (aHR) were estimated using a Cox model.

Results
Thirteen PKIs were studied. Among 49,714 new PKI users, the mean IRR of HF was 3.38 per 100 person-years, with a median time to onset of 155 days. Six PKI were significantly associated with an increased risk of heart failure occurrence: pazopanib (aHR= 2.42, 95% CI: 1.67 -3.52]), dasatinib (aHR= 2.22, 95% CI: 1.42 -3.44), ruxolitinib (aHR= 2.11, 95% CI: 1.69 -2.64), crizotinib (aHR= 1.71, 95% CI: 1.07 -2.72), everolimus (aHR= 1.45, 95% CI: 1.26 -1.67) and vemurafenib (aHR= 1.37, 95% CI: 1.01 -1.86). The median survival in patients with heart failure after the PKI exposure was 17.1 months (95% CI= [16.1; 18.2]) against 33.2 (95% CI= [32.1; 34.5]).

Conclusions
Our study provides knowledge on HF induced after a PKI exposure. Four PKI were associated with a significant increase in the risk of heart failure: dasatinib, ruxolitinib, crizotinib and everolimus. The significance of pazopanib and vemurafenib needs to be further investigated. The onset of heart failure appears to occur relatively early, with more than half of events occurring within the first 6 months after the PKI initiation. Heart failure needs to be considerate, as its onset decreased the median survival by nearly half.

PRIX HÉLÈNE STARCK POSTERS

CATÉGORIE DOCTORAT

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Increasing the efficiency of radiotherapy by targeting TRIM33 protein to increase IFN-β expression in myeloid cells infiltrating the tumor

Context & Objectives
Radiotherapy is an antitumor treatment used in more than half of cancer patients. She uses X-rays to kill cancer cells. Its efficiency also depends on its ability to trigger an antitumor response. Interferon β (IFN-β) is a protein produced after a radiotherapy, controlling this immune response. Unfortunately, its therapeutic use is limited by its toxicity. Controlling IFN-β production to increase the immune response and improve the efficiency of radiotherapy is one of the issues of innovative immunotherapies. My laboratory has shown that the inhibition of TRIM33 protein during the classical activation of certain immune cells named myeloid cells leads to an increased and sustained production of IFN-β. My project is to show that this phenomenon would increase the production of IFN-β inside the tumor during a radiotherapy, which improves the antitumor immune response and the overall efficiency of the treatment. The mechanism of regulation of IFN-β by TRIM33 in activated myeloid cells was unknown. I discovered a functional murine myeloid super-enhancer composed of 3 constitutively active enhancers that controls the activity of the IFN-β promoter in these cells. In particular, one of these enhancers is induced by LPS. The orthologous region in humans contains a polymorphism present in 30% of global population and the minus allele of this polymorphism disrupt a C/EBP-β binding site that correlates with a dysregulated expression of IFN-β in activated monocytes. It is published in Plos Genetics. To continue this work, I showed in vitro that the inhibition of TRIM33 in irradiated macrophages or macrophages exposed to irradiated tumor cells leads to an increased expression of IFN-β and I showed that it depends on cGAS/STING pathway. I have developed a murine preclinical model in which I showed that the inhibition of TRIM33 in myeloid cells increases the efficiency of radiotherapy by the cellular signalling pathway involving IFN-β. This effect of TRIM33 inhibition depends on T CD8+ cells. Now, I am studying the tumoral microenvironment before and after radiotherapy and I am tring to develop an approach with siRNA against TRIM33 delivered with lipoplexes that makes it possible to reproduce this inhibition of TRIM33 in patients treated with radiotherapy to improve the efficiency of the treatment.

Publications
A genetic variant controls interferon-β gene expression in human myeloid cells by preventing CEBP-β binding on a conserved enhancer - Plos Genetics. 2020. A Assouvie, M Rotival, J Hamroune, D Busso, P H Romeo, L Quintana-Murci, G Rousselet

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE DOCTORAT

BEKKAT Fériel
Scientific supervisor: COURAUD Pierre-Olivier
Cochin Institute, U1016, PARIS

Key roles of B cells and IL4I1 enzyme in metastatic melanoma

Context & Objectives
Despite conventional (B2) and innate-like (B1) B-cells being present in skin at homeostasis and during inflammation, the characterization of B-cells infiltrating melanoma remains poorly investigated. Here we show that B-cell depletion accelerates metastatic dissemination in RET mice, a model of spontaneous melanoma. At the earlieststage of the disease, primary tumor was mainly infiltrated by anti-tumoral B2 cells that promoted the generation of CD4+ and CD8+ memory T-cells and limited the PMN-MDSC recruitment. Expression of the IL4-induced gene 1 (IL4I1) enzyme, a negative regulator of B-cell responses in physiological setting, that was mainly upregulated in peripheral and tumor-infiltrating B2 cells during tumor development, might dampen their ability to control tumor growth. Tumor development was associated with elevated levels of CXCL13 and CXCL12 as well as that of IL4I1 possibly contributing to the differential recruitment of B1 cells and B2 cells within the tumor microenvironment. Our data may strengthen the rationale for combining current immunotherapy in metastatic melanoma with an IL4I1 antagonist, thus enhancing anti-tumoral B-cells.34.5]).

BOUYS Lucas
Scientific supervisor: BERTHERAT Jérôme
Cochin Institute, U1016, PARIS

Genetics of adrenal tumors: KDM1A inactivation causes hereditary food-dependent Cushing's syndrome

Background
Primary Bilateral Macronodular Adrenal Hyperplasia (PBMAH) is a rare disease characterized by bilateral adrenal tumors associated with variable levels of cortisol secretion. The bilateral nature of the condition and the description of familial cases has always suggested a genetic predisposition. In 2013, our team described for the first time germline heterozygous inactivating mutations of ARMC5 gene in 55% of patients treated by adrenalectomy for PBMAH associated with severe Cushing's syndrome. Since somatic mutations of ARMC5 different than the germline mutation are observed in the tumor DNA of operated adrenals, ARMC5 seems to act as a tumor suppressor gene and may be responsible for a multiple neoplasia syndrome since meningioma have been described in patients with germline inactivation of ARMC5. PBMAH is a very heterogeneous disease in terms of adrenal involvement and cortisol excess, and ARMC5 is responsible for the half of operated - thus severe - index cases, but for only 20 to 25% of all PBMAH index cases, and for around 80% of clear familial cases. The purpose of this study was to investigate other genetic predisposition potentially involved in PBMAH pathogenesis, and particularly in a rare form of PBMAH with illegitimate expression of GIP (Glucose-dependent Insulinotropic Peptide) receptor by steroidogenic cells, leading to a food-dependent Cushing's syndrome (FDCS).

Methods
A multi-omics analysis of PBMAH tissues from 36 patients treated by adrenalectomy was performed (RNAseq, SNP array, methylome, miRNome, exome sequencing).

Results
: The integrative analysis revealed three molecular groups with different clinical features: G1, 16 patients with ARMC5 inactivating variants; G2, 6 FDCS patients with GIPR ectopic expression; and G3, 14 patients with a less severe phenotype. Exome sequencing revealed germline truncating variants of KDM1A in 5 G2 patients, constantly associated with a somatic loss of the KDM1A wild-type allele on 1p, leading to a loss of KDM1A expression both at mRNA and protein levels ($p=1.2x10 - 12$ and $p<0.01$, respectively). Subsequently, KDM1A pathogenic variants were identified in 4/4 additional index cases with FDCS.

Conclusion
KDM1A inactivation explains about 90 % of FDCS PBMAH. Genetic screening for ARMC5 and KDM1A can be offered now for the majority of PBMAH operated patients and their families, opening the way to earlier diagnosis and improved management.

Publications
Update on Primary Macronodular Adrenal Hyperplasia (PBMAH) – Endocrine. 2021. L Bouys, I Chiodini, W Arlt, M Reincke, J Berthera

CABELI Vincent
Scientific supervisor: HERSEN Pascal
Curie Institute, UMR 168, PARIS

Learning causal graphs from continuous or mixed datasets of biological or clinical interest

Context & Objectives
We have developed a statistical method to extract causal links from observational data, exploiting the amount of information present in large datasets. We are particularly interested in clinical data from breast cancer patients with which we want to establish functional links between different aspects of the disease in an unbiased manner. We work in close collaboration with the clinicians responsible for the production of this data at the Curie Hospital, who complement our approach with their expert knowledge in the hope of finding ways to personalize treatments to each patient or better diagnostic tools. In addition, we also work at a more fundamental level by analyzing data generated ex vivo on tumor cells grown in microenvironments on a chip. Working with the experimental teams, we want to apply our statistical method to gain insight into the mechanisms of treatment, in particular the influence of herceptin on the behavior of cancer cells in these microenvironments.

DESIGAUX Théo
Scientific supervisor: PARIS François
Tissue Bioengineering, UMR 1026, BORDEAUX

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

Context & Objectives
Breast cancer is the most common type of cancer in women, making it a major public health issue. Depending on tumor subtype and dissemination, cancer therapy includes tumor resection, radiotherapy and various systemic treatments to avoid relapse. Recently, our understanding of microenvironment effect on not only cancer development, but also metastasis and resistance to treatment have greatly increased. Endothelial cells have been shown to secrete paracrine factors, including ceramide, in response to radio-induced oxidative stress. While it stimulates endothelial cells apoptosis, these signals also inhibit cancer proliferation. However, even if reinforced by consistent in vivo results, there is still a gap between these findings and human clinical relevance. In the last decade, biofabrication processes have emerged as a powerful tool to build in vitro tunable models using human cells and biomaterials.
Here, we discuss a 3D bioprinted breast cancer model that will be used in future work to elucidate these mechanisms in complex human microenvironments. We used MDA-MB-231 cell line in combination with Human Umbilical Vein Endothelial Cell (HUVEC) and primary fibroblasts, normal (HSF) or cancer associated (CAF) to mimic the tumor and its microenvironment. By mixing these cells with a hydrogel composed of Collagen-Methacrylate and Hyaluronic Acid Metacrylate, functionalized with laminin-derived peptides, we obtained a printable bio-ink. We then used extrusion bioprinting to deposit a cancerous core surrounded by stroma, thus building 3mm in diameter, and 500µm thick model. We first assessed the viability of cancer cells in this model and observed 80% viability at D1 post-printing, suggesting the process is not harmful to our cells. At D7 the viability is maintained in higher layers of the model but decreases in depth of the model. This viability gradient, together with a hypoxia staining, indicates the appearance of a necrotic/hypoxic core in our model. We then verified endothelial cell maturation in our model, confirmed by the presence of capillary-like structures and expression of CD31 and VE-Cadherin.
Our model then seems relevant for breast cancer-endothelial cell interaction study as it recapitulates essential parts of the tumor and its capillary microenvironment. We intend to complexify this model by integrating patient-derived cells, and to study the specific role of CAF on already known communication pathways.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE DOCTORAT

JONDREVILLE Ludovic
Scientific supervisor: NGUYEN-KHAC Florence - Cordeliers Research Center, U1138, Cell death and Drug Resistance in Hematological Disorders Team, PARIS

8p deletion in chronic lymphocytic leukemia involves the TNFRSF10A/B genes and results in fludarabine and venetoclax resistance in vitro

Context & Objectives
Genetic dissection of acquired chromosomal abnormalities has provided insight into many mechanisms of oncogenesis and treatment resistance. The deletion of the short arm of chromosome 8 (del8p) is largely unknown. It has been associated with more aggressive phenotype and resistance to ibrutinib in CLL. We constituted a monocentric cohort of 57 CLL patients with del8p. We performed genomic analyses using FISH, SNP-array and sequencing. Gene inactivations were performed by CRISPR/Cas9 on the OSU-CLL line. Gene expression was quantified using digital droplet PCR (ddPCR). Assessment of anti-CLL drugs and TRAIL responses was performed by flow cytometry. Systematic screening (FISH) of del8p in a national protocol of relapsed/refractory CLL showed a frequency of 13% (9/70). In our cohort, of the 28 untreated CLL before the discovery of del8p and compared to untreated CLL in general, there was an increased prevalence of complex and very complex karyotypes (61% and 33% vs. 15% and 5% respectively), del11q (36% vs. 6-20%), del17p (21% vs. 6%), and non-mutated IGHV status (74.5% vs. 60%). By FISH/SNPa, we showed there were 4 groups of del8p: 1. del 8p10-8pter (14%); 2. del 8p11-8pter (38%); 3. del 8p21-8pter (32%); 4. focal deletions (16%). The larger the 8p deletion, the worse the overall survival (p=0.02). The minimum common deletion region included the four TNFRSF10A/B/C/D genes, which were deleted in 91% of cases. TNFRSF10 A and B genes encode the homonymous pro-apoptotic receptors, whose ligand is TRAIL (C and D genes encode non-functional truncated receptors). In primary CLL cells, we showed by ddPCR that TNFRSF10 A and B genes were expressed, with 1.4-fold more B than A. CLL with del8p (n=11) had a decreased expression of both TNFRSF10 A and B genes compared to CLL without del8p (n=32) (p=0.072 and $p<10^{-4}$ respectively). Inactivation of TNFRSF10A or B genes in the OSU-CLL line resulted in a decreased sensitivity to TRAIL (of about 40 and 60%, respectively). Double KO cells were resistant to TRAIL. In primary CLL cells, we showed in vitro that cells with del8p (n=7) were generally resistant to TRAIL after treatment with fludarabine and venetoclax, in contrast to CLL without del8p (n=13). We found that del8p was associated with poor prognostic factors, and that a large deletion was associated with decreased survival. Del8p leads to decreased expression of apoptotic TNFRSF10A/B receptors in CLL, and in vitro resistance to fludarabine and venetoclax.

