21st

Cancéropôle Grand Sud-Ouest

Annual Meeting

November 26-28, 2025

Congress center / Agen

SEMINAR BOOKLET

Cancéropôle Grand Sud-Ouest

www.canceropole-gso.org

inca Institut National du Cancer

The Cancéropôle Grand Sud-Ouest teams warmly thanks

- **the speakers and session moderators,**
- **the coordinators and members of the Axis Steering Committees,**
- **the leaders and members of the Working Groups,**
- **the members of the GSO Scientific Steering Committee,**

for their participation and commitment in developing the program

for this 21st Annual Meeting.

GSO Scientific Steering Committee

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

Axis Steering Committees

Axis 1 – Cell signaling, microenvironment and targeting
B. Bessette, **G. Bossis**, D. Gomez, F. Lagarrigue, N. Larmonier, A. Maraver, A. Martin, **V. Moreau**, A. Penna, M. Poupot, F. Vergez, C. Vincent-Fabert

Axis 2 - Genome Dynamics & Expression
JC. Andrau, A. Cristini, T. Clouaire, D. Dupuy, C. Esnault, O. Gadal, **E. Julien**, YH. Lin, S. Péron, PYJ. Wu

Axis 3 – Therapeutic Innovation and Biomarkers
N. Béry, A. Bobrie, C. Bonnans, D. Cappellen, G. Chemin, C. Colacios, S. Dabernat, A. David, E. Deluche, D. Duluc, C. Evrard, **V. Gigoux**, V. Gire, W. Jacot, AM. Khatib, F. Lalloué, E. Liaudet-Coopman, E. Marhuenda, M. Poirot, B. Segui, **D. Tougeron**

Axis 4 - Cancers: individual and collective challenges
V. Bernad, L. Baussard, F. Cousson-Gélie, **C. Delpierre**, P. Gorry, S. Gourgou, I. Ingrand, N. Le Stang, M. Poiseuil, **F. Sordes**, B. Trétarre

Axis 5 – Health Technologies
N. Bettache, C. Bezombes, D. Bouvard, Y. Crémillieux, C. Dupin, S. Cussat-Blanc, 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

***Welcome to Agen**, which is hosting for the very first time the Annual Meeting of the Cancéropôle Grand Sud-Ouest. This 21st edition promises to be particularly rich and ambitious, reflecting the collective momentum that drives our network.*

Alongside the many researchers and clinicians from our interregional community, we are honored to welcome distinguished national and international speakers who will share their insights and expertise on the latest breakthroughs in oncology. We will have the pleasure to hear from: María CASANOVA-ACEBES from Madrid, Vijay CHUDASAMA from London, Jean ALBRENGUES from Nice, Frédéric BARD from Marseille, Florian NAUDET from Rennes, Pierre LAURENT-PUIG from Paris, Argyris PAPANTONIS from Göttingen, Kristopher LAMORE and Florent VARET from Lille.

Their contributions will enrich discussions and foster collaborations in a spirit of transdisciplinarity and openness.

***Lung cancer** will be in the spotlight this year, with a dedicated session featuring three renowned international speakers: Trever G. BIVONA from San Francisco, Montse SANCHEZ-CESPEDES from Barcelona, and David SANTAMARIA from Salamanca. We are also honored to welcome the patient advocacy group ALK/ROS1 France, whose presence will bring invaluable patient perspectives to the discussions.*

We will also have the privilege of welcoming Hervé MAISONNEUVE for a prestigious lecture entitled: "The Rise and Fall of Scientific Publications: Publish or Perish."

*A new highlight this year is the **Rising Stars** session, showcasing emerging talents from the Cancéropôle GSO. Young researchers will compete for the best oral presentation and attendees will be invited to vote for their favorite.*

This outstanding scientific program is the result of remarkable collective work. We warmly thank the members of the Scientific Steering Committee, the Axis and working group Committees, whose commitment made these three dense and exciting days possible.

The year 2025 marked a major milestone with the renewal of the Cancéropôle Grand Sud-Ouest Public Interest Group for another nine years, as approved by our General Assembly. This renewal reflects the trust placed in our shared momentum and reinforces our mission to support cancer research. It is further strengthened by a new founding agreement welcoming four new members: the Poitiers University Hospital, the University of Poitiers, the University of La Rochelle and the pharmaceutical company Bayer HealthCare. This expansion illustrates the vitality of our network and its ability to gather academic and industrial forces towards a common goal: advancing the fight against cancer.

I wish you all stimulating, friendly, and inspiring days, in the spirit of the Cancéropôle GSO community and an environment that favors collaborations and the emergence of new ideas!

Nadine Houédé
Cancéropôle Grand Sud-Ouest Director

Bienvenue à Agen, qui accueille pour la première fois les Journées Annuelles du Cancéropôle Grand Sud-Ouest. Cette 21ème édition s'annonce particulièrement riche et ambitieuse à l'image de la dynamique collective qui anime notre réseau.

Aux côtés des nombreux chercheurs et cliniciens de notre inter-région, nous avons l'honneur d'accueillir des orateurs de prestige, nationaux et internationaux, qui partageront leurs expertises et leurs regards sur les avancées les plus récentes en oncologie. Nous aurons ainsi le plaisir d'écouter : María CASANOVA-ACEBES de Madrid, Vijay CHUDASAMA de Londres, Jean ALBRENGUES de Nice, Frédéric BARD de Marseille, Florian NAUDET de Rennes, Pierre LAURENT-PUIG de Paris, Argyris PAPANTONIS de Göttingen, Kristopher LAMORE et Florent VARET de Lille.

Leurs interventions nourriront les échanges et stimuleront les collaborations dans un esprit de transdisciplinarité et d'ouverture.

Le cancer du poumon sera à l'honneur cette année, avec une session dédiée réunissant trois orateurs internationaux : Trever G. BIVONA de San Francisco, Montse SANCHEZ-CESPEDES de Barcelone et David SANTAMARIA de Salamanque ainsi que l'association ALK/ROS1 France qui apportera le point de vue précieux des patients.

Nous aurons également le privilège d'accueillir Hervé MAISONNEUVE pour une conférence de prestige intitulée : « Grandeur et décadence des publications scientifiques : publier ou mourir ».

Une nouveauté cette année : la session Rising Stars mettra à l'honneur les jeunes chercheurs du Cancéropôle GSO à travers un concours de la meilleure présentation orale, où tout le monde est invité à voter !

Ce beau programme scientifique est le fruit d'un travail collectif remarquable. Nous tenons à remercier chaleureusement les membres du Comité de Pilotage Scientifique, des Comités d'Axes et des bureaux des Groupes de travail, dont l'implication a permis de construire ces trois journées denses et passionnantes.

Cette année 2025 a été marquée par le renouvellement du Groupement d'Intérêt Public Cancéropôle GSO pour neuf ans, voté par notre Assemblée Générale. Cette reconduction témoigne de la confiance accordée à notre dynamique collective et consolide notre mission au service de la recherche en cancérologie. Il s'accompagne de la signature d'une nouvelle convention constitutive intégrant quatre nouveaux membres : le CHU de Poitiers, l'Université de Poitiers, l'Université de La Rochelle et le laboratoire pharmaceutique Bayer HealthCare. Cette évolution illustre la vitalité de notre réseau et sa capacité à fédérer des forces vives, académiques et industrielles, autour d'un objectif commun : faire progresser la lutte contre le cancer.

Je vous souhaite à tous des journées stimulantes, conviviales et inspirantes, à l'image de la communauté du Cancéropôle GSO dans un cadre propice à la collaboration et à l'émergence de nouvelles idées !

Nadine Houédé
Directrice du Cancéropôle Grand Sud-Ouest

LE PROGRAMME DE SOUTIEN A L'EMERGENCE DU CANCEROPOLE GSO

OUVERTURE DEBUT FEVRIER 2026 - 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 à 60 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 1,5 k€ maximum sous forme de

- soit une subvention financière
- soit la prise en charge d'un conférencier (déplacement et/ou hébergement)
- soit la prise en charge de l'inscription d'étudiants ou de jeunes chercheurs
- soit pour la prise en charge de prix communication orale ou poster
- soit un soutien logistique (plateforme d'inscription et d'appel à communications)

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 COURANT 2026 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 (doctorants et post-doctorants) afin de les former à la recherche translationnelle sur une thématique donnée et de les inciter aux échanges transversaux.

PROCHAINE EDITION EN 2027: 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 DU 31 MAI AU 4 JUIN 2026 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, AHU), pharmaciens (internes) et chercheurs (doctorants, 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**.

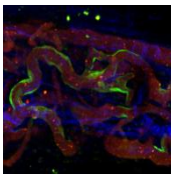
Il réunit des experts de renom et des jeunes chercheurs (post-doctorants et jeunes titulaires) sélectionnés sur leurs travaux, en format résidentiel, afin de favoriser les échanges et de permettre aux jeunes chercheurs de bénéficier d'un coaching de qualité.

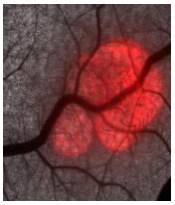
PROCHAINE EDITION : SIGNALING, MICROENVIRONEMENT AND TARGETING, 11-12 DECEMBRE 2025

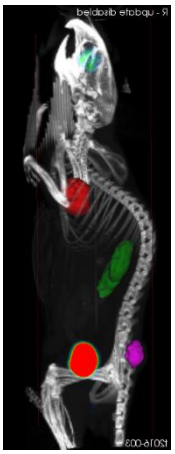
7EME ECOLE D'IMAGERIE

DU PETIT ANIMAL APPLIQUEE AU CANCER

31 mai au 4 juin 2026, Montpellier







Lieux :

- Institut de Recherche en Cancérologie de Montpellier
- Génopolys
- Plateaux techniques et visites : Institut de Génomique Fonctionnelle, Physiologie et médecine expérimentale du cœur et des muscles, Université Campus Triolet, Institute for Regenerative Medicine and Biotherapy, Institut du Cancer de Montpellier

Objectifs :

L'imagerie préclinique *in vivo* permet de mettre en évidence de nouvelles cibles thérapeutiques et d'évaluer rapidement de nouvelles stratégies médicales. Ces techniques sont mises à la disposition de la communauté scientifique sous forme de plateformes ouvertes aux académiques comme aux industriels.

La 7ème édition de cette école, organisée par le Cancéropôle Grand Sud-Ouest, PhyMedEx et l'IRCM avec l'appui des différents plateaux techniques (plateforme IPAM) abordera toutes les modalités d'imagerie *in vivo* (anatomique, fonctionnelle et moléculaire) ainsi que le suivi des animaux. Les principes théoriques des différentes modalités seront présentés par des chercheurs et médecins experts dans le domaine.

En complément, des ateliers d'imagerie en situation réelle au sein des plateaux techniques et des visites permettront une analyse exhaustive des potentialités et champs d'applications de chaque technique.

Techniques et ateliers/visites : Optique, Bioluminescence, Fluorescence, Microscopie intravitale multiphotonique, Imagerie Nucléaire, Radiomarquage, IRM, Echographie et photoacoustique, Microtomographie Rayons-X, Elastographie, Irradiation guidée par imagerie, Opto-acoustique, Imagerie de fluorescence proche infra-rouge, Onco-cardiologie, Anesthésies et confinement des animaux et des locaux, Règlementation et bien-être animal.

Responsables scientifiques : Pierre SICARD et Yan DROMARD

Intervenants : Jean-Damien ARNAUD, Elisabeth BELLARD, Anne-Laure BONNEFONT, Muriel BRENGUES, Emmanuel DESHAYES, Aurélia DROUARD, Dounia EL HAMRANI, Coralie GENEVOIS, Muriel GOLZIO, Christophe GOZE BAC, Chris JOPLING, Chrystel LAFONT, Renaud LEBRUN, Daniel NOEL, Carine PESTOURIE, Jean-Pierre POUGET, Gilles RENAULT, Guillaume REVEILLON

Prérequis : Conduire ou prévoir un projet d'imagerie *in vivo*

Public : Chercheurs, Ingénieurs, Techniciens, Post-doctorants, Doctorants

Nombre de participants : 20 maximum

Tarif : Académique : **800 €** / Industriel : **1800 €**

Le tarif inclus les déjeuners et les dîners
Surcoût hébergement chambre simple : 400 €

*Prise en charge possible dans le cadre de la **Formation Professionnelle Continue***

Validation d'unité de formation continue en expérimentation animale

Inscription avant le 15 mars 2026

Plus d'infos : imagerie.canceropole-gso.org

Program

Wednesday 26th November

12h30-14h00 **Welcome Lunch**

14h00 - 14h10 **Opening ceremony**
Nadine HOUEDE, Scientific director of Cancéropôle Grand Sud-Ouest

14h10-15h45
Session 1 - Targeting Inflammation: From Molecular Dialogues to Cellular Therapies in Oncology 10
Chairs: Abdel-Majid KHATIB & Antonio MARAVER
Lecture: **María CASANOVA-ACEBES**, *Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid (Spain)*
Tick–Tumor–Tock: Circadian Neutrophil Programs in lung cancer

- **Nadine LAGUETTE**, *Institute of Molecular Genetics of Montpellier (IGMM)* - Exploring the crosstalk between DNA repair and inflammatory responses: impact on cancer therapeutics
- **Marion LENAIN**, *Montpellier Cancer Research Institute (IRCM)*- Use of γδ T cells armed with mAbs as a novel cancer cell therapy
- **Bruno SEGUI**, *Cancer Research Center of Toulouse (CRCT)* - TNF blockade with certolizumab, but not infliximab, improves the efficacy of anti-PD-1 and anti-CTLA-4 combination therapy for melanoma

15h45-16h00
Session 2 – Cancer Research in Limoges at a glance 15
Bertrand LIAGRE, *Limoges University – LABCiS*

16h00 - 16h45 **Coffee Break**

16h45-16h55 **Société Française du Cancer**

16h55-18h15
Session 3 - Innovation in drug delivery technologies..... 17
Chairs: Sébastien BRITTON & Sébastien PAPOT
Lecture: Vijay CHUDASAMA, *University College London (UK)*
Use of "click" chemistry and native disulfide rebridging to make homogeneous ADCs, bispecifics and "synthetic" antibodies (SynAbs)

- **Gaëlle GUILLON**, *Montpellier Cancer Research Institute (IRCM)* - Targeting the TNBC tumor microenvironment with human anti-Cathepsin-D Antibody-Drug Conjugates
- **Sébastien ULRICH**, *The Institut des Biomolécules Max Mousseron (IBMM), Montpellier*- Dynamic Vectors for RNA Delivery

18h15 - 19h40 **Poster session / Icebreaker session**

Thursday 27th November

08h00-08h30 **Welcome Coffee**

08h30-10h15

Chairs: Julie PANNEQUIN & Pierre CORDELIER

Lecture: **Jean ALBRENGUES,** *Institute for Research on Cancer and Aging (IRCAN), Nice*

Neutrophil Extracellular Traps promote Cancer Initiation

- **Lorenzo SCIPIONI,** *Cancer Research Center of Toulouse (CRCT)*- Spatiotemporal omics to investigate cell state transitions in cancer
- **Thomas DAUBON**, *Institute of Cellular Biochemistry and Genetics (IBGC), Bordeaux* - Lactate Shuttle between Glioblastoma Cells and Neurons: a Cancer Neuroscience Case

10h15-11h15 **Poster Session**

11h15-12h45

Chairs: Violaine MOREAU & Guillaume BOSSIS

Lecture: **Frédéric BARD,** *Marseille Cancer Research Centre (CRCM)*

O-glycosylation drives tumor growth and activates a new surface target for Antibody Drug Conjugate

- **Ahmad SHARANEK,** *BoRdeaux Institute of Oncology (BRIC)*- Unraveling Vulnerabilities in Glioblastoma Stem Cells for Therapeutic Intervention
- **Lisa BRUNET,** *Montpellier Cancer Research Institute (IRCM)* - Targeting the TKI resistance mediated by P53 loss of function in non-small cell lung carcinoma
- **Joaquim JAVARY,** *BoRdeaux Institute of Oncology (BRIC)*- Reciprocal inhibition of NOTCH and SOX2 shapes tumor cell plasticity and therapeutic escape in TNBC

Chairs: Véronique GIGOUX & Bertrand LIAGRE

- **Frédéric FRISCOURT**, *European Institute of Chemistry and Biology and Institute of Molecular Sciences (IECB/ISM), Bordeaux*- Precision-labeling of the sialome for imaging cancer cells
- **Sacha BODIN,** *CHU de Bordeaux et Institut de Neurosciences Cognitives et Intégratives d'Aquitaine (INCIA), Bordeaux*- Improving patient selection for efficient Targeted Radionuclide Therapy, using zebrafish embryos
- **Mélanie MOREAU,** *Bordeaux Proteome* - A new spatial multiomics and multimodal workflow for deeper biological sample analysis in human pancreatic cancer
- **Israa AL JAMAL,** *Institut de Chimie des Milieux et des Matériaux de Poitiers* - Development of New Enzyme-Responsive Systems for Selective Bioorthogonal Tumor Labeling and Drug Delivery approaches
- **Chloé BAZILE**, *Cancer Research Center of Toulouse (CRCT)*- Targeting tumor associated macrophages (TAM) with vectorized magnetic nanoparticles for anticancer therapies
- **Amy GATEAU,** *Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique (Limoges)*- Surface Plasmon Resonance-based detection of EGFRvIII in circulating extracellular vesicles from glioblastoma
- **Laura EANES DA SILVA,** *Montpellier Cancer Research Institute (IRCM)* - The synergistic combination Cabozantinib and mTORi inhibits cell proliferation, translation and OXPHOS in clear cell renal cell carcinoma
- **Stéphane TREILLARD,** *Toulouse University Hospital* - Lymphoma vs. metastasis vs. non-tumoral: a multi-class classifier to evaluate H&E-stained lymph nodes

Modération : Philippe GORRY

- **Florian NAUDET,** *Université de Rennes* - Niveau de preuve ou preuves de caniveau ?
- **Jules DI SCALA,** *Université de Toulouse* - Comment caractériser la méconduite scientifique ?
- **Antoine SABOURAUD,** *Université de Bordeaux* - Favoriser l'intégrité scientifique et limiter la diffusion des rétractations : les résultats d'une enquête sur les référents intégrité scientifique français.

12h45-14h15 Lunch Break

14h15-15h45

Modérateurs: Cyrille DELPIERRE & Véronique GIGOUX

- **Jérôme BERANGER,** *Centre d'Epidémiologie et de Recherche en santé des POPulations, Toulouse* - L'impact de l'IA dans l'enseignement, la recherche et l'acquisition des savoirs en médecine
- **Thierry LAVABRE-BERTRAND,** *CHU de Montpellier et Nîmes* - IA et éthique, questions anciennes et nouvelles

15h45-16h45 Coffee Break

16h45-18h15

Chairs: Sandrine DABERNAT & Fabrice LALLOUE

Lecture: Pierre LAURENT-PUIG, *Cordeliers Research Center, Paris*

Molecular classification of colon cancer: prognostic implication

- **Frédéric SALTEL,** *BoRdeaux Institute of Oncology (BRIC)* - Proteomic Signature–Based Stratification of Patients for Predicting Therapeutic Response in Hepatic Cancers
- **Camille FRANCHET,** *Oncopole Claudius Regaud, Toulouse*

Chairs: Vera PANCALDI & Eric JULIEN

Lecture: **Argyris PAPANTONIS,** *University Medical Center Goettingen (Germany)*

Targeting transcriptional addiction to anti-senescence programs in pancreatic cancer

- **Margherita GHISI,** *Cancer Research Center of Toulouse (CRCT)* - Time-controlled CRISPR-Cas9 Screening Highlights Epigenetic Mechanisms of Drug Tolerance and Therapy Evasion in Acute Myeloid Leukemia
- **Maëlle CAROFF,** *Institute of Pharmacology and Structural Biology (IPBS), Toulouse* - Ligand Stabilization of DNA Three way Junctions for Targeted Cancer Therapy
- **Jean-Christophe ANDRAU,** *Institute of Molecular Genetics of Montpellier (IGMM)* - G-quadruplexes are promoter elements functioning as nucleosome exclusion modules in mammals

Modération : Florence SORDES

- **Kristopher LAMORE,** *Institut ONCOLille* - Baromètre cancer 2021 – Perceptions des Français sur les facteurs de risque et de protection
- **Alice DHELLEMMES-SOULAYRAC**, *Centre d'Etudes et de Recherches en PsychoPathologie et Santé (Toulouse)* - Les représentations du cancer et de ses traitements : spécificités de l'hospitalisation à domicile et des anticancéreux oraux

18h15-19h15

Chair: Nadine HOUEDE

Lecture: **Hervé MAISONNEUVE,** *Consultant, rédacteur scientifique*

Grandeur et décadence des publications scientifiques : publier ou mourir

20h00 Gala Dinner (upon registration)

Friday 28th November

08h00-08h30 **Welcome Coffee**

08h30-10h10

Session 9 - Rising Stars – Young Scientists Oral Presentation Competition 60

Chairs: Aubin PENNA, Thomas CLOUAIRE, Caroline BONNANS & Bertrand LIAGRE

- **Guillaume BELTHIER,** *Institute for Functional Genomics (IGF), Montpellier* - Characterizing the Dark Side of Cisplatin: Mechanisms Linking Treatment to Increased Colorectal Cancer Risk
- **Sarah LAVIELLE,** *Institute of Cellular Biochemistry and Genetics (IBGC), Bordeaux* - Investigating the role of gut microbiota in glioblastoma development and therapeutic resistance
- **Maxime TABAUD,** *Control of the Immune B Response and Lymphoproliferations (CRIBL), Limoges* - Study of B-cell tumor-microenvironment interactions and modulation of the immunosuppressive microenvironment by ibrutinib treatment in Waldenström macroglobulinemia-like mouse model
- **Ana Sofia VAZQUEZ URIOLA,** *BoRdeaux Institute of Oncology (BRIC)* - PCSK9: A new potential target in Gastric Cancer Stem Cells ?
- **Hiba DAHER,** *Montpellier Cancer Research Institute (IRCM)* - The pro-tumoral functions of the epigenetic enzyme SUV4-20H2 in Prostate Cancer
- **Alban RICARD,** *Cancer Research Center of Toulouse (CRCT)* - Relationship between the E3 ubiquitin ligase TRIP12 and the Mediator of DNA damage checkpoint MDC1: its impact on DNA Damage Response
- **Reem BANNOUT,** *Montpellier Cancer Research Institute (IRCM)* - Development of new class of DNA mimics to circumvent resistance to TOP1 inhibitors
- **Marcelo HURTADO,** *Cancer Research Center of Toulouse (CRCT)* - Estimating tumour microenvironment cellular states from bulk RNAseq produces biomarkers of clinical outcome across stages
- **Stefan NICOLESCU,** *Montpellier Cancer Research Institute (IRCM)* - Impact of the Pregnane X Receptor (PXR) on the sensitivity to targeted therapies in skin melanoma
- **Angela AGAËSSE,** *Cancer Research Center of Toulouse (CRCT)* - Magnetic Hyperthermia and Mechanical Ablation Induce An Anti-Tumour Immune Response In Pancreatic Adenocarcinoma

10h10-10h30 **Prize Awards**

10h30-11h15 **Coffee Break**

11h15-13h00

Session 10A - Translational Research in Thoracic Oncology / COALA project 72

Chairs: Olivier CALVAYRAC, Antonio MARAVER & Julien MAZIERES

Lecture: **Trever G. BIVONA,** *University of California San Francisco (USA)*

New insights into lung cancer pathogenesis and therapy resistance

- **Michèle CUNY & Valérie CHABRIERE,** *ALK France* - Presentation of the ALK+ & ROS1 patients association
- **Montse SANCHEZ-CESPEDES**, *Josep Carreras Leukaemia Research Institute, Barcelona (Spain)* - Genetic Factors Involved in Tumor Immune Evasion: From Mechanisms to Biomarkers
- **David SANTAMARIA,** *Centro de Investigación del Cáncer (CIC), Salamanca (Spain)* - Innovative approaches to target KRAS-driven tumours

Session 10B - Les représentations de la maladie cancéreuse au sein de la population générale 77

Modération: Florence SORDES

- **Florent VARET,** *Université Catholique de Lille* - Cancer du sein et hormonothérapie adjuvante : quand l'insatisfaction pousse à chercher ailleurs … pour le meilleur ou pour le pire. Une étude par entretiens
- **Véronique BERNAD,** *Patient en réseau* - Comprendre le vécu du cancer : comparaison des représentations entre patients, proches aidants et rôle des associations de patients
- **Brigitte TRETARRE**, *Registre des Tumeurs de l'Hérault (Montpellier)* - Situation actuelle du cancer en France : une vision optimiste de la réalité à travers les chiffres d'incidence et de survie.

13h00-14h00 **Closing Lunch**

Session 1 - Targeting Inflammation: From Molecular Dialogues to Cellular Therapies in Oncology

1 / 1

Tick-Tumor-Tock: Circadian Neutrophil Programs in lung cancer

A DE JUAN, A. DE JUAN, M. GÓMEZ, David CÁCERES, M. NOGALES, **María CASANOVA-ACEBES**

Laboratory of Cancer Immunity, Tumor Biology Program. Centro Nacional de Investigaciones Oncológicas, MADRID

In the evolving landscape of tumor immunology, the role of myeloid cells has shifted from passive support players to central orchestrators of immune suppression, stromal remodeling, and therapeutic resistance. Myeloid cells- macrophages, monocytes, neutrophils, and dendritic cell subsets- constitute a dynamic and heterogeneous compartment within the tumor microenvironment (TME). In solid tumors, they often represent the most abundant immune infiltrate, yet their complexity, plasticity, and context-dependent functions continue to pose challenges for therapeutic targeting.

Traditionally, studies have sought to understand these cells through the lens of ontogeny (what is their origin, embryonic or adult hematopoiesis?) and phenotypic markers (what do they express?). We have learned a great deal about their developmental origins, surface profiles, bulk and single-cell spatial transcriptional states. However, a critical dimension remains largely overlooked: time. Time governs biology, from embryogenesis to immune surveillance. And yet, in tumor immunology, we rarely ask: When do these cells arrive? When are they immunosuppressive? When do they become pro-tumorigenic? Is their function constant, or is it temporally gated? In my lab, we explore how temporal dynamics- both diurnal (circadian) and longitudinal (tumor progression)-shape the behavior and function of myeloid cells in solid tumors. We approach this with a central hypothesis: that immune function is not static but rather modulated by internal biological clocks and tumor stage-specific cues, which jointly orchestrate the immunological landscape of tumors.

Among the myeloid populations, neutrophils are perhaps the most understudied in the context of functional plasticity. Traditionally seen as short-lived first responders, neutrophils in cancer have been linked to both pro-tumoral (e.g., angiogenesis, immunosuppression) and anti-tumoral (e.g., tumor cell killing) functions. However, their behavior has often been interpreted as homogeneous and time-independent. Our work challenges this paradigm. Using temporally-resolved sampling in murine models of lung adenocarcinoma, we discovered that neutrophil infiltration into tumors is rhythmic, following a circadian pattern. Specifically, neutrophil numbers vary across the 24-hour cycle, peaking at defined time points that correlate with distinct functional profiles. These rhythmic infiltrations are not merely fluctuations in cell numbers. Transcriptomic profiling of time-stamped tumor-infiltrating neutrophils revealed time-dependent gene expression programs, including modules related to antigen processing and presentation, interferon signaling, and chemokine production.

One of our key findings is that antigen presentation programs in neutrophils are regulated by the core clock transcription factor BMAL1. Neutrophils infiltrating the tumor at specific circadian phases upregulate MHC class II–related genes and co-stimulatory molecules, enabling them to transiently function as antigen-presenting cells (APCs). This overturns the classical view of neutrophils as poor APCs and positions them as time-sensitive modulators of T cell priming. In parallel, we observed that neutrophil responses to type I interferons—which are central to anti-tumor immunity—are also circadian-dependent. Neutrophils recruited at specific times exhibit enhanced interferon responsiveness, marked by increased ISG expression, cytokine production, and anti-tumoral activity in vivo. Disruption of their intrinsic circadian clock (via Bmal1 deletion) abolishes these effects, underscoring the functional relevance of internal timekeeping.

Altogether, these findings redefine neutrophils as rhythmically tuned immune effectors, whose capacity to influence tumor progression is highly dependent on when they act. These insights open the door to chrono-immunotherapy, where treatments could be timed to coincide with windows of maximal neutrophil activity, or where the circadian machinery itself becomes a therapeutic target.

1 / 2

Exploring the crosstalk between DNA repair and inflammatory responses: impact on cancer therapeutics

Nadine LAGUETTE

IGMM, university of Montpellier, CNRS UMR5535, Montpellier, France

Cytosolic double-stranded DNAs (dsDNAs) are potent immune-stimulatory molecules that activate inflammatory pathways in numerous human pathologies. A central mechanism for the detection of cytosolic dsDNA involves the cyclic GMP-AMP synthase (cGAS), which produces the 2'3'-cGAMP cyclic dinucleotide (CDN) to activate the Stimulator of Interferon Genes (STING), thereby triggering type I Interferon (IFN) responses. Although 2'3'-cGAMP is a key rate-limiting second messenger in the activation of this pathway, there is, to date, no mechanism described to regulate its level in the cytosol.

Our recent work identifies the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), a key player in DNA double-strand break repair, as a regulator of intracellular 2'3'-cGAMP. We show that DNA-PKcs directly binds 2'3'-cGAMP in its catalytic domain, reducing its bioavailability for STING activation. This process is accompanied by the inhibition of DNA-PKcs catalytic activity, which may come at the expense of deficient DNA repair. Furthermore, contrary to other mechanisms that regulate extracellular 2'3'-cGAMP levels, we show that DNA-PKcs can also act on the bacterial 3'3'-cGAMP to reduce its capacity to activate STING.

The implications of this regulatory mechanism on inflammatory responses as well as DNA repair mechanisms will be discussed.

1 / 3

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

Marion LENAIN, Virginie LAFONT, Cécile DEJOU

Institut de Recherche en Cancérologie de Montpellier

Human 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 the biological functions of other immune cells, which are necessary for the initiation and establishment of an effective anti-tumor immune response. Unlike 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. This supports why γδ T cells are considered as highly attractive therapeutic targets for anti-tumor immunotherapies. Currently, many clinical trials are ongoing based on various strategies such as the use of bispecific antibodies targeting both tumor cells and γδ T cells, CAR γδ T cells, γδ T cells-activating molecules. Here, we propose a new innovative strategy of cell therapies based on the ability of γδ T cells to express low affinity receptor of IgG Fc portion (FcγRIII or CD16) and to be armed with monoclonal antibodies (mAbs) targeting specifically tumor cells. Indeed, several studies, including our own, have shown that γδ T cells can express CD16 and similar to NK cells, CD16+ γδ T cells are able to perform antibody-dependent cellular cytotoxicity (ADCC). 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 on γδ T cells differs from donor to donor and also with differentiation status. Second, we have shown that γδ T cells have cytotoxic activity against cancer cells in 2D culture models. We are currently working on the development of 3D models of different ovarian cancer lineages. Our preliminary results in 3D models showed that: 1- IL-2 and IL-15 increase the infiltration of γδ T cells of into spheres, and 2- the activation of γδ T cells by simultaneous TCR and CD16 recruitment has an additive effect on their cytotoxic activity against tumor cells. These findings are very interesting and require further investigation.

1 / 4

TNF blockade with certolizumab, but not infliximab, improves the efficacy of anti-PD-1 and anti-CTLA-4 combination therapy for melanoma

Bruno SEGUI

Université de Toulouse, CNRS, Inserm, Centre de Recherches en Cancérologie de Toulouse, Toulouse, France.

Although immune checkpoint inhibitors (ICI) enhance immune responses in melanoma, most advanced melanoma patients do not respond or relapse, and develop immune-related adverse events (irAEs). Some irAEs, such as colitis, can be treated with infliximab, which is a tumour necrosis factor-alpha inhibitor (TNFi). Given the dual role that TNF plays in immune responses and cancer progression, the impact of TNFi on immune and clinical responses remains unclear. Herein, we report the final results of the TICIMEL phase 1b clinical trial in advanced melanoma patients. This trial evaluated the safety, tolerability and efficacy of two tri-therapies comprising ipilimumab (an anti-CTLA-4) and nivolumab (an anti-PD-1), in combination with certolizumab or infliximab (two TNFi). Signs of efficacy and CD8 T cell activation were higher with ICI combined with certolizumab than with infliximab. In contrast, patients treated with ICI and infliximab exhibited a superior tolerability profile. Evidence from mouse melanoma models suggests that, unlike infliximab, certolizumab-mediated TNF blockade strongly stimulates immune and therapeutic responses to ICI. This promotes the activation of effector T cells and reduces their pre-exhaustion, as well as the proportion of regulatory T cells in tumours. We also identified the IgG1 Fc fragment of infliximab as being responsible for counteracting the benefits of TNF blockade, emphasizing the importance of selecting the correct TNF blocker to combine with ICI in melanoma.

ClinicalTrials.gov identifiers: NCT03293784; NCT05867004.

Session 2 – Cancer Research in Limoges at a glance

Cancer Research in Limoges at a glance

OmegaHealth
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CAPTuR – (Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique) – UMR Inserm-CHU 1308

CRIBL – (Contrôle de la Réponse Immune B et lymphoprolifératives) – UMR CNRS 7276 – UMR Inserm 1262

EpiMaCT – (Epidémiologie des Maladies Chroniques en Zone Tropicale) – UMR Inserm-CHU 1094 – U 270 IRD – USC INRAE 1501

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anr

Session 3 - Innovation in drug delivery technologies

3 / 1

Use of "click" chemistry and native disulfide rebridging to make homogeneous ADCs, bispecifics and "synthetic" antibodies (SynAbs)

Vijay CHUDASAMA, And CO-WORKERS

Department of Chemistry, University College London, UK

Summary of our work in the areas of cysteine and disulfide modification as applied to antibody fragments and full antibodies (https://chudasama-group.eu/publications/, Org Biomol Chem, 2022, 20, 5879-5890). How we have applied this chemistry to construct site-selectively modified antibody conjugates with a plethora of discrete payload loadings (payload to antibody ratio of 1 through to 8, Chem Sci, 2023, 14, 3752-3762), create synthetic bispecifics (Bioconjugate Chem, 2023, 34, 2215-2220) and first-in-class synthetic antibodies (ACS Cent Sci, 2023, 9, 476-487) and trispecifics (Nature Chem, 2023, 15, 1636-1647). If time permits, a few recent highlights of work in the space of regio- and chemo-selective antibody modification (Chem Sci, 2024, 15, 8557-8568), reversible cysteine modification (Chem Sci, 2023, 14, 13743-13754), and site-selective lysine modification (Chem Sci, 2025, 16, 2763-2776) will be shared.

3 / 2

Targeting the TNBC tumor microenvironment with human anti-Cathepsin-D Antibody-Drug Conjugates

Gaëlle GUILLON[1,2,3], Ilona BERESTJUK[1,2,3], Aude MALLAVIALLE[1,2,3], Valérie LAURENT-MATHA[1,2,3], Thierry CHARDÈS[1,2,3], Emmanuelle LIAUDET-COOPMAN[1,2,3]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Université de Montpellier

[3] INSERM U1194

Triple-negative breast cancers (TNBC), which account for 15% of breast cancer (BC) patients (estrogen receptor negative, progesterone receptor negative, HER2 non-amplified), are mainly treated with chemotherapy and urgently require new targeted therapies. The aspartic protease Cathepsin D (Cath-D), a poor prognostic marker in BC, including TNBC, is overexpressed by BC cells and hypersecreted in the tumor microenvironment. In BC, extracellular Cath-D exhibits pro-tumor activities through proteolytic cleavage of stromal/tumor components, and/or by acting as a binding protein interaction with cell surface receptors. Moreover, extracellular Cath-D can bind to and be internalized by mannose-6-phosphate/insulin growth factor 2 receptors (M6P/IGF2-R) or other unknown receptors that are expressed at the surface of BC and stromal cells, such as fibroblasts. We previously showed that extracellular Cath-D bound to an anti-Cath-D monoclonal antibody (mAb) is endocytosed by BC cells and also by stromal fibroblasts. In addition, tumor cell-membrane associated Cath-D was observed in 85.7% of 147 TNBC patients. These intrinsic properties of secreted Cath-D, which is reinternalized by a receptor-mediated process, suggest that it may be a promising and innovative therapeutic extracellular target in the tumor microenvironment for antibody-mediated treatment strategies, such as ADCs.

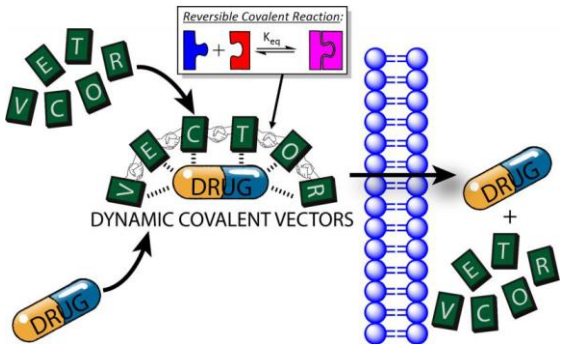
Six payloads comprising different classes of chemotherapy (topoisomerase I and II inhibitors, alkylating agents, tubulin polymerization inhibitors, DNA intercalators) were conjugated to anti-Cath-D human Ab F1M1 using Moradec technology and tested on cell lines representative of these TNBC subtypes. Cell lines from the Basal Like (BL1 and BL2) and Mesenchymal (M and MSL) subtypes exhibited increased sensitivity to these payloads, and in particular to alkylating agents (pyrrolobenzodiazepine (PBD), duocarmycin) and topoisomerase I inhibitors (deruxtecan). In partnership with Lonza, we produced two ADCs bioconjugated to PBD Tesirine and Dxd deruxtecan. These ADCs demonstrated significant cytotoxic effect in 2D and 3D TNBC models, notably on cell lines representing the BL2, MSL and M subtypes, through Caspase 3/7 activation of apoptosis and γH2AX-mediated DNA damage. The therapeutic efficacy of these ADCs was evaluated in nude mice xenografted with the SUM159 TNBC cell line, representative of the MSL subtype. Our results showed a great antitumor effect for both ADC. In addition, analysis of mouse hepatic function and complete blood counts revealed no toxicity of these ADCs. Additional in vivo studies are ongoing with the lead candidate PBD-ADCs cell lines representative of the BL2 and M subtypes, to further assess their therapeutic potential.

3 / 3
Dynamic Vectors for RNA Delivery

Sebastien ULRICH

Institut des Biomolécules Max Mousseron (IBMM, UMR 5247)
CNRS, Université de Montpellier, ENSCM, Montpellier, France

The intra-cellular delivery of anti-cancer drugs require the development of dynamic chemical systems which feature controllable assembly and disassembly processes in order to bind, transport, and release the therapeutic cargo.1, 2 In this context, we are exploring the potential of dynamic covalent chemistry for accessing such smart delivery systems. Our contribution has hitherto led to the identification of i) effective cell-selective delivery vectors of RNA (siRNA,3-6 mRNA7), and ii) photosensitizer conjugates active in photodynamic therapy. Thanks to the versatility of our design and methodology, these proof-of-concepts open up new perspectives to tackle the delivery issue in various health applications. In this presentation, I will describe our methodology and highlight the main results using these dynamic covalent vectors for the delivery of RNA.



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Session 4 - Hot topics in oncology

4 / 1

Neutrophil Extracellular Traps promote cancer initiation

Alexandra MOUSSET[1], Lola BELLONE[1], Isabelle BOURGET[1], Loan TRAN[1], Clément MOLINA[1], Lydia ARTIÈRES[1], Quentin ODET[1], Pascal LOPEZ[1], Jemima MELLERIO[2], Daniela Elena COSTEA[3], Hamid-Reza REZVANI[4], Julie PANNEQUIN[5], Cédric GAGGIOLI[1], **Jean ALBRENGUES[1]**

[1] University Côte d'Azur, CNRS UMR7284, INSERM U1081, Institute for Research on Cancer and Aging, Nice (IRCAN), Nice, France

[2] St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust, London, UK

[3] Center for Cancer Biomarkers CCBIO and Gade Laboratory of Pathology, Department of Clinical Medicine, University of Bergen, Bergen, Norway; Department of Pathology, Laboratory Clinic, Haukeland University Hospital, Bergen, Norway

[4] Univ. Bordeaux, INSERM, BRIC, Bordeaux, France; Aquiderm, Univ. Bordeaux, Bordeaux, France

[5] Université de Montpellier, Institut de Génomique Fonctionnelle, CNRS, Inserm, Montpellier, France

Inflammation predisposes individuals to cancer development, yet the underlying cellular and molecular mechanisms remain unclear. While neutrophils are the first immune cells to respond to infections and injuries, their role in cancer has only recently attracted attention.

Using multiple carcinogen-induced cancer models (DMBA/TPA and UVB for cutaneous squamous cell carcinoma, 4NQO for head and neck cancer, and AOM/DSS for colorectal cancer), we show that neutrophils promote tumor initiation through the release of Neutrophil Extracellular Traps (NETs). NETs are web-like structures composed of decondensed chromatin fibers decorated with proteins, released by activated neutrophils. While NETs were first discovered for their ability to trap and kill pathogens, we show that NETs accumulate rapidly after carcinogen exposure and targeting them during carcinogen exposure efficiently counteracts cancer initiation across models. Mechanistically, NETs favor the transition from normal to transformed epithelial cells through two complementary processes: they enhance DNA damage and suppress apoptosis, thereby allowing the survival of cells that would otherwise be eliminated. The precise molecular mechanisms underlying these effects will be discussed during the presentation.

The clinical relevance of these findings was established by identifying NETs in lesions from patients at risk of developing cancer, including those of the skin, head and neck, and colon. Altogether, our data identify NETs as critical drivers of cancer initiation and highlight them as promising targets for innovative preventive strategies.

4 / 2

ESPRESSO: Spatiotemporal Omics Based on Organelle Phenotyping Reveals Phenotypic Transitions

Lorenzo SCIPIONI[1,2], Giulia TEDESCHI[1,2], Mariana NAVARRO[3], Yunlong JIA[4], Songning ZHU[1], Lila Paige HALBERS[5], Melody DI BONA[6], X. Scott ATWOOD[4], A. Jennifer PRESCHER[3,5], Enrico GRATTON[2], A. Michelle DIGMAN[2]

[1] Centre de Recherche en Cancérologie de Toulouse, Toulouse (France)

[2] University of California, Irvine (CA, United States), Department of Biomedical Engineering, Laboratory for Fluorescence Dynamics

[3] University of California, Irvine (CA, United States), Department of Chemistry

[4] University of California, Irvine (CA, United States), Department of Developmental and Cell Biology

[5] University of California, Irvine (CA, United States), Department of Pharmaceutical Sciences

[6] Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York (NY, United States)

Omics technologies, while fundamentally revolutionizing our molecular understanding of biological systems, are inherently limited in their capacity to fully capture the complexity of life. These bulk or even single-cell snapshot methodologies often fail to account for the crucial interplay of **time and space within the living cell**, primarily due to the impossibility of following the dynamic state transition of individual cells as a function of time. This limitation means that critical, transient cellular events-such as the immediate response to a drug or the subtle shifts during differentiation-are often averaged out or missed entirely, preventing a complete mechanistic understanding of cellular decisions. To bridge this critical gap between the static molecular profile and the dynamic functional reality, we introduce **ESPRESSO (Environmental Sensor Phenotyping RElayed by Subcellular Structures and Organelles)**, a novel and powerful technique designed to achieve **high-dimensional phenotyping resolved in both space and time at the single-cell level.**

The methodology of ESPRESSO uniquely leverages the **morphological and functional information relative to the organelle network**, which acts as the cell's integrated computational hub. ESPRESSO combines advanced live-cell staining protocols utilizing a panel of **organelle-specific, environment-sensitive probes**. These innovative probes are designed to report on local biophysical conditions, not just simple presence. For robust and simultaneous data acquisition, the technique employs **confocal hyperspectral imaging** coupled with **spectral phasor unmixing**. This combination is essential, allowing us to resolve multiple, overlapping fluorescent signals with exceptional clarity and high spectral resolution, thereby enabling the necessary **high-speed temporal acquisition** required to track rapid changes within the living cell.

The output of this imaging framework is a dense, quantitative dataset. We are able to extract a vast and statistically powerful **feature set** of a dimensionality comparable to single-cell RNA sequencing. Critically, this set includes detailed **morphological properties** (e.g., organelle size, shape, and spatial distribution) alongside dynamic **functional properties** (e.g., mitochondrial membrane potential and lysosomal pH). The integration of these parameters across the organelle network generates an **organelle-based omics signature** that truly reflects the cell's integrated, active **biophysical state**, a level of functional detail currently inaccessible by pure gene or protein expression profiles.

By quantifying the dynamic reorganization of the subcellular landscape, ESPRESSO allows us to **unravel cellular heterogeneity** with unprecedented resolution, moving beyond simple molecular categories to identify distinct functional subpopulations. This capability is paramount for unveiling specific **stress and drug response pathways**, as organelle reorganization often precedes major transcriptional changes, providing an earlier and more nuanced understanding of cellular fate. Furthermore, the temporal resolution allows us to precisely **trace differentiation trajectories** in complex cultures, observing the continuous path rather than jumping between discrete endpoints. Ultimately, ESPRESSO provides a crucial, missing **bridge between molecular omics and the active physical state of the cell**, providing the context necessary to link genomic potential to realized function. Here, we will demonstrate the broad applicability of this methodology by presenting ESPRESSO applied to several critical biological and translational contexts, including the study of **phenotypic transitions in stress response, keratinocyte differentiation, macrophage polarization** and **dissecting drug response in heterogeneous breast cancer tumor spheroids**. These examples highlight the method's unparalleled power in characterizing dynamic cellular behaviors relevant to disease and development.

4 / 3

Lactate Shuttle between Glioblastoma Cells and Neurons: a Cancer Neuroscience Case

Mathis PINGLAUT[1], Claire LARRIEU[1], Yahaya YABO[1], Axell DAVOUST[1], Antonio Christian PAGANO ZOTTOLA[1], Mathieu LARROQUETTE[1], Sebastian LILLO[1], Johanna GALVIS[1], Doriane BOMONT[1], Macha NIKOLSKI[1], Océane MARTIN[1], Audrey BURBAN[1], Dieter Henrik HEILAND[2], **Thomas DAUBON[1]**

[1] IBGC CNRS UMR5095, University of Bordeaux, France

[2] MILO Laboratory, Department of Neurosurgery, Freiburg, Germany

Glioblastoma (GB) is a highly infiltrative brain tumor characterized by poor prognosis and limited median survival, even under aggressive therapeutic management. Tumor progression relies heavily on metabolic exchanges. In the healthy brain, lactate symbiosis occurs between glycolytic astrocytes and oxidative neurons, with neurons consuming astrocytic lactate to fuel the TCA cycle. We previously demonstrated that a similar lactate symbiosis exists within GB, where glycolytic and oxidative tumor cell populations cooperate to sustain growth and invasion (Guyon et al., 2022, *EMBO Mol Med*). Importantly, targeting lactate metabolism with antiepileptic agents that inhibit lactate dehydrogenase reduces GB growth, while inhibiting oxidative populations with complex I inhibitors efficiently limits tumor progression (Burban et al., 2025, *EMBO Mol Med*).

Surgical resection remains the standard of care for GB, aiming to remove the bulk of the tumor. However, we hypothesized that resection disrupts intratumoral metabolic organization, forcing residual invasive cells to undergo metabolic reprogramming. To test this, we performed spatial transcriptomics (MERSCOPE and Visium) on patient samples collected during short-term re-resections, ranging from days to weeks after surgery. We observed the emergence of a hypoxic environment, recruitment of distinct immune cell subsets, increased ROS signaling, and a metabolic switch toward oxidative phosphorylation. Mouse models undergoing GB resection confirmed these findings, and mass spectrometry imaging of recurrent xenografts revealed a sharp rise in lactate production. In vitro, simulations of lactate fluctuations reproduced this shift, showing mitochondrial downregulation and elevated ROS production. ROS acted as signaling molecules, enhancing hypoxia-inducible factor 1α (HIF1α) activity and upregulating lactate transporter MCT1. Functionally, GB cells deprived of lactate regained proliferative capacity, mirroring tumor regrowth after surgery. In vivo, treatment of resected tumors with LDH inhibitors or ROS scavengers significantly delayed recurrence, highlighting the therapeutic relevance of targeting these adaptive processes.

