Annual Meeting

Cancéropôle Grand Sud-Ouest

November 20-22, 2024

Congress Center / Perpignan

SEMINAR BOOKLET

INSTITUT NATIONAL DU CANCER

L'équipe du Cancéropôle Grand Sud-Ouest remercie vivement

- **les conférenciers et les modérateurs des sessions,**
- **les coordonnateurs et les membres des Comités de Pilotage des Axes,**
- **les copilotes et les membres des Bureaux des Groupes de Travail,**
- **les membres du Comité de Pilotage Scientifique,**

pour leur participation et leur implication dans l'élaboration du programme de ces 20èmes Journées et la qualité scientifique des présentations.

Comité de Pilotage Scientifique

E. Assénat, N. Bonnefoy, O. Calvayrac, N. Christou, S. Croce, P. Cordelier, M. Del Rio, C. Delpierre, C. Franchet, V. Gigoux, A.M Gué, N. Houédé, E. Julien, B. Liagre, V. Moreau, N. Moya, J. Pannequin, V. Randrian, F. Saltel, P. Soubeyran

Comités de pilotage des Axes

Axe 1 – Signalisation, microenvironnement et ciblage
B. Bessette, **G. Bossis**, D. Gomez, F. Lagarrigue, N. Larmonier, A. Maraver, **V. Moreau**, A. Penna, M. Poupot, F. Vergez, C. Vincent-Fabert

Axe 2 - Dynamique et expression du génome
JC. Andrau, T. Clouaire, O. Gadal, **E. Julien**, L. Linarès, V. Pancaldi, S. Péron, H. Seitz, PYJ. Wu

Axe 3 – Innovation thérapeutique et biomarqueurs
N. Bakalara, A. Bobrie, S. Dabernat, E. Deluche, **V. Gigoux**, W. Jacot, AM. Khatib, F. Lalloué, E. Liaudet-Coopman, MA. Poul, B. Segui, **D. Tougeron**

Axe 4 - Cancers : enjeux individuels et collectifs
F. Cousson-Gélie, **C. Delpierre**, P. Gorry, S. Gourgou, I. Ingrand, **F. Sordes**, B. Trétarre

Axe 5 - Technologies pour la santé
S. Bégu, N. Bettache, C. Bezombes, D. Bouvard, Y. Crémillieux, C. Dupin, S. Cussat-Blanc, M. Delarue, A. Ferrand, J. Frandon, F. Friscourt, F. Lamare, **B. Liagre**, M. Lopez, S. Mornet, M. Morris, S. Papot, A. Pothier, B. Quesson, R. Poincloux, O. Radulescu, **MP. Rols**, O. Sandre, G. Sciume, V. Sol, A. Taibi

Nous sommes ravis de vous accueillir pour la première fois à Perpignan, la belle Catalane ! pour cette 20éme édition des Journées Annuelles du Cancéropôle Grand Sud-Ouest.
Une nouvelle fois, les membres du Comité de Pilotage Scientifique, des Comités d'Axes scientifiques et des bureaux des Groupes de travail du Cancéropôle GSO se sont associés pour vous proposer un très beau programme durant ces trois jours, je les en remercie sincèrement.

Ainsi nous aurons le plaisir de recevoir des experts nationaux et internationaux de renoms tels que Thomas Bertero de Valbonne, Christoph Merten de Lausanne, José Ignacio Martin-Subero de Barcelone, Isabelle Van Seuningen et Nicolas Lebegue de Lille, Fanny Jaulin de l'IGR, Alejo Rodriguez-Fraticelli de Barcelone, Isabelle Janoueix de l'Institut Curie et Jacky Goetz de Strasbourg. Leurs présentations dans des domaines variés de la cancérologie promettent d'être passionnantes et enrichissantes pour tous.
Hervé Fridman nous fera également l'honneur de nous présenter une conférence sur le microenvironnement tumoral et la réponse à l'immunothérapie. Et nous aurons le privilège d'accueillir en conférence de prestige, Julian Carrey de l'INSA et de l'Atelier d'Écologie Politique de Toulouse dont la conférence intitulée « Le nouveau rôle de la recherche scientifique et des scientifiques face à l'urgence écologique » semble plus que jamais d'actualité.
Enfin au côté de ces prestigieux conférenciers, ces journées seront l'occasion d'écouter de nombreux chercheurs et cliniciens de notre inter-région, porte-paroles de son excellence scientifique et de son dynamisme.

Cette année 2024 sera marquée par le lancement du nouveau site internet du Cancéropôle GSO qui fait peau neuve après 20 ans d'existence. Je vous le présenterai en ouverture de la journée du jeudi 21 novembre. Vous découvrirez son nouveau look plus convivial et ses nouvelles rubriques plus interactives.
En 2024 l'équipe de direction du Cancéropôle GSO s'est renouvelée : nous avons eu le plaisir d'accueillir en avril Jean-Olivier Arnaud comme nouveau Président. Diplômé de l'EHESP, Jean Olivier a occupé pendant 40 ans des fonctions de direction d'hôpital, et en particulier directeur général des CHU de Nîmes, de Lille et de l'Assistance Publique de Marseille, profitez des journées pour faire sa connaissance.
Depuis septembre, Karine Saget nous a rejoint comme Secrétaire Générale. Karine a une grande expérience de la gestion administrative et financière ainsi que du management d'équipe après plus de 15 années passées à la Direction des Opérations et Gestion administrative de sociétés de biotechnologie. Elle dispose également d'une expérience de 10 ans en tant que Chargée de coordination scientifique au sein du SIRIC Montpellier Cancer, de la FHU EVOCAN et du CLIP2 de Montpellier. Le monde Occitan la connait bien, Nouvelle Aquitaine n'hésitez pas à l'interpeler.
Bienvenus à tous les deux au sein du Cancéropôle GSO !
En décembre, Pascale Moreau qui a veillé au bon fonctionnement de notre cancéropôle pendant plus de dix ans partira à la retraite pour une nouvelle vie, que nous lui espérons sereine et ensoleillée ! Nous profiterons d'une dernière belle soirée avec elle, jeudi soir.

Je vous remercie sincèrement d'être présents et réunis pour ces Journées, devenues incontournables dans la vie de notre Cancéropôle. Je souhaite qu'elles soient riches en échanges et l'occasion de moments de convivialité, afin de perpétuer la dynamique qui nous anime depuis plus de vingt ans.

Je souhaite à chacun d'entre vous de passer d'excellentes Journées du Cancéropôle Grand Sud-Ouest !

Nadine Houédé
Directrice du Cancéropôle Grand Sud-Ouest

LE PROGRAMME DE SOUTIEN A L'EMERGENCE DU CANCEROPOLE GSO

OUVERTURE DEBUT FEVRIER 2025 - SOUMISSION EN LIGNE

EMERGENCE DE PROJETS

OBJECTIFS	Valider les premières étapes d'un projet ou une étude de faisabilité indispensables pour une soumission à un AAP national
CRITERES	Approche nouvelle et originale, nouvelle voie d'exploration ou arrivée d'une équipe dans un nouveau champ disciplinaire
FINANCEMENT	25 k€ maximum par projet

EMERGENCE DE MODELES ET OUTILS

OBJECTIF	Soutenir la mise en place de modèles et outils innovants avec une visée technique, allant des modèles biologiques à la modélisation et au traitement des données en lien avec le cancer, afin de favoriser la mise à disposition de nouveaux modèles pour la communauté du GSO et servir de tremplin pour l'obtention de financements plus importants
CRITERES	Approche nouvelle et originale, impact du développement d'un tel modèle/outil en cancérologie
FINANCEMENT	25 k€ maximum par projet

EMERGENCE DE CONSORTIUM THEMATISE

OBJECTIFS	Soutenir le développement de projets pluri-équipes au sein du GSO qui, avant de postuler à des appels à projets nationaux, doivent disposer de données préliminaires qui valorisent la complémentarité de leurs compétences
CRITERES	Inscription dans une dynamique de mutualisation des expertises (trans- ou inter-axes), en priorisant les projets en lien avec les groupes de travail 2023-2027.
FINANCEMENT	40 k€ maximum par projet

LES PROGRAMMES DE SOUTIEN, SOUMISSION EN LIGNE AU FIL DE L'EAU

MOBILITE TECHNOLOGIQUE

OBJECTIF Acquérir une technologie originale, qu'elle soit ou non déjà présente dans le GSO.

PUBLIC ELIGIBLE Statutaires, doctorants en 1ère et 2ème année et non-statutaires (les non statutaires doivent s'engager à rester dans leur équipe de recherche au minimum pendant 12 mois après la fin de la mobilité et s'associer avec un statutaire « référent techno »).

SEJOUR 3 mois maximum **FINANCEMENT** 4 k€ maximum

ORGANISATION DE SEMINAIRES

CRITERES Séminaires organisés sur le territoire du GSO ou par des chercheurs du GSO et ouverts à l'ensemble de la communauté scientifique du GSO.

FINANCEMENT 2 k€ maximum sous forme de subvention, de prise en charge d'un conférencier ou d'inscriptions d'étudiants et de jeunes chercheurs.

SOUMISSION AU MINIMUM 4 MOIS AVANT LA DATE DE L'EVENEMENT

COLLABORATION TRANSFRONTALIERE

OBJECTIF Organiser la réunion d'équipes de recherche afin de construire un projet de recherche et servir de tremplin pour l'obtention de financements.

PAYS ELIGIBLES Pays du Sud-Ouest européen : Espagne et Portugal.

FINANCEMENT 4 k€ maximum pour un déplacement ou un cycle de déplacements sur une période d'un an impliquant plusieurs chercheurs du GSO.

API-K - INCITATION A LA RECHERCHE EN CANCEROLOGIE - GSO/GIRCI SOHO

Le **Cancéropôle GSO** et le **GIRCI SOHO** organisent annuellement un AAP Interrégional Cancer

OBJECTIF Inciter les jeunes cliniciens à la recherche clinique et/ou translationnelle

FINANCEMENT 40 k€ par projet (maximum)

SOUMISSION DEBUT 2025 AUPRES DE LA DRCI DE L'ETABLISSEMENT PARTENAIRE

LES FORMATIONS DU CANCEROPOLE GRAND SUD-OUEST

LES TRANSLATIONNELLES DU GSO

Les Translationnelles réunissent de **jeunes médecins** (internes, chefs de cliniques, AHU) et de jeunes chercheurs (fin de thèse et post-doctorants) afin de les former à la recherche translationnelle sur une thématique donnée et de les inciter aux échanges transversaux.

DERNIERE EDITION : CANCER DU PANCREAS (2022)

PROCHAINE EDITION EN 2025 : CANCER DU SEIN TRIPLE NEGATIF

L'ECOLE D'IMAGERIE DU PETIT ANIMAL APPLIQUEE AU CANCER

L'Ecole d'Imagerie du Petit Animal Appliquée au Cancer a été mise en place sur l'initiative du Club "Imagerie clinique et In Vivo " du Cancéropôle Grand Sud-Ouest. Elle présente les différentes modalités d'imagerie anatomique, fonctionnelle et moléculaire du petit animal. Elle s'appuie sur les plateformes et expertises régionales et met en avant les récentes innovations technologiques et méthodologiques en imagerie préclinique. Alternant cours et ateliers pratiques sur les plateformes d'imagerie, elle a lieu tous les 2 ans.

OBJECTIFS :

- Aborder les principes théoriques et les aspects pratiques de chaque technique d'imagerie,
- S'initier aux dernières technologies,
- Evaluer les potentialités et les limites des différentes techniques d'imagerie,
- Intégrer un réseau de scientifiques régionaux intéressés par l'imagerie médicale.

PROCHAINE EDITION EN 2025 A MONTPELLIER

*PLUS D'INFOS SUR **imagerie.canceropole-gso.org***

DEVELOPPEMENT D'UN MEDICAMENT

Organisée en alternant cours et ateliers, cette formation a pour objectif de former ensemble des jeunes médecins (internes, chefs de clinique), pharmaciens (internes) et chercheurs (fin de thèse, post-doctorants et titulaires) sur les différents aspects du développement d'un médicament en cancérologie. Elle a lieu tous les 2 ans et bénéficie du soutien institutionnel de plusieurs entreprises du médicament.

DERNIERE EDITION : DEVELOPPEMENT D'UN MEDICAMENT – IMMUNOTHERAPIES (2024)

PROCHAINE EDITION EN 2026

WORKSHOP JEUNES CHERCHEURS

Le Workshop Jeunes Chercheurs a pour objectif principal d'aider les **jeunes chercheurs à développer leurs plans de carrière** à court et moyen terme. Cet atelier vise également à **améliorer leurs projets en cours et à accroître la qualité de leurs futures publications**.

. Il réunit des experts de renom et des jeunes chercheurs (post-doctorants et jeunes titulaires) sélectionnés sur leurs travaux, en format résidentiel, afin de favoriser les échanges et de permettre aux jeunes chercheurs de bénéficier d'un coaching de qualité.

DERNIERE EDITION : SIGNALING IN CANCER (2023)

PROCHAINE ÉDITION : GENOME DYNAMICS AND EXPRESSION, 9-10 DÉCEMBRE 2024

Program

Wednesday 20th November

12h30-14h00 **Welcome Lunch**

14h00-15h45

Chairs : Guillaume BOSSIS & Dennis GOMEZ

KEYNOTE SPEAKER: Thomas BERTERO, *Institute of Molecular and Cellular Pharmacology, Valbonne* - Mechano-metabolism: From tissues to molecules

- **Océane MARTIN,** *Institute of Cellular Biochemistry and Genetics, Bordeaux* - Gut inflammation impacts glioblastoma development and therapeutic resistance
- **Myroslava SLIUSAR**, *BoRdeaux Institute of Oncology* - Role of carbohydrate-binding proteins in controlling glioblastoma stem cell fate and tumorigenesis
- **Renaud POINCLOUX**, *Pharmacology and Structural Biology Institute, Toulouse* - Macrophage mechanobiology: from tumour infiltration to the generation of protrusive forces during migration and phagocytosis
- **Grégoire MANAUD**, *BoRdeaux Institute of Oncology* - Deciphering the oncogenic properties of Fascin-1 in Hepatoblastoma

Chairs : Marie-Pierre ROLS & Bertrand LIAGRE

KEYNOTE SPEAKER: Christoph MERTEN, *Ecole Polytechnique Federale de Lausanne (Switzerland)* - Biomedical microfluidics, new approaches for drug discovery and personalized cancer therapy

- **Myriam CHAUMEIL**, *University of California, San Francisco (USA)* - Hyperpolarized 13C metabolic MRI for adaptive cancer treatment and precision medicine
- **Chloé BAZILE**, *Cancer Research Center of Toulouse* - TAM Targeting with vectorized magnetic nanoparticles for anticancer therapies

15h45-17h15 **Poster Session & Coffee Break**

Chairs : Jean-Christophe ANDRAU & Eric JULIEN

KEYNOTE SPEAKER: José Ignacio MARTIN-SUBERO, *August Pi Sunyer Biomedical Research Institute & Catalan Institution for Research and Advanced Studies, Barcelona (Spain)* - An epigenetic journey into the origin and evolution of chronic lymphocytic leukemia

- **Marta RADMAN-LIVAJA,** *Institute of Molecular Genetics of Montpellier* - In vivo chromatin footprinting with nanopore sequencing reveals a new role for the yeast heterochromatin protein Sir3 in global transcription regulation
- **Luana CINTORI**, *Molecular, Cellular and Developmental biology unit, Toulouse* - Novel optogenetic tool for targeted oxidative DNA damage generation : effect of ROS on gene transcription
- **Léa BOUTON**, *Nucleic Acids: Natural and Artificial Regulations Laboratory, Bordeaux* - Development of RNA therapeutics targeting RBM39 as an anti-cancer strategy
- **Virginie MIEULET**, *Toulouse Institute for Infectious and Inflammatory Diseases* - MAPK-mediated translational regulation of QARS contributes to DNA damage response in high-grade serous ovarian cancers

Chairs : Sandrine DABERNAT & Véronique GIGOUX

KEYNOTE SPEAKERS: Isabelle VAN SEUNINGEN, *ONCOLille* & **Nicolas LEBEGUE,** *Lille Neuroscience & Cognition, Lille* - Emerging paradigms and recent progress in targeting ErbB/HER in cancers

- **Emmanuelle LIAUDET-COOPMAN,** *Montpellier Cancer Research Institute* - Immunotherapy of triple-negative breast cancers with cathepsin D targeting antibodies
- **Angela AGAËSSE,** *Cancer Research Center of Toulouse* - Magnetic hyperthermia and magnetic-mechanical ablation, two potential strategies for inducing an anti-tumor immune response in pancreatic ductal adenocarcinoma
- **Lisa BRUNET,** *Montpellier Cancer Research Institute* - Exploiting vulnerabilities in MET-driven non-small cell lung cancer
- **Lucile BANSARD,** *Institute of Functional Genomics, Montpellier* - A potent agonist-based PROTAC targeting Pregnane X Receptor that delays colon cancer relapse
- **Isabel GALEANO-OTERO,** *BoRdeaux Institute of Oncology* - Sulconazole prevents T-cell exhaustion and promotes cancer cell malignant phenotype repression by attenuation of NF-?B and calcium signaling

19h00-20h00 **Icebreaker: Drinks & Posters**

Thursday 21st November

8h15-8h45 **Welcome Coffee**

08h45 - 09h00 **Opening ceremony**

Nadine HOUEDE, Scientific director of Cancéropôle Grand Sud-Ouest

09h00 - 10h45

Session 3 - Cancer microenvironment **24**

Chairs : Emmanuelle LIAUDET-COOPMAN & Frédéric SALTEL

KEYNOTE SPEAKER: Hervé FRIDMAN, *Centre de Recherche des Cordeliers, Paris* - Tumor microenvironment and response to immunotherapy

- **Rawan HALLAL,** *Institute of Molecular Genetics of Montpellier* - Targeting the SUMO pathway to activate an anti-tumoral response mediated by Natural Killer cells in Acute myeloid leukemia
- **Tommy CHASTEL,** *Montpellier Cancer Research Institute* - Role of Eicosanoid Receptor in Stroma - Cancer Communication
- **Marine HERNANDEZ,** *Pharmacology and Structural Biology Institute, Toulouse* - A metabolic crosstalk occurs between human bone marrow adipocytes and prostate cancer cells

10h45 - 11h15

Session 4 - Cancer Research in Bordeaux at a glance

Frédéric SALTEL, *BoRdeaux Institute of Oncology*

11h15-12h30 **Poster Session**

12h30-14h00 **Lunch**

14h00-15h30

Session 5A - Alternative models for translational research **29**

Chairs: Julie PANNEQUIN and Pierre CORDELIER

KEYNOTE SPEAKER: Fanny JAULIN, *Gustave Roussy Institute, Villejuif* - Functional personalized medicine in digestive cancers

- **Céline GONGORA**, *Montpellier Cancer Research Institute* - An in vitro heterotypic spheroid model to characterize anti-tumor immunity in chemotherapy and immunotherapy-treated urothelial carcinoma
- **Kasandra AGUILAR CAZAREZ**, *Institute for Functional Genomics, Montpellier* - Study of the reciprocal interactions between diffuse low-grade glioma IDH1 mutant cells and neuron

Session 5B - La Méthodologie et réglementation dans la recherche Interventionelle en Santé des Populations (1) **33**

Chairs : Brigitte TRETARRE & Cyrille DELPIERRE

- **Cyrille DELPIERRE**, *Centre d'épidémiologie et de recherche en santé des populations, Toulouse* & **Florence COUSSON-GELIE**, *Institut du Cancer de Montpellier* - Présentation générale du réseau SORisp - Les méthodologies en recherche interventionnelle en santé des populations.
- **Mathieu GOURLAN**, *Institut du Cancer de Montpellier* - De la théorie à la pratique : l'exemple du "Grand Défi Vivez Bougez" pour promouvoir l'activité physique des enfants.

15h30-16h30 **Coffee Break**

16h30-18h00

Chairs : Mary POUPOT & Antonio MARAVER

KEYNOTE SPEAKER: Alejo RODRIGUEZ-FRATICELLI, *IRB Barcelona, Barcelona Institute of Science and Technology and Catalan Institute for Research and Advanced Studies, Barcelona (Spain)* - Pre-existing stem cell heterogeneity as a driver of cancer evolution

- **Jérôme TORRISANI,** *Cancer Research Center of Toulouse* - The E3 ubiquitin ligase TRIP12 is required for pancreatic acinar cell plasticity and DNA damage response in pancreatic carcinogenesis
- **Anissa ZAAFOUR**, *BoRdeaux Institute of Oncology* - Modelling metastatic dormancy of cancer stem cells in gastric cancer
- **David BRACQUEMOND**, *Institut de Recherche en Cancérologie de Montpellier* - Overcoming osimertinib resistance in EGFR-driven lung cancer by targeting drug tolerant persister cells

Chairs : Brigitte TRETARRE & Cyrille DELPIERRE

- **Niamh REDMOND**, *Université Paul Sabatier, Toulouse* - DECODE : essai clinique randomisé en clusters d'une intervention de littératie en santé pour le dépistage du cancer colorectal, ciblant les médecins généralistes et les patients dans les zones défavorisées
- **Elodie NEUMANN,** *ONCODEFI, Montpellier* - PAM - Apprentissage du dépistage des cancers - Etude interventionnelle et participative avec des personnes déficientes intellectuelle
- **Morgane MARCOU DU TILLET DE VILLARS**, *IUCT Oncopole, Toulouse* - L'encadrement réglementaire des projets RISP à l'Oncopole Claudius Regaud

18h00-19h00

Chair : Véronique GIGOUX

KEYNOTE SPEAKER Julian CARREY, *National Institute of Science and Technology & ATelier d'ECOlogie POLitique, Toulouse* - The new role of scientific research and scientists facing ecological emergency

20h00 **Gala Dinner (upon registration)**

Friday 22nd November

08h00-8h30 **Welcome Coffee**

08h30-09h00 **Poster Awards Ceremony**

09h00-10h30

Session 8A - Translational research in rare cancers **47**

Chairs : Nadine HOUEDE & Fabrice LALLOUE

KEYNOTE SPEAKER: Isabelle JANOUEIX, *Institut Curie, Paris* - Non-genetic heterogeneity and phenotypic plasticity in neuroblastoma

- **Florent PEYRAUD,** *Institut Bergonié, Bordeaux* - Immunotherapy in Sarcomas : from Bench to Bedside
- **Sabrina CROCE**, *Institut Bergonié, Bordeaux*

Session 8B - L'intégration des patients partenaires en recherche **51**

Chairs : Cyrille DELPIERRE

- **Patrick LARTIGUET**, *Université Jean Jaures, Toulouse* - La participation des patients dans les projets de recherche
- **Cyril SARRAUSTE DE MENTHIÈRE**, *Institut de Génétique Humaine, UMR 9002 CNRS, Montpellier* - Patients et chercheurs, unis pour innover : L'engagement pour réinventer, ensemble, la recherche humaniste et engagée
- **Célia CARDOSO,** *Institut Imagine, Paris* - Co-construction d'un programme de partenariat patient dans un Institut Hospitalo-Universitaire : inspiration concrète

10h30-11h30 **Coffee Break**

11h30-13h00

Session 9A - Metastasis **55**

Chairs : Violaine MOREAU & Frédéric LAGARRIGUE

KEYNOTE SPEAKER: Jacky GOETZ, *Tumor Biomechanics Lab, INSERM/Unistra, CRBS, Strasbourg* - Nanoscale tracking of Metastasis

- **Inès GARROUCHE**, *Université de Poitiers, ProDiCeT* - New insights of YAP activity in brain metastases from colorectal cancer
- **Tra-Ly NGUYEN**, *BoRdeaux Institute of Oncology* - Role of immunosuppressive myeloid cells on gastric cancer stemness promotion
- **Julie PANNEQUIN**, *Institute for Functional Genomics, Montpellier* - Unraveling the metastatic process in colorectal cancer

Session 9B - Les recherches sur les soins de support **60**

Chairs :

- **Maria Claudia ADDAMIANO**, *Université Paul Sabatier, Toulouse* - AASSOAC : Améliorer l'Accès aux Soins oncologiques de Support sur la région Occitanie par l'Amélioration des connaissances des patients
- **Kerstin FARAVEL**, *Institut du Cancer de Montpellier* - La prise en charge Kiné-Yoga-ETP
- **Véronique GERAT-MULLER**, *Institut Bergonié, Bordeaux* - onCOGITE - Prise en charge des séquelles cognitives du cancer et de ses traitements

13h00 **Closing Lunch**

Session 1A - Cell signaling, microenvironment and targeting

1A / 01

Mechano-metabolism: From tissues to molecules

Thomas BERTERO

Université Côte d'Azur, CNRS, INSERM, IPMC, IHU-RespirERA, Valbonne

Dysregulation of extracellular matrix (ECM) deposition by activated fibroblasts, and cancer cell metabolism rewiring, drives solid cancers such as breast cancer (BC), by promoting key pathways controlling growth, migration, and survival. Yet, the molecular mechanisms linking the biomechanical properties of the ECM with metabolism and cancer cell behaviors during breast cancer progression have remained undefined. Since 2016 and our pioneering study demonstrating a link between cell mechanics and cell metabolism (Bertero et al, J Clin Invest 2016) our laboratory is interested to decipher how tissue mechanical properties shape - and are shaped by - cell metabolism. Here, I will highlight our recent discoveries on how the mechanical properties of the tumor niche reprogram glutamine and glucose metabolism to promote BC progression. Conversely, we will explore how glutamine metabolism supports post-translational modifications of mechanoactivated cells. Finally, I will discuss our unpublished results on how glucose-to-sorbitol metabolism regulates biomolecular condensate formation to sustain mechanotransduction. Together, our findings establish the roadmap of the main molecular events connecting the ECM with metabolism and breast cancer cell reprogramming and set the base for the discovery of novel therapies.

1A / 02

Gut inflammation impacts glioblastoma development and therapeutic resistance

Sarah LAVIELLE[1], Gauthier DELROT[1], Sebastian LILLO[1], Manon LEMAITRE[1], Doriane BOMONT[1], Ioannis PATERAS[2], Macha NIKOLSKI[1], Thomas DAUBON[1], **Océane MARTIN[1]**

[1] Institut de Biochimie et Génétique Cellulaires, Bordeaux

[2] 2nd Department of Pathology, "Attikon" University Hospital, Medical School, National and Kapodistrian University of Athen

Glioblastoma (GB) is the most common subtype of glioma in adults. Despite treatment through tumor resection associated with chemo and radiotherapies, this cancer still has a very poor prognosis. Factors contributing to etiology, pathogenesis, or treatment resistance are not well known. The significance of understanding the microbiome-gut-brain axis (MGBA) in GB, a topic that has been recently shown to be crucial in several neurodegenerative diseases, cannot be overstated. Therefore, our project aims to understand how modulation of gut physiopathology (i.e., gut inflammation or microbiota dysbiosis) affects GB development and therapeutic resistance.

We have examined the relationship between gut inflammation, microbiome modulation, GB development, and therapeutic resistance. Mice received dextran-sulfate sodium (DSS), a gut pro-inflammatory agent, and were orthotopically injected with mGB2 GB cells. Some mice were then resected and treated by radio and chemotherapy using Temozolomide (TMZ). Brain and colon samples were analyzed by RNA sequencing and histological staining. The composition of the gut microbiota was evaluated by 16S metabarcoding. Each dataset was analyzed separately and then integrated using multi-omics data integration methods.

Our results showed that DSS-treated mice had a higher GB growth than non-treated mice. Moreover, the recurrence after treatment was higher in mice bearing gut inflammation. Interestingly, we also observed on DSS-treated mice that the GB-bearing mice had lower intestinal inflammation than the control. GB growth was also associated with microbiota modifications, which were restored by the treatment.

Altogether, our results support the bidirectional communication between the gut and the brain in the context of GB. Alteration of gut physiopathology strongly impacts GB development and therapeutic resistance. This connection suggests that targeting the gut microbiome could slow down GB progression and/or improve treatment efficacy

1A / 03

Role of carbohydrate-binding proteins in controlling glioblastoma stem cell fate and tumorigenesis

Myroslava SLIUSAR[1], Ahmad SHARANEK (CHARANEK)[1], Audrey BURBAN[2], Andreas BIKFALVI[1]

[1] BRIC Team 01 Tumor and vascular biology laboratory, Bordeaux

[2] IBGC, CNRS UMR5095 GBmetabo team, Bordeaux

Introduction. Carbohydrate-binding proteins, galectins, are the family of proteins that specifically bind the β-galactoside sugars. Galectins (GAL, LGALS) are known to be associated with cancer development, including glioblastoma (GBM) - the most aggressive brain tumor. Thus, galectins, which regulate the numerous processes in the cell, can be considered worthy investigation targets for developing novel clinical approaches for GBM treatment.

Methods. Publicly available DSS and PFI data of TCGA cohorts were analyzed with SUMO software. The scRNA-seq data analysis was conducted with the R toolkit Seurat and SingleR package. For in vitro experiments we used patient-derived glioblastoma stem cells (GSCs) BTSC73 and BTSC12. Differentiation of the GSCs was reached by growth for 14 days on laminin-coated plates in the medium with 10% FBS. To study therapy resistance, GSCs were irradiated with 2 and 4 Gy. To reach hypoxic conditions, 5% CO2 and 1% O2 were maintained. The siRNA silencing was applied to achieve LGALS3 depletion. Live and apoptotic cells were counted with Annexin/PI double staining flow cytometry-based assay. EdU cell proliferation assay was used to investigate cell proliferation.

Results. We showed that LGALS1, -3, -8, and -9 are greatly expressed in glioblastoma RNA-seq TCGA datasets. The simultaneous high expression of these galectins leads to the worst prognosis for patients over other combinations. Further scRNA-seq data analysis showed that Gal3 is extensively distributed among glioblastoma cancer cells, macrophages, and T-cells. Our in vitro experiments with employed siRNA LGALS3 depletion in BTSC73 indicated a decrease in the number of live cells. This effect is related to the reduction of proliferation and not apoptosis which was shown with EDU staining and Annexin/PI assay. The role of Gal-3 in GSCs may also include stemness regulation since siLGALS3 transfection decreases the level of stem cell markers Sox2 and Nestin in BTSC73. Furthermore, Galectin-3 may control GSC differentiation since we detected an increase in LGALS3 expression during this process. We also showed that hypoxia in contrast to irradiation, increases the LGALS3 expression in BTSC73 and BTSC12.

The second branch of our investigation is dedicated to Galectin-9 which is expressed mostly in macrophages in glioblastoma scRNA-seq. Nevertheless, we showed a striking increase in LGALS9 expression during the GSC differentiation.

Conclusions. GAL-1, GAL-3, GAL-8, and GAL-9 are greatly expressed during GBM, while simultaneous high expression of these galectins is associated with poor patient survival. Both Galectin-3 and -9 might be involved in the regulation of GSC differentiation. Regardless of the others, Galectin-3 could be involved in cancer stem cell regulation by the control of proliferation. Gal-3 also affects the level of cancer stem cell markers Sox2 and Nestin. At the same time, Galectin-3 expression is regulated by hypoxia.

1A / 04

Macrophage mechanobiology: from tumour infiltration to the generation of protrusive forces during migration and phagocytosis

Renaud POINCLOUX

Institut de Pharmacologie et Biologie Structurale, CNRS UMR5089, Toulouse

Macrophages are innate immune cells that are present in all tissues to maintain the immune surveillance. They ingest particles such as bacteria or dead cells, a process called phagocytosis that involves dynamic actin reorganization and generation of forces. In addition to the amoeboid migration used by all leukocytes, we showed in vitro that macrophages use the mesenchymal migration in dense environments involving proteolysis of the extracellular matrix, compaction and ingestion of degraded matrix to create tunnels.

In most cancers, the density and stiffness of the tissue stroma are enhanced. We found in mouse fibrosarcoma in vivo and in human breast cancer ex vivo, that tumor-associated macrophages (TAM) that help tumor progression, perform the mesenchymal migration using their own matrix metalloproteases (MMPs), and perform the amoeboid migration at the tumor periphery. As a proof of concept that targeting mesenchymal migration would be a novel therapeutic strategy, we showed that MMP inhibition correlates with decreased of both TAM recruitment and tumor growth.

Podosomes are macrophage structures involved in adhesion, proteolytic degradation of the extracellular matrix and 3D mesenchymal migration. They present a submicron-size core of F-actin surrounded by an adhesion ring. Using protrusion force microscopy we showed that podosomes are mechanosensitive and could estimate the forces generated by single podosomes. We are now investigating how podosomes are organised at the nanoscale, and how this organisation regulates protrusion force generation. In particular, we employ in situ cryo-electron tomography to reveal the architecture of podosomes. Quantitative analysis of podosome architecture showed that podosome core filaments are denser, more oblique, and shorter than radial and cortical filaments. Importantly, core filaments are bent and store high elastic energy, supporting that the podosome core consists of a set of highly compressed actin filaments.

Finally, we have recently started to develop a 2.5D model of frustrated phagocytosis consisting of arrays of polyacrylamide micropillars of controlled size and stiffness in order to quantify the forces at play during phagocytosis and address the molecular mechanisms involved. In particular, we focus our attention on the involvement of podosome-like structures, which we also reported to be involved during phagocytosis.

1A- 05

Deciphering the oncogenic properties of Fascin-1 in Hepatoblastoma

Grégoire MANAUD, Lydia DIF, Violaine MOREAU

BoRdeaux Institute of Oncology

Hepatoblastoma (HB) constitutes the most common form of pediatric liver cancer, accounting for 1% of all malignancies in children. The standard of care for HB is a combination of chemotherapy and surgical resection of the liver segments affected by the tumor. Despite good efforts leading to an 80% survival at 5 years, side effects are often observed in children and negatively impacting their quality of life as well as their long-term outcomes. A distinctive genetic hallmark of HB is the high rate of CTNNB1 mutation found in 89% of cases, leading to an aberrant activation of the Wnt/β-Catenin pathway, and make it attractive as a targeted therapy for HB. However, giving the high risks of side effects, we aim to identify new β-Catenin dependent targets. In this aim, we propose to use Fascin-1 encoded by the FSCN1 gene, found to be a transcriptional target of β-Catenin and upregulated in HB. Fascin-1 an actin-bundling protein mainly localized in filopodia and thus promoting cell migration. As such, Fascin-1 is expressed in progenitors but remains absent in most of mature differentiated cells. Interestingly, we found that Fascin-1 expression was upregulated in, not all HB patients samples, but in a subset of HB with a poor prognosis characterized by the presence of undifferentiated and highly proliferative cell clusters. We demonstrated that indeed, Fascin-1 expression is correlated with hepatocyte differentiation status. To explore the underlying mechanisms, we have built the hypothesis that the cellular localization of Fascin is responsible for the alteration of hepatocyte differentiation. We use the β-Catenin-mutated HB cell lines HepG2 and Huh6 and we observed that the phospho-mimetic Fascin mutant S39E increase YAP expression and we propose that it stimulates the gene expression related to hepatocyte undifferentiated status in vitro. Thus, our results suggest a key role of Fascin-1 in HB progression and that Fascin-1 may represent a new therapeutic target in HB.

Session 1B - Precision therapeutics (1)
Health technologies

1B / 01

Biomedical microfluidics, new approaches for drug discovery and personalized cancer therapy

Christoph MERTEN

Institute of Bioengineering, School of Engineering, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

We have developed screening platforms enabling rapid identification of optimal drug cocktails for personalized cancer therapy 1,2. Results are available within 24h after surgery at consumables costs of less than 150 US$ per screen. The power of this platform has been demonstrated using cancer cell lines, xenograft mouse models and even human tumor biopsies. As a next step we are now translating the technology into a robust and easy to use diagnostic device, integrate transcriptomic readouts 3 and start investigational clinical studies.

In parallel to this, we have developed fully integrated droplet-based microfluidic platforms for the screening of therapeutic antibodies 4-7. In these systems tiny aqueous droplets (picoliter volumes) surrounded by oil serve as independent assay vessels. The technology allows the direct screening of several hundred thousand primary, non-immortalized murine or even human B-cells for the secretion of antibodies that do not just bind to a drug target, but functionally inhibit it. Taken together this should open the way for many new approaches in drug discovery, including personalized immunotherapy or the use of antibodies to control cellular pathways at will.

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1B / 02

Hyperpolarized 13C Metabolic MRI for Adaptive Cancer Treatment and Precision Medicine with a Focus on Glioblastoma

Myriam CHAUMEIL

University of California, San Francisco

Hyperpolarized (HP) 13C metabolic MRI is a cutting-edge imaging technique that has the potential to revolutionize cancer treatment and precision medicine. By amplifying signals from 13C-labeled metabolites, this technology allows real-time, non-invasive imaging of tumor metabolism. One of its most promising applications is in glioblastoma (GBM), an aggressive brain cancer with limited treatment options. Both preclinical and clinical studies are revealing how HP 13C MRI can enhance the understanding of GBM metabolism, guide adaptive treatments, and personalize therapy.

Glioblastomas exhibit significant metabolic heterogeneity, posing challenges for treatment. Tumor cells often rely on altered metabolic pathways to support their rapid growth and therapy resistance. Hyperpolarized 13C MRI enables tracking of key metabolites like pyruvate and lactate in real-time, offering insights into the Warburg effect, where tumor cells preferentially convert pyruvate to lactate, fueling malignancy.

In preclinical models, HP 13C MRI has been used to detect early metabolic responses to therapy—such as reductions in lactate production—long before conventional imaging detects changes in tumor size. This early detection is crucial for adaptive cancer treatment, allowing clinicians to modify treatment regimens in real-time, based on metabolic responses rather than waiting for structural changes.

The clinical translation of HP 13C MRI in glioblastoma is already underway, with early trials showing its feasibility and safety. These studies have provided new insights into GBM's metabolic reprogramming and demonstrated the potential to identify metabolic subtypes that could benefit from tailored therapies. For instance, tumors with high lactate production might respond better to treatments targeting glycolysis, enabling more personalized care.

Beyond glioblastoma, HP 13C MRI holds significant potential for broader cancer applications, including breast, prostate, and pancreatic cancers. Its ability to monitor metabolic responses to treatment in real-time offers a powerful tool for adaptive cancer care across different tumor types. This could allow clinicians to discontinue ineffective treatments sooner, reduce toxicity, and improve survival rates.

HP 13C MRI also aligns with the goals of precision medicine, tailoring treatments to the specific metabolic profiles of individual tumors. Its non-invasive and repeatable nature provides a valuable tool for mapping tumor metabolism in vivo, helping guide treatment decisions and optimize therapy for better patient outcomes.

In summary, hyperpolarized 13C metabolic MRI offers a transformative approach to cancer imaging and therapy. For glioblastoma, it has the potential to guide adaptive treatments and improve precision medicine approaches. As this technology becomes integrated into routine clinical care, it holds promise for improving outcomes for cancer patients across a variety of tumor types.

1B / 03

TAM Targeting with vectorized magnetic nanoparticles for anticancer therapies.

Chloé BAZILE, Mary POUPOT, Véronique GIGOUX, Pascal CLERC, Fabien GAVA, Véra PANCALDI

Centre de Recherches en Cancérologie de Toulouse

Tumor-associated macrophages (TAM) are well known as protecting tumor cells against apoptosis, immune attacks and therapies. Elimination of these pro-tumor TAM remains a challenge in cancer therapies. Several ways of TAM targeting exist, however they are not specific, potentially leading to serious adverse effects.

We produced and patented a monoclonal antibody called 6-25 capable to specifically recognize the nurse-like cells (NLC), TAM of the chronic lymphocytic leukemia (CLL), and TAM from different solid cancers. We showed that the 6-25 antibody recognizes the folate receptor beta (FRB) at the surface of these cells and is internalized in these cells without inducing any toxicity. The FR is also expressed by the M2 monocytes-derived macrophages (M2M) but not by the M1 monocytes-derived macrophages (M1M) or other myeloid cells.

The goal of the project is to produce a tool that specifically targets and kills pro-tumor TAM in the tumor in order to sensitize cancer cells to chemo- or immunotherapies.

In cancer treatment, magnetic hyperthermia represents an emerging approach with promising therapeutic potential. The magnetic hyperthermia induces an increase of the temperature following the localized application of a high frequency alternating magnetic field (AMF) to a tumor containing magnetic nanoparticles (MNP), leading to cell death. Iron oxide MNP are highly biocompatible and non-toxic (rapid degradation with iron cations recycling), which allows their combination with conventional therapies.

Thus, we developed a magnetic nanoparticle based on a PEGylated iron oxide MNP functionalized with the 6-25 mAb (MNP-6-25) as a specific tool to target pro-tumor TAM, thanks to a Michael reaction, and a fluorophore, the Cyanine 5, allowing its detection.

For this study, two cellular models were used: M2M as expressing FRB at their surface, and M1M as negative control without FRB. M2M and M1M were obtained by the culture of monocytes from healthy donors in the presence of appropriate cytokines cocktails.