LEBDY Rana
Scientific supervisor: RIBEYRE Cyril
Institute of Human Genetics, Genetic Instability and Cancer Team, MONTPELLIER

GNL3: a new player in the protection of blocked replication forks

Context & Objectives

The proper regulation of origin firing is a key mechanism to protect genomic stability when the cells are exposed to replicative stress. Here we show that GNL3/nucleostemin, a GTP-binding protein able to shuttle between the nucleolus and the nucleoplasm, limits replicative stress by limiting replication origins firing. We proved that GNL3 is in in proximity of nascent DNA and that its depletion reduces forks speed but increases forks density and replication origin firing. Consistent with this, overexpression of GNL3 leads to a decrease in origin firing. When subjected to exogenous replicative stress, cells impaired for GNL3 exhibits MRN-dependent resection and RPA phosphorylation. Strikingly, inhibition of origin firing using CDC7 inhibitor decreased resection in absence of GNL3 but not in absence of BRCA1, suggesting that GNL3 does not protect nascent strand directly. In addition, using various approaches (BioID, PLA, coIP), we established that ORC2 and GNL3 interact together in the nucleolus. We propose a model where GNL3 level is crucial to determine the correct amount of ORC2 on chromatin by sequestrating it in the nucleolus thanks to the capacity of GNL3 to shuttle between nucleoplasm and nucleolus. Our data present insights into a new role of GNL3 in the regulation of origin firing that protects genomic stability.

MATABISHI-BIBI Laura
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The chromatin remodeler ISW1 is a novel actor of the unfolded protein response

Context & Objectives

Cellular homeostasis is maintained by quality control pathways that counteract the potentially deleterious effects of stresses. This is achieved through the activation of stress responses that lead to the repair of macromolecular damages and to the restoration of cellular homeostasis. Cancer cells, in which high proliferation rates are associated with intense protein synthesis, are additionally challenged by micro-environmental conditions such as hypoxia or nutrient deprivation, which leads to endoplasmic reticulum (ER) stress, defined as the accumulation of unfolded proteins in the ER lumen. Initially characterized in yeast, the unfolded protein response (UPR) is an evolutionarily conserved adaptive response to ER stress aimed at resolving ER stress or eliminating cells in which proteostasis cannot be successfully restored. While UPR activation mitigates protein misfolding, continued ER stress induces persistent UPR signalling, leading to cell death. Chronic ER stress thus arises as central to the pathophysiology of a wide range of human diseases. In this context, understanding the molecular mechanisms involved in UPR abatement is of utmost importance. Our work identifies the yeast chromatin remodeler Isw1 as a novel critical actor of the UPR that ensures a timely termination of the signaling. The yeast UPR is set in motion by a three-component system which includes a stress sensor (Ire1), a downstream transcription factor (Hac1/XBP1), and downstream target genes. Ire1-mediated cytoplasmic splicing of the HAC1 transcript constitutes the key trigger that turns on the UPR. We report that ISW1 inactivation does not influence UPR activation but instead impairs UPR attenuation and cell viability upon ER stress. Mechanistically, we demonstrate using the CRAC technique (in vivo “UV cross-linking and analysis of cDNA”) that Isw1 directly binds the HAC1 mRNA. We identify Isw1 binding motifs in HAC1 and establish that the Isw1/HAC1 interaction restricts HAC1 mRNA nuclear export, cytoplasmic splicing and thereby UPR activation. In addition, ISW1 itself is induced by ER stress, supporting a model in which ER stress-induced Isw1 stands as a previously unrecognized key effector of the negative feedback loop that abates UPR signaling to allow for homeostatic adaptation to ER stress.

TIHY DAMEI Isabelle
Scientific supervisor: MAMI-CHOUAIB Fathia - Gustave Roussy, UMR 1186, Integrative Tumor Immunology and Genetic Oncology Team, VILLEJUIF

Role of tumor-resident memory T cells (TRM) and CD103 integrin in response to immunotherapy targeting PD-1 and CTLA-4

Context & Objectives

Understanding the mechanisms involved in anti-tumor immune response and identifying biomarkers that can predict the response to treatments targeting immune checkpoints, such as PD-1 or CTLA-4, are major issues in improving the management of cancer patients. Indeed, even if immunotherapy can give rise to very good responses, only a few percentage, around 20% of lung cancer patients treated with immune checkpoint blockade (ICB), responds to the treatment. Therefore, understanding how ICB therapy affects immune cells inside the tumor and which T-cell populations are involved in this response is important to improve the rate of patients that can get benefit from these therapies. Tumor-resident memory T (TRM) cells, defined as T cells expressing the CD103 integrin, but also CD49a and/or CD69, emerge as key T-cell subsets in clinical response to anti-PD-1 treatments. Our team have previously shown that the interaction of CD103 with its ligand, the epithelial cell marker E-cadherin, leads to an increase in the functionality of CD8+ TRM, and that an increased density of CD103+CD8+ TIL is associated with greatly improved outcome of anti-PD-(L)1-treated lung cancer patients. My PhD project aims at understanding the role of CD8+CD103+ TRM cells in the response to immunotherapies targeting PD-1 and CTLA-4 in a mouse tumor model. We first observed that CD103 and CD49a integrins defined two distinct CD8+ TRM subpopulations with expression of several T-cell exhaustion markers and cytotoxic molecules. Remarkably, these CD8+ TRM subsets are differentially involved in ICB immunotherapies, and anti-PD1 and anti-CTLA4 differentially affect CD49a+ TRM and CD103+ TRM. These results showing the impact of CD49a+ TRM and CD103+ TRM on ICB therapies in mouse and human cancer models will be presented. They may open up promising avenues to select patients for more efficient immunotherapies.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

ALPAR Lale
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Collective cell migration during epithelium folding

Context & Objectives
Forming the 3D shape of an organism relies on large scale changes in epithelial cell sheets, such as epithelial folding events or collective changes in cell contractility. Relatedly, defects in cell, tissue or organ shapes are cancer landmarks. Here we initially aimed to understand the mechanisms that drive a distinct large scale folding process that occurs at a homeotic compartment boundary and forms the Drosophila neck. We found that Toll-like receptor expression within the neck domain is under control of a homeotic gene and regulates actomyosin contractility and thus promotes neck folding. Toll-like receptors are a family of surface adhesion molecules well characterized for their role in immunity and are closely linked to cancer. Interestingly, expression of Toll-like receptors in the Drosophila dorsal thorax epithelium is not limited to the neck region, and is highly patterned. Furthermore, Toll-like receptors' role in controlling actomyosin contractility goes beyond the neck region and is also observed in other epithelia. Currently, we are expanding our studies on the morphogenetic roles of Toll-like receptors to other regions of interest where collective changes in contractility drives major morphogenetic events. Collectively, our studies provide important insights in linking patterned gene expression to patterns of morphogenesis.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

BASTIANCICH Chiara
Scientific supervisor: KHRESTCHATISKY Michel
Institute of NeuroPhysiopathology, Aix Marseille University, CNRS UMR7051, MARSEILLE

Development of a nanomedicine-loaded local treatment for glioblastoma able to target the tumor resection microenvironment andavoid the onset of recurrences (GlioRET)

Context & Objectives
Glioblastoma (GBM) is the most frequent and aggressive primary brain tumour, characterized by rapid proliferation and ability to infiltrate healthy brain tissue. The regenerative physiological responses in the brain after GBM resection and the biology of the tumor resection microenvironment (TRE) may play a key role in the formation of local recurrences which lead to patients' death. The hypothesis of this research is that the local administration of a treatment capable of killing the residual infiltrating tumour cells and reverse the exaggerated pro-tumorigenic inflammatory response at the TRE could prevent recurrence between surgery and conventional radio-chemotherapy, increasing patient's survival. Therefore, our objectives are the characterization of the TRE as therapeutic target and the development of multidrug-loaded delivery systems for the local treatment of GBM. In this work, we unraveled the TRE using different imaging and analytical techniques (intravital two-photon microscopy, nuclear imaging, histology, flow cytometry), to elucidate the key mechanisms in the onset of tumor recurrences and identify potential therapeutic targets and drug candidates for GBM treatment. At the same time, we performed in vitro screenings using 2D and 3D cellular models to select combination of molecules that could be able to act both on the TRE and kill residual cancer cells. A nanomedicine-based formulation will be formulated, characterized and its biological activity, tolerability and anti-tumor efficacy will be evaluated in vivo using adapted preclinical models.

Publications
Does local drug delivery still hold therapeutic promise for brain cancer? A systematic review - Journal of Controlled Release. 2021. C Bastiancich, E Bozzato, I Henley, B Newland

Rationally designed drug delivery systems for the local treatment of resected glioblastoma - Advanced Drug Delivery Reviews. 2021. C Bastiancich, A Malfanti, V Préat, R Rahman

Nanomedicine: A Useful Tool against Glioma Stem Cells – Cancers. 2020. E Bozzato, C Bastiancich, V Préat

CAMPOS-MORA Mauricio
Scientific supervisor: VILLALBA Martin - Regenerative Medicine and Biotherapies Research Institute, U1183, Lymphocyte differentiation, tolerance and metabolism: basis for immunotherapy Team, MONTPELLIER

Sensitization of tumor cells to NK cells by metabolic drugs

Context & Objectives
Metabolic reprogramming of tumor cells towards glycolysis is essential for cancer growth and for their mechanisms of immune evasion. Treatment with the metabolic drug dichloroacetate (DCA) have shown to shift tumor metabolism to mitochondrial oxidative phosphorylation (OXPHOS), generating an anti-oxidant response and cell stress, with subsequent membrane expression of stress ligands recognized by immune cells such as natural killer (NK) cells. We previously have observed that this anti-oxidant response is partially mediated by the MAPK ERK5 and remarkably, in cells lacking functional mitochondrial Complex I activity, DCA did not induce ERK5 expression and the anti-oxidant response. Here we aimed to study if mitochondrial complex function participates in tumor cell expression of stress ligands, analyzing whether this renders tumor cells more easily recognized by NK cells. HCT116 colorectal tumor cells and BT-20 breast tumor cells were treated with mitochondrial Complex I (CI) inhibitor Rotenone, or with Complex II (CII) inhibitors 2-Thenoyltrifluoroacetone (TTFA) and Dimethyl fumarate (DMF). Expression of stress ligands MICA/B and ULBP1 was analyzed by FACS. Gene expression was measured by qRT-PCR and tumor cell viability after co-culture with human NK cells was determined by MTT assay. By targeting CI, we observed that Rotenone treatment downregulated MICA/B and ULBP1 expression on HCT116 cells, suggesting that CI function participates in stress ligand expression as well as ERK5 expression. We observed similar results by treatment with TTFA, which downregulated MICA/B expression and decreased eNK cell cytotoxicity of treated tumor cells, even in the presence of DCA. Notably, we observed that treatment with CII inhibitor DMF upregulated MICA/B and ULBP1 expression. DMF treatment on HCT116 and BT-20 cells significantly increased in vitro NK cytotoxicity, under both control and OXPHOS conditions. Mechanistically, we found that MICA/B upregulation was dependent on oxidative stress, as treatment with antioxidant N-acetylcysteine abrogated DMF-mediated MICA/B upregulation. In addition, DMF upregulated ERK5 expression, and also upregulated NRF2 and NQO-1 which participates in the anti-oxidant response. Altogether, these results implicate that mitochondrial complex function regulates tumor stress ligand expression and NK cell recognition, supporting its targeting to improve cancer immunotherapies.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

COSGROVE Jason
Scientific supervisor: PERIE Leila
Curie Institute, UMR168, PARIS

Metabolic Heterogeneity in Hematopoietic Progenitors Fuels Innate Immunity

Context & Objectives
Recent technical advances permit metabolic profiling at the single-cell level but existing methods are destructive, making it difficult to link metabolic state to functional outcomes in vivo. Here we perform simultaneous enzyme/transporter expression and lineage tracing analysis (MetaFate) in single Hematopoietic Stem and Progenitor Cells (HSPCs), identifying metabolic heterogeneity that confers differences in lineage potential. Combined with single-cell metabolic profiling and functional assays, we characterize a myeloid-biased progenitor compartment with increased rates of oxidative phosphorylation, protein synthesis and ROS production. In addition, we demonstrate that the myeloid-biased HSPC compartment expands to produce large numbers of innate immune cells following acute infection. Together, this data shows that blood progenitors are metabolically heterogeneous, and that metabolism plays active role in the differentiation process.

COSTE Astrid
Scientific supervisor: FERVERS Béatrice
Léon Bérard Center, U1296, Radiation Defense Health Environment Team, LYON

Exposure to household pesticides at puberty and risk of testicular germ cell tumors: the TESTIS study

Background
Testicular germ cell tumors (TGCT) are the most frequent cancers in young men (15 to 45 years old). Their incidence has increased significantly in Western countries in recent decades, such as in France, where it is 2.5 times higher than in 1980, and an environmental origin of TGCT is suspected. Among the suspected environmental substances, exposure to pesticides at critical periods of genital function development, i.e., in utero and at puberty, is suspected to play a role in the development of TGCT in young adult men.

Objectives
The present study analyzes the hypothesis of an association between household pesticides use during puberty, a critical period of development, and the risk of TGCT in adulthood.

Material and methods
The TESTIS study is a multicentric case-control study, conducted between 2015 and 2018 in 20 University Hospitals in France. 454 TGCT cases were recruited and matched to 670 controls on year of birth and hospital center. TESTIS subjects were asked about their or their relatives' use of pesticides in the household at puberty. Conditional logistic regressions were performed to estimate odds ratios (OR) and 95% confidence intervals (CI).

Results
The prevalence of use was 90.3% for insecticides, 16.6% for herbicides and 28.2% for fungicides in the TESTIS controls. There was an association between domestic pesticides use and the risk of TGCT: ORnot adjusted=2.26 [95% CI 1.17-4.38]. This association was stable after stratification by category: insecticides, herbicides, and fungicides. When associations were analyzed by type of use, there was an association between herbicides use in the garden (ORnot adjusted=1.53 [95% CI 1.12-2.10]), as well as fungicides use against mold (ORnot adjusted=2.02 [95% CI 1.06-3.88]) and risk of TGCT. Analyses by histological subtypes showed that the associations observed for all TGCT tumors remained only in the non-seminoma group.