We further hypothesized that excess lactate generated in the post-resection context could be taken up by neurons, leading to neuronal hyperactivation that in turn promotes GB progression. To test this GB-neuron metabolic coupling, we disrupted the neuronal lactate transporter MCT2 in both in vitro and in vivo models. Loss of neuronal lactate uptake reduced GB cell invasion and proliferation, supporting the concept of a bidirectional lactate shuttle sustaining relapse.
In conclusion, surgical resection induces a profound metabolic reprogramming in GB, characterized by increased oxidative metabolism, ROS signaling, and altered tumor-neuron interactions. These adaptations fuel tumor recurrence. Targeting the metabolic vulnerabilities emerging after resection-such as lactate dynamics, ROS signaling, and neuron-tumor metabolic crosstalk-represents a promising therapeutic strategy to limit GB relapse and improve patient outcomes.

Session 5A - Cell signaling, microenvironment and targeting / Axis 1 session

5A / 1

O-glycosylation drives tumor growth and activates a new surface target for Antibody Drug Conjugate

Frédéric BARD

Centre de Recherche en Cancérologie de Marseille (CRCM)

Team leader GLYNTHERA, Glycosylation and New Therapies
Centre de Recherche en Cancérologie de Marseille (CRCM), 27 boulevard Leï Roure,
13009 Marseille, France, CRCM, Marseille, France
Founder and CEO, Albatroz Therapeutics, Singapore

In solid tumours, cancer cells need to remodel normal tissues to grow and metastasise and thus significantly up-regulate the degradation of extracellular matrix. Surface glycoproteins play a key role in this process. We have shown tissue remodelling and ECM degradation is highly dependent on increased O-glycosylation of surface proteins. This hyper-glycosylation is driven by the GALA signalling pathway, which controls the O-glycosylation initiation GALNTs enzymes. GALA is activated in PDAC and is essential for tumor growth. The PDAC glycoproteome activated by GALA covers over 200 proteins. Among them, the ER resident protein Calnexin is translocated to the cell surface after its glycosylation. We found that Calnexin plays a key role in ECM degradation by mediating reduction of disulfide cross-links. Surface Calnexin can be targeted by Antibody Drug Conjugates (ADC) to achieve full tumor regression in multiple CDX models. Overall, our work highlights the importance of O-glycosylation up-regulation and modification of ER-resident proteins as a critical mechanism for tumor growth and highlight a new target for cancers of the GI tract.

5A / 2

Unraveling Vulnerabilities in Glioblastoma Stem Cells for Therapeutic Intervention

Ahmad SHARANEK (CHARANEK)

University of Bordeaux, INSERM UMR1312, BRIC BoRdeaux Institute of Oncology, Bordeaux, France

Glioblastoma (GB) is the most common and aggressive primary brain tumor in adults, with median survival rarely exceeding 18 months despite surgery, radiotherapy, and chemotherapy. The persistence of glioblastoma stem cells (GSCs), a highly plastic and therapy-resistant subpopulation, drives recurrence and remains a major challenge to effective treatment. Understanding the mechanisms that sustain GSCs is therefore essential for developing new therapeutic strategies.

Metabolic plasticity is a hallmark of cancer cell survival and therapy resistance. Mitochondria support oxidative phosphorylation (OXPHOS) and adaptive responses to treatment, yet the extent of mitochondrial heterogeneity within GSC populations and its functional consequences remain unexplored. We identified mubritinib, a brain-penetrant and well-tolerated complex I inhibitor, as a potent disruptor of GSC stemness and tumor growth. Mubritinib impairs OXPHOS, disrupts AMPK/P27Kip1 signaling, and alleviates tumor hypoxia. In patient-derived and syngeneic GB models, mubritinib delayed tumor progression, prolonged survival, and enhanced response to radiotherapy and temozolomide, without detectable toxicity, highlighting its potential for clinical translation. To further investigate resistance mechanisms to mubritinib, we are performing CRISPR-based genetic screens to uncover novel resistance pathways and inform rational combinatorial strategies.

In addition to mitochondrial metabolism, cancer cells depend on aerobic glycolysis and lactate shuttling, mediated by monocarboxylate transporters (MCTs). We found that MCT1 (SLC16A1) is upregulated in GB and associated with poor prognosis. Strikingly, MCT1 knockout markedly delayed GSC growth and extended survival in intracranial GB models, whereas pharmacologic inhibition of its transport activity (AZD3965) failed to impair GSCs, suggesting a transport-independent functions. To dissect these roles, we are performing rescue experiments with wild-type and transport-inactive MCT1 constructs, alongside proteomic and phospho-proteomic analyses to identify non-canonical MCT1 mechanisms in GSCs. Together, these studies could potentially reveal exploitable vulnerabilities in GSCs and highlight novel promising targets to improve GB therapy.

5A / 3

Targeting the TKI resistance mediated by P53 loss of function in non-small cell lung carcinoma

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

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Université de Lille, CNRS, Institut Pasteur Lille, UMR 8161-M3T, Lille

[3] Université de Lille, Thoracic Onocology 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 Carcinoma (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. In this sense, clinical trials using tepotinib, a MET-TKI demonstrated that patients harboring p53 mutations respond worst to this treatment.

To understand the role of p53 in MET-TKI response, we performed p53 loss of function (LOF) in vivo in a recent developed MET-driven NSCLC model unique to our lab. 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 without p53, as it happens in patients, respond worst to the clinically relevant MET-TKI crizotinib, and strikingly, they regain sensitivity to the crizotinib upon combination with nirogacestat, a clinically relevant Notch inhibitor.

Furthermore, at the mechanistic level, we revealed that the higher activity of Notch in this genetic context was mediated by a specific Notch ligand. In collaboration with the GenAc platform at IRCM, we recently developed an antibody against this ligand that works more efficiently at pH 6.5, i.e., the one present in the NSCLC tumor microenvironment and less efficiently at normal pH 7.4, and hence we hope to treat NSCLC in this setting with a higher specificity.

5A / 4

Reciprocal inhibition of NOTCH and SOX2 shapes tumor cell plasticity and therapeutic escape in TNBC

Joaquim JAVARY[1,2,3], Morgane FOURNIER[3], Vincent ROH[4], Nadine FOURNIER[3,4], Freddy RADTKE[3]

[1] BoRdeaux Institute of Oncology

[2] Université de Bordeaux

[3] EPFL, ISREC***, Lausanne***

[4] Swiss Institute of Bioinformatics (SIB)

Triple-negative breast cancer (TNBC) represents the most aggressive subtype of breast cancer, with therapeutic options limited to chemotherapy, leading to a poor prognosis. Consequently, there is an urgent need for novel targeted therapies. Aberrant activation of the Notch signaling pathway is recurrently observed in TNBC and constitutes a promising therapeutic target with available inhibitors. The clinical potential of gamma-secretase inhibitors (GSIs), blocking Notch signaling, remains underexplored in TNBC, and their efficacy may be compromised by currently uncharacterized resistance mechanisms. Despite initial responses, cancer cell plasticity and intratumoral heterogeneity contribute significantly to the failure of chemo- and targeted therapies in TNBC. Moreover, molecular mechanisms of therapy-induced tumor cell plasticity and associated resistance are largely unknown.

Using a genome-wide CRISPR-Cas9 screen, we investigated escape mechanisms of NOTCH-driven TNBC treated with a GSI and identified SOX2 as a target of resistance to Notch inhibition. We describe a novel reciprocal inhibitory feedback mechanism between Notch signaling and SOX2, that shapes tumor cell plasticity and therapeutic escape in NOTCH-driven TNBC. Specifically, Notch signaling inhibits SOX2 transcription through its repressors target genes of the HEY family. Reciprocally, SOX2 inhibits transcription of Notch target genes through direct interaction with Notch signaling transcription factor RBPJ and binding to regulatory regions of Notch target genes. This mechanism shapes divergent cell states with NOTCH-positive TNBC exhibiting epithelial-like features, while SOX2 expression displays mesenchymal characteristics, cancer stem cell features and GSI resistance. To overcome monotherapy resistance, we evaluated rational combination therapies based on synergy drug screen and the NOTCH/SOX2 tumor status. GSI-paclitaxel and dasatinib-paclitaxel combination therapies demonstrated synergistic efficacy in GSI-sensitive and -resistant orthotopic TNBC mouse models, respectively. These distinct preventive and second-line combination therapies, dependent on NOTCH and SOX2 expression in TNBC, significantly reduced tumor growth and metastatic burden.

Altogether, we uncover a novel SOX2/NOTCH molecular axis as a central node in therapy-induced plasticity, facilitating lineage switching and treatment escape in TNBC. This work opens avenues for preventive and second-line combination treatments to avoid or overcome therapeutic resistance in TNBC patients stratified based on NOTCH and SOX2.

Session 5B - New tools for innovative biomarkers / Axis 3 & Axis 5 session

5B / 1

Precision-labeling of the sialome for imaging cancer cells

Jurgen SCHULZ[1,2], Zoeisha CHINOY[1,2], **Frédéric FRISCOURT[1,2]**

[1] Institut Européen de Chimie et Biologie, Bordeaux

[2] Institut des Sciences Moléculaires, Bordeaux

There is a growing appreciation that complex glycans, displayed on glycoproteins and glycolipids, play key roles in numerous physiological and pathological processes. Changes in the glycome of cells have been found to be associated with the onset of cancer and have been involved in tumor proliferation, invasion, angiogenesis and metastasis [1]. Consequently, aberrant glycosylation, such as **upregulation of sialosides**, offers the possibility to target novel cancer biomarkers for early diagnosis.

Previous efforts towards glycans imaging have been relying on the use of lectins (glycan-binding proteins) and monoclonal antibodies. However, lectins typically are tissue-impermeant and often toxic, raising monoclonal antibodies to specific glycans is highly challenging due to the ubiquitous presence of glycans in mammals and their inherent poor immunogenicity. Instead, **chemical biology approaches** have been developed. Notably, the use of bioorthogonal chemistry (between a chemical reporter and a bioorthogonal probe) is emerging as a versatile technology for labeling and visualizing glycans [2,3].

However, current bioorthogonal probes are often hydrophobic, which can promote their sequestration by membranes or nonspecific binding to serum proteins, thereby increasing background signal. Furthermore, some bioorthogonal probes have also been shown to react, to varying degrees, with biological functionalities such as thiols. All together, these potential non-specific fluorescence emissions significantly complicate the early detection of complex glycans.

To address these difficulties, our team has developed, via a multidisciplinary approach, novel bioorthogonal probes for precision labeling of glycans in living systems, bringing imaging of glyco-biomarkers one step closer to novel exciting cancer diagnostics.

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5B / 2

Improving patient selection for efficient Targeted Radionuclide Therapy, using zebrafish embryos

Sacha BODIN[1,2,3], Magalie HAISSAGUERRE[4], Ghoufrane TLILI[2], Elif HINDIE[2,3,5], Christophe LAURENT[6], Geneviève BELLEANNEE[7], Abdel-Majid KHATIB[8], Clément MORGAT[1,2,3]

[1] Radiopharmacy Department, Bordeaux University Hospital, Bordeaux

[2] Nuclear Medicine Department, Bordeaux University Hospital, Bordeaux

[3] Institut de neurosciences cognitives et intégratives d'Aquitaine

[4] Endocrinology Department, Bordeaux University Hospital, Bordeaux

[5] Institut Universitaire de France, Paris

[6] Digestive Surgery Department, Bordeaux University Hospital, Bordeaux

[7] Pathology Department, Bordeaux University Hospital, Bordeaux

[8] BoRdeaux Institute of Oncology

Targeted Radionuclide Therapy (TRT) consists of administering radiopharmaceutical drugs (RPDs) to specifically irradiate tumor cells throughout the body. To date, two Lutetium-177 ([^{177}Lu])-labeled RPDs have received marketing authorization for use in TRT, including [^{177}Lu]Lu-DOTATATE (Lutathera®), indicated for the treatment of inoperable or metastatic, progressive, well-differentiated (G1 and G2) gastroenteropancreatic neuroendocrine tumors (GEP-NETs) expressing somatostatin receptors in adults. These RPDs used in TRT are costly medications and their administration is complex, requiring a dedicated inpatient unit for RPD injection and management of radioactive waste emitted by the patient during the 6 hours following treatment. Eligibility for TRT is currently determined by positron emission tomography (PET) imaging using similar RPDs labeled with gallium-68 (^{68}Ga). This defines the "theranostic" concept ("to image and to treat"). However, this theranostic strategy does not necessarily predict the therapeutic efficacy of TRT on tumors (DNA damage repair mechanisms, very short physical half-life of^{68}Ga (68 minutes) which prevents medium- or long-term evaluation of tumor uptake…). In addition, the slow progression of NETs and their delayed response to TRT (over several months) mean that treatment outcomes are often only visible after completion of the four treatment cycles. In practice, nearly 20% of patients do not respond to Lutathera® therapy (phase 3 NETTER-1 data).

The strategy developed in this project therefore aims to improve the selection of patients eligible for TRT by introducing a therapeutic efficiency criterion, with the goal of moving closer to personalized medicine while controlling the medico-economic costs associated with these innovative therapies. This project relies on the use of the zebrafish (*Danio rerio*) at the embryonic stage (< 5 days), into which tumor cells derived from patient tumors (metastatic biopsy or primary lesion surgery) can be implanted. This model, which presents numerous advantages and has recently been shown to be relevant for evaluating the effects of external radiotherapy and chemotherapies, will be used to explore the feasibility of predicting the therapeutic efficacy of Lutathera® in 50 patients with metastatic NETs.

Our center treats a significant number of patients with NETs each year: approximately 50 new patients per year treated for metastatic NETs, with 35 treatment initiations per year using Lutathera). Patients will be identified by the medical endocrinologist-oncologist in collaboration with the Nuclear Medicine department. Fresh samples of biopsy or primary tumor tissue will be transferred directly-after collection and reception in the pathology department-to the zebrafish platform and the following steps will be performed: (1) Tumor cell dissociation, (2) Fluorescent labeling (transfection with an *MND-Tomato-265 lentivirus*), (3) Cell implantation at 48 hours post-fertilization. For each biopsy/tumor sample, 60 zebrafish embryos will be xenografted with approximately 500 pre-transfected fluorescent tumor cells. Among these 60 grafted zebrafish, 30 will be treated with Lutathera, while 30 will serve as an untreated control group. Thus, each biopsy/tumor sample will serve as its own control.

To evaluate the efficacy of TRT in the zebrafish model, we will quantify the amount of Lutathera taken up by each xenografted zebrafish using a gamma counter. We will then assess the distribution of radioactivity within the zebrafish by autoradiography, followed by quantification of tumor fluorescence intensity in both zebrafish groups (treated and untreated) using fluorescence microscopy and quantitative image analysis.

Primary endpoint: Efficacy of ^{177}LuTRT at 12 months in study patients (according to RECIST v1.1) as a function of fluorescence intensity measured by fluorescence microscopy in^{177}LuTRT-treated xenografted zebrafish embryos derived from these same patients' tissues.

5B / 3

A new spatial multiomics and multimodal workflow for deeper biological sample analysis in human pancreatic cancer

Mélanie MOREAU[1], Mehdi BOUBADDI[2], Jade JAUBERT[1], Samuel AMINTAS[2], Stéphane CLAVEROL[1], Caroline TOKARSKI[1,3], Sandrine DABERNAT[2], Nicolas DESBENOIT[1,3]

[1] Bordeaux Proteome, Bordeaux University, Bordeaux, France

[2] U1312 Bordeaux Institute of Oncology, CHU Bordeaux, Bordeaux University, Bordeaux, France

[3] UMR5248 CBMN, Bordeaux University, Bordeaux, France

For cancer research, fresh human samples are precious, often with limited access. Therefore, it's crucial to document the maximum information from a restricted quantity of material. We propose an original spatial multiomics and multimodal workflow combining Matrix-Assisted Laser Desorption Ionization Mass Spectrometry Imaging (MALDI-MSI) and ImmunoHistoChemistry (IHC) to obtain morphological, lipidomic and proteomic data with reduced material requirement.

To develop our workflow, we used tumoral (T) and non-tumoral (NT) pancreatic samples from patients resected for pancreatic adenocarcinoma. First, a single frozen section was analyzed for lipid detection, followed by detection of non-targeted protein, after appropriate washes. The final step in our workflow is conventional IHC.

We use an atmospheric pressure MALDI-Orbitrap, allowing acquisitions with minimum impact on sample morphology. Raw data from MS were visualized and annotated with METASPACE, using public databases for lipids and home-made databases for peptides. To build it, we used proteins identified by conventional LC-MS/MS analysis of a large number of T and NT human pancreas samples and performed in silico digestion of these proteins.

Combining these different approaches, we obtain a huge amount of data. This strategy is also suitable to visualize heterogeneity, which is not possible in a bulk sample. Indeed, different modalities are acquired over the same area allowing the overlay of results and selection of areas of interest.

Our new spatial multiomics and multimodal workflow will enable a better global analysis of tissues for research or diagnostic purposes, and opens the possibility of targeted analysis by focusing on well-defined regions such as specific cells or tissue structures.

5B / 4

Development of New Enzyme-Responsive Systems for Selective Bioorthogonal Tumor Labeling and Drug Delivery approaches

Israa AL JAMAL[1], Margaux BOSSUAT[1], Florian RAES[2], Isabelle OPALINSKI[1], Sébastien PAPOT[1]

[1] Université de Poitiers, UMR-CNRS 7285, Institut de Chimie des Milieux et des Matériaux de Poitiers (IC2MP), 86022, Poitiers, France. Equipe Labellisée Ligue Contre le Cancer

[2] University of Grenoble Alpes, INSERM, LRB, Grenoble, France

Cancer is a leading cause of death worldwide, presenting major public health challenges despite advances in detection and treatment. Conventional therapies, including surgery, chemotherapy, radiation and immunotherapy are commonly associated with substantial side effects. Therefore, the design of innovative strategies for cell membrane engineering is of prime interest to develop novel cell-based therapies in the fields of cancer, aiming to enhance treatment specificity and effectiveness.

In this context, metabolic glycoengineering, a technique that allows the incorporation of diverse bioorthogonal chemical groups onto cell-surface glycans, has become a powerful method for modifying the outer membrane of living cells. Glycoengineered cell membranes can subsequently be remodeled by introducing different molecular systems using click chemistry. This approach opening up numerous potential biomedical applications, particularly cell-based therapies.

To date, there are no established strategies for the selective *in vivo* introduction of bioorthogonal functions specifically on the surface of a particular cell population (e.g., cancer cells) or within targeted tissues (e.g., tumors). To address this limitation, we have developed a novel chemical approach based on stimuli-responsive molecular systems. These systems are programmed to covalently introduce a bioorthogonal function into targeted tissues following highly selective enzymatic activation. The molecular assemblies are composed of three key elements: an enzyme-responsive trigger, a fluorinated self-immolative linker, and a bioorthogonal function. This design enables the selective tagging of tissues overexpressing the target enzyme (e.g. solid tumors) with the desired bioorthogonal moiety.

We will present both *in vitro* and *in vivo* results demonstrating the validity of this technology in pre-targeting strategies. Our study paves the way for new drug delivery tools based on bioorthogonal chemistry, enabling the selective release of therapeutic agents specifically within malignant tissues.

5B / 5

Targeting tumor associated macrophages (TAM) with vectorized magnetic nanoparticles for anticancer therapies

Chloé BAZILE[1], Julie BORDENAVE[1], Stéphane MORNET[2], Véronique GIGOUX[1], Mary POUPOT[1]

[1] Centre de Recherches en Cancérologie de Toulouse

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

Tumor associated macrophages (TAMs) are capable to confer anti-apoptotic, proliferative and enhanced migratory properties to cancer cells, as well as protecting them against immune attacks and therapies. In lung cancer, they represent between 30 to 50% of the tumor mass and they are associated with a bad prognosis of the disease [1,2]. Targeting these pro-tumoral TAMs is a major challenge in anticancer therapies. Different strategies exist, but they are not specific, potentially leading to adverse effects. Our team produced and patented a monoclonal antibody, 6-25, capable to specifically recognize pro-tumoral TAMs displaying an M2 phenotype. We showed that the 6-25 mAb was internalized in these TAMs without inducing any toxicity. The goal of the project is to produce a tool that specifically targets and kills pro-tumoral TAMs.

In cancer treatment, magnetic hyperthermia or magnetomechanical ablation represent an emerging approach with promising therapeutic potential. The first one induces cell death for cell containing magnetic nanoparticles by increasing the temperature through a high frequency alternating magnetic while the second uses mechanical forces under low frequency rotating magnetic field (MF) [3]. We therefore developed a biocompatible and non-toxic magnetic nanoparticle functionalized with the 6-25 mAb (MNP-6-25) as a specific tool to target pro-tumoral TAMs in the tumor.

To test the feasibility of this method, we performed a robust 3D model of co-cultures with the lung cancer cell line (A549) with M2 macrophages (M2M), or M1 macrophages (M1M) as a negative control, these cells doesn't express the target of 6-25. We have studied the basal cytotoxicity, kinetics and specifity of binding of the MNP-6-25 for M2M in these models using flow cytometry and microscopy.

First, we showed that MNP-6-25 are not toxic to neither M2M nor M1M in a concentration up to 64 µg Fe2O3/mL after 72h of incubation, and bind specifically M2M but not M1M, with a maximum at 48h of incubation at 8 µg/mL. We developed 3D models with cancer cell line and M2 macrophages derived from monocytes. The M2 phenotype of macrophages is stable in our model over seven days with an increase of the CD204 M2 marker in the 3D model and M2M promote tumor cell proliferation. Replacing M1M in the 3D model promotes A549 proliferation. This is consistent with the depolarization of M1M towards an M2 phenotype.

Flow cytometry results and microscopy show the specific binding of MNP-6-25 to M2M but not to M1M in 2D and 3D models, also compare to control nanoparticles: non-vectorized nanoparticles or vectorized with the isotipic control of the 6-25 antibody.

To conclude, we showed that MNP-6-25 specifically target M2M inside 2D/3D heterotypic models. Future research will focus on the induction of TAM death in these in vitro models, as well as on the targeting and death of TAMs in an in vivo model, which has already been set up.

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5B / 6

Surface Plasmon Resonance-based detection of EGFRvIII in circulating extracellular vesicles from glioblastoma

Amy GATEAU[1], Hussein AKIL[1], Flavien BEFFARA[2], Shuwen ZENG[2,3], Joelle YOUSSEF[2], Manon GIREAU[4], Corinne CHAMPEAUX[4], Frédéric DUMAS-BOUCHIAT[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 and Nanotechnologies (L2n), CNRS-ERL 7004, Limoges

[4] Institut de Recherche sur les Céramiques, Limoges

Glioblastoma (GBM) is among the most prevalent and aggressive brain tumors, with a poor median survival rate despite advancements in diagnosis. The high heterogeneity of GBM complicates patient follow-up and therapeutic management. To overcome this problem, the identification of circulating biomarkers in liquid biopsies has become essential for GBM patients. A promising direction is based on the analysis of the contents of extracellular vesicles (EVs).

Previous studies revealed that EGFRvIII, a truncated form of the epidermal growth factor receptor present in about 40% of GBMs, can be detected in circulating EVs isolated from patient plasma. As EGFRvIII is constitutively active, it plays a role in tumorigenesis and contributes to chemoresistance. However early detection of EGFRvIII in EVs derived from liquid biopsy is not suitable with clinical routine applications: current isolation methods for EVs from plasma are labor-intensive, and existing technologies lack the sensitivity required to detect biomarkers present at very low concentrations in patients' blood.

Our preliminary technological developments on surface plasmon resonance (SPR) method offer the perspective of real-time detection of EVs from biological fluids with minimal sample preparation. Indeed, our results suggest that this technology is able to detect EGFRvIII in EVs derived from glioblastoma cell lines, demonstrating its potential as a powerful tool for biomarker detection.

This proof of concept opens the way for the development of a highly sensitive approaches with a threshold that, to our knowledge, no other available technique can currently achieve. The perspectives of this study will enable GBM patients to be monitored in order to predict the risk of recurrence following tumor resection.

5B / 7

The synergistic combination Cabozantinib and mTORi inhibits cell proliferation, translation and OXPHOS in clear cell renal cell carcinoma

Laura EANES DA SILVA[1], Candice MARCHIVE[1], Mathilde ROBIN[1], Hélène TUFFOU-HÉRAULT[1], Pauline BARRAJA[1], Véronique GARAMBOIS[1], Nadia VIE[1], Javier FLORIDO-RUIZ[1], Pierre SICARD[2], Alexandre DAVID[1], Diego TOSI[1,3], Céline GONGORA[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Physiologie et médecine expérimentale du cœur et des muscles, Montpellier

[3] Institut du Cancer de Montpellier

Clear cell renal cell carcinoma (ccRCC) is the most common subtype of renal cell carcinoma (RCC), representing about 75% of all RCC cases. Histologically, ccRCC is characterized by tumor cells with an abundant, vacuolated cytoplasm, due to the accumulation of lipid droplets containing triglycerides, esterified glycogen and cholesteryl esters. In 60-90% of sporadic ccRCC cases, loss or mutation of the Von Hippel-Lindau (VHL) tumor suppressor gene is detected, leading to the constitutive activation and accumulation of the hypoxia inducible factor alpha (HIFα), which is involved in angiogenesis, tumor growth and survival. Treatment options for advanced renal cell carcinoma include immune checkpoint inhibitors (ICI), tyrosine kinase inhibitors (TKI) mainly targeting VEGFR, and combinations of ICI and TKI. Unfortunately, treatment resistance is common and constitutes the main reason for treatment failure.

In my project, I focus on the multi-target tyrosine kinase inhibitor cabozantinib, trying to enhance the clinical efficacy of this drug. Preliminary results of RNA-Seq of cabozantinib-induced ccRCC adaptive responses showed that genes involved in lipid synthesis and regulated via mTOR were induced by the cabozantinib. Based on this data, we combined cabozantinib with an mTOR inhibitor (mTORi) and characterized the combination in vitro and in vivo using different omics tools in order to profile the interaction between these two compounds.

We found that this combination was highly synergistic in vitro and in vivo. Concerning its mechanism of action, the combination inhibits cell proliferation and cellular translation. Moreover, we observed a decrease in glycolysis and a total shutdown of the mitochondrial respiration post-treatment.

In conclusion, we found a new synergistic treatment combination for clear cell renal cell carcinoma, which affects cells proliferation through a perturbation of their metabolic status. We now aim to further investigate these metabolic effects, with a particular focus on oxidative phosphorylation and mitochondrial function.

5B / 8

Lymphoma vs. metastasis vs. non-tumoral: a multi-class classifier to evaluate H&E-stained lymph nodes

Stéphane TREILLARD[1,2,3], Robin SCHWOB[1,2,4], Raphaëlle DUPREZ-PAUMIER[5], Philippe ROCHAIX[5], Charlotte SYRYKH[1], Pierre BROUSSET[1,6], Sandrine MOUYSSET[2,6], Sylvain CUSSAT-BLANC[2,3,7], Camille FRANCHET[5,6]

[1] CHU de Toulouse

[2] Institut de Recherche en Informatique de Toulouse

[3] Université Toulouse Capitole

[4] Université Toulouse 2 Jean Jaurès

[5] Oncopole Claudius Régaud, Toulouse

[6] Université de Toulouse

[7] Institut Universitaire de France

Lymph Node (LN) assessment is part of most pathologists' routine. To assist practitioners in this task, several Artificial Intelligence (AI) models have been developed to detect LN metastases, but these approaches only consider LNs as being non-tumoral or metastatic and are unable to recognize other rare conditions such as lymphoma. Lymphoma is a type of cancer that can develop in LNs and that is particular difficult to diagnose due to the multiplicity of its subtypes, including some that closely resemble non-tumoral cases.

In this work, we developed a Deep Learning model that not only distinguishes metastatic and non-tumoral LNs, but also detects lymphomas. We used a Multiple Instance Learning (MIL) framework, with the UNI2-h foundation model as a patch feature extractor and Attention-based Multiple Instance Learning as an aggregator. We trained our model on LN slides of 6 different lymphoma subtypes (Diffuse Large B-cell Lymphoma, Hodgkin Lymphoma, T-cell Lymphoma, Small Lymphocytic Leukemia and Follicular Lymphoma) from the French Lymphopath cohort and on a local dataset of benign and metastatic slides. Our training set included 803 H&E slides from 449 patients, with both biopsies and surgical specimens from different LN localizations. We tested our model on a local dataset, on CAMELYON16 and on slides from The Cancer Imaging Archive.

Our best model obtained an AUC of 0.98 and a balanced accuracy of 0.92 on our internal test set, and an AUC of 0.95 and a balanced accuracy of 0.83 on the external test sets. Regarding lymphomas, our model reached an F1-score of 0.92 on our local test set with 6 subtypes and of 0.95 on the external test sets, which contained a single lymphoma subtype (Diffuse Large B-cell Lymphoma).

These results are promising and show that it is possible to train an LN classifier that is able to detect both metastases and rare conditions such as lymphomas. This work represents the first milestone of a larger project to develop an AI-based lymphoma diagnostic assistant for non-expert pathologists. Future work will involve further validation of the model on lymphomas, and identification of lymphoma subtypes. Our code and model weights are publicly available.

Session 5C - Mauvaises conduites en science

5C / 1
Niveau de preuve ou preuves de caniveau ?

Florian NAUDET

Université de Rennes, Rennes, France - Institut de recherche en santé, environnement et travail (IRSET, UMR_S INSERM 1085), Rennes, France

La médecine fondée sur les preuves (evidence-based medicine, EBM) est généralement présentée comme le paradigme le plus abouti de la pratique médicale. Son objectif initial était de doter la médecine clinique d'un socle de connaissances fiables, reproductibles et dignes de confiance. Les réformateurs thérapeutiques de la seconde moitié du XXe siècle ont ainsi convaincu la communauté médicale que l'essai contrôlé randomisé en double aveugle contre placebo constituait la référence absolue pour établir l'efficacité d'un traitement.

Or, ce paradigme a progressivement dérivé de ses ambitions originelles. Il tend non seulement à négliger l'importance des effets non spécifiques dans le processus de guérison, mais il peut aussi produire des représentations biaisées de la réalité clinique. Les limites méthodologiques des essais, conjuguées aux biais de publication, aux analyses sélectives et au spin dans la communication scientifique et médiatique, fragilisent la robustesse de leurs résultats. De surcroît, la tension entre l'exigence de rigueur et la pression pour innover conduit à un assouplissement préoccupant des standards de preuve.

Par ailleurs, la recherche thérapeutique se déploie dans un contexte saturé de conflits d'intérêts financiers et institutionnels. Cette situation favorise la promotion de traitements dont l'utilité réelle pour les patients est discutable, ou dont le coût exorbitant interroge la valeur. L'usage récurrent de critères de substitution, à la pertinence clinique incertaine, illustre cette dérive : il détourne l'attention des enjeux essentiels, tels que la sécurité et les bénéfices tangibles pour les patients, qui devraient rester au cœur de toute évaluation.

Là où l'on attendrait des preuves solides, reproductibles et transparentes, émergent parfois des « preuves de caniveau », issues de pratiques méthodologiques fragiles ou biaisées. Les médecins doivent reconnaître leur part de responsabilité dans ce glissement et rester vigilants face aux écueils de leur pratique thérapeutique, afin de restaurer une recherche clinique véritablement digne de confiance, guidée par la rigueur scientifique et orientée vers l'intérêt des patients.

5C / 2
Comment caractériser la méconduite scientifique ?

Alexandre CLAUSSE, **Jules DI SCALA**

Université de Toulouse

En 1942, Robert King Merton propose l'éthos de la science, un ensemble de caractères et de normes morales encadrant la production de la littérature scientifique. Celui-ci est composé de quatre piliers : le Communalisme, l'Universalisme, le Désintéressement et le Scepticisme organisé, qui assurent que la production scientifique reste neutre, désintéressée, et peut être remise en question à tout moment.

Malheureusement, le système actuel de la publication scientifique pousse certains de ses acteurs (les chercheurs, les reviewers, les éditeurs en chefs, les maisons d'éditions, et les revues scientifiques) à manquer aux principes de Merton. Chacun a des intérêts propres : par exemple, pour progresser dans leur carrières, les scientifiques sont soumis à des métriques, les encourageant à maximiser leur nombre de publications tout en étant le plus cité possible. Les maisons d'édition, elles, ont souvent des objectifs de profits économiques, les poussant à agir dans le même sens.

La pression à laquelle les chercheurs sont soumis les pousse parfois à pratiquer certaines méconduites scientifiques : celles-ci peuvent simplement concerner des pratiques douteuses, comme un manque de rigueur, des problèmes de réplication des expériences ou un manque d'accès aux données. D'autres pratiques, comme la manipulation et la falsification de données, le plagiat, et la vente d'articles, sont considérées comme frauduleuses.

Des outils permettent aujourd'hui aux scientifiques de simplifier la vérification de la littérature scientifique sur laquelle ils basent leurs travaux (PubPeer, Problematic Paper Screener, Retraction Watch), et les politiques scientifiques évoluent pour encourager la science ouverte et les bonnes conduites (plans nationaux pour la science ouverte, déclaration d'Athènes…).

5C / 3

Favoriser l'intégrité scientifique et limiter la diffusion des rétractations : enquête sur les référents intégrité scientifique français

Antoine SABOURAUD[1], Philippe GORRY[2], Pascal RAGOUET[1]

[1] Centre Emile Durkheim, Bordeaux

[2] Bordeaux school of economics / Bordeaux sciences économiques

Pour Robert Merton (1973), pionnier de la sociologie des sciences, la (supposée) quasi-absence de fraudes en science est due à une institution scientifique autorégulée par un système de peer review garantissant la rigueur des recherches. L'idée d'intégrité scientifique (IS) est longtemps perçue comme allant de soi : les scientifiques sont acquis à la recherche de la vérité et la peer review est un système favorisant la circulation des découvertes et empêchant la publication de données frauduleuses. Les premières affaires de fraude éclatent parallèlement aux remises en question d'un système d'évaluation par les pairs influencé par des facteurs sociaux, chronophage et peu valorisé.

Les recherches sur les rétractations, le développement de bases de données dédiées à les répertorier, la prise de conscience de l'importance de ce phénomène et les outils d'aide à la détection de données fabriquées, falsifiées ou plagiées révèlent l'ampleur du problème. On observe ainsi une augmentation considérable du nombre de rétractations par an et celles pour fraude se multiplient. Il faut attendre le début des années 2010 pour qu'en France l'IS devienne institutionnalisée au même titre que l'éthique et la déontologie. Depuis la mise en place de la fonction de référent à l'intégrité scientifique (RIS) en 2017 et un décret de 2021 rendant obligatoire leur nomination, la France possède un dispositif de promotion et de régulation de l'IS. Les RIS ont trois missions principales : la promotion des bonnes pratiques, la formation et la sensibilisation des personnels de recherche et le traitement des cas de manquements à l'IS.

Notre communication présente les résultats d'une enquête au cours de laquelle 43 entretiens ont été menés avec des RIS interrogés sur ce qui a motivé leur nomination, sur les formations suivies et mises en place, le volume et la diversité des cas traités ainsi que la méthodologie d'instruction des cas de manquement à l'IS. Plus globalement, les liens entre IS et peer review, science ouverte et évaluation de la recherche ont été évoqués. Cette communication donne un exemple local de la promotion de l'IS pour réfléchir aux moyens de limiter la diffusion des rétractations et favoriser les comportements intègres. Nous proposons une analyse des rôles, des outils, des pratiques et des tensions propres à l'exercice des RIS afin de comprendre comment ces acteurs contribuent à la prévention des manquements à l'IS et à la limitation de la diffusion des articles rétractés.

Notre recherche montre que si la formation des doctorants est un succès, le constat est différent pour les titulaires qui, principalement par manque de temps et parfois de volonté et d'intérêt, sont les absents du public de ces formations. La majorité des enquêtés font face à des cas de plagiat ou d'autorat et la « zone grise » - p-hacking, salami slicing, conflits d'auteurs - occupe une place centrale dans leur activité. La loi française qui confie l'administration de la sanction à la direction des établissements est source de conflits d'intérêts et de frustrations pour les RIS qui n'ont ici aucun rôle à jouer. Pour eux, les manquements à l'IS sont majoritairement dus à des facteurs structurels. Ils encouragent une modification du système d'évaluation plutôt qu'une révision du système de peer review et une promotion de la science ouverte. L'évaluation quantitative de la recherche, la course au financement et la publication comme condition de recrutement et d'attribution de financement incitent à l'hyperproductivité, à l'opportunisme, au conformisme et à la fraude. Les alternatives au système traditionnel de peer review en double aveugle - comme le preprint, l'open peer review et la post-publication peer review - ne représentent pas une solution viable pour la plupart de nos enquêtés. Les RIS alertent sur le manque de moyens mis en place pour promouvoir efficacement l'IS alors que de nouveaux enjeux comme l'IA générative émergent et soulèvent de nouvelles questions.

Session 6 - Intelligence Artificielle & Ethique (in french)

6 / 1
L'impact de l'IA dans l'enseignement, la recherche et l'acquisition des savoirs en médecine

Jérôme BERANGER

Centre d'épidémiologie et de recherche en santé des populations, Toulouse

L'intelligence artificielle (IA) transforme profondément le champ médical, bouleversant les modalités d'enseignement, les dynamiques de recherche et l'acquisition des connaissances. En médecine, ces transformations ne sont pas anecdotiques : elles redéfinissent les rôles des professionnels, les parcours de soins, et surtout, les modalités de transmission et de construction du savoir.

L'IA enrichit l'enseignement médical en introduisant des outils d'apprentissage adaptatifs, interactifs et personnalisés. Les plateformes d'e-learning intégrant des algorithmes de recommandation permettent aux étudiants de progresser à leur rythme, en ciblant leurs lacunes. L'essor des simulateurs intelligents, basés sur des réseaux neuronaux et l'analyse prédictive, rend possible la formation par scénarios cliniques réalistes, notamment pour les compétences relationnelles (ex. annonce de diagnostic) et techniques (gestes médicaux, prise en charge pluriprofessionnelle). La pédagogie active et contextualisée est également renforcée par les apports de l'IA : analyse de cas complexes, discussion à distance via des plateformes collaboratives, et suivi longitudinal des étudiants. Le développement des compétences transversales - pensée critique, éthique, analyse des données - devient central face à la délégation croissante de tâches cognitives à des machines.

De plus, l'IA bouleverse la recherche en santé en facilitant l'analyse de très grands volumes de données (big data), comme les données cliniques, génétiques ou issues de l'environnement numérique du patient (capteurs, objets connectés). En médecine générale, cette approche permet notamment d'explorer des problématiques complexes telles que la coordination ville-hôpital, le suivi des effets indésirables ou encore le repérage précoce de la fragilité. Les outils d'IA participent à la production de connaissances en classifiant automatiquement des données hétérogènes, en détectant des patterns invisibles à l'œil humain et en accélérant les revues systématiques. Cela pose toutefois des questions épistémologiques et méthodologiques nouvelles : comment garantir la reproductibilité, la fiabilité, et la robustesse des résultats ? Quel est le statut d'un savoir issu d'un algorithme non transparent ?

Par ailleurs, la médecine ne peut plus se penser comme une simple accumulation de savoirs figés. L'IA pousse à adopter une posture réflexive, intégrant en continu de nouveaux résultats, des incertitudes, et des approches centrées sur le patient. L'acquisition des savoirs devient dynamique : les professionnels doivent être formés à interpréter des scores de risque, à dialoguer avec des outils d'aide à la décision et à maintenir une culture de la preuve actualisée. L'IA ne remplace pas le jugement clinique, mais elle modifie profondément les modalités d'appropriation des connaissances médicales.

Enfin, l'intégration de l'IA dans la formation et la recherche médicales appelle une vigilance sur les biais algorithmiques, la protection des données personnelles et l'équité d'accès aux outils. Elle interroge aussi la place des savoirs expérientiels, du colloque singulier et des compétences relationnelles dans un monde de plus en plus data-centré. Il devient donc indispensable de former les étudiants et les professionnels à la littératie numérique, à la critique des outils d'IA, à l'interdisciplinarité, et l'éthique relative à la médecine digitale. L'enjeu est de taille : faire de l'IA non pas un substitut, mais un levier pour une médecine plus humaine, plus collaborative, plus pertinente, et plus éthique.

6 / 2
IA et éthique, questions anciennes et nouvelles

Thierry LAVABRE-BERTRAND

Faculté de médecine de Montpellier-Nîmes

On ne peut comprendre les questions éthiques posées aujourd'hui par l'IA sans une mise en perspective historique. La médecine hippocratique est basée sur une collection de faits, interprétés à la lumière de la théorie humorale, qui va rester prédominante, bien que d'autres approches aient été proposées. L'apparition d'une nosologie rationnelle puis de la médecine numérique, première forme de la statistique, restent dans la même ligne, où le médecin ne cherche pas à comprendre les mécanismes intimes, mais induit des faits une connaissance globale et synthétique, qu'il interprète au sein d'une théorie qu'il admet sans chercher à la maîtriser. La mise en place progressive de la démarche expérimentale répond à une volonté de compréhension objective, qui reste par nécessité analytique, accumulant à son actif d'immenses progrès au long des deux derniers siècles. Ce discours analytique a pris la place des théories antiques dans la pratique clinique quotidienne.

La montée en puissance de l'IA remet au premier plan plusieurs questions que la médecine expérimentale avait tenté de maîtriser, notamment la place d'une approche globale, la foi en un résultat obtenu sans contrôle de l'opérateur, le rôle de l'hypothèse expérimentale, la signification d'une interprétation purement probabiliste…

Face à la « boîte noire » que représente pour lui le fonctionnement de l'IA telle qu'elle est actuellement de plus en plus utilisée dans les procédures diagnostiques et thérapeutiques, le médecin garde la possibilité de créer un cadre nosologique. Sa responsabilité reste entière, et rejoint l'autonomie dont disposait le médecin « classique », avec notamment la responsabilité de confronter les données obtenues avec un discours structurant bâti sur la médecine expérimentale et pouvant prendre en compte d'autres abords.

Les choses deviendraient plus compliquées dans la pratique en présence d'une IA vraiment générative, capable de définir son propre cadre conceptuel. La place du médecin se trouverait alors reléguée au deuxième plan. Il se trouverait complètement en porte-à-faux au sein de la relation médecin-malade et aurait du mal à assurer la responsabilité éthique de la prise de décision.

Les problèmes éthiques ne se réduisent pas à la seule implication du médecin dans l'acte médical. Le regard porté par les entités extérieures (administratives, financières…) dépend largement des conceptions portées par la société. La mise en place des outils d'IA induit nécessairement une dépossession de l'autonomie médicale face au caractère algorithmique donnant une probabilité précise, permettant ainsi de définir le cadre de l'acte de soin. On retrouve là la dimension parfois ambiguë que l'on peut observer dans les RCP, à la fois progrès indiscutable mais aussi source potentielle de limitation de l'autonomie du soignant et de déresponsabilisation.

Les mêmes questionnements peuvent être transférés dans le domaine strict de la recherche, avec la place de l'autonomie du chercheur par rapport à l'outil.

Au total, c'est bien la question du cadre conceptuel où se trouve le praticien qui conditionne l'importance du risque éthique à l'utilisation de l'IA. Les problèmes posés par les versions qui deviennent aujourd'hui de pratique courante ne sont pas très différents de ce qui a pu être rencontré lors des étapes antérieures de l'histoire de la médecine. Les développements ultérieurs de l'autonomie de l'outil IA doivent par contre faire poser la question de la nature d'une intelligence pleinement humaine, tant dans son rapport au savoir que plus encore dans la relation interpersonnelle qu'est par essence l'acte de soin.

Session 7A - Biomarkers for clinical innovation

Axis 3 & Axis 5 session

7A / 1

Molecular classification of colon cancer: prognostic implication

Pierre LAURENT-PUIG[1,2]

[1] Centre de Recherche des Cordeliers, Université Paris Cité, Sorbonne Université, Inserm U1138, Institut Universitaire de France, Paris 75006, France

[2] Institut du Cancer Paris, Assistance Publique-Hôpitaux de Paris Centre, Hôpital Européen Georges Pompidou, Paris 75015, France.

The objective of our work was to establish prognostic models in stage III colon cancer (CC) based on transcriptomic signatures of the tumor microenvironment (TME) and cell cycle, using the PETACC-8 trial as a training set and the IDEA-France trial as a validation set. We performed 3'RNA sequencing in 1,733 patients from PETACC-8 and 1,248 patients from IDEA-France, focusing on four transcriptomic signatures: T-cell and macrophage M2 signatures, CXCL13 expression, and an Oncotype DX CC Recurrence Score-like index derived from stromal and cell cycle components. The Immune Proliferative Stromal (IPS) score was defined as the number of unfavorable signatures, ranging from 0 to 4. Time to recurrence (TTR) was measured from random assignment to local or metastatic relapse or death due to CC. High Oncotype-like and M2 scores, together with low CXCL13 expression and T-cell scores, were associated with shorter TTR. A multivariable model including these signatures and established prognostic factors, when applied to the IDEA-France cohort, identified patient subgroups with markedly different outcomes: 3-year recurrence-free survival ranged from 56% in the lowest quartile to 89% in the highest quartile ($P < .0001$). The IPS score remained independently associated with TTR. These findings demonstrate that transcriptomic signatures of the TME and cell cycle provide powerful complementary prognostic information. We integrate such molecular scores with circulating tumor DNA (ctDNA) analysis refine patient stratification and could guide personalized treatment strategies in stage III CC.

7A / 2

Proteomic Signature-Based Stratification of Patients for Predicting Therapeutic Response in Hepatic Cancers

Adèle DELAMARRE[1,2,#], Marie DECRAECKER[1,2,#], Jean-Frédéric BLANC[1,2], Sylvaine DI TOMMASO[3,4], Cyril DOURTHE[1,3], Jean-William DUPUY[3,5], Mélanie MOREAU[1], Nathalie ALLAIN[1], Isabelle MAHOUCHE[1], Julie GIRAUD[1], Giovanni BÉNARD[6], Claude LALOU[6], Benoît PINSON[7], Paulette BIOULAC-SAGE[1], Caroline TOULOUSE[1,2], Audrey MORISSET[8], Jérôme BOURSIER[8], Brigitte LE BAIL[1,4], Anne-Aurélie RAYMOND[1,3,*,§], **Frédéric SALTEL[1,3,*,§]**

[1] Univ.Bordeaux, Inserm UMR1312 BoRdeaux Institute of onCology (BRIC), F-33000 Bordeaux, France

[2] Department of Hepatology and Oncology, Bordeaux University Hospital, Inserm CIC 1401 F-33000 Bordeaux, France

[3] Univ. Bordeaux, CNRS, INSERM, TBM-Core, US5, UAR 3427, OncoProt, F-33000 Bordeaux, France

[4] Department of Pathology, Bordeaux University Hospital, F-33000 Bordeaux, France

[5] Univ. Bordeaux, Bordeaux Protéome, F-33000, Bordeaux, France

[6] Univ. Bordeaux, INSERM, MRGM, U1211, F-33000 Bordeaux, France

[7] Univ. Bordeaux, CNRS, INSERM, TBM-Core, US5, UAR 3427, SAM, F-33000 Bordeaux, France

[8] Department of Hepatology and Oncology, Angers University Hospital, F-49100 Angers, France

[#] These authors have contributed equally.

[*] These authors share last authorship.

[§] corresponding authors

Liver cancers encompass a wide range of entities, including both benign and malignant tumors such as hepatocellular adenomas, cholangiocarcinomas, and hepatocellular carcinomas. Among these tumors, hepatocellular carcinoma (HCC) is the most common form of liver cancer with a bad prognosis in case of advanced HCC, which are only eligible for palliative systemic therapies. After a decade of exclusive sorafenib monotherapy, with a response rate of <10%, the advent of immunotherapies represents a revolution in HCC. The combination of atezolizumab/bevacizumab is recommended as the first-line systemic treatment, with a response rate around 30%. However, there are currently no predictive factors for response to these treatment options.

We profiled, by high-resolution mass spectrometry-based proteomics combined with machine learning analysis, a selected cohort of fixed biopsies of advanced HCC. We grouped subject according to their objective response to treatments, corresponded to a tumor regression vs tumor progression at 6 months after treatment. We generated a proteome database of 100 selected HCC samples. We compared the relative protein abundance between tumoral and non-tumoral liver tissues from advanced HCC patients treated with atezolizumab/bevacizumab and sorafenib treatment, respectively. These signatures were sufficient to predict the response. Moreover, these signatures reveal the biological pathways involved in treatment resistance. Particularly, we revealed and validated a shift in tumor cell energy metabolism inducing an immunosuppressive environment involved in the resistance to atezolizumab/bevacizumab.