First, we showed that MNP-6-25 were not toxic toward M1M and M2M in a concentration up to 64 µg Fe_2O_3/mL after 72h incubation. Then, MNP-6-25 binds specifically M2M but not M1M, with a maximum of binding at 48h of incubation at 8 µg/mL. Finally, confocal microscopy imaging showed that MNP-6-25 accumulated in lysosomes of M2M.

Secondly, we performed an alternative model to study the penetration and the specificity of MNP-6-25 in a 2D and 3D co-culture model and in a same time to study the impact of M1M or M2M on the proliferation of cancer cells. We realized 3D co-cultures with M2M or with M1M and A549 (lung cancer cell line) using the technic of ultra-low-attachment plate for the formation of spheroids. We showed a higher proliferation of cancer cells with M2M than with M1M, in 2D co-culture. However, in 3D co-culture models, we observed the same profile of cancer cells proliferation with M2M or M1M, correlated with an increasing of M2M markers on M1M. These models are also developped with another cancer cell line Calu-1 of NSCLC. Furthermore, we showed in these models a specific targeting for M2M macrophages with MNP-6-25.
In perspective, we plan to evaluate the efficacy and the specificity of MNP-6-25 to kill M2M in this 3D model upon application of magnetic field and then the in vivo targeting of macrophages in a murine model of non-small cell lung cancer with MNP-6-25.

Session 2A - Genome Dynamics & Expression

2A / 01

An epigenetic journey into the origin and evolution of chronic lymphocytic leukemia

Jose Ignacio MARTIN-SUBERO[1,2,3]

[1] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

[2] University of Barcelona, Barcelona, Spain.

[3] Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

Genomics has greatly contributed to our understanding of the pathophysiology and clinical management of lymphoid neoplasms. However, beyond genomics, studies focusing on the epigenome have provided important biological insights into the origin, development and evolution of lymphoid neoplasms, and have also revealed biomarkers and signatures with diagnostic and prognostic value. From the diagnostic perspective, DNA methylation is the mark with the highest translational potential into the clinical setting. Initial studies on DNA methylation mostly focused on epigenetic silencing of specific genes, such as tumor suppressors. However, DNA methylation studies at the genome-wide scale have revealed that a large fraction of the changes does not correlate with gene expression levels. Instead, these changes reflect a kind of epigenetic memory that allows us to trace the origin and evolutionary paths of lymphoid tumors. In this context, we have observed that neoplastic B cells carry DNA methylation imprints of their cellular origin allowing the distinction of different subtypes derived from lymphocytes at distinct maturation stages. Additionally, DNA methylation changes in late replicating regions accumulate as cancer cells divide without impacting the transcriptome, allowing the development of a mitotic clock that is able to trace the past proliferative history of cancer cells. Remarkably, a recent work published as pre-print exploits the presence of CpG sites with fluctuating methylation to build models of the evolutionary dynamics of B cell tumors. These three aspects of epigenetic memory are strongly associated with disease progression. Overall, these studies and additional data that will be presented in the meeting suggest that epigenetic imprints of the past have an enormous potential to improve diagnostic accuracy of lymphoid tumors and contribute to the estimation of their future clinical behavior.

2A / 02

In vivo chromatin footprinting with nanopore sequencing reveals a new role for the yeast heterochromatin protein Sir3 in global transcription regulation

Marta RADMAN-LIVAJA

Institut de Génétique Moléculaire de Montpellier

All genomic processes are executed through protein-DNA contacts. The method of choice for the identification of specific contacts between proteins of interest and their genomic targets has been ChIP (Chromatin Immunoprecipitation), which in combination with high-throughput sequencing (ChIP-seq) has proven to be a powerful tool for mapping long lived protein-DNA high-requency contacts genome-wide. ChIP-seq can however not detect rare and/or transient protein-DNA contacts that could nevertheless have an impact on genome function.

We have now developed Nanopore-MetID, an in vivo foot printing technique based on nanopore sequencing and DamID. The protein of interest is fused to the DNA methyl transferase EcoGII which methylates any accessible Adenine. meA at sites of contact between the fusion protein and DNA are then directly detected by nanopore sequencing. Unlike for ChIP-seq which requires stable long-lived protein-DNA interactions, the residency time of the protein of interest on DNA need only be long enough to allow for EcoGII methylation of nearby Adenines. Nanopore-MetID has now revealed hundreds of new contacts between the heterochromatic yeast protein Sir3 and euchromatic genes. Moreover, our measurements of gene expression after exit from starvation reveal that Sir3 delays gene reactivation on a global scale. We propose that rare contacts between Sir3 and euchromatic genes play a direct role in delaying transcription reactivation after exit from starvation.

2A / 03

Novel optogenetic tool for targeted oxidative DNA damage generation: effect of ROS on gene transcription

Luana CINTORI, Valérie BERGOGLIO, Catherine CHAILLEUX, Didier TROUCHE, Yvan CANITROT

Unité de biologie moléculaire, cellulaire et du développement, Toulouse

The aerobic environment in which we live means that our cells are constantly exposed to reactive oxygen species (ROS), which can damage all cellular components, including DNA. This oxidative stress, which causes oxidative damage to DNA, is particularly implicated in cancer. Recent studies show that the presence of oxidative damage such as oxidized guanine (8-oxoG) and the recruitment of its repair protein OGG1 to promoters appear to be involved in modulating the expression of many genes. This project proposes a new optogenetic tool for DNA-targeted ROS induction. To achieve this, we used CRISPR technology and its ability to target selected genome sequences with guide RNAs, combined with FAP (Fluorogen activated protein), capable of producing ROS after exposure to red light following incubation with the MG2i fluorogen. To validate the tool, we demonstrated the recruitment of the XRCC1-GFP and OGG1-GFP protein involved in the oxidative damage repair pathway after light activation of FAP-MG2i. Then we performed RNAseq under oxidative stress in our cell line in order to identify genes sensitive to oxidation. Now the tool we developed aims to study the impact of targeted oxidative damage of these identified genes to better understand the role of oxidative stress on transcription regulation.

2A / 04

Development of RNA therapeutics targeting RBM39 as an anti-cancer strategy

Léa BOUTON[1], Maïlys BACHE[1], Arnaud VILLACRECES[2], Brune VIALET[1], Philippe BARTHÉLÉMY[1], Pierre-Yves DUMAS[2,3], Jean-Max PASQUET[2], Florian MALARD[1], Sebastien CAMPAGNE[1]

[1] Régulations Naturelles et Artificielles, Bordeaux

[2] BoRdeaux Institute of Oncology

[3] CHU de Bordeaux

Cell carcinogenesis is a complex process that triggers significant changes in gene expression, leading to uncontrolled cell proliferation. The RNA-binding motif 39 (RBM39), is often upregulated and essential for the survival of several cancer cells, such as Acute Myeloid Leukemia (AML) and Colorectal Cancer (CRC). The depletion of RBM39 using the CRISPR/Cas method or pharmacological molecules such as aryl sulfonamides resulted in the death of AML and CRC cells, showing that RBM39 is a validated anti-cancer target (Wang E. et al., Cancer Cell 2019; Han T. et al., Science 2017). Aryl sulfonamides have been discovered by the Eisai Company in 1999 (Owa T. et al., J Med Chem. 1999) and were shown to inhibit the proliferation of 42 human cancer cell lines in 2001. But it is only in 2017 that the mode of action of aryl sulfonamides has been elucidated (Han T. et al., Science 2017). They act as a molecular glue between RBM39 and DCAF15, which is linked to a complex with ubiquitin ligase activity. This interaction leads to the polyubiquitination of RBM39, its targeted degradation by the proteasome; thereby triggering the death of AML and CRC cancer cells. However, only 16-30% of patients responded to aryl sulfonamides treatment in clinics and the response correlated with the expression level of DCAF15, highlighting the need for new therapeutic strategies.

In this context, we recently demonstrated the molecular mechanisms of RBM39's specific RNA recognition and its autoregulation capability thanks to a negative feedback mechanism occurring at the RNA splicing level. RBM39 is required to promote the inclusion of a poison exon in its own pre-mRNA, leading to the production of a non-productive mRNA isoform (Campagne S., et al., Nature Communications 2023). Based on these results, we want to develop RNA therapeutics to decrease the intracellular level of RBM39 and trigger the death of cancer cells. This appears as a new promising therapeutic strategy. To achieve this aim, we are using two distinct strategies: a siRNA-based strategy to trigger RBM39 knockdown, and a Splicing Switch Oligonucleotide-based (SSO) strategy to manipulate the autoregulation mechanism of RBM39.

RNA therapeutics were first tested in a model cell lines (HEK293T) to study their effects of RBM39-dependent RNA splicing. The effects of siRNAs and SSOs on the splicing of the poison exon were evaluated by RT-PCR. The anti-cancer activities of the RNA therapeutics were then assessed in a CRC cell line (HCT116) using RT-PCR, colony formation assays and MTT assays. We showed that RNA therapeutics effectively killed CRC cells at low doses (between 50 and 300nM), in a dose-dependent manner, similarly to aryl sulfonamides. Our experiments show for the first time that it is possible to use RNA therapeutics acting in a DCAF15-independent manner to substitute the use of aryl sulfonamides. This offers novel therapeutic perspectives to fight against cancer.

Based on these positive results obtained during the development phase, we are now aiming at validating the anti-cancer effects of the RBM39-directed RNA therapeutics in more relevant cell lines in the context of CRC and AML, patients samples and xenograft mouse models. While the use of RNA therapeutics in the field of inherited diseases has recently shown its potential, we are aiming now to apply them in the field of cancer therapy.

2A / 05

MAPK-mediated translational regulation of QARS contributes to DNA damage response in high-grade serous ovarian cancers

Martina SERAFINI[1], Orlane MALOUDI[2], Sylvain MARTINEAU[1], Anne SALOMON[1], Stephan VAGNER[1], Manuel Daniel DIAZ MUNOZ[2], Fatima MECHTA-GRIGORIOU[1*], **Virginie MIEULET[2*]**

[1] Institut Curie, Paris

[2] Institut Toulousain des Maladies Infectieuses et Inflammatoires

F. Mechta Grigoriou* and V. Mieulet * are co-last authors

High-Grade Serous Ovarian Cancers (HGSOC) remain one of the deadliest gynecologic malignancies. After initial response to conventional therapy, most patients relapse, become resistant and die from the disease. Multi-omic approaches led to the identification of distinct molecular entities, highlighting the potential benefit of targeted therapies (Batista et al., 2013; Gentric et al., 2019; Mateescu et al., 2011; Network, 2011; Popova et al., 2012; Zhang et al., 2016). Genomic signatures are robust indicators of Homologous Recombination Deficiency (HRD), and used to identify patients likely sensitive to PARP inhibitors. We identified a metabolic heterogeneity and observed that tumors relying on oxidative phosphorylation (high-OXPHOS) are associated with HRD and are more sensitive to cisplatin-based therapies (Gentric et al., 2019; Popova et al., 2012). Proteomic studies identified signaling pathways to which distinct genomic and transcriptomic rearrangements were converging on (Gruosso et al., 2015; Zhang et al., 2016). We found that alterations in the MEK kinase MAP3K8/COT/TPL-2 is an alternative to BRAF mutations in HGSOC as it promotes tumour growth by constitutively activating the MEK/ERK pathway. Accumulation of MAP3K8 correlates with MEK/ERK activation in patients and our data indicate that MAP3K8 has a reliable predictive value for the efficiency of MEK inhibitor treatment in HGSOC although they are rarely mutated for BRAF (The Cancer Genome Atlas Research Network, 2011; Gruosso et al., 2015; Mieulet, 2014).

Most oncogenic pathways lead to translational reprogramming, providing cancer cells the ability to rapidly adapt to highly dynamic environments. We found that MAP3K8/MEK activation promotes the assembly and activity of the translation initiation complex eIF4F and confers a new translational landscape in cancer cells that is mainly involved in RNA metabolism. We decided to focus on the glutaminyl-tRNA synthetase QARS, one of the top candidates. QARS is a glutamine sensor, and glutamine is a key metabolite that fulfills energy demands in HGSOC, highlighting a potential link between QARS translational regulation and metabolic adaptation. We validated that MAP3K8/MEK controls QARS mRNA translation but not transcription in HGSOC and that QARS is associated with OXPHOS metabolism and DNA damage response (DDR) in two independent cohorts of HGSOC. We are now investigating how translational regulation of QARS downstream of MAPK signaling pathway contributes to DDR. QARS directly and specifically binds glutamine and glutaminlylates cognate tRNA for mRNA translation and/or specific proteins to control their functions. We observed that QARS overexpression prevents bleomycin-induced double strand breaks and promotes DNA repair via homologous recombination, while overexpression of a catalytic inactive QARS mutant does not, supporting that QARS is a critical glutamine sensor that controls the translation and/or the glutaminylation of key players in DDR. Potential candidates are currently tested. We expect to uncover new functions for QARS and to get a better understanding of the consequences of MAPK-mediated translational reprogramming on tumorigenesis. Inhibiting the translation machinery could be a source of new therapies for HGSOC patients that still represent a clinical challenge.

Session 2B - Precision therapeutics (2)
Therapeutic innovation and biomarkers

2B / 1

Emerging paradigms and recent progress in targeting ErbB/HER in cancers

Isabelle VAN SEUNINGEN[1], Nicolas LEBEGUE[2]

[1] ONCOLille

[2] Lille Neuroscience & Cognition

2B / 2

Immunotherapy of triple-negative breast cancers with cathepsin D targeting antibodies

Emmanuelle LIAUDET-COOPMAN

Institut de Recherche en Cancérologie de Montpellier

The prognosis of patients with triple-negative breast cancer (TNBC) is poor, mainly due to disease heterogeneity and lack of targeted therapies. Although conventional chemotherapy remains the standard treatment, immunotherapy is changing the paradigm of cancer management and is emerging as an alternative treatment for TNBC. The aspartic protease cathepsin D (cath-D) is a tumor cell-associated extracellular protein with pro-tumor activity, a marker of poor prognosis in breast cancer and in TNBC. Recently, we have shown that cath-D is a potent target for antibody-based therapy in TNBC. We have generated a panel of anti-cath-D human antibodies by screening a human scFv expression library by phage display. The first-in-class F1, a fully human anti-cath-D IgG1, localized at the tumor site and inhibited the growth of MDA-MB-231 (TNBC-derived) cell xenografts and patient-derived xenografts. Mechanistically, F1 activated natural killer (NK) cells and prevented the recruitment of M2-polarized tumor-associated macrophages (TAM) in TNBC cell xenografts in nude mice (Ashraf, Mansouri et al., J Immunother Cancer. 2019). The therapeutic effect and immunomodulatory activity of the anti-cath-D murine IgG2a antibody F1 and of its improved version F1M1 with aglycosylated Fab were then investigated in an immunocompetent mouse model of TNBC (C57BL/6 mice harboring E0771 cell grafts). We showed that anti-cath-D antibodies triggered both innate and adaptive antitumor immunity in TNBC (David et al, Brit*J. Pharmacol.*, 2023). These last years, we have improved the Fc part of our lead F1M1 antibody anti-cath-D antibody that led to the recruitment, activation and cytotoxic activity of tumor-infiltrating NK cells and demonstrated the interest of its association with paclitaxel and enzalutamide in TNBC (Desroys du Roure et al., *J ImmunoTherapy Cancer*, 2024). Altogether, our studies highlight that anti-cath-D immunotherapy could represent a new therapeutic opportunity for TNBC patients.

2B / 3

Magnetic hyperthermia and magnetic-mechanical ablation, two potential strategies for inducing an anti-tumor immune response in pancreatic ductal adenocarcinoma

Angela AGAËSSE[1], Justine JOURNAUX[1], Pascal CLERC[1], Julian CARREY[2], Olivier SANDRE[3], Stéphane MORNET[4], Véronique GIGOUX[1]

[1] Centre de Recherches en Cancérologie de Toulouse

[2] Laboratoire de Physique et Chimie de Nano-Objets, Toulouse

[3] Laboratoire de Chimie des Polymères Organiques, Pessac

[4] Institut de Chimie de la Matière Condensée de Bordeaux

Pancreatic ductal adenocarcinoma (PDAC) is a cancer with a poor prognosis, and it is predicted to be the second leading cause of cancer death within a few years. PDAC is particularly resistant to conventional therapies and characterized by the presence of a large and dense microenvironment with a key role of CAFs (Cancer-Associated Fibroblast). CAFs promote proliferation and progression of the tumor, secrete extracellular matrix proteins forming a physical barrier that limits not only the penetration and the diffusion of drugs but also the infiltration of immune cells therefore an efficient anti-tumoral immune response.

Magnetic iron oxide nanoparticles (IONPs) are innovative tools, exposed to a high-frequency alternating magnetic field, they release thermal energy, causing cell death by magnetic hyperthermia (HM). Exposed to a low-frequency rotating magnetic field, IONPs generate mechanical forces causing cell death by magnetic-mechanical ablation (MMA).

We developed IONPs, vectorized with gastrin, called NF@Gastrin, which specifically target pancreatic cancer cells and CAFs (Cancer-Associated Fibroblast) expressing the CCK2 receptor (MiaPaca2-CCK2 and CAF-CCK2). The aim of this project is to study whether local HM or MMA can stimulate immunogenic cell death and enhance an antitumor response in the PDAC. We showed that NF@Gastrin internalized and accumulated in the lysosomes of MiaPaca2-CCK2 and CAF-CCK2 cells. We demonstrated that HM and MMA specifically killed these cells in 2D culture models and 3D MiaPaca2-CCK2/CAF-CCK2 spheroids. Furthermore, we demonstrated that HM and MMA increased the expression of the Damage-Associated Molecular Pattern: Calreticulin and HSP70 at the surface of the targeted cells in 2D and 3D models. This effect was associated with an increase in phagocytosis of these cells by human THP1 macrophages in 2D and their infiltration within the spheroids, as well as an increase in the activity of Natural Killers (NK-92) when they were in contact with these cells in a 2D model. Taken together, these results strongly suggest that HM and MMA are two potential strategies capable of inducing immunogenic cell death and restoring an anti-tumor response in PDAC.

2B / 4

Exploiting vulnerabilities in MET-driven non-small cell lung cancer

Lisa BRUNET[1], Maicol MANCINI[1], Marie COLOMB[1], Zoulika KHERROUCHE[2], Alexis CORTOT[2,3], Antonio MARAVER[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] University of Lille, CNRS, Institut Pasteur de Lille

[3] University of Lille, Thoracic Oncology Department, CHU Lille

Lung cancer is a major public health problem because is responsible of the highest number of cancer deaths worldwide. Together with mutations in EGFR or KRAS, MET alterations, including MET amplification and MET skipping of exon 14, are among the most important oncogenic events in non-small-cell lung cancer (NSCLC), the main type of lung cancer accounting for more than 80% of all patients. Despite the improved clinical outcomes derived from the introduction of MET-tyrosine kinase inhibitors (TKI) to treat patients with advanced MET-driven lung cancer, their prognosis remains unfavorable because of intrinsic or acquired resistance.

Faced of the lack of in vivo models to study MET amplification, we generated a new genetic engineered mouse model that upon doxycycline induction, spontaneously develop MET-driven NSCLC in approximately 11 months. RNA sequencing analysis comparing tumors and healthy tissue showed that contrary to other oncogenic drivers as KRAS or EGFR, the Notch pathway was downregulated in tumors and the p53 was highly active, suggesting a link between these two pathways. Importantly, clinical trials using tepotinib, a MET-TKI demonstrated that patients harboring p53 mutations respond worst to this treatment. To understand the role of p53 on Notch pathway and in MET-TKI response, we performed p53 loss of function (LOF) in vivo in our new MET-driven NSCLC model. Of note, our new mouse model demonstrates that tumors lacking p53 have a higher activity on the Notch pathway, supporting a negative regulation of the Notch pathway by p53 in NSCLC. Importantly, our in vivo data using our state-of the art GEMM model showed that MET tumors lacking p53, as it happens in patients, respond worst to the clinically relevant MET-TKI crizotinib, and strikingly, they fully respond to the combination of crizotinib and nirogacestat, a clinically relevant Notch inhibitor. Together, our data suggest that a co-treatment of MET-TKIs and Notch inhibition could represent a new strategy for an unmet medical need, i.e., the treatment of p53 mutated MET-driven NSCLC patients.

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A potent agonist-based PROTAC targeting Pregnane X Receptor that delays colon cancer relapse

Lucile BANSARD[1], Guillaume LACONDE[2], Vanessa DELFOSSE[3], Tiphaine HUET[3], Margaux AYEUL[1], Emille RIGAL[4], Quentin DONATI[2], Sabine GERBAL-CHALOIN[4], Martine DAUJAT-CHAVANIEU[4], Baptiste LEGRAND[2], Alain CHAVANIEU[3], Anthony R. MARTIN[2], Julie PANNEQUIN[1], William BOURGUET[3], Muriel AMBLARD[2], Jean-Marc PASCUSSI[1]

[1] Institut de Génomique Fonctionnelle, Montpellier

[2] Institut des Biomolécules Max Mousseron, Montpellier

[3] Centre de Biologie Structurale de Montpellier

[4] Institut de Médecine Régénérative et de Biothérapies de Montpellier

Tumor recurrence is often attributed to drug-tolerant cancer stem cells. We previously demonstrated that down regulation of the Pregnane X Receptor (PXR, NR1I2) decreases chemoresistance of cancer stem cells and prevents colorectal cancer recurrence in xenograft mouse models. These is a lack of PXR antagonists that are appropriate for clinical use. In this study, we report the design and synthesis of a novel PXR agonist-based PROTAC (JMV7048) that induces polyubiquitination and degradation of human PXR protein in an E3 CRBN ubiquitin ligase- and the 26S proteasome- dependent manner. This molecule specifically degrades PXR in colon carcinoma, hepatoma, and pancreatic cancer cell lines, but not in primary cultures of human hepatocytes. Crucially, JMV7048 decreased PXR protein expression in colon cancer stem cells and sensitized them to chemotherapy significantly delaying cancer relapse in vivo. This proof of concept suggests that PROTACs targeting the PXR protein could serve as novel therapeutic agents, enhancing the sensitivity of cancer stem cells to chemotherapy.

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Sulconazole prevents T-cell exhaustion and promotes cancer cell malignant phenotype repression by attenuation of NF-κB and calcium signaling

Isabel GALEANO-OTERO[1], Simon PERNOT[1,2], Mercedes TOMÉ[1], Serge EVRARD[1,2], Iker BADIOLA[3], Frederic DELOM[1,2], Delphine FESSART[1,2], Tarik SMANI[4], Geraldine SIEGFRIED[1,2], Bruno O. VILLOUTREIX[5], Majid KHATIB[1,2]

[1] Reprograming tumor activitY and associaTed MicroenvironmEnt (Rytme)/ Bordeaux Institute of Oncology (BRIC)-UMR1312/ Inserm/ Université of Bordeaux/ Pessac

[2] Institut Bergonié/ Bordeaux

[3] Department of Cell Biology and Histology/ Faculty of Medicine and Nursing/ University of the Basque Country/ Spain

[4] Group of Cardiovascular Pathophysiology/ Institute of Biomedicine of Seville/ University Hospital of Virgen del Rocío/ University of Seville/CSIC/ Seville/ Spain

[5] Integrative Computational Pharmacology and Data Mining/ INSERM UMR 1141/ Robert-Debré Hospital/ Paris

Introduction/Objectives: The overexpression of the immunoinhibitory receptor programmed death-1 (PD1) on T-cells plays a significant role in cancer immune evasion. While anti-PD-1/PDL-1 therapies have revolutionized cancer treatment and improved patient survival, their efficacy varies widely across different tumor types and patient populations. Consequently, novel treatments are needed to interfere with the anti-tumoral immune responses and propose an adjunct therapy.

Methods: In this study, we explored the impact of the antifungal drug Sulconazole (SCZ) on PD-1 expression in activated PBMCs and T cells at both RNA and protein levels. Furthermore, we investigated SCZ's effects on NF-κB and calcium signaling pathways. Additionally, we assessed SCZ's influence on cancer cell proliferation, migration, and tumor growth using zebrafish embryo models. The drug's ability to inhibit calcium mobilization in cancer cells was also evaluated.

Results: Our results indicate that SCZ effectively inhibits PD-1 expression on activated PBMCs and T cells at both the RNA and protein levels. SCZ suppressed NF-κB and calcium signaling, crucial pathways involved in PD-1 induction. Furthermore, SCZ treatment significantly reduced cancer cell proliferation, migration, and tumor growth in vitro and in zebrafish embryos. SCZ also demonstrated an ability to inhibit calcium mobilization within cancer cells.

Conclusion: These findings highlight the potential of SCZ as a therapeutic agent, either used alone or in combination with existing treatments, to prevent T-cell exhaustion and suppress the malignant phenotype of cancer cells. This dual approach could enhance tumor eradication and improve overall cancer treatment outcomes.

Session 3 - Cancer microenvironment

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Tumor microenvironment and response to immunotherapy

Wolf Hervé FRIDMAN

Cordeliers Research Centre, INSERM U1138 and Université Paris Cité

Tumors grow within a complex microenvironment composed of immune cells, fibroblasts, endothelial cells and other non-malignant cells. The study of the composition of tumor microenvironments has led to classifications with prognostic and theranostic values, as well as to treatments modulating its composition and its functional orientation. The density, location and functional orientation of tumor-infiltrating lymphocytes form the immune contexture which composition is positively correlated in most cases with patient's survival. Colorectal cancer represents a paradigm for tumor immunology, as it is the human cancer in which it was exemplified that an adaptive immune response can control tumor growth and metastasis. A high infiltration of Th1/cytotoxic T cells is associated with longer disease or progression free and/or overall survival both in primary and metastatic sites. High infiltration by myeloid cells and fibroblats is generally associated with poor prognosis in cancer.

Immunotherapy is aimed to substitute or activate the patient's immune reactions to its tumor in order to control the disease in the long run. It has already revolutionized the management of several deadly and major cancers such as lung cancer, melanoma and hematopoietic malignancies. It shows efficacy in many other cancers including, bladder cancer, renal cell cancer, etc…

Tertiary Lymphoid Structures (TLS) are found in tissues subjected to chronic inflammation and antigen persistence in autoimmune diseases, chronic infections, graft rejection and cancers. TLS are organized lymphoid aggregates formed on a network of fibroblasts and comprising a T cell zone, in which mature dendritic cells are in contact with T cells, and a follicular B cell zone. Mature TLS are defined by the presence of a Germinal Center (GC) containing T follicular helper cells and Follicular Dendritic Cells in close contact with B cells. Recent evidence support that GC-containing mature TLS, rather than early TLS without a GC, are associated with clinical benefit and response to immunotherapy in many cancer types. The main function of the GC is to produce memory B cells and long-lived plasma cells secreting high affinity antibodies. Using spatial transcriptomics and immunochemistry, we showed that B cell maturation and plasma cell (PC) formation take place in TLS. In TLS+ tumors, IgG and IgA producing PCs disseminate into the tumor beds along fibroblastic tracks. B cell repertoire analysis revealed clonal diversification, selection, expansion in TLS and the presence of fully mature clonotypes at distance. We observed tumor cell-bound antibodies and demonstrated that TLS+ tumors exhibited not only high numbers of IgG-producing PCs but also high numbers of IgG-stained and apoptotic malignant cells, which suggests antitumor effector activity of these antibodies. Finally, therapeutic responses and progression free survival correlated with IgG stained tumor cells in patients treated with immune check-point inhibitors. Altogether, these data demonstrate intra-tumoral generation of both T and B cell immunity and antibody production that impact responses to immunotherapy.

Based on these data, we recently proposed the concept of the intra-tumoral immunity cycle enlightening the role of TLS as sites of generation and reactivation of anti-cancer immune responses, initiating tumor cell killing and amplifying the impact of immunotherapies.

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Targeting the SUMO pathway to activate an anti-tumoral response mediated by Natural Killer cells in Acute myeloid leukemia

Rawan HALLAL[1], Marion DE TOLEDO[1], Denis TEMPÉ[1], Rayane BERRAHOUANE[1,2], Ludovic GABELLIER[1,2], Guillaume BOSSIS[1]

[1] Institut de Génétique Moléculaire de Montpellier

[2] CHU de Montpellier

Objective: Acute myeloid leukemias are a group of hematological malignancies with poor prognosis. NK cells play a key role in the antitumoral immune response against AML. However, disease associated mechanism leads to alteration in circulating NK cells number and phenotype with decreased cytotoxicity and ability to produce cytokines. Several studies reported the role of SUMOylation, a posttranslational modification of the proteins, in the regulation of the innate immune response. Our team has shown that TAK981, a first in class inhibitor of SUMOylation used in various phase I/II clinical trials for solid tumors and lymphomas, upregulate the expression of the NK activating ligands on the surface of AML cells and favors their killing by NK cells. Moreover, several recent studies highlight the role of TAK981 in activating a global antitumoral immune response mediated by IFN type I induction. Here, we wondered whether TAK-981 could directly affect NK cells anti-leukemic activity.

Methods: Primary NK cells were purified from PBMCs of healthy donors or AML patients. Mock or TAK981 treated NK cells activation and cytotoxicity against AML cells lines were measured by Flow cytometry. RNAseq and RT-qPCR in NK cells upon TAK981 treatment were performed in order to understand the mechanism of action of TAK981. Cytokines production and IFN type I secretion were also quantified to categorize the interplay between NK cells and other immune cells.

Results: In this study, we show that the inhibition of SUMOylation enhances the activation of primary NK cells and increases their cytotoxicity against AML cell lines and patient cells. In addition, RNAseq analysis showed a strong enrichment of a type I Interferon signature in primary NK cells treated with TAK981. The inhibition of the type I IFN receptor suppresses this direct effect of TAK981 on NK cells activation and cytotoxicity. We also describe a cross talk between NK cells and other immune cells, mainly monocytes, leading to an indirect activation of NK cells upon TAK981 treatment mediated by IFN type I and immunomodulatory cytokines production.

Conclusion: In conclusion, we show that targeting SUMOylation induces an IFN-I dependent activation of primary NK cells, which increase their cytotoxicity against AML cells. This could pave the way to the development of new AML treatment through either the restoration of patients' NK cells activity, or by the activation of primary NK cells for autologous infusion in AML patients.

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Role of Eicosanoid Receptor in Stroma - Cancer Communication

Tommy CHASTEL[1,2]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Equipe Turtoi : Micro-environnement tumoral et résistance aux traitements

The heterotypic cell communication networks within tumors support the survivability, plasticity, and therapy resistance of cancer cells. Understanding and targeting this inter-cellular communication is essential to eradicate cancer. Cancer cell interaction with immune and vascular cells is already well-established as targetable in cancer. However, the interaction between cancer-associated fibroblasts (CAFs) and cancer cells remains clinically underdeveloped. We lack both a deep understanding of how CAFs communicate with cancer cells as well as strategies to target those interactions effectively.

The present work explores CAF cell surface receptors involved in liver cancer progression. We focus on G-protein-coupled receptors (GPCRs), and more specifically on polyunsaturated fatty acids (PUFAs) derivatives, the eicosanoids. Using public single-cell RNA sequencing data and spatial transcriptomics, we discovered a set of eicosanoid GPCRs that are specifically overexpressed by CAFs. We further focused on eicosanoid receptor EICOR1 and its cognate ligand EICO1. We confirmed using RNAscope and spatial transcriptomics that that EICOR1 is only expressed in the in the tumor microenvironment (TME) in patient-derived hepatocellular carcinoma samples. We next used the chick embryo chorioallantoic membrane (CAM) assay to decipher the role of EICOR1 in cancer progression. Activating EICOR1 in fibroblasts co-engrafted with cancer cells reduced neoangiogenesis by 50% ($p < 0.0001$). In vitro analysis further showed that the anti-angiogenic effects are possibly mediated by the simultaneous deactivation of known pro-cancerous kinases such as AKT and JNK in the fibroblasts. Metabolomics analysis from both primary and secondary liver tumors from patients revealed that the level of the natural ligand EICO1 is lower in the tumoral area when compared to adjacent normal tissue. This indicates that deactivating EICOR1 is relevant for cancer progression and is further confirmed by the positive correlation of EICOR1 expression and patient survival in liver cancer (HR = 0.51 [CI 0.3-0.84], $p = 0.0079$). Finally, proteomics analysis suggest that the anti-angiogenic effects may be mediated by the secretion of anti-angiogenic proteins by fibroblasts, such as TSP1, TIMP1 and TIMP2.

Collectively, our findings provide an incentive to develop specific therapies that will curb both primary and secondary liver cancer progression by interfering with the communication between cancer cells and CAFs. We are currently developing new compounds that could enhance this targeting, focusing on the newly discovered EICO1-EICOR1 axis.

* The exact identity of EICO1-EICOR1 will be disclosed during the GSO meeting

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A metabolic crosstalk occurs between human bone marrow adipocytes and prostate cancer cells

Marine HERNANDEZ[1], Mohammed MOUTAHIR[1], Nicolas REINA[2,3], Catherine MULLER[1], Camille ATTANE[1]

[1] Institut de Pharmacologie et de Biologie Structurale, Toulouse
[2] Département de Chirurgie Orthopédique et Traumatologique, Hôpital Pierre-Paul Riquet, CHU de Toulouse
[3] Laboratoire AMIS, UMR 5288 CNRS, Université Toulouse III-Paul Sabatier

In localized prostate cancer (PCa), we have demonstrated that periprostatic adipocytes increase tumor progression by providing cancer cells with fatty acids (FFAs) released after the activation of lipolysis, involving the hydrolysis of triglycerides (TG) [1]. In advanced PCa, the majority of metastases are found within the bone, where tumor cells can interact with bone marrow adipocytes (BMAds). However, whether a metabolic crosstalk between primary BMAds and PCa exists and favors tumor progression remains to be determined. Thanks to a collaboration with orthopedic surgeons, we obtain human bone marrow adipose tissue (BMAT) during hip replacement surgery. There are two types of BM-Ads: those contained in the red BMAT (rBMAds) and those contained in the yellow BMAT (yBMAds) [2], which have been characterized by my team [3]. Since PCa metastatic sites are frequently found in proximity to rBMAds, we established a 3D culture of these adipocytes in a fibrin matrix to preserve their viability for up to 5 days and cultured them with PCa cells.

Under coculture conditions, PCa cells exhibited an increase in neutral lipid content, primarily composed of TG. Using rBMAds loaded with fluorescent FFA, we directly demonstrated that FAs released by rBMAds and taken up by cancer cells and re-esterified into TG. These data provide the first evidence of a metabolic crosstalk between primary human rBMAds and PCa cells. However, like yBMAds [3], we found that rBM-Ads are devoid of lipolysis, one of the main function in adipocytes. This lack of lipolysis is due to a profound decrease in the expression of the last two enzymes of the lipolytic pathway. Using non-specific lipase inhibitors, we demonstrated a lipase-dependent lipid release, suggesting a novel FFA release mechanism requiring further investigation.

Cocultivated PCa cells exhibit an increase in migration abilities as compared to non-cocultivated cells. These properties are key to the progressive colonization of bone sites leading to widespread metastases. Exogenous exposure of PCa cells to FFAs reproduce these effects and it is abolished by using delipidated conditioned medium of rBM-Ads. RNAseq and gene ontology analyses of cocultivated and non-cocultivated cells reveal significant differences in migration pathways, that is consistent with functional experiments. Among the regulated genes, a target gene of PPARγ transcription factor, known to be activated by FFAs, is highly upregulated and its expression is key to the acquisition of migratory capacities upon coculture.

In conclusion, the metabolic crosstalk between rBMAds and PCa cells could contribute to the propagation of bone metastasis. Deciphering this crosstalk, could lead to pharmacological targets for the treatment of bone metastases, for which therapeutic options remain very limited.

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Session 5A - Alternative models for translational research

5A / 01

Organoids in functional precision medicine of advances digestive cancers

Jérôme CARTRY[1,2], Alice BOILEVE[1,2,3], Sabrina BEDJA[1,2], Negaar GOUDARZI[1,4], Jacques MATHIEU[1,2], Ali MOUAWIA[1], Claudio NICOTRA[5], Maud NGO-CAMUS[5], Bastien JOB[6], Karélia LIPSON[4], Valérie BOIGE[3], Marine VALERY[3], Anthony TARABAY[3], Mohamed-Amine BANI[7], Peggy DARTIGUES[7], Lambros TSELIKAS[8], Thierry DE BAERE[8], Antoine ITALIANO[5], Simona COSCONEA[9], Maximiliano GELLI[10], Elena FERNANDEZ-DE-SEVILLA[10], Maxime ANNEREAU[11], David MALKA[1,3,12], Michel DUCREUX[1,2,3], Cristina SMOLENSCHI[3,5], Antoine HOLLEBECQUE[3,5], **Fanny JAULIN[1,2]**

[1] INSERM U1279, Gustave Roussy, Villejuif

[2] Université Paris Saclay, Orsay

[3] Gustave Roussy, Département de médecine, Villejuif

[4] Gustave Roussy, plateforme organoïdes, Villejuif

[5] Gustave Roussy, DITEP, Villejuif

[6] Gustave Roussy, département de bioinformatique, Villejuif

[7] Gustave Roussy, département de pathologie morphologique, Villejuif

[8] Gustave Roussy, département de radiologie interventionnelle, Villejuif

[9] Gustave Roussy, département d'endoscopie, Villejuif

[10] Gustave Roussy, département de chirurgie, Villejuif

[11] Gustave Roussy, département de pharmacie, Villejuif

[12] Institut Mutualiste Montsouris, département d'oncologie médicale, Paris

Patient-derived organoids (PDO) have emerged as ex vivo tumor avatars and as such, represent a promising technology for functional precision medicine (FPM). Our studies aim to evaluate whether PDO can be implemented in clinical practice for the management of patients with colorectal and pancreatic carcinomas. We report the largest prospective study aiming at implementing PDO-based FPM and identify very robust predictive value in this clinical setting. In a clinically relevant turnaround-time, we identified putative hits in 91% of patients, with potential survival benefits. This remains to be confirmed in interventional precision oncology trials, yet, PDO collection are already powerful platform for preclinical studies and combinatorial therapies strategies

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5A / 02

An in vitro heterotypic spheroid model to characterize anti-tumor immunity in chemotherapy and immunotherapy-treated urothelial carcinoma

Céline GONGORA

Institut de Recherche en Cancérologie de Montpellier

5A / 03

Study of the reciprocal interactions between diffuse low-grade glioma IDH1 mutant cells and neurons

Kasandra AGUILAR CÁZAREZ[1,2], Hugues DUFFAU[1,3], Jean-Philippe HUGNOT[1,2]

[1] Institut de Génomique Fonctionnelle

[2] Université de Montpellier

[3] CHU de Montpellier

Diffuse gliomas are primary brain tumors originating from glial cells, known for their invasive growth and resistance to therapies, especially in cases with IDH1 gene mutations. These tumors primarily affect young patients.

The tumor microenvironment, particularly its interaction with neurons, plays a pivotal role in tumor progression. Neurons in the tumor environment have been shown to support glioblastoma cell growth. However, the influence of the brain environment on IDH1 mutant gliomas remains inadequately explored. Understanding the cellular and molecular mechanisms driving their invasiveness and growth is essential.

Most studies on glioma-neuron interactions focus on highly aggressive glioblastomas. Our objective is to study the reciprocal interactions between diffuse glioma cells and their surrounding tumor microenvironment, specifically with neurons. We hypothesize that IDH1 mutant glioma cells alter brain cell properties to promote tumor expansion.

To investigate this, we have co-cultured neurons derived from induced pluripotent stem cells (iPSCs) with patients' glioma cell lines. We aim to compare the behavior of different glioma lineages within this model, including astrocytomas versus oligodendrogliomas and low-grade versus high-grade gliomas, particularly regarding invasion, self-organization, integration in the neuronal network, and tumor heterogeneity. Additionally, we used tissue sections from patients to validate our in vitro results.

Our observations indicate that neurons and diffuse low-grade glioma cells form a complex and highly interactive network. We believe our work can provide valuable insights into glioma biology.

Session 5B - La Méthodologie et réglementation dans la recherche Interventionelle en Santé des Populations (1)

5B / 01

Présentation générale du réseau SORisp - Les méthodologies en recherche interventionnelle en santé des populations.