Conclusion
Our study suggests an association between the use of domestic pesticides during puberty and the risk of TGCT, particularly for non-seminomas and for the use of herbicides in the garden or fungicides against mold. However, recall bias cannot be excluded and results need to be replicated in other populations.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

DALOUL Iman
Scientific supervisor: SALEH Maya
Bordeaux University, U5164, ImmunoConcEpT, BORDEAUX

Analysis of the immune landscape by single cell transcriptomics to predict Lymphoma Relapse after CAR-T cell therapy

Context & Objectives
Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL). Although more than 50% of the patients respond to chemotherapy in combination with the anti-CD20 monoclonal antibody rituximab (R-CHOP), the prognosis of patients with refractory/relapsing DLBCL is very poor, with a median survival below one year. Chimeric antigen receptor (CAR)-T cell therapies have revolutionized the treatment of patients with hematological malignancies, including refractory B-cell acute lymphoblastic leukemia (ALL) and Non-Hodgkin Lymphoma (NHL) including DLBCL, with response rates up to 90% in some cases. Unfortunately, about 40% of patients quickly relapse after CAR-T cell infusion for largely unknown reasons. Among the potential mechanisms underlying such negative outcome is the downregulation of the CAR-T cell target antigen, i. e. CD19 in B cell malignancies, or the poor quality of patient-derived T cells used in the manufacturing of the CAR-T product. The tumor microenvironment (TME) plays a critical role in the progression of B-cell malignancy, but surprisingly it has been poorly investigated in the context of CAR-T cell therapy. In this project, we hypothesized that the TME exerts significant effects on CAR-T (as well as endogenous T) cells phenotypes and functions and is thus an important determinant of CAR-T cell therapeutic success. To characterize the TME longitudinally and unravel changes occurring under CAR-T cell immune therapy, we performed single-cell RNA sequencing (scRNAseq) on enriched innate immune cells from the blood of 10 healthy donors and 5 patients with DLBCL, 5 days before CAR-T cell infusion and 2 months after treatment. In total, we sequenced the transcriptomes of ~190 000 cells and are currently analyzing the results. We hope that this work will unravel phenotypic and functional differences of innate immune cell subsets of relapsing patients versus those achieving a durable response or complete remission and to identify biomarkers for patient stratification as well as novel therapeutic targets for combination therapy with CAR-T cells to improve DLBCL patient care.

EDWARDS Frances
Scientific supervisor: BASTO Renata
Curie Institute, UMR144, Cellular Biology and Cancer team, PARIS

Influence of centrosome amplification on the response of high-grade serous ovarian cancer to chemotherapy

Context & Objectives
Ovarian cancer is the fifth cause of cancer death in women, with frequent relapse in response to combined Paclitaxel and Carboplatin chemotherapy. Aiming for better patient stratification, the Basto lab characterized centrosomes in 110 High Grade Serous Ovarian Cancer (HGSOC) tumors. The centrosome organizes microtubules, contributing to cell polarity, trafficking and migration during interphase, and to bipolar spindle organization during mitosis. Centrosome amplification (more than two centrosomes per cell) is seen in cell lines from diverse cancer types and is suggested to favor oncogenesis by driving invasiveness and chromosomal instability. Surprisingly, the Basto team found that centrosome amplification is associated with a longer time to relapse, suggesting that in HGSOC it favors the response to chemotherapy.

My work in the Basto team comforts this hypothesis, by showing that induced centrosome amplification in HGSOC cell lines enhances their response to chemotherapy. Indeed, proliferation and viability assays show that centrosome amplification favors cell death. To understand the underlying mechanisms, I developed a microscopy assay to monitor single cell behaviors during chemotherapy, and correlate mitotic events with ensuing cell fate. This revealed that in response to Paclitaxel, a microtubule poison that perturbs mitosis, centrosome amplification favors multipolar divisions which then lead to cell death. More surprisingly, centrosome amplification also favors cell death in response to carboplatin, a DNA damaging agent that impairs replication and DNA repair. However, in this case, the behavior during mitosis isn't affected by centrosome amplification, suggesting that it influences cell fate independently of centrosomes function in building the mitotic spindle. Additionally, measuring DNA damage in these cells shows that centrosome amplification doesn't increase damage, ruling out an impact of centrosome amplification on DNA replication or repair mechanisms. This therefore suggests that centrosome amplification doesn't affect the level of genotoxic stress that carboplatin generates in these cells, but rather changes the fate chosen by these cells in response to such stress. My work therefore identifies a new factor influencing the response to chemotherapy in HGSOC, but also changes our point of view on centrosome amplification in cancer, placing it as a potential chemosensitizer.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

FABBRI Lucilla
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Curie Institute, UMR3348, RNA Biology, Signaling and Cancer Team, PARIS

Melanoma persister cells mutability

Context & Objectives
Despite the success of therapies targeting oncogenes in melanoma, clinical outcomes are limited by a small subpopulation of residual "drug-tolerant persister cells", alternatively called "minimal residual disease", that results in relapse. The emergence of these persister cells is due to non-mutational, adaptive mechanisms of resistance that allows them to dynamically and transiently escape the initial onslaught of the drug and from which permanently resistant clones may eventually evolve under continuous drug pressure. We have previously demonstrated that the insurgence of the adaptive, non-mutational drug tolerance state of BRAFV600 melanoma cells in response to lethal doses of BRAFi/MEKi targeted therapy is driven by a reversible mRNA translational reprogramming. Although these cells showed a global reduction in protein synthesis, a subset of mRNAs maintained efficient translation to sustain persister cell survival. The mechanisms by which genetic resistant clones evolve from the drug tolerant phenotype are yet to be unveiled and may provide promising targets for improving therapeutic success of melanoma. Our aim is to provide a mechanistic understanding of how these translational differences in gene expression may influence the emergence of resistance-conferring genetic alteration in melanoma cells. Here we show that one of the leading translationally regulated mRNA candidates in melanoma persister cells encodes 53BP1, a key regulator of the error-prone non-homologous end joining (NHEJ) pathway of DNA repair. This is associated with an increase in DNA damage and 53BP1 nuclear foci accumulation in persister cells and correlates with a bias towards NHEJ and increased mutagenesis in persister cells. Our studies point towards a role of a translational regulation of 53BP1 as a possible mediator of the transition from the reversible drug-tolerant persistent state into permanently resistant mutant clones driving tumor relapse. We are currently investigating the molecular mechanisms underlying the translational upregulation of the 53BP1mRNA in melanoma persister cells to identify the factors that may offer a promising therapeutic opportunity to counteract the insurgence of genetic resistance in melanoma.

Publications
The plasticity of mRNA translation during cancer progression and therapy resistance - Nat Rev Cancer. 2021. L Fabbri, A Chakraborty, C Robert, S Vagner

GANDIOSO UBIETO Albert
Scientific supervisor: GASSER Gilles - National Superior School of Chemistry of Paris, Laboratory for Inorganic Chemical Biology, PARIS

Far-Red to Near-Infrared-Absorbing Ru(II) polypyridyl complexes as Photosensitizers for Selective Photodynamic Therapy

Context & Objectives

The use of light holds tremendous potential in chemotherapy since it offers the possibility of controlling, at a desire time and location, the release of cytotoxic species from an inert pro-drug. For this reason, much efforts have been dedicated to the development of photoactivatable metal–based anticancer complexes for improving drug efficacy and, more importantly, to reduce the toxic side-effects associated with the currently approved platinum drugs. Ru(II) polypyridyl complexes have particularly emerged as promising photosensitizers for photodynamic therapy. However, some key drawbacks, such as operability in the phototherapeutic window and reactive oxygen species (ROS) production efficiency and selectivity, still hamper clinical translation.

The ground-breaking aspect of this project is based on two premises: a) the use of NIR light to activate the PS instead of UV or visible light. b) The use of monoclonal antibodies to deliver the photosensitizers specifically to cancer cells. NIR light presents higher tissue-penetration compared with shorter wavelengths. Other advantages of NIR light include minor scattering and photodamage to living cells. Finally, it is planned to conjugate this novel Ru(II) complexes to specific monoclonal antibodies. Such biomolecules have demonstrated considerable utility in the clinical treatment of cancer. Thus, there is considerable interest in arming antibodies with bioactive payloads to improve their potency and selectivity, thus increasing activity at the tumor site while sparing normal tissues.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

LE GRAND Marion
Scientific supervisor: PASQUIER Eddy
CRCM, U1068, MARSEILLE

A click chemistry-based reverse molecular pharmacology approach to unveil new therapeutic options in high-risk neuroblastoma

Context & Objectives

For successful drug repurposing strategy, identifying the right drug for the right situation, and deciphering their mechanism(s) of action in the context of cancer are essential. The REMAP (REverse MoleculAr Pharmacology) project will tackle both challenges. We developed an original strategy based on high-throughput drug repurposing screening coupled with bioinformatics, click chemistry and functional genomics to reveal new therapeutic targets. Our approach focused on high–risk neuroblastoma, a deadly childhood cancer. As a first step, our drug screening revealed 68 non-toxic drugs that could re-sensitize multi-drug resistant NB cells to standard-of-care. Then, on the one hand, bioinformatic analyses identified a list of 235 canonical targets of the identified repurposed drugs. Amongst them, 9 were found to be associated with a worse clinical outcome when highly expressed at the gene level in neuroblastoma tumors. An siRNA screening targeting those 9 genes revealed IRAK1 as the most promising factor regulating NB progression and drug resistance. On the other hand, one of the pharmacological classes identified in our drug screen is ß-blockers (5 hits out of 68). To unveil their non-canonical targets, click-chemistry approach is applied. Several clickable derivatives have been synthesized for propranolol and carvedilol. As a pre-requisite, we first ensured their conserved chemotherapy-enhancing properties in comparison to parental compounds. They were then used to assess drug penetration in cancer cells and subcellular localization by flow cytometry and confocal microscopy. Click-chemistry approach will also allow us to retrieve the clickable derivatives along with their interacting partners to molecularly dissect their mechanism(s) of action by mass spectrometry. As a next step, cellular and molecular biology techniques including CRISPR interference will be used to provide a complete characterisation of the identified targets. By deciphering the polypharmacology of repurposed drugs, the REMAP project could help better understand neuroblastoma biology and reveal key targetable pathways. It will facilitate the development of more tailored treatments and the discovery of biomarkers for neuroblastoma. Ultimately, our project will lead to the emergence of a new research field called reverse molecular pharmacology that could be applied to any cancer.

MORFOISSE Florent
Scientific supervisor: GARMY-SUSINI Barbara - Institute of Metabolic and Cardiovascular Diseases, U1048, Molecular regulations of (lymph)angiogenic growth factors in vascular diseases Team, TOULOUSE

Characterization of lymphedema-associated extracellular matrix

Context & Objectives
Secondary lymphedema, a disorder of the lymphatic vascular system, is characterized by impaired lymphatic return, swelling of the extremities and an accumulation of fat and fibrosis in a limb. Fibrosis, the pathological accumulation and disorganization of extracellular matrix (ECM), worsens lymphedema but has been poorly investigated. We aim to characterize lymphedema—induced modifications of ECM, determine how this pathological ECM disrupts lymphatic vessels and identify the molecular actor of fibrosis development. We identified the lysyl oxidase (LOX) as a key actor of lymphedema-assoiated fibrosis and extracellular matrix remodelling. We demonstrated that targeting this pathological remodeling through LOX inhibition effectively protect against lymphedema development and restore the lymphatic network. This project is expected to provide new strategies to treat lymphedema by normalizing its microenvironment.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

NAJAFI Javad
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Jacques Monod Institute, Cellular Spatial Organisation Team, PARIS

Hydrodynamics of bulk cytoplasm and division positioning

Context & Objectives
The cytoplasm of living cells is a complex material that exhibits both fluid-like viscous and solid-like elastic properties. These properties are associated with macromolecular crowding and cytoskeletal networks and may impact fundamental processes such as biochemical reaction rates or phase separation. Given that the size of components floating in the cytoplasm ranges from few nanometers for small proteins up to tens of microns for nuclei, microtubule asters, or mitotic spindles, we sought to dissect how viscoelastic properties of the cytoplasm may affect the mobility of objects with different sizes. Using large sea urchin eggs, as a model to study cytoplasm properties, we injected small magnetic beads (~1µm) and large magnetized oil droplets (10-30µm) and displaced them with calibrated magnetic tweezers in live cells. Upon displacement, we found that the cytoplasm imparted viscoelastic restoring forces that moved back these objects towards their initial position. Remarkably, cytoplasm restoring elastic stiffness was dramatically higher for larger objects. 3D COMSOL simulations confirmed this size-dependent elastic response and suggested that this effect may be caused by the hydrodynamic coupling of the object with the cell surface boundaries, which becomes increasingly more important as the object occupies more of the cytoplasm space. Modulating molecular crowding with hyper or hypo-osmotic shocks increased and respectively decreased cytoplasm elasticity and viscosity independently of object size. Interestingly, depolymerizing F-actin bulk meshworks reduced cytoplasm elasticity and viscosity but to a larger extent for bigger objects. These studies begin to establish how cytoplasm material may contribute to organelle positioning and cellular organization.