7A / 3

Camille FRANCHET

Oncopole Claudius Regaud, Toulouse

Session 7B - Genome Dynamics & Expression / Axis 2 session

7B / 1

Targeting transcriptional addiction to anti-senescence programs in pancreatic cancer

Argyris PAPANTONIS

Institute of Pathology, University Medical Center Göttingen, Germany

Pancreatic ductal adenocarcinoma (PDAC) accounts for most pancreatic cancer cases that, despite recent therapeutic advances that have ameliorated survival in other cancers, still has a 5-year survival of <13%. This is attributed to the high heterogeneity and plasticity of PDAC tumors. To address the need for alternative therapies, we focus on the abundant nuclear protein HMGB2. HMGB2 depletion is key for establishing replicative senescence in normal cells, but it is significantly overexpressed in multiple types of cancer. Here, we combine single-cell and spatial genomics with patient-derived organoids and tumor samples to show how increased HMGB2 availability represents a transcriptional addiction fueling cell cycle progression and growth. Repurposing of a small molecule inhibitor against HMGB2 allowed us to interfere with its binding to chromatin, restrict accessibility at promoters, and constrain tumor growth both in vitro and in vivo. Thus, HMGB2 overexpression represents a new and universal target for managing cancer cell overproliferation.

7B / 2

Time-controlled CRISPR-Cas9 Screening Highlights Epigenetic Mechanisms of Drug Tolerance and Therapy Evasion in Acute Myeloid Leukemia.

Mathieu LANDRY[1], Manon FAIVRE[1], Johannes SCHMOELLERL[2], Margaux OBERLING[1], Yann AUBERT[1], Emilie MONTAUT[1], Martina WEISSENBOECK[2], Florian ANDERSCH[2], Michaela FELLNER[2], Vera PANCALDI[1], Johannes ZUBER[2], **Margherita GHISI[1]**

[1] Centre de Recherches en Cancérologie de Toulouse, Inserm U1037 - CNRS UMR5071 - Université de Toulouse

[2] Research Institute of Molecular Pathology, Vienna BioCenter, Vienna, Austria

Background. Acute myeloid leukemia (AML) is an aggressive hematological cancer that remains incurable for >70% of patients. Despite major advances in our genetic and biological understanding of AML, cytarabine (AraC)-based regimens remain the backbone of clinical AML therapy. Although these regimens commonly induce disease remission, minimal residual disease (MRD) persistence and relapse after therapy are pressing problems for AML patients.

Non-genetic mechanisms of drug tolerance and adaptive survival triggered upon therapy exposure in a subset of so-called Drug Tolerant Persister (DTP) cells have emerged to play a key role in chemotherapy evasion and disease recurrence in AML and other cancer types. Unfortunately, our understanding of the biology and actional vulnerabilities of the leukemia drug tolerant state remains very limited and this is a major obstacle to the design of much needed effective and rational combination therapies to eradicate AML and prevent disease relapse. Part of the problem is that most studies today have been performed on stably resistant models or comparing patient samples at diagnosis and relapse. However, these models capture the cancer at later stages of its evolution and are not adapted to study mechanisms of adaptive drug tolerance taking place at the level of the minimal residual disease.

High-throughput loss-of-function screenings have been extensively used in recent years for probing genetic vulnerabilities and discovering new therapeutic targets in leukemia and, more in general, in cancer.

Aim. The aim of this work is to exploit the power of genetic screening to identify selective vulnerabilities and chemosensitizer genes in DTP AML cells that could be used for the design of truly rational combinatorial/sequential AraC-based regimens.

Methods. We modified one of our AML xenografts, characterized by a good initial response to chemotherapy followed invariably by disease relapse, to express a doxycycline-inducible Cas9. We then used this model of acquired resistance to perform an innovative ex-vivo time-controlled genome-wide CRISPR-Cas9 screening on DTP AML cells persisting upon a cycle of AraC-based chemotherapy in xenografted mice. In parallel, we used the same system to perform an in vitro screening on drug-naïve (DN) AML cells. ATAC-seq and RNAseq analysis were performed on DTP cells obtained from AML xenografted mice at the MRD timepoint.

Results. Beside identifying in both DTP and DN AML cells some previously described AraC sensitivity and resistance-associated genes, our ex-vivo CRISPR-Cas9 screening revealed distinct set of genes sustaining DN and DTP survival both at baseline condition and upon AraC treatment. Most importantly, our work indicated that AML DTP cells are highly dependent on chromatin modifier/remodelling factors to survive standard AraC-based chemotherapy. In particular, multiple subunits of histone acetyl-transferase complexes emerged as top hits in our screening. ATAC-seq analysis confirmed that AML cells composing the MRD undergo marked epigenetic changes upon treatment and display a more open chromatin conformation compared to untreated leukemias. Indeed, genetic inactivation or pharmacological inhibition of specific chromatin-modifier complexes substantially increased the cytotoxicity of AraC treatment in vitro in multiple AML cell lines.

Conclusions. Overall, our work strongly suggests that epigenetic changes play a key role in the persistence and drug tolerance of AML cells upon AraC-based chemotherapy and that the rational design of AraC combination therapies targeting epigenetic mechanisms could be a promising strategy to limit MRD and relapse upon standard chemotherapy.

7B / 3

Ligand Stabilization of DNA Three way Junctions for Targeted Cancer Therapy

Maëlle CAROFF[1], Aline MARNEF[2], Angélique PIPIER[3], Gaëlle LEGUBE[2], Anton GRANZHAN[4], David MONCHAUD[3], Sébastien BRITTON[1]

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

[2] Centre de Biologie Intégrative, Toulouse

[3] Institut de Chimie Moléculaire de l'Université de Bourgogne

[4] Institut Curie, Paris

Beyond the canonical B-form double helix, DNA can fold into a variety of non-canonical secondary structures, such as G-quadruplexes. Among these are DNA three-way junctions (TWJ), which adopt a Y-shaped conformation and can form within repetitive DNA sequences (1,2). Small molecules have been designed to stabilize these structures by specifically binding to the TWJ cavity, leading to the induction of toxic DNA double-strand breaks and subsequent cellular cytotoxicity (3,4). These ligands offer significant potential for therapeutic applications by inducing structure-specific DNA damage in cancer cells, presenting a more targeted alternative than broad spectrum agents, such as DNA-alkylating chemicals or radiations (3).

In this study, we aimed at characterizing the cellular effects and the mechanism by which these ligands induce DNA double-strand breaks, and at exploring their potential applications against cancer cells. Through a combination of biochemical, molecular and cellular assays, we identified that some of these ligands can be used to selectively and successfully target cancer cells enriched with secondary DNA structures resulting from repetitive DNA sequence expansion. Moreover, we also found that TWJ ligands can be combined with innovative drugs currently entering in clinical trials to create a synergistic effect which could improve therapeutic outcomes. To conclude, our work identifies TWJ ligands as promising anticancer agents to be used alone or in combination against cancers with specific genomic features.

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7B / 4

G-quadruplexes function as intrinsic nucleosome exclusion modules supporting constitutive enhancer and promoter activities

Carla HEREDIA[1], Nezih KARASU[1], Talha MAGAT[1], Amal MAKRINI[1], Cyril ESNAULT[1], Jean-Louis MERGNY[2], Salvatore SPICUGLIA[3], Yannan FAN[3], Aleksandra PEKOWSKA[4], **Jean-Christophe ANDRAU[1]**

[1] Institut de Génétique Moléculaire de Montpellier, University of Montpellier, CNRS-UMR 5535, 1919 Route de Mende, 34293 cedex 5, Montpellier, France

[2] Laboratoire d'Optique et Biosciences, Ecole Polytechnique, CNRS, Inserm, Institut Polytechnique de Paris, 91120 Palaiseau, France

[3] TAGC Marseille, INSERM, Campus de Luminy, Marseille, France

[4] Nencki Institute, Warsaw, Poland

G-quadruplexes (G4s) are stable single-stranded secondary DNA structures, alternative to Watson-Crick pairing in vitro and in vivo. Increasing evidences indicate their importance in nuclear processes such as replication, insulation and telomere structure and maintenance. Our group is interested in G4's relation to transcription at both promoters and enhancers in which they are overrepresented. In mammals up to 80% of the promoters and 20% of the enhancers carry experimentally validated G4s, using various detection methods including G4access, a method we recently developed (1). We propose that G4s and G4 clusters function as nucleosome exclusion modules at both promoters and enhancers, in which they tend to promote a constitutive activity as opposed to more activable sequences. At promoters, we have shown G4s contribute to promoter proximal pause release (2) while at enhancers, they associate to the most active sequences. At model promoters and enhancers, mutating G4 potential abolished or decreased transcription, indicating their importance in sustaining activity, most likely through chromatin opening. Intriguingly, analysis of high-resolution long-distance interactions revealed that G4 enhancers cluster with each other as well as with promoters and as opposed to other enhancers. Finally, we have observed that in the primate neural lineage, G4s tend to appear at novel and active enhancers, suggesting that are under a positive selective pressure at least in this evolutionary branch. Overall, defining G4s as critical regulatory elements of the genome make them attractive as drug targeting cancer in which such elements are abnormally used to upregulate or downregulate oncogenes or tumor suppressors respectively.

(1) Esnault, C. et al. G4access identifies G-quadruplexes and their associations with open chromatin and imprinting control regions. Nat Genet, doi:10.1038/s41588-023-01437-4 (2023).
(2) Esnault, C. et al. G-quadruplexes are promoter elements controlling nucleosome exclusion and RNA polymerase II pausing. Nat Genet 57, 1981-1993, doi:10.1038/s41588-025-02263-6 (2025).

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Session 7C - Les représentations de la maladie cancéreuse au sein de la population générale

7C / 1

Baromètre cancer 2021 - Perceptions des Français sur les facteurs de risque et de protection

Kristopher LAMORE

Laboratoire SCALab (UMR CNRS 9193), Université de Lille ; Institut ONCOLille

7C / 2

Les représentations du cancer et de ses traitements : spécificités de l'hospitalisation à domicile et des anticancéreux oraux

Alice DHELLEMMES-SOULAYRAC[1], Claudine MELAN[2], Florence SORDES[1]

[1] Université de Toulouse, laboratoire CERPPS (EA7411), Pôle 3: psychologie de la santé

[2] Université de Toulouse, laboratoire CLLE (UMR 5263)

Les patients sous anticancéreux administrés à domicile bénéficient d'une prise en charge différente en fonction de la forme du traitement : les anticancéreux i.v et injectables impliquent un contact régulier avec le personnel alors que la voie orale laisse le patient totalement autonome. Cette recherche transversale a une finalité comparative entre les représentations de la maladie et des traitements des patients bénéficiant de ces deux voies d'administration. L'échantillon se compose de 130 participants atteints de cancer dont 72 sont traités par chimiothérapie intraveineuse et 48 par voie orale. Le protocole est composé de questionnaires de représentations de la maladie (IPQ-r) et de représentations des traitements (BMQ) et le sentiment d'auto-efficacité (GSES-10). Les résultats montrent que la voie d'administration du traitement anticancéreux impacte directement les représentations de la maladie avec un phénomène de banalisation du cancer. À l'inverse, un traitement intraveineux, par son caractère invasif et chronophage, implique plus de difficultés dans l'accomplissement des rôles familiaux et professionnels. Par ailleurs, le poids des effets secondaires est corrélé avec la dangerosité perçue du traitement et avec le sentiment d'auto-efficacité. L'âge semble impacter la compréhension de la maladie. Bien plus qu'une simple différence de forme du traitement, c'est tout un parcours de soins qui se trouve remanié impliquant des conséquences psychologiques différentes qu'il semble indispensable de prendre en considération notamment dans les choix thérapeutiques ou en termes d'accompagnement des patients.

Session 8 -Prestige Conference

8 / 1

Grandeur et décadence des publications scientifiques : publier ou mourir

Hervé MAISONNEUVE

Rédacteur scientifique, Past president of European Association of Science Editors - Lyon

Depuis la fondation des premières sociétés savantes au XVIIe siècle, l'histoire des revues scientifiques illustre la construction puis la transformation profonde de la communication savante. De 1665 à 1950, ces sociétés ont créé et géré la plupart des revues, assurant quatre missions essentielles : enregistrer, évaluer, diffuser et archiver les savoirs. Ces revues, alors instruments collectifs du progrès scientifique, ont traversé les révolutions techniques, politiques et intellectuelles en incarnant la légitimité des communautés disciplinaires.

Après la Seconde Guerre mondiale, un changement de paradigme s'opère. Les éditeurs commerciaux, apparus d'abord en Europe et en Amérique du Nord, s'imposent peu à peu comme les nouveaux acteurs dominants. De nouveaux titres se multiplient, les comités éditoriaux se structurent, et la formalisation du peer review, portée par Nature entre 1960 et 1975, devient la norme. Parallèlement, des indicateurs de notoriété comme le facteur d'impact émergent et se banalisent. Rapidement adoptés par les universités pour évaluer les carrières et attribuer les financements, ces outils transforment en profondeur la finalité même de la publication scientifique. Les chercheurs et les rédacteurs apprennent à « jouer » avec ces indicateurs, ouvrant la voie à une compétition parfois dévoyée.

Dès les années 1980, après les USA, la plupart des pays mettent en évidence l'essor des Questionable Research Practices (QRPs) ou pratiques discutables en recherche, et des fraudes scientifiques. Les scandales impliquant Anil Potti, José Baselga ou Carlo Croce en cancérologie illustrent la porosité entre pressions de publication, promotion académique et intégrité scientifique. Ces dérives coïncident avec la montée d'un capitalisme éditorial où la visibilité l'emporte sur la robustesse méthodologique. La valeur marchande d'un article tend à remplacer sa valeur académique.

À partir de 1995, les technologies numériques bouleversent à nouveau le paysage. Les revues en ligne et la science ouverte favorisent l'accès à la connaissance mais déplacent le modèle économique : du lecteur-payeur à l'auteur-payeur, via la « voie dorée » de l'open access. Ce basculement, censé libérer la science, réintroduit pourtant de nouvelles inégalités et stimule la prolifération de revues douteuses. Dès 2010 apparaissent les premières revues dites « prédatrices », notamment en oncologie, exploitant la pression à publier et la méconnaissance des jeunes chercheurs. Consciente de cette fragmentation, le réseau des Académies des sciences puis l'UNESCO distinguent trois catégories : les revues de qualité reconnue (Journal of Clinical Oncology, Annals of Oncology), celles de qualité discutable (Cancers éditée par MDPI), et les revues prédatrices comme Oncotarget. L'explosion quantitative des publications depuis une décennie - sans augmentation parallèle du nombre de chercheurs ni de reviewers - exacerbe encore les dysfonctionnements du système.

Parallèlement, les sociétés savantes ont perdu le contrôle éditorial d'une grande partie des revues, désormais gérées par des consortiums privés où des universitaires servent de guest editors ponctuels. Ce déplacement du pouvoir éditorial prélude à une possible automatisation accrue : entre paper mills industriels et usages croissants de l'intelligence artificielle, la perspective de « journaux-robots pour lecteurs-robots » interroge le futur de la communication scientifique. Paper mills, review mills et citation mills deviennent difficiles à identifier car l'IA qui invente des articles progresse vite. L'histoire longue des revues savantes révèle une tension persistante entre idéal de partage des savoirs et instrumentalisation industrielle de la recherche.

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Session 9 - Rising Stars – Young Scientists Oral Presentation Competition

9 / 01

Characterizing the Dark Side of Cisplatin: Mechanisms Linking Treatment to Increased Colorectal Cancer Risk

Guillaume BELTHIER[1,2], Liza KULAEVA[3,4,5], Martina CELOTTI[3,4,5], Emilie BREEKVELDT[6], Maria AZKANAZ[2], Petur SNAEBJORNSSON[7], Maarten GEURTS[3,4,5], Hans CLEVERS[3,4,5], Ruben VAN BOXTEL[3,4,5], Monique VAN LEERDAM[6], Jacco VAN RHEENEN[2]

[1] Institut de Génomique Fonctionnelle, Montpellier

[2] Division of Molecular Pathology, Oncode Institute, Netherlands Cancer Institute, Amsterdam, The Netherlands

[3] Hubrecht Institute, Royal Netherlands Academy of Arts and Sciences (KNAW) and UMC Utrecht, Utrecht, The Netherlands

[4] Oncode Institute, Utrecht, The Netherlands

[5] The Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

[6] Department of Gastroenterology, Netherlands Cancer Institute, Amsterdam, The Netherlands

[7] Department of Pathology, Netherlands Cancer Institute, Amsterdam, The Netherlands

Cancer treatments involve a combination of surgery, radiotherapy, and chemotherapy (e.g., cisplatin), which has significantly improved survival rates. However, these benefits come with severe side effects as skin and hair issues, as well as an increased risk of developing a new primary tumor later in life. Indeed, nearly 10% of cancer survivors develop subsequent malignant neoplasms (SMNs), which are fatal in more than 50% of these cases.

This statement is particularly true for cisplatin and platinum-based chemotherapy in general. For example, cisplatin-based testicular cancer treatment has led to over 90% of patients achieving long-term survival, but these patients have a higher risk of developing SMNs such as leukemia or colorectal cancer (CRC) later in life (Hazard Ratio of 3.9). Unfortunately, experimental evidence supporting and explaining these observations remains extremely limited.

Our **objective** is to explain and decipher whether the increased risk of developing CRC after cisplatin exposure is solely due to its mechanism of action (i.e., DNA damage leading to the gain/accumulation of mutations) or if it can also affect the fate of wild-type or mutated intestinal stem cells (ISCs).

To explain the side effects of cisplatin, our **method** is based on whole-genome sequencing and computational models to detect specific cisplatin signatures in human colorectal adenomas from patient treated for a previous cancer with cisplatin and in healthy human colon organoids exposed in vitro to cisplatin. Furthermore, we used different inducible transgenic mouse models for APC inactivation in the intestinal epithelium to study the effect of cisplatin on lesion number and size. Finally, the fate of ISCs/crypts, wild-type or mutated for Kras, has been compared with or without cisplatin exposure by combining elegant traceable mouse models and intravital microscopy (IVM).

Our **results** indicate that cisplatin can create potential tumor-initiating cells through mutagenesis of CRC onco-driver genes, but not in every case. In our mouse models, we observe that cisplatin increases the number and size of lesions. In line with these results, early observations of ISCs fate upon cisplatin exposure show that ISC competition occurs faster and mutant crypt fission is boosted.

In **conclusion**, our work highlights how cisplatin potentially acts as a mutagenic compound on ISCs and/or how it disturbs the intestinal limiting steps of mutant ISCs.

9 / 02

Investigating the role of gut microbiota in glioblastoma development and therapeutic resistance

Sarah LAVIELLE, Gauthier DELROT, Maria HAYKAL, Manon LEMAITRE, Doriane BOMONT, Macha NIKOLSKI, 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. Despite the current standard of care (the **Stupp protocol**) consisting of a surgical resection, chemotherapy with temozolomide, and radiotherapy, this cancer is still associated with frequent therapeutic failure. To improve patient survival and quality of life, it is essential to identify the factors contributing to its initiation, progression, and therapeutic resistance. In this study, we focus on the gut-brain axis, 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, which has been shown to play a crucial role in several brain pathologies, including Parkinson's and Alzheimer's diseases. Emerging studies have recently suggested that the bacterial microbiota may influence glioblastoma, but the underlying mechanisms remain unclear.

To better understand the communication between the gut and glioblastoma, a first *in vivo* experiment was performed in mice to induce gut inflammation through Dextran Sulfate Sodium (**DSS**) administration. Mice with intestinal inflammation bearing a glioblastoma showed increased tumor progression and higher recurrence after Stupp protocol treatment. These results may be partly explained by a greater infiltration of anti-inflammatory macrophages into the tumors of mice with intestinal inflammation. Our work also highlights a **bidirectional communication** between the gut and the brain, as glioblastoma implantation altered gut bacterial composition, which tended to be restored following Stupp protocol treatment. Moreover, glioblastoma exerts an anti-inflammatory effect that acts systemically but also on the colon.

To further investigate the role of gut microbiota in glioblastoma progression, a second *in vivo* experiment was performed using mice treated with an **antibiotic cocktail** (streptomycin 1 g/L, neomycin 1 g/L, ampicillin 1 g/L, amphotericin B 0.1 g/L) to deplete gut bacteria. Results showed that microbiota-depleted mice exhibited significantly reduced tumor progression, associated with decreased tumoral immune cell infiltration.

Taken together, these results suggest that the gut microbiota contributes to glioblastoma progression and recurrence after treatment. We hypothesize that glioblastoma may exploit gut bacteria to promote its growth by manipulating microbiota-regulated mechanisms, such as immune responses or metabolite production. To further investigate this communication, modulation of the gut microbiota is being considered through **fecal microbiota transplantation** from healthy mice to tumor-bearing mice. In addition, analysing the gut microbiota of **responder** versus **non-responder** mice would be of interest to identify bacterial populations potentially implicated in therapeutic success or failure.

Altogether, this project opens new opportunities for therapeutic alternatives.

9 / 03

Study of B-cell tumor-microenvironment interactions and modulation of the immunosuppressive microenvironment by ibrutinib treatment in Waldenström macroglobulinemia-like mouse model

Maxime TABAUD, Quentin LEMASSON, Ophélie TETEAU, Bastien CARLE, Mina CHABAUD, Jean FEUILLARD, Nathalie FAUMONT, Christelle VINCENT-FABERT

Contrôle de la Réponse Immune B et des Lymphoprolifération, Limoges

Waldenström's macroglobulinemia (WM) is a rare, indolent lymphoproliferative disorder, genetically characterized by the presence of the *L265P* mutation in the *MYD88* gene in almost all cases, resulting in constitutive activation of NF-kappa B (NF-κB). Despite its slow progression, WM remains incurable due to the lack of specific treatments. The efficacy of therapies capable of reactivating the anti-tumour response of T cells is well documented in various solid tumours. Apart from Hodgkin's lymphoma, these therapies have very mixed effects on B-cell lymphomas, especially those with NF-κB activation. Here we used the published *Myd88L252P* mouse model which develops a WM-like disease close to human WM. By focusing on T-cell exhaustion and regulatory T-cell expansion, we show how T cells located near WM-like tumours in mice are disrupted, while *Myd88L252P* tumour B cells adopt an immunoregulatory phenotype evoking regulatory B cells. We also demonstrate, for the first time in the context of WM, the dual effect of Ibrutinib, an irreversible inhibitor of Bruton's tyrosine kinase (BTK), able to decrease B-cell activation and expansion and to partially reverse T-cell depletion in *Myd88L252P* mice. With Ibrutinib as an example, this work opens up new perspectives for the development of therapeutic combinations targeting tumour B cells while reactivating anti-tumour T cells.

9 / 04

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

Ana Sofia VAZQUEZ URIOLA[1], Anissa ZAAFOUR[1], Mai Quynh NGUYEN[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), for which only 30% are suitable for targeted immunotherapy. GC are usually detected during the metastatic stage and, 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; their metastatic properties in vivo; as well as their effect in vitro in combination with chemotherapy agents currently used in the clinics.

Results: PCSK9 inhibition caused a decrease in GC CSCs' tumorsphere formation and invasive capacity, on the GC's CD44v6 invasive marker's expression, and on the protein levels and nuclear expression of Epithelial-to-Mesenchymal Transition (EMT) transcription factors. Moreover, PCSK9 inhibition seemed to increase chemotherapy's effect on CSCs tumorigenic capacity. In vivo, PCSK9's inhibitor decreased the metastatic dissemination of GC cells.

Conclusion: Our results suggest that PCSK9 may control CSCs' tumorigenic, invasive and metastatic properties, potentially through the EMT-related signalling pathways, and it might constitute a potential new therapeutic target in GC.

9 / 05

The pro-tumoral functions of the epigenetic enzyme SUV4-20H2 in Prostate Cancer

Hiba DAHER[1,2,3], Michelle-Gracia MALANDOU-TSAMBA[2], Marine TAUZIET[2,3], Pierre DAMBRUN[2], Raphael ROMERO[2], Véronique BALDIN[2,3,4], Raghida ABOU MERHI[1], Eric JULIEN[2,3,4]

[1] Faculty of Sciences, Genomics and Surveillance Biotherapy (GSBT) Laboratory, R. Hariri Campus, Lebanese University, Hadath 1003, Lebanon.

[2] Institut de recherche en cancérologie-Montpellier (IRCM)

[3] Université de Montpellier

[4] CNRS

Despite significant progress in prostate cancer detection and treatment, this disease remains a major cause of cancer-related mortality. While localized disease can often be managed successfully, metastatic and therapy-resistant stages remain largely incurable, even after intensive multimodal regimens. Thus, understanding the molecular mechanisms driving tumor progression and therapeutic resistance is critical to develop more effective strategies. In this regard, we identified the lysine methyltransferase SUV4-20H2-responsible for catalyzing the trimethylation of histone H4 at lysine 20 (H4K20me3)-as a key driver of prostate cancer growth and resistance. Using xenografted mouse models, we demonstrate that genetic loss of SUV4-20H2 markedly impairs prostate tumor growth, in contrast to its paralog SUV4-20H1 also involved in H4K20 methylation. To investigate the underlying mechanisms, we performed transcriptomic profiling of SUV4-20H2-deficient tumors. These analyses revealed that SUV4-20H2 controls the expression of several gene networks linked to cancer progression, including metabolism, Wnt signaling, and inflammatory pathways. Notably, its loss preferentially reduced the expression of genes involved in Glutamine metabolism while having limited impact on glycolytic programs. Consistent with this, functional assays revealed that SUV4-20H2-deficient prostate cancer cells are particularly sensitive to Glutamine deprivation than to Glucose withdrawal, highlighting a metabolic shift in the source of energy sustaining tumor growth upon loss of SUV4-20H2. Importantly, the transcriptional role of SUV4-20H2 seems uncoupled from its enzymatic activity. Altogether, these results establish SUV4-20H2 as a central regulator of prostate cancer progression through a newly identified non-catalytic transcriptional role in orchestrating the balance between Glucose and Glutamine metabolism in tumor cells. By linking epigenetic regulation to metabolic plasticity, SUV4-20H2 might represent a previously unrecognized vulnerability in prostate cancer biology.

9 / 06

Relationship between the E3 ubiquitin ligase TRIP12 and the Mediator of DNA damage checkpoint MDC1: its impact on DNA Damage Response

Alban RICARD, Claire VARGAS, Damien VARRY, Pierre CORDELIER, Nicolas BÉRY, Jérôme TORRISANI

Centre de Recherches en Cancérologie de Toulouse

Pancreatic cancer (PDAC for pancreatic ductal adenocarcinoma) is a cancer with a poor prognosis and predicted to be the second cause of death by cancer in 2040. The vast majority of patients are treated by DNA damage-inducing chemotherapies combined in some cases with radiotherapy. These treatments generate DNA double-strand breaks (DSBs). DSBs detection and repair greatly contribute to the resistance of cancer cells against treatments. The Thyroid hormone Receptor Interacting Protein 12 (TRIP12) is an E3 ubiquitin ligase implicated in the plasticity of pancreatic acinar cells as well as the initiation and metastatic potential of PDAC. TRIP12 is overexpressed in preneoplastic lesions of PDAC and tightly associated with chromatin through its N-terminal intrinsically disordered region (IDR). A Bio-ID proximity assay performed in the team revealed that MDC1 is one of the most abundant proteins at the vicinity of TRIP12. The Mediator of DNA damage Checkpoint 1 (MDC1) plays a crucial role in the early DNA Damage Response (DDR) by accumulating at DSBs sites through its BRCT (BRCA C-terminus) domain, which recognizes phosphorylated serine 139 (S139) of γH2AX, one of the earliest mark of DNA damage. Our aim is to characterize the mechanistic relationship between TRIP12 and MDC1 as well as its impact on DDR and PDAC-derived cell sensitivity to DSB inducing agents. I demonstrated that a TRIP12 overexpression inhibits the accumulation of MDC1 at DSBs. Using Bioluminescence Resonance Energy Transfer 2 (BRET2), Proximity Ligation Assay (PLA), co-immunoprecipitation, Surface Plasmon Resonance (SPR) and peptide pull-down assays, we showed that this inhibition results from a direct interaction between the phosphorylated serine 77 (S77) of TRIP12 (within its IDR) and the BRCT domain of MDC1. Notably, the same MDC1 residues that recognize phosphorylated S139 of γH2AX also interact with phosphorylated S77 of TRIP12, with a comparable binding affinity. Ultimately, γH2AX kinetics analyses showed that the inhibition of MDC1 accumulation at DSBs by TRIP12 reduces DNA repair efficiency, leading to genome instability. These findings highlight a potential competition between S77 phosphorylated TRIP12 and γH2AX for MDC1 binding, thereby affecting DNA repair efficiency. To further confirm this mechanism, we are developing an intracellular antibody to specifically inhibit the TRIP12/MDC1 interaction and to assess its impact in living cells.

Therefore, the TRIP12 overexpression measured in pancreatic preneoplastic lesions could contribute in genome instability and PDAC initiation. In contrast, in advanced PDAC, a high expression of TRIP12 could participate in PDAC cell sensitivity to DSB inducing therapies. Phosphorylated S77 of TRIP12 could thus serve as a predictive marker of pancreatic cancer drug sensitivity.

9 / 07

Development of new class of DNA mimics to circumvent resistance to TOP1 inhibitors

Reem BANNOUT[1], Margaux AYEUL[1], Aurelie GARCIN[1], Bertrand BIGNOLAIS[1], Valentina CORVAGLIA[2], Madeleine BOSSAERT[3], Céline GONGORA[1], Marie-Jeanne Pillaire PILLAIRE[3], Sébastien BRITTON[3], Ivan HUC[2], Vincent PARISSI[4], Philippe POURQUIER[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Center for Integrated Protein Science, Department of Pharmacy, Ludwig-Maximilians- Universität, Munich, Germany

[3] Institut de Pharmacologie et Biologie Structurale, IPBS, Université de Toulouse, CNRS, UPS, Toulouse, France

[4] Université de Bordeaux, CNRS, Laboratoire de Microbiologie Fondamentale et Pathogénicité (UMR 5234), Bordeaux, France

Resistance and toxicity remain major obstacles to the efficacy of Topoisomerase I (Top1) inhibitors in cancer therapy, emphasizing the urgent need for agents with distinct mechanisms of action. Top1 plays a pivotal role in resolving DNA supercoiling during replication and transcription. Top1 inhibitors approved in the clinic belong to the camptothecin (CPT) family. Despite their potent antitumor activity, the efficacy of CPT derivatives is limited by dose-dependent toxicities and the development of resistant tumors harboring Top1 mutations or enhanced DNA repair. In the search for alternative strategies to counteract this resistance, DNA mimicry represents an innovative strategy to perturb DNA-Top1 interactions. Based on this concept, in collaboration with the team of Dr. Ivan Huc we developed a novel class of oligoamide-based polymers composed of repetitive dimeric units of 8-amino-2-quinolinecarboxylic acid (Q) and 8-aminomethyl-2-quinolinecarboxylic acid (mQ). In solution, these compounds fold into a helical structure that mimic the features and the charge distribution of B-DNA fragments, with tunable conformations dependent on dimer composition and side-chain chemistry. We found that these DNA mimics inhibit in a relative selective manner and in a length-dependent manner the catalytic activities of Top1. Here, we present the in-depth characterization of the molecular mechanism by which these mimics inhibit Top1 in vitro and in cellulo. Our results show that, in contrast to CPT derivatives which act as poisons by stabilizing Top1-DNA cleavage complexes (Top1cc) and preventing religation, DNA mimics bind to purified Top1 and inhibit both steps (cleavage and religation) of the Top1 reaction in vitro, suggesting a dual inhibitory activity. This was reinforced by the fact that coincubation of (mQQ4)8 with CPT resulted in additive inhibition of Top1-mediated relaxation of supercoiled DNA. Using the Immuno Complex of Enzyme (ICE) assay allowing the direct quantification of Top1cc in cells, we found that, unlike CPT, the (mQQ4)8 DNA mimic did not induce the stabilization of Top1cc in both HCT116 and LoVo colon cancer models. On the contrary, pre-treatment of cells with (mQQ4)8 led to a decrease in CPT-induced Top1cc formation, suggesting a mechanism of Top1 inhibition that differs from CPT derivatives. In accordance with this hypothesis, we found that co-treatment of HCT116 cells with SN38 and the (mQQ4)8 DNA mimic showed synergistic growth inhibition as determined by the Sulforhodamine B assay. Interestingly, we also found that SN38-resistant HCT116 cells harboring Top1 mutations and/or overexpressing drug efflux pumps, were equally sensitive to (mQQ4)8 treatment, further strengthening our hypothesis. Additionally, we demonstrated that Top1 contributes, at least in part, to DNA mimics-induced cytotoxicity as Top1-deficient ovarian (OVCAR4), breast (MCF7) or colon (HCT116) cancer cell lines showed resistance to the (mQQ4)8 DNA mimic as compared to their wild-type counterparts. DNA mimics-induced cytotoxicity was accompanied with late apoptosis as measured by the annexin V/7AAG markers, but was not associated with a significant increase of H2AX phosphorylation, indicating that cell death occurs independently of DNA breakage by a mechanism that remains to be elucidated. Collectively, these findings establish DNA mimics as a novel class of Top1 inhibitors with a dual mechanism of action that could be used as an alternative to counteract resistance to CPT derivative used in the clinic. Future work is dedicated to the identification of structural determinants of activity to optimize DNA mimics potency towards Top1 and to the vectorization of these heavily charged molecules to optimize their delivery to cancer cells.

9 / 08

Estimating tumour microenvironment cellular states from bulk RNAseq produces biomarkers of clinical outcome across stages

Marcelo HURTADO[1], Elisa GOBBINI[2,3], Laurent GREILLIER[4], Leila KHAJAVI[5], Abdelmounim ESSABBAR[1], Michael KAMMER[1,6], Anne PRADINES[1,7], Anne CASANOVA[1,7], Anna KRUCZYNSKI[8], Sandrine GOUIN[9], Estelle TARANCHON-CLERMONT[1,9], Maria Fernanda SENOSAIN[10,11], Yong ZOU[10,11], Stephen DEPPEN[10,11], Eric GROGAN[10,11], Shillin ZHAO[12], Lionel FALCHERO[13], Jean BERNARD AULIAC[14], Marie BERNARDI[15], Sophie BAYLE[16], Marie MARCQ[17], Julian PINSOLLE[18], Stéphane HOMINAL[19], Olivier BYLICKI[20], Sabine VIEILLOT[21], Fabrice BARLESI[22], Frédérique PENAULT-LLORCA[23], Gilles FAVRE[1], Fabien MALDONADO[10], Francisco CRUZALEGUI[8], Olivier DELFOUR[8], Jenny VALLADEAU-GUILEMOND[2], Julien MAZIÈRES[1,9], Vera PANCALDI[1]

[1] Univ Toulouse, CNRS, INSERM, CRCT, Toulouse, France

[2] Centre de Recherche en Cancérologie de Lyon, Centre Léon Bérard, Université de Lyon, Université Claude Bernard Lyon 1, PLASCAN, INSERM 1052, CNRS 5286, Lyon, France

[3] Oncology Department, Institut Curie, Paris, France

[4] Aix-Marseille University, Marseille, France; Department of Multidisciplinary Oncology and Therapeutic Innovations, APHM, Hôpital Nord, Marseille, France; Department of Multidisciplinary Oncology and Therapeutic Innovations, Hôpital Nord, Marseille, France

[5] Bioinformatics Department, Evotec, Toulouse, France

[6] Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States

[7] Laboratory Medicine, Oncopole Claudius Regaud, Toulouse, France

[8] Institut de Recherche Pierre Fabre, Toulouse, France

[9] Pulmonology Department, Larrey Hospital, University Hospital of Toulouse, Toulouse, France

[10] Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States

[11] Cancer Early Detection and Prevention Initiative, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, United States

[12] Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, United States

[13] Service de pneumologie, Centre Hospitalier de Villefranche de Rouergue, Villefranche, France

[14] Service de pneumologie, CHI Créteil, Créteil, France

[15] CH Aix en provence, service pneumologie

[16] CHU St Etienne ; service pneumologie

[17] CH Vendée la roche sur Yon, service pneumologie

[18] CH Chamberry, service pneumologie

[19] CH annecy genennois, service pneumologie

[20] Service de Pneumologie, Hôpital d'instruction des armées Sainte-Anne, Toulon, France

[21] Centre Catalan Oncologie, service oncologie

[22] Institut Gustave Roussy - Paris

[23] Centre Jean Perrin - Clermont-Ferrand

Background: We still lack predictive biomarkers of response for lung cancer, a complex and heterogeneous disease for which there is a need for better predictive biomarkers for personalized therapies. A better understanding of the tumor microenvironment (TME) is needed to improve patient outcomes. Here, we propose a novel computational approach that leverages bulk RNA-seq to infer clinically relevant patient-specific cell groups and states, which are normally detectable only with more costly and complex single-cell assays.

Methods: We developed an integrated computational approach based on cell type deconvolution and transcription factor activity estimation combined with an advanced machine learning framework to extract clinically relevant features from bulk RNAseq data. We analyzed a cohort of 62 primary lung adenocarcinoma (LUAD) samples from IUCT patients across disease stages (Hurtado et al. 2024). As validation, we use an independent RNA-seq cohort of early-stage LUAD with 77 RNAseq and 15 scRNA-seq samples collected at Vanderbilt University (Senosain et al. 2023). To assess the potential for this approach in late stage samples, we applied it to a multicenter French cohort with 130 advanced NSCLC patients treated with immunotherapy (IT) (N=90) or chemotherapy (N=40) in first-line setting (E. Gobbini, GFPC and UNICANCER).

Results: Our results identified cell populations associated with immune response and evasion (Hurtado et al. 2024). In early-stage samples, we observed a dual role of natural killer cells, suggesting their involvement in both immune activation and suppression. This dual behavior was linked to patient survival, highlighting natural killer cells as important players (Figure 1AB). In the late stage cohort we identified cell type groups significantly associated with immunotherapy response (p-value = 0.025, F-statistic = 5.188, effect size = 0.051) which predicted response with better performance than several existing approaches.

Conclusion: Our approach characterizes RNA-seq based TME profiles through immune cell states and interactions, which enhances patient stratification. It identifies immune cell phenotype and interaction biomarkers linked to survival and progression that are validated across independent cohorts.

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9 / 09

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

Stefan NICOLESCU[1], Alice MATHEUX[1], Mihaly LEIWOLF[1], Marina GRIMALDI[1], Abdel BOULAHTOUF[1], Laura TALLEVAST[1], Julia TOUCHEBOEUF[1], Fanny LEENHARDT[1], Litaty MBATCHI[1,2], Céline GONGORA[1], Philippe POURQUIER[1], Alexandre EVRARD[1,2]

[1] IRCM, Univ Montpellier, ICM, INSERM, Montpellier, France

[2] CHU de Nîmes

The difficulty in treating malignant metastatic melanoma resides in the resistance to therapies and the risk of recurrence. Understanding the mechanisms by which tumors adapt to treatment is crucial, as they directly influence therapeutic efficacy. Our immunohistochemical analyses revealed, for the first time, significant and heterogeneous expression of the nuclear receptor PXR (Pregnane X Receptor) in patients' melanoma samples. In addition, drug screening experiments on cell models overexpressing PXR showed that PXR can be activated by BRAF inhibitors (BRAFi) that are currently used in the clinic. PXR is known to regulate the expression of genes involved in drug metabolism and drug transport. Thus, PXR may alter the sensitivity of cancer cells to kinase inhibitors and affect the therapy efficacy. Using BRAF-V600E-mutated human melanoma cell lines, we showed that stable overexpression of PXR induces a sensitization to treatments combining BRAFi and MEK inhibitors (MEKi). RNA sequencing analysis reveals that this overexpression contributes to the phenotype switching of the melanoma cells, which could modulate the tumor response to the BRAFi/MEKi combination. The aim of my project is to leverage PXR as a predictive biomarker of therapeutic response to targeted therapies, contributing to the optimization of the treatments used for melanoma.

9 / 10

Magnetic Hyperthermia and Mechanical Ablation Induce An Anti-Tumour Immune Response In Pancreatic Adenocarcinoma

Angela AGAËSSE[1], Justine JOURNAUX[1], Pascal CLERC[1], Megi BEJKO[2], Julien CARREY[3], Auriane BAGUR[2], Olivier SANDRE[2], Stéphane MORNET[4], Mary POUPOT[1], Véronique GIGOUX[1]

[1] Centre de Recherches en Cancérologie de Toulouse

[2] Laboratoire de Chimie des Polymères Organiques, Bordeaux

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

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

Pancreatic ductal adenocarcinoma (PDAC) is a cancer with a poor prognosis, resistant to conventional therapies, and characterized by a dense microenvironment, with a key role of CAFs (Cancer-Associated Fibroblast). This physical barrier not only limits the penetration and diffusion of therapies, but also the infiltration of immune cells restricting an effective anti-tumor 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 internalize and accumulate 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. Finally, 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 as well as an increase in the cytotoxic activity of Natural Killers (NK-92) when they were in contact with these cells in 2D model. Moreover, the infiltrations of THP1 macrophages and Natural Killers (NK-92) were observed within the MiaPaca2-CCK2/CAF-CCK2 spheroids. 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.

Session 10A - Translational Research in Thoracic Oncology / COALA project

10A / 1

New insights into lung cancer pathogenesis and therapy resistance

Trever G. BIVONA

University of California San Francisco

10A / 2

Cure Oncogene-Addicted Lung Cancer (COALA) project presentation

•Michèle CUNY & Valérie CHABRIERE, ALK France

France Patient Association ALK/ROS1

10A / 3

Genetic Factors Involved in Tumor Immune Evasion: From Mechanisms to Biomarkers

Montse SANCHEZ-CESPEDES

Cancer Genetics Group, Josep Carreras Leukaemia Research Institute (IJC), IJC Building, Campus ICO-Germans Trias i Pujol, Ctra de Can Ruti, Camí de les Escoles s/n, 08916 Badalona, Barcelona, Spain

Immune evasion is an important hallmark of tumor development that enables cancer cells to avoid or bypass recognition and elimination by the host immune system. The specificity of T-cell activation against tumor cells relies on the recognition of tumor cognate neoantigens, which are processed and properly presented by the HLA-I complex on the surface membrane of cancer cells. The HLA-I complex consists of a heavy chain (HLA-I) molecule and an invariant light chain (B2M). We showed the presence of recurrent B2M inactivation in lung cancer, associated with impaired anchoring of the HLA-I complex to the cell surface. B2M loss-of-function mutations or low HLA-I expression levels are involved in resistance to immune checkpoint blockade (ICB) treatment. Furthermore, alterations affecting the response to interferon gamma (IFNγ), which can directly inhibit tumor cell growth and promote apoptosis, also contribute to immune evasion. IFNγ is a cytokine produced predominantly by T-lymphocytes and natural killer cells in response to a variety of inflammatory or immune stimuli. We have shown the presence of genetic defects in IFNGR1/2 or JAK1/2 in lung cancer that render tumor cells refractory to IFNγ. Expression of IFNγ-responsive genes was found to be necessary, but not always sufficient, to produce a clinical benefit from ICB treatment. We also reported a deficient transcriptional response to IFNγ in some lung cancer cells, together with constitutively low levels of IFNγ-stimulated genes related to oncogenic activation of MYC, which was also associated with a lower response to ICBs. Thus, tumor-intrinsic genetic alterations contribute to immune evasion mechanisms that facilitate cancer development and can also serve as biomarkers for predicting response to ICBs.

10A / 4

Innovative approaches to target KRAS-driven tumours

Alberto MARTÍN[1], Silvia RODRÍGUEZ-LÓPEZ[1], Ines M. GARCÍA-PÉREZ[2], Sonia SAN JOSÉ[1], Antonio GÓMEZ[3], David MOREIRA[3], Stéphanie CABANTOUS[4], Cristina MAYOR RUIZ[2], **David SANTAMARIA[1]**

[1] Molecular Mechanisms of Cancer Program, Centro de Investigación del Cáncer (CIC), CSIC-Universidad de Salamanca, Salamanca, Spain

[2] Institute for Research in Biomedicine (IRB Barcelona), the Barcelona Institute of Science and Technology (BIST), Barcelona, Spain

[3] Kaertor Foundation, Campus Vida, Santiago de Compostela, Spain

[4] Centre de Recherche en Cancérologie de Toulouse (CRCT), INSERM, Université de Toulouse, UPS, CNRS, Toulouse, France

Recent drug discovery breakthroughs led to the approval of KRAS G12C inhibitors in lung adenocarcinoma (LUAD). Unfortunately, clinical responses are often hampered by the rapid resistance onset underlying the need to develop novel therapeutic approaches ideally based on varied modes of action. Proteolysis-targeting chimeras (PROTACs) have emerged as promising alternatives to traditional inhibition. However, there is limited mechanistic understanding of KRAS degradation in vivo. Here, we developed a preclinical LUAD mouse model and demonstrated that targeted oncogenic KRAS degradation induces rapid tumour regression primarily due to cancer cell-intrinsic mechanisms. Yet, transcriptional, histological, and immunophenotypic analyses revealed a substantial remodelling of the tumour microenvironment. Notably, disease relapse observed during prolonged degrader treatment stems mostly from proteolysis machinery dysregulation, indicating resistance mechanisms distinct from those reported upon KRAS inhibition. Collectively, our findings highlight the therapeutic potential of KRAS degradation in LUAD, providing insights into both cell-intrinsic and -extrinsic mechanisms that accompany antitumor responses and support the ongoing clinical exploration of this approach.

In parallel, the capacity of KRAS to self-organize into membrane nanoclusters is a well-established phenomenon essential for the fidelity and amplification of its downstream signalling output. Despite this recognition, the precise molecular mechanisms guiding KRAS nanocluster assembly remain incompletely defined. Evidence suggests that scaffold proteins could play a pivotal role by facilitating the activity of GTP-bound KRAS at the plasma membrane. To interrogate these mechanisms, in collaboration with Stéphanie Cabantous we engineered an inducible tripartite split-GFP system as a surrogate marker of KRAS nanocluster formation. This fluorescent readout was combined with multiplexed CRISPR knockout targeting an educated list of potential scaffold proteins, enabling functional screening of nanocluster modulators. Ongoing work extends this analysis to KRAS-dependent and -independent lung cancer cell lines, aiming to validate the specificity and generality of key scaffold dependencies. The split-GFP A549 model further enabled high-content chemical screening, allowing identification of small molecule inhibitors that diminish KRAS nanocluster integrity. Through this integrated approach, the project seeks to advance a mechanistic understanding of how KRAS nanoclusters are regulated and to catalyze the development of therapeutic strategies targeting resistant KRAS-driven cancers. Ultimately, these findings have the potential to inform new avenues for intervention in cases where direct KRAS inhibitors are ineffective due to resistance mechanisms.

Session 10B - Les représentations de la maladie cancéreuse au sein de la population générale

10B/1

Cancer du sein et hormonothérapie adjuvante : quand l'insatisfaction pousse à chercher ailleurs … pour le meilleur ou pour le pire. Une étude par entretiens

Léo TOUSSARD[1], Valentyn FOURNIER[2], Katell MAGUET[3], Kristopher LAMORE[4], François CHERIFI[5], Sylvain DELOUVÉE[6], **Florent VARET[1]**

[1] ANTHROPO-LAB - ETHICS EA7446, Université Catholique de Lille, F-59000 Lille, France

[2] Centre intégré universitaire de santé et de services sociaux de l'Est-de-l'Île-de-Montréal : Montreal, CA

[3] Patiente co-chercheuse indépendante, Amsterdam, Pays-Bas

[4] Univ. Lille, CNRS, UMR 9193 - SCALab - Sciences Cognitives et Sciences Affectives, Lille, France

[5] Comprehensive Cancer Center François Baclesse, Breast Cancer Unit, UNICANCER, Institut Normand du Sein, Caen, France

[6] LP3C (Laboratoire de Psychologie : Cognition, Comportement, Communication), Université Rennes 2, Rennes, France

L'adhésion thérapeutique à l'hormonothérapie adjuvante (HTA) constitue un enjeu majeur dans la prise en charge du cancer du sein hormono-dépendant, son interruption prématurée augmentant le risque de récidive (Lambert-Côté et al., 2020). Or, certaines patientes expriment une insatisfaction vis-à-vis de la médecine conventionnelle et se tournent vers d'autres sources d'information ou de soins. La littérature suggère que l'exposition à la désinformation et certaines croyances conspirationnistes peuvent contribuer à ce phénomène, en renforçant la défiance envers les traitements et les professionnels de santé, et en valorisant certaines pratiques non conventionnelles (Fournier & Varet, 2024 ; Varet, Fournier & Delouvée, 2025 ; Swire-Thompson & Johnson, 2024). Peu d'études ont toutefois exploré ces dynamiques dans des populations de patientes suivies en oncologie.