Cyrille DELPIERRE[1], **Florence COUSSON-GELIE[2]**, Linda CAMBON[3], François ALLA[4], Véronique REGNIER[5], Mathieu GOURLAN[6]

[1] EQUITY Inserm UMR 1295 CERPOP Université de Toulouse

[2] Epsylon EA 4556, Université Paul-Valéry Montpellier 3 & Epidaure, département prévention de l'Institut du Cancer de Montpellier

[3] EVIDANS Inserm U1219, CHU Bordeaux

[4] EVIDANS Inserm U1219, Université de Bordeaux & CHU Bordeaux

[5] Centre Hygée Institut PRESAGE, Université Jean Monnet à Saint-Etienne

[6] Epidaure, département prévention de l'Institut du Cancer de Montpellier

Plus de 40% des cancers sont liés à nos comportements et à notre environnement au sens large du terme. L'objectif de la stratégie décennale de lutte contre les cancers 2021-203 est de réduire de 60 000 par an le nombre de cancers évitables, à horizon 2040. Pour cela, il est nécessaire de disposer d'interventions et d'organisations préventives efficaces, efficientes et intégrées. Or, les stratégies actuellement déployées en France sont peu étayées scientifiquement ou théoriquement, peu ou mal évaluées, tiennent peu compte des inégalités sociales et territoriales de santé, et sont essentiellement centrées sur le recours aux soins et les comportements individuels. Dans ce cadre, le recours à des travaux de recherche interventionnelle menés de manière ancrée (en contexte) et participative (en collaboration avec les intervenants et les populations) est un moyen de développer des stratégies plus efficaces, plus équitables et plus pérennes. Il s'agit plus précisément de mobiliser dans ce cadre la recherche interventionnelle en santé des populations (RISP), définie comme l'utilisation des méthodes scientifiques pour produire des connaissances concernant les interventions en santé publique. L'enjeu est donc de promouvoir des méthodologies éprouvées et de développer de nouveaux outils de recherche pour développer, implémenter, évaluer et accompagner la mise à l'échelle d'interventions « evidence-based » dans le domaine de la prévention primaire des cancers, tout en n'augmentant pas les inégalités sociales de santé.

La complexité de la RISP la rend néanmoins difficile à adopter par la communauté de recherche. Il est nécessaire d'innover sur ses approches et méthodes et d'accompagner les chercheurs dans cette démarche pour qu'ils l'investissent dans la prévention primaire des cancers. C'est ce que proposent 4 équipes de recherche investies et reconnues en France en RISP et très impliquées dans la prévention primaire des cancers, en alliance avec un opérateur de la prévention des cancers : EVIDANS Inserm U1219, Université de Bordeaux & CHU Bordeaux ; Epsylon EA 4556, Université Paul-Valéry Montpellier 3 ; EQUITY Inserm UMR 1295 CERPOP Université de Toulouse ; Centre Hygée Institut Presage, Université Jean Monnet à Saint-Etienne ; Epidaure, département prévention de l'Institut du Cancer de Montpellier. Ces équipes ont souhaité allier leurs expertises au service de la RISP dans le champ de la prévention primaire des cancers afin de répondre aux objectifs suivants : 1) contribuer collectivement à avancer sur les grandes questions portant sur les concepts et méthodes en RISP ; 2) produire des outils en RISP afin de mobiliser davantage la communauté de chercheurs ; 3) développer une animation scientifique et la formation des chercheurs et des doctorants ; 4) développer le lien recherche/acteurs/décisions notamment par un transfert de connaissances fondé sur les dernières avancées de la recherche.

L'objectif de cette communication est de présenter le réseau SORISP, de discuter des enjeux méthodologiques en RISP en s'appuyant sur des exemples concrets de recherche.

Le réseau est soutenu par l'Institut National du Cancer (INCa), l'Institut de Recherche en Santé Publique (IReSP) et a bénéficié du soutien du GSO dans le cadre de son appel à projet Action Structurante.

5B / 02

De la théorie à la pratique : l'exemple du « Grand Défi Vivez Bougez » pour promouvoir l'activité physique des enfants

Mathieu GOURLAN[1], Florence COUSSON-GELIE[1,2]

[1] Epidaure, Prevention Department of the Institut régional du Cancer de Montpellier (ICM), Montpellier
[2] Université Paul-Valéry Montpellier 3, Laboratoire Epsylon

La majorité des enfants à l'école primaire ne sont pas suffisamment actifs pour atteindre les recommandations d'une heure d'activité physique (AP) quotidienne (Verdot et al., 2022). Dans un tel contexte, la promotion de l'AP chez les enfants d'âge scolaire est reconnue comme une priorité de santé publique (OMS, 2022).

S'appuyer sur des théories de changement de comportement pour comprendre les déterminants de l'AP et développer des interventions efficaces est recommandé par de nombreux auteurs (Hagger et al., 2020). Cette présentation mettra en avant le programme de recherche associé au Grand Défi Vivez Bougez (GDVB), une intervention de promotion de l'AP à destination des enfants âgés de 6 à 11 ans basée sur la théorie du comportement planifié (TCP, Ajzen, 2011).

Dans un premier temps, seront présentées les recherches observationnelles basées sur la TCP afin de mieux comprendre les déterminants de la pratique d'AP chez l'enfant (Gourlan et al., 2018 ; Roux et al., 2020). Ces recherches ont confirmé la pertinence de la TCP et ont notamment indiqué que les attitudes (i.e., sentiments positifs ou négatifs), les normes subjectives (i.e., perceptions de ce que pensent et font les proches) et le contrôle perçu (i.e., capacités perçues pour adopter le comportement) étaient associés aux intentions (i.e., motivations) de pratiquer des AP, elles-mêmes associées au niveau d'AP des enfants (ps < 0,05). Ces études ont également permis de quelque peu compléter et affiner la TCP, en révélant notamment des effets d'interaction entre certains déterminants des intentions (i.e., attitudes*contrôle perçu, normes subjectives*contrôle perçu) ainsi que des différences dans la force des liens entre certaines variables en fonction du genre et de l'âge des enfants (ps < 0,05).

Fort de ces premiers résultats, la construction du GDVB en tant qu'intervention de promotion de l'AP basée sur la TCP sera présentée. En lien avec les recommandations existantes sur le développement des interventions ancrées théoriquement (Michie & Prestwich, 2010), chaque contenu éducatif proposé aux enfants dans le cadre du GDVB cible une des variables de la TCP. Les séances proposées peuvent consister à présenter les bienfaits de la pratique d'AP (i.e., attitudes), sensibiliser aux recommandations en matière d'AP (i.e., normes subjectives) ou demander aux enfants d'enregistrer les « cubes énergie » (i.e., 15 minutes d'AP pratiquée en continu) qu'ils cumulent chaque jour afin de prendre conscience de leur niveau de pratique (i.e., contrôle perçu). De plus, des événements « Grand Défi » sont également organisés afin de promouvoir la transformation des intentions de pratique en comportement concret (Ajzen, 2020).

Dans un troisième temps, les résultats d'un essai contrôlé randomisé en cluster sur deux années scolaires seront présentés (Cousson-Gélie et al., 2019). Cet essai avait pour objectif de (1) tester l'impact du GDVB sur les variables de la TCP et la pratique de l'AP des enfants, et (2) évaluer le rôle médiateur des variables du TCP pour expliquer l'impact du GDVB sur l'AP. Les analyses ont révélé que, par rapport au groupe contrôle, le groupe intervention rapportait une augmentation significativement plus importante de l'AP sur les deux années, ainsi qu'une augmentation plus importante des attitudes au cours de la première année (ps < 0,01). A la fin des deux années de suivi, près de 80% des enfants du groupe intervention respectaient les recommandations d'AP d'une heure par jour (Bull et al., 2020). Les analyses ont également révélé que la relation entre les intentions et l'AP était significativement plus forte pour les enfants du groupe intervention que pour ceux du groupe contrôle (Critical Ratios > 1,96).

La conclusion de cette présentation portera sur l'efficacité du GDVB pour promouvoir l'AP des enfants ainsi que sur les difficultés à identifier les mécanismes sous-jacents à cette efficacité.

Session 6A - Cellular plasticity

6A / 01

Pre-existing stem cell heterogeneity as a driver of cancer evolution

Alejo E. RODRIGUEZ FRATICELLI[1,2]

[1] IRB Barcelona, Barcelona Institute of Science and Technology, Barcelona, Spain

[2] Catalan Institute for Research and Advanced Studies (ICREA), Barcelona, Spain

Cancer cells display wide phenotypic variation even across patients with the same driver mutations. Non-genetic differences across cancer cells could be derived from pre-existing heterogeneity in the cells of origin. We developed STRACK (simultaneous tracking of recombinase activation and clonal kinetics) to unbiasedly identify clonal trajectories of early cancer initiation events. Our model combines state-of-the-art ex vivo primary stem cell cultures, prospective activation of recombinases, and simultaneous tracking of thousands of barcoded cells using longitudinal single-cell profiling. Using STRACK, we traced the dynamics of gene expression and clonal expansion in response to two leukemia driver mutations, Dnmt3a-R882H (R878H in mice), and Npm1-cA. Intriguingly, the response to each mutation was different, and variable across pre-existing origin states. Differentiation biased stem cells, which normally become outcompeted through time, can efficiently expand with both mutations and display a strong clonal fitness effect. Npm1-cA mutations displayed the largest clone-to-clone heterogeneity, giving rise to either mature and immature cancer states. We propose a clonal « reaction norm », in which pre-existing clonal states dictate cancer phenotypic potential. We are currently dissecting how pre-existing states drive differences in cancer cell plasticity across various conditions.

6A / 02

The E3 ubiquitin ligase TRIP12 is required for pancreatic acinar cell plasticity and DNA damage response in pancreatic carcinogenesis

Manon BRUNET[1,2], Claire VARGAS[1,3], Alban RICARD[1], Damien VARRY[1], Marjorie FANJUL[1], Naïma HANOUN[1], Dorian LARRIEU[1], Laetitia PIERUCCIONI[4], Guillaume LABROUSSE[1], Hubert LULKA[1], Florence CAPILLA[5], Janick SELVES[6], Anne COUVELARD[7], Laetitia LIGAT[1], Manon FARCÉ[1], Alexandre STELLA[8,9], Odile BURLET-SCHILTZ[8,9], Henrik LAURELL[2], Véronique GIGOUX[1], Nicolas BERY[1], Pierre CORDELIER[1], Julie GUILLERMET-GUIBERT[1], Marlène DUFRESNE[1], **Jérôme TORRISANI[1]**

[1] CRCT, Université de Toulouse, Inserm, CNRS, Université Toulouse III-Paul Sabatier, Centre de Recherches en Cancérologie de Toulouse
[2] Institut National de la Santé et de la Recherche Médicale (INSERM), U1297, Institut des Maladies Métaboliques et Cardiovasculaires, Toulouse
[3] German Cancer Research Center (DKFZ), Division Chromatin Networks, Im Neuenheimer Feld 280, Heidelberg, Germany
[4] Centre de recherches RESTORE, Université de Toulouse, INSERM, CNRS, EFS, ENVT, Toulouse
[5] Service d'Histopathologie expérimentale, INSERM US006-CREFRE, Toulouse
[6] Département de Pathologie, Institut Universitaire du Cancer Toulouse Oncopole, CHU Toulouse
[7] Département de Pathologie Beaujon-Bichat, Hôpital Bichat, APHP and Université Paris Cité, Paris
[8] Institut de Pharmacologie et de Biologie Structurale, Université de Toulouse, CNRS, Université Toulouse III-Paul Sabatier
[9] Infrastructure nationale de protéomique, ProFI, FR 2048, Toulouse

The E3 ubiquitin ligase Thyroid hormone Receptor Interacting Protein 12 (TRIP12) has been involved in pancreatic adenocarcinoma (PDAC) by inducing the degradation of Pancreas Transcription Factor 1a (PTF1a), a transcription factor essential for acinar differentiation state that is lost in the early steps of pancreatic carcinogenesis. However, TRIP12 implication in pancreatic carcinogenesis has not been completely demonstrated. Herein, we demonstrate that TRIP12 protein is markedly overexpressed in human pancreatic preneoplastic lesions. Acinar-to-ductal cell metaplasia (ADM) is a reversible process that reflects the high plasticity of acinar cells. ADM becomes irreversible in the presence of oncogenic Kras mutations and leads to the formation of preneoplastic lesions. Using two genetically modified murine models, we showed that a loss of TRIP12 prevents acini from developing ADM in response to pancreatic injury. Additionally, we noticed that TRIP12 overexpression is heterogeneous in PDAC samples as well as PDAC cell lines that we explain, at least in part, by an altered cell cycle regulation. We further demonstrate that TRIP12 is required for PDAC cell line growth by controlling the expression of E2F-targeted genes. With two additional murine models, we further showed that the loss of TRIP12 prevents the formation of KrasG12D-induced preneoplastic lesions and impairs metastasis formation in the presence of mutated KrasG12D and TP53R172H. In parallel, we established the TRIP12 proxisome and unveiled its pleiotropic role in chromatin regulation. Notably, we discovered that TRIP12 controls DNA damage response by inhibiting the accumulation of the Mediator of DNA Damage Checkpoint 1 (MDC1) at DNA break sites.

In summary, our study identifies an overexpression of TRIP12 from the early stages of pancreatic carcinogenesis and proposes this E3 ubiquitin ligase as a novel regulator of acinar plasticity with important roles in initiation, metastatic steps of PDAC and DNA damage response.

6A / 03

Modelling metastatic dormancy of cancer stem cells in gastric cancer

Anissa ZAAFOUR, Nina REITANO FERBER, Tra Ly NGUYEN, Christine VARON

BoRdeaux Institute of Oncology

Metastasis is the leading cause of cancer-related death. At the core of this process are cancer stem cells (CSCs), a highly plastic subpopulation of cancer cells with the ability to invade the bloodstream and colonize organs distant from the primary tumor. CSCs are resistant to conventional treatments, and some can remain dormant, a state of near quiescence in which cells survive with very little growth and are not detectable by current imaging techniques, for several months or even years before triggering local or metastatic tumor recurrence. Despite the magnitude of the problem, the underlying mechanisms of CSC dormancy in the context of gastric adenocarcinoma (GC) are still largely unknown. Indeed, even in the case of early diagnosis of GC, the risk of recurrence remains elevated at around 60% despite surgical resection of the primary tumor (1). Two recurrence peaks are observed after surgery at 3 and 7.5 years, suggesting the presence of residual dormant GC cells that may awaken years after treatment (1). This emphasizes the crucial need to understand CSC dormancy in GC.

In the context of GC, our objectives are to: 1) elucidate the molecular mechanisms controlling CSC entry into dormancy and awakening by modelling it in vitro. This will allow us to understand how extracellular signals such as the hypoxic environment and external factors including ATRA, GAS6, and LIF influence the plasticity of CSCs from entry into dormancy to proliferative and invasive states. 2) To target the molecular mechanisms of dormancy in GC by focusing on NR2F1, one of the master regulators of dormancy described in the literature (2,3).

Various GC cell lines were exposed to dormancy inducers, including ATRA, LIF, TGF-B2, BMP7, and hypoxia, as described in the literature and based on previous works done in our laboratory (4). Our preliminary results indicate notably a potential role of ATRA and hypoxia in GC dormancy mechanisms. GC cells under ATRA treatment or hypoxic condition showed a lower proliferation rate in both proliferation and colony-forming unit assays compared to the control. However, no increase in cell death was observed, suggesting that the cells might be arrested and surviving. This was confirmed by flow cytometry which showed an increase in the percentage of cells blocked in the G0/G1 phase of the cell cycle. We also observed variations in the protein expression and localization of dormancy markers such as NR2F1 and p27 by western blot and immunofluorescence.

In conclusion, these preliminary results are encouraging but require further experimentations, which are currently ongoing, such as RTqPCR to obtain the GC dormancy signature and senescence assay. Additionally, tests with shRNA against NR2F1 are being conducted to target dormancy mechanisms in GC cells. Finally, this research project aims to develop and validate original models for the study of dormancy in the GC. Our ultimate goal is to identify the molecular signature of dormancy, and to elucidate the underlying mechanisms of dormant metastatic CSCs, thereby opening new perspectives for improving the therapeutic management of GC.

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6A / 04

Overcoming osimertinib resistance in EGFR-driven lung cancer by targeting drug tolerant persister cells

David BRACQUEMOND[1], Xavier QUANTIN[2], Maicol MANCINI[1], Antonio MARAVER[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Institut du Cancer de Montpellier

Patients diagnosed with EGFR-mutated lung adenocarcinoma are treated with specific EGFR-inhibitors such as osimertinib. However, inevitably, almost all patients relapse. A subpopulation of slow-to-non-cycling cells called Drug Tolerant Persisters (DTP) seems to be responsible for the tumour recurrence. Our aim is to establish whether DTPs are associated with the NOTCH pathway, a crucial pathway in lung adenocarcinoma.

EGFR-driven cells were treated with a combination of EGFR and NOTCH inhibitors. We transduced these cells with the FUCCI system to be able to follow the cell cycle. Additionally, we labelled cells to monitor HES1 expression (read-out of Notch pathway activity) by cytometry upon different drug treatment. Tet-on-EGFRT790M/L858R transgenic mice have been treated with the combination of EGFRi and NOTCHi by oral gavage 5 days per week.

Upon EGFRi treatment, we observe i) an arrest of the cell cycle in G1, ii) the appearance of a subpopulation likely in G0 and iii) a fluctuation of the NOTCH pathway activity over time. Initially, HES1 drops drastically in DTPs, then, once DTPs are expending, the trend is reversed. In vitro, EGFRi/NOTCHi combination delays the expansion of DTPs compared to EGFRi alone. In vivo, the same combination demonstrates a strong acute response and significantly delays the relapse compare to EGFRi alone.

EGFRi treatment affects the NOTCH pathway activity and targeting NOTCH in combination with EGFR brings therapeutic benefit as it delays the relapse in vitro in EGFR-mutated cell lines and in vivo in Tet-on EGFRT790M/L858R transgenic mice. Since both treatments seems to strongly impact the cell cycle, we intend to shed light into the exact mechanism of how HES1 levels mediates DTPs status.

Session 6B - La Méthodologie et réglementation dans la recherche Interventionelle en Santé des Populations (2)

6B / 01

DECODE : essai clinique randomisé en clusters d'une intervention de littératie en santé pour le dépistage du cancer colorectal, ciblant les médecins généralistes et les patients dans les zones défavorisées

Niamh REDMOND[1,2], Maria Claudia ADDAMIANO[1], Aurore LAMOUROUX[3,4], Raphaël FENNI[1], Myriam KAOU[5], Zineb DOUKHI[6], Françoise COURANJOU[3], Raoudha GRAMI[5], Amalia MARTINEZ[1], Marie BICHARA[7], Valérie ZIMMERLÉ[8], Michel ROTILY[3,4], Aurélie BOURMAUD[9], Anne-Marie SCHOTT[5], Isabelle AUGER-AUBIN[9], Adèle FRACHON[9], Catherine EXBRAYAT[10], Christian BALAMOU[10], Grosclaude PASCALE[1,11,12], Nora MOUMJID[13], Julie HAESEBAERT[5], Helene DELATTRE MASSY[14], Julia BARDES[14], Patricia MARINO[15], Julien MANCINI[16], Cyrille DELPIERRE[1], Marie-Anne DURAND[17,18]

[1] Centre d'épidémiologie et de recherche en santé des populations
[2] Bristol Medical School/ARC West, University of Bristol, UK
[3] Assistance Publique - Hôpitaux de Marseille
[4] Comité Départemental d'Éducation pour la Santé de Vaucluse (CoDES 84), Avignon
[5] INSERM, UMR 1290 RESHAPE Université Lyon 1
[6] INSERM, UMR-S 1123 ECEVE Université de Paris
[7] Centre Régional de Coordination du Dépistage des Cancers (CRCDC-Occitanie)
[8] Centre Régional de Provence-Alpes-Côte d'Azur (CRCDC-PACA)
[9] Département de Médecine Générale, Université de Paris
[10] Centre Régional de Coordination du Dépistage des Cancers Auvergne-Rhônes-Alpes (CRCDC-AuRA)
[11] Faculté de médecine - Département Universitaire de Médecine Générale, Toulouse
[12] Institut Claudius Regaud, IUCT-O, Registre des cancers du Tarn, Toulouse
[13] Université Lyon 1, P2S EA4129, Centre Léon Bérard, Lyon
[14] Centre Régional de Coordination du Dépistage des Cancers d'Ile de France (CRCDC-IDF)
[15] Institut Paoli Calmettes, SESSTIM UMR1252, Marseille
[16] Aix-Marseille Université, CEReSS-Health Service Research and Quality of Life Center
[17] The Dartmouth Institute for Health Policy & Clinical Practice, Dartmouth College, NH, USA.
[18] Unisanté, Centre universitaire de médecine générale et santé publique, Lausanne, Switzerland

Le taux de participation au dépistage du cancer colorectal (CCR) reste faible en France (environ 34%) et atteint même 12% dans certaines régions de France. La participation est socialement graduée, les personnes vivant dans les zones les plus défavorisées au niveau socio-économique affichant les taux de dépistage les plus faibles.
Le manque de la « littératie en santé » (LS), c'est-à-dire la capacité à comprendre et à gérer les informations sur la santé et le système de soins, est un facteur majeur d'inégalité dans le dépistage du CCR, car il constitue un obstacle à la participation. Cibler la LS pourrait contribuer à améliorer les taux de dépistage et à réduire les inégalités sociales de santé. L'objectif de DECODE était d'évaluer l'impact d'une intervention combinée de LS pour les médecins généralistes (MG) et les patients sur la participation au dépistage du CCR dans les zones défavorisées en France.
DECODE est un essai contrôlé randomisé, multicentrique, à deux, en clusters, mené en collaboration avec 4 centres régionaux de coordination des dépistages des cancers (CRCDC), avec une approche de recherche participative. Les cabinets de MG de 4 régions françaises (Auvergne Rhône Alpes, Ile de France, Occitanie et PACA) ont été invités à participer, en utilisant l'European Deprivation Index (EDI) pour sélectionner les zones les plus défavorisées (EDI 4/5). Les MG ont été randomisés en bloc, stratifiés par région et par cluster (cabinet ou MG).
L'intervention consistait en 1) une formation interactive pour les MG sur le CCR, LS et les stratégies pour communiquer visant les patients, et 2) une brochure illustrée (co-construite avec un groupe de recherche participative) et une vidéo expliquant comment faire le test à la maison, pour les patients. Les MG du groupe contrôle ont été invités à proposer un test FIT aux patients recrutés selon leur méthode habituelle. Six mois après leur inclusion, les MG du groupe intervention ont reçu une session de formation interactive Booster.
Le résultat principal était le recours au dépistage du CCR après un an. Les résultats secondaires comprenaient l'intention de faire le test, des mesures LS standardisées et validées, une mesure de « l'activation du patient » et le niveau de précarité. Des données sociodémographiques ont également été recueillies via un questionnaire en ligne ou par téléphone. Un service d'interprète était disponible pour les non-francophones. Les participants ont été suivis une semaine et un an après la consultation de recrutement. Le recours au test FIT auto-déclaré après 1 an a été confirmé par les dossiers médicaux des cabinets MG et par les partenaires CRCDC.
52 MG de 27 cabinets ont été randomisés dans les groupes contrôle ou intervention. Le recrutement des participants a duré 18 mois à partir d'octobre 2021. 1065 participants ont été recrutés avec succès (494 intervention, 571 contrôle ; la cible était de 1024) et les données de 1022 participants ont été analysées. 83% (849/1022) des participants ont été contactés après 1 semaine et 68% (693/1022) après 1 an. Des différences ont été constatées en termes de région (plus des patients dans le groupe contrôle en IDF) et de sexe (plus de femmes) entre les deux groupes au moment du recrutement. Les premiers résultats seront présentés.
L'essai DECODE a réussi à recruter des MG et des participants dans des zones défavorisées de 4 régions différentes en France pendant l'épidémie de COVID-19. Les participants ont été suivis avec des taux de rétention et de collecte de données plus élevés que prévu. La lutte contre le faible niveau de LS et la réalisation d'études de recherche interventionnelle ciblées dans des zones défavorisées, comme DECODE, pourraient avoir le potentiel de réduire les inégalités de santé. Ces résultats pourraient avoir un impact positif sur les services de prévention du CCR, le recours du test et avoir des implications importantes pour les politiques de santé publique en matière de prévention du cancer.

6B / 02

PAM - Apprentissage du dépistage des cancers - Etude interventionnelle et participative avec des personnes déficientes intellectuelles

Elodie NEUMANN[1], Amaelle OTANDAULT[1], Genevieve PETITPIERRE[2], Caroline PITAVY[1], Haifaa KEZBAR[1], Marc PALPACUER[1], Elisangela OLIVIER[1], Anais LECLUSE[3], Xavier HEBER-SUFFRIN[4], Brigitte TRETARRE[1,5,6], Chris SERRAND[7], Daniel SATGE[1,8]

[1] ONCODEFI
[2] Département de Pédagogie spécialisée, Université de Fribourg, Suisse
[3] Association "Nous Aussi"
[4] ESAT l'Envol de Castelnau-le-Lez, Montpellier, Association UNAPEI 34
[5] Registre des Tumeurs de l'Hérault
[6] Equipe constitutive du CERPOP, UMR 1295, Université Paul Sabatier, Toulouse
[7] Département de biostatistique, épidémiologie clinique, santé publique et innovation méthodologique (BESPIM), CHU Nîmes
[8] L'Institut Desbrest d'Épidémiologie et de Santé Publique

Contexte : Les personnes atteintes d'une déficience intellectuelle (PDI) caractérisée par des difficultés cognitives et adaptatives apparues avant l'âge de 18 ans, présentent un risque de cancer similaire à celui de la population générale. Les cancers du côlon et du sein sont, chez elles, souvent détectés à un stade avancé. De plus, leur participation aux dépistages organisés des cancers (DOC) est faible, faute d'information. Très peu de recherches impliquent activement des PDI. L'étude PAM (Prévention/dépistage - Amélioration - Mesure) coconstruite avec les PDI avait pour objet d'évaluer, après une sensibilisation adaptée, les capacités d'apprentissage, de mémorisation et de mise en pratique du DOC chez des PDI.

Méthode : PAM est un essai contrôlé randomisé en cluster à deux groupes parallèles, en ouvert. Il a été mené auprès de 618 personnes DI de 38 établissements médico-sociaux dans 3 départements : Hérault, Gard et Aude sur 3 années (2022-2024). Les capacités d'apprentissage, de mémorisation et la mise en pratique du DOC par les PDI après une sensibilisation (diaporama, suivi de discussions, ateliers et livre explicatif) ont été évaluées par un questionnaire complété quatre fois : avant (J-15), pendant (J-0) et après (J+3mois et J+1an) le jour de la sensibilisation. L'étude été construite avec les conseils des PDI, de professionnels d'établissements médico-sociaux, un méthodologiste et une experte en apprentissage spécialisée auprès de ce public. Les PDI, particulièrement les membres de l'association « Nous Aussi », ont été intégrés à toutes les phases de l'étude. A) Au moment de la conception, elles ont évalué la faisabilité des réunions d'information et proposé des modifications. B) Elles sont intervenues dans la création des supports de communication en Facile à lire et à comprendre (FALC). Elles ont aménagé les textes, évalué le diaporama, modifié le questionnaire en supprimant certaines images qui facilitaient trop la réponse. Elles avaient aussi participé à la création du livret de dépistage remis à chaque participant. C) Au cours de l'étude, face à des difficultés de recrutement de participants, elles ont proposé de réaliser des affiches et se sont impliquées dans le recrutement. D) A la fin de l'étude, elles ont pris connaissance des résultats et fait des propositions pour leur diffusion et communication.

Résultats : L'étude a montré une augmentation significative des connaissances et des intentions de pratique du dépistage des cancers à J0 ($p<0,001$). Cette augmentation était encore statistiquement significative 3 mois après la sensibilisation ($p= 0,001$). Les PDI ont témoigné un grand intérêt pour l'étude et les questions de santé. Sur une période d'un an, le taux d'attrition est inférieur à 19%, et seulement 4% des participants (n=24) ont arrêté l'étude, les autres pour maladies, organisation dans l'institution, vacances et décès. Les PDI ont permis d'augmenter le nombre de participants, elles ont amélioré la communication et la qualité du questionnaire.

Conclusion : La collaboration avec les PDI et une experte en matière d'apprentissage spécialisé a été essentielle pour la mise en œuvre et la faisabilité de cette recherche participative. L'étude a montré, pour la première fois à notre connaissance, que des informations relatives au dépistage des cancers adaptées aux besoins des PDI, peuvent être communiquées avec succès. Elle montre aussi que ces personnes sont capables de retenir ce type d'information au moins sur une période de trois mois ; de les assimiler et de les appliquer. Ces importants résultats incitent à intensifier les actions qui favorisent le dépistage organisé des cancers chez les PDI. Travail soutenue par l'INCa et le CPAM de l'Hérault.

6B / 03

L'encadrement réglementaire des projets RISP à l'Oncopole Claudius Regaud

Morgane MARCOU DU TILLET DE VILLARS, Ambre MARCONATO, Guillaume JAUFFRET, Bettina COUDERC, Muriel POUBLANC

IUCT Oncopole, Toulouse

L'Oncopole Claudius Regaud (OCR) est un centre de lutte contre le cancer alliant un centre de recherche et un centre de soin en cancérologie. Il compose, avec plusieurs équipes du CHU de Toulouse, l'Institut Universitaire du Cancer de Toulouse-Oncopole (IUCT-O). L'IUCT-O traite plus de 10 000 nouveaux patients chaque année et plus d'un patient sur huit est inscrit dans des études cliniques.

Dans le cadre des activités de recherche au sein de l'OCR, l'épidémiologie est l'une des typologies de projets les plus récentes que la Direction de la Recherche et de l'Innovation (DRI) est amenée à accompagner. Comprendre les finalités et adapter la mise en conformité réglementaire de ces projets est un enjeu pour un centre de soin dans lequel la recherche clinique est prépondérante. Les recherches interventionnelles en santé des populations (RISP) génèrent de nouvelles modalités d'organisation, de collecte de données, d'analyses et d'interventions hors des murs de l'établissement. Il convient de les encadrer juridiquement car elles entrent la plupart du temps dans la catégorie des recherches non interventionnelles sur la personne humaine (RNIPH) de la loi Jardé mais sont souvent non conformes au cadre réglementaire défini par une méthodologie de référence de la Commission Nationale de l'Informatique et des Libertés (CNIL). Elles sont relativement éloignées des profils de recherches initialement menées à l'OCR.

A partir de notre expérience dans la mise en œuvre des projets de recherche épidémiologique et des RISP, nous avons soulevé un certain nombre de questions et de freins dans leur mise en conformité réglementaire et identifié des éléments clés -juridiques et organisationnels- pour la réaliser. Nous aborderons des cas d'usage et livrerons une synthèse des mesures adaptées, adoptées en concertation avec la DRI, la direction des Affaires Juridiques et le Comité d'Ethique Recherche de l'établissement.

Session 7 -Prestige Conference

7 / 1

The new role of scientific research and scientists facing ecological emergency

Julian CARREY

National Institute of Science and Technology & ATelier d'ECOlogie POLitique, Toulouse

During the first part of this seminar, we will provide concrete information on ecological emergency, based on scientific literature, in particular that cited in the IPCC and IPBES reports.
In a second part we will look at the particular role of higher education and research in this context.

Firstly, scientific research contributes directly to greenhouse gas emissions, as does any human activity: figures will be provided, based on the greenhouse gas balances of French and European higher education establishments and laboratories.

Next, the indirect impacts of scientific research will be discussed: given the way our society and research system currently operate, a large number of scientific themes contribute indirectly to the increase in environmental damage, notably via the rebound effect, whose preponderance in the technological trajectory of our society has never been denied over the last three centuries, including, for example, in the digital domain: any innovation leading to an increase in energy efficiency ultimately leads to an increase in energy consumption.

What's more, many basic research projects require increasing amounts of energy, at a time when calls for energy conservation from scientists themselves are becoming ever more pressing. This puts us scientists in a delicate situation, where philosophical questions about neutrality, ethics, the nature of "Progress", and our role in the life of the city seem to be impossible to ignore.

Based on these considerations, the various roles that scientists can play facing emergency will be discussed.
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Session 8A - Translational research in rare cancers

8A / 1

Non-genetic heterogeneity and phenotypic plasticity in neuroblastoma

Isabelle JANOUEIX-LEROSEY

Institut Curie, Paris

Neuroblastoma is a malignant tumor of young children that arises from the peripheral sympathetic nervous system, a tissue derived from neural crest cells. The clinical hallmark of neuroblastoma is heterogeneity, which has been described for decades and the long-term survival of children with a high-risk clinical phenotype remains below 40%. Several drivers of neuroblastoma oncogenesis have been identified, including the MYCN, ALK and TERT genes.

In addition to the mutations observed at the genetic level, other mechanisms related to the epigenetic states of tumor cells may be involved in tumor phenotype and response to treatment in neuroblastoma. Through the characterization of the super-enhancer and transcriptomic landscapes of neuroblastoma cell lines and human neural crest cells, we uncovered two distinct cell identities (Boeva et al, Nature Genetics, 2017). Cells of the two identities, called NORadrenergic and MESenchymal, showed notable differences in their behavior in vitro, particularly in terms of chemotherapy resistance and invasion abilities. We further deciphered the core regulatory circuitry governing the NOR cell identity, showing that it includes the PHOX2B, GATA3 and HAND2 transcription factors, known to be crucial for the specification of the NOR sympathetic neurons during development.

In several neuroblastoma models, we documented spontaneous and reversible plasticity between the two identities, associated with epigenetic reprogramming. Our data revealed that intrinsic factors and signals from the microenvironment dictate cell identity in this pediatric cancer (Thirant et al, Nature Communications, 2023). Indeed, we showed that several growth factors such as EGF and TNFa could promote a NOR to MES transition in vitro whereas tumors of NOR identity are observed following engraftment of MES cells in mice. This plasticity is reminiscent but different from the well described Epithelial to Mesenchymal Transition (EMT), and its reverse process, MET. Subsequent analysis of a cohort of 18 tumor biopsies from neuroblastoma patients by single-cell transcriptomics indicated that most tumor cells exhibited a NOR identity; yet, in a few cases a subpopulation of NOR tumor cells presented with expression of some MES genes.

Recently, we have deciphered the transcriptional network regulating the MES identity in neuroblastoma and further characterized plasticity between the NOR and MES states. Our data show that YAP, TAZ, and their target genes are marked by super-enhancers and are strongly and specifically expressed in MES tumor cells. Using ChIP-seq experiments of both transcription factors and histone marks, we characterized a core regulatory circuitry that controls gene expression linked to a MES identity in neuroblastoma. We further functionally explored the role of key actors of this circuitry in MES neuroblastoma cells and in the plasticity between the NOR and MES states.

The identification of extrinsic and intrinsic factors that govern neuroblastoma cell identity and behavior during disease progression appears fundamental to develop new therapeutic strategies that could intercept the disease before its dissemination or systematically eradicate all tumor cells in high-risk neuroblastoma patients

8A / 2

Immunotherapy in Sarcomas: from Bench to Bedside

Florent PEYRAUD

Institut Bergonié, Bordeaux

Soft-tissue sarcomas (STS) are rare and heterogeneous tumors with a limited response to standard immunotherapies due to their generally low mutational burden and immunosuppressive tumor microenvironment (TME). Recent advancements in the immune classification of STS, particularly through the identification of sarcoma immune classes (SICs), have led to a new understanding of TME's role in immunotherapy response. Among the SICs, the presence of tertiary lymphoid structures (TLS) and B-cell signatures in the TME of certain sarcoma subtypes has been associated with improved outcomes and response to immune checkpoint inhibitors.

In this presentation, we explore the shift from targeting tumor cells to focusing on immune cell modulation in sarcoma treatment. Traditional paradigms have emphasized tumor-centric strategies, but recent evidence underscores the importance of enhancing the TME to achieve meaningful therapeutic responses. Immunotherapy approaches, including anti-PD-1/PD-L1, have demonstrated limited efficacy in sarcoma overall, but emerging insights on TLS as biomarkers for treatment response indicate a promising avenue for personalized immunotherapy. Data from studies like PEMBROSARC and others show that TLS-positive sarcomas display higher rates of objective response, supporting TLS as a predictive biomarker.

This presentation will discuss the latest findings on TLS's prognostic impact and the immune-rich sarcoma subtypes most likely to benefit from immune checkpoint blockade. It will also outline the challenges and future directions in tailoring immunotherapy for sarcoma patients, focusing on combining immune-based treatments to exploit the unique TME of sarcoma and improve patient outcomes

8A / 3

Translational research in Gynecological Rare Sarcomas: examples of ongoing translational projects

Sabrina CROCE[1,2], Nathalène TRUFFAUX[1]

[1] Département de Biopathologie, Institut Bergonié, Bordeaux

[2] BRIC (BoRdeaux Institute of onCology), INSERM U1312

Session 8B - L'intégration des patients partenaires en recherche

8B / 01

Le partenariat avec les patients dans la recherche en santé : un défi épistémologique, éthique et démocratique !

Patrick LARTIGUET[1,2]

[1] Université Toulouse 2 Jean Jaurès

[2] Institut pour la promotion des patients et aidants partenaires en Santé

« Les sciences et recherches participatives sont des formes de production de connaissances scientifiques auxquelles participent, aux côtés des chercheurs, des acteurs de la société civile, à titre individuel ou collectif, de façon active et délibérée. »

Si les recherches participatives dans le domaine de la santé suscitent un véritable engouement en France et à l'international il n'empêche que cette terminologie est polysémique et revêt des visions disparates de la participation des acteurs de la société civile, des patients/personnes accompagnées comme des proches aidants. Plusieurs modèles existent sous les noms de recherches collaboratives, partenariales, interventionnelles, recherche-action, sciences citoyennes…

Les recherches participatives relèvent de plusieurs enjeux :
- utilitaristes : réponse aux appels à projets et recherche de financement.
- épistémologiques : valorisation de la pluralité des savoirs et remise en cause du monopole du savoir scientifique dans la production de connaissances ; valorisation du croisement des savoirs avec la reconnaissance des savoirs issus du vécu avec la maladie ; valorisation d'une science utile à l'action dans une visée praxéologique (lien sciences-société).
- éthiques : réduction des injustices épistémiques ; valorisation du patient, de la personne accompagnée comme sujet en soin.
- démocratique : valorisation d'une véritable démocratie en santé dans la recherche.
- émancipatoire : modification des relations sociales qui sous-tendent la production de connaissances.

En référence au continuum de l'engagement des usagers dans le système de santé (HAS, septembre 2020), un parallèle peut être établi avec la recherche participative :
- Information : recueil du consentement auprès de la personne lors de la phase du recueil de données dans une recherche qualitative (observation, questionnaires, entretiens).
- Consultation : participation de patients (associations) pour faciliter le recueil de données (accès au terrain, intelligibilité du mode de recueil de données…).
- Collaboration : participation de patients (associations) à certains stades la recherche (problématisation, méthodologie de recherche, analyse des résultats, valorisation de la recherche…)
- Partenariat : participation de patients à tous les stades de la recherche avec co-leadership, co-décision, co-mise en œuvre, co-responsabilité.

Pour autant, l'opérationnalisation du partenariat avec les patients dans la recherche en santé nécessite un changement de paradigme afin de promouvoir le(s) savoir(s) patient(s) dans la production de connaissance en santé. Un défi épistémologique, éthique et démocratique !

8B / 02

Patients et chercheurs, unis pour innover : L'engagement pour réinventer, ensemble, la recherche humaniste et engagée

Cyril SARRAUSTE DE MENTHIÈRE

Co-responsable du label « Mon Réseau Cancer Colorectal » de l'association Patients en Réseau, Membre du bureau de Digestive Cancers Europe (DiCE), Membre de la Commission de Déontologie de l'UFR Médecine Paris Saclay, Membre du Comité Patients du Paris-Saclay Cancer Cluster, Membre du COPIL du SIRIC Montpellier, Membre des conseils scientifiques de React-therapeutics et Depist&Vous, Membre du consortium de recherche 4P, SESSTIM - université Aix-Marseille

L'intégration des patients dans la recherche en santé est aujourd'hui un pilier essentiel pour construire une recherche plus humaniste et orientée vers les besoins réels des patients. Ce mouvement vers une recherche collaborative répond au besoin de recentrer les projets scientifiques autour des attentes des individus directement concernés par la maladie. L'implication des patients peut s'étendre tout au long du processus de recherche, depuis la définition des priorités jusqu'à la communication des résultats. Leur participation commence souvent par la co-définition des priorités de recherche. Les patients apportent une connaissance intime des défis et impacts quotidiens liés à la maladie, ce qui aide les chercheurs à cibler des problématiques pertinentes pour améliorer la qualité de vie. Par exemple, en cancérologie, les patients peuvent orienter la recherche vers des traitements moins toxiques ou vers des solutions de support pour gérer les effets secondaires. En s'alignant sur ces priorités, la recherche devient plus significative pour les patients et améliore le taux d'adhésion aux projets.