POILLET-PEREZ Laura
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Cancer Research Center of Toulouse (CRCT), U1037, TOULOUSE

Involvement of autophagy in the regulation of metabolism and chemoresistance of acute myeloid leukemia (AML)

Context & Objectives

The prognosis is poor in human acute myeloid leukemia (AML) due to the high frequency of relapses, mainly caused by the growth of relapse-initiating chemoresistant leukemic cells (RICs). AML cells, similar to numerous cancer cells, are able to reprogram their metabolism. My laboratory and others demonstrated that RICs have an increased oxidative metabolism and relies on fatty acids and amino acids metabolism to grow and survive to chemotherapy. We hypothesized that autophagy could be responsible of this reprogramming and resistance. Autophagy is a catabolic process allowing degradation and recycling of damaged proteins and organelles to feed metabolism and support cancer cell biology. Earlier studies on autophagy and tumor growth mainly focused on cell-autonomous autophagy (tumor autophagy). However, similar to tumor autophagy, non cell-autonomous autophagy (host/microenvironment autophagy) has also been recently implicated in tumor growth promotion of melanoma, lung cancer or pancreatic cancer by supplying substrates required for their growth. Moreover, our laboratory recently showed that tumor autophagy is necessary for AML metabolism and growth regulation. However, the exact mechanisms by which autophagy controls the metabolic dialog between AML cells and their microenvironment and the consequences on therapeutic resistance still remain unknow. Thus, I aim to investigate whether tumor and/or host autophagy can support AML growth and therapeutic resistance by modulating tumor metabolism. Using innovating in vitro and in vivo models for autophagy deficiency, I wish to 1) evaluate the role of tumor and host autophagy in tumor growth and resistance to therapy and 2) identify the underlying mechanisms. Thus, I expect that modulating the identified targets will sensitize the AML cells to therapy. This knowledge will provide a deeper understanding on the molecular mechanisms involved in AML resistance especially in vivo and help to develop new selective treatments eradicating RLCs to overcome AML patient relapses.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

ROSINSKA Sara
Scientific supervisor: GAVARD Julie - Cancer and Immunology Research Center of Nantes-Angers, U1232, Laboratory of Signaling Oncogenese Permeability and Angiogenesis, NANTES

Involvement of JAM-C in Communication between Glioblastoma Stem-like Cells and Brain Endothelial Cells

Context & Objectives

Glioblastoma (GBM) is the most aggressive and common malignant primary brain tumor in adults with a high recurrence and mortality rate. The presence of Glioblastoma Stem-like Cells (GSCs) is suspected to be responsible for tumor initiation, expansion, recurrence and resistance to current therapies. Moreover, GSCs are localize in close proximity to the brain blood vessels which supports not only their growth, but also allows GSCs to migrate along blood vessels and to invade healthy tissues. Invasive nature of GSCs on brain vasculature is related to the GBM intracranial spreading and poor patient survival. The adhesion molecules engaged in direct tethering of GSCs to the brain endothelial cells (EC) that lines blood vessels, are not identified so far as well as the mechanism of invasion.

Our transcriptomic analysis identified Junctional Adhesion Molecules C (JAM-C) as a putative adhesion partner between GSCs and ECs. We therefore investigated the impact of JAM-C on the tumor vascular niche, by developing ex vivo human models. First, RNA silencing (knock-down, KD) or gene deletion (knock-out, KO) of JAM-C in GSCs hampers adhesion to EC monolayers. Moreover, JAM-C KO reduced the levels of SOX2 and NESTIN stemness markers. JAM-C KO GSCs undergo Epithelial-to-Mesenchymal Transition (EMT) displaying up-regulation of EMT markers on protein and mRNA levels, as well as up-regulation of vimentin and integrin beta 1 activity. This was accompanied by an elevated differentiation ability of GSCs, in terms of morphological and molecular differentiation, adhesion and sprouting migratory behavior from 3D spheroids.

Our results established that JAM-C acts at the level of both GSC/GSC and GSC/EC interaction, impacting their binding and migratory behavior and the stem-like properties of GSCs. Future studies will decipher whether JAM-C disruption benefits to tumor expansion and/or invasion either in vitro as in vivo.

SIMULA Luca
Scientific supervisor: DONNADIEU Emmanuel
Cochin Institute, U1016, Cancer and Immune Response team, PARIS

Improving the intra-tumoral motility of T cells by targeting their metabolism

Context & Objectives
The tumor microenvironment markedly limits intra-tumoral T cell motility and the contact with tumor cells. Such a defective intra-tumoral motility of T cells is one of the main reasons explaining why current treatments based on reinvigoration/infusion of T or CAR T cells to fight human solid cancers are unsuccessful. Metabolic reactions support T cell migration, which requires a fine-tuned regulation of cytoskeletal rearrangements, a process highly energy-expending. Indeed, both glycolysis- and mitochondria-generated ATP are required to sustain T cell motility.Of note, metabolism is severely altered within the tumor microenvironment. Several nutrients are sequestered by tumor cells, which at the same time release several metabolites inhibiting the immune response. Consequently, T cell metabolism is severely de-regulated within different tumor areas, but if and how this specifically affects intra-tumoral T cell motility is unknown. This aspect is important, since the metabolism of tumor-infiltrating T cells could be in principle easily modulated, opening a window of opportunity to improve current immunotherapy approaches against solid cancers, whose ineffectiveness is often associated with a poor intra-tumoral T cell motility.

Objectives
By this project, I aim at understanding (i) if and how the altered intra-tumoral metabolism of T cells is responsible for their defective ability to infiltrate tumor islets, and (ii) how to manipulate the metabolism of intra-tumoral endogenous T cells and CAR T cells to improve their motility and anti-cancer response.

Methods
I will take advantage of fresh human tumor biopsies in which resident T cell motility will be monitored thanks to an innovative methodological approach to obtain viable vibratome-cut tissue sections. In addition, multiparametric immunohistochemistry approaches and fluorescent biosensors will be used to measure in the same cells several metabolic parameters. Also, the effects of metabolites on T cell motility will be assessed using 3D in vitro models.

Expected Benefits
The findings of this project will provide new insights into (i) how to improve the metabolic regimen of human cancer patients to increase T cell infiltration within tumor islets (this has broad-range implications for all cancer patients), and (ii) how to boost the infiltration of both endogenous and CAR T cells by modulating their metabolism.

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

VASSAUX Maxime
Scientific supervisor: CANTAT Isabelle
Physic Institute, « Matière Molle » Department, RENNES

In silico multiscale models of microenvironment to explore invasiveness of osteosarcomas

Context & Objectives
Bone sarcomas are extremely invasive tumours, at the expense of patients prognosis. Precision of ablation of pathological tissue during surgical treatment can largely be improved and novel signalling pathways targeted by poly-chemotherapy must be discovered. The purpose of my project is to explore fundamental mechanisms underlying bone and Ewing sarcomas aggressiveness by means of computer-based simulations at the tissue and molecular scales. We have recently hypothesised that sarcomas proliferation results from the double catalysis of sarcomas by bone tissue and bone tissue by sarcomas. The spectacular morphology of the remodelled bone tissue in presence of tumour cells may well be induced by this synergetic effect triggered by signalling molecules released by sarcomas. We have developed a simple model based on a cellular automaton of the evolution of bone tissue and sarcoma morphology accounting for both catalytic effects. Simulations results show the dependence of the morphology to the double catalysis. This demonstration orients our recent research toward clarifying the specific molecular signals capable of triggering this synergetic mechanism. To that extent, I am now pursuing our investigations at the molecular scale by investigating the mechanisms of mineralisation of collagen fibrils altered by such potential molecular signalling. I perform molecular dynamics simulations of the hydration of collagen microfibrils to determine how mineral transport and deposition occurs. These simulations will help us understand in detail the catalytic effect of sarcoma on bone tissue remodelling, and in particular why its results in weakly mineralised collagen structures similar to osteoid.

VOISIN Allison
Scientific supervisor: GRINBERG-BLEYER Yenkel - Cancer Research Center of Lyon (CRCL), UMR 5286, Molecular regulation of cancer immunity Team, LYON

Understanding the roles of NF-κB subunits on effector CD8+ T cell functions and response to anti-PD-1 checkpoint blockade therapy in cancer.

Context & Objectives
Cancer progression is greatly influenced by a delicate balance between immunity and tolerance to tumors. In particular, CD8+ effector T lymphocytes (Teff) play a central role in the elimination of tumors. Despite recent advances in the comprehension of the immune cell subsets controlling tumor growth, which have led to the development of ground-breaking cancer immunotherapies, the signal transduction pathways and transcription factors orchestrating Teff cell function in cancer remains largely unknown. Our recent reports demonstrated that the transcription factor Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB) is a critical modulator of immunity and tolerance to cancer. However, NF-κB is in fact a family of transcription factors composed of 5 distinct subunits and the contribution of individual subunits to CD8+ effector T cell functions has never been addressed. Here we aim at deciphering the contribution of RelA and c-Rel, two of the canonical NF-kB subunits, in CD8+ T-cell response to cancer and cancer immunotherapies.

Results
Using a CRISPR/Cas9 approach and unique mouse models, we first investigated the effect of RelA and c-Rel ablation in human and murine CD8+ T cells at steady-state. We found that RelA and c-Rel had distinct contributions to the proliferation, cytokine production and gene expression pattern of CD8+ T cells. In the context of cancer, we made the unexpected observation that CD8+ T cell-restricted ablation of RelA, but not c-Rel, strongly decreased the burden of transplanted colon carcinoma; this was associated with increased T-cell cytotoxicity. However, neither the ablation of RelA or c-Rel impacted the clinical response to anti-PD-1 checkpoint blockade therapy in this model. This suggested that RelA may have a deleterious function in tumor-infiltrating CD8+ T cells.

Conclusion & Perspectives
Our experiments delineated specific CD8+ T-cell functions and gene expression patterns controlled by discrete NF-κB subunits. We are now investigating the molecular mechanisms underlying these selective contributions by using multi-omics analyses. These results provide proof-of-concept evidences that manipulation of specific NF-κB subunits can shape immune responses in cancer and could represent possible therapeutic targets. Publications:

Publications
The many-sided contributions of NF-κB to T-cell biology in health and disease - International Review of Cell and Molecular Biology. 2021. V Allison and G-B Yenkel

PRIX HÉLÈNE STARCK POSTERS
CATÉGORIE POST-DOCTORAT

YAMAGUCHI Kohsuke
Scientific supervisor: DEFOSSEZ Pierre-Antoine
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Controlled epigenetic disturbances induce senescence in cancer cells

Context & Objectives
The advances of cancer genomics have clearly established that mutation of epigenetic regulators can drive transformation. Among the epigenetic marks, DNA methylation has long been recognized as a key phenomenon that could be targeted pharmaceutically to regulate cancer cells. In this regard, a large amount of attention has been given to the DNMTs, the enzymes that methylate DNA, but more recent work has identified another key factor: the protein UHRF1. UHRF1 ensures the maintenance of DNA methylation by recruiting and activate DNMT1. Remarkably, UHRF1 is also known as an oncogene. The overexpression of UHRF1 causes cancer in animal models, and its expression is required for growth of tumor cells. Understanding how UHRF1 works in cancer cell can inform the general question: «how does an epigenetic regulator become oncogenic?».However, the currently used tools for loss-of-function analysis are not well adapted to answer the question: siRNA gives a transient and incomplete effect, while CRISPR does not affect all cells in the population and does not act rapidly.To overcome these limitations, we used advanced genetic methods to render the endogenous UHRF1 or DNMT1 protein of cancer cells rapidly degradable upon addition of an inducer (Auxin-Inducible Degron method), then prepared 3 cell lines (UHRF1-AID, DNMT1-AID, UHRF1/DNMT1-AID) using HCT116. In these cell lines, the endogenous UHRF1 or DNMT1 was rapidly and completely removed from cancer cell nuclear after 2 hours incubation with auxin. Using this system, we tested 1) the cell proliferation and cell cycle, 2) the DNA methylation and histone modifications state, and 3) the kinetics analysis with RNA-seq after UHRF1 or DNMT1 remove. With above studies, we found the main phenotype after UHRF1 or DNMT1 remove was senescence. This work will help better understand an epigenetic oncogene, and provide new tools for the epigenetic treatment of oncogenesis.

POSTERS

HORS PRIX

BOUTEGRABET Warda – Doctorat
Scientific supervisor: PIOT Olivier - INSERM U1113, Fundamental and Applied Research Interface in Cancerology (IRFAC), Strasbourg, 2EA7506, Translational BioSpectroscopy (BioSpecT), Reims

Development of a new unsupervised feature selection based on genetic algorithm: application on the FTIR images of human colon cancer

Context & Objectives
Spectral histopathology is a mature analytical technique based on two pillars: vibrational spectroscopy and chemometrics. Multivariate analysis in chemometrics aims at building a mathematical model linking the molecule vibrations (expressed in wavenumbers) to a biological objective. So far, the majority of spectral histology studies based on vibrational spectroscopy exploits all the information contained in the recorded spectra, i.e. several hundreds, even thousands, of wavenumbers [1]. The analysis of hyperspectral data is complex because usually a small subset of wavenumbers is really informative for the designed task. Selecting the most informative spectral features is thus essential, in particular to improve the efficiency of prediction models, as stated by several authors [1-2].

The aim of this study is to propose a new unsupervised method of feature selection based on genetic algorithm (GA) combined with KMeans clustering in order to identify main biomarkers of histological structures from human colon cancer tissue sections. In particular, we have proposed a new «fitness» function based on the use of validity indices computed from KMeans partitions.

The performance of our proposed approach has been evaluated on simulated data, then validated on real mid-infrared datasets of colon cancer available within U1113 INSERM-IRFAC (Strasbourg) and University Hospital of Reims. The results have been compared with and without feature selection using GA in terms of accuracy and time. Our proposed method has been proved stable and able to perfectly estimate a small list of discriminant wavenumbers for an equivalent accuracy. Furthermore, these spectral descriptors ease the biochemical interpretation of the results since only few spectral bands are highlighted by our algorithm.
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Publications
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GIRAUD Julie – Post Doctorat
Scientific supervisor: SALEH Maya
Bordeaux University, U5164, ImmunoConcEpT, BORDEAUX

Exploiting immunity of hepatocellular carcinoma to improve the treatment of patients

Context & Objectives
Hepatocellular carcinoma (HCC) is the most common liver tumor and among the deadliest cancers worldwide. Environmental risk factors for developing HCC include viral infection (HBV and HCV), alcohol abuse and the metabolic syndrome. While there is evidence that boosting the activity of tumor-specific T cells might benefit patients with HCC, the underlying liver soil (cirrhosis, NASH) renders the tumor microenvironment of this cancer somewhat unique. Despite a significant therapeutic advance in the treatment of advanced HCC with immune checkpoint inhibitors, ~75% of patients do not respond to these immunotherapies for unclear reasons. Such a heterogenous response highlights the need to further explore etiology- and organ-specific immunity towards improved patient stratification and the development of new combination therapies.
Here, we set to characterize the innate immune landscape of HCC with respect to etiology. We employed droplet-based 3' single-cell RNA sequencing (scRNA-seq) to profile CD45+panTCRαβ-CD19- cells in tumoral and adjacent non-tumoral tissue freshly isolated from 10 HCC patients with different etiologies. In parallel, we performed spatial transcriptomics (stRNA-seq) using the 10x Genomics Visium technology.
Analysis of the transcriptomes of 100,000 innate immune cells revealed a remarkable diversity of myeloid cells and natural killer (NK) cells and lead to the identification of etiology-dependent subsets that were either depleted or enriched in HCC. In particular, we identified novel subsets of tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) with immunosuppressive properties and associated with bad prognosis in HCC patients.
The integration of scRNA-seq and stRNA-seq is underway and is hoped to elucidate spatial information of the newly characterized clusters and their microenvironmental interactions, with respect to liver zonation, fibrosis and etiology of the disease.
Collectively, our work uncovered interesting immunotherapeutic targets as potential novel therapeutic entry points for improved HCC patient care.