L'objectif principal de cette étude est d'identifier et de décrire, chez des patientes en rémission d'un cancer du sein, les déterminants psychosociaux de la non-adhésion à l'HTA, en lien avec leurs comportements informationnels, leurs croyances et leurs représentations des médecines conventionnelle et non-conventionnelles.

Vingt-cinq entretiens de recherche semi-directifs ont été conduits en visioconférence auprès de patientes en rémission d'un cancer du sein non métastatique pour lesquelles un traitement par HTA était prescrit, recrutées via les réseaux sociaux et des associations. Les verbatims ont fait l'objet d'une analyse qualitative préliminaire selon la méthode de l'analyse thématique du contenu (Braun & Clarke, 2006, 2021).

Les résultats préliminaires font ressortir plusieurs thèmes principaux. Les patientes décrivant une communication perçue comme distante ou peu centrée sur leur bien-être, leurs effets secondaires ou leur santé mentale, rapportent plus souvent une insatisfaction vis-à-vis de la prise en charge et une tendance à chercher des informations et du soutien social en dehors du système de soin conventionnel. Cette recherche peut s'exercer auprès de proches, d'associations, sur internet ou via des praticiens en soins non conventionnels. Ces démarches semblent pouvoir être bénéfiques lorsqu'elles apportent information et soutien de qualité, mais elles semblent également exposer certaines patientes à des informations erronées ou à des pratiques à risque (ex. : dilution homéopathique du traitement sans en informer le médecin). Les patientes les plus insatisfaites semblent également moins tolérer les effets secondaires de l'HTA et plus enclines à envisager une réduction, une pause ou un arrêt du traitement. À l'inverse, certaines rapportent que les soins de support ou certaines approches complémentaires les aideraient à mieux tolérer l'HTA et à maintenir leur adhésion thérapeutique.

Seront discutées les implications pratiques (formation à la communication centrée sur le patient, développement de supports d'information adaptés, encadrement des soins de support) et théoriques (relations entre variables d'intérêts), ainsi que les perspectives pour approfondir ces résultats (analyses croisées, validation par les participantes, analyses quantitatives exploratoires).

10B/2

Comprendre le vécu du cancer : comparaison des représentations entre patients, proches aidants et rôle des associations de patients

Veronique BERNAD

Patiente partenaire - Association Patients en Réseau

1. Présentation de l'association Patients en réseau et de sa plateforme de soutien et d'information Mon réseau cancer accessible gratuitement sur le web et sur application mobile. L'association est une association d'intérêt général fondée et animée par des patients , anciens patients, et proches aidants. Trois missions principales :
- soutien aux patients touchés par un cancer du sein, gyneco, colorectal et du poumon et aux proches de malades de tous types de cancer , par partage d'expérience et par l' accès à une information actualisée et sourcée pour mieux comprendre la maladie et le parcours de soin
- proposition de soins de supports en ligne : ateliers thématiques, séances d'activité physique adaptée , rencontres et groupes d'échanges , …
- actions de démocratie en santé : enquêtes , plaidoyers , participation des patients partenaires de l'association au sein d'instances publiques , de recherche et aussi co-pirteurs de projets innovants qui accompagnent les patients et leurs proches notamment l'art51 parcours Ako@dompicto , serious game mon immuno poumon.

2. Enquête vécu et représentation du cancer chez les patients et leurs proches aidants : convergences, divergences et rôle des associations de patients
Cette enquête a été diffusée du 20/10/25 au 16/11/25 de façon large au sein d'associations de patients et/ou d'aidants tous types de cancer et hors association : espace patients et aidants en établissement de santé , salle d'attente hôpitaux et maisons de santé.
1179 personnes ont participé avec 939 réponses exploitables.
Cette enquête vise à explorer la manière dont les patients atteints de cancer et leurs proches aidants se représentent la maladie en tenant compte des cinq dimensions du modèle de Leventhal (identité, cause, chronologie, conséquences, contrôle/guérison) et la dimension émotionnelle.
L'étude analyse également l'impact de l'adhésion ou non à une association de patients sur ces représentations : partage d'expériences, sentiment de maîtrise, espoir et soutien mutuel.
L'objectif est de mieux comprendre les différences et convergences patients/proches.

10B/3

Situation actuelle du cancer en France : une vision optimiste de la réalité à travers les chiffres d'incidence et de survie.

Brigitte TRETARRE

Registre des Tumeurs de l'Hérault

Auteur + Réseau Francim

Introduction
Le cancer demeure une priorité de santé publique en France, représentant l'une des principales causes de morbidité et de mortalité. Les données d'incidence et de survie, issues des registres et des estimations nationales, constituent des indicateurs clés pour évaluer l'évolution de la maladie. Au-delà de la gravité qu'elle représente, ces chiffres mettent également en évidence des progrès significatifs, porteurs d'une vision plus optimiste.

Méthodologie
Les données d'incidence et de survie proviennent des registres de cancers métropolitains du réseau Francim qui couvrent de 19 à 22 départements selon le cancer étudié. Nous présentons dans ce travail une extraction des dernières données publiées par Francim: I) Estimations d'incidence 2023 et tendances 1990-2023 (1) ; II) Survie des personnes atteintes de cancer en France métropolitaine 1989-2018 avec date de point au 30/06/2018 (2) ; III) Tendances d'incidence chez les adolescents et jeunes adultes âgés de 15 à 39 ans entre 2000 et 2020 (3).

Résultats
En 2023, environ 433 000 nouveaux cas de cancer ont été estimés en France. L'incidence tend à se stabiliser chez les hommes et reste en légère augmentation chez les femmes. Les cancers de la prostate, du sein, du poumon et du côlon-rectum restent les plus fréquents. Sur ces 4 principales localisations, 3 montrent des tendances à la baisse grâce aux efforts de prévention et de dépistage (sein, côlon-rectum et prostate). On observe en particulier pour les cancers induits en partie par le tabac, (cancers de l'ensemble lèvre-bouche-pharynx, de l'œsophage, du poumon ou de la vessie), une diminution de l'incidence chez l'homme. A l'inverse, chez la femme, l'incidence augmente pour le cancer du poumon, de l'ensemble lèvre-bouche-pharynx et pour les cancers de l'œsophage, en lien étroit avec l'évolution de la consommation de tabac. Pour le cancer du col utérin, le dépistage par frottis mis en place depuis les années 80 a permis de réduire considérablement l'incidence de ce cancer, même si les taux semblent s'être stabilisés depuis 2010. Comme pour le dépistage, l'amélioration des méthodes de diagnostic s'accompagne généralement d'une hausse de l'incidence, souvent suivie d'une diminution. C'est le cas pour les cancers de la thyroïde.

La survie à 5 ans s'est nettement améliorée au cours des deux dernières décennies : elle atteint environ 90 % pour le cancer du sein et de la prostate, 65 % pour le cancer colorectal, et plus de 80 % pour les leucémies de l'enfant. Ces résultats reflètent l'impact des dépistages organisés, des avancées thérapeutiques (immunothérapie, thérapies ciblées) et d'une meilleure prise en charge globale des patients.

Avec 54 735 nouveaux cas diagnostiqués en 21 ans chez les adolescents et jeunes adultes, les cancers restent rare comparés à ceux chez les ≥ 60 ans. Chez les 15-39 ans, l 'incidence a augmenté de 1,6 % par an entre 2000 et 2014, mais cette tendance est ensuite suivie par une baisse de -0,8 % par an entre 2015 et 2020. Seules 6 localisations sont en augmentation significative (cancers du rein, du sein, du colo-rectum, glioblastomes, liposarcomes et lymphomes de Hodgkin) avec des causes encore mal établies, mais plusieurs facteurs de risque émergents sont suspectés (obésité, mode de vie, expositions environnementales, alimentation, diagnostics plus précoces, améliorations dans la détection…). Ces évolutions se basent toutefois sur de très petits chiffres, sans que l'on constate une « explosion » des cas, comme cela a été mentionné dans les médias.

Conclusion
Le cancer reste un défi majeur, marqué par des inégalités persistantes et la progression de certains cancers liés au tabagisme et aux modes de vie. Toutefois, les données d'incidence et de survie soulignent des avancées notables et continues, ouvrant la voie à une perspective plus optimiste : davantage de patients vivent plus longtemps et avec une meilleure qualité de vie après un cancer.

Posters – Axis 1
Signaling, Microenvironment and Targeting

P101

Targeting metabolic vulnerability to increase electrochemotherapy efficacy

Coralie CAYRON, Géraldine ALBEROLA, Jelena KOLOSNJAJ-TABI, Muriel GOLZIO, Marie-Pierre ROLS

Institut de Pharmacologie et de Biologie Structurale, Toulouse

INTRODUCTION

Electroporation is a non-invasive strategy for cancer treatment. Based on the use of locally applied electric pulses that induce reversible or irreversible membrane permeabilization, it has fewer side effects than conventional treatments. Electrochemotherapy (ECT) based on the combination of electroporation and chemotherapy is used to favour the cytotoxicity of poorly permeant drugs, as the electrical field facilitates the entry of chemotherapeutic agent into tumour cells. The efficacy of ECT in clinic has been reported for therapeutic agents such as bleomycin, cisplatin, mitomycin c or 5-FU. In the absence of ECT, these therapeutic agents are known to induce metabolic adaptations that allow tumour cells to resist to treatment. In addition, electroporation disrupts cell homeostasis, of which oxidative stress is a major component. Recently, the combination of metformin, an inhibitor of the mitochondrial respiratory chain, with electrical pulses has been shown to have a synergistic effect to enhance their anticancer effect, suggesting a metabolic adaptation induced by the electrical pulse [1]. Although ECT induces complete or partial responses in more than 80% of melanoma patients, approximately 20% fail to respond [2]. Elucidating the resistance mechanisms in non-responders is critical to enhance their tumour sensitivity to ECT. This project aims to show that ECT induces metabolic adaptations in tumours, to characterize these changes, and to target them to reduce resistance rate.

MATERIALS AND METHODS

We focus our research on human skin tumours because ECT is currently used to treat melanoma, and because we can easily study the metabolic effects of treatments on normal neighbouring cells. To this end, we firstly characterise the effects of electroporation and ECT on the oxidative stress and metabolism of melanoma cells using 2D cell cultures. More complex models and more physiological models as 3D melanoma cell culture, reconstructed epidermis and reconstructed skin containing melanoma cells could be used to better characterise the effects [3]. To further characterise the changes in metabolism, exometabolomics and transcriptomics analysis are carried out to determine the changes in cell signalling involved in the metabolic changes after electroporation or ECT treatment.

RESULTS

Our first results show a decrease of melanoma cell viability after ECT treatment using bleomycin or cisplatin. Moreover, the mitochondrial function characterisation reveals the induction of an important mitochondrial stress post-ECT treatment characterised by the presence of an important mitochondrial network and a decrease of mitochondrial membrane potential suggesting that ECT favours mitochondrial dysfunction. In addition, post-ECT treatment melanoma cells present an increase of oxidative stress both in the mitochondria and in the cytosol. The first results on long term resistant melanoma cells revealed that the mitochondrial dysfunction is maintained 10 days post-ECT bleomycin.

CONCLUSION

ECT treatment in melanoma cells induces oxidative stress and mitochondrial dysfunction in resistant cells. Targeting the resulting metabolic vulnerabilities could enhance treatment efficacy and further decrease resistant cell viability.

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P102

Deciphering the role of metabolic exchanges between tumor cells and neurons during glioblastoma development

Mathis PINGLAUT[1,2], Mathieu LARROQUETTE[1,2], Doriane BOMONT[1,2], Gauthier DELROT[1,2], Ignacio FERNANDEZ MONCADA[3], Guillaume DURANTHON[1,2], Camille RUFFIER[4,5], Clémentine BOSCH-BOUJU[4,5], Macha NIKOLSKI[1,2], Audrey BURBAN[1,2], Thomas DAUBON[1,2]

[1] Institut de Biochimie et Génétique Cellulaires, Bordeaux

[2] CNRS

[3] Neurocentre Magendie, Bordeaux

[4] NutriNeuro, Bordeaux

[5] INRAE

Glioblastomas (GB) are the most common and aggressive primary brain tumors in adults and represent a public health problem due to their very high lethality despite treatments. A hallmark of GB is its diffuse infiltration into healthy brain tissue, driven by glioma stem-like cells (GSCs) that resist therapy and promote recurrence. Recent studies reveal that neurons actively promote GB progression through paracrine signalling and even direct electrochemical synapses with tumor cells. Our lab previously demonstrated that GSCs rely on lactate to fuel invasion. Intriguingly, neurons metabolize lactate as an energy source under normal conditions, raising the question: Could neuronal uptake of tumor-derived lactate create a feedback loop that amplifies GB aggressiveness? To answer that question, we developed an in vitro model of purified neurons cultures. Cocultures of patient-derived GSCs with purified neurons that were inhibited or not for MCT2 (neuron-specific lactate transporter) were studied. We observed that, in coculture condition, GB cells tend to increase their proliferative and invasive capacities as well as their mitochondrial metabolism and stemness. Same effect of coculture on tumor progression was observed in vivo thanks to orthotopic xenografts experiments in mice. Interestingly this increase of aggressive capacities in vitro and in vivo was found partially lost when neurons were inhibited for MCT2. These results support a model where GB hijacks neuronal metabolism via lactate shuttling, creating a vicious cycle of tumor growth.

P103

Highlight of a distinct, yet reversible, quinone redox state in cancerous cells

Aude BRUNEL[1], Mélanie MARTINS PINTO[1,2], Patrick PAUMARD[1], Stéphane ARBAULT[2], Laurent SCHWARTZ[3], Anne DEVIN[1]

[1] Institut de Biochimie et Génétique Cellulaires, Bordeaux

[2] Institut de Chimie & Biologie des Membranes & des Nano-objets, Bordeaux

[3] Assistance publique des hôpitaux de Paris

Cancer has been a widespreading field of research over the last few decades. Despite many efforts and advances, it is still one of the major cause of death worldwilde. Hence the importance to highlight new insights on cancer screening and appropriate therapeutic care. Cell energetics is an interesting way to address these questions. Indeed, since O. Warburg (Warburg et. al, 1925), the particular cell metabolism of cancer cells has been well described, but yet not completely understood. Cancerous cells mostly use aerobic glycolysis as the main source of ATP, even though mitochondria are the predominant source of ATP in the cells. Cellular energetic metabolism includes both degradation (i.e. catabolism) and synthesis (i.e. anabolism) pathways supporting biomass generation and cell growth. This metabolism is mostly controlled by both cellular redox potential (NAD+/NADH ratio) and phosphate potential (ATP/ADP.Pi ratio). As mitochondria play a key role in maintaining those two parameters through the oxydative phosphorylations in the inner mitochondrial membrane (IMM), we focused on mitochondrial quinones, which are lipophilic molecules embedded in the IMM, found as Q_{10} in mammals. Quinones are key elements in the mitochondrial respiratory chain (RC) since they are at the crossroad between complexes I-II and complex III to ensure the electron transfer. Their redox state depends on substrate availability and the presence of O_2, the final electron acceptor and is also thought to reflect the RC activity (Martins Pinto et. al, 2024). We therefore hypothesized that the quinone redox state could be a marker of the cellular redox state. That is why, based on previous works on plants (Moore et. al, 1988 ; Rigoulet et. al, 1985), we developed an indirect method to monitor in real-time the quinone redox state, using electrochemistry. However, since Q_{10} is embedded in the IMM, we used a shorter-length, hydrosoluble quinone as redox mediator (Q_2), which will reach a redox equilibrium with the endogenous quinones. The reduced form Q_2H_2 diffuses then back in solution and is oxidized at a carbon electrode. This method is combined with the O_2 consumption measurement using a Clark electrode.

We previously showed (Martins Pinto et. al, 2024), in yeast isolated mitochondria, that quinone redox state is a good marker of mitochondrial energetic metabolism. Here, we conducted similar experiments on cancerous cells, compared to non-cancerous cells. After characterizing the different cell lines in terms of energetics (i.e. O_2 consumption, quinone redox state, glycolysis, etc…), our results highlighted different quinone redox state signatures depending on the cell type. This enables to point out if the cells are to be considered cancerous or non-cancerous. We then tried to modulate this quinone redox state to study its effect on cellular energetics and functions. To do so, we used different approaches such as changing the carbon source in the medium or pharmacological treatment. We found that we were able to induce a variation in the percentage of reduced quinones, i.e. a decrease of the endogenous quinone redox state. These results show the effectiveness of our electrochemical approach to study cellular redox state and its diagnosis and/or prognosis potential on the long term.

P104

Deciphering the oncogenic properties of Fascin-1 in Hepatoblastoma

Grégoire MANAUD[1], Lydia DIF[1], Isabelle MAHOUCHE[1], Anne-Aurélie RAYMOND[2], Cyril DOURTHE[1,2], Sylvaine DI TOMMASO[2], Jean-William DUPUY[2], Violaine MOREAU[1]

[1] BoRdeaux Institute of Oncology

[2] TBMCore

Hepatoblastoma (HB) constitutes the most common form of primary liver malignancy in children, accounting for 1% of all pediatric malignancies. We recently published that Fascin-1, is overexpressed in undifferentiated and aggressive HB cells. Fascin-1 is important in cell migration and invasion; and we also demonstrated that Fascin-1 controls HB cell differentiation but the way Fascin-1 plays this role remains to be explored. Fascin-1 exist in two different states, bound or unbound to actin. Based on this state, we hypothesize that Fascin-1 has distinct role and localization in the cell: 1) Migration and invasion when bound to actin; 2) Control of cell differentiation when free from actin. To investigate these two forms, we used phospho-mutants of Fascin-1. The Fascin-S39E is mimicking the presence of phosphorylation (unbound to actin). We use this mutant to investigate new partners of Fascin-1 and we observed that it directly interacts with the complex V of the mitochondria. Moreover, our preliminary results indicate that this form of Fascin-1 reduces the cell respiration. In parallel, we have performed proteomic analysis on laser-microdissected tumors from a mouse model recapitulating human HB phenotype where Fascin-1 expression correlates with an undifferentiated phenotype. We found a proteomic signature suggesting that the cells are switching to a glycolytic metabolism. The production of lactate may be used to modify histones through the addition of lactyl group on lysines and therefore modifying gene expression.

P105

Keep lung cancer in check by targeting drug tolerant persister cells.

David BRACQUEMOND[1], Céline BOUCLIER[1], Xavier QUANTIN[1,2], 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 (EGFRi), but inevitably, all patients relapse within approximately 1 year. The current dogma suggests that a subpopulation of slow-to-non-cycling cells, called Drug Tolerant Persisters (DTP), is responsible for the tumour recurrence. Our aim is to abolish or at the very least delay the appearance of resistance and increase patient's survival.

The entrance in DTPs state of EGFRi treated cells coincides with a drastic downregulation of the NOTCH pathway activity (HES1 drop). This pattern is reversed once DTPs begin to expand (DTEPs), thus tumour relapse. In parallel, we monitored cell cycle progression through the FUCCI reporter system: EGFRi promotes G0/G1 cell cycle arrest and an upregulation of cell cycle inhibitors. Interestingly, combining NOTCHi and EGFRi abolishes DTPs expansion in vitro and prolongs the previously described DTPs features.

In vivo, we took advantage of the Tet-On-EGFRT790M/L858R genetically engineered mouse model (GEMM) to assess the combination of clinically relevant EGFRi/NOTCHi molecules. This combination demonstrated a superior objective response rate (100% vs 71%) when compared to the EGFRi monotherapy and significantly delayed tumour relapse with a 40% increase in the median overall survival (11.6 vs 8.6 months). Similarly, when using EGFR-driven Patient Derived Xenografts (PDX), the benefit of the combination was even more striking in promoting tumour regression and almost doubled mice survival when compared to EGFRi monotherapy (94 vs 50 days).

In conclusion, EGFRi treatment affects the NOTCH pathway activity and therefore combining NOTCH and EGFR inhibition confers a therapeutic benefit as it delays the relapse both in vitro and in vivo. We are at the moment dissecting how HES1 levels mediates DTPs status that might identify new targets to tackle DTPs more efficiently.

P106

p190A/ARHGAP35 and p190B/ARHGAP5 proteins in endometrial cancer, a novel cancer-relevant paralog interplay

Mathilde PINAULT[1], Capucine HERAUD[1], **Mélissa CORREIA DE OLIVEIRA[1]**, Véronique NEAUD[1], Valérie VALESCO[2], Valérie PROUZET-MAULEON[3], Béatrice TURCQ[3], Anne-Aurélie RAYMOND[1,4], Sabrina CROCE[2], Valérie LAGREE[1], Violaine MOREAU[1]

[1] BRIC (BoRdeaux Institute of onCology), UMR1312, INSERM, Univ. Bordeaux, F-33000, Bordeaux, France

[2] Department of Biopathology, Institut Bergonié, 33076 Bordeaux, France

[3] CRISP'Edit, UAR 005 TBMcore, Bordeaux, F-33076, France

[4] Oncoprot, UAR 005 TBMcore, Bordeaux, F-33076, France

ARHGAP35/p190A and *ARHGAP5*/p190B are paralogs and major regulators of small GTPases of the Rho family. Several studies highlight *ARHGAP35* as a new significantly mutated gene in endometrial cancer, which is one of the main gynecological malignancies worldwide, with an estimated 320 000 new cases annually. By analyzing human endometrial cancer samples, we found a co-occurrence of mutations in *ARHGAP35* and *ARHGAP5* genes and we reported that both are less expressed at the mRNA level in tumoral samples compared to healthy tissues. We were interested in understanding the impact of p190A/B under-expression in endometrial cancer and the relationship between the two paralogs. To do so, we have used CRISPR/Cas9 technology to generate HEC-1-A knockout cells for p190A and p190B. We showed that removal of each paralog led to a similar actin remodeling phenotype with the formation of Cross-Linked Actin Networks (CLANs), dependent on the Rho/ROCK pathway. Moreover, proteomic analysis of p190A and p190B knockout cells highlighted similar affected cell functions. Finally, our study demonstrates a synthetic lethality between p190A and p190B where removal of both paralogs is deleterious in endometrial cancer cells, unveiling a potential actionable vulnerability.

~~P107~~

~~A dynamic 3D interface model to study proliferation and invasion during Hepatocellular Carcinoma progression~~

Lucile ROUYER

BoRdeaux Institute of Oncology

During tumorigenesis, cancer cells acquire competitive advantages over surrounding non-tumoral cells through constant interactions with their microenvironment, particularly at interface zones where they encounter other cells or structural elements such as extracellular matrices. These contact zones critically influence cancer development, metastatic spread, and aggressiveness. Hepatocellular carcinoma (HCC) is a highly heterogeneous malignancy that develops over extended periods within pathological liver tissue. We hypothesize that the surrounding hepatic microenvironment plays a crucial role in HCC progression.

This project aims to develop a 3D in vitro model that recapitulates the dynamic interface between healthy hepatocytes and tumor cells, enabling investigation of bidirectional cellular influences over time and providing insights into proliferation and invasion mechanisms in liver tumor progression. To reproduce the mechanical constraints of liver parenchyma on tumor growth, we established a co-culture 3D spheroid model using HepaRG or AML12 hepatocytes and HUH7 HCC cells in varying ratios, organized as tumor cores surrounded by healthy cells.

We characterized this model through immunohistochemistry, live-cell imaging (IncuCyte), confocal microscopy, and functional assays measuring proliferation and apoptosis. The model maintained excellent viability for two weeks without core hypoxia or apoptosis. Notably, tumor cell proliferation was significantly reduced in co-culture compared to HUH7 monoculture spheroids, inversely correlating with the number of surrounding normal cells. Direct co-culture was essential for this effect, as HepaRG pressure through indirect co-culture or conditioned media proved insufficient, suggesting the importance of direct cell-cell contact and molecular competition.

Proteomic analysis comparing non-proliferative and proliferative conditions revealed molecular processes controlling tumor progression. Selected targets identified through proteomics are currently being validated using silencing and overexpression strategies. This model provides a robust platform for studying HCC progression mechanisms and testing therapeutic interventions targeting tumor-microenvironment interactions.

P108

Role of PARD3, a newly identified target of Syk kinase in mammary tumour invasion

Pauline BARRAJA[1], Fatima LAKIS[1,2], Charlotte GAVARD[1], Alain MANGE[1], Gilles FREISS[1], Peter COOPMAN[1], Marion PETER[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Laboratory of Cancer Biology and Molecular Immunology, Faculty of Sciences-I, Lebanese University, Hadath, Lebanon

Breast cancer is the most common invasive cancer in women and metastatic spread is the main cause of treatment failure and mortality. In this cancer, we are interested in the signalling pathways controlled by the Syk tyrosine kinase. Our laboratory first established Syk tumour suppressor role in breast cancer. Recently, we have shown that Syk is involved in the control of intercellular adhesion. We therefore hypothesise that the onco-suppressive effect of Syk is mediated in particular by effectors and/or substrates that regulate intercellular adhesion, such as junction proteins. By phospho-proteomic analysis, new direct or indirect targets of Syk have been significantly identified. Many of these proteins are involved in intercellular adhesion, including PARD3 (Par-3 family cell polarity regulator).

We have thus investigated PARD3 regulation in cells and in vitro, in relation to Syk. In different breast cancer cell lines, a partial co-localisation at cell-cell junctions of PARD3 with Syk was detected at the endogenous level. Furthemore we have shown that Syk seems to promote PARD3 recruitment and stabilisation at cell-cell junctions. Besides, PARD3 was co-immunoprecipitated with Syk following overexpression in MCF7 cells. Moreover, we showed that PARD3 is an vitro substrate of Syk. PARD3 tyrosine residues regulated by Syk were identified by mass spectrometry. Following the obtention of PARD3 phosphorylation site mutants and their expression in different cell lines, we are now studying the consequences of the interaction and phosphorylation of PARD3 by Syk on its function and on cell-cell junctions. To do so, we are currently studying PARD3 localisation, recruitment, stability and dynamics using different methods, such as FRAP (Fluorescence Recovery After Photobleaching).

P109

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], Sébastien GIRAUD[4], Julien TAÏEB[5], Serge MILIN[1,6], Michel WAGER[7], Jean-François EMILE[8], Olivier BOUCHE[9], Côme LEPAGE[10], David TOUGERON[1,11], Lucie KARAYAN-TAPON[1,3], Pierre-Olivier GUICHET[1,3]

[1] Laboratoire ProDiCeT, UR 24144, Université de Poitiers

[2] CHU Poitiers, Service d'Oncologie Médicale, F-86000 Poitiers, France.

[3] CHU Poitiers, Laboratoire de Cancérologie Biologique, F-86000 Poitiers, France

[4] Université de Poitiers, INSERM IRMETIST U1313, CHU de Poitiers, Service de Biochimie, Poitiers, France

[5] Gastroentérologie et Oncologie Digestive, Georges-Pompidou Hôpital Européen, Assistance Publique-Hôpitaux de Paris (AP-HP-Paris Centre), Université de Paris, Paris, France

[6] CHU de Poitiers, Service d'Anatomie et de Cytologie Pathologiques, F-86000 Poitiers, France

[7] CHU de Poitiers, Service de Neurochirurgie, F-86000 Poitiers, France

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

[9] CHU Reims, Service d'Oncologie Digestive, F-51100 Reims, France

[10] Département d'Oncologie Digestive, CHU Dijon, Université de Burgundy et Franche Comté, Dijon, France

[11] CHU Poitiers, Service d'Hépato-gastro-entérologie, F-86000 Poitiers, France

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 transcriptomic approach that this coactivator was strongly expressed in tumor area with metabolic changes. Notably, YAP inhibition led to decreased mitochondrial respiration and activity, with reduced expression of mitochondrial markers, suggesting a role of YAP in regulation of cellular respiration. Altogether, our results highlight a potential role of YAP in CRC progression, particularly in BM stem cells.

Key-words: Brain metastases, colorectal cancer, stem cells, YAP.

P110

Inhibiting mRNA Translation with MYC Degraders Counteracts Drug-Tolerant Persister Cells During KRAS G12D Inhibition in PDAC

Léa FEVRIER[1], Morgane LEBRAS[1], Mehdi LIAUZUN[1], Clémence GUILLON[2], Bertrand FABRE[2], Corinne BOUSQUET[1], Yvan MARTINEAU[1]

[1] Centre de Recherches en Cancérologie de Toulouse

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

Drug-tolerant persister (DTP) cells, which arise under targeted therapies, survive in a reversible quiescent-like state and frequently drive progression toward acquired resistance. Various non-genetic mechanisms contribute to DTP emergence, including adaptive changes in mRNA translation [1].

In pancreatic ductal adenocarcinoma (PDAC), the recently developed KRAS G12D inhibitor MRTX1133 (G12Di) has shown potent activity, yet therapy resistance also emerges in cell culture and preclinical mouse models [2]. To address this challenge, we examined the formation of DTPs during sustained G12Di exposure and investigated the role of translational control in this process. Given the established function of MYC as a regulator of protein synthesis in cancer, we further explored whether MYC degraders could prevent the establishment of persister cells during G12Di treatment.

Extended G12Di exposure in PDAC cells induced a transient global reduction in protein synthesis accompanied by proliferative arrest. Upon drug withdrawal, surviving cells resumed proliferation and regained drug sensitivity, confirming the reversibility of this phenotype consistent with a DTP state. Strikingly, co-treatment with G12Di and MYC degraders (A80.2HCl) markedly reduced the emergence of DTPs, an effect associated with a strong suppression of protein synthesis. Beyond the direct effect of MYC degraders, further analysis revealed additional regulators of translation contributing to the suppression of DTP cells.

Taken together, our findings demonstrate that prolonged KRAS G12Di treatment promotes a reversible DTP state in PDAC cells, closely linked to reduced protein synthesis. Importantly, co-treatment with MYC degraders effectively suppresses DTP development, providing a mechanistic rationale for combination strategies. These results pave the way for future evaluation of dual KRAS G12Di and MYC degrader therapy in preclinical PDAC models.

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P111

The vitamin K-dependent anticoagulant factor Protein S regulates the expression of the receptor tyrosine kinase AXL via the Hippo/YAP pathway in primary and brain-metastatic colorectal cancer cell models

Yousra KAISSOUNI[1], Konstantin MASLIANTSEV[1,2], Pierre-Olivier GUICHET[1,2], Lucie KARAYAN-TAPON[1,2], Omar BENZAKOUR[1], Fatima DKHISSI[1]

[1] UR24144 PRODICET, Université de Poitiers, CHU Poitiers, Poitiers, France

[2] Laboratoire de Cancérologie Biologique, CHU de Poitiers, Poitiers, France

Background. Brain metastases (BM) from colorectal cancer (CRC) are rare (≈1-3%) but are associated with a poor prognosis, and their molecular mechanisms remain poorly understood. Protein S (PROS1), a vitamin K-dependent anticoagulant factor, is also a ligand for the TAM receptor tyrosine kinase family (TYRO3/AXL/MERTK). We have previously provided evidence that PROS1 acts as a major regulator of vascular, immune/phagocytic, and neural processes relevant to the brain niche, including vascular permeability, neural stem/progenitor cell (NSPC) migration and apoptotic-cell clearance. Alterations in Hippo signaling, with YAP as a central effector, can induce AXL transcription and are associated with several steps of the metastatic cascade.

Objective. We undertook the present study to investigate whether PROS1/TAM signaling interfaces with Hippo/YAP signaling in primary and brain-metastatic colorectal cancer cell models.

Methods. We used established colorectal cancer cell lines (HT29, SW480, SW620) and patient-derived brain-metastatic CRC cell line (BM-SC-CRC). Baseline expression of AXL, MERTK, and TYRO3 was quantified by Western blot on whole-cell lysates and normalized to β-actin. Cells were then stimulated with recombinant human PROS1 or vehicle. TAM activation was measured by phospho-specific immunoblotting (p-MERTK, p-TYRO3) and expressed as phospho/total ratios versus matched controls. Hippo/YAP activity was determined by (i) YAP immunofluorescence, (ii) Western blot of phospho-YAP and total YAP (p-YAP/total YAP), and (iii) qPCR of canonical YAP targets (CTGF, CYR61, AXL, BIRC5 (Survivin)), normalized to GAPDH using the ΔΔCt method.

Results. In terms of responsiveness to PROS1 and with respect to Hippo signaling, clear differences were consistently observed between established CRC cell lines (HT29, SW480, SW620) and a patient-derived brain-metastatic CRC line. In CRC cell lines -but not in the brain-metastatic line-PROS1 reduced YAP phosphorylation at Ser127 and Ser397. However, across all cell lines examined, PROS1 promoted YAP nuclear translocation and increased the mRNA levels of YAP target genes (AXL, CTGF, CYR61, BIRC5/Survivin). These differences in PROS1-induced YAP phosphorylation suggest that, in established CRC cell lines, PROS1 reduces YAP phosphorylation at Ser127 and Ser397, thereby promoting its nuclear localization, whereas in the patient-derived, brain-metastatic CRC line, PROS1-induced YAP nuclear translocation may depend on phosphorylation at other, as-yet unexamined residues, possibly tyrosine (e.g., Y444).

Conclusion. Our study suggests that regulation of the YAP pathway and, subsequently, AXL receptor expression may be a novel mechanism by which PROS1 could contribute to colorectal cancer progression and dissemination. Therefore, combined targeting of YAP and the PROS1/TAM system may represent a promising therapeutic approach for colorectal cancer and warrants further investigation.

P112

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

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

[1] BoRdeaux Institute of Oncology

[2] CNRS

Background: Galectins, carbohydrate-binding proteins, are a family of proteins recognized for their β-galactoside-binding activity. Several galectins (GALs, LGALS) have emerged as critical modulators of tumorigenesis, with growing evidence in glioblastoma (GB). Nevertheless, their precise role in GB remains barely understood, particularly within glioblastoma stem cells (GSC) - pivotal drivers of recurrence and tumour progression.

Material and Methods: Publicly available TCGA and CCGA datasets were analyzed with SUMO software and R. scRNA-seq data analysis was conducted with the R toolkit Seurat and the SingleR package. As cellular models, we used patient-derived glioblastoma stem cells (GSCs) - BTSC73, BTSC53, and BTSC12. Genetic depletion was achieved using siRNA-mediated silencing and CRISPR-Cas9 genome editing. Pharmacological inhibition was performed using the selective inhibitor GB1107. Protein localization in BTSC was assessed by immunostaining with GAL-3, mtHSP70 as a mitochondrial marker, and DAPI for nuclei, and images were acquired using confocal microscopy. Cell viability was assessed by flow cytometry (FACS) using propidium iodide (PI) staining. Cell death was quantified using an Annexin/PI double staining assay. Cell cycle analysis was performed using PI staining followed by FACS. Proliferation was assessed by EDU staining. BTSC were treated with temazolomide (TMZ) and irradiated with 2 Gy, followed by a 7-day culture phase to assess post-treatment responses.

Results: We first conducted an in silico analysis for LGALS1, -3, -8, and -9 expressions in GB. We found that a combination of high expression of these GALs is associated with the poorest prognosis in GB patients compared to other combinations. The scRNA-seq analysis has revealed that GALs are distributed heterogeneously in GB, where GAL-3 is expressed in tumour cells, macrophages, and T-cells. Furthermore, Kaplan-Meier survival analysis demonstrated that patients with low LGALS3 expression exhibited improved prognosis. We then conducted in vitro experiments to assess the role of GAL-3. BTSC immunostaining highlighted the broad distribution of GAL3 within the cell. Both genetic and pharmacological LGALS3 depletion led to a decrease in BTSC12 and BTSC73 numbers, which is related to an effect on proliferation but not apoptosis. Cell cycle analysis revealed that CRISPR knockout cells exhibited an accumulation in the G1 phase 22 hours after seeding. RNA-sequencing of BTSC73 followed by GAL-3 knockout showed that this effect can be attributed to upregulation of expression of SFRP2, known to antagonize the Wnt signaling cascade. Western blot analysis validated the increased level of SFRP2 in CRISPR knockout cells. Notably, growth factor deprivation of these cells resulted in the opposite phenotype, characterized by increased proliferation and a decreased G1-phase cell fraction. The same outcome was recapitulated while using pharmacological inhibition of GAL-3 in BTSC73, BTSC12, and BTSC53. Subsequent studies have demonstrated that TMZ treatment, as well as irradiation of BTSC73 and BTSC12 following GAL-3 knockout, result in a bigger decrease in cell viability compared to the control condition. However, subsequent experiments revealed no alterations in the migratory or invasive capacities of CRISPR knockout cells. Besides, oxygen consumption rate also remained unchanged in CRISPR knockout cells compared to control BTSC73.

Conclusion: Our findings indicate that GAL-3 contributes to GB development by regulating GSC proliferation, cell cycle progression, and the response to growth factor deprivation, TMZ treatment, and irradiation.

P113

Study of interactions between Sézary Syndrome derived patient's cells and monocytes/macrophages

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

[1] BRIC (BoRdeaux Institute of onCology), UMR1312, INSERM, Univ. Bordeaux, F-33000, Bordeaux, France

[2] Dermatology Department, Bordeaux University Hospital, F-33000 Bordeaux, France

[3] Tumor Bank and Tumor Biology Laboratory, Bordeaux University Hospital, F-33600 Pessac, France

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 (SS) (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)). Recent publications have demonstrated significant macrophage infiltration in patient skin biopsies (Han et al, JCI Insight, 2023 (PMID: 37427589)).

Flow cytometry was used to assess the impact of SS cells derived from 4 patient samples on primary CD14+ monocyte differentiation after co-culture. The immunosuppressive activity of « educated » macrophages derived from monocytes (MDMs) was determined by co-culture with healthy CD4+ T lymphocyte and analysis of their ability to inhibit CD4+ T lymphocyte activation. Then, the functions of « educated » MDMs on SS cells properties were investigated.

We observed that MDMs PD-L1 expression was increased after direct or indirect culture with SS cells. This is associated with an increase in the immunosuppressive activity of the "educated" MDMs on CD4+ T cells, which may contribute to tumor escape. Secretome analysis allowed us to identify soluble factors secreted by SS cells that could induce PD-L1 expression on MDMs and their immunosuppressive phenotype. In turn, preliminary results suggested a pro-survival and pro-proliferative function of the PD-L1high MDMs on SS cells.

Overall, these results reveal that SS-derived patient cells differentiate MDMs into a PD-L1high and immunosuppressive phenotype. Finally, this study will enable us to better understand the impact of monocytes/macrophages on tumor survival and immune escape in SS in order to propose alternative therapies.

P114

Evidence of immunosuppressive and pro-tumoral interactions between tumor cells and macrophages in cutaneous diffuse large B-cell lymphomas.

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

[1] BRIC (BoRdeaux Institute of onCology), UMR1312, INSERM, Univ. Bordeaux, team 5, F-33000, Bordeaux, France

[2] Hematology and cell therapy department, CHU Bordeaux, F-33000 Bordeaux, France

[3] Tumor Bank and Tumor Biology Laboratory, CHU Bordeaux, F-33000 Bordeaux, France

[4] Dermatology Department, CHU Bordeaux, F-33000 Bordeaux, France

Introduction: Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) is an aggressive rare disease affecting the elderly, with limited therapeutic options. It harbors an ABC-DLBCL signature and commonly exhibits *MYD88* and/or *CD79B* and/or *PIM1* mutations that rely to the MCD genetic cluster. Regarding their microenvironment, our team previously demonstrated that biopsy samples of PCDLBCL-LT are particularly enriched in tumor-associated macrophages that express a pro-tumoral phenotype. We aimed to decipher the relationships between tumor cells and macrophages in PCDLBCL-LT.

Material and Methods: The unique PCDLBCL-LT ARSI cell line and patient-derived xenografts (PDXs) were used as PCDLBCL-LT models. Macrophages were generated from primary monocytes or the THP-1 cell line. We used co-culture systems, secretome analysis, flow cytometry, immunosuppressive assays, and neutralizing antibodies to mechanistically dissect these interactions.

Results: We demonstrated that ARSI cells induced phenotypic changes in macrophages toward a pro-tumoral state ($CD163^{high}$, $PD\text{-}L1^{high}$, $CD80^{high}$, $HLA\text{-}DR^{low}$) with immunosuppressive functions. These changes occurred independently of direct cell-cell contact. We revealed that ARSI cells expressed and secreted high amounts of a specific cytokine and that blocking this cytokine-driven interaction inhibits macrophage polarization induced by tumor cells. These findings were reproduced when macrophages were co-cultured with PCDLBCL-LT cells from different PDXs.

Conclusions: Our findings highlight the critical role of a specific cytokine in modeling lymphoma microenvironment, especially on macrophages. These results emphasize the robustness of this model to study lymphoma cell and macrophage interplays. This study may help define specific features in the context of microenvironment-targeted therapies.

P115

The matricellular protein periostin is a novel substrate of cathepsin D in triple-negative breast cancers

Isaure DOUAT[1,2,3], Aude MALLAVIALLE[1,2,3], Cindy DIERYCKX[4,5,6,7,8,9,10], Frédéric DELOLME[4,5,6,7,8,9,10], Thomas REINHECKEL[11,12], Catherine MOALI[4,5,6,7,8,9,10], Emmanuelle LIAUDET-COOPMAN[1,2,3]

[1] Institut de Recherche en Cancérologie de Montpellier
[2] Inserm U1194
[3] Université de Montpellier
[4] Université de Lyon
[5] CNRS UMR5305
[6] Tissue Biology and Therapeutic Engineering Laboratory (LBTI), F-69367 Lyon
[7] ENS de Lyon
[8] INSERM US8
[9] CNRS UMS3444
[10] SFR Biosciences, F-69366 Lyon
[11] Institute of Molecular Medicine and Cell Research
[12] Faculty of Medicine, Albert-Ludwigs-University Freiburg, Germany

Triple-negative breast cancers (TNBC) represent 15 to 20% of breast cancers. TNBCs are characterized by the lack of estrogen (ER) and progesterone receptors (PR) and no amplification of human epidermal growth factor receptor 2 (HER2). Chemotherapy is the primary systemic treatment, but resistance is common. Thus, alternative therapeutic strategies based on tumor-specific molecular targets are urgently needed. Matricellular proteins (MCPs) have emerged as promising targets to restructure the tumor microenvironment (TME). Among them, periostin, an anti-adhesive MCP highly secreted in the stroma of TNBC, is of major interest. Its poor prognosis value and its pro-tumoral roles in multiple cancer hallmarks suggest that it could be a potent target for new therapies. The proteolytic cleavage of periostin in the tumor stroma has been poorly studied and the biological functions of its resulting cleaved fragments remain unknown. The protease cathepsine-D (cath-D), a marker of poor prognostic in TNBC, is overexpressed mainly by cancer cells and is hypersecreted in the stroma of TNBC. Secreted cath-D plays numerous pro-tumoral roles, notably by cleaving extracellular factors at the acidic pH of the tumor stroma, promoting TME remodeling.

Our preliminary analysis, by N-TAILS proteomics (N-terminal amine isotopic labeling of substrates), of the extracellular degradome at acidic pH of an inducible *ctsd−/−* murine MMTV-PyMT mammary cancer cell line revealed that periostin is a potential substrate of cath-D.

The objective of my thesis is to demonstrate that human periostin is a substrate of human cath-D in TNBC stroma, and to determine whether one or more periostin fragments may exhibit enhanced pro-tumoral roles, in order to determine a novel promising cleaved stromal target for new antibody-based therapies.

We have confirmed the autocrine and paracrine cleavages of secreted human periostin in TNBC cell lines monoculture and in coculture with cancer-associated fibroblasts (CAFs). The specificity of this cleavage by cath-D in the secretome of TNBC cell lines is currently investigated using siRNA and MDA-MB-231 cath-D CRISPR knock out cell line. Our *in vitro* proteolytic cleavage assays using the two human recombinant proteins periostin and cath-D, analyzed by western blot and silver staining, demonstrated that periostin is a substrate of cath-D. Six main periostin fragments, ranging from 50 to 15 kDa, were detected. Using ATOMS-iTraq™ proteomic technology, three sites of cleavage of recombinant human periostin by recombinant human cath-D were identified. These data support the selection and production of the main POSTN fragments for functional studies, including biological and signaling analyses.

P116

Receptor tyrosine kinase-mediated regulation of glioblastoma stem cell maintenance, therapy resistance, and tumor progression

Nour KHAIRALLAH *[1], Malak SENOUCI *[1], Maxime TOUJAS *[1], Ludivine JOURDAN[1], Joris GUYON[1], Ahmad SHARANEK ‡[1], Audrey BURBAN ‡[2]

[1] University of Bordeaux, INSERM UMR1312, BRIC BoRdeaux Institute of Oncology, Bordeaux, France.

[2] University of Bordeaux, CNRS, IBGC, UMR5095, Bordeaux, France.

Glioblastoma (GB) is the most aggressive primary brain tumor, with a median survival of less than 15 months despite maximal surgical resection, temozolomide chemotherapy, and radiotherapy. Treatment failure is largely driven by tumor heterogeneity and intrinsic resistance mechanisms. Glioblastoma stem cells (GSCs) are a self-renewing population capable of regenerating all tumor subpopulations and driving recurrence, representing a major therapeutic challenge. Identifying essential regulators of GSCs is therefore critical for the development of novel treatment strategies.

GSCs rely on multiple context-specific pathways to survive under diverse microenvironmental conditions and therapeutic pressures. Cell-surface proteins, particularly receptor tyrosine kinases (RTKs), play central roles in transmitting extracellular signals and mediating interactions with the tumor microenvironment, making them attractive therapeutic targets. Through surface protein profiling, we identified an RTK that is highly expressed in GSCs compared with non-oncogenic neural stem cells. Analysis of patient datasets revealed that this RTK is overexpressed in GB relative to normal brain tissue, and higher expression correlates with poorer patient survival. However, its functional role in GB had not been defined.

Functional assays demonstrated that genetic deletion or pharmacological inhibition of this RTK reduces GSC proliferation and self-renewal, with variable sensitivities observed across patient-derived GSCs. Activation of the RTK reinforced GSC dependency and increased their vulnerability to inhibition. Notably, RTK depletion or inhibition impaired mitochondrial morphology and reduced oxidative phosphorylation, suggesting a critical role in GSC metabolism. Combination studies further showed that targeting this RTK sensitizes GSCs to radio- and chemotherapy. In vivo intracranial tumor assays revealed that RTK knockdown reduces tumor growth and extends survival. Together, these findings establish this RTK as a central regulator of GSC biology and underscore its potential as a therapeutic target in GB.

* Co-first authors
‡ Co-corresponding authors

P117

Role of thrombospondin-1 in the metabolic exchanges between astrocytes and glioblastoma during tumor development and invasion.

Eva EPINETTE[1], Shannon Sherwin MOREINO[2], Hrvoje MILETIC[2], Thomas DAUBON[1]

[1] Institut de Biochimie et Génétique Cellulaires, Bordeaux

[2] Department of Biomedicine, University of Bergen, Bergen, Norway

Glioblastoma is an aggressive and invasive grade IV glioma that is associated with a poor prognosis with a median survival around 15 months despite the current treatments available. Part of this low survival is due to relapse which happens in 90% of cases (1). This is why it is essential to find therapeutic targets that would help to improve the disease outcome for patients.

Thrombospondin-1 (TSP1) is protein of the extracellular matrix that has been found upregulated in the glioblastoma tumor microenvironment and is associated with poor prognosis for the patients. This protein has been implicated in the formation of microtubes which are enabling glioblastoma cells to exchange ions, proteins and organelles, such as mitochondria, with each other (2)(3).

More recently, a study revealed that astrocytes can also transfer their mitochondria to glioblastoma cells through microtubes (3). Astrocytes are essential to maintain the brain homeostasis and are known to metabolically support neurons with lactate through a lactate shuttle (4). Such phenomenon is also suggested between the glioblastoma cells from glycolytic and oxidative areas of the tumor (5).

Considering those elements, this project aim is to determine if astrocytes metabolically support glioblastoma progression and the role of the thrombospondin-1 protein in these interactions.