Le partenariat actif dans la conception et la mise en œuvre des protocoles de recherche est une autre dimension cruciale. Les patients partenaires contribuent à concevoir des études réalistes, plus faciles à suivre et moins contraignantes. Par exemple, ils peuvent proposer des aménagements pratiques dans le cadre d'essais cliniques pour limiter les déplacements ou réduire le nombre de procédures invasives. Cette approche est particulièrement pertinente pour les essais en cancérologie, où la fatigue et la vulnérabilité des patients peuvent compliquer la participation. En collaborant directement avec les chercheurs, les patients aident à ajuster les protocoles pour qu'ils soient en phase avec leur réalité.

En parallèle, les patients partenaires jouent un rôle clé dans la diffusion et la vulgarisation des résultats de la recherche. Ils contribuent à rendre les données accessibles et compréhensibles pour un public plus large, incluant les autres patients et le grand public. En tant que témoins directs des enjeux de la maladie, ils aident à sensibiliser et à attirer l'attention sur des domaines spécifiques qui nécessitent davantage d'investissements. Leur témoignage personnel et leur engagement renforcent la crédibilité et l'impact des messages auprès des décideurs publics, des financeurs et de la société en général.

Cependant, l'implication des patients dans la recherche comporte des défis. Il peut être difficile de gérer l'équilibre entre leur rôle de patients et celui de partenaires, en évitant les surcharges émotionnelles. De même, des questions éthiques peuvent surgir, notamment en ce qui concerne la confidentialité et la gestion des données personnelles. Il est crucial d'élaborer des cadres éthiques clairs pour protéger les patients partenaires et s'assurer que leurs droits et leur vie privée sont respectés tout au long du processus.

L'union entre patients et chercheurs pour réinventer la recherche en santé est une démarche innovante, mais surtout nécessaire. En valorisant l'expérience vécue des patients et en mobilisant leur expertise, la recherche devient plus humaniste et mieux adaptée. Elle s'enrichit de perspectives nouvelles et propose des solutions plus proches des réalités de vie des patients. Ainsi, la collaboration patients-chercheurs trace le chemin vers une science en santé plus inclusive, au service des individus, et tournée vers l'impact réel de chaque découverte.

8B / 03

Co-construction d'un programme de partenariat patient dans un Institut Hospitalo-Universitaire : inspiration concrète

Célia CARDOSO

Institut Imagine - Paris

Dans sa volonté d'ouverture à la société, le programme de travail WP7 « Sciences humaines et sociales et rôle sociétal » de l'IHU Institut Imagine, premier centre de recherche sur les maladies génétiques, porte un projet de partenariat avec les patients en recherche. Ce projet a été coconstruit entre juin et décembre 2023, en groupe de travail pluridisciplinaire (TFPPR pour TaskForce Partenariat Patient en Recherche), constituée de représentants de centres de référence maladies rares, de laboratoires de recherche, d'associations de patients, de la direction, avec une valence éthique et juridique. Il était co-piloté par Maura Samarani, chargée d'animation des programmes éducation et société et par Célia Cardoso, présidente de l'association de patients Tintamarre-Grandir avec une malformation ano-rectale et patiente partenaire, rémunérée par l'Institut Imagine dans le cadre de cette mission.

En se basant sur le « Montréal model », le groupe de travail TFPPR a développé une méthodologie, enrichie par des données obtenues via un questionnaire en ligne partagé à tous ses personnels et à des membres d'associations de patients, par des entretiens menés auprès de volontaires parmi les laboratoires de recherche et des associations, par un atelier d'idéation qui a abouti à l'identification des étapes d'un projet de recherche, des missions qui pourraient être confiées à des patients partenaires ainsi que les compétences nécessaires associées à ces missions. En parallèle, de nombreux échanges et rencontres ont eu lieu avec des chercheurs partenaires et des patients partenaires en recherche, en France et au Canada.

Le groupe de travail TFPPR a décidé de continuer le travail commencé en 2023 et de se constituer en groupes de réflexion thématiques pour permettre aux équipes de l'Institut Imagine qui le souhaitent de s'engager dans une démarche de recherche partenariale. Pour coordonner ce projet un poste de Coordinateur du partenariat patient en recherche a été créé, avec des missions spécifiques, notamment celle de conduire la gestion de projet du PPR en termes de coordination, d'animation des forces internes, de collaborations en externes afin de développer des synergies avec les équipes, experts ou institutions développant des démarches similaires, de veille stratégique, de documentation et d'évaluation de la démarche pour le bon déploiement du projet du PPR. Ce poste a été confiée à la patiente partenaire qui co-pilotait ce projet dès ses débuts.

Session 9A - Metastasis

9A / 01
Nanoscale tracking of tumor metastasis

Jacky GOETZ

Tumor Biomechanics Lab, INSERM/Unistra, CRBS Strasbourg (www.goetzlab.fr)

A better understanding of tumor metastasis is required for improving therapies that remain largely inefficient to prevent the lethality of cancer. My lab has embarked on proving an accurate view, via microscopy and functional experiments in animal models, of the most discrete steps of metastasis. We developed intravital correlative microscopy for tracking metastasis in zebrafish and mouse models (Karreman et al. JCS, 2016; Karreman et al., TCB, 2016; Follain et al. JCS 2016). Doing so, we have identified a new mechanism for metastatic extravasation (i.e. intraluminal endothelial remodeling; Follain et al. Developmental Cell, 2018; Follain-Osmani et al. Sci Rep, 2021, Karreman et al. Cancer Research, 2023). My group is also focused on dissecting the biomechanics of the metastasis cascade. We recently identified the contribution of hemodynamic forces to tumor cell arrest and extravasation preceding metastasis formation (Follain et al. Developmental Cell, 2018; Osmani et al. Cell Reports, 2019, Follain-Osmani et al. Sci Rep, 2021). These studies demonstrate that fluid & cell mechanics are key regulators of tumor metastasis (reviewed in Goetz, Science, 2018; Follain et al., Nature Reviews Cancer, 2020; Gensbittel et al. Dev Cell 2021, Mittelheisser et al. Nat Nanotechnology 2024). We very recently dissected the contribution of platelets to tumor metastasis with the discovery of a very late contribution of these blood components (Garcia-Leon et al. Nat Comm 2024). My group is also interested in elucidating the mechanisms driving the establishment of pre-metastatic niches in vivo. We have recently demonstrated that Ral1 controls biogenesis and secretion of tumor extracellular vesicles (Hyenne et al. JCB 2015) and demonstrated that the zebrafish embryo can be used for tracking, at high spatio-temporal resolution, the fate and function of extracellular vesicles in vivo (Hyenne et al. Dev Cell, 2019; Verweij et al. Dev Cell, 2019; Verweij et al. TCB, 2019; Verweij et al. Nat Meth, 2021). We unraveled an important role for RalGTPases and the adhesive potential of Extracellular Vesicles in priming metastatic niches during breast cancer progression (Ghoroghi et al. eLife, 2021) and recently demonstrated that the uptake of EVs by endothelial cells is sensitive to hemodynamic forces (Mary et al. EMBO Rep 2023). My talk will focus on unpublished work along these lines of research.

9A / 02

New insights of YAP activity in brain metastases from colorectal cancer

Inès GARROUCHE[1], Sheik EMAMBUX[1,2], Konstantin MASLIANTSEV[1,3], Amandine DESETTE[1,3], Julien TAÏEB[4], Serge MILIN[1,5], Michel WAGER[1,6], Jean-François EMILE[7], Pierre-Laurent PUIG[4], Olivier BOUCHE[8], Côme LEPAGE[9], David TOUGERON[1,10], Lucie KARAYAN-TAPON[1,3], Pierre-Olivier GUICHET[1,3]

[1] Université de Poitiers, ProDiCeT, UR 24144

[2] CHU Poitiers, Service d'Oncologie Médicale

[3] CHU Poitiers, Laboratoire de Cancérologie Biologique

[4] Department of Gastroenterology and Digestive Oncology, Georges-Pompidou European Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP-Paris Centre), Université de Paris

[5] CHU de Poitiers, Service d'Anatomie et de Cytologie Pathologiques

[6] CHU de Poitiers, Service de Neurochirurgie

[7] Paris-Saclay University, Versailles SQY University, EA4340-BECCOH, Assistance Publique-Hôpitaux de Paris (AP-HP), Ambroise-Paré Hospital, Pathology department, Boulogne

[8] CHU Reims, Service d'Oncologie Digestive

[9] Department of Digestive Oncology, University Hospital Dijon, University of Burgundy and Franche Comté

[10] CHU de Poitiers, Service d'Hépato-gastro-entérologie

Brain metastases (BM) represent the majority of malignant intracranial tumors and a life-threatening complication for patient with colorectal cancers (CRC). Currently, YAP and TAZ, belonging to the Hippo signaling pathway, are considered as crucial malignancy factors in many solid tumors. In this work, we studied the impact of the transcriptional coactivator YAP in two different cohorts of CRC patients (PETACC8 cohort including 327 patients with grade III and a local cohort from Poitiers with 79 grade IV patients with BM) as well as its role in brain metastasis stem cells derived from CRC patients (BM-SC-CRC). First, we found that YAP expression was significantly higher in the BM cohort and associated with the tumor stage at diagnosis. However, we did not find a significant association with patient prognosis in both cohorts. In vitro, we showed that YAP was involved in proliferation and survival as its selective inhibition by verteporfin reduced the viability of BM-SC-CRC cultures. To get insight into the role of YAP in brain metastasis, we found using spatial transciptomic approach that this coactivator was strongly expressed in tumor area with metabolic changes. Altogether, our results highlight a potential role of YAP in CRC progression particularly in BM stem cells.

9A / 03

Role of immunosuppressive myeloid cells on gastric cancer stemness promotion

Tra-Ly NGUYEN[1], Klara SCHOTTGEN[1], Anissa ZAAFOUR[1], Coralie GENEVOIS[1,2], Lornella SEENEEVASSEN[1], Ana-Sofia VAZQUEZ[1], Thomas BOYER[3], Alexandra MOISAND[3], Elodie SIFRÉ[1], Alban GIESE[1], Jérôme GUIGNARD[1], Pierre DUBUS[1], Nicolas LARMONIER[3], Christine VARON[1]

[1] BoRdeaux Institute of Oncology
[2] TBMCore, Bordeaux
[3] IMMUNOLOGY from CONCEPT and EXPERIMENTS to TRANSLATION, Bordeaux

Gastric cancer (GC) ranks as the 4th leading cause of cancer-related deaths globally. Our research has identified and characterized cancer stem cells (CSCs) that drive tumor initiation and contribute to chemoresistance in GC, including a mesenchymal subpopulation of CSCs detected as metastatic circulating tumor cells (CTCs).

CSCs represent a small, crucial subpopulation of cancer cells within tumors that give rise to the various differentiated cancer cells comprising the tumor mass. These cells are marked by the expression of markers of immaturity, such as CD44-a cell surface glycoprotein-and are pivotal in tumor initiation, growth, chemoresistance, and metastasis through the epithelial-to-mesenchymal transition (EMT). Our team has identified a highly invasive mesenchymal-like CSC subpopulation expressing the surface markers CD44v3/CD44v6, which can be detected as circulating and metastatic tumor cells. This subpopulation may represent metastasis-initiating cells (MICs), similar to those reported in breast cancer (Liu et al., Stem Cell Rep. 2014) and colorectal cancer (Todaro et al., Cell Stem Cell 2014). Research indicates that these cells can be found either as single cells or in clusters (Heeke et al., Cells 2019). Interestingly, certain tumor-promoting immune cells, such as neutrophils or myeloid-derived suppressor cells (MDSCs), can associate with these CSCs, protecting and escorting them to distant sites to facilitate metastasis (Heeke et al., Cells 2019). However, the characterization of the cellular partners within these CTC/MIC-immune cell/MDSC circulating clusters, as well as the nature of their interactions in promoting MIC emergence, survival, homing, and metastasis development in distant organs, remains poorly understood. This emerging research field seeks to develop new targeted strategies to inhibit metastasis by focusing on these cells and clusters.

Project Overview: This project aims to investigate the impact of MDSCs on the tumorigenic and invasive properties of gastric CSCs, particularly the MIC subpopulation, both *in vitro* and *in vivo*. We utilized various GC cell lines co-cultured with human monocyte-derived suppressor cells (HuMoSCs), an *in vitro*model for MDSCs. Preliminary results suggest that HuMoSCs can induce stemness features in GC cells through contact-dependent mechanisms, as evidenced by 3D tumorsphere and transwell assays. Flow cytometry analysis revealed an increased percentage of CD44v3/CD44v6+ cells, corresponding to the MIC subpopulation. Additionally, initial immunofluorescence results indicated an increase in ZEB1 nuclear localization upon HuMoSC co-culture. Furthermore, HuMoSCs may also contribute to GC tumor formation*in vivo*, as suggested by subcutaneous tumor models.

Conclusion: Our promising preliminary results suggest that HuMoSCs enhance both tumorsphere initiation and growth *in vitro*. These findings will be validated using CD33+ myeloid cells purified from GC patients. Additionally, scRNA-seq analysis will elucidate the mechanisms underlying the acquisition and promotion of cancer stemness induced by HuMoSCs/MDSCs. Ultimately, this project seeks to develop new therapeutic strategies targeting CSC/MIC-MDSC interactions, offering novel tools for diagnosis and prognosis in gastric cancer.

9A / 04

Unraveling the metastatic process in colorectal cancer

Julie PANNEQUIN

Institut de Génomique Fonctionnelle, Montpellier

Even though metastatic disease kills 10 million people worldwide, there remain many points that are not well understood. The timing of tumor dissemination, in particular, has raised many questions, and several teams, have demonstrated that it can begin at very early stages of tumorigenesis. Another question that concerns gastroenterologists is how to predict whether a colon polyp will progress into cancer or not. In our laboratory, we had previously shown that there are two distinct transcriptomic signatures of polyps, one of which is highly immune and strikingly resembles that of actual tumors. We thus hypothesized that early dissemination could be a component of the progression of polyps into cancer. To validate this hypothesis, we have, for the very first time, demonstrated in mice and patients with intestinal polyps that early dissemination does occurs during intestinal tumorigenesis and these cells have a significant impact on the formation of late metastasis. Altogether these results induce a dogma change that could have an impact on standard of care of patients with polyps.

Session 9B - Les recherches sur les soins de support

9B / 01

AASSOAC : Améliorer l'Accès aux Soins oncologiques de Support sur la région Occitanie par l'Amélioration des connaissances des patients

Sébastien LAMY[1,2,3], Marie-Ange LEOPHONTE[4], **Maria Claudia ADDAMIANO**[3], Camille JOANNES[3], Morgane MARCOU DU TILLET DE VILLARS[1], Florence DALENC[1], Julien MAZIERES[5], Loic MOUREY[1], Nathalie CAUNES-HILLARY[1], Charlotte MOREL[6], Pascale MANUELLO[7], Thomas FILLERON[1], Cyrille DELPIERRE[3]

1 IUCT Oncopole
2 Registre des cancers du Tarn
3 Équipe EQUITY, CERPOP, UMR 1295, Inserm, Université Paul Sabatier Toulouse
4 CD 31 Ligue contre le cancer
5 Institut Universitaire du Cancer de Toulouse - Hôpital Larrey
6 Dispositif Spécifique Régional du Cancer ONCO-Occitanie
7 Laboratoire interdisciplinaire solidarités, sociétés, territoires, UMR 5193 CNRS Université Toulouse 2

Les soins oncologiques de support (SOS) font partie intégrante du parcours de soins des patients atteints de cancer et se définissent comme « l'ensemble des soins et soutiens nécessaires aux personnes malades tout au long de la maladie conjointement aux traitement oncologiques ou onco-hématologiques spécifiques lorsqu'il y en a » (DHOS/SDO 2005). L'institut National du Cancer (INCa) définit un panier de SOS considérés comme indispensables au parcours de soins du patient en distinguant des soins « socles » et les soins de support complémentaires.

Pourtant, selon l'Association Francophone pour les soins en oncologie de support (AFSOS), le recours à ces dispositifs est améliorable. Les études AFSOS menées en 2013 et 2017 (Scotté et al. 2017) mettent en évidence une méconnaissance de la part des patients des SOS en général, et relèvent une hétérogénité dans l'organisation des SOS et dans leur accessibilité pour les patients avec des disparités entre l'hôpital et la ville. Ces résultats ne permettent pas d'évaluer si cette méconnaissance varie en fonction des caractéristiques sociales des individus. Pourtant, on peut faire l'hypothèse que la connaissance des SOS est liée à la position sociale des individus en se basant sur les travaux montrant un lien entre le niveau d'étude et le niveau de littératie en santé et son impact sur les comportements de santé (Friis et al. 2016, Levy and Janke 2016, Svendsen et al. 2020). Ces éléments placent l'amélioration des connaissances des patients sur les SOS, en particulier via l'accès à l'information, comme un enjeu majeur pour renforcer l'accès à ces dispositifs (Regnier Denois et al. 2017).

Des outils existent déjà pour informer les patients sur les SOS, édités par la Ligue Contre le Cancer, les DSRC (Dispositif Spécifique Régional du Cancer) de chaque région, ou encore par les établissements prenant en charge les patients directement. En Occitanie, le DSRC Onco-Occitanie a, par exemple, élaboré des annuaires de l'offre en SOS proposés dans les établissements autorisés à prendre en charge les cancers, ainsi qu'en ville, par des acteurs associatifs (https://onco-occitanie.fr/annuaires/). Ces dispositifs n'ont néanmoins jamais fait l'objet d'une évaluation quant à leur identification et leur mobilisation par les patients, ni en termes d'impact sur le recours aux SOS.

Dans ce contexte, le projet AASSOAC vise à identifier les populations les plus éloignées de l'information sur les SOS, et de co-construire un plan d'action adapté. La première phase vise à :
Evaluer le niveau de connaissance des patients sur ce que sont les SOS, sur l'offre en SOS disponible à proximité, ainsi que leur connaissance des outils d'information existants. Nous étudions également le recours aux SOS et la façon dont les patients ont été orientés vers le SOS.

Etudier les facteurs liés aux patients associés à la connaissance sur les SOS et l'offre disponible, en particulier le profil de patients en termes de position dans le parcours de soin, mais aussi en termes de milieu social.

Evaluer les ressources mobilisées par les patients pour faire face à la maladie, et la place des SOS parmi celles-ci.

La seconde phase exploitera les résultats de la première étape, en particulier quant aux profils les plus à risque de méconnaissance, pour co-construire, avec les acteurs du terrain et les usagers, un plan d'actions pour améliorer la connaissance des patients sur les SOS et sur l'offre disponible et de proposer une stratégie d'implémentation régionale.

9B / 02

La prise en charge Kiné-Yoga-ETP

Kerstin FARAVEL, Cédric GUILLAUMON, Marta JARLIER, Muriel THOMASO, Pierre SENESSE, Maguy DEL-RIO, Laetitia MEIGNANT, William JACOT, Anne STOEBNER, Sylvain DEMONTOY, Estelle GUERDOUX

Institut du Cancer de Montpellier, Montpellier

A l'ICM nous avons mené l'étude de faisabilité **SKYPE**, Suivi en Kinésithérapie et Yoga- Projet Educatif, entre 2018-2019. L'intervention de Kiné-Yoga-ETP (éducation thérapeutique du patient) propose aux patientes des séances de yoga encadrées par une kinésithérapeute, ainsi que des séances en autonomie à domicile, afin de lutter contre les douleurs liées à l'hormonothérapie (HT) après un cancer du sein. En effet, 50% des patientes sous HT souffrent de douleurs, ce qui constitue un risque d'interruption de traitement. L'étude SKYPE a été financé par le Cancéropôle-Emergence et l'adhésion à 83% de la part des patientes à l'intervention a validé la faisabilité. Concernant les objectifs secondaires, 58% des patientes ont vu leur douleur diminuer de 2 points sur l'échelle visuelle analogique (EVA). Toutes les patientes ont amélioré leur souplesse en flexion en avant, avec un gain médian de 8 cm.

Ces résultats nous ont permis de monter l'étude **SKYPE 2**, une étude randomisée, multicentrique, financé par un PHRIP (2020). A ce jour, nous avons inclus 64 patientes sur les 108 attendues dans les six centres participants. Le protocole a été publié dans BMJ Open. Nous avons également créé des outils éducatifs à destination des patientes (livret, enregistrement audio et carnet de bord) ainsi qu'un guide d'animation pour les kinésithérapeutes, afin de garantir la reproductibilité de l'intervention.

Nous avons ensuite adapté l'intervention Kiné-Yoga-ETP au contexte très particulier de l'immobilisation prolongée (3-5 jours) nécessaire pour les patientes traitées par curiethérapie dans le cadre d'un cancer du col de l'utérus. Une étude a en effet montré que 40% des patientes traitées par curiethérapie présentent des symptômes de stress post-traumatique trois mois après le traitement L'étude **KYOCOL**, une étude randomisée, multicentrique, financé par un PHRIP (2022), propose une intervention expérimentale de Kiné-Yoga-ETP dans l'objectif de réduire le stress et l'inconfort physique liés à l'alitement. A ce jour, nous avons inclus 14 patientes sur les 80 attendues dans les trois centres participants. Le protocole de cette étude est en cours de rédaction pour publication.

Le projet d'établissement 2023-2027 de l'Institut du Cancer de Montpellier (ICM) identifie clairement une orientation stratégique pour développer la recherche paramédicale. Nous sommes convaincus que son développement sera bénéfique pour tous : avant tout les patients, mais également les soignants et l'établissement. Le Comité de Recherche en Soins de Support (CORESS) existe depuis 2017 à l'ICM. C'est un comité pluri-professionnel a récemment évolué pour devenir le CORESP, en intégrant la recherche paramédicale. L'objectifs de ce comité est d'examiner les projets à venir et d'aider les porteurs à améliorer leur projet avant de le soumettre à un appel à projet.

Nous avons poursuivi et renforcé la structuration de la recherche paramédicale en créant le Groupe de Recherche Paramédicale. Ce groupe est composé de professionnels paramédicaux de divers services (soins de support, radiothérapie, médecine, hôpital de jour, chirurgie etc.) ainsi qu'un patient partenaire. Les missions de ce groupe sont les suivantes :

- Communiquer, informer, rendre visible les projets existants
- Sensibiliser et former les paramédicaux à la recherche,
- Recueillir des idées de projets auprès des soignants sur le terrain,
- Accompagner les soignants pour faciliter l'émergence de projets (aide méthodologie, recherche bibliographique et rédaction de synopsis),
- Valoriser et présenter les résultats des projets, et de représenter la recherche paramédicale lors des congrès ou d'autres événements.

En conclusion, la structuration de la recherche paramédicale a pour objectif de donner plus de visibilité à cette activité, à la valoriser, et à permettre à un plus grand nombre de paramédicaux de développer leurs compétences et de participer, de près ou de loin, à des projets de recherche.

9B / 03

Prise en charge des séquelles cognitives du cancer et de ses traitements

Véronique GERAT-MULLER[1], Pedro-Alejandro RODRIGUEZ[2], Virginie POSTAL[3]

[1] Dr en Psychologie Clinique et Psychopathologie, DU Neurosciences, Directrice Recherche et Méthode Association onCOGITE
[2] Neuropsychologue, Doctorant en psychologie cognitive, Labpsy UR 4139, Université de Bordeaux.
[3] Pr en Psychologie et Neuropsychologie, Labpsy UR 4139, Université de Bordeaux

Contexte : Les avancées thérapeutiques en oncologie ont permis une amélioration significative du taux de survie des patients traités pour une pathologie cancéreuse. La prévalence totale du cancer - soit le nombre de personnes de 15 ans et plus vivantes et ayant eu un cancer au cours de leur vie - continue de croître et l'augmentation de la survie a permis la prise de conscience de symptômes secondaires et/ou séquelles à plus ou moins long terme nourrissant une préoccupation quant à la qualité de vie et la réhabilitation socio-professionnelle des personnes.

Les troubles cognitifs post-traitements oncologiques ou Cancer Related Cognitive Impairment (CRCI), aussi appelés chemobrain ou chemofog, longtemps sous-diagnostiqués, apparaissent pré, per ou post traitement contre le cancer de tropisme non cérébral. Ils regroupent les troubles mnésiques, d'apprentissage, de concentration, de raisonnement, de vitesse de traitement ainsi que les dysfonctionnements touchant les fonctions exécutives et les capacités visuo-spatiales des patients.

Développement d'une prise en charge : Dans les suites d'une étude exploratoire menée sur des patients en post-traitement, le programme onCOGITE propose depuis 2020 une prise en charge au niveau national. Il est axé sur la stimulation des fonctions fragilisées, l'apprentissage de nouveaux automatismes et de nouvelles stratégies, l'aménagement de l'environnement et l'éducation aux troubles, sur une durée de 4 à 6 mois.

La prise en charge est assurée par des neuropsychologue formés, garantissant une clinique d'expertise en regard d'activités aux consignes complexes.

Les patients accèdent, via la plateforme numérique, à leurs séances distancielles structurées par des supports d'animation digitalisés dont les activités multiniveaux pilotées par le professionnel, sont conçues pour un travail en groupe ouvert de 8 à 12 personnes.
L'accès en visio garantit l'assiduité et réduit les inégalités géographiques. La plateforme permet aux patients d'organiser leur parcours et leurs inscriptions aux séances hebdomadaires.

La web-application onCOGITIEL propose de plus aux patients ayant acquis une autonomie de réentraînement, des activités en ligne développées en intelligence adaptative, permettant une intensification du renforcement entre les séances hebdomadaires en groupe et un maintien des performances à l'issue du parcours.

Le programme onCOGITE spécifiquement créé avec et pour cette population se différencie des solutions actuellement proposées, conçues pour des patients cérébrolésés, ou souffrant pathologies neurodégénératives ou psychiatriques ; en effet, ces programmes non adaptés à une population en oncologie risquent de les confronter rapidement à un effet plafond.

Evaluation de la méthode : Les effets du programme onCOGITE sont évalués par une recherche interventionnelle, randomisée, menée sur un échantillon de 164 patientes suivis pour un primo cancer du sein. Cette étude multicentrique est coordonnée par l'Université de Bordeaux, l'Institut Bergonié en étant le promoteur. Les analyses sont en cours.

Par ailleurs, une étude d'impact quantitative et qualitative sur la prise en charge des CRCI et la reprise professionnelle est en cours de réalisation auprès d'une population de 2500 bénéficiaires.

Enfin, le programme onCOGIT'aja axé sur une méthode adaptée aux Adolescents-Jeunes Adultes permet d'ouvrir cet accompagnement à une population en devenir, nécessitant un accompagnement très spécifique pour la reprise des études ou l'entrée dans la vie professionnelle.

Conclusion : La stratégie décennale de lutte contre les cancers 2021-2030 fixe de réduire de deux tiers à un tiers la part des patients souffrant de séquelles 5 ans après un diagnostic. Les séquelles cognitives altèrent la qualité de vie et entravent la réhabilitation sociale et professionnelle. Créer et évaluer des programmes de remédiation cognitive adaptés est une nécessité à inscrire dans les soins de supports, quel que soit l'âge des patients.

Posters – Axis 1
Signaling, Microenvironment and Targeting

P101

Study of the reciprocal interactions between diffuse low-grade glioma IDH1 mutant cells and neurons

Kasandra AGUILAR CÁZAREZ[1,2], Hugues DUFFAU[2,3], Jean-Philippe HUGNOT[1,2]

[1] Université de Montpellier

[2] Institut de Génomique Fonctionnelle, Montpellier

[3] CHU de Montpellier

Diffuse gliomas are primary brain tumors originating from glial cells, known for their invasive growth and resistance to therapies, especially in cases with IDH1 gene mutations. These tumors primarily affect young patients.

The tumor microenvironment, particularly its interaction with neurons, plays a pivotal role in tumor progression. Neurons in the tumor environment have been shown to support glioblastoma cell growth. However, the influence of the brain environment on IDH1 mutant gliomas remains inadequately explored. Understanding the cellular and molecular mechanisms driving their invasiveness and growth is essential.

Most studies on glioma-neuron interactions focus on highly aggressive glioblastomas. Our objective is to study the reciprocal interactions between diffuse glioma cells and their surrounding tumor microenvironment, specifically with neurons. We hypothesize that IDH1 mutant glioma cells alter brain cell properties to promote tumor expansion.

To investigate this, we have co-cultured neurons derived from induced pluripotent stem cells (iPSCs) with patients' glioma cell lines. We aim to compare the behavior of different glioma lineages within this model, including astrocytomas versus oligodendrogliomas and low-grade versus high-grade gliomas, particularly regarding invasion, self-organization, integration in the neuronal network, and tumor heterogeneity. Additionally, we used tissue sections from patients to validate our in vitro results.

Our observations indicate that neurons and diffuse low-grade glioma cells form a complex and highly interactive network. We believe our work can provide valuable insights into glioma biology.

~~P102~~

P103

Role of Eicosanoid Receptor in Stroma - Cancer Communication

Tommy CHASTEL[1,2]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Equipe Turtoi : Micro-environnement tumoral et résistance aux traitements

The heterotypic cell communication networks within tumors support the survivability, plasticity, and therapy resistance of cancer cells. Understanding and targeting this inter-cellular communication is essential to eradicate cancer. Cancer cell interaction with immune and vascular cells is already well-established as targetable in cancer. However, the interaction between cancer-associated fibroblasts (CAFs) and cancer cells remains clinically underdeveloped. We lack both a deep understanding of how CAFs communicate with cancer cells as well as strategies to target those interactions effectively.

The present work explores CAF cell surface receptors involved in liver cancer progression. We focus on G-protein-coupled receptors (GPCRs), and more specifically on polyunsaturated fatty acids (PUFAs) derivatives, the eicosanoids. Using public single-cell RNA sequencing data and spatial transcriptomics, we discovered a set of eicosanoid GPCRs that are specifically overexpressed by CAFs. We further focused on eicosanoid receptor EICOR1 and its cognate ligand EICO1. We confirmed using RNAscope and spatial transcriptomics that that EICOR1 is only expressed in the in the tumor microenvironment (TME) in patient-derived hepatocellular carcinoma samples. We next used the chick embryo chorioallantoic membrane (CAM) assay to decipher the role of EICOR1 in cancer progression. Activating EICOR1 in fibroblasts co-engrafted with cancer cells reduced neoangiogenesis by 50% ($p < 0.0001$). In vitro analysis further showed that the anti-angiogenic effects are possibly mediated by the simultaneous deactivation of known pro-cancerous kinases such as AKT and JNK in the fibroblasts. Metabolomics analysis from both primary and secondary liver tumors from patients revealed that the level of the natural ligand EICO1 is lower in the tumoral area when compared to adjacent normal tissue. This indicates that deactivating EICOR1 is relevant for cancer progression and is further confirmed by the positive correlation of EICOR1 expression and patient survival in liver cancer (HR = 0.51 [CI 0.3-0.84], $p = 0.0079$). Finally, proteomics analysis suggest that the anti-angiogenic effects may be mediated by the secretion of anti-angiogenic proteins by fibroblasts, such as TSP1, TIMP1 and TIMP2.

Collectively, our findings provide an incentive to develop specific therapies that will curb both primary and secondary liver cancer progression by interfering with the communication between cancer cells and CAFs. We are currently developing new compounds that could enhance this targeting, focusing on the newly discovered EICO1-EICOR1 axis.

* The exact identity of EICO1-EICOR1 will be disclosed during the GSO meeting.

P104

Time series analysis of cellular interactions through gene regulatory network inference

Hugo CHENEL[1,2], Malvina MARKU[1], Julie BORDENAVE[1], Marcin DOMAGALA[1], Mary POUPOT[1], Loic YSEBAERT[3], Andrei ZINOVYEV[2], Véra PANCALDI[1]

[1] Centre de Recherches en Cancérologie de Toulouse

[2] EVOTEC France, Toulouse

[3] IUCT Oncopole, Toulouse

Gene regulatory networks (GRNs) are crucial to understand the complex regulatory mechanisms underlying cancer development and progression. They provide insights into molecular mechanisms driving cancer, such as identifying key driver genes, molecular pathways, and the identification of novel therapeutic targets. In the context of the tumor microenvironment (TME), the complex interactions between immune and cancer cells give rise to a cascade of regulatory processes at different levels, defining the cellular behavior and response to external stimuli and to treatments. This project aims to investigate how regulatory interactions between genes characterize cellular behavior. A detailed molecular description of cancer cell behavior and state transitions during interactions with immune cells is presented.

Using an in vitro model of Chronic Lymphocytic Leukemia (CLL), a blood cancer characterized by the aberrant proliferation of malignant B lymphocytes in the lymph nodes, we studied CLL cell interactions with immune cells. In the lymph node, CLL cells interact with monocytes, promoting their differentiation into macrophages that promote CLL cell survival, similar to tumor associated macrophages in solid cancers. We conducted experiments in three conditions (CLL patient blood, monocytes from healthy individuals with CLL cells, and B-CLL cells alone) and obtained a 14-day gene expression time-course bulk RNAseq of CLL cells.

GRNs were inferred for each condition to identify involved genes. Structural analysis and gene set enrichment analysis revealed significant differences in CLL cell responses to macrophages and immune cells, identifying novel transcription factors involved in CLL-immune cell crosstalk.

We applied various analytical tools to the experimental setups including ImpulseDE2, which analyzes continuous changes in gene expression across multiple time points, capturing subtle shifts and trends, and BIODICA, which uses Independent Component Analysis to decompose complex signals/profiles into independent components, representing underlying biological processes.

These analyses provide a comprehensive view of CLL cell interactions with immune cells in our in-vitro co-culture system. The integration of multi-omics data using multilayer networks could enhance our understanding of CLL by jointly considering several data types to understand the complex dynamics of cancer-immune cell interactions and identify novel therapeutic strategies. This approach highlights the power of integrating multiple analytical tools to enhance our understanding of cancer biology in the context of the tumor microenvironment.

P105

Telocyte dynamics in Squamous Cell Carcinoma

Julie CLACHET, Muriel CARIO, François MOISAN, Léa PECHTIMALDJIAN

BoRdeaux Institute of Oncology

The skin, being the largest organ in humans, is susceptible to various diseases, including cancer. Among these, skin cancer, encompassing carcinomas and melanomas, ranks as one of the most prevalent globally. Preceding the onset of squamous cell carcinoma (cSCC), pre-cancerous lesions may occur, often making accurate prognostication of their progression difficult.

The epidermis, primarily affected by irradiation, undergoes changes that extend into the dermis, where critical cellular components reside. Notably, telocytes (TC), a recently discovered cell type distinct from fibroblasts, undergo modifications concurrent with dermal structural alterations. As lesions evolve into cancer, a cascade of events unfolds, culminating in invasion into the dermis and remodeling of the extracellular matrix (ECM) through interactions between cancer cells, neighboring cells, and the ECM.

Literature has established the essential role of fibroblasts in cancer progression, while the role of telocytes remains unexplored. This study aims to identify telocytes as potential markers for the fate of pre-cancerous lesions and elucidate the communication networks among cancer cells, telocytes, and the ECM at various stages of skin cancer progression.

The first part of this PhD project will investigate telocyte behavior during carcinoma progression by identifying telocytes using immunohistochemistry (IHC) staining on cSCC samples at different stages. Concurrently, an in vitro study will focus on the behavior of TC. The mutual effects of telocytes and A431 cells (cSCC cell line) will be examined on proliferation and invasion assays in both 2D and 3D models, as part of a comprehensive characterization process of this particular cell type.

In conclusion, this work aims to highlight the role of telocytes in the progression of squamous cell carcinoma and provide new insights into this poorly understood and little-known cell type.

P106

Role of BIGH3 in Cancer-Associated Cachexia and Its Potential as a Major Tumor Target

Claire CRAMPES[1], Bilguun ERKHEM-OCHIR[2], Pascal POMIÈS[3], Marie-Alix POUL*[1], Takehiko YOKOBORI[2], Andrei TURTOI*[1,2]

[1] Tumor Microenvironment and Resistance to Treatment Lab, Institut de Recherche en Cancérologie de Montpellier, INSERM U1194

[2] Division of Gene Therapy Science, Gunma University Initiative for Advanced Research (GIAR), Japan

[3] PhyMedExp (Physiologie et médecine expérimentale du cœur et des muscles), University of Montpellier

A least 20% of cancer deaths are due to cancer-associated cachexia (CAC) [1], a complex and poorly understood metabolic syndrome characterized by muscle and adipose tissue loss. Occurring in more than 50% of advanced cancers, cachexia is a major public health issue leading to poor quality of life, bad treatment tolerance, and survival. Unfortunately, no treatment is available to curb this multifactorial syndrome, reflecting the necessity of understanding the biological mechanisms of CAC.

Macrophages are known to play a crucial role in cachexia. They induce tissue wasting in patients suffering from CAC by producing inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are key effectors in cachexia. On the other hand, the Transforming Growth Factor β (TGF-β) signaling pathway is implicated in cachexia by promoting fibrosis and muscle tissue degradation. Macrophages stimulated by TGF-β produce TGF-β induced Gene Human 3 (BIGH3 or TGFBI), an extracellular matrix protein that promotes cell adhesion, migration, and metastasis. [2]

Our research team studied the role of BIGH3 in cancer and, particularly, showed its overexpression in metastatic colorectal cancer (CRC). [3] [4] Thereafter, we obtained a panel of anti-BIGH3 antibody clones which were injected into the colon 26 CRC mouse model. Interestingly, targeting BIGH3 with antibodies significantly reduced cachectic symptoms such as muscle weakness and body mass loss. These in vivo unpublished data thus indicate that BIGH3 may be a central factor in CAC. In vitro, we observed that targeting BIGH3 reduces the production of IL-6 and TNF-α by macrophages, whereas the recombinant BIGH3 increases the production of both IL-6 and TNF-α. These preliminary data show that BIGH3 might be involved in the production of key inflammatory cytokines involved in cachexia through macrophages.
Our project aims to clarify the contribution of BIGH3 in macrophage-mediated muscle wasting and uncover the related downstream signaling during cachexia. More globally, we have the ambition to explore the possibility of positioning BIGH3 as a drug target for cachexia treatment.

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P107

Study of the bidirectionnal interaction between gut microbiome and gliobalstoma through multi-omics data integration methods

Gauthier DELROT, Sarah LAVIELLE, Thomas DAUBON, Océane MARTIN, Macha NIKOLSKI

Institut de Biochimie et Génétique Cellulaires, Bordeaux

The communication between the central nervous system (CNS), the enteric nervous system, and the gut microbiome via the microbiome-gut-brain axis is well established and has been implicated in several neurodegenerative diseases, including Parkinson's and Alzheimer's diseases. This study aims to investigate the connection between the **gut microbiome** and **glioblastoma** (GB) development through a bioinformatics analysis of multi-omics data. Glioblastoma, the most common primary brain tumor in adults, has a poor prognosis, with a survival rate of less than 5% five years post-diagnosis.

To explore this connection, the experimental design was structured as follows: a subset of mice received dextran sulfate sodium (DSS), an agent that induces **gut inflammation** , to assess the effect of gut inflammation on the microbiome and glioblastoma development. Then, a subset of DSS and non-DSS mice were implanted with **murine glioblastoma stem cells** (mGB2). Finally, a subset of the implanted groups was treated with the **Stupp protocol** , the standard treatment for glioblastoma, composed of tumor resection followed by chemo- and radiotherapies. Fecal samples were collected at each time point, enabling precise characterization of gut microbiome profiles under different conditions, and brains and intestines were collected at the final time point.

This experimental setup generated various datasets from different modalities. These datasets were analyzed separately and then integrated using **multi-omics data integration** methods to gain a deeper understanding of the communication between these tissues.

The first aim of this project is to investigate the connection between the gut microbiome and glioblastoma development; then a brain **bulk RNA-Seq** dataset and a **16S metabarcoding** gut microbiome dataset were produced. Initial **single-omics** analyses confirmed that gut inflammation led to a **decrease** of gut microbiome's **alpha diversity** , and revealed **distinct gut microbiome profiles** in the GB implanted groups.

To identify gut bacteria capable of modulating brain transcriptomics, **statistical correlation** methods were employed. Given the distance between the brain and gut, the focus then shifted to understanding how these bacteria might communicate with the CNS, particularly through **metabolism** . As the 16S metabarcoding method does not provide information on bacterial gene content, **metabolic pathway inference** methods were used. These inferred pathways were subsequently subjected to differential abundance analysis to investigate how variations in gut microbiome composition could impact metabolism.

The same analytic workflow will be used on intestine RNA-Seq datasets to understand 1) how changes in microbiome profiles can affect intestine transcriptomics and 2) are these transcriptomics changes related to brain transcriptomics modulations ?

This project aims to better understand the gut-brain axis's role in glioblastoma development and to find potential treatment improvements, notably through the modulation of the gut microbiota.