Publications
Landscape and the Potential of Immunotherapies. Front Immunol. 2021, J Giraud, D Chalopin, J.F Blanc, M Saleh.

KARA-ALI Ghania - Doctorat

Scientific supervisor: DIMANCHE-BOITREL Maie-Thérèse
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The E3-Ubiquitin ligase TRIM21 acts as a brake on hepatocellular carcinoma development in hypoinsulinemic mice with non-alcoholic steatohepatitis.

Context & Objectives

The tripartite motif protein 21 (TRIM21) is an E3 ubiquitin ligase already known to be implicated in different biological processes such as cell cycle, cell death, and immune response. In the oncology field, a low expression of TRIM21 has been linked to poor survival rates in cancers such as diffuse large B-cell lymphoma, breast cancer, and hepatocellular carcinoma (HCC). However, the implicated mechanisms remain to be unraveled. Using a mouse model that mimics the emergence of HCC in humans in the context of non-alcoholic steatohepatitis (NASH), we investigated the role of TRIM21 throughout this pathology. Briefly, male mice, developing hypoinsulinemia induced by streptozotocin injection at the neonatal stage, were fed with a high-fat high-cholesterol diet (HFHCD) for 4, 8, or 12 weeks, promoting systematic HCC development on NASH. Results show that Trim21-KO mice exhibited greater liver damage after 12 weeks under HFHCD, as quantified by serum transaminases, and developed more HCC nodules than their Trim21-WT littermates. At 4 weeks of HFHCD, the liver microenvironment in Trim21-KO mice exhibited a more pronounced pro-inflammatory and pro-survival signature. Later, at 12 weeks of HFHCD, the overall hepatic immune infiltrates were more significantly reduced in Trim21-KO mice. Furthermore, intrasplenic CD4+PD1+ and CD8+PD1+ lymphocytes were increased in Trim21-KO at 12 weeks under HFHCD. Besides, an analysis carried out on HCC from patients suffering from metabolic syndrome revealed a positive correlation between TRIM21 expression and immune infiltrates in HCC tumors, supporting our in vivo results. Overall, our data show that the E3 ubiquitin ligase TRIM21 contributes to the establishment of an appropriate liver immune microenvironment able to limit HCC nodule emergence.

POSTERS
HORS PRIX

KASIKCI Yasenya - Doctorat

Scientific supervisor: GRONEMEYER Hinrich - Institute of Genetic and Molecular and Cellular Biology (IGBMC), Functional Genomics and Cancer Team, ILLKIRCH

Patient-matched analysis identifies deregulated networks in prostate cancer to guide personalized therapeutic intervention

Context & Objectives

Prostate cancer (PrCa) is the second most common malignancy in men. More than 50% of advanced prostate cancers display the TMPRSS2-ERG fusion. Despite extensive cancer genome/transcriptome data, little is known about the impact of mutations and altered transcription on regulatory networks in the PrCa of individual patients. Using patient-matched normal and tumor samples, we established somatic variations and differential transcriptome profiles of primary ERG-positive prostate cancers. Integration of protein-protein interaction and gene-regulatory network databases defined highly diverse patient-specific network alterations. Different components of a given regulatory pathway were altered by novel and known mutations and/or aberrant gene expression, including deregulated ERG targets, and were validated by using a novel in silico methodology. Consequently, different sets of pathways were altered in each individual PrCa. In a given PrCa, several deregulated pathways share common factors, predicting synergistic effects on cancer progression. Our integrated analysis provides a paradigm to identify druggable key deregulated factors within regulatory networks to guide personalized therapies.

NICOLLE Amandine - Doctorat

Scientific supervisor: WANG Xiaobo
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Loss of PKCθ drives cancer cells into p53-independent senescence

Context & Objectives

Triple negative breast cancer (TNBC) is a subtype of breast cancer characterized by absence of estrogen and progesterone receptors and absence of amplification of HER2. TNBCs accounts for about 15% of all breast cancers, they display aggressive and invasive characteristics. Thus, there is an urgent need to identify signaling pathways driving this aggressiveness in order to develop new therapeutic strategies. Protein kinase C θ (PKCθ), a serine/theronine kinase well known for its role in the immune system is highly expressed in TNBCs. We and other groups have previously found that PKC θ inhibition reduces the proliferation ability of breast cancer cells. Here, we have explored the molecular mechanism by which PKCθ controls cell proliferation.We found that PKCθ loss lead to a proliferation arrest in G1 phase along with a cellular senescence-like phenotype in TNBC cells. PKCθ regulates the expression of genes involved in cell proliferation such as p16 and p21 (slight increase) and a strong accumulation of p27. P27 inhibition partially rescue the phenotype induced by PKCθ depletion suggesting p27 is the main driver of the PKCθ loss-induced senescence. Surprisingly we found that during PKCθ loss, Growth Arrest and DNA Damage inducible alpha(Gadd45α) is down regulated. Indeed, Gadd45α silencing demonstrate features similar to PKCθ inhibition including proliferation arrest in G1 phase, cellular senescence-like phenotype and accumulation of p27.The loss of PKCθ-Gadd45α axis initiates a proliferation arrest and a senescence response in TNBC cells harbouring a p53 mutation. A better understanding of this mechanism and the role of PKCθ is important, since this aggressive subtype of cancer has a poor prognosis and is currently mainly treated with chemotherapy. PKCθ could be a potential good target due to its limited expression in normal cells (lymphoid cells and skeletal muscle cells).

PIECYK Marie - Doctorat

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Pemetrexed Hinders Translation Inhibition upon Low Glucose in Non-Small Cell Lung Cancer Cells

Context & Objectives

Genetic alterations in non-small cell lung cancers (NSCLC) stimulate the generation of energy and biomass to promote tumor development. However, the efficacy of the translation process is finely regulated by stress sensors, themselves often controlled by nutrient availability and chemotoxic agents. Yet, the crosstalk between therapeutic treatment and glucose availability on cell mass generation remains understudied. Herein, we investigated the impact of pemetrexed (PEM) treatment, a first-line agent for NSCLC, on protein synthesis, depending on high or low glucose availability. PEM treatment drastically repressed cell mass and translation when glucose was abundant. Surprisingly, inhibition of protein synthesis caused by low glucose levels was partially dampened upon co-treatment with PEM. Moreover, PEM counteracted the elevation of the endoplasmic reticulum stress (ERS) signal produced upon low glucose availability, providing a molecular explanation for the differential impact of the drug on translation according to glucose levels. Collectively, these data indicate that the ERS constitutes a molecular crosstalk between microenvironmental stressors, contributing to translation reprogramming and proteostasis plasticity.

Publications

Pemetrexed Hinders Translation Inhibition upon Low Glucose in Non-Small Cell Lung Cancer Cells. Metabolites. 2021. M Piecyk, M Triki, P.A Laval, H Dragic, L Cussonneau, J Fauvre, C Duret, N Aznar, T Renno, S.N Manié, C Chaveroux, C Ferraro-Peyret

WATZKY Manon - Doctorat
Scientific supervisor: MIOTTO Benoit
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Dissecting Hexokinase 2 functions in cancer: from cell metabolism to the regulation of stemness and chemo-resistance

Context & Objectives
Elevated glucose uptake is one of the hallmarks of cancer cells. This metabolic change, commonly referred as the "Warburg effect", is mainly due to the increased expression and activity of glycolytic enzymes, especially Hexokinase 2 (HK2). HK2 overexpression has been reported in many cancers and often associated with poor prognosis and drug resistance. HK2 plays a central role in tumor initiation and progression, highlighted by the many observations that its deletion impairs cancer cells proliferation and genetically-induced tumors development in mice models. Although many projects aimed at developing inhibitors of hexokinases activity, none of these studies identified compounds that selectively inhibit HK2 and exhibit clear beneficial effects in clinical trials. A better understanding of HK2 functions in cancer cells is thus needed to find ways to specifically target this key enzyme. To achieve this goal, we though to describe in deep the cellular and molecular functions of HK2 and we established a stable cell line overexpressing HK2 using poorly tumorigenic osteosarcoma cells as a model. We demonstrated that HK2 overexpression is sufficient to enhance cell proliferation and promote colony formation and anchorage-independent growth. The cells overexpressing HK2 also acquired the ability to form 3D spheroids, a characteristic of cancer stem like cells (CSC). We further validated the existence of the CSC population by flow cytometry and described that these cells highly express key pluripotency factors as well as multidrug resistance proteins important for drug efflux and chemotherapy resistance. The use of competitive inhibitors of hexokinases activity, such as 2-deoxyglucose, only partially impair the tumorigenic capacities promoted by HK2 overexpression. We thus postulated that HK2 may have additional functions beyond glycolysis. A label-free proteomic analysis highlighted the proteome changes triggered by HK2 overexpression in cancer cells. The cells overexpressing HK2 exhibit alterations of components involved in cytoskeleton network, cell junctions and cell adhesion as well as nuclear factors. Moreover, by combining high throughput single-cell analysis and confocal microscopy, we described that HK2 protein shuttles between the cytoplasm and the nucleus. Importantly, we showed that this regulation may be dependent on phosphorylation by oncogenic kinases and might imply a nuclear function of HK2. Our work provides new insights into the function of HK2 in cancer cells and identifies unsuspected targets of the kinase in the cytoplasm and the nucleus. Some of these factors are essential for tumor initiation, stemness and chemotherapy resistance, consistent with our assays showing a key role of HK2 in these processes in an osteosarcoma model. We currently envision to use this new information to target HK2 function in cancer cell models.

WILSON Têtê Norbert - Doctorat
Scientific supervisor: ROQUELAURE Yves
Faculty of Health, Ester Team, ANGERS

Effectiveness of physical activity interventions on return to work after a cancer diagnosis: a systematic review of intervention studies

Purpose
The aim of this systematic review is to assess the effects of physical activity (PA) intervention on return to work (RTW) in cancer patients and determine the dose of PA needed to improve this outcome.

Methods
A systematic review was conducted according to PRISMA guidelines. We included PA intervention studies that aimed to assess RTW in cancer patients (≥18 years). Six electronic databases were searched for relevant studies including PubMed, EMBASE, Web of Science, CENTRAL (Cochrane), PsycINFO, and Scopus from inception to March 8, 2021. We also searched grey literature, and health organization websites; hand-searched reference list of previous reviews; and consulted additional experts. Two review authors independently screened records based on the eligibility criteria, extracted data from the included studies and assessed risk of bias using navigation guide tools.

Results
A total 2405 records were identified, of which 8 intervention studies were included. The sample size of the included studies varied between 41 and 240, for a total 1087 participants aged between 18 and 75 years, diagnosed with breast cancer (mainly), prostate cancer, colorectal, upper gastrointestinal, Hodgkin lymphoma and ovarian cancers. Altogether, the included studies reported beneficial effects of PA intervention on RTW compared to usual care. Of these, 2 studies reported statistically significant effects of PA intervention increasing the rate of RTW corresponding to weekly exercise dose comprised between 7.6 METs.h/week and 15 METs.h/week.

Conclusion
Findings from the individual studies suggested that there exists some evidence that PA intervention have positive effects, thereby increasing the rate of RTW among cancer survivors.

Keywords
Intervention, return to work, cancer, physical activity, systematic review.

PRIX KERNER

Anaïs ASSOUVIE — CEA - FONTENAY-AUX-ROSES

1 PERSONNALISER LES THÉRAPIES ANTICANCÉREUSES : QUAND LA GÉNÉTIQUE S'EN MÊLE

Au Commissariat à l'Énergie Atomique et aux Énergies Alternatives (CEA) de Fontenay-aux-Roses, la doctorante Anaïs ASSOUVIE s'est intéressée durant sa thèse à améliorer l'efficacité d'un traitement largement utilisé pour éliminer certaines tumeurs.

Quel est l'objectif de votre thèse ?

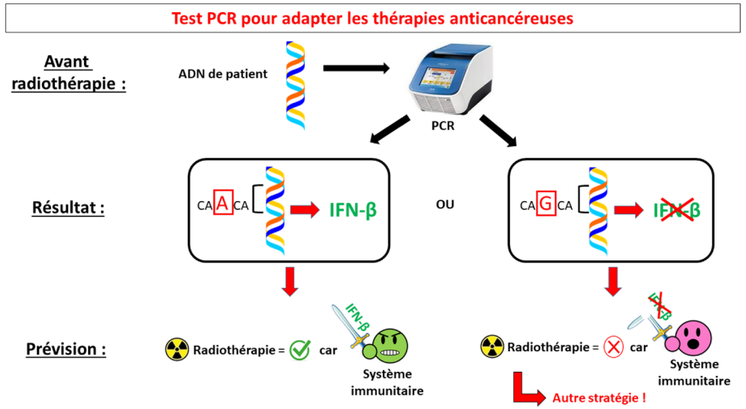
L'objectif de ma thèse est d'améliorer l'efficacité d'un traitement utilisé chez la moitié des patients atteints de cancers localisés. Ce traitement est la thérapie par les rayons X, aussi appelée radiothérapie. Et oui, les rayons X ne servent pas uniquement à scanner vos valises à l'aéroport ou votre squelette lors d'une fracture mais également à éliminer les cancers.