To achieve this, patient-derived glioblastoma stem-like cells (P3) expressing the eGFP protein and Normal Human Astrocytes (NHA) with red fluorescent mitochondria (mitoDSRed) were used. Migration experiments of P3 spheroids on a NHA monolayer were realized and then fixed to perform immunofluorescent staining to study mitochondrial transfer and the expression patterns of proteins associated to lactate metabolism.

Preliminary results reveal that astrocytes seem to support glioblastoma cell migration. Moreover, expression patterns of the LDHA and LDHB enzymes as well as MCT1 and MCT4 lactate transporters in P3 and NHA cells during P3 migration seem coherent with the hypothesis of a potential lactate shuttle from astrocytes to glioblastoma cells. Finally, mitochondrial transfer from NHA to glioblastoma cells were observed during glioblastoma cell migration, a phenomenon that seems to be supported by TSP1 since its knock-down in P3 cells reduced the number of mitochondrial transfers observed.

These results could suggest a potential metabolic support from the astrocytes to the glioblastoma cells which could be supported by the action of the TSP1 protein.

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P118

The Impact of the Immune Microenvironment on the Therapeutic Response to Combined Chemotherapy and ATR Inhibition in Pancreatic Cancer

Clara FREIXINOS[1], Thomas BESSEDE[1], Clotilde LIGNON[1], Véronique GARAMBOIS[1], Laurent GROS[1], Virginie LAFONT[1], Garett DUNSMORE[2], Florent GINHOUX[2], Céline GONGORA[1], Christel LARBOURET[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Institut Gustave Roussy, Villejuif

Pancreatic ductal adenocarcinoma (PDAC) is an incurable cancer when diagnosed at advanced stages due to its marked resistance to conventional therapies (Gemcitabine and FOLFIRINOX) and immunotherapies. Only patients diagnosed at an early stage can benefit from surgical resection. This resistance is largely attributed to its tumor microenvironment (TME), which consists of a dense stroma (accounting for 80% of the tumor mass) heavily reliant on the presence of cancer-associated fibroblasts (CAFs) and exhibits immunosuppressive properties. The main infiltrating immune cells (ICs) include macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T lymphocytes.

To date, strategies aimed at disrupting this desmoplastic stroma and targeting immunosuppressive pathways have largely failed. Therefore, there is an urgent need to (i) better understand the role of the stroma, particularly that of CAFs, which are a major TME component and play a central role in therapy resistance, in order to design new therapies capable of modulating the immune cell infiltrate and sensitizing the tumor to immunomodulatory therapies, and (ii) develop new therapeutic combinations to improve patient survival.

In our laboratory, we have demonstrated a synergistic effect of combining FOLFIRINOX with VE-822 (an ATR inhibitor targeting DNA damage repair pathways) in various 3D co-culture models (immortalized or primary CAFs and pancreatic tumor cells) and in an immunocompetent mouse model orthotopically grafted with the murine KPC cell line (KrasG12D/+/P53-/-/Pdx1-Cre). This therapeutic effect was associated with strong immune cell infiltration, particularly macrophages and T lymphocytes, in tumors treated with the combination compared to FOLFIRINOX alone. CD8+ T cell depletion in mice treated with the combination significantly reduced the therapeutic response, though not completely, suggesting the involvement of other immune cells. Beyond the direct cytotoxic effect of the drugs, we aim to investigate the role of macrophages in this response, as tumor-associated macrophages are one of the most abundant populations and play a key role in tumor development and therapy response.

The proposed project aims to (i) further characterize the anti-tumor responses mediated by infiltrating immune cell populations, with a particular focus on macrophages; (ii) investigate the interactions between macrophages, cancer-associated fibroblasts (CAFs), and tumor cells following treatment; and (iii) explore strategies to modulate these immune cells to enhance therapeutic efficacy. Given that our immunocompetent model exhibits low murine CAF infiltration (10-15%), we developed a 3D heterotypic spheroid model in the laboratory composed of tumor cells, primary CAFs, PBMCs and/or macrophages, closely mimicking the pathophysiological characteristics of pancreatic tumors.

Our results show that all immune cells can infiltrate spheroids and that macrophages are able to differentiate into M1-like and M2-like phenotype. Furthermore, we observe a pronounced M2-like phenotype due to the cross-talk between macrophages and CAFs in favor of an immunosuppressive immunoenvironment, as observed in patients. Upon administration of our combination therapy, an M1-like macrophage phenotype is induced, accompanied by a reduction in M2-like macrophage populations. We are currently evaluating immune cell functionality within treated spheroids, as well as profiling cytokine secretion. Finally, using single-cell RNA sequencing (scRNA-seq) analysis in the KPC mouse model, we plan to conduct an in-depth investigation of the nature and role of immune infiltration following treatment with FOLFIRINOX combined with ATR inhibition.

P119

Analysis of the impact of macrophage polarization on the stemness in glioblastoma

Léa DECOUX, Léa SCARAMUZZINO, Amy GATEAU, Damien OTT DE NUSSAC, Andreea ANDREEV, Lucas COUTURIER, Stéphanie DURAND, Paul-François GALLET

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

Glioblastoma multiforme (GBM) is the most aggressive and most common tumor of the central nervous system (CNS) in adults. Its strong tendency to recur is partly attributable to a subpopulation of cancer stem cells (CSCs), capable of resisting standard treatments and reigniting tumorigenesis. The immune compartment is a key component of the GBM tumor microenvironment: it includes microglia (resident CNS macrophages) and infiltrating macrophages that can traverse the blood-brain barrier under pathological conditions. These macrophages, regardless of their origin, exhibit great plasticity, able to polarize in response to their environmental context toward M1 (antitumor) or M2 (protumor) phenotypes.

These macrophages/microglia interact with tumor cells via cytokines (interleukins such as IL-10, etc.), through direct contact, as well as by secreting small extracellular vesicles (EVs) called exosomes. These EVs are particles measuring between 30 and 150 nm in diameter that reflect the contents of their parent cell.

We hypothesize that EVs released by polarized (or non-polarized) macrophages/microglia have a significant impact on the phenotype of CSCs in GBM: EVs from M1-polarized cells will reduce CSC-associated phenotypes (lower proportion of CSCs, decreased self-renewal and invasion capacities), while EVs from M2-polarized cells will promote the maintenance or expansion of CSCs.

To investigate this, macrophage and microglial cell lines are polarized in vitro. EVs from these polarized cells are isolated by differential ultracentrifugation, and then glioblastoma tumor cells are treated with these EVs to assess the proportion of CSCs.

Overall, this study aims to elucidate the role of microglia/macrophage-derived EVs in modulating the CSC phenotype in glioblastoma and to identify potential therapeutic targets to disrupt pro-tumoral signals emanating from the tumor microenvironment.

P120

The carboxyamidotriazole calcium channel inhibitor reduces stem like properties in glioblastoma stem cells

Théo BRANCHU, Valérie CORONAS, Nadine DELIOT, Laëtitia COUSIN, Thomas HARNOIS, Bruno CONSTANTIN

Canaux & Connexines dans les Cancers et Cellules Souches, Poitiers

Glioblastoma (GBM) is the most aggressive form of malignant brain tumors, occurring mainly in adults. It is characterized by rapid growth and a high capacity to invade brain tissue. Treatment for GBM relies on a combination of surgery, radiation therapy, and chemotherapy with temozolomide (TMZ), but the prognosis remains generally poor, with an overall survival rate limited to approximately 12 to 15 months. In addition, the relapse rate of approximately 90% and resistance to treatment remain major challenges, and despite extensive ongoing research, therapeutic options are still very limited. These characteristics of GBMs are now associated with glioblastoma stem cells (GSCs), which have important proliferation and self-renewal properties and are responsible for tumor initiation and progression. In addition, GSCs resist conventional treatments such as radiotherapy and chemotherapy, and owing to their stem cell properties, they rebuild the tumour.

Previous work of the laboratory showed that Ca2+ influx can regulate GSCs activities. In non-excitable cells, store-operated channels (SOCs) are the major pathway for Ca2+ influx. SOC inhibition reduces proliferation and self-renewal capacity of these cells (1). Interestingly, carboxyamidotriazole (CAI), a non-voltage-dependent calcium channel inhibitor, when combined with TMZ improved survival in patients with GBM and was well tolerated in a phase Ib clinical trial (2). But the target and the cellular impacts of CAI are not known.

In this study, human glioblastoma stem cells were used to analyze CAI effects. Our data show that CAI inhibited SOC mediated calcium entries which led to a reduction in proliferation and self-renewal. No impact on mitochondrial membrane potential could be detected. To complete the work of the clinical trial, the effects of a co-treatment with CAI and TMZ have been evaluated on GSC characteristics such as proliferation, self-renewal and senescence. Our results suggest that SOC could be a relevant therapeutic target for GSCs to treat GBM.

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P121

Regulation of Normal and Leukemic Hematopoiesis By G-Protein Coupled Receptors

Tala MAASSARANI[1,2], Elodie RICHARD[1,2], Stephania CONTRERAS[1,2], Catherine SAWAI[1,2], Bruno CARDINAUD[1,2]

[1] Université de Bordeaux

[2] BoRdeaux Institute of Oncology

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder driven by the expression of the BCR::ABL1 fusion protein, encoded by the Philadelphia chromosome. CML is treated with tyrosine kinase inhibitors (TKIs) such as imatinib. While TKIs effectively eliminate most BCR::ABL1+ cells, quiescent leukemic stem cells (LSCs) often persist, leading to disease relapse upon treatment discontinuation. In CML, LSCs share many properties with normal hematopoietic stem cells (HSCs), which reside in a specialized bone marrow microenvironment, where they receive diverse signals from surrounding and distant cells through ligand-receptor interactions that regulate their quiescence, proliferation, and differentiation. This so-called 'niche' is thought to promote LSC survival during TKI therapy. Our lab performed single-cell RNA sequencing data from normal and leukemic HSCs and progenitor cells isolated from a transgenic mouse model of CML we recently developed. The analysis, validated by RT-qPCR, revealed that 37 G-protein coupled receptors (GPCRs) are significantly expressed in both normal and leukemic HSCs, along with their associated signaling partners. Similarly, RT-qPCR showed that human CD34+ cells , the counterpart of murine hematopoietic and progenitor cells, express the same GPCRs. Literature suggests that several GPCRs may regulate HSC proliferation and quiescence, although this gene family has received relatively little attention. Our research investigates the role of selected GPCRs identified in HSC and LSC biology, and whether pharmacological targeting of these GPCRs has an effect on LSC quiescence, proliferation and differentiation as well as sensitivity to TKIs. Because of limiting numbers of cells, we used bulk LSC-enriched fractions of bone marrow and spleen cells from transgenic mice and treated these cells ex vivo with GPCR-targeting drugs alone or in combination with TKIs. We assessed the treatment impact on LSC functions using cell viability assays, colony forming unit assays, phenotypic characterization, and cell cycle analysis. Preliminary results revealed certain combinations that increase the sensitivity of LSCs and CD34+ cells to imatinib. Similarly, CFUs assays demonstrate a reduction in the number of colonies upon some combination treatments. This approach provides further understanding to the role of GPCRs in LSC/HSC biology which might be a potential target for CML treatment outcomes.

P122

T-cell engager antibodies with pH-dependant targeting: Enhancing safety in solid cancer immunotherapy

Lucile SAUVAGE[1], Tristan MANGEAT[1,2], Diego BARBA[1], Daouda MOUSTAPHA ABBA MOUSSA[3], Pierre MARTINEAU[1], Bruno ROBERT[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Mabqi

[3] Institute for Regenerative Medicine & Biotherapy (IRMB), Montpellier

Bispecific T cell engagers (TCEs) have emerged as a powerful immunotherapeutic strategy, enabling targeted T cell-mediated lysis of tumor cells through simultaneous binding to tumor-associated antigens (TAAs) and the CD3 receptor on T lymphocytes. Since the approval of Blinatumomab in 2015, the clinical development of TCEs has rapidly expanded for hematological cancer, with 12 antibody approved in the US or Europe.

In solid tumors, TCE development is more challenging due in particular to the expression of TAA in healthy tissues, leading to greater on-target, off-tumor toxicities than in hematologic malignancies. In addition, activating T lymphocytes using bispecific TCEs or chimeric antigen receptor T cells (CAR-T cells) requires careful modulation of their activity. This is essential to reduce immune-related toxicities, such as cytokine release syndrome (CRS).

To address these limitations, my thesis project consists of developing bispecific antibodies with enhanced safety profiles. These antibodies exploit a key metabolic hallmark of solid tumors: the extracellular acidification driven by the Warburg effect. By engineering pH-dependent antibodies, we enable selective high-affinity binding to TAAs, such as EGFR (Epidermal Growth Factor Receptor) or HER2 in the acidic tumor microenvironment (pH 5.8-6.7), while maintaining minimal binding at physiological pH (7.2-7.4), thus limiting off-tumor toxicity.

To achieve these objectives, we developed our TCE candidates in a simple, monovalent diabody format (anti-EGFR × anti-CD3) using a selection of anti-EGFR with either pH-dependent or pH-independent binding, to screen their selective tumor cell killing in vitro. Furthermore, we are implementing an avidity-based targeting approach, optimizing multivalent interactions to selectively cells with high TAA density. This added layer of specificity enhances discrimination between cancerous and healthy cells

In parallel, we anticipate in vivo testing in non-humanized murine models by performing phage display selections to isolate murine CD3-specific antibodies with pH-dependent binding properties. This additional specificity aims to limit T cell activation and therefore reduce the risk of CRS of the best TCE candidates.

Through these different strategies, our ultimate goal is to improve the therapeutic window by balancing effective antitumor activity and improved safety.

P123

Role of Telocytes in the physiopathology of cutaneous Squamous Cell Carcinoma

Julie CLACHET[1], Léa PECHTIMALDJIAN[1], François MOISAN[1], Muriel CARIO[1,2]

[1] BoRdeaux Institute of Oncology

[2] Aquiderm

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. Among these are **telocytes** (**TC**), a recently discovered cell type distinct from fibroblasts. TC undergoes structural and functional changes alongside dermal alterations. Previous studies have described TCs as a disappearing population in parallel with the loss of tissue homeostasis, but reappearing after treatment in conditions such as psoriasis, suggesting that **TCs act as a sensor of tissue homeostasis**. Furthermore, their numbers are reduced in several cancer types, including peritumoral tissues.

While fibroblasts are well-established drivers of cancer progression, the role of telocytes remains largely unexplored. This PhD project aims to investigate TCs as a potential marker of pre-cancerous lesion fate and to elucidate their interactions with cancer cells and the extracellular matrix (ECM) during cSCC progression.

In the first phase, we demonstrated a progressive decrease of telocytes during carcinoma progression using immunohistochemistry (IHC) on cSCC samples at different stages. To further dissect the relation between cancer and TC, we established a protocol for isolating telocyte from fresh skin samples and cocultured them with cSCC cell lines. Unexpectedly, TCs promoted tumor cells growth on both 2D and 3D models, while tumor cells enhanced telocyte proliferation. In addition, tumor cells induced morphological changes in TC within 3D fibrin-based hydrogel models, suggesting possible differentiation. This hypothesis is currently being investigated through RNA and protein analyses, with preliminary results supporting it. Complementary proteomics studies are ongoing to identify novel markers, and contribute to a more comprehensive characterization of this particular cell type.

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

P124

Study of the crosstalk between sensory neurons and tumor cells in colorectal cancer

Nicolas DI GLERIA--PILLARD, Pierre-Francois MERY, Julie PANNEQUIN, Emmanuel BOURINET, Caroline BONNANS

IGF, Univ Montpellier, CNRS, Inserm, Montpellier, France

Colorectal cancer (CRC) is one of the leading causes of cancer-related mortality worldwide, with an increasing incidence, including among young adults. While immunotherapy has revolutionized the treatment of many cancers, only ~15% of CRCs exhibiting microsatellite instability (MSI) respond to it, unlike the more common microsatellite-stable (MSS) tumors, whose tumor microenvironment is highly immunosuppressive. A better understanding of this microenvironment is therefore crucial. Growing evidence suggests that sensory neurons contribute to tumor progression by releasing neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P, which directly modulate immune surveillance. However, their involvement in CRC remains poorly explored. We hypothesize that colorectal tumors at different stages are innervated by sensory neurons that actively remodels the TME by interacting with tumor cells. By using different animal models, we demonstrated a significant innervation of the healthy small intestine and colon by sensory nerve fibers Nav1.8+, but also in the Peyer's patches and in the lamina propria, suggesting an interaction between these neurons and immune cells. We observed that sensory fibers appeared to infiltrate tumors at different stages of the disease progression and that these neurons expressed CGRP. Furthermore, CGRP neurotransmitter concentrations are increased in polyps, strongly suggesting the presence of sensory neurons within the colon tumors themselves. We also developed an in vitro 3-dimensional model to study direct interactions between sensory neurons and tumoroids. This revealed neurite growth toward tumor structures and close contacts between both cell types. The presence of Nav1.8/CGRP-positive neurons within tumors, together with their observed interactions with epithelial cells, suggest a potential role for sensory neurons in tumorigenesis. While further investigations are needed, these preliminary data open the possibility that neuronal pathways and their neuromediators could become relevant therapeutic targets in cancer. Research on the role of CGRP in CRC is still relatively recent, but it suggests that this neuropeptide, which is highly abundant in the intestine, may influence tumor progression, inflammation, and the response to immunotherapy in MSS colorectal cancer.

P125

Src promotes tumor cell invasion by hijacking the translation machinery

Benjamin BONNARD[1], **Anouk CHATEFAU[1]**, Cyril DOURTHE[1], Anne-Aurélie RAYMOND[1,2], Violaine MOREAU[1], Arnaud JABOUILLE[1], Anne BLANGY[3], Yvan MARTINEAU[4], Frédéric SALTEL[1]

[1] Bordeaux Institute of Oncology

[2] Oncoprot Platform, TBM-Core

[3] Montpellier Cell Biology research center, CRBM

[4] Centre de Recherche en Cancérologie de Toulouse (CRCT)

The Src oncogene controls cancer cell invasiveness by promoting invadosome formation and extracellular matrix degradation (ECM).

Invadosomes are enriched in the eukaryotic translation initiation factor 3 (eIF3) complex associated with a local mRNA translation activity mandatory for their maintenance.

Here, we show that Src regulates mRNA translation by controlling the expression of eIF3 subunits. Among them, eIF3h/e/d are essential for invadosome formation and ECM degradation.

We demonstrate that Src controls the canonical mTOR/eIF4E and the non-canonical eIF3d cap-dependent translation initiation pathways. We show that both pathways are necessary for invadosome formation and their ECM degradation function.

Finally, we highlighted a correlation between Src and eIF3h/e/d overexpression, which is associated with poor prognosis in hepatocellular carcinoma (HCC) patients and controls the ECM degradation and invasive properties of HCC cells. These findings identify Src as a major regulator of translation initiation pathways, which leads to invadosome formation, ECM degradation and tumor cell invasion.

P126

Glioblastoma and the gut-brain axis: exploring the role of peripheral serotonin and the enteric nervous system

Maria HAYKAL[1], Sarah LAVIELLE[1,2], Océane MARTIN[1,2]

[1] Institut de Biochimie et Génétique Cellulaires, Bordeaux

[2] Université de Bordeaux

Glioblastoma is the most aggressive primary brain tumor in adults, with a poor prognosis despite the standard Stupp protocol. Increasing evidence highlights the gut-brain axis as a key modulator of brain diseases, with communication occurring through immune, metabolic, and neural pathways. Among these, the neural route via the enteric nervous system (ENS) and peripheral serotonin (5-HT) is of particular interest, as more than 90% of 5-HT is produced by intestinal enterochromaffin cells under ENS control.

Here, we used TPH1 knock-out (TPH1-/-) mice, deficient in peripheral 5-HT, and wild-type controls (TPH1+/+). Mice were orthotopically implanted with mGB2 glioblastoma cells and treated or not with the Stupp protocol (surgery, temozolomide, irradiation). Both colonic and cerebral landscapes were analyzed.*In vitro*, indirect co-cultures were established using normal colonic epithelial cells stimulated or not with metabolites, or their conditioned medium, in combination with GB spheroids, to investigate how gut-derived signals affect tumor behavior.

TPH1-/- mice developed significantly larger tumors compared to wild-type animals. Tumor volume negatively correlated with circulating 5-HT levels, supporting a protective role for peripheral serotonin. Interestingly, glioblastoma implantation induced an increase of serotonin content in colonic enterochromaffin cells, suggesting a feedback regulation along the gut-brain axis. We are currently analyzing the cerebral immune landscape to determine whether this effect involves immunosuppression, as well as investigating ENS alterations in this context.

Our data demonstrate that peripheral serotonin and the ENS contribute to glioblastoma progression and potentially to therapy response. Ongoing investigations aim to decipher the mechanisms underlying this neuro-immune communication. Also, we are currently developing a gut-brain-on-chip model that will provide a unique and controlled platform to dissect these mechanisms, integrating intestinal, neuronal, and tumoral compartments. This approach will allow us to move beyond animal models, refine mechanistic understanding, and ultimately explore novel therapeutic strategies for glioblastoma.

P127

Deletion of MonoCarboxylate Transporter 1 in myeloid cells favours glioblastoma development

Sebastian LILLO[1], Cédric PAPE[1], Marie-Alix DERIEPPE[2], Julie MARTINEAU[1], Doriane BOMONT[1], Maialen ARRIETA[1], Macha NIKOLSKI[1], Océane MARTIN[1], Thomas DAUBON[1]

[1] University Bordeaux, CNRS, IBGC, UMR 5095, Bordeaux, France

[2] Animal Facility, University Bordeaux, Pessac, France

Glioblastoma (GB) is the most aggressive brain tumor, with a median survival of less than 15 months after diagnosis. Despite surgical resection and radio-chemotherapy, patients suffer from a high rate of tumor recurrence explained by an enriched immune environment in myeloid cells possessing pro-tumoral properties. GB cells release large amounts of lactate, responsible for immuno-metabolic modifications of immune cells in other cancers. Altogether, TAM abundancy and lactate concentration may impact tumor development and patient's outcome. However, lactate's specific effects on myeloid cell phenotypes and functions within GB tumor microenvironment is poorly understood. In vivo experiments of mouse models deficient for MonoCarboxylate Transporter 1 (MCT1), a lactate transporter in myeloid cells (Mct1Δmye), show significantly larger tumors compared to WT mice and highlight enriched pro-tumoral TAMs by flow-cytometry in male. Interestingly, histology revealed significantly higher and a tendency towards a higher proportion of pro-tumoral macrophages (IBA1+, ARG1+) in Mct1Δmye mice. In vitro, Bone Marrow-derived macrophages (BMDMs) from WT or Mct1Δmye mice showed no differential response when challenge with sodium-lactate, for phagocytosis or co-cultured with mGB2 for tumor cell invasion. Metabolic analysis between WT and Mct1Δmye BMDMs is currently under investigation. Together, these results question lactate's role in myeloid cells in glioblastoma development.

P128

Single-cell timecourse analysis of an in-vitro model of Chronic Lymphocytic Leukemia

Augustine BLANC-BOEKHOLT[1,2], Malvina MARKU[3], Hugo CHENEL[1,2], Julie BORDENAVE[1,2], Loïc PAULEVÉ[4], Victoria BRUNING[5], Andrei ZINOVYEV[6], Loïc YSEBAERT[3], Laurence CALZONE[5], Vera PANCALDI[1,2]

[1] CRCT, Université de Toulouse, Inserm, CNRS, Toulouse, France

[2] La Ligue Contre le Cancer - Comité de Haute-Garonne

[3] Institut Universitaire du Cancer de Toulouse-Oncopole, Toulouse, France

[4] LaBRI, CNRS, Bordeaux, France

[5] Institut Curie, Paris, France

[6] Evotec, Toulouse, France

Chronic lymphocytic leukemia (CLL) is a malignancy of B lymphocytes characterized by their progressive accumulation within lymph nodes. To better elucidate cellular dynamics in CLL, we investigated interactions between malignant B cells and immune cells using an in vitro model designed to mimic the lymph node microenvironment.

We established an in vitro model consisting of peripheral blood mononuclear cells (PBMCs) to which we added purified neutrophils extracted from the same sample, and profiled samples at five time points (D1, D4, D8, D11, D14) from three untreated CLL patients using CITE-seq, which combines single-cell RNA sequencing with surface protein quantification. Multiple preprocessing pipelines and R-based analytical tools were applied to pre-process the sequencing data, identify cell clusters and annotate cell types. Despite methodological variations, results were highly concordant across workflows (≥91% exact label matching for the single cells; clustering structure measured by ARI ≥0.76). Cell type annotation was performed by integrating automated methods with manual annotation based on RNA, surface protein (ADT), and reference datasets.

We observe the presence of a cluster of cells located between CLL and macrophages in patients 2 and 3. These bridging populations expressed predominantly myeloid transcriptional programs while displaying both lymphoid and myeloid surface markers. Additionally, a cluster of cells located between the T cell and CLL clusters was detected exclusively in patient 3. This intermediate cluster is primarily composed of T cells, predominantly $CD4^+$ cells. Analysis of clusters at each time point revealed that both the CLL-macrophage cluster and the CLL-T cell cluster emerged around day 4 of the culture. The CLL-macrophage cluster persisted throughout the experiment until day 14, whereas the CLL-T cluster remained stable up to day 11 but disappeared by day 14, likely due to CLL cells shifting toward the alternative trajectory. Temporal trajectory inference supported a progressive evolution of malignant B cells toward macrophage-like states. This trajectory inference reveals a linear progression from the CLL cluster directly toward the macrophage cluster. The cellular transition becomes particularly evident at days 8 and 11, where pseudotime highlights a clearer shift in cell states. The analysis of both timepoints and the overall computational trajectory appeared consistent and mutually supportive.

Notably, this observation is consistent with recent evidence that T-bet, classically a master regulator in T cells, can be induced in malignant B cells, where it exerts tumor-suppressive functions [1]. Moreover, CLL cells have been shown to express myeloid programmes [2] and this might explain how CLL patients can present secondary tumours that exhibit myeloid features [3].

Collectively, these results highlight the plastic nature of immune interactions in CLL and suggest that subsets of malignant B cells may acquire myeloid-like features, potentially reflecting microenvironmental influences and transcriptional reprogramming.

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P129

Effect of Calcium-dependent channels' inhibition on Gastric Cancer Stem Cells Tumorigenic Properties

Coralie GENEVOIS[1], Orane LE GALLAIS[1], Anissa ZAAFOUR[1], Valérie CORONAS[2], Bruno CONSTANTIN[2], Christine VARON[1]

[1] BoRdeaux Institute of Oncology

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

Introduction.

Stomach cancer is currently the 5th cause of mortality by cancer in the world. The majority of cases are gastric adenocarcinomas (GC). Diagnosed late most often at advanced stages, the chances of remission are low. This gloomy prognosis is the consequence of the strong aggressiveness of GCs and their resistance to current conventional treatments of chemo and radiotherapy. Recent work by the research team has identified a rare subpopulation of cancer stem cells (CSC) within tumors, responsible for the initiation, progression, chemoresistance and dissemination of GCs. The team showed that the use of a general calcium flux inhibitor, Verapamil, made it possible to sensitize CSCs to current chemotherapy treatments in *in vitro* culture models. Store-operated calcium channels (SOCs) consist of stromal interaction molecules (STIM1/2 proteins), which act as endoplasmic reticulum (ER) Ca2+ sensors, and Orai1/2/3 proteins, which form the structure of calcium release-activated calcium (CRAC) channels in the plasma membrane (PM). The two main Ca2+ influx channels of non-excitable cells are the ORAI and TRPC families of Ca2+ channels. The objective of this project was to study the impact of SOCs inhibition on the tumorigenic properties of gastric CSCs *in vitro*.

Methods.

Subpopulations of epithelial-like and mesenchymal-like CSC from different GC cell lines and patients derived tumors were analyzed by transcriptomic analysis to study the expression of calcium channels genes. To assess the effect of calcium channels inhibition, two strategies were compared. First, inhibitors targeting different categories of calcium channels were tested on GC lines rich in CSCs (MKN45) or poor in CSCs (MKN74) *in vitro* : two pharmacological (called SKF and YM) inhibitors inhibit both ORAI1 and TRPC channels ; one inhibitor (called GSK) target more specifically ORAI1 channel. Second, GC cell lines KO for ORAI1 channel were obtained by CRISPR-Cas9 technologies. Effects of these two inhibition strategies on CSC properties were determined by proliferation assays, 3D cultures as tumorspheres, flow cytometry analysis of stem cell markers and invasion assays.

Results.

Transcriptomic analysis showed that ORAI1 was overexpressed in epithelial-like CSCs and TRPC6 was overexpressed in mesenchymal-like CSCs. Proliferation assays showed a dose dependent effect of SKF inhibitor on both cell lines while only a slight effect was observed with the others inhibitors. Tumorspheres assays showed that preventive treatment of cells with SKF and YM decreased the number of tumorspheres formed attesting a decrease of the CSCs population. Specific ORAI1 inhibition, by GSK inhibitor or by CRISPR-Cas9 technology, had no effect on the tumorspheres initiation. However ORAI1 inhibition seems to have an impact on the invasion capacity of the CSCs. The KO of ORAI1 decreased the size of tumorspheres in presence of chemotherapy meaning that it has an impact on CSC's self-renewal capacity.

Conclusion.

We demonstrate that SOCs inhibiton has an influence on tumorspheres initiation properties, invasion capacity, chemoresistance and self-renewal properties of CSC in GC. Molecular mechanisms of action of SOCs and particularly ORAI1 in invasion and chemoresistance properties of CSC will be analyzed to understand their role in the context of GC.

P130

The Hallmarks of Cancer Metabolism: A Semi-quantitative Approach

Jean-Pierre MAZAT[1], Maxime MAHOUT[2], Sabine PÉRÈS[3], Stephane RANSAC[1]

[1] Institut de Biochimie et Génétique Cellulaires, Bordeaux

[2] UMR CNRS MIVEGEC, Maladies infectieuses et vecteurs, Montpellier

[3] Laboratoire de Biométrie et de Biologie Évolutive, CNRS UMR 5558, Université Claude Bernard Lyon 1

To provide an accessible and simple tool to describe cancer cell metabolism, we developed a reduced metabolic model of central carbon and nitrogen metabolism, M(CM)2, with 75 reactions, 58 internal metabolites, and three compartments. This model takes into account the actual stoichiometry of the reactions, including the stoichiometric role of cofactors and the irreversibility of some reactions. Furthermore, to accurately model the oxidative phosphorylation, the proton gradient across the inner mitochondrial membrane is modeled by two pseudo-metabolites: DPH (representing the pH difference, ΔpH) and DPSI (representing the membrane potential, Δψ).

We then use data from the literature to define the metabolism of an "average cancer cell in culture", particularly the metabolites exchanges with the medium [Jain et al. Science 2012].

Flux Balance Analysis (FBA) with these exchange fluxes as constraints and biomass maximization as the objective function highlights the hallmarks of cancer metabolism in a quantitative way at least on the "average cancer cell in culture". More precisely we show:

- The mechanisms underlying the Warburg effect
- The Glutamine addiction and the reductive glutaminolysis
- The citrate output and the FA synthesis to eliminate the redox load of the cancer cell
- The role of amino acids for the proliferation of cancer cells
- The importance of the one-carbon metabolism with exchanges of serine and glycine with the medium
- The existence of metabolic cycles between mitochondria and cytosol
- Different metabolic phenotypes following mutations in oxidative phosphorylation (mitochondrial diseases)

In all our simulations, it clearly appears that NADH reoxidation is the major challenge for proliferating cells. We identify metabolic cycles involving electron transfers between mitochondrial NADH (NADHm) and cytosolic NADPH (NADPHc), as well as mitochondrial citrate export that promotes fatty acid synthesis, acting as a metabolic safety valve.

To better understand the metabolic rewiring of cancer cells, we express the steady-state metabolic fluxes of the average cancer cell as the sum of a small number of elementary flux modes (EFMs), i.e., minimal metabolic pathways (e.g., aerobic glycolysis, oxidative glycolysis, glutaminolysis, etc.). This decomposition is performed using our software tool, aspefm [Mahout, Carlson & Peres, 2020], which computes, on-demand, a relevant subset of EFMs based on specified properties. This is of major interest as enumerating all possible EFMs is computationally infeasible, even for simplified models like ours. We therefore show that the metabolic pathways of the "average cancer cell in culture" can be expressed as a linear combination of a few EFMs with a biological meaning.

This highlights the interest of using a core model, which allows different theoretical and quantitative approaches of the metabolism of cancer cells and more generally of proliferating cells and metabolic diseases.

Posters – Axis 2
Genome Dynamics and Expression

P201

Overcoming challenges to advance genomic research in breast cancer in sub saharian Africa

Mohamad CHKEIR[1], Freddy GNANGNON[2], Gilbert FASSINOU[3], Sylvain LACORRE[4], Maeva CHAUMET[4], Valere Belle MBOU[4], Romulus TAKIN[5], Mahiné IVANGA[6], Sidonie NGUIZI-OGOULA[6], Edgard Brice NGOUNGOU[1], Tchin DARRÉ[7], Alain CHAUNAVEL[4], Karine DURAND[4], Pierre-Marie PREUX[1], Anatole LALEYE[8], Véronique BLANQUET[1], Alexis PARENTÉ[1,2]

[1] Inserm U1094, IRD UMR270, Univ. Limoges, CHU Limoges, EpiMaCT - Epidemiology of Chronic Diseases in Tropical Areas, Institute of Epidemiology and Tropical Neurology, OmegaHealth, Limoges, France

[2] Laboratory of Epidemiology of Chronic and Neurological Diseases, University of Abomey-Calavi, Cotonou, Benin

[3] Lagoon Mother and Child University Hospital, CHU-MEL, Cotonou, Benin

[4] Department of Pathology, Dupuytren University Hospital, Limoges, France

[5] Department of Pathology, Troyes Hospital Center, Troyes Cedex, France

[6] Institut de Cancérologie d'Akanda, Akanda, BP 23902 Gabon

[7] Department of Pathology, University Teaching Hospital of Lomé, Lomé, Togo

[8] Laboratory of Histology, Reproductive Biology, Cytogenetics and Medical Genetics, Faculty of Health Sciences, University of Abomey-Calavi, Cotonou, Benin

The EpiMaCT team focuses on the epidemiology of chronic diseases in tropical regions to improve population health. Sub-Saharan African women often develop breast cancer at a younger age and have higher mortality. Aggressive subtypes, especially triple-negative breast cancer (TNBC), are common. In Benin, Gabon, and Togo, TNBC represents more than 30% of cases, compared to 10% in France. This disparity suggests a genetic contribution. However, African populations remain underrepresented in genomic research.

To address this gap, we launched the first high-throughput NGS study on breast cancer samples in Benin, Gabon, and Togo. FFPE samples are essential resources for NGS research. Initially, we evaluated DNA from FFPE blocks collected in local pathology laboratories. Although extraction was possible, DNA integrity was impaired: qPCR revealed degradation and NGS libraries showed low coverage and high duplication rates, reflecting local infrastructural constraints.

To overcome these limitations, we implemented a new preservation protocol. Biopsies were initially stored in physiological saline at -20 °C (for up to one year), then re-embedded in FFPE via standardized protocols. This cost-effective approach maintained tissue histology and provided DNA of quality comparable to that from frozen biopsies, while also enabling the selection of tumor areas. FFPE-frozen biopsies showed similar qPCR and NGS metrics to frozen biopsies, with only slightly reduced coverage, but far superior to conventional West African FFPE samples.

NGS analysis then allowed us to establish the first mutational catalogue of breast cancer in Benin. The most frequently mutated genes were FANCD2 (96%), TP53 (62%), CDK12, RAD51B, and BRCA2. Intron variants predominated (>50%), followed by missense mutations (~33%). In this catalogue, we identified novel variants which are currently undergoing functional validation.

This adapted strategy not only improves sample preservation in resource-limited settings but also enables large-scale genomic studies. Our results provide a starting point for genomic research in West Africa, contribute to global efforts to understand the overrepresentation of TNBC in African women and lay the groundwork for precision oncology.

P202

Development of RNA therapeutics targeting RBM39 as an alternative to aryl sulfonamides in the context of colorectal cancer

Léa BOUTON[1], Sébastien CAMPAGNE[1], Brune VIALET[1], Viet-Ha PHAN[1], Philippe BARTHÉLÉMY[1], Jeanne LEBLOND-CHAIN[1], Samuel AMINTAS[2], Isabelle MORANVILLIER[2], Isabelle LAMRISSI[2]

[1] Régulations Naturelles et Artificielles, Bordeaux

[2] BoRdeaux Institute of Oncology

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 many 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. The structure of the indisulam degradation complex revealed that the degrader achieves its specificity at the interface between RBM39 and DCAF15 (Bussière et al., Nat. Chem. Biol. 2020), explaining how a single point mutation in RBM39 triggers indisulam resistance. It also explained the poor clinical efficiency of aryl sulfonamides. Indeed, 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 developed two strategies to decrease the intracellular level of RBM39 and trigger the death of colorectal cancer cells: an Antisense Oligonucleotide (ASO) Splicing Switch to manipulate the autoregulation pathway of RBM39, and a RNA-PROTAC to trigger the degradation of RBM39, independently of DCAF15. We demonstrated that both RNA therapeutics induced a loss of function of RBM39 in poison exon splicing regulation, reduced the amount of RBM39 in CRC cells, and resulted in the loss of their proliferation capacity. Altogether, our data show, for the first time, that it is possible to use RNA therapeutics acting in a DCAF15-independent manner to deplete RBM39 from CRC cells and therefore substitute the use of aryl sulfonamides. This offers novel therapeutic perspectives to fight against cancer.

P203

Ligand Stabilization of DNA Three way Junctions for Targeted Cancer Therapy

Maëlle CAROFF[1], Aline MARNEF[2], Angélique PIPIER[3], Gaëlle LEGUBE[2], Anton GRANZHAN[4], David MONCHAUD[3], Sébastien BRITTON[1]

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

[2] Centre de Biologie Intégrative, Toulouse

[3] Institut de Chimie Moléculaire de l'Université de Bourgogne

[4] Institut Curie, Paris

Beyond the canonical B-form double helix, DNA can fold into a variety of non-canonical secondary structures, such as G-quadruplexes. Among these are DNA three-way junctions (TWJ), which adopt a Y-shaped conformation and can form within repetitive DNA sequences (1,2). Small molecules have been designed to stabilize these structures by specifically binding to the TWJ cavity, leading to the induction of toxic DNA double-strand breaks and subsequent cellular cytotoxicity (3,4). These ligands offer significant potential for therapeutic applications by inducing structure-specific DNA damage in cancer cells, presenting a more targeted alternative than broad spectrum agents, such as DNA-alkylating chemicals or radiations (3).

In this study, we aimed at characterizing the cellular effects and the mechanism by which these ligands induce DNA double-strand breaks, and at exploring their potential applications against cancer cells. Through a combination of biochemical, molecular and cellular assays, we identified that some of these ligands can be used to selectively and successfully target cancer cells enriched with secondary DNA structures resulting from repetitive DNA sequence expansion. Moreover, we also found that TWJ ligands can be combined with innovative drugs currently entering in clinical trials to create a synergistic effect which could improve therapeutic outcomes. To conclude, our work identifies TWJ ligands as promising anticancer agents to be used alone or in combination against cancers with specific genomic features.

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P204

How cohesin and transcription cooperate to organize the genome ?

Maximilien NDJAMI MAKANDA, Sophie QUEILLE, Olivier GADAL, Frédéric BECKOUET, Christophe CHAPARD

Centre de Biologie Intégrative de Toulouse

The 3D arrangement of eukaryotic genomes and the dynamics of spatial chromosome organisation are functionally capital for processes such as gene expression, replication and DNA segregation, which are directly involved in many cancers. Cohesin is an essential actor of chromosome folding, by making long-range intra-chromosomal DNA loops, in addition to allowing chromosome segregation in a timely manner. Cohesin also ensures a dynamic regulation of gene expression in mammals by promoting the interaction between distal regulatory elements, such as enhancers, and promoters. It has recently been shown that RNA polymerase II is also able to organize the genome in Saccharomyces cerevisiae by forming DNA loops and promoting contacts between active genes. However, the mechanisms by which transcription regulates genome folding by interacting with cohesin are poorly understood. The hypotheses are that active transcription can act as a barrier to cohesin translocation on the DNA, or that it can regulate its loading. The goal of my project is to dissect the mechanisms by which transcription and the cohesin complex, and their interaction organise of Saccharomyces cerevisiae's genome. This is done by using both in vivo and in vitro approaches.

P205

The oncogenic role of m6A reader IGF2BP2 in Acute Myeloid leukemia

Sarah DUCHAMP[1], Manon DOS SANTOS[1], Valérie LAGARDE[1], Elodie RICHARD[1], Manuel Daniel DIAZ MUNOZ[2], Catherine SAWAI[1]

[1] Bordeaux Research in Translational Oncology

[2] Institut Toulousain des Maladies Infectieuses et Inflammatoires

N6-methyladenosine (m6A), the most abundant epitranscriptomic modification, is a key regulator of gene expression programs that control cell fate and function. m6A is dynamically regulated through deposition, removal, and recognition by "writers" (e.g., METTL3), "erasers" (e.g., ALKBH5, FTO), and "readers" (e.g., YTH and IGF2BP families). Dysregulation of this pathway has been implicated in acute myeloid leukemia (AML), contributing to impaired differentiation, increased self-renewal, and therapy resistance. While the methyltransferase METTL3 has been proposed as a therapeutic target, the role of m6A "readers" remains less understood. Among the readers, IGF2BP2 is markedly overexpressed in AML, and its expression correlates with poor prognosis. However, the downstream targets and functional consequences of IGF2BP2-m6A interactions remain largely unknown. This work aims to establish an IGF2BP2 knockdown model in AML cell lines to investigate its role in leukemic cell survival, identify the target genes underlying its oncogenic effects, and elucidate the mechanisms by which these targets are regulated.

P206

Hypertranscription in the adaptive response to targeted therapies in lung cancer

Eglantine FAGET[1], Lara FERNADEZ MARTINEZ[1], Gilles FAVRE[1,2], Olivier SORDET[1], Agnese CRISTINI[1]

[1] Centre de Recherches en Cancérologie de Toulouse

[2] IUCT Oncopole, Toulouse

Targeted therapies are effective for lung cancer patients harboring oncogenic mutations. However, their efficacy is limited by the acquisition of resistance. This can be due to few tumour cells with no pre-existing mutations, which adapt to treatment and enter a pseudo-dormant "drug-tolerant" state (DTCs for 'drug-tolerant cells') before acquiring resistance mechanisms and re-establishing the tumour. Multiple heterogeneous DTC populations coexist together and to date, which specific DTC population acquire resistance and how it is able to proliferate under treatment remain unclear. Transcription defines cell identity and is necessary for reprogramming and cell cycle progression. A global increase in nascent RNA synthesis, referred to as hypertranscription, has been shown to mediate key cell state transitions during development, such as the switch from quiescence to proliferation. Using lung cancer as a model, we show that targeted therapies induce hypertranscription in a specific DTC subpopulation across different oncogenic contexts. This hypertranscribing subpopulation exhibits a specific regulation of transcription and chromatin structure. Furthermore, a partial decrease of global transcription delays the emergence of resistance. Altogether, our preliminary results suggest that hypertranscription could play a role in the acquisition of resistance to targeted therapies, with potential implications for therapeutic strategies aimed at preventing relapse.

P207

Relationship between the E3 ubiquitin ligase TRIP12 and the Mediator of DNA damage checkpoint MDC1: its impact on DNA Damage Response

Alban RICARD, Claire VARGAS, Damien VARRY, Pierre CORDELIER, Nicolas BÉRY, Jérôme TORRISANI

Centre de Recherches en Cancérologie de Toulouse

Pancreatic cancer (PDAC for pancreatic ductal adenocarcinoma) is a cancer with a poor prognosis and predicted to be the second cause of death by cancer in 2040. The vast majority of patients are treated by DNA damage-inducing chemotherapies combined in some cases with radiotherapy. These treatments generate DNA double-strand breaks (DSBs). DSBs detection and repair greatly contribute to the resistance of cancer cells against treatments. The Thyroid hormone Receptor Interacting Protein 12 (TRIP12) is an E3 ubiquitin ligase implicated in the plasticity of pancreatic acinar cells as well as the initiation and metastatic potential of PDAC. TRIP12 is overexpressed in preneoplastic lesions of PDAC and tightly associated with chromatin through its N-terminal intrinsically disordered region (IDR). A Bio-ID proximity assay performed in the team revealed that MDC1 is one of the most abundant proteins at the vicinity of TRIP12. The Mediator of DNA damage Checkpoint 1 (MDC1) plays a crucial role in the early DNA Damage Response (DDR) by accumulating at DSBs sites through its BRCT (BRCA C-terminus) domain, which recognizes phosphorylated serine 139 (S139) of γH2AX, one of the earliest mark of DNA damage. Our aim is to characterize the mechanistic relationship between TRIP12 and MDC1 as well as its impact on DDR and PDAC-derived cell sensitivity to DSB inducing agents. I demonstrated that a TRIP12 overexpression inhibits the accumulation of MDC1 at DSBs. Using Bioluminescence Resonance Energy Transfer 2 (BRET2), Proximity Ligation Assay (PLA), co-immunoprecipitation, Surface Plasmon Resonance (SPR) and peptide pull-down assays, we showed that this inhibition results from a direct interaction between the phosphorylated serine 77 (S77) of TRIP12 (within its IDR) and the BRCT domain of MDC1. Notably, the same MDC1 residues that recognize phosphorylated S139 of γH2AX also interact with phosphorylated S77 of TRIP12, with a comparable binding affinity. Ultimately, γH2AX kinetics analyses showed that the inhibition of MDC1 accumulation at DSBs by TRIP12 reduces DNA repair efficiency, leading to genome instability. These findings highlight a potential competition between S77 phosphorylated TRIP12 and γH2AX for MDC1 binding, thereby affecting DNA repair efficiency. To further confirm this mechanism, we are developing an intracellular antibody to specifically inhibit the TRIP12/MDC1 interaction and to assess its impact in living cells.

Therefore, the TRIP12 overexpression measured in pancreatic preneoplastic lesions could contribute in genome instability and PDAC initiation. In contrast, in advanced PDAC, a high expression of TRIP12 could participate in PDAC cell sensitivity to DSB inducing therapies. Phosphorylated S77 of TRIP12 could thus serve as a predictive marker of pancreatic cancer drug sensitivity.

P208

The pro-tumoral functions of the epigenetic enzyme SUV4-20H2 in Prostate Cancer

Hiba DAHER[1,2,3], Michelle-Gracia MALANDOU-TSAMBA[1], Marine TAUZIET[1,2], Pierre DAMBRUN[1], Raphael ROMERO[1], Véronique BALDIN[1,2,4], Raghida ABOU MERHI[3], Eric JULIEN[1,2,4]

[1] Institut de recherche en cancérologie-Montpellier (IRCM)

[2] Université de Montpellier

[3] Faculty of Sciences, Genomics and Surveillance Biotherapy (GSBT) Laboratory, R. Hariri Campus, Lebanese University, Hadath 1003, Lebanon.

[4] CNRS

Despite significant progress in prostate cancer detection and treatment, this disease remains a major cause of cancer-related mortality. While localized disease can often be managed successfully, metastatic and therapy-resistant stages remain largely incurable, even after intensive multimodal regimens. Thus, understanding the molecular mechanisms driving tumor progression and therapeutic resistance is critical to develop more effective strategies. In this regard, we identified the lysine methyltransferase SUV4-20H2-responsible for catalyzing the trimethylation of histone H4 at lysine 20 (H4K20me3)-as a key driver of prostate cancer growth and resistance. Using xenografted mouse models, we demonstrate that genetic loss of SUV4-20H2 markedly impairs prostate tumor growth, in contrast to its paralog SUV4-20H1 also involved in H4K20 methylation. To investigate the underlying mechanisms, we performed transcriptomic profiling of SUV4-20H2-deficient tumors. These analyses revealed that SUV4-20H2 controls the expression of several gene networks linked to cancer progression, including metabolism, Wnt signaling, and inflammatory pathways. Notably, its loss preferentially reduced the expression of genes involved in Glutamine metabolism while having limited impact on glycolytic programs. Consistent with this, functional assays revealed that SUV4-20H2-deficient prostate cancer cells are particularly sensitive to Glutamine deprivation than to Glucose withdrawal, highlighting a metabolic shift in the source of energy sustaining tumor growth upon loss of SUV4-20H2. Importantly, the transcriptional role of SUV4-20H2 seems uncoupled from its enzymatic activity. Altogether, these results establish SUV4-20H2 as a central regulator of prostate cancer progression through a newly identified non-catalytic transcriptional role in orchestrating the balance between Glucose and Glutamine metabolism in tumor cells. By linking epigenetic regulation to metabolic plasticity, SUV4-20H2 might represent a previously unrecognized vulnerability in prostate cancer biology.