P108

Transfer of functional FOLR2 from Nurse-like cells to CLL cells contributes to their activation and proliferation

Marcin DOMAGALA[1], Bastien GERBY[1], Pauline GRAVELLE[1,2], Chloe BAZILE[1], Nathalie VAN ACKER[2], Camille LAURENT[1,2], Véra PANCALDI[1], Loic YSEBAERT[1,2], Mary POUPOT[1]

[1] Centre de Recherches en Cancérologie de Toulouse

[2] IUCT Oncopole, Toulouse

Chronic lymphocytic leukemia (CLL) is one of the most common adult blood cancer in Western world, and is characterized by a clonal accumulation of malignant $CD5^+$, mature-like B cells in lymphoid tissues and periphery. These CLL cells show an almost complete dependence on the tumor microenvironment (TME), required for their survival and proliferation. When cultured in vitro CLL cells become quiescent and prone to spontaneous apoptosis. CLL TME, located in lymphoid tissues, especially bone marrow and lymph nodes (LNs) is among others, composed of: T cells, stromal cells, endothelial cells and Nurse-like cells (NLCs) - a subtype of M2-like tumor-associated macrophages (TAMs). NLCs play a critical role in cancer cell homing, survival, proliferation and chemoresistance. They can support cancer cells by release of soluble factor and a direct contact. While the NLCs secretome and its effect on cancer cells is well established, the exact nature of direct interactions between NLCs and CLL cells requires further insight.

In this study, we discovered that pro-tumoral NLCs express a high level of folate receptor beta (FOLR2), a myeloid cell-specific protein that allows an efficient uptake of folates (vit. B9). Moreover, we demonstrated that CLL cells could acquire a functional FOLR2 from NLCs by trogocytosis - a peculiar type of direct cell-cell interaction. Thus, we aimed to further characterize the trogocytosis between NLCs and CLL cells, and establish its potential advantage for activation and proliferation of cancer cells.

Phenotyping of CLL cells following long-term PBMC cultures containing NLCs, revealed a presence of $FOLR2^+$ cancer cells. Further tests confirmed that NLCs are the source of FOLR2 detected on cancer cells, and that CLL cells employ trogocytosis to acquire this protein. Initial characterization of trogocytic $FOLR2^+$ CLL cells showed their increased potential for the uptake of folic acid. Moreover, experiments with CD40L+IL-15 priming showed a significant enrichment of trogocytic FOLR2+ CLL cells in the fraction of activated and proliferating cancer cells. Finally, using mIF staining of the LNs from CLL patients, we confirmed the presence of trogocytic $FOLR2^+$ CLL cells in vivo, suggesting a clinical relevance of the in vitro results.

Presented work demonstrates a novel type of protumoral direct cell-cell interaction between NLCs and CLL cells, relying on the transfer of functional FOLR2 from NLCs to cancer cells by trogocytosis. As a result, the trogocytic $FOLR2^+$ CLL shows increased capacity for the uptake of folic acid, and upon activation with CD40L+IL-15, a significant enrichment in the fraction of proliferating cells in vitro. These results shed a light on the underappreciated role of trogocytosis in the increasing adaptability of malignant cells upon a contact with TME. Further characterization of the cellular content exchanged between NLCs and CLL cells during trogocytosis represent a next step in deciphering this interaction, identifying its role in pathogenesis of CLL and potentially translating these findings to other cancers.

P109

High-resolution imaging of brain tumor invasion

Emmanuelle GEORGET[1], Yulia DEMBITSKAYA[2], Jérémie TEILLON[3], Thomas DAUBON[4], Valentin NÄGERL[2], Andreas BIKFALVI[1]

[1] BoRdeaux Institute of Oncology

[2] Institut Interdisciplinaire de Neurosciences, Bordeaux

[3] Bordeaux Neurocampus

[4] Institut de Biochimie et Génétique Cellulaires, Bordeaux

Glioblastoma (GBM) is the most aggressive adult brain tumor, characterized by its highly invasive nature and devastating impact on patient quality of life. The mechanisms that underlie GBM's ability to infiltrate healthy brain tissue (parenchyma) along diverse trajectories, including blood vessels, white matter tracts, and the leptomeningeal space are still poorly understood. Recent advances in high-resolution tissue imaging techniques offer new possibilities to dissect these invasion mechanisms.

We have developed an experimental pipeline to investigate the interactions between GBM cells and their brain tissue environment, focusing on the migratory pathways of invading tumor cells. To this end, we used two distinct glioblastoma animal models: a syngenic model using adherent mouse cell line (CT2A) injected into C57BL6/N mice, and a xenogenic model using human GBM cells (BTSC73) injected into immuno-deficient (RAGɣ) mice. In both cases, the tumor cells were fluorescently labeled with YFP.

We used 2-photon shadow imaging (TUSHI) in somatosensory and motor cortex in vivo and in acute brain slices to track the invading tumor cells and to visualize the anatomical tissue context at different stages of tumor progression. Notably, perivascular spaces of capillaries were larger in RAGɣ mice injected with GBM cells than in control mice, while capillary diameters did not differ.

To track tumor progression on a macroscale level we implemented a brain clearing protocol (Adipoclear+) and used light-sheet microscopy to visualize proliferation and migration of GBM cells in the entire brain.

Overall, this project leverages cutting-edge microscopy techniques to elucidate the complex mechanisms of GBM invasion, paving the way for the development of novel therapeutic strategies to combat brain cancer.

P110

A metabolic crosstalk occurs between human bone marrow adipocytes and prostate cancer cells

Marine HERNANDEZ[1], Mohammed MOUTAHIR[1], Nicolas REINA[2,3], Catherine MULLER[1], Camille ATTANE[1]

[1] Institut de Pharmacologie et de Biologie Structurale, Toulouse

[2] Département de Chirurgie Orthopédique et Traumatologique, Hôpital Pierre-Paul Riquet, CHU de Toulouse

[3] : Laboratoire AMIS, UMR 5288 CNRS, Université Toulouse III-Paul Sabatier

In localized prostate cancer (PCa), we have demonstrated that periprostatic adipocytes increase tumor progression by providing cancer cells with fatty acids (FFAs) released after the activation of lipolysis, involving the hydrolysis of triglycerides (TG) [1]. In advanced PCa, the majority of metastases are found within the bone, where tumor cells can interact with bone marrow adipocytes (BMAds). However, whether a metabolic crosstalk between primary BMAds and PCa exists and favors tumor progression remains to be determined. Thanks to a collaboration with orthopedic surgeons, we obtain human bone marrow adipose tissue (BMAT) during hip replacement surgery. There are two types of BM-Ads: those contained in the red BMAT (rBMAds) and those contained in the yellow BMAT (yBMAds) [2], which have been characterized by my team [3]. Since PCa metastatic sites are frequently found in proximity to rBMAds, we established a 3D culture of these adipocytes in a fibrin matrix to preserve their viability for up to 5 days and cultured them with PCa cells.

Under coculture conditions, PCa cells exhibited an increase in neutral lipid content, primarily composed of TG. Using rBMAds loaded with fluorescent FFA, we directly demonstrated that FAs released by rBMAds and taken up by cancer cells and re-esterified into TG. These data provide the first evidence of a metabolic crosstalk between primary human rBMAds and PCa cells. However, like yBMAds [3], we found that rBM-Ads are devoid of lipolysis, one of the main function in adipocytes. This lack of lipolysis is due to a profound decrease in the expression of the last two enzymes of the lipolytic pathway. Using non-specific lipase inhibitors, we demonstrated a lipase-dependent lipid release, suggesting a novel FFA release mechanism requiring further investigation.

Cocultivated PCa cells exhibit an increase in migration abilities as compared to non-cocultivated cells. These properties are key to the progressive colonization of bone sites leading to widespread metastases. Exogenous exposure of PCa cells to FFAs reproduce these effects and it is abolished by using delipidated conditioned medium of rBM-Ads. RNAseq and gene ontology analyses of cocultivated and non-cocultivated cells reveal significant differences in migration pathways, that is consistent with functional experiments. Among the regulated genes, a target gene of PPARγ transcription factor, known to be activated by FFAs, is highly upregulated and its expression is key to the acquisition of migratory capacities upon coculture.

In conclusion, the metabolic crosstalk between rBMAds and PCa cells could contribute to the propagation of bone metastasis. Deciphering this crosstalk, could lead to pharmacological targets for the treatment of bone metastases, for which therapeutic options remain very limited.

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P111

Is ARID3A a key player in malignant B-cell hematologic disorders ?

Pierre HIRT[1], Morgane THOMAS[2], Jérôme MOREAUX[2], Eric PINAUD[1]

[1] Contrôle de la Réponse Immune B et des Lympho-proliférations, Limoges

[2] Epigenome modifications and genomic instability in normal and malignant B cells

ARID3A is a key transcription factor (TF) in embryonic development and early lymphopoiesis. While its role is well-established during these early phases, its involvement in the later stages of B cell differentiation remains largely unexplored, mainly due to the embryonic lethality associated with its deletion, which has limited studies on its role in the late phases of lymphoid development.

However, our data in mice, consistent with the literature, show a significant increase in ARID3A expression in the B cell lineage, starting from B cell activation, and this expression persists through the late stages of differentiation into plasma cells. This expression kinetics suggests a potential role for ARID3A in the late stages of B cell lineage differentiation. Moreover, ARID3A is among the most differentially expressed genes in numerous solid and diffuse cancers, particularly in activated B cell-like diffuse large B-cell lymphomas (DLBCL-ABC) and multiple myelomas (MM). These observations suggest a possible involvement of ARID3A in the oncogenic mechanisms of hematologic cancers.

Given these findings, our objective is to evaluate the role of ARID3A in activated B cells and its contribution to tumor survival, with a particular focus on DLBCL-ABC. Our data, obtained from primary murine and human cultures, show that ARID3A is crucial for B cells to establish a complete differentiation program and mount an effective humoral response. Transcriptomic analysis of patient cohorts with DLBCL-ABC indicates that poor prognosis correlates with high ARID3A gene expression. This correlation aligns with literature data suggesting that the sustained expression of ARID3A is required for the survival of certain DLBCL-ABC cell lines. These results lead us to consider ARID3A not only as an essential protein for the terminal maturation program of the B cell lineage but also as a potential therapeutic target in certain types of hematologic malignancies.

P112

Impact of 5-Fluorouracil on cell plasticity

Laura JENTSCHEL[1], Mounira CHALABI[2], Olivia VILLERONCE[1], Jihane VITRE[1], Nicole DALLA-VENEZIA[2], Jean-Jacques DIAZ[2], Julie PANNEQUIN[1]

[1] Institut de Génomique Fonctionnelle, Montpellier

[2] Centre de Recherche de Cancérologie de Lyon

The 5-Fluorouracil (5-FU), an agent used in all combinations of chemotherapy for colorectal cancer (CRC) as well as in many other cancers, is often associated with resistance and consequently tumor recurrence. Indeed, nearly half of CRC patients experience recurrence within 5 years of their treatment.

Surprisingly, for one of the oldest and most widely used chemotherapies, some aspects of its mode of action remain to be deciphered in detail. Over the past few years, our team in collaboration with Dr. Jean-Jacques Diaz's team at the Lyon Cancer Research Center has revealed the ability of 5-FU to integrate into ribosomal RNA, leading to drastically modified translation. Indeed, ribosomes continue to produce proteins, but only those potentially crucial for cell survival.

We have demonstrated that this modified translation induces cellular reprogramming towards a pluripotent phenotype allowing cells to survive. This study is a proof of concept and only the tip of the iceberg, as single-cell RNA sequencing before and after treatments has revealed the presence of about ten subpopulations.

Our study sheds light on the response and adaptation of cells to 5-FU. These findings highlight the complex nature of cellular responses to 5-FU and could contribute to a deeper understanding of tumor plasticity and treatment resistance.

Introduction and objectives: The 5-Fluorouracil (5-FU), an agent used in all combinations of chemotherapy for colorectal cancer (CRC) as well as in many other cancers, is often associated with resistance and consequently tumor recurrence. Indeed, nearly half of CRC patients experience recurrence within 5 years of their treatment.

Surprisingly, for one of the oldest and most widely used chemotherapies, some aspects of its mode of action remain to be deciphered in detail. Over the past few years, our team in collaboration with Dr. Jean-Jacques Diaz's team at the Lyon Cancer Research Center has revealed the ability of 5-FU to integrate into ribosomal RNA, leading to drastically modified translation.

The objective of this study was to determine whether this modified translation lead to cancer cell plasticity and thus to drug resistance or not.

Methods: Cells were transduced with the lentiviral pGreenZeo Reporter Vector in which NANOG gene promoter controlled the expression of GFP. A readout of cell plasticity was achieved by exposing transduced cells to 5-FU and counting cells highly expressing GFP: GFPhigh by FACS.

Results: We have demonstrated that this modified translation induces cellular reprogramming towards a pluripotent phenotype allowing cells to survive.

Conclusion / Discussion: This study is a proof of concept and only the tip of the iceberg, as single-cell RNA sequencing before and after treatments has revealed the presence of about ten subpopulations.

P113

β-Catenin Phosphorylation by AKT at Serine 552: A Novel Mechanism for CDT Modulation

Ruxue JIA[1], Mariana SARAIVA[1], Lamia AZZI-MARTIN[1,2], Elodie SIFRE[1], Christine VARON[1,2], Pierre DUBUS[1,2,3], Armelle MENARD[1]

[1] University of Bordeaux, INSERM UMR1312, BoRdeaux Institute of oncology BRIC
[2] Univ. Bordeaux, UFR des Sciences Médicales
[3] CHU de Bordeaux, Institut de Pathologie et de Biologie du Cancer

Some strains of bacteria can produce toxins, such as colibactin and cytolethal distending toxin (CDT). These toxins induce DNA damage and inflammation, well-established risk factors for cancer, particularly colorectal cancer. The Wnt/β-catenin signaling pathway plays a crucial role in cancer development and progression, driving tumor initiation, growth, and metastasis.

In the present study, we examined the impact of the cytolethal distending toxin active subunit, CdtB, on the Wnt/β-catenin pathway in human intestinal and hepatic epithelial cell lines.

CdtB exposure resulted in the loss of adherens cell junctions (β-catenin and E-cadherin). Additionally, CdtB exposure increased the phosphorylation of β-catenin at serine 552. This phosphorylation correlated with β-catenin's nuclear localization and its enhanced transcriptional activity, as confirmed by microarray analysis, RT-qPCR analyses and TOP/FOP-Flash luciferase reporter assay.

Metformin, a commonly prescribed oral medication for type 2 diabetes, inhibits the phosphorylation of β-catenin at Serine 552 through the AMPK/PI3K/AKT pathway. This compound mitigated the CdtB-induced loss of β-catenin at cell-cell junctions, decreased β-catenin phosphorylation at Ser552, and reduced its nuclear accumulation and transcriptional activity. These findings were further supported by similar observations with MK2206, a highly selective and allosteric direct inhibitor of AKT.

Overall, these findings indicate that CdtB activates the AKT signaling pathway, leading to the phosphorylation of β-catenin at Ser552. This phosphorylation facilitates β-catenin's dissociation from cell-cell junctions and subsequent nuclear translocation, preventing cytoplasmic degradation, and ultimately resulting in increased β-catenin transcriptional activity.

P114

Investigating the role of Gut Microbiota in Glioblastoma development

Sarah LAVIELLE, Manon LEMAÎTRE, Bomont DORIANE, Thomas DAUBON, Océane MARTIN

Institut de Biochimie et Génétique Cellulaires, Bordeaux

Glioblastoma is the most common and aggressive **brain tumor** in adults, characterized by a poor prognosis, with a median survival of approximately 14 to 15 months and frequent therapeutic failure [1]. To improve patient survival and quality of life, it is essential to identify the factors contributing to the initiation, progression, and therapeutic resistance of this cancer. In this study, we focus on the gut-brain axis [2], specifically by exploring the potential role of the **bacterial microbiota**, in glioblastoma progression. The bacterial microbiota refers to the diverse community of bacteria that colonizes the gut [3], which has been shown to play a crucial role in several brain pathologies, including Parkinson's disease and Alzheimer's disease [4]. More recently, emerging studies have suggested that the bacterial microbiota may influence glioblastoma, but the underlying mechanisms remain unclear [5].

This project has two main objectives:

1 Evaluate the effect of bacterial microbiota depletion on glioblastoma progression.

2 Investigate the mechanisms by which gut bacteria influence glioblastoma, by studying tumor immune system modulation *in vivo* and the impact of gut-derived metabolites on glioblastoma stem cells *in vitro*.

To achieve this, **C57BL/6 mice** were implanted or not with murine **glioblastoma stem cells** (mGB2) and treated or not with **antibiotics** to deplete their gut microbiota.

Tumor growth was monitored by bioluminescence imaging. **Macrophages** and **T-cells** infiltration into the tumor was analyzed using RNAscope multiplex staining. Finally, the effect of two metabolites (**serotonin** and **butyrate**), which are either produced or regulated by the gut microbiota, was tested *in vitro* on murine (mGB2) and patient derived (P3) glioblastoma stem cells to assess their impact on cellular **invasion** and **proliferation**.

The results showed reduced tumor progression in microbiota-depleted mice. Additionally, antibiotic-treated mice exhibited a significant decrease of immune cell infiltration at the tumor site. *In vitro*, glioblastoma cells treated with serotonin proliferated more but exhibited reduced invasion. In contrast, butyrate significantly decreased proliferation but increased invasion.

These findings suggest a role of bacterial microbiota on glioblastoma progression. Bacteria may stimulate the recruitment of immune cells into the tumor, benefiting its growth. The tumor could also exploit certain bacterial metabolites to promote its development.

This project aims to contribute to a better understanding of the gut-brain axis in glioblastoma and may help identify novel therapeutic strategies targeting bacterial microbiota to improve treatment outcomes for patients with this aggressive cancer patients.

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P115

Slit/Robo signaling in glioblastoma invasion

Teo LEBOUCQ, Thomas MATHIVET, Andreas BIKFALVI, Laura CHAILLOT, Wilfried SOULEYREAU

BoRdeaux Institute of Oncology

Glioblastoma (GBM) is the most common malignant brain tumor worldwide. Blood vessel development (angiogenesis) drives GBM progression. Blocking a single angiogenic growth factor VEGF slows GBM progression in patients, demonstrating that anti-angiogenic therapy is a viable option to inhibit tumor growth. However, tumors evade inhibition suggesting that other factors besides VEGF must drive tumor vascularization. In addition, tumor cell infiltration contributes to tumor recurrence.

We have identified the guidance factor Slit2 as a novel angiogenic factor in mice. Moreover, we lately demonstrated, in glioma context, that Slit2 promotes myeloid cell recruitment in the tumor microenvironment, which in turn abnormalizes blood vessels morphology and function, supporting tumor progression.

Lately, we evidenced that tumor cells themselves express Robo receptors at the leading edge of the tumor invading front. We propose that Slit2 may also affect, directly or indirectly, glioma cells infiltration.

Our study shows the chemoattractant effect of Slit2, via Robo receptors, on patient derived tumor cells in vitro and in vivo. In vitro, Slit2 promotes orientated migration and tumor spheroid invasion via Src kinase signaling, effects which is lost in tumor cells depleted for their expression of Robo receptors using an anti-sens strategy. In vivo, the depletion of Robo receptors induces an impressive tumor growth delay of patient derived tumor cell spheroid implanted orthotopically in Raggamma mice, which might be explained by direct invasion miss-guidance, but also an alteration of the full invadosome mechanism, as suggested by a downregulation of MMP signaling in Robo depleted tumor cells which are required for matrix degradation prior invasion.

This study provides the first comprehensive examination of Slit-Robo-signaling in GB cells, with the goal to develop innovative therapy strategies to prevent GB invasion.

P116

Identification of bispecific aptamers targeting gastric cancer cells

Gorann LEPIED[1,2], Mengyuan CAO[1], Anissa ZAAFOUR[2], Pierre DUBUS[2,3], Christine VARON[2], Jeanne LEBLOND CHAIN[1]

[1] Régulations Naturelles et Artificielles, Bordeaux

[2] BoRdeaux Institute of Oncology

[3] CHU Bordeaux, Tumor Biology

In 2020, gastric cancer diagnoses reached a significant 1.1 million count around the world, ranking it as the fifth most recurrent cancer worldwide. 90% of these cancers are gastric adenocarcinomas, a specific tumoral subtype affecting the stomach epithelial tissues. Numerous treatments have been explored and now range from conventional chemotherapy to personalized targeted therapy or immunotherapy. Despite these consistent improvements, multiple treatment resistance patterns have been identified and appear to emerge from gastric cancer stem cells (GCSCs). C. Varon's team has characterized several GCSC's biomarkers such as EpCAM (CD326) or CD44(v9). These receptors are overexpressed on gastric cancer cells which reinforces their interest for accurate targeting.

In this project, we aim at developing dual-targeted therapies against these specific GCSCs biomarkers to improve GCSC diagnostic and chemotherapy targeting.

Aptamers are synthetic DNA or RNA sequences with high affinity and specificity for their target. As compared to antibodies, they display a better thermal stability, are easier and safer to synthesize, especially for bivalent aptamers as compared to fastidious synthesis of bivalent antibodies. Here, we developed bi-specific aptamer assemblies to improve the selective recognition of GCSCs.

In a first step, CD44v9 binding aptamer (Apt4) was hybridized with an EpCAM binding aptamer (SYL3C) through hybridization of a 15-nucleotides linker and various spacer designs, which were added during the synthesis. The assembly formation was assessed by native PAGE.

Then, the targeting ability of the single aptamers was evaluated on 4 gastric cancer cell lines - AGS, NCI-N87, MKN74 and MKN45 - by flow cytometry and compared to conventional antibodies for both CD44 and EpCAM receptors, in order to select the best model for EpCAM+/CD44(v9)+ GCSCs.

The binding curves of both EpCAM and CD44(v9) single aptamers were established by flow cytometry and showed affinity values close to literature reports. Spacer and linker addition during the synthesis did not show significant loss in aptamer/target interaction.

Finally, the single aptamers were compared with the various designs of SYL3C-Apt4 assemblies in flow cytometry for their targeting capacity of EpCAM+/CD44(v9)+ GCSCs.

The next steps of this work will focus on the specificity of such assemblies, the diagnosis potential of these bispecific aptamers for GCSCs and the conjugation of chemotherapeutics for targeted drug delivery.

P117

Cancer stemness induction by immunosuppressive cells in NSCLC

Mathilde MADÉRY

IMMUNOLOGY from CONCEPT and EXPERIMENTS to TRANSLATION, Bordeaux

Regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) are immunosuppressive cells induced by many cancers, which participate to the mechanisms of cancer escape from immune recognition and elimination. Beyond their ability to inhibit antitumor-immunity, these cells can exert multiple tumorpromoting functions including the promotion of cancer cell survival, invasion and metastasis. They therefore represent major obstacles for efficient cancer therapies. One pro-tumoral property of suppressive myeloid cells that has emerged recently is their ability to induce cancer stemness. Whether Treg may also be endowed with similar potential however remains to be determined. In the current study, we demonstrated that both MDSC and Tregs are capable of inducing cancer cells exhibiting cancer-stem cell-like properties.

We further identified the underlying mechanism, which requires a direct cell to cell. Our data also indicate that blockade of the TGFβ pathway significantly impaired the capability of Treg, but not of MDSC to promote cancer stemness suggesting different mode of action of these two subpopulations.

P118

Deciphering the oncogenic properties of Fascin-1 in Hepatoblastoma

Grégoire MANAUD, Lydia DIF, Violaine MOREAU

BoRdeaux Institute of Oncology

Hepatoblastoma (HB) constitutes the most common form of pediatric liver cancer, accounting for 1% of all malignancies in children. The standard of care for HB is a combination of chemotherapy and surgical resection of the liver segments affected by the tumor. Despite good efforts leading to an 80% survival at 5 years, side effects are often observed in children and negatively impacting their quality of life as well as their long-term outcomes. A distinctive genetic hallmark of HB is the high rate of CTNNB1 mutation found in 89% of cases, leading to an aberrant activation of the Wnt/β-Catenin pathway, and make it attractive as a targeted therapy for HB. However, giving the high risks of side effects, we aim to identify new β-Catenin dependent targets. In this aim, we propose to use Fascin-1 encoded by the FSCN1 gene, found to be a transcriptional target of β-Catenin and upregulated in HB. Fascin-1 an actin-bundling protein mainly localized in filopodia and thus promoting cell migration. As such, Fascin-1 is expressed in progenitors but remains absent in most of mature differentiated cells. Interestingly, we found that Fascin-1 expression was upregulated in, not all HB patients samples, but in a subset of HB with a poor prognosis characterized by the presence of undifferentiated and highly proliferative cell clusters. We demonstrated that indeed, Fascin-1 expression is correlated with hepatocyte differentiation status. To explore the underlying mechanisms, we have built the hypothesis that the cellular localization of Fascin is responsible for the alteration of hepatocyte differentiation. We use the β-Catenin-mutated HB cell lines HepG2 and Huh6 and we observed that the phospho-mimetic Fascin mutant S39E increase YAP expression and we propose that it stimulates the gene expression related to hepatocyte undifferentiated status in vitro. Thus, our results suggest a key role of Fascin-1 in HB progression and that Fascin-1 may represent a new therapeutic target in HB.

P119

G-CSF in the treatment of breast cancers: friend or foe ?

Alexandra MOISAND

IMMUNOLOGY from CONCEPT and EXPERIMENTS to TRANSLATION, Bordeaux

Many chemotherapeutic agents are typically associated with febrile neutropenia as a result of neutrophil depletion. To prevent the risk of infection associated with neutropenia, patients receiving chemotherapy are often concomitantly treated with G-CSF, a recognized hematopoietic stimulant capable of replenishing the pool of immune cells. However, apart from its beneficial role, few studies have suggested that G-CSF may also exert unexpected effects on antitumor immunity by promoting immunosuppressive myeloid cells (MDSC). The current study aims at exploring the impact of G-CSF on myeloid cells in a murine breast cancer model over the course of tumor development. We present results suggesting that G-CSF promotes the expansion of granulocytic but not monocytic subpopulations of MDSC in the spleen, lungs, and bone marrow of tumor-bearing mice. The kinetic of accumulation of MDSC in the pre- then post- metastatic lungs is not modified by G-CSF. Functional attributes of MDSC such as their suppressive activity and their ability to promote the emergence of cancer cells exhibiting stem-like features were also evaluated, but no significant role of G-CSF in their modulation was identified.

P120

Cells derived from primary cutaneous diffuse large B cell lymphoma-leg type polarize macrophages towards an immunosuppressive phenotype which in turn induce tumor cell survival.

Rémi PEANNE[1], Jean GALTIER[1,2], Valérie LE MORVAN[1], Thibaut BLONDY[1], Maylis MELANE[1], Aurore BIDON[1], Amandine ROUSSEL[1], Martina CARLOTTI[1], Sandrine POGLIO[1], Jean-Philippe MERLIO[1,3], Audrey GROS[1,3], Anne PHAM-LEDARD[1,4], Marie BEYLOT-BARRY[1,4], Laurence BRESSON-BEPOLDIN[1,4]

[1] BRIC (BoRdeaux Institute of onCology), UMR1312, INSERM, Univ. Bordeaux, team 5

[2] Hematology and cell therapy department, CHU Bordeaux

[3] Tumor Bank and Tumor Biology Laboratory, CHU Bordeaux

[4] Dermatology Department, CHU Bordeaux

Diffuse large-cell B lymphomas are due to the proliferation of large B lymphocytes. They most often develop in the lymph nodes, but also in other organs such as the skin, corresponding to "cutaneous large B-cell lymphoma, leg type" (BL-LT). BL-LT is a rare and aggressive disease. The patients are currently treated with a combination of immunotherapy and polychemotherapy, but 50% are refractory or relapse. Although they grow within the skin that offers a very different microenvironment than for DLBCL developing in the lymph node niche, no specific medical management for BL-LT exists. Our team has shown a macrophagic infiltrate in BL-LT tumors microenvironment suggesting the crucial role of macrophage-tumor lymphocyte dialog in this ecosystem. Until recently, the lack of representative BL-LT model prevented functional studies to elucidate its physiopathology. Thanks to the first BL-LT models developed by our team, consisting both in a cell line and patient-derived xenografts in mice, we obtained data revealing that BL-LT secreted cytokines polarizing monocytes towards a M2-like phenotype. Using proteome profiler technology, we identified IL-10 as cytokine responsible for polarization of macrophages. The role of IL-10 in macrophage polarization has been confirmed by functional analyses using neutralizing anti-IL-10 antibody. Finally, we revealed that in turn, macrophages promoted the BL-LT cell proliferation and survival. In conclusion, our study highlights the crucial role of BL-LT-macrophage dialog in the physiopathology of this cancer and suggests that the targeting of this dialog could provide new therapeutic strategies suitable for BL-LT patients.

P121

Study of myeloid tumor microenvironment in cutaneous T-cell lymphomas

Amandine ROUSSEL[1], Thibaut BLONDY[1], Martina PROCHAZKOVA-CARLOTTI[1], Laurence BRESSON-BEPOLDIN[1], Rémi PEANNE[1], Jean-Philippe MERLIO[1,2], Marie BEYLOT-BARRY[1,3], Anne PHAM-LEDARD[1,3], Sandrine POGLIO[1]

[1] BRIC (BoRdeaux Institute of onCology), UMR1312, INSERM, Univ. Bordeaux

[2] Tumor Bank and Tumor Biology Laboratory, Bordeaux University Hospital, Pessac

[3] Dermatology Department, Bordeaux University Hospital

Cutaneous T-cell lymphomas (CTCL) correspond to an abnormal accumulation of T-cells primarily in the skin and represent 70% of cutaneous lymphomas composed of entities with variable prognosis. Some are indolent for several years, others are aggressive either with development of tumors in the skin, or with the expansion of leukemic T-cells in the blood, this last form corresponding to Sézary syndrome (Werner Kempf, Hematol Oncol, 2021 (PMID: 34105822)). With the exception of hematopoietic stem cell transplantation (only for patients under 65 who have achieved complete remission of their disease), there are no effective or sustainable therapies for advanced CTCL (De Masson et al, Lancet, 2023 (PMID: 37105210)) even if the development of targeted immunotherapies such as mogamulizumab has been shown to improve prognosis of patients with Sézary syndrome (Bozonnat et al, EClinicalMedicine, 2024 (PMID: 39007062). This lack of efficient therapies could be due to immune state of the tumor microenvironment (TME) (Phillips et al, Nature communications, 2021 (PMID: 34795254)).

In this context, our team, focusing on TME and particularly on tumor associated macrophages (TAMs), has demonstrated a huge CD163+ macrophages infiltration in patient skin biopsies. The first aim of our project is to better characterize the TAMs using an immunofluorescence multiplex panel (TOX, CD4, CD68, CD163, PD-1, PD-L1) in patients, comparing subgroups of patient's biopsies with indolent stage to advanced stages. Then, we have co-cultivated in 2D culture healthy CD14+ monocytes/macrophages with CTCL cells derived from patient samples (Oncodermatology unit, Bordeaux University hospital) to evaluate their influence on each-other and study the dialog between TAMs and CTCL cells.

Using flow cytometry, we observed that macrophages increase PD-L1 expression when they are in presence of tumors cells. To better understand the functional influence of tumor cells on macrophages, we started to investigate the functions of these macrophages by immunomodulation assays on CD4+ T lymphocytes from healthy donors. Preliminary results suggested an increased immunosuppression activity of the monocytes/macrophages in co-culture or "educated" by tumor cells, that may contribute to tumor escape. The next step will be to use a 3D spheroid culture models including extracellular matrix, already developed in the lab, (Lamaison C, Blood Advances, 2021 (PMID: 34555842)) to better characterize the dialog of CTCL cells and macrophages in more relevant model, closer to the architecture of skin tumors. This work will allow us to better understand the role of these TAMs on CTCL properties and vice versa, to better understand the impact of TME on tumor survival and escape, and develop alternative therapies.

P122

Invasive properties of breast cancer cells transferred via miRNAs in collagen-tracks

Lucile ROUYER[1], Léa NORMAND[1], Elodie RICHARD[1], Sylvaine DI-TOMMASO[2], Cyril DOURTHE[1,2], Anne-Aurélie RAYMOND[1,2], Jean- William DUPUY[2], Reini LUCO[3], Kévin MOREAU[3], Nathalie ALLAIN[1], Anthony BOUTER[4], Alexandre FAVEREAUX[5], Violaine MOREAU[1], Manon ROS[1], Frédéric SALTEL[1]

[1] University of Bordeaux, Inserm, UMR1312, BRIC, BoRdeaux Institute of onCology

[2] Oncoprot, UAR 005 TBMcore, Bordeaux

[3] Institut Curie (UMR3348) - Centre de Recherche et Universitaire Rue Henri Becquerel , Orsay

[4] University of Bordeaux, Institute of Chemistry and Biology of Membranes and Nano-Objects, UMR 5248, CNRS, IPB, Pessac

[5] University of Bordeaux, CNRS, Interdisciplinary Institute for Neuroscience, IINS, UMR 5297

Metastasis is the leading cause of breast cancer-related deaths. During this process, tumor cells acquire invasive and migratory capacities in order to invade surrounding tissues. To achieve this, the tumor microenvironment (TME) including the extracellular matrix (ECM) are alter to facilitate cancer cell proliferation and dissemination. One of the most abundant component of this ECM is the collagen. Thanks to the collagen receptor, cancer cells can attach to the ECM in order to migrate and invade, during the process cell membrane fragments are pull out under the effect of mechanical forces. In parallel, cancer cells have the ability to produce vesicles in the TME involved in cell-cell communication and tumor progression.

Here we highlight that some depositions, name collagen-tracks, can be formed by cancer cells during migration and specifically attached along collagen fibers. Collagen-tracks are identified by discoidin receptor 1 (DDR1) enrichment and their formation is promoted when cell-ECM interactions are increased, such as in tumor microenvironment. We characterized these collagen-tracks, their ultrastructure as well as their molecular composition in terms of proteins and nucleic acids, showing that they are different from classical other extracellular vesicles known so far. Indeed, migrasomes have been recently discovered, they are vesicles formed at the end of retraction fibers of migrating cells on fibronectin ECM.

Moreover, collagen-tracks are very stable structures and can be internalize by surrounding cells. After internalization, they modify the differentiation status and the phenotype of recipient cells, promoting epithelial to mesenchymal transition, matrix degradation, and invasion. We highlight that these effects are drive by the miRNA cargo present in collagen-tracks. Thus, we identified a function of these membrane deposits playing a role in cell-cell communication by transferring invasive properties. Consequently, cancer-related collagen-tracks could be a new player in the tumor invasion process.

P123

Role of carbohydrate-binding proteins in controlling glioblastoma stem cell fate and tumorigenesis

Myroslava SLIUSAR[1], Ahmad SHARANEK (CHARANEK)[1], Audrey BURBAN[2], Andreas BIKFALVI[1]

[1] BRIC Team 01 Tumor and vascular biology laboratory, Bordeaux

[2] IBGC, CNRS UMR5095 GBmetabo team, Bordeaux

Introduction. Carbohydrate-binding proteins, galectins, are the family of proteins that specifically bind the β-galactoside sugars. Galectins (GAL, LGALS) are known to be associated with cancer development, including glioblastoma (GBM) - the most aggressive brain tumor. Thus, galectins, which regulate the numerous processes in the cell, can be considered worthy investigation targets for developing novel clinical approaches for GBM treatment.

Methods. Publicly available DSS and PFI data of TCGA cohorts were analyzed with SUMO software. The scRNA-seq data analysis was conducted with the R toolkit Seurat and SingleR package. For in vitro experiments we used patient-derived glioblastoma stem cells (GSCs) BTSC73 and BTSC12. Differentiation of the GSCs was reached by growth for 14 days on laminin-coated plates in the medium with 10% FBS. To study therapy resistance, GSCs were irradiated with 2 and 4 Gy. To reach hypoxic conditions, 5% CO2 and 1% O2 were maintained. The siRNA silencing was applied to achieve LGALS3 depletion. Live and apoptotic cells were counted with Annexin/PI double staining flow cytometry-based assay. EdU cell proliferation assay was used to investigate cell proliferation.

Results. We showed that LGALS1, -3, -8, and -9 are greatly expressed in glioblastoma RNA-seq TCGA datasets. The simultaneous high expression of these galectins leads to the worst prognosis for patients over other combinations. Further scRNA-seq data analysis showed that Gal3 is extensively distributed among glioblastoma cancer cells, macrophages, and T-cells. Our in vitro experiments with employed siRNA LGALS3 depletion in BTSC73 indicated a decrease in the number of live cells. This effect is related to the reduction of proliferation and not apoptosis which was shown with EDU staining and Annexin/PI assay. The role of Gal-3 in GSCs may also include stemness regulation since siLGALS3 transfection decreases the level of stem cell markers Sox2 and Nestin in BTSC73. Furthermore, Galectin-3 may control GSC differentiation since we detected an increase in LGALS3 expression during this process. We also showed that hypoxia in contrast to irradiation, increases the LGALS3 expression in BTSC73 and BTSC12.

The second branch of our investigation is dedicated to Galectin-9 which is expressed mostly in macrophages in glioblastoma scRNA-seq. Nevertheless, we showed a striking increase in LGALS9 expression during the GSC differentiation.

Conclusions. GAL-1, GAL-3, GAL-8, and GAL-9 are greatly expressed during GBM, while simultaneous high expression of these galectins is associated with poor patient survival. Both Galectin-3 and -9 might be involved in the regulation of GSC differentiation. Regardless of the others, Galectin-3 could be involved in cancer stem cell regulation by the control of proliferation. Gal-3 also affects the level of cancer stem cell markers Sox2 and Nestin. At the same time, Galectin-3 expression is regulated by hypoxia.

P124

PCSK9: A new potential target in Gastric Cancer Stem Cells?

Ana Sofia VAZQUEZ URIOLA[1], Anissa ZAAFOUR[1], Tra-Ly NGUYEN[1], Coralie GENEVOIS[1,2], Jérôme GUIGNARD[1], Abdel-Majid KHATIB[3], Christine VARON[1]

[1] Team 04 - Helicobacter-associated digestive cancers, cancer stem cells and therapeutic strategies - U1312 INSERM - BoRdeaux Institute of Oncology (BRIC) - Université de Bordeaux

[2] VIVOPTIC TBM-Core, CNRS UAR3427 INSERM US005, Université de Bordeaux

[3] Team 02 - Reprograming tumor activity and associated microenvironment - RYTME - U1312 INSERM - BoRdeaux Institute of Oncology (BRIC) - Université de Bordeaux

Background: Gastric cancer is the fifth leading cause of cancer-related death worldwide (IARC, 2022). Most cases are gastric adenocarcinomas (GC) that are usually detected during the metastatic stage; thus, the number of relapses is high, with a five-year survival rate lower than 20%. Increasing evidence suggests that GC's bad prognosis is caused by cancer stem cells (CSCs), which are a small tumor cell subpopulation with the capacity of inducing GC's initiation, growth, chemo-resistance, relapse and metastasis. Recent studies have shown that in GC the expression of the Proprotein Convertase Subtilisin/Kexin 9 (PCSK9), a member of the proprotein convertases (PCs) family, is correlated with cancer progression and poor prognosis, and it seems to have a role in GC cell functions. In our laboratory, it was shown that PCSK9 is highly overexpressed in GC CSCs. In this context, our objective is to study the potential role of PCSK9 on the tumorigenic, invasive and metastatic properties of CSCs in GC.

Methods: PCSK9's pharmacological inhibitor R-IMPP and siRNAs were used to evaluate the impact of PCSK9 inhibition on GC CSCs' stemness, tumorigenic and invasive properties in vitro; and their metastatic properties in vivo.

Results: PCSK9 inhibition caused a decrease in GC CSCs' tumorsphere formation and invasive capacity, on the GC's invasive marker's expression, and on the protein levels and nuclear expression of Epithelial-to-Mesenchymal Transition (EMT) transcription factors. In vivo, PCSK9's inhibitor dramatically decreased the metastatic dissemination of GC cells. Moreover, PCSK9's inhibition decreased YAP/TAZ protein levels and their nuclear expression on GC cells. The impact on the TEAD transcriptional activity is currently under investigation.

Conclusion: Our results suggest that PCSK9 may control CSCs' tumorigenic, invasive and metastatic properties through the EMT and probably the YAP/TAZ pathway, and it could constitute a potentially new therapeutic target in GC.

P125

Modelling metastatic dormancy of cancer stem cells in gastric cancer

Anissa ZAAFOUR, Nina REITANO FERBER, Tra Ly NGUYEN, Christine VARON

BoRdeaux Institute of Oncology

Metastasis is the leading cause of cancer-related death. At the core of this process are cancer stem cells (CSCs), a highly plastic subpopulation of cancer cells with the ability to invade the bloodstream and colonize organs distant from the primary tumor. CSCs are resistant to conventional treatments, and some can remain dormant, a state of near quiescence in which cells survive with very little growth and are not detectable by current imaging techniques, for several months or even years before triggering local or metastatic tumor recurrence. Despite the magnitude of the problem, the underlying mechanisms of CSC dormancy in the context of gastric adenocarcinoma (GC) are still largely unknown. Indeed, even in the case of early diagnosis of GC, the risk of recurrence remains elevated at around 60% despite surgical resection of the primary tumor (1). Two recurrence peaks are observed after surgery at 3 and 7.5 years, suggesting the presence of residual dormant GC cells that may awaken years after treatment (1). This emphasizes the crucial need to understand CSC dormancy in GC.