Comment ces rayons X qui ne détruisent pas nos valises ou notre squelette éliminent-ils les cancers ?

Avec les rayons X, tout est une question de dose ! En thérapie, la dose utilisée est plus élevée que pour les scanners et peut donc avoir des effets sur les cellules. Mais ne vous inquiétez pas ! Les cellules cancéreuses sont plus sensibles aux rayons X que les cellules saines. En effet, les fortes doses de rayons X entraînent des dommages à l'ADN qui sont mortels pour nos cellules. Ils sont généralement mieux réparés lorsque les cellules sont saines. Mais les cellules cancéreuses ont du mal à réparer ces dommages. C'est pour cela qu'elles meurent.

Puisque la radiothérapie est déjà efficace, pourquoi vouloir l'améliorer ?

Malgré son efficacité, la radiothérapie a des limites. En effet, certains patients ne répondent pas du tout à ce traitement. Cela est en partie dû au fait que pour être efficace, la radiothérapie doit déclencher une réponse immunitaire en plus de détruire directement les cellules cancéreuses. On s'est aperçu que le patrimoine génétique des patients qui ne déclenchent pas cette réponse est en cause.



Avant de traiter les patients par radiothérapie, on récupère leur ADN. Par un test PCR, on détermine s'ils ont la variation A ou G. La variation A permet une radiothérapie efficace par un système immunitaire armé par la production d'IFN-β tandis que la variation G entraine une radiothérapie moins efficace par un système immunitaire désarmé à cause de l'absence de production d'IFN-β. Pour la variation G, une stratégie différente de la radiothérapie doit être envisagée.

Comment le patrimoine génétique peut-il influencer la réponse immunitaire après radiothérapie ?

Cette réponse est coordonnée par la production d'une protéine appelée interféron-β (IFN-β). Durant ma thèse, j'ai découvert une variation génétique responsable d'une absence de production d'IFN-β dans les cellules immunitaires appelées cellules myéloïdes. Notre ADN est composé d'une succession de quatre molécules simplifiées par les lettres A, T, C et G et cette succession varie selon les individus. J'ai montré sur une petite cohorte de patients qu'à une position précise de cette succession, certains ont un A et d'autres ont un G : la présence du G empêche la production d'IFN-β dans les cellules myéloïdes et la réponse à la radiothérapie se trouve affaiblie.

Comment intervenir ?

On peut identifier la présence du A ou du G par un simple test PCR avant d'utiliser la radiothérapie comme stratégie de soin. Un brevet a d'ailleurs été déposé par mon laboratoire sur la détection de cette variation pour orienter le choix de la thérapie. On parle de médecine personnalisée.

Quelle est la suite de votre projet ?

La suite du projet est de réaliser ce test PCR sur de grandes cohortes de patients afin de valider à grande échelle ce nouvel outil d'orientation de thérapie mais il faudrait obtenir des financements importants et mon laboratoire ne les a pas encore obtenus. Parallèlement, j'ai découvert un moyen d'augmenter la production d'IFN-β chez les patients ayant la variation A. En plus d'améliorer la réponse immunitaire, cette stratégie permettrait de diminuer les doses de radiothérapie et d'en limiter les effets secondaires néfastes.

Blandine BAUDON — Institut Curie - PARIS

2 EXPLOITER LE GÉNOME SILENCIEUX POUR AMÉLIORER LES PROTOCOLES D'IMMUNOTHÉRAPIE

Les cellules cancéreuses peuvent se distinguer des cellules saines en créant de nouvelles protéines. Blandine Baudon, doctorante à l'Institut Curie, étudie les mécanismes qui conduisent les cellules cancéreuses à créer de nouvelles protéines qui les rendent reconnaissables par les cellules du système immunitaire.

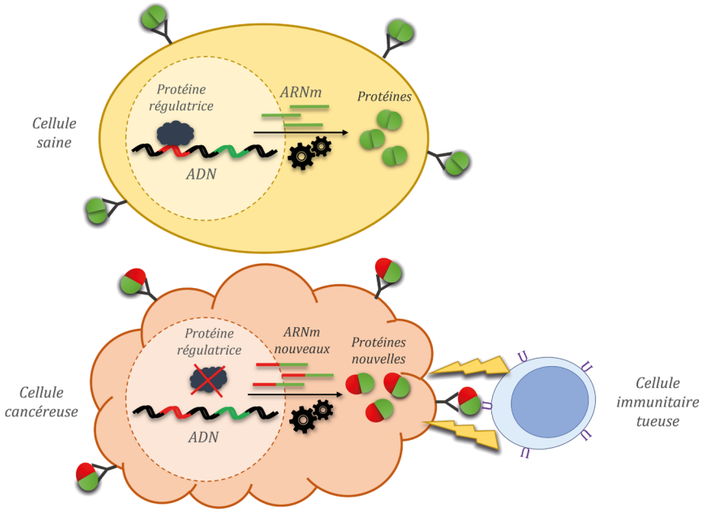
Qu'est-ce qui distingue les cellules cancéreuses des cellules saines ?

Nos cellules ont une membrane qui les enveloppe et les protège ainsi qu'un noyau qui contient notre patrimoine génétique sous forme de longues molécules d'ADN. L'ADN contient l'information nécessaire à la production des protéines, constituants essentiels au bon fonctionnement de la cellule. Ces protéines, produites à l'intérieur de la cellule, sont aussi présentes à la surface de la membrane. Une molécule intermédiaire est nécessaire pour que les machineries de la cellule sachent quelle protéine elles doivent créer. Cette molécule est un messager capable de copier une petite partie de l'information génétique contenue dans l'ADN et de se rendre sur les lieux de la création des protéines, c'est l'ARN messager.

Dans les cellules saines, des protéines régulatrices maintiennent endormies des portions d'ADN. Cependant, dans les cellules cancéreuses, ces protéines régulatrices sont parfois absentes : des parties de l'ADN endormi peuvent alors se réveiller. Elles vont s'associer aux portions d'ADN habituellement utilisées pour former l'ARN messager. Un nouvel ARN messager est ainsi formé. Il conduit à la création de nouvelles protéines absentes des cellules saines. Ces nouvelles protéines se retrouvent aussi à la surface des cellules cancéreuses et les différencient des cellules saines.

Comment le système immunitaire peut-il reconnaître les cellules cancéreuses ?

Des cellules du système immunitaire sont capables de reconnaître les protéines à la surface des cellules. Quand les cellules immunitaires rencontrent des protéines inconnues à la surface des cellules cancéreuses, elles peuvent détruire ces cellules. La recherche de nouvelles protéines spécifiques des cellules



Dans le noyau des cellules saines, des protéines régulatrices maintiennent endormies certaines portions d'ADN. Leur absence dans des cellules cancéreuses induit la création de protéines nouvelles. Les protéines nouvelles peuvent être exposées sur la membrane de la cellule. Lorsqu'elles détectent ces protéines nouvelles, les cellules du système immunitaire peuvent tuer ces cellules cancéreuses.

cancéreuses est, pour cette raison, un défi majeur pour le développement de nouvelles thérapies.

Quels sont les objectifs de vos travaux ?

L'un d'entre eux est d'explorer les mécanismes moléculaires qui induisent le réveil de l'ADN endormi. Par ailleurs, je vais chercher à confirmer que ces protéines nouvelles des cellules cancéreuses les rendent plus susceptibles d'être détruites par le système immunitaire.

Comment procédez-vous pour étudier ces mécanismes ?

Dans les journaux scientifiques, certaines protéines régulatrices sont connues pour empêcher le réveil des parties endormies de l'ADN. J'ai établi une liste de ces protéines puis j'ai enlevé ces protéines régulatrices de cellules cancéreuses de mélanomes. Ensuite, j'ai analysé les ARN messagers de ces cellules pour savoir s'il existe des ARN messagers nouveaux. J'ai constaté que deux protéines régulatrices semblent moduler la présence d'ARN messagers nouveaux. Il me reste à approfondir ces résultats et à étudier la réponse immune contre les tumeurs où ces nouvelles protéines sont présentes à la surface cellulaire.

3 LE MEILLEUR TRAITEMENT CIBLE DANS UN CANCER RARE DES JEUNES

Le Dr Charlotte Degoutte, en Master 2 à l'Institut Necker Enfants Malades à Paris, nous fait part de son travail de comparaison de nouveaux médicaments dans un cancer rare des sujets jeunes.

Pouvez-vous tout d'abord nous parler de la maladie sur laquelle portent vos travaux ?

Je travaille sur un lymphome particulier. Un lymphome est un cancer des lymphocytes, un type de globules blancs présents dans les ganglions. Comme il existe de nombreux types de lymphomes, une classification a été établie permettant de les définir selon leurs caractéristiques. Mon travail porte sur un lymphome rare appelé « lymphome anaplasique à grandes cellules ALK-positif », dont les caractéristiques sont les suivantes : 1) les cellules tumorales ont un aspect typique lorsqu'on les regarde au microscope et 2) la survenue de ce lymphome est liée au dérèglement d'une protéine appelée « ALK ».

Pourquoi travaillez-vous sur ce lymphome ?

Il s'agit d'une maladie agressive, touchant surtout des enfants et des jeunes adultes (entre 10 et 35 ans). Les patients chez lesquels la chimiothérapie ne fonctionne pas (20-30% des cas) ont un pronostic sombre. Pour ces patients, il est impératif de trouver de nouveaux traitements.

Des médicaments particuliers, les inhibiteurs de ALK, ont récemment été développés dans certains cancers des poumons, eux aussi liés à un dérèglement de la protéine ALK. Ces médicaments ciblent et bloquent la protéine ALK, ce qui provoque la mort des cellules du cancer des poumons. Les inhibiteurs de ALK sont utilisés en pratique courante dans ces cancers, mais il y a très peu de données dans le lymphome que j'étudie, beaucoup plus rare.

Pourquoi avez-vous voulu comparer ces médicaments ?

Ce lymphome est trop rare pour que l'on puisse comparer les différents inhibiteurs de ALK dans une étude chez les patients. L'objectif était donc de sélectionner au laboratoire celui qui serait le plus efficace et qu'il faudrait étudier en priorité chez les patients.

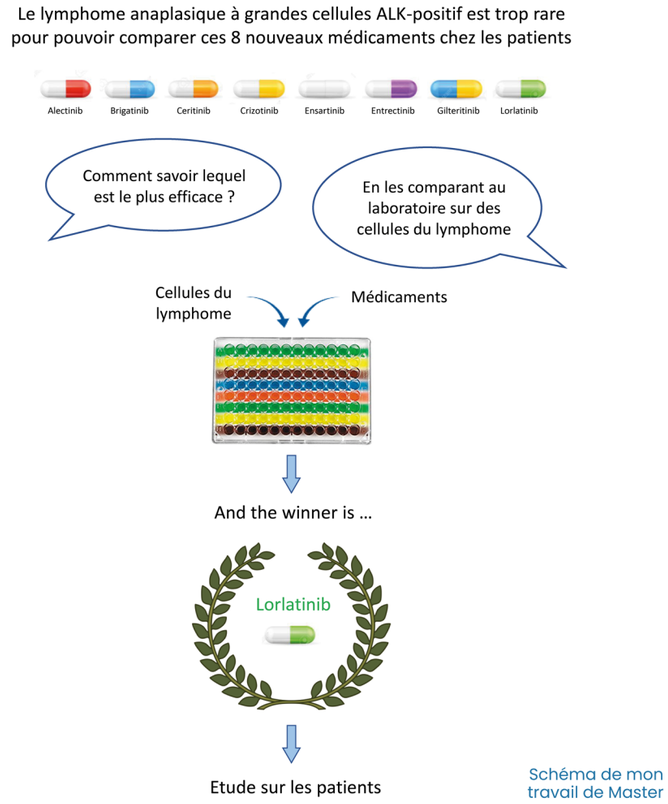


Schéma de mon travail de Master

Comment les avez-vous comparés ?

J'ai testé 8 inhibiteurs de ALK sur des cellules de lymphome anaplasique à grandes cellules ALK-positif. Il s'agit de cellules cancéreuses provenant de différents patients atteints de ce lymphome. Au laboratoire, ces cellules peuvent se multiplier hors du corps humain, dans un milieu de culture, c'est-à-dire un liquide nutritif comprenant ce dont la cellule a besoin pour survivre. J'ai ajouté les différents inhibiteurs de ALK dans le milieu de culture et j'ai comparé leurs effets sur les cellules cancéreuses, notamment leur capacité à les tuer.

Un des médicaments testés semble-t-il plus efficace que les autres ?

Oui, parmi les 8 inhibiteurs de ALK, le lorlatinib a donné les meilleurs résultats.

Quelles sont les perspectives de votre travail ?

Notre objectif est maintenant d'évaluer le lorlatinib au cours d'une étude clinique, avec l'espoir d'améliorer le pronostic de nos jeunes patients qui ont encore tant de choses à vivre.

4 CANCER DU SEIN : L'IMPRIMER EN 3D POUR MIEUX L'ÉTUDIER

Au sein de l'Accélérateur de Recherche Technologique de Bordeaux, Théo Desigaux, étudiant en doctorat, reproduit par impression 3D des tumeurs du sein. L'objectif est double : répondre à des questions fondamentales sur cette maladie qui échappe encore trop souvent aux traitements et aider aux décisions cliniques.

Pourquoi utiliser l'impression 3D pour travailler sur le cancer ?

Actuellement, une des limitations majeures de la recherche en cancérologie est d'étudier la tumeur dans sa globalité. Cela inclut bien sûr les cellules cancéreuses, mais aussi ce qui les entourent, les vaisseaux sanguins, graisses, le système immunitaire et bien d'autres. C'est tout ce qu'on appelle le microenvironnement tumoral.