P209

Structural organization of self-assembled lamina: a network analysis framework

Hadiya Abdul HAMEED[1,2], Ata Utku ÖZKAN[2], Aykut ERBAŞ[2]

[1] Centre de Recherches en Cancerologie de Toulouse

[2] UNAM-National Nanotechnology Research Center and Institute of Materials Science and Nanotechnology, Bilkent University, Ankara 06800, Turkey

The nuclear lamina, composed of fibrous lamin proteins, forms a two-dimensional protein meshwork that preserves the structural integrity, elasticity, and morphology of the nucleus. These lamins-A/C-type and B-type-assemble into dynamic, mechanically responsive networks with distinct structural properties (Nmezi et. al, 2019, *PNAS*). 3D structured illumination microscopy reveals that B-type lamins form a loosely packed outer meshwork, characterized by larger meshwork faces compared to the more uniform, denser A/C-type network (Shimi et. al, 2015, *MBoC*).

Lamina meshwork assembly can be disrupted in several diseases, including laminopathies, premature aging syndromes, and cancer. For instance, in Progeria, mutated lamin A proteins (progerin) assemble into closely packed nematic phases at the nuclear periphery, in contrast to the relatively more randomly oriented isotropic microdomains in healthy cells (Dahl et. al, 2006, *PNAS*). Progerin also indirectly alters the B-type lamin meshwork, triggering further enlargement of mesh faces (Kim et. al, 2024, *PNAS*). Other laminopathic mutations can lead to the formation of lamin aggregates or thicker paracrystalline lamin filaments. These changes not only disrupt the organization of the lamina but also affect the mechanical properties and morphology of the nucleus. Despite these biological insights, the polymer physical mechanisms that govern lamin network formation, phase behavior, and mechanical response are largely unexplored. Image analysis and reconstruction studies provide valuable insights into structural features-such as edge lengths, the number of edges per face, and node distribution-of the lamina. Nevertheless, they cannot resolve the molecular-level interaction cascades or the stoichiometric conditions that govern its assembly and overall structural organization.

In this study, we present a coarse-grained molecular dynamics (MD) model to model the self-assembly of the lamina meshwork in healthy and diseased nuclei. Lamin fibers are modeled as semiflexible polymers confined within an elastic nuclear shell (Hameed et. al, 2025, *arxiv*). Keeping the lamin concentration high enough to observe network configurations (Hameed et. al, 2025, *JCP*), we systematically manipulate inter-lamin interactions, lamin-shell associations, and fiber lengths. We analyze the resulting meshwork configurations using a network reconstruction-based framework, representing lamin network segments in a node-edge representation. This network-based analysis enables quantitative characterization of lamina topology and allows direct correlation of network features with the underlying physical interactions.

Our results also suggest that the ratio of lamin-lamin to lamin-nuclear shell interaction leads to a plethora of meshwork architectures with varying face size, shape, and edge characteristics. We also propose that diseased nuclei, with nematic phases (Hameed et. al, 2025, *JCP*), might require the formation of additional, longer and/or thicker fibers, via weaker lamin-nuclear shell interactions, and introducing interacting domains besides the canonical sticky lamin ends. Overall, our computational results provide insights into how altered lamin interactions could affect the mesoscale architecture of the lamina in disease. Overall, our integrative MD and network analysis framework provides a quantitative platform to study the principles of lamina assembly, the structural consequences of laminopathies, and the relationship between network topology and nuclear mechanical function. These findings may inform future therapeutic strategies aimed at modulating lamin interactions to mitigate disease hallmarks. Future studies will extend this model to incorporate spatial chromatin organization, alongside lamin-chromatin interactions, to better capture disease-associated hallmarks and nuclear shape anomalies.

Posters – Axis 3
Therapeutic Innovation & Biomarkers

P301

Development of New Enzyme-Responsive Systems for Selective Bioorthogonal Tumor Labeling and Drug Delivery approaches

Israa AL JAMAL[1], Margaux BOSSUAT[1], Florian RAES[2], Isabelle OPALINSKI[1], Sébastien PAPOT[1]

[1] Université de Poitiers, UMR-CNRS 7285, Institut de Chimie des Milieux et des Matériaux de Poitiers (IC2MP), 86022, Poitiers, France. Equipe Labellisée Ligue Contre le Cancer

[2] University of Grenoble Alpes, INSERM, LRB, Grenoble, France

Cancer is a leading cause of death worldwide, presenting major public health challenges despite advances in detection and treatment. Conventional therapies, including surgery, chemotherapy, radiation and immunotherapy are commonly associated with substantial side effects. Therefore, the design of innovative strategies for cell membrane engineering is of prime interest to develop novel cell-based therapies in the fields of cancer, aiming to enhance treatment specificity and effectiveness.

In this context, metabolic glycoengineering, a technique that allows the incorporation of diverse bioorthogonal chemical groups onto cell-surface glycans, has become a powerful method for modifying the outer membrane of living cells. Glycoengineered cell membranes can subsequently be remodeled by introducing different molecular systems using click chemistry. This approach opening up numerous potential biomedical applications, particularly cell-based therapies.

To date, there are no established strategies for the selective *in vivo* introduction of bioorthogonal functions specifically on the surface of a particular cell population (e.g., cancer cells) or within targeted tissues (e.g., tumors). To address this limitation, we have developed a novel chemical approach based on stimuli-responsive molecular systems. These systems are programmed to covalently introduce a bioorthogonal function into targeted tissues following highly selective enzymatic activation. The molecular assemblies are composed of three key elements: an enzyme-responsive trigger, a fluorinated self-immolative linker, and a bioorthogonal function. This design enables the selective tagging of tissues overexpressing the target enzyme (e.g. solid tumors) with the desired bioorthogonal moiety.

We will present both *in vitro* and *in vivo* results demonstrating the validity of this technology in pre-targeting strategies. Our study paves the way for new drug delivery tools based on bioorthogonal chemistry, enabling the selective release of therapeutic agents specifically within malignant tissues.

P302

Function of sortilin in early-stage non-small cell lung cancer

Andreea ANDREEV[1,2,3], Hussein AKIL[1,2,3], Thomas NAVES[1,2,3], François VINCENT[1,2,3], Amandine ROVINI[1,2,3], Fabrice LALLOUE[1,2,3]

[1] Institut OmegaHealth, Limoges

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

[3] Université de Limoges

Context:

Non-small cell lung cancer (NSCLC) is the most represented type of lung cancer, mainly diagnosed at advanced stages which reduces overall survival. However, ~20% of patients relapse even after early-stage diagnosis, toward more aggressive disease[1]. Predicting relapse in this subgroup of patients would represent a major advance, enabling tailored therapy and improved patient care. Identifying molecular signatures with prognostic value for recurrence could also foster the development of new treatments. Our team previously identified a tumor-suppressor function of sortilin, a protein member of the VPS10-domain sorting receptor family, in late-stage and metastatic lung adenocarcinoma[2]. As sortilin expression is higher in NSCLC early-stage compared to late-stage, its downregulation in early stages may drive recurrence. However, the mechanism involved in sortilin downregulation is still unknown. Moreover, studies on other cancer models suggest that sortilin is linked to the expression and maintenance of cancer stem cells (CSCs) traits[3,4]. Thus, variation in sortilin expression in CSCs could be associated with poor prognosis and increased relapse risk.
In this work, we aim at investigating the role of sortilin in CSCs from early- versus late-stage NSCLC and define a sortilin-dependent molecular profile with potential prognostic value. This study will allow characterizing a sortilin-dependent molecular profile that could possess a prognostic value to prevent recurrence.

Methods:

Five different lung adenocarcinoma cell lines representing early and late stages were grown in basal media (BM) or defined media (DM) to enrich the CSC population. One late-stage cell line (H1975) was engineered with a Tet-On system (H1975 tet-on), allowing inducible over-expression of sortilin. Sortilin levels and CSC markers were analyzed by Western Blot and Flow Cytometry.

Results:

Results showed that sortilin is more expressed in early versus late-stage cells. Interestingly, in DM, sortilin expression increased in late-stage cells but tended to decrease in early-stage cells. Moreover, over-expression of sortilin in H1975 tet-on cells grown in DM led to a decrease in glycosylated CD133, a known CSC marker, when compared to levels of glycosylated CD133 in wilt-type H975.

Conclusion:

Sortilin expression and CSC emergence appear to be interconnected. Sortilin decreases levels of glycosylated CD133, though further investigation is required to determine if sortilin function is more of a cause or a consequence to the CSC phenotype. Its expression profile is stage-dependent in NCSLC cell lines, suggesting a stage-dependent function. Future studies will use loss-of-function models of sortilin in order to analyse consequences on CSCs characteristics. If sortilin functions as a "stemness" inhibitor, it may serve as a prognostic marker to predict recurrence in early-stage NSCLC.

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P303

Understanding and Targeting ATF3-Mediated Resistance Mechanisms to Improve Therapeutic Outcomes in Upper Tract Urothelial Carcinoma

Margaux AYEUL[1], Margot MACHU[2], Lucas RIBOULLON[1], Alexandra FAUVRE[3], Baptiste LEGRAND[4], Pascal VERDIE[4], Anthony MARTIN[4], Muriel AMBLARD[4], Nadine HOUÉDÉ[1,5], Céline GONGORA[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Institut Immunologie et Nouveaux Concepts en Immunothérapie (INCIT), Nantes

[3] Mass General Cancer Center

[4] Institut des Biomolécules Max Mousseron, Montpellier

[5] CHU de Nîmes

Urothelial carcinoma can be classified into two main types: bladder cancer, which represents about 90% of cases, and upper tract urothelial carcinoma (UTUC). Although UTUC have a distinct molecular signature from bladder cancers, they are managed similarly, mainly by administering platinum-based chemotherapies combined with gemcitabine for metastatic cancers, Cisplatin-Gemcitabine (Cisgem) or Carboplatin-Gemcitabine (CarboGem). However, UTUC is a particularly aggressive tumor with poor response rates to conventional chemotherapy, leading to relapse in more than 50% of patients. The addition of anti PD-1/PD-L1 immunotherapies has shown partial benefit, but their efficacy remains limited, due to the "cold" immune microenvironment of UTUC, characterized by low infiltration of immune cells. A recent study from C. Gongora's team (A. Fauvre et al., Clin Transl Med., 2024) identified a resistance mechanism involving the transcription factor ATF3 (Activating transcription factor 3), which is strongly induced by chemotherapy. Under physiological conditions, ATF3 regulates the expression of multiple genes and contributes to glucose and lipid metabolism, immune regulation, and cell cycle control. In the UTUC cell line UM-UC-14, ATF3 inhibits the production of interferon beta (IFN-β), a cytokine essential for the activation and infiltration of the immune system, thus preventing the establishment of an effective immune response against the tumor. In this context, this project aims to better understand the role of ATF3 in treatment resistance and to develop new targeted therapeutic strategies against this factor.

We investigate the induction mechanisms of ATF3 in vitro. Using Western blotting, RT-qPCR, and specific inhibitor, we demonstrated that the p38 MAPK pathway contributes to CisGem-mediated ATF3 expression. In parallel, we analyzed RNA-seq data from UM-UC-14 cells (untreated vs. CisGem) previously generated in our team. Our objective was to identify the transcription factors that can induce ATF3 after treatment, as well as to discover targets downstream of ATF3 after its induction. For this, we screened all up- and downregulated transcription factors to determine whether they contained a binding site within the ATF3 promoter sequence. This analysis identified two relevant transcription factors, ERG1 and cJUN, both validated by ChIP-seq data in HCT116 cell lines. We then examined up- and downregulated genes carrying an ATF3 binding motif in their promoter regions, which highlighted two potential candidates: MAGI1 and TTC28.

Finally, we developed peptide inhibitors targeting ATF3, in collaboration with M. Amblard's team at IBMM. For this, we use the first ATF3 inhibitor described in the literature, the ATF3W_eag peptide (M.Yo et al., ACS chem biol. 2024). We confirmed its interaction with ATF3 in cells using CETSA (Cellular Thermal Shift Assay) and we restored the production of IFNb by cancer cells. From this prototype peptide, we are now designing stapled analogs to enhance its stability and efficacy. The next step will be to evaluate whether these inhibitors can promote immune cell infiltration in our heterotypic spheroid models, with the ultimate goal of improving treatment response.

This interdisciplinary project could significantly improve the management of UTUC by proposing new therapeutic strategies. By specifically targeting ATF3, it aims to overcome tumor resistance to existing treatments and optimize the efficacy of immunotherapies.

P304

Development of new class of DNA mimics to circumvent resistance to TOP1 inhibitors

Reem BANNOUT[1], Margaux AYEUL[1], Aurelie GARCIN[1], Bertrand BIGNOLAIS[1], Valentina CORVAGLIA[2], Madeleine BOSSAERT[3], Céline GONGORA[1], Marie-Jeanne Pillaire PILLAIRE[3], Sébastien BRITTON[3], Ivan HUC[2], Vincent PARISSI[4], Philippe POURQUIER[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Center for Integrated Protein Science, Department of Pharmacy, Ludwig-Maximilians- Universität, Munich, Germany

[3] Institut de Pharmacologie et Biologie Structurale, IPBS, Université de Toulouse, CNRS, UPS, Toulouse, France

[4] Université de Bordeaux, CNRS, Laboratoire de Microbiologie Fondamentale et Pathogénicité (UMR 5234), Bordeaux, France

Resistance and toxicity remain major obstacles to the efficacy of Topoisomerase I (Top1) inhibitors in cancer therapy, emphasizing the urgent need for agents with distinct mechanisms of action. Top1 plays a pivotal role in resolving DNA supercoiling during replication and transcription. Top1 inhibitors approved in the clinic belong to the camptothecin (CPT) family. Despite their potent antitumor activity, the efficacy of CPT derivatives is limited by dose-dependent toxicities and the development of resistant tumors harboring Top1 mutations or enhanced DNA repair. In the search for alternative strategies to counteract this resistance, DNA mimicry represents an innovative strategy to perturb DNA-Top1 interactions. Based on this concept, in collaboration with the team of Dr. Ivan Huc we developed a novel class of oligoamide-based polymers composed of repetitive dimeric units of 8-amino-2-quinolinecarboxylic acid (Q) and 8-aminomethyl-2-quinolinecarboxylic acid (mQ). In solution, these compounds fold into a helical structure that mimic the features and the charge distribution of B-DNA fragments, with tunable conformations dependent on dimer composition and side-chain chemistry. We found that these DNA mimics inhibit in a relative selective manner and in a length-dependent manner the catalytic activities of Top1. Here, we present the in-depth characterization of the molecular mechanism by which these mimics inhibit Top1 in vitro and in cellulo. Our results show that, in contrast to CPT derivatives which act as poisons by stabilizing Top1-DNA cleavage complexes (Top1cc) and preventing religation, DNA mimics bind to purified Top1 and inhibit both steps (cleavage and religation) of the Top1 reaction in vitro, suggesting a dual inhibitory activity. This was reinforced by the fact that coincubation of (mQQ4)8 with CPT resulted in additive inhibition of Top1-mediated relaxation of supercoiled DNA. Using the Immuno Complex of Enzyme (ICE) assay allowing the direct quantification of Top1cc in cells, we found that, unlike CPT, the (mQQ4)8 DNA mimic did not induce the stabilization of Top1cc in both HCT116 and LoVo colon cancer models. On the contrary, pre-treatment of cells with (mQQ4)8 led to a decrease in CPT-induced Top1cc formation, suggesting a mechanism of Top1 inhibition that differs from CPT derivatives. In accordance with this hypothesis, we found that co-treatment of HCT116 cells with SN38 and the (mQQ4)8 DNA mimic showed synergistic growth inhibition as determined by the Sulforhodamine B assay. Interestingly, we also found that SN38-resistant HCT116 cells harboring Top1 mutations and/or overexpressing drug efflux pumps, were equally sensitive to (mQQ4)8 treatment, further strengthening our hypothesis. Additionally, we demonstrated that Top1 contributes, at least in part, to DNA mimics-induced cytotoxicity as Top1-deficient ovarian (OVCAR4), breast (MCF7) or colon (HCT116) cancer cell lines showed resistance to the (mQQ4)8 DNA mimic as compared to their wild-type counterparts. DNA mimics-induced cytotoxicity was accompanied with late apoptosis as measured by the annexin V/7AAG markers, but was not associated with a significant increase of H2AX phosphorylation, indicating that cell death occurs independently of DNA breakage by a mechanism that remains to be elucidated. Collectively, these findings establish DNA mimics as a novel class of Top1 inhibitors with a dual mechanism of action that could be used as an alternative to counteract resistance to CPT derivative used in the clinic. Future work is dedicated to the identification of structural determinants of activity to optimize DNA mimics potency towards Top1 and to the vectorization of these heavily charged molecules to optimize their delivery to cancer cells.

P305

Identifying new mediators of liver carcinogenesis using proteomic profiling and functional CRISPRa/i screening

Daniel BARROSO ALVES

BoRdeaux Institute of onCology - Inserm U1312

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and the fourth leading cause of cancer-related mortality worldwide. In Europe, most cases arise in the context of alcoholic and/or metabolic cirrhosis, through a multistep process that progresses from low- and high-grade dysplastic nodules to early and advanced HCC. A critical diagnostic challenge remains the assessment of cirrhotic macronodules (7-20 mm), where current imaging and histological approaches often fail to distinguish benign from malignant lesions. This uncertainty directly impacts clinical management and eligibility for liver transplantation, so much so that only 20% of patients are eligible for first treatment. Yet, no validated biomarkers are known to predict malignant transformation, highlighting an urgent unmet need.

The project aims to identify and functionally validate a proteomic signature of malignant transformation in cirrhotic nodules, and with the ultimate goal of establishing clinically translatable biomarkers for early HCC diagnosis by pioneering an integrated strategy that bridges clinical proteomics and functional genomics.

To this end, we assembled a unique cohort of early lesions from cirrhotic explants from patients with alcoholic/metabolic cirrhosis obtained from the CRB-K biobank at Bordeaux University Hospital. These samples, rigorously characterized by our expert pathologists at CHU de Bordeaux, span the full sequence of hepatocarcinogenesis and provide paired non-tumoral controls, reducing inter-individual variability. Using laser microdissection coupled with state-of-the-art LC-MS/MS, we are generating quantitative proteomic profiles to identify differential signatures distinguishing benign from malignant nodules.

In parallel, we developed a robust functional screening strategy based on HepaRG cells, a non-tumorigenic hepatocyte model optimized for 3D growth assays as a readout of malignant transformation. First, CRISPRa/i systems were successfully integrated and validated, demonstrating no interference with baseline growth parameters. Pilot studies confirmed that CRISPRa-mediated activation of MYC and EGFR, or CRISPRi-mediated repression of PTEN and RB1, all known as critical mediators of hepatocarcinogenesis, accurately induce malignant phenotypes in vitro. Our data validate the system as a robust functional assay and establishes proof-of-concept for large-scale functional screening of candidate proteins identified in the proteomic signature.

In the next phase, targeted CRISPRa/i libraries will interrogate 50-100 deregulated proteins predicted to drive hepatocarcinogenesis identified by proteomic profiling.

Functional hits will be prioritized based on their interactions and role in key signaling pathways, strong enrichment in malignant nodules, and clinical detectability in tissue. To ensure translational impact, validation will be performed by in vitro experiments on independent patient cohorts, including a set of well-charactarized and validated samples with the ultimate goal of establishing reliable biomarkers that can be implemented in clinical surveillance protocols.

By combining high-resolution proteomics with functional CRISPR-based screening, this project aims to provide an unprecedented strategy to uncover the molecular determinants of hepatocarcinogenesis. The expected outcome is the identification of a small set of clinically actionable biomarkers enabling accurate and minimally invasive diagnosis of malignant transformation in cirrhotic nodules.

P306

Dual regulation of immune checkpoints by Furin and PCSK7: A novel strategy to boost T cell based-cancer therapy

Marta BORNEZ[1], Chloé PORCHERON[1], Alexia FRANÇOIS[1], John CREEMERS[2], Nabil SEIDAH[3], Serge EVRARD[4], Simon PERENOT[4], Géraldine SIEGFRIED[1], Abdel-Majid KHATIB[1]

[1] Bordeaux Research in Translational Oncology

[2] KU Leuven, Belgium

[3] IRCM, Montreal, Canada

[4] Institut Bergonié, Bordeaux

T cell-based immunotherapies have revolutionized cancer treatment but are often limited by T-cell dysfunction and high expression of immune checkpoint proteins (ICPs). We previously identified a critical role for the proprotein convertase Furin in regulating ICP expression and T-cell infiltration in established tumors. Here, we uncover a novel role for proprotein convertase subtilisin/kexin type 7 (PCSK7) in modulating ICP expression and T-cell cytotoxic function, acting in concert with Furin. Furin and PCSK7 are the predominant convertases expressed in T cells and positively correlate with ICPs including LAG3, CTLA4, PD1, and TIGIT. Genetic deletion of PCSK7 or Furin in T cells reduced surface ICP expression and decreased the proportion of T cells co-expressing multiple ICPs. PCSK7-deficient mice exhibited enhanced CD8+ T-cell antitumor activity and markedly reduced tumor growth. Notably, repression of Furin and PCSK7 potentiated the antitumor efficacy of chemotherapy and immunotherapy in vivo. In vitro analyses using organoids, PBMCs, and isolated T cells further confirmed the importance of Furin and PCSK7 in regulating T-cell function and tumor progression. Collectively, these findings indicate that targeting PCSK7 and/or Furin modulates ICP expression and T-cell activity, providing a promising strategy to enhance cancer therapy, alone or in combination with existing treatments.

P307

Mechanisms of radiation-induced cell death in patient lymphocytes

Laura BOURILLON[1,2,3], Chloé BUCHALET[1,2,3], Nicolas MIR[1,2,3], Tiphany GOUVEIA[1,2,3], Barbara MOHA[1,2,3], Marion LARROQUE[1,2,3], Virginie LAFONT[1,2,3], Alain MANGE[1,2,3], Céline BOURGIER[1,2,3], David AZRIA[1,2,3], Muriel BRENGUES[1,2,3]

[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 >20% 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 healthy samples 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. 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. All together these results showed a correlation between radiation-resistance and lymphocytes activation and the possible involvement of survivin in the radiation-resistance lymphocyte apoptosis. These data will need to be further validated on a larger cohort of patients.

To further investigate, we developed the PROBA clinical trial, coordinated by ICM, which will include three cohorts: healthy donors, breast cancer patients, and patients with inflammatory bowel disease. The study aims to compare intrinsic radiosensitivity, lymphocyte differentiation, activation, functionality, and apoptotic rates across these groups.

The data from this project will allow us to understand why lymphocytes from different patients react differently to ionizing radiation and thus explain the variations in RILA values (highs and lows). In the longer term, these results will help understand the link between the resistance of lymphocytes to radiation-induced apoptosis and the development of breast fibrosis in these patients.

P308

Optimization of combinations including hormone therapy, chemotherapy and radiotherapy in oligo-metastatic prostate cancers

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

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Institut du Cancer de Montpellier

[3] CHU de Nîmes

Prostate cancer is one of the most common malignant tumors in men. Around 25% of men with prostate cancer will develop a metastatic form. Despite ongoing clinical trials, there is currently no standard treatment. The aim of this project is to optimize therapeutic combinations to improve patient survival and quality of life, while seeking to identify biomarkers involved in responses to the different treatments. To this end, we are currently evaluating the potential benefits of sequential administration compared with concomitant administration of chemotherapy, stereotaxic radiotherapy and hormonal therapy in oligometastatic forms of prostate cancers.

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. 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. In addition, in vivo experiments revealed a slightly improved survival rate in mice receiving the sequential treatment compared with those given the concomitant regimen.

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

ATP5F1C, a metabolic vulnerability in Sézary Syndrome

Carel CHERFAN[1], Anne PHAM-LEDARD[1,2], Maxime DESLANDES[1], Jean-Philippe MERLIO[1,3], Martina PROCHAZKOVA-CARLOTTI[1], Marie BEYLOT-BARRY[1,2], Valérie LE MORVAN[1], Laurence BRESSON-BEPOLDIN[1], Nasir ABBASI[1], Edith CHEVRET[1], Audrey GROS[1,3]

[1] BRIC (BoRdeaux Institute of onCology), UMR1312, INSERM, Univ. Bordeaux, team 5, F-33000, Bordeaux, France

[2] Dermatology Department, CHU Bordeaux, F-33000 Bordeaux, France

[3] Tumor Bank and Tumor Biology Laboratory, CHU Bordeaux, F-33000 Bordeaux, France

Cutaneous T-cell lymphomas (CTCLs) represent the most common form of primary cutaneous lymphomas (PCLs). Among CTCLs entities, SS represents a rare subtype (~2%) and is characterized by the proliferation of a malignant clone of TCD4+ lymphocytes with circulating and tissue-homing properties, allowing their localization in the blood, skin and lymph nodes. Although certain targeted immunotherapies have improved its prognosis, SS remains a very complex disease due to its inter- and intra-heterogeneity that limits both the specificity of identified biomarkers, as well as the development of effective curative treatments (PMID: 36226409 and 30525758). Hence, a deeper understanding of the molecular events that initiate or drive disease progression may enable the development of innovative therapeutic strategies.

Numerous transcriptomic studies have been conducted to identify differentially expressed genes and pathways, and decipher tumor-specific signatures that distinguish tumor cells from their healthy and non-malignant inflammatory counterparts. Interestingly, while single-cell RNA sequencing confirmed SS heterogeneity, it showed that oxidative phosphorylation (OXPHOS) is a commonly upregulated pathway, suggesting a potential shared feature across SS patients (PMID: 35421230). Moreover, scRNA-seq analysis identified potential markers exclusively expressed in tumor TCD4+ lymphocytes, including the mitochondrial subunit ATP5F1C, thereby supporting the enhanced OXPHOS phenotype (PMID: 31010835). Such disease-specific expression highly suggests that ATP5F1C may be considered as a potential diagnostic marker and an interesting candidate for targeted therapy. This subunit is an integral component of the mitochondrial electron transport chain's (ETC) complex V (also known as ATP synthase), which plays an essential role in OXPHOS and cellular ATP synthesis in the mitochondria.

Considering previous published studies that have proven the overexpression of this subunit in SS, and given its involvement in several pathologies (PMID: 25938092 and 39814280), ATP5F1C represents an interesting candidate for further investigation. The main objective of our study is to evaluate the role of ATP5F1C in tumorigenic properties of Sézary cells. Our experiments revealed indeed an exclusive protein expression of ATP5F1C in Sézary cells isolated from patient samples (n=6), compared to TCD4+ cells from healthy donors (n=5). Additionally, Sézary cell lines that were previously established in our laboratory (PMID: 33106625) also showed high ATP5F1C protein expression (n=9). This tumor-specific expression prompted us to investigate the functional role of ATP5F1C. Pharmacological inhibition of the respiratory complex V, hosting the subunit of interest, resulted in a cytostatic effect on tumor cells, highlighting its contribution to tumor cell proliferation. Based on these findings, our next step will be to specifically target this subunit using shRNA-mediated knockdown. The functional consequences of its inhibition, whether pharmacological or genetic, will be assessed through comprehensive analyses of mitochondrial energy metabolism, cellular viability, and the migratory and invasive properties of tumor cells in vitro and in vivo. These findings are expected to provide us with novel insights into the metabolic mitochondrial dependencies of Sézary cells and potentially pave the way for the development of innovative targeted metabolic therapies in SS.

P310

Metabolic adaptations of glioblastoma cells during tumor relapse

Axell DAVOUST[1], Claire LARRIEU[1], Antonio Christian PAGANO ZOTTOLA[2], Doriane BOMONT[1], Yanis ZIREM[3], Isabelle FOURNIER[3], Michel SALZET[3], Dieter Henrik HEILAND[4], Thomas DAUBON[1]

[1] Institut de Biochimie et Génétique Cellulaires, Bordeaux

[2] BoRdeaux Institute of Oncology

[3] PRISM, INSERM, Université de Lille

[4] Friedrich-Alexander University (FAU) Erlangen-Nürnberg, Germany

Background: Glioblastoma (GB) is the most common primary tumour in the adult brain. Despite surgical excision of the tumour followed by radiotherapy and chemotherapy, patients' prognoses remain unfavourable, with a high relapse rate and an overall survival of 15 months. Tumour recurrence takes its source in the infiltrative nature of some GB cells that escaped resection, among which were revealed GB stem-like cells (GSCs). Extending the lactate shuttle model of astrocyte-neuron metabolic coupling proposed by Pellerin et al. (Dev Neurosci., 1998), recent work has uncovered a metabolic symbiosis within GB: cells from the core of the tumour and invasive populations exchange lactate to support growth and invasion (Guyon J. et al., EMBO Mol. Med., 2022). Resection, while pivotal, disrupts this spatial and metabolic equilibrium established between cells within the tumour core and the invasive population, potentially driving metabolic reprogramming in the residual invasive cells that seed recurrence.

Methods: We hypothesized that tumour resection, through the disturbance of the intratumoral metabolic organization, induces a metabolic reprogramming of the remaining GB invasive cells. An *in vitro* model of resection was engineered through the chronic treatment/removal of lactate. The link between post-resection metabolic adaptation and tumour regrowth was further explored *in vivo* through novel resection models in mice harbouring intracranial GB. An inducible knockdown system was employed to study a protein of interest: MCT1. Patient-derived GB cells P3 were transduced with pLV-based IPTG-inducible shRNA vectors targeting MCT1.

Results: Spatial transcriptomics correlated with Mass Spec Imaging was performed to determine global metabolic adaptations in post-resection GB. *In vitro* results showed behavioural modulations in GB cells P3 deprived of lactate, tending towards a reprise of proliferation and a reduction of the invasion, thus correlating with tumour recurrence in patients after surgery. Though different GB cell lines exhibit heterogeneous behaviours, we observed consistent modulations of proteins linked to the lactate metabolism, such as the LDHs, CD147/Basigin, and MCT1. MCT1 is a lactate transporter that tends to be upregulated under tumour resection or lactate deprivation. This increase appears alongside its chaperone, CD147, suggesting that MCT1 is correctly positioned and active in the membrane. Knocking down MCT1 provoked a decrease in GB cells P3 proliferation and invasion capacities.

Conclusion: When the core of the GB tumour is resected, the remaining invasive population is starved from its preferred substrate: lactate. This lactate starvation seems to trigger a metabolic switch in GSCs. Using our *in vitro* resection model based on lactate starvation, we identified a concomitant upregulation of the lactate transporter MCT1 and its chaperone Basigin. Knockdown of MCT1 reduced both proliferation and invasion *in vitro*. Building on these results, *in vivo*assays will evaluate the impact of MCT1 knockdown in our mouse model. We are now assessing MCT1 and Basigin inhibitors approved by the EMA (European Medicines Agency) and FDA (Food and Drug Administration) with the aim of identifying candidates for therapeutic repurposing.

P311

Assessment of minimal residual disease using liquid biopsy in patients with EGFR-mutated lung cancer treated with osimertinib

Célia DELAHAYE

Centre de Recherches en Cancérologie de Toulouse

Introduction. Drug tolerance is one of the major mechanisms driving resistance to targeted therapies (TT), but the dynamics and molecular heterogeneity underlying the adaptive drug response in patients is still unknown. Here, we used iterative liquid biopsies from lung cancer patients to characterize minimal residual disease (MRD) and predict treatment outcome using circulating tumor DNA (ctDNA) and circulating tumor cells (CTC).

Methods. LUNG-RESIST (NCT04222335) is a prospective research study enrolling EGFR-mutant adenocarcinoma patients treated by osimertinib frontline. We collected blood samples at baseline, 1 month and every 3 months until progression. The initial EGFR mutation (EGFRm) was monitored in ctDNA by digital PCR. CTC were enriched and isolated based on their size, absence of leucocyte staining and viability, to perform single-cell transcriptomic.

Results. 40 patients were enrolled with a median progression-free survival (mPFS) of 14.5 months (95%CI, 8.5-24.5 months). 70% patients had detectable EGFRm in ctDNA at baseline, and complete clearance at 1 month was associated with a favourable mPFS. Clinical relapse could be anticipated 3 months ahead based on ctDNA increase for 9/20 patients. CTC-like cells were collected at baseline and MRD from respectively 31/40 and 29/40 patients, and at clinical progression for 12/22 patients who relapsed, for a total number of 1,510 cells. The single-cell transcriptomic data on CTC will be presented at the congress, and should provide a better insight into the dynamics of molecular events occurring throughout the adaptive response in patients.

Conclusion. We report the first molecular profiling of ctDNA and CTC during the adaptive response to osimertinib in lung cancer patients. Monitoring the response and predicting the clinical outcome for EGFR-mutant lung cancer patients undergoing TT treatment can be done using ctDNA level as a biomarker. The isolation of CTC-like cells represents a non-invasive approach to study drug tolerance and ultimately develop new combinatory treatments to prevent relapse.

P312

Novel HSD3B1-bioactivated prodrugs against prostate cancer

Bastien DUMAIS[1], Nadège PREUILH[1], Stéphanie BALLEREAU[2], Patrick SEIGNEUR[2], Jon BOUVET[2,3], Carine RACCA[1], Emmanuelle MARTIN-MOTHES[3], Alicia VOGE[3], Margaux BOSSUAT[2,3], Valérie MARAVAL[3], Vania BERNARDES-GÉNISSON[3], Yves GENISSON[2], Sébastien BRITTON[1]

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

[2] Synthèse et physico-chimie de molécules d'intérêt biologique, Toulouse

[3] Laboratoire de Chimie de Coordination, Toulouse

Nature provides a valuable source of bioactive molecules that inspire the development of innovative therapeutics. Recent studies have revealed that natural and bioinspired lipids bearing a terminal alkynylcarbinol motif can act as prodrugs, bioactivated through enantiospecific oxidation by members of the Short-chain Dehydrogenase/Reductase (SDR) superfamily. This process generates intracellular reactive electrophiles that disrupt protein homeostasis, induce endoplasmic reticulum stress, and trigger apoptosis. Importantly, these studies established that novel prodrugs can be selectively activated by distinct SDR enzymes, enabling cell-type-specific targeting. Among human SDRs, HSD3B1 (aka 3β-HSD1 or 3β-Hydroxysteroid dehydrogenase/Δ5-4 isomerase type 1) represents an attractive target since it is a critical SDR enzyme in androgen metabolism catalyzing key steps in testosterone and dihydrotestosterone synthesis. HSD3B1-specific prodrugs could prove particularly useful to treat castration-resistant prostate cancer, since the stabilized N367T variant of HSD3B1 (rs1047303), found in ~30% of the population, has been associated with resistance to Androgen-Deprivation Therapy by enabling prostate cancer cells to maintain self-sufficient production of pro-proliferative androgens.

Here we describe how we discovered and optimized the first prodrugs selectively bioactivated by HSD3B1. Using our lead, we establish how these compounds affect cellular homeostasis to trigger HSD3B1-dependent cell death. We also report a clickable probe that we use to establish the mechanism of action of this novel family of anticancer agents. Finally, we show that these prodrugs can serve as probes to identify HSD3B1-specific inhibitors and/or characterize them in terms of activity and selectivity. This work highlights the potential of SDR-targeted prodrug design not only as a strategy for cancer therapy, but also as a versatile platform to expand the repertoire of enzyme-specific inhibitors for precision medicine.

P313

The synergistic combination Cabozantinib and mTORi inhibits cell proliferation, translation and OXPHOS in clear cell renal cell carcinoma

Laura EANES DA SILVA[1], Candice MARCHIVE[1], Mathilde ROBIN[1], Hélène TUFFOU-HÉRAULT[1], Pauline BARRAJA[1], Véronique GARAMBOIS[1], Nadia VIE[1], Javier FLORIDO-RUIZ[1], Pierre SICARD[2], Alexandre DAVID[1], Diego TOSI[1,3], Céline GONGORA[1]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Physiologie et médecine expérimentale du cœur et des muscles, Montpellier

[3] Institut du Cancer de Montpellier

Clear cell renal cell carcinoma (ccRCC) is the most common subtype of renal cell carcinoma (RCC), representing about 75% of all RCC cases. Histologically, ccRCC is characterized by tumor cells with an abundant, vacuolated cytoplasm, due to the accumulation of lipid droplets containing triglycerides, esterified glycogen and cholesteryl esters. In 60-90% of sporadic ccRCC cases, loss or mutation of the Von Hippel-Lindau (VHL) tumor suppressor gene is detected, leading to the constitutive activation and accumulation of the hypoxia inducible factor alpha (HIFα), which is involved in angiogenesis, tumor growth and survival. Treatment options for advanced renal cell carcinoma include immune checkpoint inhibitors (ICI), tyrosine kinase inhibitors (TKI) mainly targeting VEGFR, and combinations of ICI and TKI. Unfortunately, treatment resistance is common and constitute the main reason for treatment failure.

In my project, I focus on the multi-target tyrosine kinase inhibitor cabozantinib, trying to enhance the clinical efficacy of this drug. Preliminary results of RNA-Seq of cabozantinib-induced ccRCC adaptive responses showed that genes involved in lipid synthesis and regulated via mTOR were induced by the cabozantinib. Based on this data, we combined cabozantinib with an mTOR inhibitor (mTORi) and characterized the combination in vitro and in vivo using different omics tools in order to profile the interaction between these two compounds.

We found that this combination was highly synergistic in vitro and in vivo. Concerning its mechanism of action, the combination inhibits cell proliferation and cellular translation. Moreover, we observed a decrease in glycolysis and a total shutdown of the mitochondrial respiration post-treatment.

In conclusion, we found a new synergistic treatment combination for clear cell renal cell carcinoma, which affects cells proliferation through a perturbation of their metabolic status. We now aim to further investigate these metabolic effects, with a particular focus on oxidative phosphorylation and mitochondrial function.

P314

Targeting the TNBC tumor microenvironment with human anti-Cathepsin-D Antibody-Drug Conjugates

Gaëlle GUILLON[1,2,3], Ilona BERESTJUK[1,2,3], Aude MALLAVIALLE[1,2,3], Valérie LAURENT-MATHA[1,2,3], Thierry CHARDÈS[1,2,3], Emmanuelle LIAUDET-COOPMAN[1,2,3]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Université de Montpellier

[3] INSERM U1194

Triple-negative breast cancers (TNBC), which account for 15% of breast cancer (BC) patients (estrogen receptor negative, progesterone receptor negative, HER2 non-amplified), are mainly treated with chemotherapy and urgently require new targeted therapies. The aspartic protease Cathepsin D (Cath-D), a poor prognostic marker in BC, including TNBC, is overexpressed by BC cells and hypersecreted in the tumor microenvironment. In BC, extracellular Cath-D exhibits pro-tumor activities throught proteolytic cleavage of stromal/tumor components, and/or by acting as a binding protein interaction with cell surface receptors. Moreover, extracellular Cath-D can bind to and be internalized by mannose-6-phosphate/insulin growth factor 2 receptors (M6P/IGF2-R) or other unknown receptors that are expressed at the surface of BC and stromal cells, such as fibroblasts. We previously showed that extracellular Cath-D bound to an anti-Cath-D monoclonal antibody (mAb) is endocytosed by BC cells and also by stromal fibroblasts. In addition, tumor cell-membrane associated Cath-D was observed in 85.7% of 147 TNBC patients. These intrinsic properties of secreted Cath-D, which is reinternalized by a receptor-mediated process, suggest that it may be a promising and innovative therapeutic extracellular target in the tumor microenvironment for antibody-mediated treatment strategies, such as ADCs.

Six payloads comprising different classes of chemotherapy (topoisomerase I and II inhibitors, alkylating agents, tubulin polymerization inhibitors, DNA intercalators) were conjugated to anti-Cath-D human Ab F1M1 using Moradec technology and tested on cell lines representative of these TNBC subtypes. Cell lines from the Basal Like (BL1 and BL2) and Mesenchymal (M and MSL) subtypes exhibited increased sensitivity to these payloads, and in particular to alkylating agents (pyrrolobenzodiazepine (PBD), duocarmycin) and topoisomerase I inhibitors (deruxtecan). In partnership with Lonza, we produced two ADCs bioconjugated to PBD Tesirine and Dxd deruxtecan. These ADCs demonstrated significant cytotoxic effect in 2D and 3D TNBC models, notably on cell lines representing the BL2, MSL and M subtypes, through Caspase 3/7 activation of apoptosis and γH2AX-mediated DNA damage. The therapeutic efficacy of these ADCs was evaluated in nude mice xenografted with the SUM159 TNBC cell line, representative of the MSL subtype. Our results showed a great antitumor effect for both ADC. In addition, analysis of mouse hepatic function and complete blood counts revealed no toxicity of these ADCs. Additional in vivo studies are ongoing with the lead candidate PBD-ADCs cell lines representative of the BL2 and M subtypes, to further assess their therapeutic potential.

P315

Estimating tumour microenvironment cellular states from bulk RNAseq produces biomarkers of clinical outcome across stages

Marcelo HURTADO[1], Elisa GOBBINI[2,3], Laurent GREILLIER[4], Leila KHAJAVI[5], Abdelmounim ESSABBAR[1], Michael KAMMER[1,6], Anne PRADINES[1,7], Anne CASANOVA[1,7], Anna KRUCZYNSKI[8], Sandrine GOUIN[9], Estelle TARANCHON-CLERMONT[1,9], Maria Fernanda SENOSAIN[10,11], Yong ZOU[10,11], Stephen DEPPEN[10,11], Eric GROGAN[10,11], Shillin ZHAO[12], Lionel FALCHERO[13], Jean BERNARD AULIAC[14], Marie BERNARDI[15], Sophie BAYLE[16], Marie MARCQ[17], Julian PINSOLLE[18], Stéphane HOMINAL[19], Olivier BYLICKI[20], Sabine VIEILLOT[21], Fabrice BARLESI[22], Frédérique PENAULT-LLORCA[23], Gilles FAVRE[1], Fabien MALDONADO[10], Francisco CRUZALEGUI[8], Olivier DELFOUR[8], Jenny VALLADEAU-GUILEMOND[2], Julien MAZIÈRES[1,9], Vera PANCALDI[1]

[1] Univ Toulouse, CNRS, INSERM, CRCT, Toulouse, France

[2] Centre de Recherche en Cancérologie de Lyon, Centre Léon Bérard, Université de Lyon, Université Claude Bernard Lyon 1, PLASCAN, INSERM 1052, CNRS 5286, Lyon, France

[3] Oncology Department, Institut Curie, Paris, France

[4] Aix-Marseille University, Marseille, France; Department of Multidisciplinary Oncology and Therapeutic Innovations, APHM, Hôpital Nord, Marseille, France; Department of Multidisciplinary Oncology and Therapeutic Innovations, Hôpital Nord, Marseille, France

[5] Bioinformatics Department, Evotec, Toulouse, France

[6] Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States

[7] Laboratory Medicine, Oncopole Claudius Regaud, Toulouse, France

[8] Institut de Recherche Pierre Fabre, Toulouse, France

[9] Pulmonology Department, Larrey Hospital, University Hospital of Toulouse, Toulouse, France

[10] Division of Allergy, Pulmonary, and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States

[11] Cancer Early Detection and Prevention Initiative, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, United States

[12] Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, United States

[13] Service de pneumologie, Centre Hospitalier de Villefranche de Rouergue, Villefranche, France

[14] Service de pneumologie, CHI Créteil, Créteil, France

[15] CH aix en provence, service pneumologie

[16] CHU St étienne ; service pneumologie

[17] CH Vendée la roche sur Yon, service pneumologie

[18] CH Chamberry, service pneumologie

[19] CH annecy genennois, service pneumologie

[20] Service de Pneumologie, Hôpital d'instruction des armées Sainte-Anne, Toulon, France

[21] Centre Catalan Oncologie, service oncologie

[22] Institut Gustave Roussy - Paris

[23] Centre Jean Perrin - Clermont-Ferrand

Background: We still lack predictive biomarkers of response for lung cancer, a complex and heterogeneous disease for which there is a need for better predictive biomarkers for personalized therapies. A better understanding of the tumor microenvironment (TME) is needed to improve patient outcomes. Here, we propose a novel computational approach that leverages bulk RNA-seq to infer clinically relevant patient-specific cell groups and states, which are normally detectable only with more costly and complex single-cell assays.

Methods: We developed an integrated computational approach based on cell type deconvolution and transcription factor activity estimation combined with an advanced machine learning framework to extract clinically relevant features from bulk RNAseq data. We analyzed a cohort of 62 primary lung adenocarcinoma (LUAD) samples from IUCT patients across disease stages (Hurtado et al. 2024). As validation, we use an independent RNA-seq cohort of early-stage LUAD with 77 RNAseq and 15 scRNA-seq samples collected at Vanderbilt University (Senosain et al. 2023). To assess the potential for this approach in late stage samples, we applied it to a multicenter French cohort with 130 advanced NSCLC patients treated with immunotherapy (IT) (N=90) or chemotherapy (N=40) in first-line setting (E. Gobbini, GFPC and UNICANCER).

Results: Our results identified cell populations associated with immune response and evasion (Hurtado et al. 2024). In early-stage samples, we observed a dual role of natural killer cells, suggesting their involvement in both immune activation and suppression. This dual behavior was linked to patient survival, highlighting natural killer cells as important players (Figure 1AB). In the late stage cohort we identified cell type groups significantly associated with immunotherapy response (p-value = 0.025, F-statistic = 5.188, effect size = 0.051) which predicted response with better performance than several existing approaches.

Conclusion: Our approach characterizes RNA-seq based TME profiles through immune cell states and interactions, which enhances patient stratification. It identifies immune cell phenotype and interaction biomarkers linked to survival and progression that are validated across independent cohorts.

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P316

Understanding Tumor Response to Propranolol in Angiosarcoma: A Combined Approach of Experimental Biology and Mathematical Modeling

Faiza LAANANI[1,2], Tiphaine DELAUNEY[2,3], Léa PECHTIMALDJIAN[1,2], Christele ETCHEGARAY[2,3], Annabelle COLLIN[2,3], François MOISAN[1,2]

[1] BoRdeaux Institute of Oncology

[2] Université de Bordeaux

[3] Inria Bordeaux Sud-Ouest

Angiosarcoma is a rare and aggressive vascular malignancy of cutaneous and subcutaneous tissues for which therapeutic options remain very limited. Recent clinical observations suggest that propranolol, a nonselective β-adrenergic receptor antagonist successfully used in infantile hemangiomas (IH), may also have therapeutic potential in angiosarcoma. However, patient stratification criteria and optimal dosing remain undefined, highlighting the need for further investigation.

This project explores propranolol's effects on angiosarcoma through a combined approach of biological experimentation and mathematical modeling. While propranolol's mechanisms of action have been partially elucidated in IH, current preclinical models of angiosarcoma are insufficient to capture its effects. To address this gap, we are developing a novel strategy that employs in vitro 3D tumor spheroid assays alongside in vivo mouse models, designed to examine propranolol's sometimes unexpected influence on tumor growth. In addition, we use shB2 cells, in which the β2-adrenergic receptor (ADRB2) is silenced, to dissect the specific role of β-adrenergic signaling in tumor biology and connect propranolol's effects to its molecular targets.

The biological studies also include wound-healing assays to assess cell migration in 2D, as well as analyses of cell trajectory and adhesion. Complementary proteomic profiling is being performed to identify signaling pathways modulated by propranolol, with particular attention to Integrins, VEGF, and Aquaporin-1 (AQP1), a water channel involved in cell migration and invasion, appears to converge with ADRB2 signaling and may represent a key mediator of the antitumor response to propranolol.

In parallel, a mathematical model is being developed to describe tumor spheroid dynamics under treatment, with the aim of clarifying underlying mechanisms and identifying predictive factors of therapeutic response.

Altogether, this research advances understanding of propranolol's effects on angiosarcoma and offers perspectives for developing personalized treatment approaches for this rare malignancy. Beyond angiosarcoma, it contributes to a broader effort to define the role of beta-blockers in vascular tumors, potentially expanding their applications in oncology.

P317

Integrating Lymphocyte Responses and Cellular Senescence in Late Radiation-Induced Side Effects.