In the context of GC, our objectives are to: 1) elucidate the molecular mechanisms controlling CSC entry into dormancy and awakening by modelling it in vitro. This will allow us to understand how extracellular signals such as the hypoxic environment and external factors including ATRA, GAS6, and LIF influence the plasticity of CSCs from entry into dormancy to proliferative and invasive states. 2) To target the molecular mechanisms of dormancy in GC by focusing on NR2F1, one of the master regulators of dormancy described in the literature (2,3).

Various GC cell lines were exposed to dormancy inducers, including ATRA, LIF, TGF-B2, BMP7, and hypoxia, as described in the literature and based on previous works done in our laboratory (4). Our preliminary results indicate notably a potential role of ATRA and hypoxia in GC dormancy mechanisms. GC cells under ATRA treatment or hypoxic condition showed a lower proliferation rate in both proliferation and colony-forming unit assays compared to the control. However, no increase in cell death was observed, suggesting that the cells might be arrested and surviving. This was confirmed by flow cytometry which showed an increase in the percentage of cells blocked in the G0/G1 phase of the cell cycle. We also observed variations in the protein expression and localization of dormancy markers such as NR2F1 and p27 by western blot and immunofluorescence.

In conclusion, these preliminary results are encouraging but require further experimentations, which are currently ongoing, such as RTqPCR to obtain the GC dormancy signature and senescence assay. Additionally, tests with shRNA against NR2F1 are being conducted to target dormancy mechanisms in GC cells. Finally, this research project aims to develop and validate original models for the study of dormancy in the GC. Our ultimate goal is to identify the molecular signature of dormancy, and to elucidate the underlying mechanisms of dormant metastatic CSCs, thereby opening new perspectives for improving the therapeutic management of GC.

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P126

SK3 in the quiescent state of IDH1 mutant gliomas cells

Valérie CORONAS[1], Clémentin JACQUES[1], Aurélien CHATELIER[2], Laura BRARD[1], Donovan PINEAU[3], Bruno CONSTANTIN[1], Jean-Philippe HUGNOT[3]

[1] Canaux & Connexines dans les Cancers et Cellules Souches, Poitiers

[2] Laboratoire PRéTI, UR 24184 - Université de Poitiers

[3] Institut de Génomique Fonctionnelle, Montpellier

IDH1 mutant gliomas are a subtype of brain tumors. These incurable tumors affect young patients in their second or third decade. They are diagnosed as slow-growing tumors (grade II), but progress inexorably to high-grade gliomas (grade IV) leading to death.

Like many cancers, gliomas comprise both actively proliferating and quiescent cells. Being resistant to treatment, quiescent cells can re-enter the cell cycle, leading to tumor relapse. Quiescent cells are therefore a major target for improving the prognosis of gliomas. In a previous study, we identified by differential RNA profiling of proliferating versus quiescent cells, a group of genes highly specific to the quiescent state in our cell lines, including SK3 which is a Ca^{2+}-activated K^+ channel. These data, together with our previous studies showing that Ca^{2+}signaling plays a critical role in high-grade gliomas, prompted us to explore SK3 in LGG stem cells.

To this end, we analyzed the presence of functional SK3 in the LGG275 cell line isolated from a low-grade glioma. LGG275 low grade glioma cells were grown in a defined medium containing the growth factors EGF and FGF-2 (proliferative cells). Quiescence was induced by removal of the growth factors. SK3 expression was analyzed by western-blot and immunocytochemistry, and its activity by patch-clamp using apamin, an antagonist of SK3 channels.

Our western-blot data confirmed the overexpression of SK3 in quiescent LGG275 cells compared with proliferating cells. Immunostaining analysis showed the presence of SK3 at the cell membrane, particularly on the lamellipodia of bipolar cells. Patch clamp analysis was performed using an intracellular Ca^{2+}concentration that allowed SK3 to open. The results showed the presence of a current that reverses near the K^+equilibrium potential, at -80mV, and is abolished by barium, indicating that it corresponds to a K^+ current. This current was reduced by apamin, an antagonist of SK channels.

Physiologically, SK3 is activated by Ca^{2+} influxes that occur in response to extracellular signals. Among these, we focused on endothelin as our data indicate that the endothelin receptor is increased in quiescent LGG275 cells compared to proliferating cells. Using calcium imaging with the fura-2AM ratiometric probe, we showed that 40% of quiescent cells exhibit spontaneous Ca^{2+} oscillations compared with 10% of proliferating cells. Both endothelin and endothelin receptor B agonist induced Ca^{2+} influx in 40% of quiescent cells versus 20% of proliferating cells.

In conclusion, our data show that quiescent low-grade glioma cells display a outward current sensitive to apamine and express SK3 protein, exhibit spontaneous Ca^{2+} oscillations and endothelin-induced Ca^{2+} responses. The link between endothelin and SK3 will be further explored to better characterize quiescent LGG cells, which will help the design of new therapeutic strategies.

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P127

The Hippo pathway terminal effector TAZ mediates oxaliplatin sensitivity in p53 proficient colon cancer cells

Lisa HERON-MILHAVET, Vera SLANINOVA, Céline GONGORA, Alexandre DJIANE

Institut de Recherche en Cancérologie de Montpellier

YAP and TAZ, the Hippo pathway terminal transcriptional activators, are frequently upregulated in cancers. In tumor cells, they have been mainly associated with increased tumorigenesis controlling different aspects from cell cycle regulation, stemness, or resistance to chemotherapies. In fewer cases, they have also been shown to oppose cancer progression, including by promoting cell death through the action of the p73/YAP transcriptional complex, in particular after chemotherapeutic drug exposure. Using colon cancer cell lines, we show that oxaliplatin treatment led to core Hippo pathway down-regulation and nuclear accumulation of TAZ. We further show that TAZ was required for the increased sensitivity of colon cancer cells to oxaliplatin, an effect that appeared independent of p73, but which required the nuclear relocalization of TAZ. Accordingly, Verteporfin and CA3, two drugs affecting the activity of YAP and TAZ, showed antagonistic effects with oxaliplatin in co-treatments. Importantly, using several colorectal cell lines, we show that the sensitizing action of TAZ to oxaliplatin is dependent on the p53 status of the cells. Our results support thus an early action of TAZ to sensitize cells to oxaliplatin, consistent with a model in which nuclear TAZ in the context of DNA damage and p53 activity pushes cells towards apoptosis.

~~P128~~

P129

Identification and characterization of host factors that drive oncolytic virus infection in pancreatic cancer cells

Guillaume LABROUSSE[1], Nina SUAREZ[1], Adèle NEVOT[1], Nelson DUSETTI[2], Louis BUSCAIL[1], **Pierre CORDELIER[1]**

[1] Centre de Recherches en Cancérologie de Toulouse

[2] Centre de Recherches en Cancérologie de Marseille

Oncolytic viruses (OV) whether they arise naturally or are genetically engineered, possess the unique ability to selectively replicate within and eliminate cancer cells. Furthermore, they hold the potential to propagate within the cancerous cell population and trigger a potent anti-tumor immune response, capable of overcoming immune tolerance and rendering "cold" tumors receptive to immunotherapy. OV often thrive in cancer cells due to inherent defects in their antiviral defense mechanisms. Nevertheless, the precise molecular underpinnings governing the preference of OV for tumor cells remain incompletely understood. This work is dedicated to the exploration and characterization of host factors associated with the rat H-1PV parvovirus, a virus of therapeutic interest in cancer treatment, especially for the management of highly resistant neoplasms including pancreatic adenocarcinoma (PDAC). Following a genome-wide Cas9 loss-of-function screening conducted in primary cell cultures derived from PDAC patients, we identified that TGN46 (TransGolgiNetwork 46) knockdown completely protects PDAC cells from oncolysis. We generated primary PDAC cells depleted for, or overexpressing TGN46 and found that modulating TGN46 expressing has no impact on the formation of endocytic vesicles, nor on clathrin-mediated endocytosis. On the other hand, TGN46 is essential and fosters H-1PV productive infection of PDAC primary cells. In greater details, TGN46 drives H-1PV entry into cells, and colocalizes with the virus within infected cells. In silico modelling and functional studies using TGN46 protein mutants indicate that H-1PV directly binds to the luminal domain 1 of the protein. We also found that sialylation is essential for viral entry. Our results strongly suggest that TGN46 is the long-expected H-1PV receptor that allows for cancer cell infection. By establishing a host factor that is essential to the effectiveness of oncolytic therapy in PDAC, this research has the potential to significantly enhance the precision in selecting patients who are most likely to benefit the most from virotherapy.

Posters – Axis 2
Genome Dynamics & Expression

P201

Novel optogenetic tool for targeted oxidative DNA damage generation: effect of ROS on gene transcription

Luana CINTORI, Valérie BERGOGLIO, Catherine CHAILLEUX, Didier TROUCHE, Yvan CANITROT

Unité de biologie moléculaire, cellulaire et du développement, Toulouse

The aerobic environment in which we live means that our cells are constantly exposed to reactive oxygen species (ROS), which can damage all cellular components, including DNA. This oxidative stress, which causes oxidative damage to DNA, is particularly implicated in cancer. Recent studies show that the presence of oxidative damage such as oxidized guanine (8-oxoG) and the recruitment of its repair protein OGG1 to promoters appear to be involved in modulating the expression of many genes. This project proposes a new optogenetic tool for DNA-targeted ROS induction. To achieve this, we used CRISPR technology and its ability to target selected genome sequences with guide RNAs, combined with FAP (Fluorogen activated protein), capable of producing ROS after exposure to red light following incubation with the MG2i fluorogen. To validate the tool, we demonstrated the recruitment of the XRCC1-GFP and OGG1-GFP protein involved in the oxidative damage repair pathway after light activation of FAP-MG2i. Then we performed RNAseq under oxidative stress in our cell line in order to identify genes sensitive to oxidation. Now the tool we developped aims to study the impact of targeted oxidative damage of these identified genes to better understand the role of oxidative stress on transcription regulation.

P202

Functional characterisation of Special AT-rich binding protein 1 (SATB1) in B cell nuclei

Jean-Yves FRAYSSINHES, Claire CARRION, Morgane THOMAS, Pierre HIRT, Ophélie MARTIN, Tiffany MARCHIOL, Sandrine LE NOIR, Eric PINAUD

Contrôle de la Réponse Immune B et des Lymphoprolifération, Limoges

Special AT-rich binding protein 1 (SATB1) is a member of the MAR-binding protein family that functions as a chromatin organizer and transcriptional regulator in T lymphocytes.

In T lymphocyte nuclei, SATB1 recruitment to specialized genomic binding sites, called matrix attachment regions (MARs), tethers portions of chromatin to the nuclear skeleton and contributes to genome organization.

Using these mechanical forces, the SATB1 transcription factor orchestrates the expression of many genes by both remodeling the chromatin architecture into specific loop domains and contributing to transcription to ensure proper T-cell development.

Although SATB1 is less expressed in B cells than in T cells, its expression occurs at different stages of B cell differentiation.

Surprisingly, using conditional KO of SATB1 in mouse B cells (cKOSatb1), we recently showed that loss of SATB1 does not affect early B cell development, but identified a dual function of this nuclear factor on IgH gene expression; SATB1 acts as either an activator or repressor on resting and activated B cells, respectively. While depletion of SATB1 in activated B cells has no effect on class switch recombination, we observed a higher frequency of mutations at IgH, Bcl6 and Pim1 loci.

Consistent with the increased mutation rate in B cell oncogenes, we hypothesize that the absence of SATB1 contributes to a level of genomic instability that may promote tumorigenesis.

In our current work, we have shown that SATB1 expression is atypical, as its protein levels are rather stable over time, but not its mRNA levels. Second, we identified multiple SATB1 isoforms in B cells, including transcriptional and splicing variants with potentially different biochemical properties. Third, preliminary FISH analysis showed that the IgH and Bcl6 loci in cKOSatb1 are more distant from each other in resting B cells. In addition, SATB1-depleted resting B cells are less susceptible to DNA double-strand breaks (DSBs) repair when quantifying P-Ser 139 γH2A.X nuclear foci after DBS-induction with bleomycin sulfate.

Taken together, our results show that SATB1 regulates the positioning of immunoglobulin genes and oncogene loci in B cells. By such a change in the spatial regulation of loci subject to DNA repair in B cells, SATB1 could be considered as a factor protecting the B cell genome.

P203

Role and regulation of the SUV4-20H family of epigenetic enzymes in aggressive forms of prostate cancer

Michelle Gracia MALANDOU TSAMBA, Hiba Daher, Pierre Dambrun, Véronique Baldin, Eric Julien

INSERM U1194 Institut de Recherche en Cancérologie de Montpellier

Methylation of lysine 20 on histone H4 (H4K20me) is frequently altered in cancer, primarily due to dysregulated expression of the SUV4-20H1 and SUV4-20H2 enzymes, which are responsible for H4K20me2 and H4K20me3. These enzymes are chromatin-associated and remain stable throughout the cell cycle. While both enzymes share general physiological functions, their roles in prostate tumor development diverge: SUV4-20H1 is mutated in cancer and potentially acts as a tumor suppressor, whereas SUV4-20H2 is upregulated and could function as a pro-oncogene. This highlights the need to explore how these enzymes regulate cancer related mechanisms and whether they could constitute attractive targets for new therapeutic strategies. Through RNA sequencing of various DU145 cell lines knockout for each enzyme or both, we found that loss of SUV4-20H1 and SUV4-20H2 has opposing effects on gene expression. Genes such as PLAGL1, HKDC1, and MET are upregulated in SUV4-20H1 knockout (KO) cells but downregulated in SUV4-20H2 depleted cancer cells. Additionally, oncogenes like TGFa, CDH1, and NOTCH1 were found to be upregulated in the absence of SUV4-20H1 in a manner dependent on its catalytic activity. Interestingly, other genes, including inflammatory mediators PTGER1 and PTGER2, which are not linked to the enzyme's catalytic function, may also contribute to its tumor-suppressive effects. Building on these findings, my thesis project aims to elucidate the transcriptional role of SUV4-20H1, the connection with tumor suppression mechanisms and the cancer-associated SUV4-20H1 mutations.

P204

Impact of the overexpression of EIF3 subunit on the dynamics regulation of other subunits of the complex and cancer-associated cellular phenotypes

Ibrahim SAHEBALLY

BoRdeaux Institute of Oncology

In recent years, translation control has emerged as a major actor in cancer development. This process, which is highly regulated and limiting, requires numerous eukaryotic initiation factors (eIFs). Of all the eIFs, eIF3 is the largest and the most complex of all eIFs, comprising 13 non-identical protein subunits (eIF3a-m). The expression of eIF3 subunits is frequently dysregulated in many cancers. Although eIF3 plays a role in canonical translation, its specialized subunits can also drive non-canonical translation pathways in a variety of physiological and pathological contexts. Interestingly, it has recently been shown that the knock-down of eIF3 subunits leads to the dysregulation of other subunits, altering the dynamic assembly of the whole complex and leading to the formation of new sub-complexes whose role in tumor development is still unknown [1]. Our aim is therefore to understand, in a context of eIF3 subunits overexpression, how the eIF3 dynamic assembly is remodelled and what is its impact on tumour development. First of all, the expression analysis of all eIF3 subunits (mRNA and protein) in the public TCGA database and in different cellular models, allowed us to identify different signatures of eIF3 subunits overexpression in certain cancers (hepatocellular carcinoma - HCC, glioblastoma - GBM, invasive breast carcinoma - CIS). In order to understand the functional role of these different signatures on the biology of the complex, we overexpressed some of the eIF3 subunits identified in these signatures (3E, 3H, 3D and 3M) in a single or combined manner in HEK293A. Our results show that the level as well as the combination of overexpressed eIF3 subunits leads to a different co-regulation of the other subunits of the complex. Interestingly, by Optiprep gradient fractionation approaches, we observed that these different overexpressions and associated co-regulations of subunits lead to the formation of new eIF3 subcomplexes independent of the overall complex. Furthermore, we also observed that certain combinations have opposite phenotypic effects on multiple cellular parameters related to tumor development such as 3D cell growth and resistance to apoptosis, and globally deregulate protein synthesis. Overall, our data suggest that the different combinations of overexpressed eIF3 subunits observed in certain cancers, by altering the overall stoichiometry of the complex, could lead to the formation of eIF3 subcomplexes. The latter could have an impact on specific cellular functions important for tumor development in relationship with translational reprogramming.

~~P205~~

P206

Exploring dynamically the Role of Hybrid E/M States in Cancer Stemness by IVM

Guillaume BELTHIER, Laura BORNES, Jacco VAN RHEENEN

Nederlands Kanker Instituut

Epithelial-to-mesenchymal transition (EMT) is a cellular program which leads to cells losing epithelial features, including cell polarity, cell-cell adhesion, and attachment to the basement membrane, while gaining mesenchymal characteristics, such as invasive properties and stemness. Over the years, the role of EMT in cancer progression has been heavily debated, and the requirement of this process in metastasis even has been disputed. The overall topic is even more complicated since EMT has been shown as extremely dynamic in term of intermediate or hybrid E/M states[1] and reversible[2]. Furthermore, a significant portion of the literature focuses on specific mutation or permanent EMT activation, blocking the spontaneous and dynamic aspect of EMT. Latest publications suggest that, physiologically, stemness is acquired or strengthened in an hybrid state[3]. However, most stemness assays are based on transplantation models, which are also heavily disputed[4].

Here, we combine transgenic mouse models and intravital microscopy to study EMT, hybrid E/M and stemness states in the unperturbed and physiological in vivo setting. Our data suggest that cells undergoing a full EMT program lose complete self-renewing potential (i.e. stemness). Moreover, our data shows that cells in a hybrid E/M state acquire a hybrid stemness state, leading to long-lived clones with limited expansion capacity.

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Posters – Axis 3
Therapeutic Innovation & Biomarkers

P301

Magnetic hyperthermia and magnetic-mechanical ablation, two potential strategies for inducing an anti-tumor immune response in pancreatic ductal adenocarcinoma

Angela AGAËSSE[1], Justine JOURNAUX[1], Pascal CLERC[1], Julian CARREY[2], Olivier SANDRE[3], Stéphane MORNET[4], Véronique GIGOUX[1]

[1] Centre de Recherches en Cancérologie de Toulouse

[2] Laboratoire de Physique et Chimie de Nano-Objets, Toulouse

[3] Laboratoire de Chimie des Polymères Organiques, Pessac

[4] Institut de Chimie de la Matière Condensée de Bordeaux

Pancreatic ductal adenocarcinoma (PDAC) is a cancer with a poor prognosis, and it is predicted to be the second leading cause of cancer death within a few years. PDAC is particularly resistant to conventional therapies and characterized by the presence of a large and dense microenvironment with a key role of CAFs (Cancer-Associated Fibroblast). CAFs promote proliferation and progression of the tumor, secrete extracellular matrix proteins forming a physical barrier that limits not only the penetration and the diffusion of drugs but also the infiltration of immune cells therefore an efficient anti-tumoral immune response.

Magnetic iron oxide nanoparticles (IONPs) are innovative tools, exposed to a high-frequency alternating magnetic field, they release thermal energy, causing cell death by magnetic hyperthermia (HM). Exposed to a low-frequency rotating magnetic field, IONPs generate mechanical forces causing cell death by magnetic-mechanical ablation (MMA).

We developed IONPs, vectorized with gastrin, called NF@Gastrin, which specifically target pancreatic cancer cells and CAFs (Cancer-Associated Fibroblast) expressing the CCK2 receptor (MiaPaca2-CCK2 and CAF-CCK2). The aim of this project is to study whether local HM or MMA can stimulate immunogenic cell death and enhance an antitumor response in the PDAC. We showed that NF@Gastrin internalized and accumulated in the lysosomes of MiaPaca2-CCK2 and CAF-CCK2 cells. We demonstrated that HM and MMA specifically killed these cells in 2D culture models and 3D MiaPaca2-CCK2/CAF-CCK2 spheroids. Furthermore, we demonstrated that HM and MMA increased the expression of the Damage-Associated Molecular Pattern: Calreticulin and HSP70 at the surface of the targeted cells in 2D and 3D models. This effect was associated with an increase in phagocytosis of these cells by human THP1 macrophages in 2D and their infiltration within the spheroids, as well as an increase in the activity of Natural Killers (NK-92) when they were in contact with these cells in a 2D model. Taken together, these results strongly suggest that HM and MMA are two potential strategies capable of inducing immunogenic cell death and restoring an anti-tumor response in PDAC.

P302

Development of a new class of DNA mimics to counteract the resistance to anticancer treatments.

Reem BANNOUT

Institut de Recherche en Cancérologie de Montpellier

Numerous essential biomolecular processes require the recognition of DNA surface features by proteins. Therefore, molecules mimicking these features could potentially interfere with protein-DNA interactions as it was shown for several naturally occurring DNA-mimicking proteins. In the search for new DNA mimics molecules that could target pharmacologically or therapeutically relevant proteins, the group of I. Huc synthetized tunable oligoamide-based molecules that mimic the charge surface of double-stranded DNA. In solution, these mimics fold into single helical conformations and display a double helical array of negatively charged residues in positions that match the phosphate moieties in B-DNA. We previously showed that in vitro, these mimics inhibit several enzymes possessing non-sequence-selective DNA-binding properties, notably DNA topoisomerase 1 (Top1). Top1 is a nuclear enzyme that is essential for the removal of torsional constraints associated with many DNA processes including replication, transcription, DNA repair or recombination. Top1 is the target of Top1 poisons from the camptothecin (CPT) family that stabilize the enzyme-DNA covalent complexes, leading to cytotoxic replication-mediated DNA double strand breaks. We also showed that DNA mimics could inhibit the growth of cancer cells, this effect being observed only in the presence of a transfection agent due to the polyanionic nature of these molecules and their poor lipophilicity.

The thesis project will be divided in three main objectives: (1) The first aim will be to identify at the molecular level the precise mechanism of Top1 inhibition in vitro by using dedicated oligonucleotide-based assays that were developed to study the effects of Top1 inhibitors on the two steps of the Top1 reaction (cleavage and religation). This part of the project will also study whether Top1 inhibition also occurs in cells and whether it is involved in the cytotoxicity of the DNA mimics. (2) The second objective of the thesis project is part of a larger program aimed at developing new strategies to improve the delivery of the DNA mimics since their charge prevents their free diffusion into cells. We will specifically focus on the development of new Antibody-Drug Conjugates (ADCs) in collaboration with N. Joubert's team (University of Tours) within the Labex MabImprove. (3) The third objective of the thesis is based on preliminary results obtained using an RNAseq approach to identify genes/pathways that are triggered following transfection with DNA mimics.

P303

A potent agonist-based PROTAC targeting Pregnane X Receptor that delays colon cancer relapse

Lucile BANSARD[1], Guillaume LACONDE[2], Vanessa DELFOSSE[3], Tiphaine HUET[3], Margaux AYEUL[1], Emille RIGAL[4], Quentin DONATI[2], Sabine GERBAL-CHALOIN[4], Martine DAUJAT-CHAVANIEU[4], Baptiste LEGRAND[2], Alain CHAVANIEU[3], Anthony R. MARTIN[2], Julie PANNEQUIN[1], William BOURGUET[3], Muriel AMBLARD[2], Jean-Marc PASCUSSI[1]

[1] Institut de Génomique Fonctionnelle, Montpellier

[2] Institut des Biomolécules Max Mousseron, Montpellier

[3] Centre de Biologie Structurale de Montpellier

[4] Institut de Médecine Régénérative et de Biothérapies de Montpellier

Tumor recurrence is often attributed to drug-tolerant cancer stem cells. We previously demonstrated that down regulation of the Pregnane X Receptor (PXR, NR1I2) decreases chemoresistance of cancer stem cells and prevents colorectal cancer recurrence in xenograft mouse models. These is a lack of PXR antagonists that are appropriate for clinical use. In this study, we report the design and synthesis of a novel PXR agonist-based PROTAC (JMV7048) that induces polyubiquitination and degradation of human PXR protein in an E3 CRBN ubiquitin ligase- and the 26S proteasome- dependent manner. This molecule specifically degrades PXR in colon carcinoma, hepatoma, and pancreatic cancer cell lines, but not in primary cultures of human hepatocytes. Crucially, JMV7048 decreased PXR protein expression in colon cancer stem cells and sensitized them to chemotherapy significantly delaying cancer relapse in vivo. This proof of concept suggests that PROTACs targeting the PXR protein could serve as novel therapeutic agents, enhancing the sensitivity of cancer stem cells to chemotherapy.

P304

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) in a rabbit model of gastric peritoneal metastases

Sylvia M. BARDET[1,2], Marie-Laure PERRIN[1], Matteo BRANDY[1,2], Catherine YARDIN[1], Sylvaine DURAND-FONTANIER[1,2], Abdelkader TAIBI[1,2]

[1] XLIM Limoges

[2] Groupe Biosanté

The primary objective was to assess the safety and viability of repetitive PIPAC procedures in a rabbit model exhibiting gastric peritoneal metastases. The rabbits, as per the model by Pascal et al. (2017), were subjected to PIPAC treatments with serum physiological solutions on Days 8, 15, and 21. Preceding euthanasia on Day 26, a PIPAC procedure incorporating trypan-blue-dye was conducted.Evaluation of the well-being status was carried out before each PIPAC session. Abdominal CT scans were performed prior to the first PIPAC and post the third PIPAC. During each PIPAC, ascites volume and Peritoneal Cancer Index (PCI) were quantified, alongside biopsy sampling from at least three nodules. Morbidity and mortality outcomes were documented. Histological scrutinization employing HES and Microscopic Multiphoton Imaging was undertaken.The well-being score of all three rabbits decreased to below 2 points after the series of PIPAC interventions. A wound in the intestine was sutured without consequence, and no rabbit died during the experiment. Histological analysis revealed an increased presence of collagen in the peritoneum following PIPAC compared to control rabbits; however, no heightened tissue inflammation was observed in either the peritoneum or liver parenchyma. The distribution pattern of the blue dye post-PIPAC application displayed homogeneity across the parietal peritoneum, small intestine peritoneum, and colon while showing weaker diffusion in the diaphragmatic-cupola and Douglas' cul-de-sac.In conclusion, our findings indicate that PIPAC is both feasible and safe within a rabbit model featuring gastric peritoneal metastases. This model holds promise for evaluating novel chemotherapy protocols involving PIPAC applications.

P305

Mechanisms of radiation-induced cell death in patient lymphocytes

Laura BOURILLON[1,2], Marion LARROQUE[1,2], Tiphany GOUVEIA[1,2], Virginie LAFONT[2], Alain MANGE[2,3], Céline BOURGIER[1,2], David AZRIA[1,2], Muriel BRENGUES[1,2]

[1] Institut du Cancer de Montpellier

[2] Institut de Recherche en Cancérologie de Montpellier

[3] Université de Montpellier

Fifty percent of cancers patients will benefit from radiotherapy (RT) as part of their treatment. Approximately 5 to 10% of all patients undergoing RT will develop serious late side effects. Early identification of these patients is therefore essential. The development of the radiation-induced lymphocyte apoptosis (RILA) assay showed that it was possible to predict the intrinsic radiosensitivity of patients suffering from a cancer based on the rates of radiation-induced T lymphocytes apoptosis. A prospective multicenter study involving more than 500 patients showed that patients with a high RILA >16% do not develop breast fibrosis in the long term while patients with a low RILA <12% have a risk of developing a side effect.

This project is dedicated to understanding the mechanisms of individual radiosensitivity of healthy tissues. Until now, no data have been published on the mechanisms that could explain these differences between low and high RILA values among patients. Our hypothesis is that patients' lymphocytes with a low RILA were subjected to a stress which could have activated lymphocyte stimulation causing radiation-resistance.

We first validated on patient samples that stimulated lymphocytes have a lower rate of radiation-induced apoptosis than unstimulated lymphocytes, showing as in the literature that stimulated lymphocytes are more radiation-resistant. We also observed that T lymphocytes after stimulation undergo a decrease in their RILA value compared to the same unstimulated T lymphocytes. Next, we analyzed in patients' samples the activation state of lymphocyte sub-types by flow cytometry. We observed more CD25+ cells in the CD8 patients' lymphocytes with low RILA indicating a greater activation state of T lymphocytes in these patients.

In order to identify biomarkers involved in radiation-induced and radiation-resistant lymphocytes apoptosis signaling pathway, we used a Reverse Protein Phase Array (RPPA) approach. Several proteins over or under-expressed due to lymphocyte stimulation were selected for further validation. One of them, the survivin, an anti-apoptotic factor known to be overexpressed in patients with chronic inflammatory disease happened to be overexpressed as well in stimulated lymphocytes. This result was confirmed by Western Blot and Proteome Profiler.

P306

Glucose-Independent Effects of Metformin on Cancer Stem Cell in Colorectal Cancer

Marie BOUTAUD[1], Abdulkerim BILGIN[1], Niki CHRISTOU[1,2], Mireille VERDIER[1]

[1] Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique, Limoges

[2] Service de Chirurgie Digestive, Centre Hospitalier Universitaire de Limoges

Colorectal cancer (CRC) is the second cause of cancer-related deaths worldwide, with a high recurrence rate, even in early stages. This is mostly due to cancer stem cells (CSCs), which drive tumor progression and resistance to treatments. These CSCs are characterized by the expression of specific markers and their ability to self-renew and metastases. Metformin, primarily utilized in type 2 diabetes management due to its actions on mitochondrial metabolism and AMPK, has been studied for its inhibitory effects on CSCs across various cancers, yet its impact on CRC remains relatively evasive.

In this study, we investigated the impact of metformin on three colorectal cancer cell lines (HCT-116, SW-480, SW-620) cultured in 2D and on two colorectal cancer cell lines (HCT-116, SW-480) in 3D cultures. In 2D cultures we investigate the effect of metformin on CSC gene and proteins expression, migration capacities and cell cycle whereas the effect on CSC gene and proteins expression, clonogenicity and invasion were checked in 3D cultures. In the light of these results, we explored the effect of the metformin on epithelial mesenchymal transition. The role of AMPK in metformin's action was also explored using AMPK-targeting siRNA. To evaluate the influence of glucose levels on metformin's ability to inhibit CSCs, all experiments were conducted under both normoglycemic (7.8 mM) and hyperglycemic (17.5 mM) conditions.

Our results show that metformin significantly reduces CSCs sub-population whatever cells were cultured (2D or 3D). The drug also decreased the migratory and invasive properties of the cancer cells in both glucose conditions. In addition, we observed a better effect of metformin on migratory and invasive capacity in early-stage cancer.

In conclusion, this study highlights metformin's potential to slow down colorectal cancer progression by targeting CSCs in a glucose-independent manner. The most significant effects were observed in early-stage CRC, suggesting that metformin could be a valuable adjuvant therapy for early-stage CRC in both diabetic and non-diabetic patients. Although further validation is required, these results offer encouraging prospects for the use of metformin in developing new therapeutic strategies.

P307

Overcoming osimertinib resistance in EGFR-driven lung cancer by targeting drug tolerant persister cells

David BRACQUEMOND[1], Xavier QUANTIN[2], Maicol MANCINI[1], Antonio MARAVER[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Institut du Cancer de Montpellier

Patients diagnosed with EGFR-mutated lung adenocarcinoma are treated with specific EGFR-inhibitors such as osimertinib. However, inevitably, almost all patients relapse. A subpopulation of slow-to-non-cycling cells called Drug Tolerant Persisters (DTP) seems to be responsible for the tumour recurrence. Our aim is to establish whether DTPs are associated with the NOTCH pathway, a crucial pathway in lung adenocarcinoma.

EGFR-driven cells were treated with a combination of EGFR and NOTCH inhibitors. We transduced these cells with the FUCCI system to be able to follow the cell cycle. Additionally, we labelled cells to monitor HES1 expression (read-out of Notch pathway activity) by cytometry upon different drug treatment. Tet-on-EGFRT790M/L858R transgenic mice have been treated with the combination of EGFRi and NOTCHi by oral gavage 5 days per week.

Upon EGFRi treatment, we observe i) an arrest of the cell cycle in G1, ii) the appearance of a subpopulation likely in G0 and iii) a fluctuation of the NOTCH pathway activity over time. Initially, HES1 drops drastically in DTPs, then, once DTPs are expending, the trend is reversed. In vitro, EGFRi/NOTCHi combination delays the expansion of DTPs compared to EGFRi alone. In vivo, the same combination demonstrates a strong acute response and significantly delays the relapse compare to EGFRi alone.

EGFRi treatment affects the NOTCH pathway activity and targeting NOTCH in combination with EGFR brings therapeutic benefit as it delays the relapse in vitro in EGFR-mutated cell lines and in vivo in Tet-on EGFRT790M/L858R transgenic mice. Since both treatments seems to strongly impact the cell cycle, we intend to shed light into the exact mechanism of how HES1 levels mediates DTPs status.

P308

Combination of chemotherapy, hormonal therapy and radiotherapy in oligo-metastatic prostate cancers treatment

Tiphany GOUVEIA[1,2], Laura BOURILLON[1,2], Hanane AGHERBI[3], Véronique GARAMBOIS[2], Salima ATIS[1,2], Nadine HOUEDE[2,3], Céline GONGORA[2], David AZRIA[1,2], Philippe POURQUIER[2], **Muriel BRENGUES[1,2]**

[1] Institut du Cancer de Montpellier

[2] Institut de Recherche en Cancérologie de Montpellier

[3] CHU de Nîmes

This study aims to optimize combinations including hormonal therapy, taxane-based chemotherapy, and radiotherapy in the treatment of prostate cancer. The objective is to determine whether this triple combination could be used in oligo-metastatic situations for which stereotaxic irradiation of metastases is considered, but for which there are currently no standard treatments. A preliminary in-vitro study on the LNCaP (Lymph Node Carcinoma of the Prostate) and VCaP (Vertebral-Cancer of the Prostate) cell lines allowed us to determine that the most effective triple combination was the one in which docetaxel was administered 24 hours before the radiotherapy plus enzalutamide combination, the triple concomitant association being less effective. In order to identify biomarkers involved in the different response between concomitant and sequential treatment, we used a Reverse Protein Phase Array (RPPA) approach. The first validated results show a differential expression of certain proteins (phosphorylated or not) with a significant increase in H2AX in the sequential treatment, indicating an increase in DNA damage with this treatment. Furthermore, we observed a difference in the expression of several key proteins from different signaling pathways, in particular an inhibition of Akt1 phosphorylation in the sequential treatment. The in-vivo validation of these results is in process.

The results will allow a better understanding of the mechanisms of action of combination treatments and will be used to identify new biomarkers and/or new targets whose inhibition could improve the tumor response to this triple combination. These data will also be useful to consider using this treatment for oligometastatic prostate cancer in order to improve its effectiveness.

P309

Exploiting vulnerabilities in MET-driven non-small cell lung cancer

Lisa BRUNET[1], Maicol MANCINI[1], Marie COLOMB[1], Zoulika KHERROUCHE[2], Alexis CORTOT[2,3], Antonio MARAVER[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] University of Lille, CNRS, Institut Pasteur de Lille

[3] University of Lille, Thoracic Oncology Department, CHU Lille

Lung cancer is a major public health problem because is responsible of the highest number of cancer deaths worldwide. Together with mutations in EGFR or KRAS, MET alterations, including MET amplification and MET skipping of exon 14, are among the most important oncogenic events in non-small-cell lung cancer (NSCLC), the main type of lung cancer accounting for more than 80% of all patients. Despite the improved clinical outcomes derived from the introduction of MET-tyrosine kinase inhibitors (TKI) to treat patients with advanced MET-driven lung cancer, their prognosis remains unfavorable because of intrinsic or acquired resistance.

Faced of the lack of in vivo models to study MET amplification, we generated a new genetic engineered mouse model that upon doxycycline induction, spontaneously develop MET-driven NSCLC in approximately 11 months. RNA sequencing analysis comparing tumors and healthy tissue showed that contrary to other oncogenic drivers as KRAS or EGFR, the Notch pathway was downregulated in tumors and the p53 was highly active, suggesting a link between these two pathways. Importantly, clinical trials using tepotinib, a MET-TKI demonstrated that patients harboring p53 mutations respond worst to this treatment. To understand the role of p53 on Notch pathway and in MET-TKI response, we performed p53 loss of function (LOF) in vivo in our new MET-driven NSCLC model. Of note, our new mouse model demonstrates that tumors lacking p53 have a higher activity on the Notch pathway, supporting a negative regulation of the Notch pathway by p53 in NSCLC. Importantly, our in vivo data using our state-of the art GEMM model showed that MET tumors lacking p53, as it happens in patients, respond worst to the clinically relevant MET-TKI crizotinib, and strikingly, they fully respond to the combination of crizotinib and nirogacestat, a clinically relevant Notch inhibitor. Together, our data suggest that a co-treatment of MET-TKIs and Notch inhibition could represent a new strategy for an unmet medical need, i.e., the treatment of p53 mutated MET-driven NSCLC patients.

P310

Role of H-1PV oncolytic virus on pancreatic cancer microenvironment

Margaux VIENNE, Charlène LOPEZ, Adele NEVOT, Naïma HANOUN-ZIANE, Louis BUSCAIL, **Pierre CORDELIER**

Centre de Recherches en Cancérologie de Toulouse

Oncolytic viruses (OVs) show great potential in modulating the tumor microenvironment (TME) to enhance cancer treatment. These viruses selectively infect and kill cancer cells, but their effects extend beyond direct oncolysis. They can stimulate a potent immune response by altering the TME, often converting it from an immunosuppressive to an immunogenic state. Pancreatic ductal adenocarcinoma (PDAC) is notoriously resistant to immunotherapies due to its highly immunosuppressive TME, characterized by a dense stromal barrier, low immunogenicity, and poor infiltration of immune cells such as T cells. PDAC also features high levels of immunosuppressive cells, such as regulatory T cells and myeloid-derived suppressor cells (MDSCs), which further inhibit immune responses. In this study, we found that the PDAC-enhanced H-1PV virus, generated by directed evolution, successfully inhibited the progression of orthotopic primary human pancreatic cancer tumors engrafted in athymic mice. We further explored the potential of H-1PV in immune-competent models of this cancer. Primary murine PDAC cells derived from spontaneous tumors were implanted subcutaneously in C57/bl6 mice. While H-1PV failed to kill murine pancreatic cancer cells directly, intratumoral injection of H-1PV resulted in a significant reduction in tumor growth.Flow cytometry (FACS) analysis revealed that H-1PV repolarizes murine PDAC tumors to promote antitumor immunity, with increased numbers of CD4+ T cells, CD206-negative macrophages, and a reduction in regulatory T cells (Tregs), as well as a general decrease in immune cell exhaustion. We then combined H-1PV infection with a PD-1-targeted IL-2 variant complex (PD1-IL2v), a bispecific immune molecule designed to promote the proliferation, migration, activation, and function of CD8+ T cells within tumors. This therapeutic combination significantly decreased tumor growth and reduced tumor size. Collectively, our results demonstrate that the H-1PV oncolytic virus is a promising approach in cancer immunotherapy for PDAC, especially when combined with other treatments like immune checkpoint inhibitors.

P311

Quantification of radiosensitizing gadolinium-based nanoparticle concentration in patients with glioblastoma using a routine clinical imaging protocol

Audrey LAVIELLE, Noël PINAUD, **Yannick CRÉMILLIEUX**

Institut des Sciences Moléculaires

Objectives: Measuring the concentration of Gd-based nanoparticles (NPs) administered as radiosensitizers prior to radiotherapy sessions in patients with glioblastoma (GBM) is essential for determining the therapeutic efficacy of these NPs and the safety regarding healthy tissue. The objectives of this study were to generate T1 (longitudinal relaxation time) maps, to compute NP concentration from MR images obtained with the magnetization-prepared rapid gradient echo (MPRAGE) sequence and to generate concentration level maps in order to study the biodistribution of NPs in patients with GBM (1).

Materials and Methods: The computation of T1 maps from MPRAGE sequences was carried out using a theoretical approach described in Lavielle et al. (2). The Gd^{3+} concentration maps were computed using the relationship between the T1 value, the longitudinal relaxivity of the T1 agent and its concentration C. Additionally, maps illustrating the varying levels of Gd^{3+} concentration were generated. Voxels within the gross tumor volume (GTV) ROI from all patients were used to compute a global histogram. To characterize this histogram, a 4-Gaussian mixture model was employed that captured the characteristic concentration distributions in biological tissues. Subsequently, the Gaussians in the model were sorted, and an automatic Otsu's method was applied to determine the optimal threshold that effectively separates two consecutive Gaussians while minimizing intra-class intensity variance (3). These determined thresholds were then used to define the ranges of concentration used for classifying voxels.