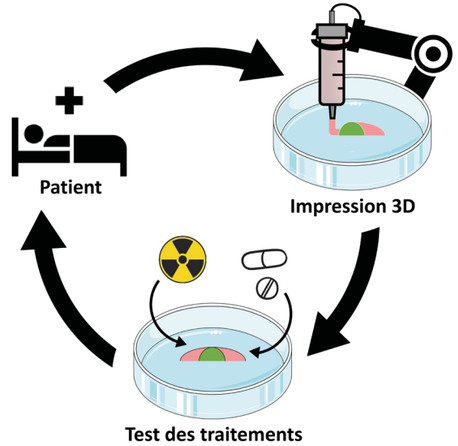
Malheureusement, cet ensemble est dur à étudier chez les patients. Beaucoup de recherches se font chez la souris, mais il est plus intéressant de pouvoir travailler avec des cellules humaines, pour tirer des conclusions qui s'appliquent à l'humain.

Grâce à l'impression 3D, je peux recopier une tumeur avec son microenvironnement de manière simplifiée à partir des cellules des malades. C'est en quelque sorte un modèle de ce cancer. Je peux ensuite m'en servir pour étudier l'effet des traitements et mieux comprendre l'impact du microenvironnement.

Qu'étudiez-vous plus précisément grâce à ce modèle ?

Il y a encore beaucoup de rechutes chez les patientes atteintes de cancer du sein, malgré les énormes progrès faits ces dernières décennies. Je suis intéressé par les mécanismes qui permettent au cancer de résister aux traitements.

Pour la radiothérapie, traitement qui utilise la radioactivité pour cibler et tuer les cellules cancéreuses, mes collaborateurs ont identifié un de ces mécanismes. Les cellules des vaisseaux sanguins envoient des signaux aux cellules cancéreuses qui vont s'en servir pour mieux survivre. Dans mon modèle, j'essaie de comprendre comment d'autres cellules influent sur cette interaction.



Le cycle du patient au patient

À partir des cellules de patients, un modèle de cancer du sein est créé par impression 3D. Au centre, les cellules tumorales (en vert) sont entourées de leur microenvironnement (en rose). Cette dernière partie contient principalement des vaisseaux sanguins. Des tests de traitements sont ensuite effectués sur le modèle afin d'étudier sa réaction. Enfin, cette meilleure compréhension permet de mieux accorder le traitement du patient à la façon dont ses cellules y réagissent et de mieux comprendre l'impact du microenvironnement.

Un autre objectif plus direct, est de se servir de nos modèles pour aider à choisir les traitements. On part des cellules d'une patiente et on identifie la thérapie qui a le plus de chance de lui réussir. Si ça fonctionne et que notre modèle permet de prédire et donc réduire les échecs thérapeutiques, cela pourrait être une pierre de plus sur le chemin d'une médecine plus personnalisée.

Comment fonctionne l'impression 3D d'un cancer, en pratique ?

Le meilleur moyen de visualiser cette technique est de penser à une impression classique.

D'abord il nous faut le plan de ce qu'on souhaite imprimer. Moi, je veux un centre qui contiendra surtout des cellules tumorales, et un cercle qui l'entoure avec des vaisseaux sanguins.

Ensuite il me faut une encre. Je prends dans un premier temps des cellules humaines qui viennent des opérations chirurgicales. J'y mélange des matériaux, que l'on trouve naturellement autour des cellules et qui modulent la rigidité de l'ensemble, du collagène par exemple. J'obtiens une mixture gélatineuse que je peux mettre dans une seringue et accrocher au bras robotique de mon imprimante.

Celle-ci va enfin suivre le tracé que je lui ai indiqué et j'obtiens, dans une boite en plastique, mon modèle de tumeur.

Cette méthode est adaptable à la majorité des cancers dits solides, qui forment une tumeur. Les perspectives de cette technologie sont donc immenses.

Camille LANDRAGIN — Institut Curie - PARIS

5 LA CACOPHONIE DE L'ÉPIGÉNOME IMPLIQUÉE DANS LE DÉVELOPPEMENT DES TUMEURS DU SEIN

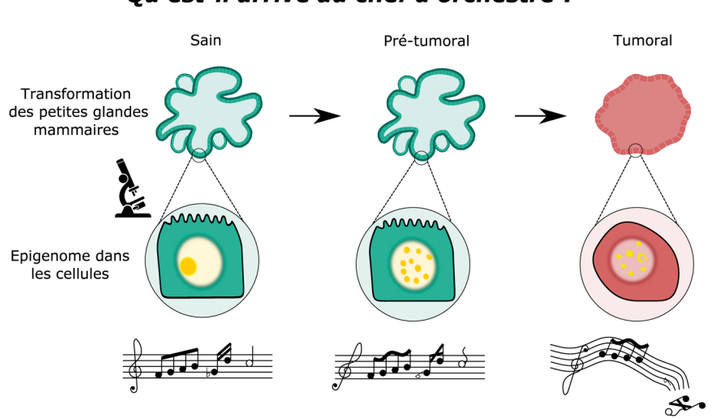
Au sein d'un jeune laboratoire de l'Institut Curie à Paris, Camille Landragin, doctorante, s'intéresse aux premiers stades de développement des tumeurs du sein. Elle s'interroge sur les mécanismes qui conduisent les cellules saines à se transformer en cellules tumorales. Elle observe notamment les modifications de l'épigénome, le chef d'orchestre qui dicte l'identité des cellules normales, mais aussi tumorales.

Quel est l'objectif de vos travaux de recherche ?

Aujourd'hui on peut noter que une femme sur huit est touchée par un cancer du sein. Les médecins et les chercheurs connaissent bien ces tumeurs. On sait les décrire et les catégoriser. Par contre, les connaissances sur les éléments qui déclenchent la formation de ces tumeurs sont beaucoup plus obscures. L'objectif de ma thèse est donc de retracer le film des événements qui permettent aux cellules de perdre leur identité normale et d'acquérir une identité tumorale, donc de se transformer dans les premières étapes de formation de la tumeur. Or, ces étapes sont difficiles à observer car, lors du diagnostic d'un cancer chez une patiente, la tumeur est déjà formée, on ne peut donc plus analyser le point de départ de la formation de la tumeur.

Comment est mis en place l'identité des cellules dans l'organisme ?

En fait, le corps est constitué de cellules différentes qui sont spécialisées dans des tâches spécifiques. Les cellules de la peau ou des muscles par exemple ne se ressemblent pas car elles ont des rôles différents, on parle d'identité cellulaire. Pourtant, toutes ces cellules ont le même ADN, les mêmes gènes. Alors pour se différentier les unes des autres, les gènes ne vont pas être tous lus de la même façon. On peut comparer ça à de la musique, une même série de notes peut avoir un rythme différent et donner des mélodies variées. Dans les cellules c'est pareil, des molécules viennent s'accrocher à l'ADN pour le compacter ou l'étendre. Ceci modifie considérablement le rythme de lecture des gènes et permet de définir une carte d'identité de la cellule, c'est ce qu'on appelle l'épigénome. L'épigénome est donc, en quelque sorte, le chef d'orchestre de l'identité des cellules !



L'épigénome (représenté en jaune) est le chef d'orchestre de la lecture des gènes, il s'altère avant même l'apparition de tumeur, suggérant qu'il joue un rôle primordial dans la transformation des cellules lors du développement des tumeurs.

Comment avez-vous fait pour étudier les premières étapes de développement de la tumeur ?

Pour pouvoir analyser les étapes précoces, j'ai adapté au laboratoire une technique qui me permet de reproduire plein de petites glandes mammaires dans des boites spécifiques. Pour cela, je découpe en très petits morceaux des échantillons de glande mammaire provenant d'une souris qui a déjà développé une tumeur. Je les laisse pousser pour reformer des nouvelles petites glandes. Au fur et à mesure, elles se transforment en tumeur, ce qui me permet de faire des analyses à différents moments de transformation tumorale, et donc en particulier dans les étapes pré-tumorales, juste avant que la tumeur ne se développe.

Quels sont les résultats obtenus et leur intérêt ?

J'ai regardé au microscope l'épigénome des cellules. J'ai vu que sa structure était totalement perturbée dans les cellules tumorales. Mais de manière surprenante, j'ai aussi découvert que des modifications de l'épigénome étaient déjà visibles dans les cellules pré-tumorales. Mes résultats montrent que l'épigénome joue un rôle avant même la formation des tumeurs. Il induit la transformation des cellules avec une identité normale en les obligeant à se diviser de manière incontrôlée pour former la tumeur. Ces découvertes nous permettent d'imaginer des nouveaux traitements préventifs qui empêcheraient les modifications de l'épigénome, permettant ainsi de garder les cellules au diapason pour empêcher l'apparition des tumeurs chez les femmes qu'on sait à risque.

Marion LE GRAND — CRC - MARSEILLE

6 RÉVÉLER LES SECRETS DES MÉDICAMENTS POUR AIDER LES ENFANTS ATTEINTS DE CANCER

Au Centre de Recherche en Cancérologie de Marseille, une équipe de biologistes, médecins et pharmaciens met au point une stratégie prometteuse pour trouver de nouveaux traitements pour les enfants atteints de cancer. Pour nous expliquer ce projet, nous avons rencontré Marion Le Grand, pharmacien-chercheur.

Pouvez-vous nous dire quelques mots sur les cancers pédiatriques ?

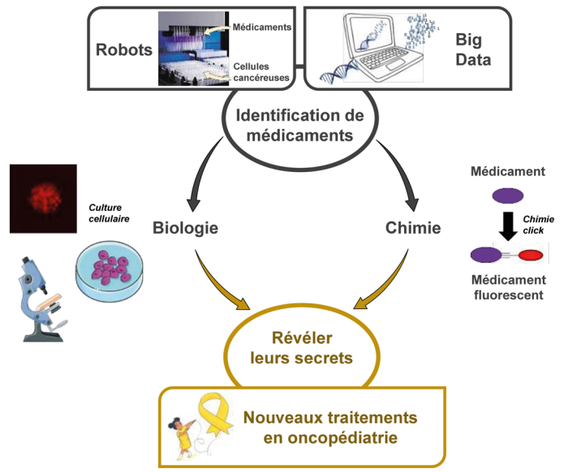
Chaque année en France, 500 enfants décèdent des suites d'un cancer. Les tumeurs pédiatriques, définies comme des maladies du développement, ont des caractéristiques différentes des cancers de l'adulte. C'est pourquoi, il est primordial d'avoir des projets de recherche qui leur sont dédiés ; et de développer des traitements qui leur sont spécifiques.

Comment en êtes-vous venue à travailler sur cette thématique ?

Après avoir validé mon cursus de pharmacie et passé ma thèse de Science, je suis partie en Australie pour travailler dans un institut dédié à la lutte contre les cancers pédiatriques. L'énergie et la combativité des enfants malades que j'ai pu rencontrer m'ont donné l'envie de les aider. C'est donc tout naturellement que je me suis tournée vers la recherche en oncopédiatrie pour développer des traitements à la fois plus efficaces et ayant moins d'effets secondaires.

Développer de nouveaux traitements, qu'entendez-vous par là ?

Nous utilisons une approche appelée « le repositionnement de médicaments ». Je cherche à identifier des médicaments utilisés avec succès dans d'autres maladies, telles que la migraine ou le diabète, et qui pourraient être efficaces pour traiter les cancers de l'enfant. Une fois ces médicaments trouvés, j'étudie comment ils agissent contre le cancer, pour mieux comprendre leurs effets encore inconnus. C'est ce que j'appelle « révéler leurs secrets ». Ceci va me permettre de savoir dans quel cancer les administrer et comment les employer avec les traitements actuellement utilisés en clinique.



Comment faites-vous pour identifier ces médicaments ?

Les robots ont fait leur entrée dans nos laboratoires me permettant de tester un grand nombre de médicaments rapidement. J'ai pu ainsi évaluer sur cellules cancéreuses plus de 3600 composés seuls ou en association avec les traitements actuellement utilisés. Les médicaments qui tuent le plus de cellules cancéreuses et qui augmentent l'efficacité des traitements de référence sont alors sélectionnés pour la suite du projet.

Et pour ensuite révéler leurs secrets ?

Je dois rentrer au cœur des cellules cancéreuses pour trouver comment les médicaments agissent. Pour cela, j'utilise plusieurs techniques dont une qui consiste à interroger ce qu'on appelle les « Big Data ». Nous avons désormais accès à des millions de données sur internet, et notamment sur les médicaments que j'ai testés. Ces données me permettent de mieux comprendre comment ils agissent dans les cellules. Une autre technique est basée sur la chimie click. L'idée est de modifier chimiquement le médicament à étudier pour l'associer par exemple avec une molécule fluorescente. Ceci va alors me permettre de visualiser le médicament dans les cellules par des techniques de biologie pour étudier ses effets.

Quels sont les avantages du repositionnement de médicaments en oncologie ?

L'objectif de mon équipe est de proposer rapidement de nouvelles solutions aux médecins. Étant utilisés chez l'Humain depuis parfois plusieurs décennies, nous connaissons déjà certaines caractéristiques de ces médicaments telles que les effets secondaires mais aussi les voies d'administration possibles chez les patients. Ceci va nous permettre de réduire les délais de développement. Le repositionnement de médicaments a aussi pour avantage d'aboutir au développement de traitements à faible coût, pouvant donc être accessibles à tous, y compris aux enfants dans les pays en voie de développement. C'est notre but final, pouvoir venir en aide à tous les enfants atteints de cancer.

Luca SIMULA — Institut Cochin - PARIS

7 OPTIMISER L'ALIMENTATION DES CELLULES POUR COMBATTRE LE CANCER

À l'Institut Cochin à Paris, on étudie comment aider certaines cellules du système immunitaire à obtenir l'énergie pour se mouvoir de façon efficace dans les tumeurs afin de trouver et tuer les cellules tumorales.

Bonjour M. Simula, comment votre projet de recherche est-il lié à la lutte contre le cancer ?