Marion LARROQUE[1,2], Alain MANGE[1,3], Julien FAGET[1,4], Stanislas DU MANOIR[1,4], Florence BOISSIERE[1,2], Tiphany GOUVEIA[1,2], Laura BOURILLON[1,2], David AZRIA[1,2], Muriel BRENGUES[1,2]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Institut du Cancer de Montpellier

[3] Université de Montpellier

[4] Institut National de la Santé Et de la Recherche Médicale

Radiation therapy (RT) is a cornerstone of cancer treatment, with 50-60% of patients receiving RT after a primary diagnosis. However, 5-10% of these patients develop severe late toxicities that can significantly impair long-term quality of life. Anticipating which patients are at risk would enable personalized therapeutic strategies to reduce permanent side effects.

The Radiation-Induced Lymphocyte Apoptosis (RILA), has shown that patients with higher levels of radiation-induced apoptosis in T-lymphocytes are less likely to develop late toxicities such as fibrosis. In contrast, low RILA values reflect radioresistant lymphocytes and correlate with an increased risk of chronic inflammation and radiation-induced tissue damage.

To further explore the biological mechanisms underlying these outcomes, we focused on the role of lymphocytes and cellular senescence in radiation-induced fibrosis. An 18-color flow cytometry panel was designed to characterize lymphocyte subsets, their differentiation, and their activation status (CD25, PD-1, ICOS) in patients with or without late radiation effects. Senescence, triggered by irreversible DNA damage and oxidative stress, contributes to a proinflammatory and pro-fibrotic microenvironment. To assess this, β-galactosidase activity was measured in patient PBMCs, and expression of p21 was evaluated in breast tissue biopsies.

Finally, transcriptomic profiling of 40 patients was performed to identify cellular signatures with the objective to complement and validate the flow cytometry findings. Together, these approaches aim to uncover biomarkers predictive of late radiation-induced toxicity and to improve patient stratification for personalized RT.

P318

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

Marion LENAIN, Virginie LAFONT, Cécile DEJOU

Institut de Recherche en Cancérologie de Montpellier

Human 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 the biological functions of other immune cells, which are necessary for the initiation and establishment of an effective anti-tumor immune response. Unlike 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. This supports why γδ T cells are considered as highly attractive therapeutic targets for anti-tumor immunotherapies. Currently, many clinical trials are ongoing based on various strategies such as the use of bispecific antibodies targeting both tumor cells and γδ T cells, CAR γδ T cells, γδ T cells-activating molecules. Here, we propose a new innovative strategy of cell therapies based on the ability of γδ T cells to express low affinity receptor of IgG Fc portion (FcγRIII or CD16) and to be armed with monoclonal antibodies (mAbs) targeting specifically tumor cells. Indeed, several studies, including our own, have shown that γδ T cells can express CD16 and similar to NK cells, CD16+ γδ T cells are able to perform antibody-dependent cellular cytotoxicity (ADCC). 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 on γδ T cells differs from donor to donor and also with differentiation status. Second, we have shown that γδ T cells have cytotoxic activity against cancer cells in 2D culture models. We are currently working on the development of 3D models of different ovarian cancer lineages. Our preliminary results in 3D models showed that: 1- IL-2 and IL-15 increase the infiltration of γδ T cells of into spheres, and 2- the activation of γδ T cells by simultaneous TCR and CD16 recruitment has an additive effect on their cytotoxic activity against tumor cells. These findings are very interesting and require further investigation.

P319

Targeting Furin-TGF-β1-COX-2 axis represses malignancy and enhances chemosensitivity in KRAS- and BRAF-mutant colorectal cancer

Yiyang LIU[1], Géraldine SIEGFRIED[1], John CREEMERS[2], Abdel-Majid KHATIB[1]

[1] BoRdeaux Institute of Oncology

[2] KU LEUVEN

Colorectal cancers (CRC) with KRAS or BRAF mutations remain a major therapeutic challenge due to their resistance to standard treatments. In this study, we identify genetic and pharmacological inhibition of Furin in KRAS-mutant (KPN) and BRAF-mutant (BPN) CRC models led to marked reductions in tumor growth, angiogenesis, and survival in preclinical mouse models, accompanied by enhanced infiltration of cytotoxic lymphocytes. Furin inhibition in these cells disrupted the proteolytic activation of IGF-1 receptor and TGF-β1 precursors, leading to impaired signaling and downstream disruption of multiple serine/threonine and tyrosine kinase pathways associated with KRAS and BRAF oncogenic activity. This was accompanied by downregulated expression of COX-2, whereas stable COX-2 overexpression reciprocally increased tumor growth as well as TGF-β1 and Furin expression, establishing a pro-tumorigenic feedback loop. While KPN- and BPN organoids with repressed Furin are more sensitizes to 5-FU, oxaliplatin, and irinotecan, the expression of Furin was found positively correlated with KRAS, BRAF, TGF-β1, and COX-2 in CRC patients. These findings revealed, targetable Furin-dependent signaling axis in KRAS- and BRAF-mutant CRC and support the translational potential of Furin inhibition as a personalized therapeutic strategy to enhance therapy responsiveness in patients.

P320

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

Stefan NICOLESCU[1], Alice MATHEUX[1], Mihaly LEIWOLF[1], Marina GRIMALDI[1], Abdel BOULAHTOUF[1], Laura TALLEVAST[1], Julia TOUCHEBOEUF[1], Fanny LEENHARDT[1], Litaty MBATCHI[1,2], Céline GONGORA[1], Philippe POURQUIER[1], Alexandre EVRARD[1,2]

[1] IRCM, Univ Montpellier, ICM, INSERM, Montpellier, France

[2] CHU de Nîmes

The difficulty in treating malignant metastatic melanoma resides in the resistance to therapies and the risk of recurrence. Understanding the mechanisms by which tumors adapt to treatment is crucial, as they directly influence therapeutic efficacy. Our immunohistochemical analyses revealed, for the first time, significant and heterogeneous expression of the nuclear receptor PXR (Pregnane X Receptor) in patients' melanoma samples. In addition, drug screening experiments on cell models overexpressing PXR showed that PXR can be activated by BRAF inhibitors (BRAFi) that are currently used in the clinic. PXR is known to regulate the expression of genes involved in drug metabolism and drug transport. Thus, PXR may alter the sensitivity of cancer cells to kinase inhibitors and affect the therapy efficacy. Using BRAF-V600E-mutated human melanoma cell lines, we showed that stable overexpression of PXR induces a sensitization to treatments combining BRAFi and MEK inhibitors (MEKi). RNA sequencing analysis reveals that this overexpression contributes to the phenotype switching of the melanoma cells, which could modulate the tumor response to the BRAFi/MEKi combination. The aim of my project is to leverage PXR as a predictive biomarker of therapeutic response to targeted therapies, contributing to the optimization of the treatments used for melanoma.

P321

New proteomic signature in circulating extracellular vesicles from tumor-draining and peripheral veins of patients with lung adenocarcinoma

Jérémy TRICARD[1], Stéphanie DURAND[1], **Amandine ROVINI[1]**, Amy GATEAU[1], Luc NÉGRONI[2], Alain CHAUNAVEL[3], Anaelle CHERMAT[3], Marie-Odile JAUBERTEAU[1], Massimo CONTI[4], Fabrice LALLOUÉ[1]

[1] Institut OmegaHealth, Limoges

[2] Institut de génétique, biologie moléculaire et cellulaire, Illkirch-Graffenstaden

[3] CHU de Limoges

[4] Université Laval

The identification of noninvasive prognostic biomarkers for monitoring relapse in patients with locally advanced lung cancer remains a primary objective. Tumor-draining vein (TDV) plasma samples are known to be enriched in cancer biomarkers compared to peripheral vein (PV) samples. In this study, we investigated both proteomic profile from tumor and non-tumor tissues and from extracellular vesicles (EVs) purified from TDV and PV plasma samples in patients undergoing surgery for lung adenocarcinoma. Twenty patients operated for a lung adenocarcinoma were enrolled and their EVs from TDV and PV plasma samples were characterized for size distribution and concentration using nanoparticles tracking analysis. Proteomic profiling of both tissue and EVs was performed using mass spectrometry (nanoLC-MS/MS) analysis.

EVs from TDV plasma were significantly smaller and more concentrated than those from PV. Proteomic analysis revealed that 9 of the 10 most upregulated proteins in TDV-derived EVs compared to PV-derived EVs were linked to lung cancer diagnosis and prognosis. Notably, SRPRB was the only protein upregulated in both tumor tissues and TDV-derived EVs.

Altogether our data showed that this subset of proteins carried by EVs from TDV plasma, may represent promising circulating biomarkers for early-stage lung adenocarcinoma prognosis.

P322

Chalcones: a potential scaffold for the design of multi-targeted anticancer drugs?

François-Xavier TOUBLET, Aurélie LAURENT, Aurélie LÉVÊQUE, Aline PINON, Bertrand LIAGRE, Christelle POUGET

Laboratoire des Agroressources, Biomolécules et Chimie pour l'Innovation en Santé, Limoges

LABC*i*S team has long been engaged in the development of innovative therapeutic agents, with a primary focus on two highly prevalent cancers: prostate cancer and colorectal cancer.
Natural products have always been considered to be invaluable sources of inspiration for drug design. Thus, chalcones are polyphenolic compounds belonging to the vast family of flavonoids, widely distributed in the plant kingdom, fruits and vegetables. Chalcones are open-chain molecules in which two aromatic rings (A and B) are joined by a three-carbon α,β-unsaturated carbonyl system. They received significant attention due to their wide range of biological activities, especially anti-cancer properties [1]. The in vitro antiproliferative activity against cancer cell lines has been mostly reported and is associated with interfering with the activity of several mechanisms and targets such as aromatase, VEGF, JAK/STAT signaling pathways, tubulin, topoisomerase-II [2,3].
Structure-activity relationship studies have highlighted the importance of a trimethoxyphenyl ring for the anticancer activity of chalcones, particularly in the inhibition of tubulin polymerization [4]. Consequently, part of our previous and ongoing research focuses on the synthesis of original trimethoxylated chalcones through pharmacomodulation of the B aromatic ring. The biological activities of these compounds are evaluated in vitro against colorectal and prostate cancer cell lines [5].
In parallel, additional targets are being explored. Pharmacomodifications of isoliquiritigenin (ISL), a natural chalcone with a strong antiproliferative effect, are being developed to specifically target mitochondria and thereby mitigate chemoresistance [6,7].
Furthermore, it is well established that chemotherapeutic agents designed to act on single targets are generally insufficient to effectively treat multigenic diseases such as cancer. Polychemotherapy therefore remains a preferred strategy, although it is frequently associated with adverse effects, largely due to the lack of selectivity of conventional anticancer agents. In this context, strategies based on multi-target compounds are gaining considerable momentum. These approaches offer several key advantages, including the ability to overcome clonal heterogeneity, reduce the risk of "multidrug resistance" (MDR), decrease drug toxicity, and ultimately minimize side effects [8].
The overarching aim of this research is to design small molecules that integrate the properties of targeted therapies (such as protein kinase inhibitors or anti-EGF agents) with those of chemotherapeutic agents directed against classical targets, including tubulin, mitochondria, and topoisomerases. Furthermore, chalcones, owing to their enone motif, can act as versatile intermediates in the synthesis of a wide variety of heterocyclic compounds, thereby enabling the diversification of chemical libraries. Since many protein kinase inhibitors possess a heterocyclic core, such scaffolds represent particularly promising structures within the framework of this project [9].

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P323

Restoring Iodine Sensitivity in Resistant Thyroid Cancer: Role of PXR and Kinase Inhibitors

Julia TOUCHEBOEUF[1], Stefan NICOLESCU[1], Marina GRIMALDI[1], Abdelhay BOULAHTOUF[1], Florence BOISSIERE-MICHOT[2], Amélie GUDIN-DE-VALLERIN[2], Marie VINCHES[3], Cyril FERSING[3,4], Céline GONGORA[1], Alexandre EVRARD[1,5], Philippe POURQUIER[1], Fanny LEENHARDT[1,3]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Translational Research Unit, ICM, Montpellier

[3] Institut du Cancer de Montpellier

[4] Institut des Biomolécules Max Mousseron, Montpellier

[5] CHU de Nîmes

Thyroid cancer is the most common endocrine malignancy. In metastatic settings, its treatment relies on radioiodine therapy (RAI), the effectiveness of which is limited by resistance mechanisms that are not yet fully understood. One such mechanism involves the downregulation of the NIS (Sodium/Iodide Symporter) transporter, which is essential for intracellular iodine uptake. For patients with RAI-refractory thyroid cancer harboring the BRAF V600E mutation, an alternative treatment option is the combination of dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor). This combination has been shown to partially restore radioiodine sensitivity in a subset of patients with a tumor control in 90% of patients (MERAIODE clinical trial).

Our team recently demonstrated that dabrafenib is a potent agonist of the nuclear receptor PXR (Pregnane X Receptor), a transcription factor that regulates the expression of a wide range of genes involved in xenobiotic metabolism and transport. Moreover, PXR has been shown to modulate the response to various kinase inhibitors.

Our project aims to: (1) assess the expression of PXR and NIS in thyroid cancer patient samples; (2) investigate the influence of PXR on sensitivity to BRAF and MEK inhibitors; and (3) to validate, at the functional level, whether the increased expression of NIS is linked to PXR activation by dabrafenib, suggesting that NIS is a direct transcriptional target of PXR.

Using immunohistochemistry, we analyzed a commercial Tissue Microarray (TMA) comprising 70 thyroid tumor samples and showed that PXR is detected in approximately 90% of the samples. H-score analysis, which accounts for staining intensity and the proportion of positive cells, revealed that PXR is expressed at varying levels: no expression in 13% of samples, low expression (H-score > 0-100) in 59% of samples, moderate expression (H-score > 100-200) in 26%, and high expression (H-score >200) in 3% of samples.

Using the BCPAP cell line (harboring the BRAF V600E mutation) as a first model, we demonstrated that the dabrafenib/trametinib combination acts synergistically. We also showed that stable expression of PXR in this cell line was accompanied by increased NIS protein expression. Interestingly, this overexpression was further enhanced when cells were treated with the PXR agonist dabrafenib (10 nM, 24h). These preliminary results support our hypothesis and need to be confirmed in additional BRAF-mutated thyroid cancer cell lines.

Further investigations are also ongoing to study the impact of stable PXR overexpression on intracellular iodine uptake, which will help establish the functional role of PXR in restoring sensitivity to radioiodine therapy. Additionally, a ChIP-seq analysis is underway to determine whether NIS overexpression is directly regulated by PXR or whether it is mediated through an indirect mechanism.

P324

Aptamer selection for detection of Trombospondin-1 in Glioblastoma

Anielle VILLERONCE[1], Emma ALLARD[1], Jean-Baptiste CHARPENEL[1], Thomas DAUBON[2], Jeanne LEBLOND CHAIN[1], Laurent AZÉMA[1]

[1] Univ. Bordeaux, CNRS, INSERM, ARNA, UMR 5320, U1212, F-33000 Bordeaux, France

[2] Univ. Bordeaux, CNRS, IBGC, UMR 5095, F-33000 Bordeaux, France

AIM. Aptamers are small synthetic oligonucleotides obtained through Systematic Evolution of Ligands by EXponential enrichment (SELEX), a powerful combinatorial method leading to the identification of high affinity ligands for a specific target. SELEX allows the screening of libraries containing up to 10^{15} different candidates, either regular or chemically modified. Molecular Aptamers Beacons (MABs) combine the recognition properties of aptamers with the switching ability of Molecular Beacons, by triggering a fluorescence signal for imaging or drug release in a specific environment, with an improved signal/noise ratio. However, MABs designed from previous aptamers by trial-and-error or strand displacement can be tedious and do not ensure a successful candidate. Developing a SELEX method that can directly provide MABs without major post-SELEX modification is valuable. In this project, we aim to develop a MAB SELEX method to detect Thrombospondin-1 (TSP1), a relevant biomarker of Glioblastoma, for theranostic purposes.

METHODS. We designed a library bearing FRET pair (DABCYL/FAM). First, regular SELEX rounds were achieved using human recombinant TSP-1 immobilized on magnetic beads to reduce the diversity required for the next step. Then, functional selection rounds were realized where monoclonal beads were produced by emulsion PCR and fluorophores grafted through NHS chemistry. The beads were incubated with TSP1; beads exhibiting fluorescence enhancement were sorted by FACS. A negative selection was used to discard sequences switching in absence of TSP-1.

The most promising candidates were deciphered through bioinformatic analysis. Binding and affinity for TSP-1 was assessed by MicroScale Thermophoresis (MST), BioLayer Interferometry (BLI) and Fluorescence using human recombinant TSP-1. Live cell analysis was performed with P3 glioblastoma stem-like cells.

RESULTS. Four rounds of selection were conducted followed by four rounds of functional selection. After sequencing of all SELEX round, 18 candidates were identified and synthesized in DNA chemistry and conjugated to FRET pair to assess their molecular beacon properties. Seven candidates (A1; A10; A14; A15; A16; A17; A18) exhibited significant affinity for TSP-1 by MST, and some were confirmed with BLI (A1; A16; A17; A18). Furthermore, fluorescent labeled DNA candidates (A10; A14; A15) allowed to detect TSP-1 in P3 glioblastoma stem-like cells. Some candidates are still undergoing evaluation by BLI and Live cells analysis. Further investigations will focus on the switching properties of the selected candidates using Fluorescence.

Posters – Axis 4
Cancers : enjeux individuels et collectifs

P401

Prise en charge des tumeurs de vessie non infiltrant le muscle dans un département français (Hérault)

Brigitte TRETARRE[1,2], Stéphanie TROUCHE-SABATIER[1], Anne-Sophie FOUCAN[1], Grégoire POINAS[3], Xavier REBILLARD[3], David AZRIA[4], François IBORRA[1,5]

[1] Registre des Tumeurs de l'Hérault

[2] Centre d'épidémiologie et de recherche en santé des populations

[3] Département d'urologie, Clinique Beau Soleil, Montpellier, France

[4] Institut national de la santé et de la recherche médicale U 1194, institut du cancer, université Montpellier, France

[5] Département d'urologie, centre hospitalier universitaire Lapeyronie, Montpellier, France

Objectifs

En raison de la pénurie mondiale de BCG depuis 2012, cette étude vise à analyser la prise en charge des patients atteints d'une tumeur de vessie non infiltrant le muscle (TVNIM) dans un département français (l'Hérault) et à évaluer le respect des recommandations actuelles du CCAFU (Comité de Cancérologie de l'Association Française d'urologie).

Méthodes

Nous avons utilisé les données de RHESOU (registre français d'onco-urologie) comprenant les cas de TVNIM diagnostiqués entre 2017 et 2022. Les patients ont été classés en quatre groupes de risque : faible (primo-diagnostic, pTa, bas grade, < 3 cm, pas de CIS), intermédiaire (sans critères de faible risque ou de risque élevé), élevé (pT1 et/ou haut grade/G3 et/ou CIS) et très élevé (pT1G3+CIS, pT1G3 multifocal, pT1G3 > 3 cm, pT1G3 + envahissement lympho-vasculaire, pT1G3 de l'urètre prostatique, variants histologiques). Les patients dont le risque était indéterminé ont été exclus. Nous avons analysé les réunions de consultation pluridisciplinaire (RCP), les re-résections transurétrales de la vessie (re-RTUV) et les primo-traitements.

Résultats

Parmi les 2 096 patients atteints de TVNIM (1 755 hommes, 341 femmes) : 537 présentaient un risque faible, 451 un risque intermédiaire, 873 un risque élevé et 235 un risque très élevé. Une RCP a été réalisée pour 47,2% des patients à risque intermédiaire, 43,1 % pour les patients à risque élevé et 46,8 % pour le très haut risque.

• Risque faible : la cystoscopie seule prédominait (93,9 %), tandis que la chimiothérapie intravésicale précoce (IPOP) était de 0,7 %.

• Risque intermédiaire : seuls 40,6 % ont reçu des instillations intravésicales dont 31.9% de la mitomycine, 7.5% du BCG et 1.2% d'autres agents.

• Risque élevé : une re-RTUV a été réalisée chez 23 %. Le BCG a été utilisé chez 65,4 %, tandis que 27,9 % ont subi une cystoscopie seule.

• Risque très élevé : une re-RTUV a été réalisée chez 55,3 % des patients. Le BCG était le traitement principal (76,2 %), 4,3 % des patients ayant subi une cystectomie.

Conclusion

La prise en charge des TVNIM dans l'Hérault n'était pas toujours conforme aux recommandations du CCAFU, en particulier pour les groupes de faible risque et de risque intermédiaire. Pour ces groupes, la cystoscopie seule était la stratégie prédominante, tandis que l'IPOP était sous-utilisée. Cependant, malgré la pénurie mondiale de BCG, son utilisation a été plus strict dans les groupes à risque élevé et très élevé. Le traitement d'entretien par BCG n'a pas toujours été bien précisé. Ces résultats soulignent la nécessité d'optimiser la prise en charge des TVNIM par une meilleure adhésion aux recommandations du CCAFU.

P402

Améliorer les connaissances et la participation des personnes avec une déficience intellectuelle au dépistage des cancers ? Oui, c'est possible

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

[1] ONCODEFI

[2] Département de Pédagogie spécialisée, Université de Fribourg, Fribourg, Suisse

[3] Association Nous aussi

[4] Association UNAPEI ESAT l'Envol, Castelnau-le-Lez

[5] Registre des tumeurs de l'Hérault, Montpellier

[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] Institut Desbrest d'Epidémiologie et de Santé Publique UMR 1302 INSERM, Université Montpellier, Montpellier

Contexte : Les personnes qui ont une déficience intellectuelle (PDI) développent autant de cancers que les personnes dans la population générale, mais les diagnostics sont tardifs. Ces personnes participent peu aux dépistages des cancers. Pourtant, les cancers ciblés par les dépistages organisés : du sein du colon-rectum, sont ceux qui surviennent le plus fréquemment chez les adultes DI ; et les lésions précancéreuses du col utérin sont en augmentation. Le dépistage est fondamental pour ces personnes chez qui les symptômes sont souvent atypiques et les diagnostics difficiles. Les rares études conduites pour améliorer leur participation aux dépistages du cancer ne fournissent pas d'information sur la compréhension, la mémorisation, et l'intention de mise en pratique du message. Elles ne se basent pas sur une théorie d'apprentissage établie.

Objectif : Evaluer les capacités d'apprentissage des PDI sur les connaissances et le comportement à adopter vis-à-vis du dépistage de cancer.

Méthode : Cet essai contrôlé randomisé en grappes à deux groupes parallèles, en ouvert, a été co-construit avec les PDI. Il analyse l'effet d'une sensibilisation au dépistage des cancers menée directement auprès des PDI (petits groupes de 8 à 12 personnes). L'intervention qui est basée sur les théories d'apprentissage de Bandura, de Vygotski et de Piaget, associe des approches : visuelle, auditive, tactile, ludique, par la coopération et donne une place très importante aux discussions. Des outils adaptés en langage Facile à Lire et à Comprendre (normes européennes FALC) ont été coconstruits avec les PDI : livret, jeu, diaporama, ateliers, film. Le groupe testé a reçu une sensibilisation sur le dépistage des cancers, le groupe contrôle une intervention sur l'hygiène bucco-dentaire. Un questionnaire a été complété quatre fois par les participants : quinze jours avant l'intervention (J-15), le jour de l'intervention (J0), 3 mois après (J+3 mois) et 1 an après (J+1an). Il évalue les connaissances sur le dépistage des cancers (score 1) et les intentions de comportement face au dépistage des cancers (score 2).

Résultats : Dans 36 établissements médico-sociaux de l'Hérault, du Gard et de l'Aude, 608 adultes avec DI légère ou moyenne ont été inclus. Dans le groupe testé (n=306) en comparaison du groupe témoin (n=302) la progression des connaissances (score 1) est significative à J0 ($p<0,001$), à trois mois ($p<0,001$) et un an ($p<0,001$) après l'intervention. Les intentions de pratique (score 2), ont progressé à J0 ($p<0,001$), persistent mais de manière non significative 3 mois plus tard, et sont observées comme une tendance à un an ($p=0,068$). La faible attrition (17% sur un an) et la participation active des PDI lors des discussions montrent leur intérêt pour les questions sur le cancer, elles ont remis en question des préjugés sur leurs capacités intellectuelles. Nous n'avons pas observé de réaction anxiogène particulière.

Conclusion : 1) Une intervention sur le dépistage du cancer directement auprès des personnes qui ont une déficience intellectuelle (PDI) est réalisable, et peut faire progresser les connaissances mémorisées jusqu'à une année. 2) Une approche multimodale combinant un appel à la vision, à l'audition, au jeu, à la coopération et faisant une large place aux discussions qui impliquent activement les apprenants est à recommander. 3) La participation des PDI au comité de pilotage a permis d'accroître l'efficacité de l'étude.

Etude soutenue par l'INCa et la caisse primaire d'assurance maladie de l'Hérault.

P403

ACERCA : analyse de 933 questionnaires évaluant les connaissances des éducateurs des personnes avec déficience intellectuelle sur le cancer - Dépistage et repérage des symptômes

Samira BLAIZE[1], Sarah HABIB HADEF[1], Amaëlle Cherone OTANDAULT AVIVIANI[1], Debbie WYATT[2], Elise BASTSELÉ[3], Anne-Sophie FOUCAN[4], Louisa ALLOUCHE[1], Anne STOEBNER-DELBARRE[1,5,6], Brigitte TRETARRE[1,4,7], Daniel SATGE[1,5]

[1] ONCODEFI

[2] Faculty Credit Co-ordinator (APL) and Faculty of Health and Social Care, Chester, UK

[3] Département d'orthopédagogie, Université de Mons, Belgique

[4] Registre des Tumeurs de l'Hérault

[5] L'Institut Desbrest d'Épidémiologie et de Santé Publique

[6] L'Institut du cancer Montpellier ICM

[7] Equipe constitutive du CERPOP, UMR 1295, Université Paul Sabatier, Toulouse

Contexte : Les personnes présentant une déficience intellectuelle (PDI) font autant de cancers que les personnes dans la population générale. Chez ces personnes les cancers sont différents, par leur répartition dans l'organisme, leur mode de révélation, l'âge de survenue souvent plus précoce. Ils sont mal connus et souvent découverts à un stade avancé. Cela accroit les souffrances des patients, réduit leurs chances de guérison, provoque une importante augmentation du travail d'accompagnement pour les aidants professionnels, et complique la prise en charge par les équipes oncologiques. En raison de leurs difficultés à communiquer, notamment pour exprimer la douleur, les PDI, lorsqu'elles vivent en institution, dépendent fortement des aidants professionnels (AP) (éducateurs, aides médico-psychologiques). Ces derniers jouent un rôle essentiel en étant particulièrement bien placés pour repérer les symptômes, les transmettre aux professionnels de santé et encourager le dépistage.

Objectif : Evaluer les connaissances des aidants professionnels qui travaillent en institution sur la détection des cancers (dépistage et repérage des signes précoces) chez les personnes présentant une déficience intellectuelle.

Méthode : Evaluation des connaissances des aidants professionnels (sans formation médicale) sur le cancer par un questionnaire anonyme en 4 pages. Le questionnaire a été remis à des établissements qui prennent en charge les PDI, répartis sur 11 départements (Aude, Bas-Rhin, Côtes d'Armor, Gard, Gironde, Hérault, Île-de-France, Loire, Loire-Atlantique, Lozère, Nord) et sélectionnés par tirage au sort afin d'assurer une représentativité nationale. Le questionnaire (testé auparavant pour une étude au Royaume-Uni par une des co-auteurs DW) recueillait les informations démographiques des participants et leurs réponses aux questions générales sur le cancer, notamment sur le dépistage et le repérage des symptômes. Il suscitait une autoévaluation des aidants sur leurs connaissances, leur formation et leur besoin d'information sur le cancer. Le test statistique de Welch a comparé les résultats (score de connaissances) avec ceux d'un groupe témoin composé de 153 questionnaires distribués à la population générale (PG).

Résultats : 933 questionnaires sur 1628 initialement distribués (taux de réponse exceptionnellement bon à 57.3%) issus de 65 établissements médico-sociaux. Des connaissances inférieures à celle dans la PG ont été constatées pour le dépistage (8.07 AP vs 8.64 PG) (p=0.006) et le repérage des symptômes (11.25 AP vs 12.38 PG) (p=0.042).

Conclusion : L'enquête met en évidence des connaissances inférieures à celle de la population générale sur le dépistage et le repérage des signes précoces de cancer chez les aidants accompagnant les personnes DI. Ceci peut expliquer, au moins en partie, les importants retards de diagnostic de cancer observés chez les PDI. Ces données suggèrent qu'il est nécessaire de renforcer la formation initiale et continue sur le cancer pour les professionnels du secteur médico-social.

Etude soutenue par AG2R- la mondiale, Le Comité National Coordination Action Handicap (CCAH) et par la Caisse Nationale de Solidarité pour l'Autonomie (CNSA).

P404

Comment les expériences de terrain conduisent à la recherche : le parcours d'ONCODEFI

Marc PALPACUER[1], Brigitte TRETARRE[1], Anne STOEBNER[1,2], Louisa ALLOUCHE[1], Samira BLAIZE[1], Anne-Sophie FOUCAN[3], Sarah HABIB HADEF[1], Elodie NEUMANN[1], Elisangela OLIVIER[1], Amaëlle Cherone OTANDAULT AVIVIANI[1], Chris SERRAND[4], Daniel SATGE[1,5]

[1] ONCODEFI

[2] Centre d'épidémiologie et de recherche en santé des populations

[3] Registre des Tumeurs de l'Hérault

[4] Département de biostatistique, épidémiologie clinique, santé publique et innovation méthodologique (BESPIM), CHU Nîmes

[5] L'Institut Desbrest d'Épidémiologie et de Santé Publique

Contexte : Les cancers des personnes qui ont un trouble du développement intellectuel (PDI) sont fréquents, mal connus et différents de ceux observés dans la population générale. A toutes les étapes il est nécessaire d'adapter la prise en charge en s'appuyant sur des données scientifiques. Des travaux menés chez des PDI documentent leur participation au dépistage, la fréquence de leurs cancers, la mortalité induite par leurs cancers et leurs difficultés de soins. D'autres études sont nécessaires pour adapter des actions de terrain, voire initier des interventions encore non menées.

Méthode : Les actions conduites par Oncodéfi depuis 13 ans sont basées sur une analyse de la littérature médicale et scientifique (recherches et méta-analyses). Pour répondre aux problématiques rencontrées lors d'accompagnements, Oncodéfi conduit des études en collaboration avec des équipes de recherche en Hérault, au niveau national et à l'international. Toutes ces études montrent des résultats intéressants et novateurs.

Résultats : Sur la fréquence et la répartition des cancers : L'analyse des 260 cancers recensés a confirmé un profil tumoral particulier chez les PDI (CHAID).

Oncodéfi a établi que malgré une espérance de vie réputée réduite, les cancers sont encore fréquents après 55 ans (ADICAN-collaboration Université de Lund -Suède).

Sur le dépistage : Sur la base des données de l'INSERM, Oncodéfi a montré que les cancers du sein sont aussi fréquents et ceux du côlon probablement un peu plus fréquent chez les PDI qu'en population générale en France alors que la pratique du dépistage est nettement inférieure à celle de la population générale pour les cancers du côlon et du col utérin (INDEP).

Oncodéfi a aussi montré que les connaissances sur le dépistage par les travailleurs sociaux des institutions médicosociales sont inférieures à celles de la population générale (ACERCA-en collaboration avec l'Université de Chester-Royaume Uni et l'Université de Mons-Belgique).

Une autre étude d'Oncodéfi a montré que les PDI comprennent et mémorisent (jusqu'à un an) les notions de dépistage, permettant d'envisager des actions directes auprès de ces personnes (PAM-collaboration Université de Fribourg-Suisse).

Sur les retards au diagnostic : Oncodéfi est, à l'international, la première équipe (2014) qui a documenté les retards diagnostiques pour les cancers du sein, du colon et des mélanomes malins (étude CHAID). Ces retards ont récemment été confirmés en Angleterre (2022) et au Canada (2024) (MELADY, GYNDI, COLODI).

Sur les soins : En l'absence d'études conduites sur un grand nombre de patients, Oncodéfi a repéré et quantifié les difficultés et les éléments facilitateurs de soins (OSO collaboration Epidaure, article soumis).

Sur la prévention : Oncodéfi a mis en évidence une moins bonne connaissance de la prévention des cancers de la part des aidants professionnels en institution (ACERCA).

Discussion : Les résultats de ces recherches confirment la nécessité de faire progresser la participation des PDI au dépistage organisé des cancers car ces tumeurs sont découvertes à un stade avancé et qu'elles sont observées à l'âge du dépistage. Actuellement la participation au dépistage des PDI est trop basse, nécessitant une formation des aidants professionnels et de mettre à profit les capacités sous-estimées des PDI, qui sont de plus sont intéressées par leur santé. Pour les soins, des pistes ont été proposées pour améliorer la prise en charge des patients DI.

Conclusion : Les différentes études menées par Oncodéfi ont été initiées devant les difficultés observées sur le terrain lors des sensibilisations et lors de l'accompagnement de résidants DI touchés par un cancer dans les institutions médico-sociale. Ces études ont permis d'innover en développant des interventions directement auprès des PDI et même en les faisant collaborer aux recherches mises en place. Les résultats montrent que les actions sur le dépistage et sur la prévention doivent être poursuivies et intensifiées.

P405

Survie des cancers du sein par sous type moléculaire dans l'Hérault : étude en population entre 2012 et 2021

Claudine GRAS-AYGON[1], Anne Sophie FOUCAN[1], Brigitte TRETARRE[1,2]

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

Contexte.
Le cancer du sein est le cancer le plus fréquent chez la femme. Il est traditionnellement classé selon le type histologique. Les progrès technologiques ont permis de définir des sous-types moléculaires distincts en fonction du profil moléculaire intrinsèque, qui influencent le choix des traitements. L'objectif de ce travail est d'analyser la survie du cancer du sein féminin selon les sous-types moléculaires dans le département de l'Hérault.

Méthode.
Tous les nouveaux cas de cancers du sein invasifs féminins diagnostiqués entre 2012 et 2021 ont été extraits de la base de données du registre des tumeurs de l'Hérault et inclus dans l'analyse de survie avec une date de point au 30 juin 2024.Les sous types moléculaires ont été regroupés en 4 classes :
1. Luminal A : RE + ; HER2 - ; Ki67 faible (< 20%) et/ou grade I/II et/ou RP élevé
2. Luminal B :
• RE + ; HER2 +
• RE + ; HER2 - ; Ki67 élevé (< 20%) et/ou grade III et/ou RP faible
3. HER2+ : RE - ; RP - ; HER2+
4. TN (triple négatif) : RE- ; RP - ; HER2 –
La survie globale à 5 ans a été estimée à l'aide de la méthode de Kaplan-Meier. Les facteurs (âge, sous type moléculaire, stade au diagnostic, type histologique, score de précarité, période) ont été évalués dans un modèle de régression de Cox. Les rapports de risque (HR) sont présentés avec des intervalles de confiance (IC) à 95 %.

Résultats.
Sur la période 2012-2021, 10 320 femmes ont eu un diagnostic de cancer du sein invasif dans l'Hérault, dont 288 (2.7%) n'ont pu être classées au niveau moléculaire. L'étude de survie porte donc sur 10 032 cas. A 5 ans le nombre de perdues de vue vivant était de 461 (4.5%) et 1 372 décédés (13.6%). Sur le 10 032 patientes, 6 120 (61%) avaient un type moléculaire luminal A, 2 543 (25%) un luminal B, 390 (3.9%) une HER2+ et 976 (9.7%) un type moléculaire triple négatif. Le taux de survie global à 5 ans des cancers du sein était de 84.9 % (IC95% : 84.2 ; 85.7). Le risque de décès était élevé chez les patientes âgées de plus de 75 ans (HR = 4.45, IC95 % : 3.3 ; 5.9) par rapport au moins de 40 ans. Il y a un effet significatif du type moléculaire sur la survie (p<0.001) : La survie à 5 ans chez les patientes ayant une tumeur type luminal A était de 88.7 % (IC95% : 87.9 ; 89.6) et de 70.2 % (IC95% : 67.2 ; 73.3) pour les triples négatifs. Il n'y a pas d'effet période sur la survie. Le risque augmentait avec les stades péjoratifs (stade III vs I HR = 7.1 [IC95 % : 6.0 ;8.4) ; stade IV vs I HR = 19.5 [IC95 % : 16.6 ;22.8). Les résultats étaient identiques lors de l'analyse multivariée.

Conclusion :
Le cancer du sein sous-type luminal A est le plus courant et présente le meilleur pronostic à 5 ans, tandis que le cancer du sein triple négatif (TN) présente une survie à 5 ans significativement plus faible. Cette étude fournit des données réelles permettant d'évaluer la survie du cancer du sein, soulignant l'importance de déterminer le statut des récepteurs pour affiner le pronostic et guider la prise en charge thérapeutique.

Posters – Axis 5
Health Technologies

P501

Targeting tumor associated macrophages (TAM) with vectorized magnetic nanoparticles for anticancer therapies

Chloé BAZILE[1], Julie BORDENAVE[1], Stéphane MORNET[2], Véronique GIGOUX[1], Mary POUPOT[1]

[1] Centre de Recherches en Cancérologie de Toulouse
[2] Institut de Chimie de la Matière Condensée de Bordeaux

Tumor associated macrophages (TAMs) are capable to confer anti-apoptotic, proliferative and enhanced migratory properties to cancer cells, as well as protecting them against immune attacks and therapies. In lung cancer, they represent between 30 to 50% of the tumor mass and they are associated with a bad prognosis of the disease [1,2]. Targeting these pro-tumoral TAMs is a major challenge in anticancer therapies. Different strategies exist, but they are not specific, potentially leading to adverse effects. Our team produced and patented a monoclonal antibody, 6-25, capable to specifically recognize pro-tumoral TAMs displaying an M2 phenotype. We showed that the 6-25 mAb was internalized in these TAMs without inducing any toxicity. The goal of the project is to produce a tool that specifically targets and kills pro-tumoral TAMs.

In cancer treatment, magnetic hyperthermia or magnetomechanical ablation represent an emerging approach with promising therapeutic potential. The first one induce cell death for cell containing magnetic nanoparticles by increasing the temperature through a high frequency alternating magnetic while the second uses mechanical forces under low frequency rotating magnetic field (MF) [3]. We therefore developed a biocompatible and non-toxic magnetic nanoparticle functionalized with the 6-25 mAb (MNP-6-25) as a specific tool to target pro-tumoral TAMs in the tumor.

To test the feasibility of this method, we performed a robust 3D model of co-cultures with the lung cancer cell line (A549) with M2 macrophages (M2M), or M1 macrophages (M1M) as a negative control, these cells doesn't express the target of 6-25. We have studied the basal cytotoxicity, kinetics and specifity of binding of the MNP-6-25 for M2M in these models using flow cytometry and microscopy.

First, we showed that MNP-6-25 are not toxic to neither M2M nor M1M in a concentration up to 64 µg Fe2O3/mL after 72h of incubation, and bind specifically M2M but not M1M, with a maximum at 48h of incubation at 8 µg/mL. We developed 3D models with cancer cell line and M2 macrophages derived from monocytes. The M2 phenotype of macrophages is stable in our model over seven days with an increase of the CD204 M2 marker in the 3D model and M2M promote tumor cell proliferation. Replacing M1M in the 3D model promotes A549 proliferation. This is consistent with the depolarization of M1M towards an M2 phenotype.

Flow cytometry results and microscopy show the specific binding of MNP-6-25 to M2M but not to M1M in 2D and 3D models, also compare to control nanoparticles: non-vectorized nanoparticles or vectorized with the isotipic control of the 6-25 antibody.

To conclude, we showed that MNP-6-25 specifically target M2M inside 2D/3D heterotypic models. Future research will focus on the induction of TAM death in these in vitro models, as well as on the targeting and death of TAMs in an in vivo model, which has already been set up.

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P502

Surface Plasmon Resonance-based detection of EGFRvIII in circulating extracellular vesicles from glioblastoma

Amy GATEAU[1], Hussein AKIL[1], Flavien BEFFARA[2], Shuwen ZENG[2,3], Joelle YOUSSEF[2], Manon GIREAU[4], Corinne CHAMPEAUX[4], Frédéric DUMAS-BOUCHIAT[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 and Nanotechnologies (L2n), CNRS-ERL 7004, Troyes

[4] Institut de Recherche sur les Céramiques, Limoges

Glioblastoma (GBM) is among the most prevalent and aggressive brain tumors, with a poor median survival rate despite advancements in diagnosis. The high heterogeneity of GBM complicates patient follow-up and therapeutic management. To overcome this problem, the identification of circulating biomarkers in liquid biopsies has become essential for GBM patients. A promising direction is based on the analysis of the contents of extracellular vesicles (EVs).

Previous studies revealed that EGFRvIII, a truncated form of the epidermal growth factor receptor present in about 40% of GBMs, can be detected in circulating EVs isolated from patient plasma. As EGFRvIII is constitutively active, it plays a role in tumorigenesis and contributes to chemoresistance. However early detection of EGFRvIII in EVs derived from liquid biopsy is not suitable with clinical routine applications: current isolation methods for EVs from plasma are labor-intensive, and existing technologies lack the sensitivity required to detect biomarkers present at very low concentrations in patients' blood.

Our preliminary technological developments on surface plasmon resonance (SPR) method offer the perspective of real-time detection of EVs from biological fluids with minimal sample preparation. Indeed, our results suggest that this technology is able to detect EGFRvIII in EVs derived from glioblastoma cell lines, demonstrating its potential as a powerful tool for biomarker detection.

This proof of concept opens the way for the development of a highly sensitive approaches with a threshold that, to our knowledge, no other available technique can currently achieve. The perspectives of this study will enable GBM patients to be monitored in order to predict the risk of recurrence following tumor resection.

P503

Isolation and characterization of extracellular vesicles from glioblastoma cancer stem cells using field-flow fractionation techniques

Damien OTT DE NUSSAC[1], Amani BEN AZZOUZ[2], Axel BOUKREDINE[1], Valentin DE CARSALADE DU PONT[2], Amy GATEAU[1], Tiffany DARBAS[1], Léa DECOUX[1], Barbara BESSETTE[1], Fabrice LALLOUE[1], Mireille VERDIER[1], Elise DELUCHE[1], Paul-François GALLET[1], Stéphanie DURAND[1], Serge BATTU[1], Gaëtane LESPES[2], Gaëlle BEGAUD[1]

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

[2] Institut des Sciences Analytiques et de Physico-Chimie pour l'Environnement et les Matériaux, Pau

Glioblastoma (GB) is an aggressive brain tumor characterized by frequent relapse and high resistance to current therapies, mainly due to cancer stem cells (CSCs). CSCs contribute to tumor progression and therapy resistance, in part through the secretion of extracellular vesicles (EVs) that mediate cell communication.

However, isolating CSC-derived EVs remains difficult because of their low abundance and the high heterogeneity of EVs populations. To address this, we developed a strategy using Field-Flow Fractionation (FFF) techniques.

We demonstrated that we could obtain a population enriched in CSCs using Sedimentation Field-Flow Fractionation (SdFFF). Asymmetrical Flow FFF (AF4) enabled size-based separation of EVs, with vesicle size progressively increasing over the elution time. We demonstrated that EVs can resist different osmotic pressures and remain stable in ultrapure water, supporting their use in separation protocols.

Finally, cyclical Electrical FFF (cy-ElFFF) was applied to discriminate EVs subpopulations according to their surface charge, thereby reflecting differences in their membrane composition.

This new instrumental and methodological approach is an important innovation that allows both isolation and characterization of EVs subpopulations, opening the door to novel diagnostic and therapeutic approaches.

P504

A new spatial multiomics and multimodal workflow for deeper biological sample analysis in human pancreatic cancer

Mélanie MOREAU[1], Mehdi BOUBADDI[2], Jade JAUBERT[1], Samuel AMINTAS[2], Stéphane CLAVEROL[1], Caroline TOKARSKI[1,3], Sandrine DABERNAT[2], Nicolas DESBENOIT[1,3]

[1] Bordeaux Proteome, Bordeaux University, Bordeaux, France

[2] U1312 Bordeaux Institute of Oncology, CHU Bordeaux, Bordeaux University, Bordeaux, France

[3] UMR5248 CBMN, Bordeaux University, Bordeaux, France

For cancer research, fresh human samples are precious, often with limited access. Therefore, it's crucial to document the maximum information from a restricted quantity of material. We propose an original spatial multiomics and multimodal workflow combining Matrix-Assisted Laser Desorption Ionization Mass Spectrometry Imaging (MALDI-MSI) and ImmunoHistoChemistry (IHC) to obtain morphological, lipidomic and proteomic data with reduced material requirement.

To develop our workflow, we used tumoral (T) and non-tumoral (NT) pancreatic samples from patients resected for pancreatic adenocarcinoma. First, a single frozen section was analyzed for lipid detection, followed by detection of non-targeted protein, after appropriate washes. The final step in our workflow is conventional IHC.

We use an atmospheric pressure MALDI-Orbitrap, allowing acquisitions with minimum impact on sample morphology. Raw data from MS were visualized and annotated with METASPACE, using public databases for lipids and home-made databases for peptides. To build it, we used proteins identified by conventional LC-MS/MS analysis of a large number of T and NT human pancreas samples and performed in silico digestion of these proteins.

Combining these different approaches, we obtain a huge amount of data. This strategy is also suitable to visualize heterogeneity, which is not possible in a bulk sample. Indeed, different modalities are acquired over the same area allowing the overlay of results and selection of areas of interest.

Our new spatial multiomics and multimodal workflow will enable a better global analysis of tissues for research or diagnostic purposes and opens the possibility of targeted analysis by focusing on well-defined regions such as specific cells or tissue structures.

P505

λ-Carrageenan Oligosaccharide-Based Magnetic Nanoparticles: A Novel Dual MRI Imaging and Hyperthermia/Magneto-Mechanical Therapeutic Agent for Triple-Negative Breast Cancer

Céline KIEU[1], Manon PORTA ZAPATA[2], Hugo GROULT[2], Veronique GIGOUX[1]

[1] Centre de Recherches en Cancérologie de Toulouse

[2] LIttoral ENvironnement et Sociétés

Triple-negative breast cancer (TNBC) is characterized by an aggressive phenotype, with high metastatic potential, altered metabolic regulation, and strong resistance to current therapies, resulting in poor overall survival and underscoring the urgent matters for novel therapeutic methods (1). In current medical research, the development of advanced multifunctional nanotherapeutics (NP) represents one of the most promising strategies, offering opportunities for targeted delivery, synergistic therapeutic effects, and imaging modalities.

Recently, we demonstrated that oligosaccharide derivatives (λ-COS) of λ-carrageenan, a marine sugar derived from red algae, can serve as a scaffold for the preparation of highly stable hybrid NP embedding free Mn2+ ions and extremely small ferrite cores (λ-COS NP). These λ-COS NP display a favorable biosafety profile for in vivo use, MRI contrast capability for none-invasive tracking, and promising pharmacokinetic properties evaluated in healthy mice. Interestingly, preliminary results in an MDA-MB-231 xenograft model indicated moderate tumor accumulation of these nanoparticles after intravenous administration (2). Encouraged by these results, we next investigated the multifunctional therapeutic potential of λ-COS NP highlighting their selective cytotoxic effect assisted by magnetic hyperthermia or magneto-mechanical approaches in TNBC model.

In the in vitro studies, high doses of λ-COS NPs (higher than 50 µg/mL) were highly toxic to both TNBC (MDA-MB-231) and healthy epithelial (hTERT-HME1 [ME16C]) breast cells. However, at low non-cytotoxic doses (2-10 µg/mL), λ-COS NPs induce cell death and decrease cell proliferation of MDA-MB-231 cells, only under high-frequency alternating magnetic fields (AMF) and low-frequency rotating magnetic fields (RMF). Interestingly, no side effects were observed on healthy hTERT-HME1 [ME16C] cells at these effective doses. These results indicate that λ-COS NPs heating or motion, respectively induced in response to AMF or RMF, have specific anti-proliferative effects against cancer cells.

This study establishes the proof-of-concept that extremely small magnetic nanoparticles coated with oligosaccharides derivatives from red alae can specifically eradicate cancer cells through magnetic hyperthermia or mechanical forces, therefore opening new opportunities for TBNC therapy.