Results: All patients demonstrated an increase in signal intensity in GTV on T1-weighted MRI after Gd-based NPs injection. Gd^{3+} concentration maps highlighted NPs accumulation specifically within the tumor. The average, minimum, and maximum mean Gd^{3+}concentrations in the tumors were 84.9 (± 40.3), 54.5, and 160.3 µM. Average mean Gd^{3+} concentrations in healthy occipital withe matter and vitreous body eyeball (10.9 ± 12.9 and -12.6 ± 7.3 µM, respectively) were below the limits of detection.
Three thresholds were determined for the biodistribution in four levels: 0-36 (low), 36-123 (moderate), 123-291 (high), and 291-550 (very high) µM. In the concentration level maps, voxels classified at the same level are usually found in the same region of the GTV. Regions with the highest concentration (> 123 µM) were predominantly found at the border of the GTV, while regions of lower concentration (< 36 µM) were primarily located at the center of the GTV.
Analyzing the proportion of each region in relation to the total GTV volume per patient, we noted that regions with high (123-291 µM) or very high (> 291 µM) concentration accounted in average for 26.8 ± 19.3 % of the GTV, and up to 66.9 % for patient #4. Regions with low (< 36 µM) and moderate (36-123 µM) concentration accounted in average for 34.5 ± 13.3 % and 38.7 ± 12.9 %, respectively.

Conclusions: The concentration of MRI-traceable NPs can be assessed in GBM using a MPRAGE acquisition. This study highlighted that theconcentration of NPs differed significantly between patients and within different regions of the tumor, highlighting the importance of considering the heterogeneity in the vascularization of GBM for treatment planning and outcome prediction. For patients treated with radiotherapy, the concentration maps will be used to correlate the NP concentration with the magnitude of the therapeutic effect and will offer the possibility of adjusting an external therapeutic modality to the concentration of the radiosensitizing NPs.

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P312

Sulconazole prevents T-cell exhaustion and promotes cancer cell malignant phenotype repression by attenuation of NF-κB and calcium signaling

Isabel GALEANO-OTERO[1], Simon PERNOT[1,2], Mercedes TOMÉ[1], Serge EVRARD[1,2], Iker BADIOLA[3], Frederic DELOM[1,2], Delphine FESSART[1,2], Tarik SMANI[4], Geraldine SIEGFRIED[1,2], Bruno O. VILLOUTREIX[5], Majid KHATIB[1,2]

[1] Reprograming tumor activitY and associaTed MicroenvironmEnt (Rytme)/ Bordeaux Institute of Oncology (BRIC)-UMR1312/ Inserm/ Université of Bordeaux/ Pessac

[2] Institut Bergonié/ Bordeaux

[3] Department of Cell Biology and Histology/ Faculty of Medicine and Nursing/ University of the Basque Country/ Spain.

[4] Group of Cardiovascular Pathophysiology/ Institute of Biomedicine of Seville/ University Hospital of Virgen del Rocío/ University of Seville/CSIC/ Seville/ Spain.

[5] Integrative Computational Pharmacology and Data Mining/ INSERM UMR 1141/ Rob-ert-Debré Hospital/ Paris

Introduction/Objectives: The overexpression of the immunoinhibitory receptor programmed death-1 (PD1) on T-cells plays a significant role in cancer immune evasion. While anti-PD-1/PDL-1 therapies have revolutionized cancer treatment and improved patient survival, their efficacy varies widely across different tumor types and patient populations. Consequently, novel treatments are needed to interfere with the anti-tumoral immune responses and propose an adjunct therapy.

Methods: In this study, we explored the impact of the antifungal drug Sulconazole (SCZ) on PD-1 expression in activated PBMCs and T cells at both RNA and protein levels. Furthermore, we investigated SCZ's effects on NF-κB and calcium signaling pathways. Additionally, we assessed SCZ's influence on cancer cell proliferation, migration, and tumor growth using zebrafish embryo models. The drug's ability to inhibit calcium mobilization in cancer cells was also evaluated.
Results: Our results indicate that SCZ effectively inhibits PD-1 expression on activated PBMCs and T cells at both the RNA and protein levels. SCZ suppressed NF-κB and calcium signaling, crucial pathways involved in PD-1 induction. Furthermore, SCZ treatment significantly reduced cancer cell proliferation, migration, and tumor growth in vitro and in zebrafish embryos. SCZ also demonstrated an ability to inhibit calcium mobilization within cancer cells.

Conclusion: These findings highlight the potential of SCZ as a therapeutic agent, either used alone or in combination with existing treatments, to prevent T-cell exhaustion and suppress the malignant phenotype of cancer cells. This dual approach could enhance tumor eradication and improve overall cancer treatment outcomes.

P313

New insights of YAP activity in brain metastases from colorectal cancer

Inès GARROUCHE[1], Sheik EMAMBUX[1,2], Konstantin MASLIANTSEV[1,3], Amandine DESETTE[1,3], Julien TAÏEB[4], Serge MILIN[1,5], Michel WAGER[1,6], Jean-François EMILE[7], Pierre-Laurent PUIG[4], Olivier BOUCHE[8], Côme LEPAGE[9], David TOUGERON[1,10], Lucie KARAYAN-TAPON[1,3], Pierre-Olivier GUICHET[1,3]

[1] Université de Poitiers, ProDiCeT, UR 24144

[2] CHU Poitiers, Service d'Oncologie Médicale

[3] CHU Poitiers, Laboratoire de Cancérologie Biologique

[4] Department of Gastroenterology and Digestive Oncology, Georges-Pompidou European Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP-Paris Centre), Université de Paris

[5] CHU de Poitiers, Service d'Anatomie et de Cytologie Pathologiques

[6] CHU de Poitiers, Service de Neurochirurgie

[7] Paris-Saclay University, Versailles SQY University, EA4340-BECCOH, Assistance Publique-Hôpitaux de Paris (AP-HP), Ambroise-Paré Hospital, Pathology department, Boulogne

[8] CHU Reims, Service d'Oncologie Digestive

[9] Department of Digestive Oncology, University Hospital Dijon, University of Burgundy and Franche Comté, Dijon

[10] CHU de Poitiers, Service d'Hépato-gastro-entérologie

Brain metastases (BM) represent the majority of malignant intracranial tumors and a life-threatening complication for patient with colorectal cancers (CRC). Currently, YAP and TAZ, belonging to the Hippo signaling pathway, are considered as crucial malignancy factors in many solid tumors. In this work, we studied the impact of the transcriptional coactivator YAP in two different cohorts of CRC patients (PETACC8 cohort including 327 patients with grade III and a local cohort from Poitiers with 79 grade IV patients with BM) as well as its role in brain metastasis stem cells derived from CRC patients (BM-SC-CRC). First, we found that YAP expression was significantly higher in the BM cohort and associated with the tumor stage at diagnosis. However, we did not find a significant association with patient prognosis in both cohorts. In vitro, we showed that YAP was involved in proliferation and survival as its selective inhibition by verteporfin reduced the viability of BM-SC-CRC cultures. To get insight into the role of YAP in brain metastasis, we found using spatial transciptomic approach that this coactivator was strongly expressed in tumor area with metabolic changes. Altogether, our results highlight a potential role of YAP in CRC progression particularly in BM stem cells.

P314

Development of a new technology based on surface plasmon resonance to detect circulating tumor biomarkers in extracellular vesicles released by glioblastoma

Amy GATEAU[1], Hussein AKIL[1], Flavien BEFFERA[2], Shuwen ZENG[2,3], Mireille VERDIER[1], Frédéric DUMAS-BOUCHIAT[4], Manon GIREAU[4], Georges HUMBERT[2], Barbara BESSETTE[1], Fabrice LALLOUE[1]

[1] Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique, Limoges

[2] XLIM Limoges

[3] Light, Nanomaterials & Nanotechnologies (L2n), CNRS-ERL 7004, Université de Technologie de Troyes

[4] Institut de Recherche sur les Céramiques, Limoges

Glioblastoma (GBM) is the most common and most aggressive brain tumor, with a very limited median survival rate despite advances in diagnosis. The complexity of this cancer is due to tumor heterogeneity, which makes patient follow-up and management particularly difficult. To overcome this problem, it is essential to have circulating biomarkers accessible by liquid biopsy in GBM. A new method of liquid biopsy based on analysis of the contents of extracellular vesicles (EVs) is currently emerging. Previous studies have shown that the truncated EGFR variant (EGFRvIII) present in 40% of GBMs is secreted into circulating EVs in patients' plasma. EGFRvIII is constitutively activated, contributing to tumorigenicity and promoting resistance to chemotherapeutic treatments. Our preliminary results show variations in the expression of this variant between different sub-populations of EVs. Early detection of EGFRvIII in EVs by liquid biopsy using current methods is not compatible with clinical routine applications and lacks the sensitivity to detect biomarkers at low concentrations in patient blood. Our preliminary technological developments on improving the surface plasmon resonance (SPR) method offer the prospect of label-free, real-time detection of EVs from biological fluids with minimal preparation. Our aim is to improve the detection sensitivity of circulating biomarkers in extracellular vesicles derived from human glioblastomas using SPR technology.

P315

Photodynamic Therapy Against Colorectal Cancer Using Porphin-Loaded Arene Ruthenium Cages

Suzan GHADDAR[1,2], Aline PINON[1], Manuel GALLARDO-VILLAGRAN[1,3], Jacquie MASSOUD[1], Catherine OUK[4], Claire CARRION[4], Mona DIAB-ASSAF[2], Bruno THERRIEN[3], Bertrand LIAGRE[1]

[1] Univ. Limoges, LABCiS, UR 22722, Faculté de Pharmacie

[2] Doctoral School of Sciences and Technology, Lebanese University, Hadath, Beirut, Lebanon

[3] Institut de Chimie, Université de Neuchâtel, Avenue de Bellevaux 51, Neuchâtel, Switzerland

[4] Univ. Limoges, CNRS, Inserm, CHU Limoges, BISCEm, UAR 2015, US 42

Colorectal cancer (CRC) is the third most common cancer in the world with an ongoing rising incidence. Despite secure advancements in CRC treatments, challenges such as side effects and therapy resistance remain to be addressed. Photodynamic therapy (PDT) emerges as a promising modality, clinically used in treating different diseases, including cancer. Among the main chal-lenges with current photosensitizers (PS), hydrophobicity and low selective uptake by the tumor remain prominent. Thus, developing an optimal design for PS to improve their solubility and en-hance their selective accumulation in cancer cells is crucial for enhancing the efficacy of PDT. Targeted photoactivation then triggers the production of reactive oxygen species (ROS) which promote an oxidative stress within cancer cells and ultimately lead to their death. Ruthenium (Ru)-based compounds, known for their selective toxicity towards cancer cells, hold potential as anti-cancer agents. In this study, we investigated the effect of two distinct arene-Ru assemblies, which lodge porphin PS in their inner cavity and tested them as PDT agents on HCT116 and HT-29 human CRC cell lines. The cellular internalization of the porphin-loaded assemblies was confirmed by fluorescence microscopy. Additionally, significant photocytotoxicity was observed in both cell lines after photoactivation of the porphin in the cage systems, inducing apoptosis through caspase activation and cell cycle progression disruptions. These findings suggest that arene-Ru assemblies lodging porphin PS are potent candidates for PDT of CRC.

P316

Time to use the right classification to predict the severity of Checkpoint Inhibitor-induced Liver Injury

Lina HOUNTONDJI, Alexandre MARIA, Lucy MEUNIER

CHU de Montpellier

Background and Aims: While immune checkpoint inhibitors are revolutionizing cancer therapy, Checkpoint Inhibitor-induced Liver Injury is a significant immune-related side effect of this immunotherapy. This study focuses on the severity classifications and characteristics of patients with Checkpoint Inhibitor-induced hepatitis.

Methods: A retrospective analysis of patients with severe Checkpoint Inhibitor-induced hepatitis grade 3 and 4 according to the recommended Common Terminology Criteria for Adverse Events classification was conducted. Data on clinicobiological characteristics, treatment and outcomes were collected from 3 university hospitals, and causality was assessed by using the updated Roussel Uclaf Causality Assessment Method. The severity of hepatitis was assessed using the Model for End-stage Liver Disease score, the Drug-Induced Liver Injury Network, and the Drug-Induced Liver Injury International Expert Working Group classifications.

Results: We retrospectively included 100 patients presenting various hepatitis patterns with a median time to onset of 20 days after checkpoint inhibitors. Severity grading varied significantly among the classifications used. A lower incidence of severe cases was observed when using the Drug-Induced Liver Injury classifications instead of the recommended Common Terminology Criteria for Adverse Events classification, and this was correlated with outcomes.

Conclusions: This retrospective study challenges the efficacy of the Common Terminology Criteria for Adverse Events classification in defining the severity of Checkpoint Inhibitor-induced hepatitis and suggests that the traditional hepatology-focused scores may be more relevant. The Common Terminology Criteria for Adverse Events classification is inconsistent and gives equal weight to jaundice and elevated transaminases, which leads to steroid overtreatment and limits the rechallenge of immune checkpoint inhibitors.

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Ursodeoxycholic acid alone is effective and safe to treat cholestatic Checkpoint Inhibitor-induced Liver Injury (U-CHILI): a proof of concept

Lina HOUNTONDJI, Alexandre MARIA, Lucy MEUNIER

CHU de Montpellier

Background: CHeckpoint Inhibitor-induced Liver Injury (CHILI) is an immune-related adverse event secondary to immune checkpoint inhibitors (ICIs). Corticosteroids are recommended in first line, but ESMO guidelines have also recommended UDCA in ICI-related cholangitis. Furthermore, ICI-induced cholangiopathy may be resistant to corticosteroids. Thus, we analyzed real-world data on the off-label use of first-line UDCA alone in CHILI to assess its efficacy in CHILI.

Methods: We collected data among patients presented at the "Toximmun" multidisciplinary meeting. Patients treated with first-line UDCA were included. The hepatitis pattern was calculated with the ratio (R) = (ALT/ULN)/(ALP/ULN). Response criteria to UDCA treatment was defined as decrease in ALP and GGT ≥ 50%. Recurrent CHILI (rCHILI) was defined as ALP ≥ 50 % after ALP improvement (i.e. response to UDCA treatment), and chronic CHILI was defined as ALP>2 x ULN or ALT>5 x ULN after 6 months.

Results: This study included 21 patients treated with first-line UDCA. A cholestatic pattern was observed in 20 patients (95.2%). We found that patients with macroscopic bile duct tract injury had significantly more recurrent CHILI (n= 4, 57.1%; p= 0.006), and higher levels of eosinophil polynuclear (p= 0.04) compared to patients without macroscopic bile duct injury. Finally, 18 patients (85.7%) improved with UDCA only, and 4 patients had chronic CHILI (19.1%). ICI was rechallenged in 13 patients (61.9%).

Conclusion: We highlight that cholestatic and mixed CHILI may benefit from UDCA treatment alone in first line, instead of corticosteroids. Further prospective studies are needed to precise the indication in this condition.

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Mechanisms involved in early tumor dissemination in colorectal cancer, and validation in patients

Tinhinan LAHLOU[1], Zeinab HOMAYED[1], Guillaume BELTHIER[1], Szimonetta HIDEG[1], Jean François BOURGAUX[2], Adam PROST[2], Frederic LAGARRIGUE[3], Jean ALBRENGUES[4], Caroline BONNANS[1], Julie PANNEQUIN[1]

[1] Institut de Génomique Fonctionnelle, Montpellier

[2] CHU de Nîmes

[3] Institut de Pharmacologie et de Biologie Structurale, Toulouse

[4] Institut de recherche sur le cancer et le vieillissement de Nice (IRCAN), Nice

Colorectal cancer (CRC) is the third most common cancer in men and the second in women, making it the second leading cause of cancer-related deaths globally. Early diagnosis significantly improves outcomes, with a 5-year survival rate of 90% for stage 1, compared to just 14% in cases with metastases. While 80% of CRCs develop from benign polyps, only 20% progress to adenocarcinomas, emphasizing the need for better biomarker identification to predict high-risk lesions and limit unnecessary surveillance.

Our study explores the early dissemination of tumor cells (eDTCs) in CRC. Using an inducible mouse model with intestinal epithelial cells marked by TdTomato and an APC gene mutation, we detected eDTCs in the liver. These cells, in synergy with systemic factors such as TIMP-1, SDF-1, CXCL2, and M-CSF, drive hepatic remodeling by recruiting myeloid cells, particularly macrophages and neutrophils, which primes the liver for metastasis. TIMP-1 plays a pivotal role in this recruitment process, as confirmed in both our murine model and in patients with intestinal polyps who exhibited elevated plasma levels of TIMP-1.

One of the key findings of our study involves SerpinE1, which could potentially play a significant role in early tumor dissemination. High SerpinE1 expression was observed in circulating tumor cells (CTCs) from patients with adenomas, correlating with increased NETosis, a process by which neutrophils form extracellular traps (NETs) that capture CTCs. SerpinE1 may also enhance the epithelial-mesenchymal transition (EMT), facilitating tumor cell migration and invasion. Functionally, in vitro tests demonstrated that the addition of SerpinE1 to adenoma cells promoted cell migration and EMT marker expression, while TGF-β stimulation led to heightened SerpinE1 secretion.

In conclusion, our study highlights the critical roles of TIMP-1 and the potential involvement of SerpinE1 in early CRC dissemination and metastatic niche formation.

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Use of γδ T cells armed with monoclonal antibodies as a novel cancer cell therapy

Marion LENAIN[1,2], Anna MACMANUS[1,2], Cécile DEJOU[1,2], Nathalie BONNEFOY[1,2], Virginie LAFONT[1,2]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Institut du Cancer de Montpellier

γδ T cells are involved in the anti-tumor response of many solid and hematological cancers (e.g., myeloma, lymphoma, melanoma, breast, colon, lung, ovarian and prostate). Their anti-tumor properties are based on a direct cytotoxic activity against tumor cells and their ability to stimulate/regulate the biological functions of other immune cells, such as dendritic cells (DC), CD8 T cells and NK cells, which are necessary for the initiation and establishment of an effective anti-tumor immune response. In contrast to conventional αβ T cells, γδ T cells: (i) display a potent MHC-independent reactivity against a broad panel of tumors, (ii) show limited if any alloreactivity and (iii) can be massively and specifically expanded from samples (e.g. peripheral blood). This supports why γδ T cells are considered as highly attractive therapeutic targets for anti-tumor immunotherapies. Although a strong reactivity against tumor cells has been reported for human Vδ1+, Vδ2+ and Vδ3+ T cell subsets, γδ T cell-based immunotherapies have primarily targeted the Vδ2+ subset (mainly represented by the Vγ9Vδ2 T cells) due to their easy isolation from blood and their amplification with specific molecules. Initial clinical trials have been based on adoptive transfer of *ex vivo* stimulated Vγ9Vδ2 T cells or on their *in vivo* stimulation with clinical grade agonists and have shown their safety for the patients but only objective responses in 10 to 33% of patients with hematological and solid malignancies. Several means have been used to improve the anti-tumor activity of γδ T cells based on increasing their cytotoxic activity, better targeting of tumor cells or even better recruitment into tumors. Currently, clinical trials based on γδ T cell therapies, are using CAR γδ T cells or novel activating molecules or other γδ T cell subsets. To improve both the cytotoxic activity of γδ T cells and their targeting of tumor cells, we are considering their ability to express the low affinity receptor to IgG (FcγRIII) or CD16 as a new way to use them. Indeed, several studies, including our own, have shown that γδ T cells can express CD16 and similarly to NK cells, CD16+ γδ T cells are able to perform antibody-dependent cellular cytotoxicity (ADCC). Furthermore, their unique property of not being MHC-restricted allows them to be used in allogeneic conditions. We hypothesized that γδ T cells could be "armed" by binding of CD16 with monoclonal antibodies selected to recognize tumor-specific antigens and lyse tumor cells via their ADCC capability. Our first results show that the expression of CD16 in γδ T cells differs depending on their differentiation status. Second, we have shown that γδ T cells have cytotoxic activity against cancer cells in 2D culture models. Currently, we are working on the development of 3D models of different ovarian cancer lineages. Our preliminary results in 3D models show some promising results on the ability of γδ T cells to infiltrate the spheroids. These results are very interesting and require further investigation.

P320

The Furin/ TGFβ1/ PTGS2 axis promotes oncogenesis in KRAS/BRAF-mutated colorectal cancer

Yiyang LIU[1], Zongsheng HE[2], Sabine TEJPAR[3], Abhishek D. GARG[4], Torsten STEINMETZER[5], John CREEMERS[1], Abdel-Majid KHATIB[6]

[1] Laboratory for Biochemical Neuroendocrinology, Department of Human Genetics, KU Leuven, Belgium

[2] Department of Gastroenterology, Daping Hospital, Army Medical University, Chongqing, China

[3] Digestive Oncology, Department of Oncology, KU Leuven, Belgium

[4] Laboratory for Cell Stress & Immunity (CSI), Department of Cellular & Molecular Medicine, KU Leuven, Belgium

[5] Department of Pharmaceutical Chemistry, Philipps-University Marburg, Germany

[6] INSERM, LAMC, UMR 1029, Pessac & Institut Bergonié, Bordeaux

Colorectal cancer (CRC) is a leading malignancy and the second-highest cause of cancer-related deaths globally. Genetic factors, aging, and lifestyle significantly contribute to CRC risk, with common mutations in oncogenes such as KRAS and BRAF driving tumor progression through continuous activation of signaling pathways like MAPK and PI3K/Akt. These mutations complicate treatment responses and highlight the need for targeted therapeutic approaches. Furin, a proprotein convertase, is broadly expressed and is pivotal in activating numerous substrates, including growth factors and adhesion molecules, which are crucial for tumor growth and metastasis. Notably, Furin's regulation of PTGS2 has been implicated in tumorigenesis and inflammation in KRAS/BRAF mutated CRC. This study investigates the mechanisms by which Furin modulates PTGS2 expression and examines the involvement of the TGFβ1 signaling pathway in this process. Our findings reveal that the Furin/TGFβ1/PTGS2 axis functions as a proto-oncogene regulator in CRC, suggesting that targeting this pathway could offer new therapeutic strategies for patients with KRAS/BRAF mutations. Understanding the molecular interplay between Furin and PTGS2 provides valuable insights into CRC progression and opens avenues for developing more effective, personalized treatments.

P321

Impact of the Pregnane X Receptor (PXR) on the sensitivity of skin melanoma to targeted therapies

Stefan NICOLESCU[1], Alice MATHEUX[1], Mihaly LEIWOLF[1], Laura TALLEVAST[1], Fanny LEENHARDT[1], Litaty MBATCHI[1,2], Philippe POURQUIER[1], Alexandre EVRARD[1,2]

[1] IRCM, Univ Montpellier, ICM, INSERM

[2] CHU Nîmes-Carémeau

The difficulty in effectively treating patients suffering from skin melanoma resides in the resistance of tumors to therapies and the associated risk of recurrence. The mechanisms by which the tumor could modify drug pharmacokinetics are poorly studied and may influence the tumor's adaptation to treatment. Immunohistochemical analysis revealed, for the first time, significant and heterogeneous expression of the nuclear receptor PXR (Pregnane X Receptor) in skin melanoma samples. In addition, drug screening experiments on cell models overexpressing PXR have shown that PXR can be activated by several BRAF inhibitors (BRAFi) that are currently used in the clinic, including dabrafenib, which has been shown to be a potent agonist. Once activated, the receptor can directly regulate the expression of numerous genes involved in the metabolism and membrane transport of xenobiotics. Thus, PXR-mediated regulation may alter the sensitivity of cancer cells to kinase inhibitors (KIs) and affect the response to therapy. We are using A375 and SK-MEL-28 melanoma cell lines carrying a BRAF V600E mutation to study the impact of PXR expression. Proliferation assays showed that cancer cells overexpressing PXR were more sensitive in vitro to treatments combining BRAFi and MEK inhibitors (MEKi), compared with wild-type cancer cells. This major observation led us to hypothesize that PXR activation in melanoma patients treated with dabrafenib could modulate the success of the BRAFi/MEKi combination used in routine therapy for this pathology. Therefore, the identification of PXR as a potential molecular marker for therapy selection and response efficacy may contribute to the optimization of therapeutic strategies for patients suffering from skin melanoma, in order to improve the efficacy of KI-based targeted therapies.

P322

What is the therapeutic efficacy of pressurised intraperitoneal aerosol chemotherapy in a rabbit model of gastric peritoneal metastases?

Abdelkader TAIBI[1,2], Marie Laure PERRIN[2], Catherine YARDIN[1,2], Sylvia M BARDET[2], Sylvaine DURAND FONTANIER[1,2]

[1] CHU de Limoges

[2] XLIM Limoges

This study presents an experimental investigation of the feasibility in a rabbit model with gastric peritoneal metastases, evaluating the efficacy of PIPAC oxaliplatin (n=5) compared to PIPAC cisplatin-doxorubicin (n=5), and a group treated with physiological saline, on D8, D15, and D21. Assessment of the animals' well-being score was undertaken prior to each PIPAC procedure. Abdominal CT-Scans were performed before PIPAC1 and after PIPAC3. During each PIPAC session, ascites volume and Peritoneal Cancer Index (PCI) were determined, along with biopsies from at least three nodules. Evaluation of Histological Response (HR) based on the Peritoneal Regression Grading Score (PRGS), were performed. Additionally, a detailed histological examination using Microscopic-Multiphoton-imaging was conducted.

The overall well-being score showed improvement in all groups (0.6 +- 0.55 for control group; 6 +- 2.24 for Cisplatin-Doxorubicin; and 7 +- 2.74, NS). The PCI score decreased solely in the Oxaliplatin group between PIPAC1 and PIPAC3 (11 +- 1.7 vs 8 +- 2.8 p=0.01). It remained stable in the Cisplatin-Doxorubicin group (11 +- 1.3 vs 11 +- 3.1 NS) but significantly increased in the control group (8 +-1.9 vs 21+-1.8 p=0.001). The PCI score post-PIPAC3 was notably elevated in the control group compared to the Oxaliplatin and Cisplatin-Doxorubicin groups (21+-1.8 vs 8+-2.8 vs 11+-3.1, respectively, p<0 .05). The median PRGS was recorded as being 2 for both Oxaliplatin and Cisplatin-Doxorubicin groups but significantly higher in the Control group (3.25 p=0 .0003). This experimental inquiry confirms the therapeutic impact of Oxaliplatin and Cisplatin-Doxorubicin administered via PIPACs on gastric peritoneal metastasis.

Posters – Axis 4
Cancers : enjeux individuels et collectifs

P401

Prise en charge thérapeutique des cancers colorectaux chez les personnes âgées dans l'Hérault : étude en population entre 2014 et 2021

Claudine GRAS-AYGON, Anne-Sophie FOUCAN, Brigitte TRÉTARRE

Registre des Tumeurs de l'Hérault

Contexte :
La population française est vieillissante, or l'incidence des cancers augmente avec l'âge. Désormais, plus de la moitié des cas sont diagnostiqués après 70 ans. Le cancer colorectal est le deuxième cancer en termes d'incidence chez les personnes âgées de plus de 80 ans. Le primo-traitement est décidé en Réunion de Concertation Pluridisciplinaire (RCP), il dépend de l'histologie, du stade de la maladie, de l'âge, des comorbidités et des préférences du patient. Seuls les registres de cancer peuvent évaluer les prises en charge thérapeutiques initiales en vie réelle.
L'objectif de cette étude est d'analyser les prises en charge thérapeutiques des cancers colorectaux chez les personnes âgées de plus de 70 ans et leurs évolutions au cours du temps.

Méthode :
Tous les nouveaux cas de cancers colorectaux diagnostiqués entre 2014 et 2021 chez les personnes âgées de plus de 70 ans ont été extraits de la base de données du registre des tumeurs de l'Hérault.
L'âge est regroupé en 5 catégories : 70-74, 75-79, 80-84, 85-89 et les 90 ans et plus.
Les primo-traitements possibles sont, pour le cancer du côlon et du tiers supérieur du rectum (haut rectum) : chirurgie, chimiothérapie, pour le cancer du rectum (moyen et bas rectum) : chirurgie, chimiothérapie et radiothérapie.

Résultats :
Sur la période 2014-2021, 3 742 nouveaux cas de cancer colorectal chez les plus de 70 ans ont été inclus dans l'analyse dont 80.6% de cancer du côlon et 19.4% de cancer du rectum.

• Le stade est renseigné pour 3 510 patients de plus de 70 ans (94%). Plus l'âge augmente, plus le cancer colorectal est diagnostiqué à un stade avancé et plus il y a de stades inconnus ($p < 0.001$). Chez les 90 ans et plus, 6.8% sont diagnostiqués au stade I contre 21.9% chez les 70-74 ans. Chez les 90 ans et plus, 29% sont diagnostiqués à un stade IV, 21.6% ont un stade inconnu.
• Prise en charge thérapeutique initiale :
- Pour le cancer du côlon, 87.4% des 70 à 74 ans ont bénéficié d'une chirurgie, ce taux diminue pour les 80-89 ans autour de 70% et baisse à 54% chez les plus de 90 ans. Les stades I, âgés entre 70 et 89 ans, étaient tous opérés et il n'y a pas d'effet du temps. En revanche pour les 90 ans et plus 42% étaient opérés en 2014-2015 contre 100% en 2020-2021. Pour les stades IV, 53% des 70-74 ans étaient opérés contre 29% chez les plus de 85 ans sans effet période. Il y a un effet de l'âge sur la réalisation de la chimiothérapie passant de 42.7 % chez les 70-74 ans à 8.7% pour les 85-89 ans et 2.8% pour les plus de 90 ans.
- Pour le cancer du rectum, près de 76% des 70 à 74 ans ont bénéficié d'une chirurgie, ce taux diminue pour les plus 80-89 ans autour de 60% et baisse à 23% chez les plus de 90 ans. Quatre-vingt-quinze pourcents des stades I, âgés entre 70 et 74 ans, ont eu une chirurgie, en revanche pour les 90 ans et plus le taux était de 66%. Pour les stades IV, 31% des 70-74 ans étaient opérés contre 14% chez les 85-89 et aucun chez les 90 ans et plus. Il y a un effet de l'âge sur la réalisation de la chimiothérapie passant de 71.1% chez les 70-74 ans à 20% pour les 85-89 ans et 4.65% pour les plus de 90 ans. Il y a un effet de l'âge sur la réalisation de la radiothérapie passant de 54% chez les 70-74 ans à 41.7% pour les 85-89 ans et 23.6% pour les plus de 90 ans. Ce taux augmente de manière significative selon les années pour les 90 ans et plus.

Conclusion :
Cette étude de population fournit des caractéristiques des cancers colorectaux chez les personnes âgées de plus de 70 ans dans l'Hérault : stades plus péjoratifs avec l'âge qui augmente et plus de stades inconnus ; diminution de la chirurgie avec l'âge mais près de 54 % des 90 ans et plus ayant un cancer du côlon ; la chimiothérapie est peu utilisée chez les plus de 85 ans ; pour le cancer du rectum la radiothérapie diminue avec l'âge, mais le taux augmente avec les années.

P402

Modèles de prescription et d'utilisation de médicaments psychoactifs chez les patients atteints de cancer dans les pays à revenu faible et intermédiaire (PRFI) : revue systématique

Tassadit MERABTINE[1,2], Dieu Donné GNONLONFOUN[2,3], Zeinab TARHINI[4], Niki CHRISTOU[4,5], Jeremy JOST[1,6]

[1] Inserm U1094, IRD UMR270, Univ. Limoges, CHU Limoges, EpiMaCT - Epidémiologie des maladies chroniques en zone tropicale, Institut d'Epidémiologie et de Neurologie Tropicale, OmegaHealth, Limoges
[2] Laboratoire d'Epidémiologie des Maladies Chroniques et Neurologiques (LEMACEN), Faculté des Sciences de la Santé, Université d'Abomey-Calavi, Cotonou, Bénin.
[3] Centre National Hospitalier et Universitaire Hubert KM de Cotonou, Bénin
[4] Laboratoire Inserm U1308 CAPTuR - Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique, CHU de Limoges
[5] Service de chirurgie digestive, CHU de Limoges
[6] Service de pharmacie, CHU de Limoges

Introduction :
Les patients atteints de cancer font souvent face à des troubles psychologiques tels que l'anxiété et la dépression, rendant l'utilisation de traitements psychoactifs essentielle pour améliorer leur qualité de vie et leur bien-être émotionnel. Cependant, dans les pays à revenu faible et intermédiaire (PRFI), la prescription et l'utilisation de ces médicaments rencontrent des obstacles majeurs. Le diagnostic tardif du cancer, fréquent dans ces régions, complique la prise en charge globale des patients. De plus, la santé mentale des patients cancéreux n'est pas systématiquement évaluée, et même lorsqu'elle l'est, elle est souvent mal diagnostiquée en raison d'absence d'outils validés. Ces difficultés sont accentuées par des inégalités dans les pratiques de prescription et d'utilisation, influencées par la situation géographique et les régimes d'assurance, ce qui crée d'importantes disparités dans l'accès aux traitements. Cette étude vise à identifier les schémas de prescription et d'utilisation des médicaments psychoactifs chez les patients cancéreux dans les PRFI.

Méthodes :
Cette revue systématique a été réalisée conformément aux lignes directrices PRISMA. Le protocole de l'étude a été enregistré PROSPERO sous le numéro d'enregistrement CRD42024560300. Une recherche exhaustive a été effectuée dans six bases de données électroniques : PubMed, Scopus, Google Scholar, SciELO, AJOL et APA PsychArticles. Les critères d'inclusion se sont concentrés sur des études observationnelles qui examinent la prescription et l'utilisation de médicaments psychoactifs chez les patients cancéreux dans les PRFI selon la classification de la Banque mondiale. Les études éligibles étaient celles qui exploraient spécifiquement l'utilisation de ces médicaments pour gérer des troubles psychologiques tels que l'anxiété, la dépression et d'autres conditions de santé mentale liées chez les patients cancéreux.

Résultats :
Sur 1237 articles identifiés, dix études ont été incluses, comprenant deux études de cohorte et huit études transversales menées en Chine, en Inde, au Brésil et en Malaisie. la majorité des études étaient menées dans un contexte hospitalier. Les médicaments psychoactifs les plus couramment prescrits et utilisés étaient les antidépresseurs, les benzodiazépines, les antipsychotiques et les hypnotiques, principalement utilisés pour traiter la dépression, l'anxiété et les troubles du sommeil. La prescription et l'utilisation de ces médicaments étaient influencées par des facteurs tels que les comorbidités, la polypharmacie, l'âge avancé, la multimorbidité, les disparités géographiques et la couverture d'assurance santé. L'utilisation potentiellement inappropriée des antidépresseurs et des benzodiazépines a été fréquemment observée, en particulier chez les patients âgés souffrant de multimorbidité. Plusieurs études ont également noté que le faible taux de prescription de médicaments psychotropes chez les patients cancéreux pourrait être dû à un diagnostic tardif du cancer, à un sous-diagnostic de la dépression ou à une prudence accrue dans la prescription de ces médicaments. La plupart des prescriptions étaient basées sur les symptômes et initiées par des non-psychiatres, ce qui entraînait souvent un traitement inadéquat.

Conclusion :
En conclusion, la revue met en évidence des défis significatifs dans la prescription et l'utilisation de médicaments psychoactifs chez les patients cancéreux dans les PRFI, notamment en raison d'un sous-diagnostic des troubles mentaux chez ces patients. Des facteurs tels que les comorbidités, les disparités géographiques et la multi morbidité contribuent à l'utilisation inappropriée de ces médicaments, en particulier chez les personnes âgées. Il est essentiel de renforcer la collaboration entre les services d'oncologie et de santé mentale afin d'optimiser l'évaluation et la prise en charge des troubles psychologiques chez les patients cancéreux.

P403

Les soins oncologiques de support pour les personnes avec un trouble du développement intellectuel (PDI) : Bilan d'un secteur à développer

Elisangela OLIVIER, Elodie NEUMANN, Amaelle OTANDAULT, Marc PALPACUER, Daniel SATGE

ONCODEFI, Montpellier

Contexte : La mortalité par cancer chez les personnes avec un trouble du développement intellectuel (PDI) est 1.5 fois plus élevée que dans la population générale. Ce trouble correspond à une limitation du fonctionnement intellectuel et des comportements adaptatifs apparus avant l'âge de 18 ans. Le parcours de soins des PDI en cancérologie est complexe, nécessitant l'intervention de plusieurs catégories de professionnels de santé, sociaux et médicosociaux. Les soins oncologiques de support (SOS) sont destinés à améliorer la qualité de vie et à gérer les conséquences de la maladie et des traitements. L'équipe médicale repère dans un premier temps les besoins. Les SOS se répartissent en 4 soins "socle" : prise en charge de la douleur, suivi diététique et nutritionnel, soutien psychologique et accompagnement social ; et de 5 soins complémentaires : développement de l'activité physique, conservation de la fertilité, correction de troubles de la sexualité et conseils d'hygiène de vie ainsi que soutien psychologique des proches et des aidants. Les soins palliatifs (SP), nécessaires quand plus aucun traitement curatif n'est envisageable, font aussi partie des SOS. Nous avons évalué les informations relatives aux soins de support en oncologie chez les PDI.

Résultats : Aucun document, à notre connaissance, ne met à disposition des équipes oncologiques l'information nécessaire pour faire bénéficier les PDI des SOS. Cela traduit la rareté des études sur le sujet. Deux grands thèmes ont été explorés : la douleur et les soins palliatifs. Chez les PDI, la douleur est souvent méconnue et difficile à évaluer, plusieurs échelles sont maintenant disponibles, mais mal connues. Les soins palliatifs ont été largement étudiés par une équipe anglaise (I.Tuffrey-Wijne) et dans le cadre d'une recherche européenne dans 13 pays qu'a coordonné l'European Association for Palliative Care, les connaissances sont rapportées dans le " livre blanc des soins palliatifs" gratuitement accessible (https://oncodefi.org/wp-content/uploads/2022/03/Livre-Blanc-de-lEAPC.pdf). Les autres thèmes : nutrition, soutien psychologique, soutien social, développement de l'exercice physique, soins socio-esthétiques etc. n'ont pas fait l'objet de travaux publiés.

Discussion : Les PDI sont, par définition, dépendants de leur entourage familial et professionnel. Le cancer est très mal connu des professionnels du secteur médicosocial. Les équipes oncologiques n'ont pas reçu d'enseignement sur les patients DI. Dans ce contexte, les besoins des PDI ne sont pas identifiés. Quand bien même ils le seraient, les informations de base font défaut. Il est nécessaire, pour combler ces lacunes, d'adapter les dispositifs accessibles à la population générale aux PDI en tenant compte de leurs spécificités. Par exemple, les études sur l'activité physique adaptée qui existent pour la prévention du cancer chez les PDI pourraient être proposées dans le cadre des SOS. Il est aussi très important de sensibiliser le secteur oncologique aux moyens d'améliorer la qualité de vie de ces personnes lorsqu'elles sont soignées pour un cancer.

Conclusion : Alors que les besoins en accompagnement d'un cancer pour les personnes avec un trouble du développement intellectuel sont plus importants qu'en population générale et que le parcours de soin est plus complexe, ces personnes ont très peu accès aux soins de support. La gestion de la douleur et l'accompagnement en soins palliatifs ont fait l'objet d'études et sont documentés dans la littérature médicale et médico-sociale. Afin d'alléger les souffrances et d'améliorer la qualité de vie de ces personnes il est important 1) de développer des recherches et des actions pour faire le bilan des possibilités 2) d'informer les professionnels des équipes oncologiques et du secteur médico-social des besoins et des possibilités accessibles.

P404

Prise en charge des Cancers de Prostate localisés chez les hommes jeunes dans l'Hérault et suivi à un an des plaintes fonctionnelles après prostatectomie

Brigitte TRETARRE[1,2], Stéphanie TROUCH-SABATIER[1], Anne-Sophie FOUCAN[1], François IBORRA[1]

[1] Registre des Tumeurs de l'Hérault
[2] Centre d'épidémiologie et de recherche en santé des populations

Introduction : Le cancer de la prostate (CaP) se situe au 1er rang des cancers chez l'homme. Il représente 25 % de l'ensemble des cancers incidents masculins et survient dans 66 % des cas chez des hommes âgés de 65 ans et plus. Il touche également des hommes plus jeunes pour lesquels la principale prise en charge montrée dans la littérature est la prostatectomie radicale (PR). Notre étude s'intéresse à la prise en charge de patients jeunes (55 ans et moins) diagnostiqués d'un CaP localisé (CaPL) et aux plaintes fonctionnelles (continence, fonction érectile) qui persistent un an après une prostatectomie.