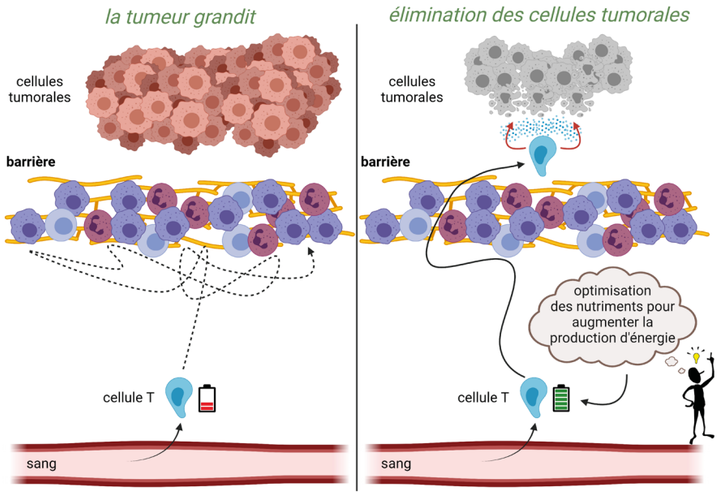
Bonjour, j'étudie des cellules du système immunitaire qu'on appelle les cellules T. Au cours d'une infection, ces cellules sont capables de tuer les microbes qui en sont responsables. Ce qui est très intéressant, c'est que les cellules T peuvent également reconnaitre et tuer les cellules cancéreuses et donc elles sont idéalement très utiles pour lutter contre les tumeurs. Hélas, à l'exclusion des tumeurs du sang et de la moelle osseuse, dans les autres tumeurs, qu'on appelle « les tumeurs solides » parce qu'elles forment des masses de cellules dans nos organes (par exemple, le cancer du sein, du poumon, du colon, du rein) et qui constituent 90% des toutes les tumeurs, les cellules T n'arrivent pas à tuer les cellules tumorales de façon efficace.

Et pourquoi ?

Pour que les cellules T tuent les cellules tumorales, elles doivent rentrer en contact direct avec ces cellules-ci. Le problème, dans toutes les tumeurs solides, est que les cellules tumorales sont souvent entourées par une barrière composée par des fibres et par d'autres cellules de l'organisme qui les aident à survivre, et donc les cellules T doivent d'abord traverser et surmonter cette barrière.

Et s'agit-il d'une tâche difficile à accomplir ?

Malheureusement, cette barrière est très difficile à traverser par les cellules T parce que la plupart de ces cellules n'ont pas assez d'énergie pour la surmonter. Pour en comprendre la difficulté, imaginez que vous êtes assis dans un train bondé. Pour réussir à descendre au prochain arrêt avant que les portes aillent se refermer très rapidement, il faut dépenser de l'énergie, jouer des coudes pour trouver un passage jusqu'au quai. En plus, si les cellules T échouent à tuer



Dans les tumeurs, une barrière de fibres et d'autres cellules de l'organisme empêche les cellules T de rentrer en contact avec les cellules tumorales. Le projet vise à augmenter la production d'énergie des cellules T pour les aider à surmonter cette barrière et à tuer les cellules tumorales

les cellules cancéreuses, celles-ci continueront à proliférer et la tumeur à grandir. Donc, trouver des stratégies pour aider les cellules T à obtenir l'énergie suffisante pour traverser rapidement cette barrière est important pour éradiquer ces tumeurs.

Que pensez-vous faire au regard de cette problématique ?

Si vous avez besoin d'énergie, vous devez d'abord manger et ensuite transformer la nourriture en énergie. C'est pareil pour les cellules T. Mon projet de recherche vise à comprendre comment les cellules T utilisent les nutriments dont elles disposent pour produire l'énergie qui leur faut pour bouger. Si on comprend bien cela, on pourra aussi comprendre comment améliorer l'alimentation de ces cellules pour les aider à bouger de façon plus efficace dans les tumeurs solides et donc leur permettre de tuer les cellules tumorales.

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

Je veux comprendre comment optimiser le régime alimentaire des patients atteints de tumeurs solides pour maximiser la capacité de leur cellules T à atteindre et tuer les cellules tumorales. En plus, de nos jours, il y a des thérapies antitumorales basées sur le prélèvement des cellules T d'un patient atteint de cancer. Après les avoir faite grandir hors du corps, on les réinjecte en grande quantité au patient pour l'aider à combattre la tumeur. Pendant qu'on laisse les cellules T grandir hors du corps, nous pourrions optimiser les nutriments qu'on donne aux cellules pour augmenter leur production d'énergie. L'idée est de produire des cellules T plus rapides, et donc plus efficaces, avant de les réinjecter au patient.

Isabelle TIHY-DAMEI — Gustave Roussy - VILLEJUIF

8 IMMUNOTHÉRAPIE : À LA RECHERCHE D'UN FACTEUR PRÉDICTIF

Aujourd'hui, nous avons rencontré Isabelle TIHY-DAMEI, doctorante au sein de l'Institut Gustave Roussy à Villejuif. Soucieuse de voir la lutte contre le cancer avancer, elle nous a parlé de ses travaux de recherche visant à identifier des facteurs qui permettent de prédire l'efficacité des immunothérapies.

Pourquoi avoir choisi d'étudier ces traitements ?

Ces thérapies, très prometteuses, sont déjà utilisées chez certains patients atteints d'un cancer. Quelle espérance de voir qu'elles peuvent faire gagner aux malades des mois voire des années de vie dans le cas de cancers très agressifs comme celui de la peau ou du poumon. Cependant, ces traitements restent inefficaces pour quatre patients sur cinq. Comprendre pourquoi permettrait d'administrer ces thérapies de manière plus ciblée. Ainsi, les autres patients pourraient être redirigés rapidement vers des traitements plus adaptés.

Sur quoi portent vos recherches ?

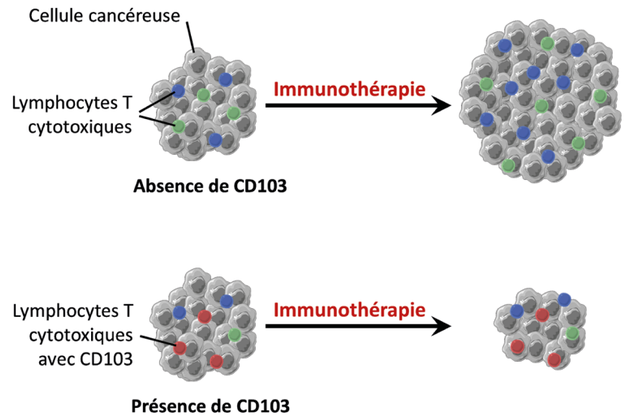
Je travaille tout particulièrement sur des cellules du système immunitaire, les lymphocytes T cytotoxiques. En leur sein, on distingue plusieurs sous-populations avec des caractéristiques différentes. Certains sont capables de détruire les cellules cancéreuses. C'est dans cette diversité que nous avons trouvé un des facteurs clés de l'efficacité des immunothérapies.

Quel est le lien entre les lymphocytes T cytotoxiques et les immunothérapies ?

Les cellules cancéreuses pour se protéger des lymphocytes T cytotoxiques mettent en place différentes stratégies. L'une d'elles est de les bâillonner pour les empêcher d'agir. Les immunothérapies que j'étudie permettent de délier certains lymphocytes T cytotoxiques leur permettant à nouveau de détruire les cellules cancéreuses.

Et qu'avez-vous découvert plus précisément ?

Comme je vous le disais précédemment, les lymphocytes T cytotoxiques ne sont pas tous identiques et ils n'ont pas tous les mêmes fonctions. Un des facteurs qui peut les rendre particulièrement actifs est la présence d'une



Évolution de la tumeur après l'administration d'une immunothérapie en présence ou non de lymphocytes T cytotoxiques porteurs de l'intégrine CD103.

molécule appelée intégrine CD103. Les lymphocytes T cytotoxiques n'en sont pas tous porteurs et leur nombre varie pour chaque patient. Après quatre années de recherche, j'ai pu démontrer que l'intégrine CD103 est indispensable pour que certaines immunothérapies soient efficaces.

Comment avez-vous découvert cela ?

Pour y parvenir, j'ai mené de nombreuses expériences et analyses en laboratoire. Sur certaines souris développant des tumeurs, j'ai bloqué ou supprimé l'intégrine CD103. J'ai ensuite administré aux souris malades des immunothérapies, tout en gardant un groupe témoin sans traitement. J'ai alors suivi l'évolution des tumeurs chez les unes et chez les autres. Lorsque l'intégrine CD103 est présente en quantité suffisante, le traitement par immunothérapie permet de ralentir la croissance de la tumeur. Mais, de manière intéressante, j'ai observé que lorsque cette intégrine n'est pas, ou trop peu présente, la tumeur grossit aussi vite qu'en l'absence de traitement.

Quelles sont les applications médicales de cette découverte ?

En effectuant, en amont, des analyses chez les patients, nous pouvons dénombrer les lymphocytes T cytotoxiques porteurs de l'intégrine CD103 dans les tumeurs. Nous avons ainsi un nouveau facteur de choix permettant de mieux cibler les immunothérapies à mettre en œuvre. Cela me réjouit et me motive de savoir que dans la course contre le cancer, nous pourrions ainsi orienter les patients plus rapidement vers les traitements les plus appropriés.

Que pouvons-nous espérer pour la suite ?

Nos recherches ne s'arrêtent pas là, nous essayons d'ores et déjà d'induire l'intégrine CD103 sur davantage de lymphocytes T cytotoxiques, ainsi nous devrions permettre à davantage de patients de bénéficier de ces immunothérapies, ce qui est très encourageant pour l'avenir !

9 LE BIG DATA AU SERVICE DE LA SANTÉ

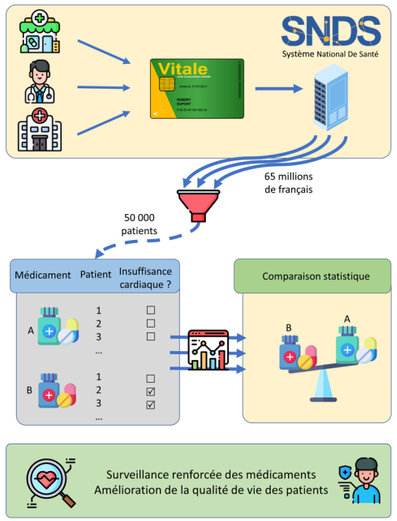
Les Mégadonnées, ou « Big Data », sont de plus en plus présentes dans notre quotidien et notamment dans le domaine de la santé. Yoann nous présente comment elles peuvent être utilisées à bon escient afin de mieux connaître les effets des médicaments.

Qu'entendez-vous par « les données de santé » ?

À chaque fois que vous prenez un médicament à la pharmacie, que vous consultez votre médecin ou lorsque vous êtes hospitalisé, une demande de remboursement est transmise à l'assurance maladie via votre carte vitale. Cette demande contient des données comme votre date de naissance, quels médicaments vous prenez et quand vous les avez récupérés, vos dates et motifs d'hospitalisations, etc. C'est ce que l'on appelle les « données de santé ». En France, le Système National des Données de Santé (SNDS) regroupe l'ensemble des données de santé de la quasi-totalité des Français, soit près de 65 millions de personnes et constitue l'une des plus grandes bases de données médicales dans le monde. Depuis cinq ans, nous pouvons accéder à ces données préalablement anonymisées à des fins de recherche encadrées par des organismes experts, comme la CNIL (Commission Nationale Informatique & Liberté). La pharmaco-épidémiologie s'intéresse ainsi à l'évaluation du médicament dans des conditions d'utilisation réelles dans la population.

Comment pouvons-nous identifier des effets indésirables à partir de ces données ?

Tout d'abord, on appelle « effet indésirable » un effet non souhaité d'un médicament, comme par exemple une réaction allergique ou des nausées qui sont provoquées par la prise d'un médicament. Certains peuvent entrainer une hospitalisation que nous pouvons détecter grâce à ces données. En plus, nous pouvons en identifier de nouveaux qui pourraient ne pas être détectés dans les essais cliniques, qui sont souvent trop limités en nombre de patients pour détecter les effets rares et/ou d'une durée trop courte pour en identifier certains à long-terme. Nous pouvons ainsi prolonger et renforcer la surveillance des médicaments.



Les données de santé, de leurs sélections jusqu'à leurs analyses : la Pharmaco-Épidémiologie en schéma !

Sur quel effet votre équipe a-t-elle travaillé ?

Ces dernières années, des inquiétudes concernant de potentiels effets indésirables cardiaques après prise de nouveaux médicaments anticancéreux ont été signalées. Cependant, nous manquons encore d'informations précises sur ce risque et c'est pourquoi nous avons utilisé la puissance du SNDS afin d'en savoir plus.

Dans mon étude, j'ai pu retracer le parcours des patients prenant des médicaments anticancéreux par voie orale. J'ai d'abord sélectionné ceux qui n'avaient préalablement pas d'insuffisance cardiaque. Ensuite, j'ai regardé quand ils avaient débuté leur traitement et s'ils avaient développé dans les mois qui suivent cet effet indésirable. Pour cela, j'ai regardé s'ils avaient été hospitalisés ou inscrits à l'affection longue durée (ALD) en lien avec une insuffisance cardiaque. Ainsi, nous avons les fréquences et délais de survenue de cet effet pour chaque médicament et nous pouvons les comparer entre eux par des méthodes statistiques.

Qu'avez-vous appris de ces données ?

Suite à ces analyses, j'ai pu mettre en évidence que certains médicaments sont effectivement plus à risques d'induire une insuffisance cardiaque. C'est le cas du dasatinib, du ruxolitinib, du crizotinib et de l'everolimus. Ils sont largement utilisés dans différents cancers et restent très efficaces. Néanmoins, la survenue de cet effet cardiaque a un impact majeur sur la santé du patient, puisqu'elle diminuait son espérance de vie de moitié dans notre étude. Notre objectif est donc désormais d'informer les équipes de soins en oncologie et cardiologie afin de mieux surveiller cet effet indésirable pour qu'il soit détecté plus tôt et ainsi améliorer la qualité de vie des malades durant leur combat contre le cancer.

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Aujourd'hui, elle entend notamment accélérer en priorité le développement de la médecine de précision (thérapies ciblées, immunothérapies, chirurgie mini-invasive…) et l'amélioration de la prise en charge des enfants et adolescents atteints de cancer.

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