Matériel et méthodes : Notre étude a inclus les patients de 55 ans et moins résidant dans l'Hérault, diagnostiqués entre 2017 et 2021 d'unicancer de prostate localisé (cT1-cT2N0M0).
Les variables d'intérêt retenues étaient le PSA au diagnostic et le facteur de risque selon la classification de D'Amico(faible risque (PSA <10ng/ml et ISUP 1 et cT1-2a), risque intermédiaire (PSA compris entre 10 et 20ng/ml ou ISUP 2/3 ou cT2b) et haut risque (PSA supérieur à 20ng/ml ou ISUP 4/5 ou cT2c)). En l'absence de certains paramètres, ce facteur a été noté «non évaluable». Les traitements de ces patients ont été : prostatectomie radicale (PR), surveillance active (SA) ou autres traitements (radiothérapie ± hormonothérapie, curiethérapie, …). Pour les patients traités par PR, les plaintes fonctionnelles telles que la continence et la fonction érectile ont aussi été analysées avec un recul d'un an après leur intervention chirurgicale.

Résultats : Notre étude a concerné 156 patients : 146 dépistés par un dosage du PSA, 6 suite à une RTUP (résection trans-urétrale de la prostate) pour une hypertrophie bénigne de la prostate (HBP) et 4 suite à une CPT (cystoprostatectomie) pour cancer de vessie invasif. Pour les patients avec un diagnostic de CaP après RTUP, 5 (83,3%) ont été placés enSA et 1 (16,7%) a bénéficié d'un autre traitement
(radiothérapie associée à une hormonothérapie). Les quatre patients diagnostiqués sur CPT ont été mis en surveillance avec un contrôle du PSA.
Pour les 146 patients dépistés par un dosage du PSA, 140 (95,9%) avaient un PSA au diagnostic supérieur à 4ng/ml. Selon la classification de D'Amico, 55 (37,7%) étaient de faible risque, 65 (44,5%) de risque intermédiaire, 23 (15,7%) de haut risque et 3 (2,1%) de risque non évaluable. Quatre-vingt-dix-neuf patients (67,8%) ont eu une PR versus 27 (19,2%) mis en SA et 19 (13,0%) ayant eu un autre traitement.
Sur 70 patients ayant eu une PR avec un suivi post-chirurgical d'un an et plus, 50 sont continents (71,4%), 11 (15,7%) présentent toujours une incontinence et 9
(12,9%) cas ne sont pas renseignés. Pour 50 patients (71,4%), il persiste une dysfonction érectile dont 13 (18,6%) classés en faible risque de D'Amico.

Conclusion : Notre étude a montré que les CaP localisés chez les sujets jeunes dans l'Hérault étaient principalement traités par PR (N= 103 cas, CPT inclus) qui est le traitement conseillé pour les CaP de risque intermédiaire et haut risque. Les patients de faible risque de notre étude ont bénéficié aussi bien d'une SA que d'une PR, ce qui correspond aux recommandations préconisées par le CCAFU 2018-2022. Notre étude a également montré qu'un an après une PR les plaintes fonctionnelles chez ces hommes jeunes étaient fréquentes, notamment en ce qui concerne la dysfonction érectile. Afin de prendre en considération les séquelles post-chirurgie chez les sujets jeunes, il serait intéressant de prendre en considération l'âge du patient au diagnostic et de les inclure dans les critères de sélection de SA (PSA, ISUP, Toucher Rectal, pourcentage de biopsies envahies, …) et en particulier pour les CaP de faible risque.

Posters – Axis 5
Health Technologies

P501

TAM Targeting with vectorized magnetic nanoparticles for anticancer therapies

Chloé BAZILE, Mary POUPOT, Véronique GIGOUX, Pascal CLERC, Fabien GAVA, Véra PANCALDI

Centre de Recherches en Cancérologie de Toulouse

Tumor-associated macrophages (TAM) are well known as protecting tumor cells against apoptosis, immune attacks and therapies. Elimination of these pro-tumor TAM remains a challenge in cancer therapies. Several ways of TAM targeting exist, however they are not specific, potentially leading to serious adverse effects.

We produced and patented a monoclonal antibody called 6-25 capable to specifically recognize the nurse-like cells (NLC), TAM of the chronic lymphocytic leukemia (CLL), and TAM from different solid cancers. We showed that the 6-25 antibody recognizes the folate receptor beta (FRB) at the surface of these cells and is internalized in these cells without inducing any toxicity. The FR is also expressed by the M2 monocytes-derived macrophages (M2M) but not by the M1 monocytes-derived macrophages (M1M) or other myeloid cells.

The goal of the project is to produce a tool that specifically targets and kills pro-tumor TAM in the tumor in order to sensitize cancer cells to chemo- or immunotherapies.

In cancer treatment, magnetic hyperthermia represents an emerging approach with promising therapeutic potential. The magnetic hyperthermia induces an increase of the temperature following the localized application of a high frequency alternating magnetic field (AMF) to a tumor containing magnetic nanoparticles (MNP), leading to cell death. Iron oxide MNP are highly biocompatible and non-toxic (rapid degradation with iron cations recycling), which allows their combination with conventional therapies.

Thus, we developed a magnetic nanoparticle based on a PEGylated iron oxide MNP functionalized with the 6-25 mAb (MNP-6-25) as a specific tool to target pro-tumor TAM, thanks to a Michael reaction, and a fluorophore, the Cyanine 5, allowing its detection.

For this study, two cellular models were used: M2M as expressing FRB at their surface, and M1M as negative control without FRB. M2M and M1M were obtained by the culture of monocytes from healthy donors in the presence of appropriate cytokines cocktails.

First, we showed that MNP-6-25 were not toxic toward M1M and M2M in a concentration up to 64 µg Fe2O3/mL after 72h incubation. Then, MNP-6-25 binds specifically M2M but not M1M, with a maximum of binding at 48h of incubation at 8 µg/mL. Finally, confocal microscopy imaging showed that MNP-6-25 accumulated in lysosomes of M2M.

Secondly, we performed an alternative model to study the penetration and the specificity of MNP-6-25 in a 2D and 3D co-culture model and in a same time to study the impact of M1M or M2M on the proliferation of cancer cells. We realized 3D co-cultures with M2M or with M1M and A549 (lung cancer cell line) using the technic of ultra-low-attachment plate for the formation of spheroids. We showed a higher proliferation of cancer cells with M2M than with M1M, in 2D co-culture. However, in 3D co-culture models, we observed the same profile of cancer cells proliferation with M2M or M1M, correlated with an increasing of M2M markers on M1M. These models are also developped with another cancer cell line Calu-1 of NSCLC. Furthermore, we showed in these models a specific targeting for M2M macrophages with MNP-6-25.

In perspective, we plan to evaluate the efficacy and the specificity of MNP-6-25 to kill M2M in this 3D model upon application of magnetic field and then the in vivo targeting of macrophages in a murine model of non-small cell lung cancer with MNP-6-25.

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k-mer based exploration of large RNA sequencing datasets and applications to biomarkers, diagnosis and prognosis in cancers with Transipedia.org

Thérèse COMMES, Chloé BESSIERE, Raissa DA SILVA, Florence RUFFLE, Benoit GUIBERT, Anthony BOUREUX, Cédric RIEDEL, Camelia SENNAOUI, Jerome REBOUL, Nicolas GILBERT

Bio2M, Institut de Recherche en médecine regeneratrice, INSERM U1183 Hôpital Saint-Eloi, Montpellier

Large scale transcriptome analysis from public RNA-seq datasets is a key challenge to identify transcriptional aberrations and new biomarkers in cancer. Efficient methods are required to circumvent accessiblity of this huge amount of data. We wanted to facilitate their access while providing a better capture of the transcriptome complexity using indexing techniques based on k-mers approaches. We recently demonstrated that arbitrary RNA sequences can be quantified in seconds through their decomposition into k-mers, with a precision similar to that of conventional RNA quantification methods (Bessiére et al, Genome Biol, 2024). For this purpose, we developed Transipedia, a framework based on k-mers, constructed with several modules: the RNAseq indexing with Reindeer (Marchet et al, 2020); a module to generate specific k-mers as signature of transcripts (Kmerator; Riquier et al, 2021) and a supporting website **Transipedia.org.**

The indexing process provides ultra-fast performance in the query step while indexing thousands of RNAseq and retains all the quantitative information contained in the raw fastq files. We showcase several applications by exploring an index of the Cancer Cell Line Encyclopedia (CCLE) collection consisting of 1019 RNA-seq samples. Transipedia website is available to facilitate queries and sharing by biologists. It now includes several thousands of datasets, mainly for cancer applications, including the Acute myeloid leukemia (AML) and Lung cohort (NSLC). This large scale quantification of cancer promising biomarkers is necessary to check for their specificity comparing normal and tumor datasets or to select them regarding different patient groups as recently demonstrated by Ruffle et al, NARgab, 2024. Moreover indexing and counting kmers open the way to apply Machine learning models (Da Silva et al, 2024) and many perspectives in personnalised medecine for patient follow-up and drug response prediction.

Posters – Platforms

P601

OrgaPrint: A 3D Bioprinting facility in Poitiers

Maleaume SOULARD[1], Konstantin MASLIANTSEV[1,2], Lucie KARAYAN-TAPON[1,2], Pierre-Olivier GUICHET[1,2]

[1] Université de Poitiers

[2] CHU de Poitiers

In response to a scientific and technological need to consolidate expertise and federate research in oncology at the University of Poitiers, a new facility dedicated to the genesis of tumor organoids by 3D Bioprinting has been created in 2023 with the support of the Canceropole GSO and the University of Poitiers.

Currently, several projects are in progress allowing us to test different settings on the printer or composition of matrices for different cell types. Thus, we develop different models to study the impact of mechanical constraints in brain tumorigenesis. We also develop a model to study the interface between tumor cells and cells of the microenvironment. Finally, we have developed a model to print muscle cells allowing us to orient them lengthwise and potentialize the formation of mature myotubes.

List of Participants

Name	Affiliation	City	Email
Maria Claudia ADDAMIANO	CERPOP	TOULOUSE	maria-claudia.addamiano@univ-tlse3.fr
Angela AGAËSSE	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	angela.agaesse@inserm.fr
Kasandra AGUILAR CÁZAREZ	Institut de Génomique Fonctionnelle	MONTPELLIER	kasandra.aguilar@igf.cnrs.fr
Soha ALLIOUI	Université de Montpellier	MONTPELLIER	soha.allioui01@etu.umontpellier.fr
Diane AMINTAS	Université de Montpellier	MONTPELLIER	diane.amintas@etu.umontpellier.fr
Jean-Christophe ANDRAU	Institut de Génétique Moléculaire Montpellier	MONTPELLIER	jean-christophe.andrau@igmm.cnrs.fr
Eden ANDUJAR	Université de Montpellier	MONTPELLIER	eden.andujar@etu.umontpellier.fr
Margaux AYEUL	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	ayeul.margaux@gmail.com
Reem BANNOUT	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	reem.bannout@inserm.fr
Lucile BANSARD	Institut de Génomique Fonctionnelle	MONTPELLIER	Lucile.Bansard@igf.cnrs.fr
Diego BARBA	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	diego.barba@inserm.fr
Marion BARBIER	Université de Montpellier	LE VERNEIL	barbier.marion73@gmail.com
Corentin BARBOT	Institut de Génétique Moléculaire Montpellier	MONTPELLIER	corentin.barbot@igmm.cnrs.fr
Sylvia BARDET	XLIM Limoges	LIMOGES	sylvia.bardet@unilim.fr
Daniel BARROSO ALVES	BoRdeaux Institute of Oncology	BORDEAUX	daniel.barralv@hotmail.com
Laia BASSAGANYAS BARS	Institut de Génomique Fonctionnelle	MONTPELLIER	laia.bassaganyas@igf.cnrs.fr
Chloé BAZILE	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	chloe.bazile@inserm.fr
Guillaume BELTHIER	NKI	AMSTERDAM	g.belthier@nki.nl
Justine BERDUCOU	Université de Bordeaux	TALENCE	justine.berducou@etu.u-bordeaux.fr
Valérie BERGOGLIO	CBI-UMR 5077	TOULOUSE	valerie.bergoglio@univ-tlse3.fr
Alix BERNET	Université de Montpellier	MONTPELLIER	alix.bernet@gmail.com
Thomas BERTERO	Université Côte d'Azur, CNRS, INSERM, IPMC, IHU-RespirERA	VALBONNE	
Barbara BESSETTE	CAPTuR, UMR Inserm 1308	LIMOGES	barbara.bessette@unilim.fr
Yannick BESSIN	Institut des Biomolécules Max Mousseron	MONTARNAUD	yannick.bessin@gmail.com
Nadir BETTACHE	Institut des Biomolécules Max Mousseron	MONTPELLIER	nadir.bettache@umontpellier.fr
Samira BLAISE	ONCODEFI	MONTPELLIER	samira.blaise@oncodefi.org
Caroline BONNANS	Institut de Génomique Fonctionnelle	MONTPELLIER	caroline.bonnans@igf.cnrs.fr
Nathalie BONNEFOY	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	nathalie.bonnefoy@inserm.fr
Guillaume BOSSIS	Institut de Génétique Moléculaire Montpellier	MONTPELLIER	guillaume.bossis@igmm.cnrs.fr
Laura BOURILLON	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	laura.bourillon@icm.unicancer.fr
Cléo BOUSSAU	Université de Bordeaux	BORDEAUX	cleo.boussau@gmail.com
Marie BOUTAUD	CAPTuR, UMR Inserm 1308	LIMOGES	marie.boutaud@etu.unilim.fr
Léa BOUTON	Régulations Naturelles et Artificielles	BORDEAUX	lea.bouton@u-bordeaux.fr
Thaïs BOUVIER	Université de Montpellier	MONTPELLIER	thais.bouvier@etu.umontpellier.fr

David BRACQUEMOND	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	david.bracquemond@inserm.fr
Nina BRAQUET	Université de Bordeaux	BORDEAUX	ninabraquet@gmail.com
Muriel BRENGUES	Institut en Cancérologie de Montpellier	MONTPELLIER	muriel.brengues@icm.unicancer.fr
Lisa BRUNET	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	lisa.brunet@inserm.fr
Chloé BUCHALET	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	chloebuchalet@gmail.com
Laurelly CALIARI	Université de Bordeaux	BORDEAUX	laurellycaliari@gmail.com
Olivier CALVAYRAC	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	olivier.calvayrac@inserm.fr
Yvan CANITROT	Unité de biologie moléculaire, cellulaire et du développement	TOULOUSE	yvan.canitrot@univ-tlse3.fr
Julian CARREY	Laboratoire de Physique et Chimie de Nano-Objets	TOULOUSE	
Claire CARRION	Contrôle de la Réponse Immune B et des Lymphoprolifération	LIMOGES	claire.carrion@unilim.fr
Vincent CAVAILLES	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	vincent.cavailles@inserm.fr
Tommy CHASTEL	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	tommy.chastel@inserm.fr
Myriam CHAUMEIL	University of California	SAN FRANCISCO	myriam.chaumeil@nvision-imaging.com
Carine CHAVEY	Institut de Génétique Moléculaire Montpellier	MONTPELLIER	carine.chavey@igmm.cnrs.fr
Hugo CHENEL	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	hugo.chenel@inserm.fr
Nina CHOUBLIER	BoRdeaux Institute of Oncology	BORDEAUX	nina.choublier@inserm.fr
Luana CINTORI	Unité de biologie moléculaire, cellulaire et du développement	TOULOUSE	luana.cintori@univ-tlse3.fr
Julie CLACHET	BoRdeaux Institute of Oncology	BORDEAUX	julie.clachet@u-bordeaux.fr
Thomas CLOUAIRE	Unité de biologie moléculaire, cellulaire et du développement	TOULOUSE	thomas.clouaire@univ-tlse3.fr
Marie COLOMB	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	marie.colomb@icm.unicancer.fr
Therese COMMES	Institut de Médecine Régénérative et de Biothérapies de Montpellier	MONTPELLIER	therese.commes@inserm.fr
Bruno CONSTANTIN	Canaux & Connexines dans les Cancers et Cellules Souches	POITIERS	Bruno.Constantin@univ-poitiers.fr
Pierre CORDELIER	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	pierre.cordelier@inserm.fr
Marie CORDONNIER	Faculté des Sciences de Montpellier	MONTPELLIER	marie.cordonnier@etu.umontpellier.fr
Valérie CORONAS	Canaux & Connexines dans les Cancers et Cellules Souches	POITIERS	valerie.coronas@univ-poitiers.fr
Florence COUSSON-GELIE	Institut du Cancer de Montpellier	MONTPELLIER	florence.cousson-gelie@icm.unicancer.fr
Claire CRAMPES	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	claire.crampes@inserm.fr
Yannick CREMILLIEUX	Institut des Sciences Moléculaires	TALENCE	yannick.cremillieux@u-bordeaux.fr
Sabrina CROCE	Institut Bergonié	BORDEAUX	s.croce@bordeaux.unicancer.fr
Sandrine DABERNAT	BoRdeaux Institute of Oncology	BORDEAUX	sandrine.dabernat@u-bordeaux.fr
Boutaina DAHER	MATWIN	BORDEAUX	boutaina.daher@matwin.fr
Chloe DEL BOVE	Université de Montpellier	MONTPELLIER	chloe_delbove@yahoo.fr

Cyrille DELPIERRE	CERPOP	TOULOUSE	cyrille.delpierre@inserm.fr
Gauthier DELROT	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	gauthier.delrot@u-bordeaux.fr
Nicolas DI GLERIA--PILLARD	Université de Montpellier	MONTPELLIER	nicolas.di-gleria-pillard@etu.umontpellier.fr
Selma DJILALI-SALAH	Université de Montpellier	BORDEAUX	selma.djilali-salah@etu.u-bordeaux.fr
Marcin DOMAGALA	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	marcin.domagala@inserm.fr
Laura EANES DA SILVA	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	laura.eanes-da-silva@inserm.fr
Fabrice ESCAFFIT	Unité de biologie moléculaire, cellulaire et du développement	TOULOUSE	fabrice.escaffit@univ-tlse3.fr
Solen FAIDHERBE	Université des sciences de Montpellier	MONTPELLIER	solen.faidherbe@etu.umontpellier.fr
Kerstin FARAVEL	Institut du Cancer de Montpellier	MONTPELLIER	kerstin.faravel@icm.unicancer.fr
Isabelle FERNANDEZ	Institut national du cancer	BOULOGNE-BILLANCOURT	ifernandez@institutcancer.fr
Anne FERNANDEZ-VIDAL	Centre de Biologie Intégrative	TOULOUSE	anne.fernandez2@univ-tlse3.fr
Jean-Yves FRAYSSINHES	Contrôle de la Réponse Immune B et des Lymphoprolifération	LIMOGES	jean-yves.frayssinhes@unilim.fr
Clara FREIXINOS	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	clara.freixinos@etu.umontpellier.fr
Hervé FRIDMAN	Centre de Recherche des Cordeliers	PARIS	
Olivier GADAL	Centre de Biologie Intégrative	TOULOUSE	olivier.gadal@univ-tlse3.fr
Emilie GADAY	Université de Montpellier	MONTPELLIER	emilie.gaday@etu.umontpellier.fr
Lise GAILLARD--TABLIN	Université de Bordeaux	BORDEAUX	lise.gaillard-tablin@etu.u-bordeaux.fr
Isabel GALEANO-OTERO	BoRdeaux Institute of Oncology	BORDEAUX	isabel.galeano-otero@inserm.fr
Inès GARROUCHE	Université de Poitiers, Laboratoire ProDiCeT	POITIERS	ines.garrouche@univ-poitiers.fr
Amy GATEAU	CAPTuR, UMR Inserm 1308	LIMOGES	amy.gateau@gmail.com
Emmanuelle GEORGET	BoRdeaux Institute of Oncology	BORDEAUX	emmanuelle.georget@u-bordeaux.fr
Véronique GERAT-MULLER	onCOGITE	BORDEAUX	v.gerat.muller@oncogite.com
Suzan GHADDAR	Laboratoire des Agroressources, Biomolécules et Chimie pour l'Innovation en Santé	LIMOGES	Suzan.ghaddar@etu.unilim.fr
Véronique GIGOUX	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	veronique.gigoux@inserm.fr
Jacky GOETZ	Centre de Recherche en Biomédecine de Strasbourg	STRASBOURG	
Dennis GOMEZ	Institut de Pharmacologie et de Biologie Structurale	TOULOUSE	dennis.gomez@ipbs.fr
Céline GONGORA	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	celine.gongora@inserm.fr
Lou GOUIN	Université de Bordeaux	BORDEAUX	lou.gouin29@gmail.com
Mathieu GOURLAN	Institut du Cancer de Montpellier	MONTPELLIER	mathieu.gourlan@icm.unicancer.fr
Tiphany GOUVEIA	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	tiphany.gouveia@inserm.fr

Claudine GRAS-AYGON	Registre des Tumeurs de l'Hérault	MONTPELLIER	dr.gras.aygon@gmail.com
Damien GREGOIRE	Institut de Génétique Moléculaire Montpellier	MONTPELLIER	damien.gregoire@igmm.cnrs.fr
Pierre-Olivier GUICHET	Université de Poitiers	POITIERS	pierre-olivier.guichet@inserm.fr
Rawan HALLAL	Institut de Génétique Moléculaire Montpellier	MONTPELLIER	rawan.hallal@igmm.cnrs.fr
Marine HERNANDEZ	Institut de Pharmacologie et de Biologie Structurale	TOULOUSE	marine.hernandez@ipbs.fr
Lisa HERON-MILHAVET	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	lisa.heron-milhavet@inserm.fr
Valeria HERRERA ROJAS	Université de Montpellier	MONTPELLIER	valeherrerarojas@hotmail.com
Pierre HIRT	Contrôle de la Réponse Immune B et des Lymphoprolifération s	LIMOGES	pierre.hirt@unilim.fr
Lina HOUNTONDJI	CHU de Montpellier	MONTPELLIER	lina.hountondji@outlook.fr
Isabelle JANOUEIX	Institut Curie	PARIS	
Fanny JAULIN	Institut Gustave Roussy	VILLEJUIF	
Laura JENTSCHEL	Institut de Génomique Fonctionnelle	MONTPELLIER	Laura.jentschel@etu.umontpellier.fr
Ruxue JIA	BoRdeaux Institute of Oncology	BORDEAUX	ruxue.jia@u-bordeaux.fr
Eric JULIEN	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	eric.julien@inserm.fr
Marie-Louise JUNG	Greenpharma business development	ORLÉANS	marielouise.jung@greenpharma.com
Abdel-Majid KHATIB	BoRdeaux Institute of Oncology	BORDEAUX	majid.khatib@inserm.fr
Virginie LAFONT	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	virginie.lafont@inserm.fr
Frédéric LAGARRIGUE	Institut de Pharmacologie et de Biologie Structurale	TOULOUSE	frederic.lagarrigue@ipbs.fr
Tinhinan LAHLOU	Institut de Génomique Fonctionnelle	MONTPELLIER	tinhinan.lahlou@igf.cnrs.fr
Fabrice LALLOUE	CAPTuR, UMR Inserm 1308	LIMOGES	fabrice.lalloue@unilim.fr
Christel LARBOURET	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	christel.larbouret@inserm.fr
Nicolas LARMONIER	IMMUNOLOGY from CONCEPT and EXPERIMENTS to TRANSLATION	BORDEAUX	nicolas.larmonier@u-bordeaux.fr
Marion LARROQUE	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	marion.larroque@icm.unicancer.fr
Patrick LARTIGUET	Université Toulouse 2 Jean Jaurès	TOULOUSE	patrick.lartiguet@savoirspatients.org
Sarah LAVIELLE	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	sarah.lavielle@u-bordeaux.fr
Nicolas LEBEGUE	Lille Neuroscience & Cognition	LILLE	
Teo LEBOUCQ	BoRdeaux Institute of Oncology	BORDEAUX	teo.leboucq@u-bordeaux.fr
Theo LECOQ	Université de Bordeaux	BORDEAUX	theo.lecoq2003@bbox.fr
Marion LENAIN	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	marion.lenain@inserm.fr
Gorann LEPIED	Régulations Naturelles et Artificielles	BORDEAUX	gorann.lepied@u-bordeaux.fr
Sabrina LEVERRIER-PENNA	Canaux & Connexines dans les Cancers et Cellules Souches	POITIERS	sabrina.penna@univ-poitiers.fr
Bertrand LIAGRE	Laboratoire des Agroressources, Biomolécules	LIMOGES	bertrand.liagre@unilim.fr

	et Chimie pour l'Innovation en Santé		
Emmanuelle LIAUDET-COOPMAN	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	emmanuelle.liaudet-coopman@inserm.fr
Yiyang LIU	BoRdeaux Institute of Oncology	BORDEAUX	yiyang.liu@kuleuven.be
Eva LLES	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	eva.lles@inserm.fr
Jeanne LOISEAU	Université de Montpellier	MONTPELLIER	jeanneloiseau4545@gmail.com
Marie LOPEZ	Institut des Biomolécules Max Mousseron	MONTPELLIER	marie.lopez@cnrs.fr
Mathilde MADÉRY	IMMUNOLOGY from CONCEPT and EXPERIMENTS to TRANSLATION	BORDEAUX	mathilde.madery@u-bordeaux.fr
Michelle Gracia MALANDOU TSAMBA	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	michelle-gracia.malandou-tsamba@inserm.fr
Lisa MALARD	Université de Montpellier	MONTPELLIER	lisa.malard@etu.umontpellier.fr
Grégoire MANAUD	BoRdeaux Institute of Oncology	BORDEAUX	gregoire.manaud@inserm.fr
Maicol MANCINI	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	maicol.mancini@inserm.fr
Antonio MARAVER	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	antonio.maraver@inserm.fr
Tiffany MARCHIOL	Contrôle de la Réponse Immune B et des Lymphoprolifération	LIMOGES	tiffany.marchiol@unilim.fr
Morgane MARCOU DU TILLET DE VILLARS	IUCT Oncopole	TOULOUSE	marcoudutilletdevillars.morgane@iuct-oncopole.fr
Emilie MARHUENDA	CBMN - Bordeaux INP	BORDEAUX	emilie.marhuenda@bordeaux-inp.fr
Océane MARTIN	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	oceane.martin@u-bordeaux.fr
Pierre MARTINEAU	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	pierre.martineau@inserm.fr
Jose Ignacio MARTIN-SUBERO	IDIBAPS & ICREA	BARCELONA	
Konstantin MASLIANTSEV	ProDiCeT	POITIERS	konstantin.masliantsev@univ-poitiers.fr
Thomas MATHIVET	BoRdeaux Institute of Oncology	BORDEAUX	thomas.mathivet@inserm.fr
Dehbia MATOUB	Université de Montpellier	MONTPELLIER	dehbia.matoub@etu.umontpellier.fr
Camille MAZET	Université de Montpellier	MONTPELLIER	mcamy@orange.fr
Tassadit MERABTINE	Institut d'épidémiologie des maladies chroniques en zones tropicales	LIMOGES	tassadit.merabtine@etu.unilim.fr
Christoph MERTEN	Ecole Polytechnique Federale de Lausanne	LAUSANNE	
Virginie MIEULET	Institut Toulousain des Maladies Infectieuses et Inflammatoires	TOULOUSE	virginie.mieulet@inserm.fr
Alexandra MOISAND	IMMUNOLOGY from CONCEPT and EXPERIMENTS to TRANSLATION	BORDEAUX	alexandra.moisand@u-bordeaux.fr
Violaine MOREAU	BoRdeaux Institute of Oncology	BORDEAUX	violaine.moreau@inserm.fr
Thibault MORIN	Université de Bordeaux	BORDEAUX	morin.tib@orange.fr
May MORRIS	Institut des Biomolécules Max Mousseron	MONTPELLIER	may.morris@umontpellier.fr

Lesa Faith NDAYISABA	Université de Bordeaux	BORDEAUX	lesafaithndayi@gmail.com
Elodie NEUMANN	ONCODEFI	MONTPELLIER	elodie.neumann@oncodefi.org
Tra-Ly NGUYEN	BoRdeaux Institute of Oncology	BORDEAUX	tra-ly.nguyen@u-bordeaux.fr
Mai Quynh NGUYEN	Université de Bordeaux - Sciences et technologies	PESSAC	maiquynh.biology@gmail.com
Stefan NICOLESCU	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	stefan.nicolescu@inserm.fr
Elisangela OLIVIER	ONCODEFI	MONTPELLIER	elisangela.olivier@oncodefi.org
Marc PALPACUER	ONCODEFI	MONTPELLIER	marc.palpacuer@oncodefi.org
Liudmyla PAMBUKHCHIAN	Université de Bordeaux	BORDEAUX	lyudochka1206@gmail.com
Julie PANNEQUIN	Institut de Génomique Fonctionnelle	MONTPELLIER	julie.pannequin@igf.cnrs.fr
Rémi PEANNE	BoRdeaux Institute of Oncology	BORDEAUX	remi.peanne@u-bordeaux.fr
Aubin PENNA	Canaux & Connexines dans les Cancers et Cellules Souches	POITIERS	aubin.penna@univ-poitiers.fr
Zurab PETROSIAN	Université de Bordeaux	T'BILISI	petrosianizura.tsmu@gmail.com
Florent PEYRAUD	Institut Bergonié	BORDEAUX	f.peyraud@bordeaux.unicancer.fr
Eric PINAUD	Contrôle de la Réponse Immune B et des Lymphoprolifération	LIMOGES	eric.pinaud@unilim.fr
Sandrine POGLIO	BoRdeaux Institute of Oncology	BORDEAUX	sandrine.poglio@u-bordeaux.fr
Renaud POINCLOUX	Institut de Pharmacologie et de Biologie Structurale	TOULOUSE	Renaud.Poincloux@ipbs.fr
Marie-Alix POUL-PEARSON	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	marie-alix.poul@inserm.fr
Mary POUPOT	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	mary.poupot@inserm.fr
Philippe POURQUIER	Centre de Recherches en Cancérologie de Toulouse	MONTPELLIER	philippe.pourquier@inserm.fr
Dimitri PUREUR	Université de Montpellier	MONTPELLIER	d-pureur@chu-montpellier.fr
Rofaida RABAHI	Université de Montpellier	MONTPELLIER	rofaida.rabahi98@gmail.com
Marta RADMAN-LIVAJA	Institut de Génétique Moléculaire Montpellier	MONTPELLIER	marta.radman-livaja@igmm.cnrs.fr
Antoine RAGOIN	Université de Bordeaux	BORDEAUX	antoine.ragoin@gmail.com
Patrice RAVEL	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	patrice.ravel@umontpellier.fr
Debjeet RAY	Université de Bordeaux	BORDEAUX	raydebjeet@gmail.com
Niamh REDMOND	CERPOP	TOULOUSE	niamh.redmond@inserm.fr
Lucas RIBOULLON	Université de Montpellier	MONTPELLIER	lucas.riboullon01@etu.umontpellier.fr
Lucie ROBERT	Université de Montpellier	MONTPELLIER	lucie.robert01@etu.umontpellier.fr
Lou ROBINO	Université de Bordeaux	BORDEAUX	lou.robino@etu.u-bordeaux.fr
Alejo E. RODRIGUEZ FRATICELLI	IRB & ICREA	BARCELONA	
Pedro Alejandro RODRIGUEZ NUNEZ	EA4139	BORDEAUX	pedro.rodriguez-nunez@u-bordeaux.fr
Marie-Pierre ROLS	Institut de Pharmacologie et de Biologie Structurale	BALMA	marie-pierre.rols@ipbs.fr
Amandine ROUSSEL	BoRdeaux Institute of Oncology	BORDEAUX	amandine.roussel@u-bordeaux.fr
Lucile ROUYER	BoRdeaux Institute of Oncology	BORDEAUX	lucile.rouyer@u-bordeaux.fr
Amandine ROVINI	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	amandine.rovini@unilim.fr
Doriane RUIZ	Université de Montpellier	MONTPELLIER	dorianeruiz@yahoo.com
Ibrahim SAHEBALLY	BoRdeaux Institute of Oncology	BORDEAUX	ibrahim.sahebally@inserm.fr

Frederic SALTEL	BoRdeaux Institute of Oncology	BORDEAUX	frederic.saltel@inserm.fr
Cyril SARRAUSTE	Institut de Génétique Humaine	MONTPELLIER	cyril.s@patientsenreseau.fr
Daniel SATGE	ONCODEFI	MONTPELLIER	daniel.satge@oncodefi.org
Catherine SAUTES-FRIDMAN	Centre de Recherche des Cordeliers	PARIS	
Lucile SAUVAGE	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	lucile.sauvage@inserm.fr
Yaële SAUVAGE	Université de Montpellier	MONTPELLIER	yaele.sauvage@gmail.com
Bruno SEGUI	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	bruno.segui@inserm.fr
Malak SENOUCI	Université de Bordeaux	BORDEAUX	senoucim222@gmail.com
Myroslava SLIUSAR	BoRdeaux Institute of Oncology	BORDEAUX	myroslava.sliusar@u-bordeaux.fr
Florence SORDES	Université Toulouse Jean Jaurès	TOULOUSE	sordes@univ-tlse2.fr
Pierre SOUBEYRAN	BoRdeaux Institute of Oncology	BORDEAUX	p.soubeyran@bordeaux.unicancer.fr
Maleaume SOULARD	ProDiCeT	POITIERS	maleaume.soulard@univ-poitiers.fr
Abdelkader TAIBI	XLIM Limoges	LIMOGES	abdelkader.taibi@chu-limoges.fr
Lisa TELLIER	Université de Montpellier	MONTPELLIER	lisa.tellier@etu.umontpellier.fr
Jérôme TORRISANI	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	jerome.torrisani@inserm.fr
Hélène TOURRIERE	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	helene.tourriere@inserm.fr
Brigitte TRETARRE	Registre des Tumeurs de l'Hérault	MONTPELLIER	tretarre.brigitte@registre-tumeurs-herault.fr
Olivia TRIBILLAC	Université de Montpellier	MONTPELLIER	olivia.tribillac@outlook.fr
Isabelle VAN SEUNINGEN	ONCOLille	LILLE	
Ella VANNIEUWENHUYSE	Université de Montpellier	MONTPELLIER	ellavannieuw@gmail.com
Ana Sofia VAZQUEZ URIOLA	BoRdeaux Institute of Oncology	BORDEAUX	ana-sofia.vazquez-uriola@u-bordeaux.fr
Nadia VIE	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	nadia.vie@icm.unicancer.fr
Pauline VIGNERESSE	Université de Bordeaux	BORDEAUX	pauline.vigneresse@etu.u-bordeaux.fr
Carole VOLAND	CHU de Montpellier	MONTPELLIER	BB-LRO@chu-montpellier.fr
Anissa ZAAFOUR	BoRdeaux Institute of Oncology	BORDEAUX	anissa.zaafour@u-bordeaux.fr

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Dates importantes

1er décembre 2024 date limite du dépôt de dossier

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La FHU s'inscrit dans un écosystème structurant de soins *via* la Fédération de Cancérologie, le Centre de Coordination en Cancérologie (3C), le réseau Onco-Occitanie et de recherche en oncologie *via* le SIRIC Montpellier Cancer et le LabEx d'Excellence MAbImprove.

Ses principales missions :

- Fédérer, structurer, former étudiants et professionnels de santé et promouvoir la recherche translationnelle dans le domaine des immunothérapies appliquées au cancer *via* le co-financement de projets de recherche et de bourses de Master et la contribution à l'organisation de formations et séminaires.

- Promouvoir l'excellence des soins dans ce domaine en permettant au plus grand nombre de patients d'avoir un accès précoce à ces traitements novateurs.

Son programme scientifique :

Axe 1 : Etudier comment le métabolisme des cellules cancéreuses, l'instabilité génétique, les dérégulations épigénétiques et épitranscriptomiques influencent l'écosystème tumoral et impactent la réponse aux immunothérapies.

Axe 2 : Développer des outils et plateformes d'analyse de l'écosystème tumoral, notamment des approches spatiales, pour accélérer l'identification de facteurs prédictifs et le suivi de la réponse aux immunothérapies.

Pour plus d'informations : FHU EVOCAN - evocan - CHU de Montpellier (chu-montpellier.fr)

Coordination : Pr Guillaume CARTRON, CHU de Montpellier
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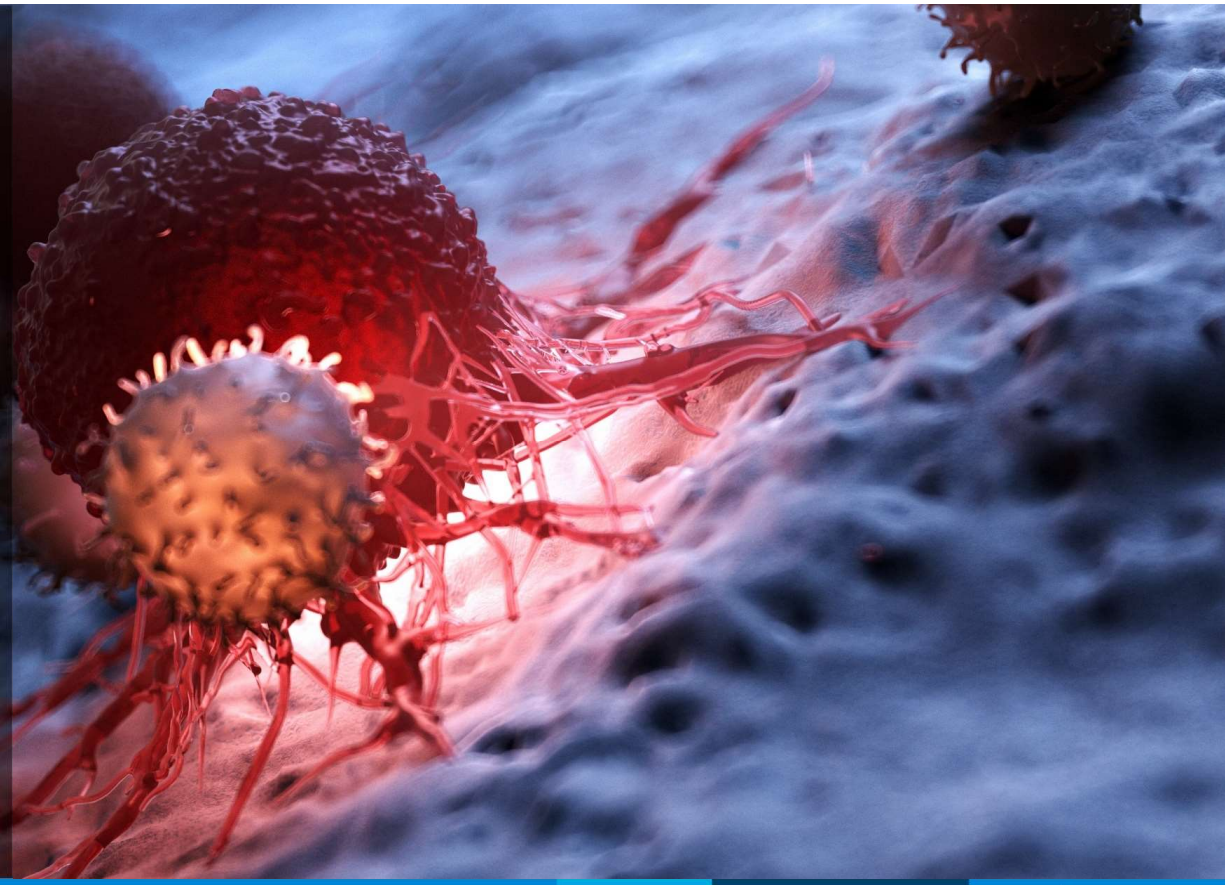

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Président	Jean-Olivier ARNAUD
Directrice	Nadine HOUEDE
Secrétaire Générale	Karine SAGET (Montpellier) karine.saget@canceropole-gso.org
Adjoint à la Secrétaire Générale	Jean-Philippe BORGES (Toulouse) jeanphilippe.borges@canceropole-gso.org
Chargé(e)s de Mission	
Innovation thérapeutique et biomarqueurs (Axe 3)	Alice BEIGBEDER (Toulouse) alice.beigbeder@canceropole-gso.org
Technologies pour la santé (Axe 5)	Jean-Philippe BORGES (Toulouse) jeanphilippe.borges@canceropole-gso.org
Signalisation, microenvironnement et ciblages (Axe 1) Dynamique et expression du génome (Axe 2) Cancers : enjeux individuels et collectifs (Axe 4)	Karine MARENDZIAK (Montpellier) karine.marendziak@canceropole-gso.org Jeanne RAMBAUD (Toulouse) jeanne.rambaud@canceropole-gso.org

Bureau Toulouse
Oncopole – Bât. Maison Commune - 1er étage
5 Avenue Irène Joliot-Curie
31100 Toulouse

Bureau Montpellier
IRCM - Bâtiment F1 - RdC
124 avenue des Apothicaires
34090 Montpellier

Cancéropôle Grand Sud-Ouest
5 Avenue Irène Joliot-Curie 31100 Toulouse
contact@canceropole-gso.org
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