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P506

Lymphoma vs. metastasis vs. non-tumoral: a multi-class classifier to evaluate H&E-stained lymph nodes

Stéphane TREILLARD[1,2,3], Robin SCHWOB[1,2,4], Raphaëlle DUPREZ-PAUMIER[5], Philippe ROCHAIX[5], Charlotte SYRYKH[1], Pierre BROUSSET[1,6], Sandrine MOUYSSET[2,6], Sylvain CUSSAT-BLANC[2,3,7], Camille FRANCHET[5,6]

[1] CHU de Toulouse

[2] Institut de Recherche en Informatique de Toulouse

[3] Université Toulouse Capitole

[4] Université Toulouse 2 Jean Jaurès

[5] Oncopole Claudius Régaud, Toulouse

[6] Université de Toulouse

[7] Institut Universitaire de France

Lymph Node (LN) assessment is part of most pathologists' routine. To assist practitioners in this task, several Artificial Intelligence (AI) models have been developed to detect LN metastases, but these approaches only consider LNs as being non-tumoral or metastatic and are unable to recognize other rare conditions such as lymphoma. Lymphoma is a type of cancer that can develop in LNs and that is particular difficult to diagnose due to the multiplicity of its subtypes, including some that closely resemble non-tumoral cases.

In this work, we developed a Deep Learning model that not only distinguishes metastatic and non-tumoral LNs, but also detects lymphomas. We used a Multiple Instance Learning (MIL) framework, with the UNI2-h foundation model as a patch feature extractor and Attention-based Multiple Instance Learning as an aggregator. We trained our model on LN slides of 6 different lymphoma subtypes (Diffuse Large B-cell Lymphoma, Hodgkin Lymphoma, T-cell Lymphoma, Small Lymphocytic Leukemia and Follicular Lymphoma) from the French Lymphopath cohort and on a local dataset of benign and metastatic slides. Our training set included 803 H&E slides from 449 patients, with both biopsies and surgical specimens from different LN localizations. We tested our model on a local dataset, on CAMELYON16 and on slides from The Cancer Imaging Archive.

Our best model obtained an AUC of 0.98 and a balanced accuracy of 0.92 on our internal test set, and an AUC of 0.95 and a balanced accuracy of 0.83 on the external test sets. Regarding lymphomas, our model reached an F1-score of 0.92 on our local test set with 6 subtypes and of 0.95 on the external test sets, which contained a single lymphoma subtype (Diffuse Large B-cell Lymphoma).

These results are promising and show that it is possible to train an LN classifier that is able to detect both metastases and rare conditions such as lymphomas. This work represents the first milestone of a larger project to develop an AI-based lymphoma diagnostic assistant for non-expert pathologists. Future work will involve further validation of the model on lymphomas, and identification of lymphoma subtypes. Our code and model weights are publicly available.

P507

Magnetic Hyperthermia and Mechanical Ablation Induce An Anti-Tumour Immune Response In Pancreatic Adenocarcinoma

Angela AGAËSSE[1], Justine JOURNAUX[1], Pascal CLERC[1], Megi BEJKO[2], Julien CARREY[3], Auriane BAGUR[2], Olivier SANDRE[2], Stéphane MORNET[4], Mary POUPOT[1], Véronique GIGOUX[1]

[1] Centre de Recherches en Cancérologie de Toulouse

[2] Laboratoire de Chimie des Polymères Organiques, Bordeaux

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

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

Pancreatic ductal adenocarcinoma (PDAC) is a cancer with a poor prognosis, resistant to conventional therapies, and characterized by a dense microenvironment, with a key role of CAFs (Cancer-Associated Fibroblast). This physical barrier not only limits the penetration and diffusion of therapies, but also the infiltration of immune cells restricting an effective anti-tumor 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 internalize and accumulate 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. Finally, 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 as well as an increase in the cytotoxic activity of Natural Killers (NK-92) when they were in contact with these cells in 2D model. Moreover, the infiltrations of THP1 macrophages and Natural Killers (NK-92) were observed within the MiaPaca2-CCK2/CAF-CCK2 spheroids. 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.

P508

Platinum nanoparticles as radiosensitizers to boost conventional radiotherapy for pancreatic adenocarcinoma treatment

Manon BOULET[1], Adeline PHAM[2], Simon TRICARD[2], Véronique GIGOUX[1]

[1] Centre de Recherches en Cancérologie de Toulouse

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

Pancreatic adenocarcinoma (PDAC) is one of the most aggressive cancers. It is the fourth leading cause of cancer death in the Western world and will become the second leading cause of cancer death by 2030. It is highly lethal (9% survival at 5-years), due to late diagnosis making patients poor candidates (~15%) for surgical treatment. Pancreatic adenocarcinoma is known to be highly resistant to chemotherapy and radiotherapy (RT). A few studies suggest that RT may have a positive impact on pathological response, although the effect on survival is not always efficient. Therefore, the identification of new radiosensitizers is critical to improve the efficacy of RT. Few studies have been conducted to identify such radiosensitizers for the treatment of PDAC. For example, resveratrol and capsaicin radiosensitize pancreatic cancer cells in vitro, indicating that radiosensitization of pancreatic adenocarcinoma is thus an option to be further explored. Recently, nanoparticles containing heavy atoms, such as platinum and gold, have emerged as potential radiosensitizers for high-energy X-ray RT. Moreover, nanoparticles present the advantage to preferentially accumulate in the tumor by enhanced permeability or retention effect, offering the possibility to increase radiotherapy effect on the tumor site.

Here, we investigate, the effect of platinum nanoparticles (Pt NPs) radiosensitization on PDAC cells. The advantage of using Pt NPs is the possibility to specifically functionalize their surface by biocompatible polymers (PEG), responsive molecules (luminescent), or functional molecules (chemotherapy agents). We demonstrated that Pt@PEG NPs did not present any cytotoxicity up to 500 µM and were internalized by pancreatic cancer cells. Moreover, we showed that X-ray irradiation of the Pt NPs decrease the viability of pancreatic cancer cells more importantly than irradiation or Pt NPs alone, strongly suggesting that Pt NPs can act as radiosensitizers by enhancing the efficacy of X-ray irradiation. We hope that this strategy will offer new therapeutic opportunity to treat PDAC using Pt NPs as radiosensitizer, which will specifically act at the tumor site and metastasis.

P509

A collaborative Landmark Annotation and Registration Tool for Longitudinal Brain Tumor Imaging

Gayane KHARATYAN[1,2], **Amel AISSAOUI[2]**, Wafae LABRIJI[2], Lotfi CHAARI[2]

[1] Université française en Arménie (UFAR)

[2] Institut de Recherche en Informatique de Toulouse

Longitudinal magnetic resonance imaging (MRI) is essential for monitoring brain tumors and guiding clinical decision-making [1]. A promising application lies in predicting relapse after resection, where temporal imaging captures subtle patterns of tumor recurrence. However, annotated datasets with ground-truth correspondences across time points remain scarce. One approach to address this gap is to exploit tumor information available in follow-up scans as reference annotations for baseline scans [2,3], enabling predictive modeling of recurrence patterns. The success of this approach depends critically on accurate image registration to ensure reliable alignment of the evolving tumor environment.

Conventional registration algorithms [4,5], mostly optimized for healthy anatomy, often fail under the complex deformations induced by neurosurgical interventions, including tumor growth, cavity formation, tissue resorption, and post-operative remodeling. Existing validation strategies are also limited: synthetic deformations lack clinical realism, while visual inspection is subjective and irreproducible. Moreover, the shortage of annotated datasets constrains the development and benchmarking of robust registration models in neuro-oncology.

To overcome these limitations, we introduce LandMatch [6], a lightweight, collaborative annotation tool for establishing ground-truth point correspondences across 3D longitudinal medical images. LandMatch enables radiologists to identify and validate anatomically consistent landmarks between time points through synchronized visualization across modalities (T1, T1CE, T2, FLAIR) and anatomical planes. It provides an integrated benchmarking framework that automatically evaluates registration algorithms using standardized metrics such as Target Registration Error (TRE) and Robustness. Beyond benchmarking, LandMatch supports multi-user collaboration, inter-observer consistency assessment, and standardized data export, promoting reproducibility and dataset sharing. The generated landmarks can also serve as supervision signals for training data-driven registration models or as spatial references for relapse prediction. By bridging manual clinical expertise with quantitative algorithmic evaluation, LandMatch offers a scalable and clinically relevant foundation for registration and outcome prediction in brain tumor longitudinal studies.

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Posters – Platforms

P601

Vivoptic, a preclinical optical imaging platform for in vivo evaluation of diagnostic and therapeutic strategies

Coralie GENEVOIS

TBMCore, Bordeaux

Vivoptic is an approved platform for preclinical experimentation located at the Bordeaux Biomedical Imaging Institute. Labeled France Life Imaging (FLI), it offers not only access to optical imaging equipment for small animals after user training, but also experimental models (genetically modified lines, in vivo tumor models) as well as a set of therapeutic devices. This L1 biological level platform (no pathogens) has fully equipped surgery and animal preparation rooms (anesthesia stations, monitoring (ECG, T°, respiratory rate), micro-injector, stereotaxic frame, etc.). Vivoptic can also help you design the in vivo experiment, support you throughout your project and analyze the results.

1/ Vivoptic an optical imaging platform
Optical imaging is widely used in cancer research, cardiology and neurology and is a convenient tool for first pharmacological and biodistribution evaluations of nanoparticles labeled with fluorescent dyes, targeting assessment and new therapies. After an initial training, Vivoptic offers you free access to optical imaging devices for bioluminescence and fluorescence imaging
- Lumina III (Perkin Elmer) for 2D bioluminescence and fluorescence 2D imaging
- FMT4000 (Perkin Elmer) for fluorescence molecular tomography (3D)
- Fluobeam (Fluoptic) a per-operatory probe for free and live monitoring of fluorescence signals including during surgery.
- A clinical/preclinical ultrasound system (Aixplorer) (B mode, Doppler, elastography) including a mouse probe available at the platform, useful for developing therapeutic strategies and image-guided surgery.

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3/ Vivoptic, a place to share preclinical therapy devices Therapeutic devices for in vivo gene therapies (electroporation), magnetic hyperthermia, photodynamic therapies (PDT) and high intensity focused ultrasound are also available at Vivoptic.

Vivoptic is a certified place for animal experiment, why not consider Vivoptic to install your own preclinical therapeutic setup ?

List of Participants

Name	Affiliation	City	Email
Angela AGAËSSE	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	angela.agaesse@inserm.fr
Amel AISSAOUI	Institut de Recherche en Informatique de Toulouse	TOULOUSE	amel.aissaoui@irit.fr
Israa AL JAMAL	Institut de Chimie des Milieux et Matériaux de Poitiers	POITIERS	israa.al.jamal@univ-poitiers.fr
Virginie ALBINET	CHU de Toulouse	TOULOUSE	albinet.v@chu-toulouse.fr
Jean ALBRENGUES	Institute for Research on Cancer and Aging	NICE	jean.albrengues@univ-cotedazur.fr
Soha ALLIOUI	Institut de Génétique Moléculaire de Montpellier	MONTPELLIER	soha.allioui@gmail.com
Jean-Christophe ANDRAU	Institut de Génétique Moléculaire de Montpellier	MONTPELLIER	jean-christophe.andrau@igmm.cnrs.fr
Andreea ANDREEV	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	andreea.andreev@unilim.fr
Jean Olivier ARNAUD	Cancéropôle GSO	NIMES	jean.olivier.arnaud@gmail.com
Lolarose ASELIN	Université de Bordeaux	BORDEAUX	lola.at.1013@gmail.com
Margaux AYEUL	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	margaux.ayeul@inserm.fr
Lamia AZZI-MARTIN	BoRdeaux Institute of Oncology	BORDEAUX	lamia.azzi-martin@u-bordeaux.fr
Reem BANNOUT	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	reem.bannout@inserm.fr
Diego BARBA	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	diego.barba@inserm.fr
Frédéric BARD	Centre de Recherche en Cancérologie de Marseille	MARSEILLE	frederic.bard@inserm.f
Pauline BARRAJA	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	pauline.barraja@inserm.fr
Daniel BARROSO ALVES	BoRdeaux Institute of Oncology	BORDEAUX	dbarrosoalve@u-bordeaux.fr
Serge BATTU	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	serge.battu@unilim.fr
Chloé BAZILE	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	chloe.bazile@inserm.fr
Guillaume BELTHIER	Institut de Génomique Fonctionnelle	MONTPELLIER	g.belthier@gmail.com
Jessim BENHAMMOUDA	Université de Montpellier	MONTPELLIER	jessim.benhammouda@etu.umontpellier.fr
Jérôme BERANGER	Centre d'épidémiologie et de recherche en santé des populations	TOULOUSE	jeromeberanger@hotmail.com
Lydie BERGEAU	Registre général des cancers de la Gironde	BORDEAUX	lydie.bergeau@u-bordeaux.fr
Véronique BERNAD	Ass. Patients en réseau	RODEZ	veronique.bernad191@orange.fr
Nicolas BERY	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	nicolas.bery@inserm.fr

Barbara BESSETTE	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	barbara.bessette@unilim.fr
Christine BEZOMBES	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	christine.bezombes@inserm.fr
Trever BIVONA	University of California	SAN FRANCISCO	trever.bivona@ucsf.edu
Samira BLAIZE	ONCODEFI	MONTPELLIER	samira.blaize@oncodefi.org
Augustine BLANC-BOEKHOLT	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	augustine.blanc-boekholt@inserm.fr
Sacha BODIN	Institut de neurosciences cognitives et intégratives d'Aquitaine	BORDEAUX	sacha.bodin@u-bordeaux.fr
Doriane BOMONT	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	doriane.bomont@ibgc.cnrs.fr
Caroline BONNANS	Institut de Génomique Fonctionnelle	MONTPELLIER	caroline.bonnans@igf.cnrs.fr
Marta BORNEZ	BoRdeaux Institute of Oncology	PESSAC	marta.martin-bornez@inserm.fr
Guillaume BOSSIS	Institut de Génétique Moléculaire de Montpellier	MONTPELLIER	guillaume.bossis@igmm.cnrs.fr
Bernard BOTIN	Ligue contre le Cancer Lot et Garonne	AGEN	
Céline BOUCLIER	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	celine.bouclier@inserm.fr
Manon BOULET	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	manon.boulet@inserm.fr
Laura BOURILLON	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	laura.bourillon@icm.unicancer.fr
Nicolas BOURMEYSTER	Université de Poitiers/CHU de Poitiers	POITIERS	nicolas.bourmeyster@univ-poitiers.fr
Léa BOUTON	Acides Nucléiques : Régulations Naturelles et Artificielles	BORDEAUX	lea.bouton@inserm.fr
David BRACQUEMOND	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	david.bracquemond@inserm.fr
Théo BRANCHU	Canaux & Connexines dans les Cancers et Cellules Souches	POITIERS	theo.branchu@univ-poitiers.fr
Muriel BRENGUES	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	muriel.brengues@icm.unicancer.fr
Lucie BRISSON	BoRdeaux Institute of Oncology	BORDEAUX	lucie.brisson@inserm.fr
Sébastien BRITTON	Institut de Pharmacologie et de Biologie Structurale	TOULOUSE	sebastien.britton@ipbs.fr
Aude BRUNEL	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	aude.brunel@ibgc.cnrs.fr
Lisa BRUNET	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	lisa.brunet@inserm.fr
Audrey BURBAN	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	audrey.burban@u-bordeaux.fr
Jean CALABET	Ligue contre le Cancer Lot et Garonne	AGEN	jeancalabet@orange.fr
Olivier CALVAYRAC	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	olivier.calvayrac@inserm.fr
Yvan CANITROT	MCD CNRS UMR5077 University of Toulouse	TOULOUSE	yvan.canitrot@univ-tlse3.fr
Bruno CARDINAUD	BoRdeaux Institute of Oncology	BORDEAUX	bruno.cardinaud@u-bordeaux.fr

Maëlle CAROFF	Institut de Pharmacologie et de Biologie Structurale	TOULOUSE	maelle.caroff@ipbs.fr
Elisa CASABURO	Université de Montpellier	MONTPELLIER	elisacasaburo@gmail.com
Maria CASANOVA-ACEBES	CNIO	MADRID	mcasanova@cnio.es
Coralie CAYRON	Institut de Pharmacologie et de Biologie Structurale	TOULOUSE	coralie.cayron@ipbs.fr
Valérie CHABRIÈRE	ALK/ROS1 France	TOULOUSE	valerie.chabriere@gmail.com
Benjamin CHANRION	Institut de Recherche Pierre Fabre	TOULOUSE	benjamin.chanrion@pierre-fabre.com
Anouk CHATEFAU	BoRdeaux Institute of Oncology	BORDEAUX	anouk.chatefau@inserm.fr
Myriam CHAUMEIL	NVision Imaging Technologies GmbH	ULM	myriam.chaumeil@nvision-imaging.com
Carine CHAVEY	Institut de Génétique Moléculaire de Montpellier	MONTPELLIER	carine.chavey@igmm.cnrs.fr
Guillaume CHEMIN	Laboratoire des Agroressources, Biomolécules et Chimie pour l'Innovation en Santé	LIMOGES	guillaume.chemin@unilim.fr
Carel CHERFAN	BoRdeaux Institute of Oncology	BORDEAUX	carel.cherfan@u-bordeaux.fr
Mohamad CHKEIR	Laboratoire EpiMaCT	LIMOGES	mohamad.chkeir@etu.unilim.fr
Niki CHRISTOU	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	christou.niki19@gmail.com
Vijay CHUDASAMA	Department of Chemistry, University College London	LONDON	v.chudasama@ucl.ac.uk
Julie CLACHET	BoRdeaux Institute of Oncology	BORDEAUX	julie.clachet@u-bordeaux.fr
Greg CLEMENCEAJ	Université de Montpellier	MONTPELLIER	greg.clemenceau@gmail.com
Thomas CLOUAIRE	Centre de Biologie Intégrative	TOULOUSE	thomas.clouaire@utoulouse.fr
Ilona COMINO	Université de Bordeaux	TALENCE	ilona.comino@etu.u-bordeaux.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
Mélissa CORREIA DE OLIVEIRA	BoRdeaux Institute of Oncology	BORDEAUX	melissa.correia-de-oliveira@u-bordeaux.fr
Lucas COUTURIER	Yomi Pharma	LIMOGES	lucas.couturier@unilim.fr
Yannick CREMILLIEUX	Institut des Sciences Moléculaires	TALENCE	yannick.cremillieux@u-bordeaux.fr
Agnese CRISTINI	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	agnese.cristini@inserm.fr
Elodie CULERIER	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	elodie.culerier@inserm.fr
Michèle CUNY	ALK/ROS1 France	TOULOUSE	michelemonastir937@gmail.com

Sandrine DABERNAT	BoRdeaux Institute of Oncology	BORDEAUX	sandrine.dabernat@u-bordeaux.fr
Hiba DAHER	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	hiba.daher@inserm.fr
Thomas DAUBON	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	thomas.daubon@u-bordeaux.fr
Axell DAVOUST	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	axell.davoust@ibgc.cnrs.fr
Lea DECOUX	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	lea.decoux@unilim.fr
Cécile DEJOU	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	cecile.dejou@inserm.fr
Célia DELAHAYE	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	celia.delahaye@inserm.fr
Théo DELMOTTE	Université de Bordeaux	BORDEAUX	theo.delmotte@mydi.fr
Cyrille DELPIERRE	Galenix Innovations	TOULOUSE	cyrille.delpierre@inserm.fr
Amandine DESETTE	Université de Poitiers - CHU POITIERS - PROCIDET UR 24144	POITIERS	amandine.desette@univ-poitiers.fr
Alice DHELLEMMES	Psychologie de la santé	TOULOUSE	alicedhellemmes@gmail.com
Nicolas DI GLERIA--PILLARD	Institut de Génomique Fonctionnelle	MONTPELLIER	nicolas.di-gleria-pillard@igf.cnrs.fr
Jules DI SCALA	Institut de Recherche en Informatique de Toulouse	TOULOUSE	jules.di-scala@irit.fr
Emma DONATI	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	emma.dnti@gmail.com
Isaure DOUAT	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	isaure.douat@inserm.fr
Sarah DUCHAMP	BoRdeaux Institute of Oncology	BORDEAUX	sarah.duchamp@u-bordeaux.fr
Bastien DUMAIS	Institut de Pharmacologie et de Biologie Structurale	TOULOUSE	bastien.dumais@ipbs.fr
Marjorie DUNET	Université de Montpellier	MONTPELLIER	marjorie.dunet@etu.umontpellier.fr
Stéphanie DURAND-PANTEIX	BISCEm	LIMOGES	stephanie.durand-panteix@unilim.fr
Laura EANES DA SILVA	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	laura.eanes-da-silva@inserm.fr
Hicham ECH-CHARFI	Université de Montpellier	MONTPELLIER	hicham.ech-charfi@etu.umontpellier.fr
Frédéric EGHIAIAN	Akoya		feghiaian@akoyabio.com
Mirella EL-KHOURY	Akoya		melkhoury@quanterix.com
Eva EPINETTE	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	eva.epinette@u-bordeaux.fr
Fabrice ESCAFFIT	Unité de biologie moléculaire, cellulaire et du développement	TOULOUSE	fabrice.escaffit@utoulouse.fr
Eglantine FAGET	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	eglantine.faget@inserm.fr

Thaïs FAVODON	Université de Montpellier	MONTPELLIER	thaisfavodon@icloud.com
Léa FÉVRIER	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	lea.fevrier@inserm.fr
Camille FRANCHET	IUCT Oncopole	TOULOUSE	franchet.camille@iuct-oncopole.fr
Clara FREIXINOS	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	clara.freixinos@inserm.fr
Frédéric FRISCOURT	Institut Européen de Chimie et Biologie	PESSAC	frederic.friscourt@u-bordeaux.fr
Ioana GABOR	Université de Bordeaux	BORDEAUX	ioana-carolina.gabor@etu.u-bordeaux.fr
Olivier GADAL	Centre de Biologie Intégrative	TOULOUSE	olivier.gadal@utoulouse.fr
Fani GALIATSATOU	Université de Bordeaux	TALENCE	galiatsatoufani@yahoo.com
Inès GARROUCHE	Université de Poitiers, Laboratoire ProDiCeT, UR 24144	POITIERS	ines.garrouche@univ-poitiers.fr
Amy GATEAU	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	amy.gateau@unilim.fr
Coralie GENEVOIS	BoRdeaux Institute of Oncology	BORDEAUX	coralie.genevois@u-bordeaux.fr
Mohamed GHERMI	ICG- CHU de Nimes	NIMES	mohamed.ghermi@chu-nimes.fr
Margherita GHISI	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	margherita.ghisi@inserm.fr
Nyere GIBSON	Université de Bordeaux	TALENCE	nyere.gibson@etu.u-bordeaux.fr
Véronique GIGOUX	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	veronique.gigoux@inserm.fr
Charlotte GLADEN	Université de Bordeaux	BORDEAUX	charlotte.gladen@gmail.com
José Eduardo GOMES	Université de Bordeaux	BORDEAUX	jose-eduardo.gomes@u-bordeaux.fr
Céline GONGORA	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	celine.gongora@inserm.fr
Philippe GORRY	Bordeaux school of economics	PESSAC	philippe.gorry@u-bordeaux.fr
Lucie GOURET	BoRdeaux Institute of Oncology	BORDEAUX	lucie.gouret@u-bordeaux.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	gras-aygon.claudine@registre-tumeurs-herault.fr
Ewelyna GUCA	MedChemExpress		ewelina.guca@medchemexpress.com
Yanis GUECHE	Université de Montpellier	MONTPELLIER	gueche.yanis@gmail.com
Gaëlle GUILLON	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	gaelle.guillon@inserm.fr
Hadiya Abdul HAMEED	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	abdul.hameed@bilkent.edu.tr
Maria HAYKAL	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	maria.haykal@u-bordeaux.fr
Nadine HOUEDE	CHU de Nîmes	NIMES	nadine.houede@chu-nimes.fr

Marc PALPACUER	ONCODEFI	MONTPELLIER	marc.palpacuer@oncodefi.org
Vanessa WEHBI	Institut de Recherche Pierre Fabre	TOULOUSE	vanessa.wehbi@pierre-fabre.com
Arnaud JABOUILLE	BoRdeaux Institute of Oncology	BORDEAUX	arnaud.jabouille@inserm.fr
Joaquim JAVARY	BoRdeaux Institute of Oncology	BORDEAUX	joaquim.javary@inserm.fr
Eric JULIEN	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	eric.julien@inserm.fr
Yousra KAISSOUNI	Université de Poitiers	POITIERS	yousra.kaissouni@univ-poitiers.fr
Nour KHAIRALLAH	BoRdeaux Institute of Oncology	BORDEAUX	nour.khairallah@u-bordeaux.fr
Roudaina KHALIL	Université de Montpellier	MONTPELLIER	roudaina.khalil@etu.umontpellier.fr
Abdel-Majid KHATIB	BoRdeaux Institute of Oncology	BORDEAUX	majid.khatib@inserm.fr
Céline KIEU	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	celine-trinh-le-vi.kieu@inserm.fr
Faiza LAANANI	BoRdeaux Institute of Oncology	BORDEAUX	faiza.laanani@u-bordeaux.fr
Camille LABADIE	Université de Montpellier	MONTPELLIER	camillelabadie@yahoo.com
Maxime LACOUR	Université de Montpellier	MONTPELLIER	lacour.mx@gmail.com
Sophie LACROIX	Pierre Fabre		sophie.lacroix@pierre-fabre.com
Frédéric LAGARRIGUE	Institut de Pharmacologie et de Biologie Structurale	TOULOUSE	frederic.lagarrigue@ipbs.fr
Nadine LAGUETTE	Institut de Génétique Moléculaire de Montpellier	MONTPELLIER	nadine.laguette@igmm.cnrs.fr
Fabrice LALLOUE	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	fabrice.lalloue@unilim.fr
Kristopher LAMORE	SCAlab	LILLE	kristopher.lamore@univ-lille.fr
Christel LARBOURET	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	christel.larbouret@inserm.fr
Marion LARROQUE	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	marion.larroque@icm.unicancer.fr
Claude LAURENS	Ligue contre le Cancer Lot et Garonne		claude.laurens@gmail.com
Pierre LAURENT-PUIG	Centre de recherche des Cordeliers	PARIS	pierre.laurent-puig@parisdescartes.fr
Thierry LAVABRE-BERTRAND	CHU Montpellier / Nimes	MONTPELLIER	thierry.lavabre-bertrand@umontpellier.fr
Sarah LAVIELLE	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	sarah.lavielle@u-bordeaux.fr
David LEGER	Laboratoire des Agroressources, Biomolécules et Chimie pour l'Innovation en Santé	LIMOGES	david.leger@unilim.fr
Emma LEHIR	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	emmalhr2@gmail.com
Marion LENAIN	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	marion.lenain@inserm.fr

Domitille LEROUGE	Université de Bordeaux	BORDEAUX	domitille.lerouge@icloud.com
Sabrina LEVERRIER-PENNA	Canaux & Connexines dans les Cancers et Cellules Souches	POITIERS	sabrina.penna@univ-poitiers.fr
Bertrand LIAGRE	Laboratoire des Agroressources, Biomolécules et Chimie pour l'Innovation en Santé	LIMOGES	bertrand.liagre@unilim.fr
Sébastian LILLO	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	sebastian.lillo@u-bordeaux.fr
Yiyang LIU	BoRdeaux Institute of Oncology	BORDEAUX	yiyang.liu@kuleuven.be
Gaby LONGUY-GENEBES	Université de Bordeaux	TALENCE	gabylonguy@gmail.com
Marie POISEUIL	Registre régional des cancers de la Gironde	BORDEAUX	marie.poiseuil@u-bordeaux.fr
Tala MAASSARANI	BoRdeaux Institute of Oncology	BORDEAUX	tala.maassarani@u-bordeaux.fr
Pierre MAHE	Université de Montpellier	MONTPELLIER	pierre.mahe@etu.umontpellier.fr
Juliette MAIRESSE	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	juliette.mairesse@inserm.fr
Hervé MAISONNEUVE	Rédaction médicale	LYON	hervemaisonneuve@gmail.com
Grégoire MANAUD	BoRdeaux Institute of Oncology	BORDEAUX	gregoire.manaud@inserm.fr
Antonio MARAVER	Oncogenic pathways in lung cancer	MONTPELLIER	antonio.maraver@inserm.fr
Christelle MARCEROU	Ligue contre le Cancer Lot et Garonne		Christelle.Marcerou@ligue-cancer.net
Émilie MARHUENDA	Institut de Chimie & Biologie des Membranes & des Nano-objets	PESSAC	emilie.marhuenda@bordeaux-inp.fr
Océane MARTIN	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	oceane.martin@u-bordeaux.fr
Yvan MARTINEAU	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	yvan.martineau@inserm.fr
Konstantin MASLIANTSEV	Université de Poitiers - CHU Poitiers - UR24144	POITIERS	konstantin.masliantsev@univ-poitiers.fr
Thomas MATHIVET	BoRdeaux Institute of Oncology	BORDEAUX	thomas.mathivet@inserm.fr
Jean-Pierre MAZAT	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	jean-pierre.mazat@u-bordeaux.fr
Julie PANAL	Université de Montpellier	MONTPELLIER	julie.panal@etu.umontpellier.fr
Giorgio MAZZARESE	Université de Bordeaux	BORDEAUX	giomazzarese@gmail.com
Miriam MELONI	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	meloni.miriam@hsr.it
Sydney MERCIER	Université de Montpellier	MONTPELLIER	sydney.mercier@etu.umontpellier.fr
Anne MERVIEL	Université de Montpellier	MONTPELLIER	anne.merviel@etu.umontpellier.fr
Donia MOCHO	Université de Bordeaux	BORDEAUX	donia.mocho@gmail.com
Valérie MONTAGNY	ALK/ROS1 France	TOULOUSE	v.montagny@gmail.com
Mélanie MOREAU	Bordeaux Protéome	BORDEAUX	melanie.moreau.1@u-bordeaux.fr
Violaine MOREAU	BoRdeaux Institute of Oncology	BORDEAUX	violaine.moreau@inserm.fr
Alexandre MOTTA	Fosca BioTech	MOULEYDIER	a.motta@fosca.tech

Mark Alvin MULINDWA	Université de Montpellier	MONTPELLIER	mulindwamarkalvin0@gmail.com
Florian NAUDET	Irset	RENNES	floriannaudet@gmail.com
Maximilien NDJAMI MAKANDA	Centre de Biologie Intégrative	TOULOUSE	maximilien.ndjami-makanda@utoulouse.fr
Elodie NEUMANN	ONCODEFI	MONTPELLIER	elodie.neumann@oncodefi.org
Stefan NICOLESCU	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	stefan.nicolescu@inserm.fr
Chantal NOUHAUD	Ligue contre le Cancer Lot et Garonne		Chantale.Nouhaud@ligue-cancer.net
Damien OTT DE NUSSAC	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	damien.ott@etu.unilim.fr
Yousra OUAZZANI-TOUHAMI	BoRdeaux Institute of Oncology	BORDEAUX	ouazzaniyousra@gmail.com
Nael OUYOUSSEF	Université de Montpellier	MONTPELLIER	nael.ouyoussef@etu.umontpellier.fr
Antonio Christian PAGANO ZOTTOLA	BoRdeaux Institute of Oncology	PESSAC	antonio.pagano-zottola@u-bordeaux.fr
Marcelo HURTADO	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	marcelo.hurtado@inserm.fr
Julie PANNEQUIN	Institut de Génomique Fonctionnelle	MONTPELLIER	julie.pannequin@igf.cnrs.fr
Véra PANCALDI	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	vera.pancaldi@inserm.fr
Julien MAZIERES	CHU de Toulouse	TOULOUSE	mazieres.j@chu-toulouse.fr
Argyris PAPANTONIS	Institute of Pathology, University Medical Center	GOTTINGEN	argyris.papantonis@med.uni-goettingen.de
Cédric PAPE	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	cedric.pape@etu.u-bordeaux.fr
Sébastien PAPOT	Institut de Chimie des Milieux et Matériaux de Poitiers	POITIERS	sebastien.papot@univ-poitiers.fr
Alexis PARENTE	Université de Limoges	LIMOGES	alexis.parente@unilim.fr
Jean-Marc PASCUSSI	Institut de Génomique Fonctionnelle	MONTPELLIER	jean-marc.pascussi@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
Sophie PERON CHEMIN	Contrôle de la Réponse Immune B et des Lymphoprolifération	LIMOGES	sophie.peron@unilim.fr
Mathis PINGLAUT	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	mathis.pinglaut@u-bordeaux.fr
Sandrine POGLIO	BoRdeaux Institute of Oncology	BORDEAUX	sandrine.poglio@u-bordeaux.fr
Laura POILLET	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	laura.poillet@inserm.fr
Marie-Laure SCHNEIDER	10x Genomics		marielaure.schneider@10xgenomics.com
Mary POUPOT	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	mary.poupot@inserm.fr
Philippe POURQUIER	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	philippe.pourquier@inserm.fr
Mathilde RABET	Registre général des cancers de la Gironde	BORDEAUX	mathilde.rabet@u-bordeaux.fr

Brenna RAMM	Université de Montpellier	MONTPELLIER	brenna-renay.ramm@etu.umontpellier.fr
Patrice RAVEL	Université de Montpellier	MONTPELLIER	patrice.ravel@umontpellier.fr
Lisa RENAUDET--KELLER	BoRdeaux Institute of Oncology	BORDEAUX	lisa.renaudet-keller@u-bordeaux.fr
Mathilde REY-TRICHOT	Université de Bordeaux	BORDEAUX	mathilde.rey-trichot@etu.u-bordeaux.fr
Alban RICARD	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	alban.ricard@inserm.fr
Guillaume RINQUIN	Université de Bordeaux	BORDEAUX	rinquin.guillaume@gmail.com
Clara ROUAULT	Université de Montpellier	MONTPELLIER	clara.rouault@gmail.com
Amandine ROUSSEL	BoRdeaux Institute of Oncology	BORDEAUX	amandine.roussel@u-bordeaux.fr
Amandine ROVINI	Contrôle de l'Activation cellulaire, Progression Tumorale et Résistance thérapeutique	LIMOGES	amandine.rovini@unilim.fr
Noémie SABOIE	Université de Bordeaux	BORDEAUX	noemie.saboie@gmail.com
Antoine SABOURAUD	Centre Emile Durkheim	BORDEAUX	antoine.sabouraud@u-bordeaux.fr
Frédéric SALTEL	BoRdeaux Institute of Oncology	BORDEAUX	frederic.saltel@inserm.fr
Montse SANCHEZ-CESPEDES	Josep Carreras Leukaemia Research Institute	BARCELONA	mscespedes@carrerasresearch.org
David SANTAMARIA	Centro de Investigación del Cáncer	SALAMANCA	d.santamaria@usal.es
Lucile SAUVAGE	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	lucile.sauvage@inserm.fr
Yaële SAUVAGE	Institut de Génétique Moléculaire de Montpellier	MONTPELLIER	yaele.sauvage@gmail.com
Marie LOPEZ	Institut des Biomolécules Max Mousseron	MONTPELLIER	marie.lopez@cnrs.fr
Lorenzo SCIPIONI	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	scipioni.lorenzo@gmail.com
Bruno SEGUI	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	bruno.segui@inserm.fr
Anthony SEILLER	Université de Montpellier	MONTPELLIER	anthony.seiller01@etu.umontpellier.fr
Irinka SÉRAUDIE	Institut de Biochimie et Génétique Cellulaires	BORDEAUX	irinka.seraudie@u-bordeaux.fr
Ahmad SHARANEK	BoRdeaux Institute of Oncology	BORDEAUX	ahmad.charanek@inserm.fr
Tanguy SIRIMA	Université de Montpellier	MONTPELLIER	tanguy.sirima@etu.umontpellier.fr
Myroslava SLIUSAR	BoRdeaux Institute of Oncology	BORDEAUX	myroslava.sliusar@u-bordeaux.fr
Florence SORDES	Université Toulouse 2 Jean Jaurès	TOULOUSE	sordes@univ-tlse2.fr
Mai Linh SORROCHE	Université de Montpellier	MONTPELLIER	mailinhs@yahoo.com
Pierre SOUBEYRAN	Institut Bergonié	BORDEAUX	p.soubeyran@bordeaux.unicancer.fr
Maxime TABAUD	Contrôle de la Réponse Immune B et des Lymphoprolifération	LIMOGES	maxime.tabaud@unilim.fr
Samuel TERKI	Université de Montpellier	MONTPELLIER	samuel.terki@etu.umontpellier.fr
Catherine TEYSSIER	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	catherine.teyssier@inserm.fr
Fabien THOREAU	Institut de Chimie des Milieux et Matériaux de Poitiers	POITIERS	sebastien.papot@univ-poitiers.fr
Jérôme TORRISANI	Centre de Recherches en Cancérologie de Toulouse	TOULOUSE	jerome.torrisani@inserm.fr

François-Xavier TOUBLET	Laboratoire des Agroressources, Biomolécules et Chimie pour l'Innovation en Santé	LIMOGES	francois-xavier.toublet@unilim.fr
Julia TOUCHEBOEUF	Université de Montpellier	MONTPELLIER	stefan.nicolescu@inserm.fr
Hélène TOURRIERE	Institut de Recherche en Cancérologie de Montpellier	MONTPELLIER	helene.tourriere@inserm.fr
Emeline TRANCHET	Registre général des cancers de la Gironde	BORDEAUX	emeline.tranchet@u-bordeaux.fr
Stéphane TREILLARD	CHU de Toulouse	TOULOUSE	stephanefj.treillard@gmail.com
Maïna TRELOHAN	Université de Bordeaux	BORDEAUX	maina.trelohan@gmail.com
Brigitte TRETARRE	Registre des Tumeurs de l'Hérault	MONTPELLIER	tretarre.brigitte@registre-tumeurs-herault.fr
Sébastien ULRICH	Institut des Biomolécules Max Mousseron	MONTPELLIER	sebastien.ulrich@cnrs.fr
Florent VARET	Institut Catholique de Lille	LILLE	florent.varet@univ-catholille.fr
Christine VARON	BoRdeaux Institute of Oncology	BORDEAUX	christine.varon@u-bordeaux.fr
Ana Sofia VAZQUEZ URIOLA	BoRdeaux Institute of Oncology	BORDEAUX	ana-sofia.vazquez-uriola@etu.u-bordeaux.fr
Paola VECINO	MedChemExpress		paola.vecino@medchemexpress.com
Oscar VERGNAUD	Université de Bordeaux	BORDEAUX	oscar.vergnaud@etu.u-bordeaux.fr
Marion VIALA	Université de Montpellier	MONTPELLIER	marion.viala@etu.umontpellier.fr
Chrisitine VIEIRA LUZIO	Université de Bordeaux	BORDEAUX	christinecordeiro@hotmail.fr
Anielle VILLERONCE	Régulations Naturelles et Artificielles	BORDEAUX	anielle.villeronce@u-bordeaux.fr
Christelle VINCENT-FABERT	Contrôle de la Réponse Immune B et des Lymphoprolifération s	LIMOGES	christelle.vincent-fabert@unilim.fr
Jihane VITRE	Institut de Génomique Fonctionnelle	MONTPELLIER	jihane.vitre@igf.cnrs.fr
Van Tuat HUYNH	Université de Montpellier	MONTPELLIER	tuathuynh2702@gmail.com
Anna WOJCIK	Université de Montpellier	MONTPELLIER	anna.wojcik@etu.umontpellier.fr
Gabriela XAVIER	Université de Montpellier	MONTPELLIER	gabriela.xavier@etu.umontpellier.fr

PROGRAMME IA POUR LA SANTÉ

QUAND LES CHERCHEURS EN IA RENCONTRENT LES ACTEURS DU MONDE MEDICAL

CONTEXTE

Basées sur des approches hybrides et multidisciplinaires, combinant des techniques d'apprentissage automatique et des modèles logiques, biologiques ou physiques, les avancées dans les différents domaines de l'IA sont au cœur de la médecine du futur. Mises à profit dans de nombreux secteurs de la santé, elles permettent notamment l'amélioration de la qualité des soins, une meilleure prise en charge des patients, ou encore la conception de nouveaux traitements adaptés à chaque personne. Ainsi, parce que l'application de l'IA au domaine de la santé est vaste, les questions autour de l'acceptabilité sociale de ces approches, le respect de la confidentialité des données et de la vie privée ainsi que l'éthique doivent inévitablement être réfléchies. Pour s'attaquer à ces défis, la région Occitanie décide de financer le Programme IA pour la Santé porté par l'Université de Toulouse et ANITI (Artificial and Natural Intelligence Toulouse Institute).

PROPOSITION

→ Fédérer les acteurs régionaux de la recherche, de la formation, du monde socio-économique et de l'innovation autour des techniques d'application de l'IA dans la Santé au sein d'un programme financé par la Région Occitanie et porté par la COMUE de Toulouse et ANITI.

PERIMETRE SCIENTIFIQUE

Le programme "IA pour la Santé" regroupe plusieurs laboratoires de recherche de la région dans le numérique et dans la santé autour de techniques de l'intelligence artificielle pour améliorer la précision des diagnostics, la qualité des soins ou encore le suivi des patients.

- Basées sur des données de santé annotées et fiabilisées.
- Appliquées à la cancérologie, les gérosciences, les maladies infectieuses émergentes et l'exposomique, même si d'autres applications peuvent être proposées.
- Visant la mise au point de méthodes d'IA qui améliorent les techniques de l'état de l'art (par exemple: parcimonie des données, performance, détection de biais, robustesse, explicabilité...).

SOUTIENS FINANCIERS PROPOSÉS

Appel à projet d'amorçage

Financement de projets interdisciplinaires entre académiques et industriels autour des techniques d'application de l'IA dans la santé

Budget compris entre 15 000€ et 20 000€

Clôture le 14 décembre 2025

Appel à projet de stage de recherche de niveau Master 2

Financement de stage de 6 mois sur un sujet qui concerne les problématiques de l'IA en application à la santé et au médical.

Financement de 6 mois de gratification de stage

Soutien d'évènements scientifiques

Financement de l'organisation d'un évènement scientifique ou de diffusion de la culture scientifique dont le sujet s'inscrit dans la stratégie du programme

Participation jusqu'à 1200€

CONTACT

Charlotte Dahlem - Cheffe de projet - charlotte.dahlem@univ-toulouse.fr

Fondation
SILAB - Jean PAUFIQUE

Aide à la Recherche sur les pathologies cutanées

La Fondation d'Entreprise SILAB - Jean PAUFIQUE a pour objectif d'apporter un soutien actif et constant à la Recherche fondamentale et appliquée au diagnostic, au pronostic et au traitement des pathologies dermatologiques et plus particulièrement des cancers de la peau.

La Fondation alloue à ses lauréats sous forme d'aide à la recherche un montant de 20 000 euros par an, reconductible sur 3 ans maximum.

Ce dispositif s'adresse aux structures de recherche d'établissements publics ou aux associations reconnues d'utilité publique.

Chaque année, la Fondation d'Entreprise SILAB - Jean PAUFIQUE soutient une jeune équipe méritante dans l'étude des thérapies des maladies de la peau en offrant un **prix de poster « Jeune chercheur »** lors des Journées du Cancéropôle Grand Sud-Ouest.

Informations complémentaires sur :

fondation.silab.fr

De la vision à l'action

« La Ligue contre le cancer »

La Ligue trouve son origine dans l'idée d'une élève de Marie Curie, le Dr Sonia Fabre, et dans l'impulsion donnée par Justin Godart, avocat puis député et sénateur du Rhône, accompagné d'Henri Hartmann et Claudius Regaud.

Le 14 mars 1918 est constituée « la ligue franco-anglo-américaine contre le cancer », devenue par la suite Ligue Nationale contre le Cancer. Justin Godart en sera le président pendant 38 ans.

En fait, pendant la première guerre mondiale les poilus blessés étaient pris en charge par le Service de santé militaire, mais ce dernier ignorait les malades du cancer. Il a fallu le courage sans faille de quelques médecins pour faire évoluer une organisation rigide et impliquer les pouvoirs publics.

Très tôt, dès 1919, la Ligue franco-anglo-américaine édite des affiches alertant la population sur des signes pouvant traduire l'existence d'un cancer et conseille de se faire examiner.

En 1922, le cancer devient cause nationale à l'initiative de Paul Strauss, ministre de l'Hygiène, assistance et prévoyances sociales. Dans les trois ans qui suivent sont créés en France dix centres anticancéreux.

Aujourd'hui, La Ligue contre le cancer, forte de 103 comités, y compris l'Outre-mer est un acteur important de lutte, de la prévention et de l'aide aux malades.

Depuis de longues années, elle est le premier financeur privé de la recherche contre le cancer.

Le Comité de la Ligue contre le cancer du Lot-et-Garonne

est né en 1962 et fait partie des 103 Comités Départementaux en France. Nos objectifs sont d'œuvrer pour les malades et la recherche.
Chaque euro qui arrive à notre Comité par don, leg ou bien lors de manifestations sert à la lutte contre le cancer ou est dirigé vers nos patients Lot-et Garonnais. C'est un point indiscutable de notre fonctionnement.

Dans le Lot et Garonne, des soins de support offerts pendant et après la maladie sont proposés à toutes personnes atteintes d'un cancer, à raison de 4 soins par an :
Soins de socio-coiffure, socio-esthétique, soutien psychologique, activité physique adaptée (espace dédié pour le Pilates et la gym douce), atelier de nutrition, autant de lieux qui sont propice à l'écoute et au partage, où l'on peut aussi pratiquer de la sophrologie
Récemment des ateliers de musique, ateliers d'autohypnose ont été mis en place au sein de notre comité.
En complément de ces actions, des soins à domicile où au cabinet de nos prestataires sont également proposés.

Des manifestations de prévention dans le cadre du cancer du sein (octobre rose), du cancer colorectal (mars bleu) ou des cancers pédiatriques (septembre en Or et opération Leclerc) sont déployées dans tout le département.

Notre Comité situé au 33 rue Camille Desmoulins à Agen vous accueille, vous informe et vous accompagne du lundi au vendredi de 9h à 12h30 et 13h30 à 17h.

La Société Française du Cancer, fondée en 1906, est la plus ancienne société savante française sur le cancer

Société Française du Cancer

La Société Française du Cancer œuvre sans relâche pour accompagner les professionnels de santé et chercheurs à avancer sur la lutte contre le cancer

La SFC a trois missions principales pour lesquelles elle mène de nombreuses actions :

FORMATION

- Organisation de la Journée scientifique Louise Harel
- Formation des internes de médecine à la recherche translationnelle
- Mobilité internationale pour les chercheurs et cliniciens
- Subvention de congrès réunissant chercheurs et médecins

INFORMATION

- Publication du Bulletin du cancer (journal scientifique indexé PubMed)
- Cycle de webinaires mensuels réalisés par des experts
- Envoi de Newsletter sur l'actualité du cancer

EXPERTISE

- Participation aux comités d'expertise et groupe de travail (notamment INCa et HAS)

Pourquoi devenir membre de la Société Française du Cancer ?

Etre adhérent à la **Société Française du Cancer** vous permet de participer aux nombreux événements qu'elle organise : **webinaires mensuels**, **Journée scientifique Louise Harel**, session(s) de formation, **IFODS**, etc.

Cela vous permet également de rester informé des dernières actualités du cancer par :

- Un abonnement au Bulletin du Cancer
- La Newsletter du cancer
- La mise à jour des AMM
- Les interviews, articles, tribunes et groupes de travail relayés sur le site et les réseaux sociaux

Information & adhésion **www.sfc.asso.fr**

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Akoya Biosciences is a pioneering company in the field of Spatial Biology. Founded by researchers from Stanford, Akoya offers an array of solutions for fluorescence-based phenotyping at medium to high multiplex (>100 biomarkers are possible with PhenoCycler Fusion), with applications ranging from discovery to translational and clinical research. Akoya solutions enable rapid characterization of the tissue microenvironment in solid tumor biopsies, leading to new discoveries, and offering possibilities for stratification of patient cohorts with an unprecedented level of precision.

This year, Quanterix and Akoya has jointed forces. Quanterix is the inventor of the SiMoA technology, which provides a solution to the unmet need for sub-femtomolar sensitivity in protein biomarker detection, and facilitates measurement of low abundance biomarkers in a variety of easily accessible biofluids such as blood, saliva and urine. Akoya and Quanterix become the first commercial supplier of advanced detection of biomarkers in both solid and liquid biopsies.

Le Cancéropôle GSO : une équipe pour vous accompagner

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)	Karine MARENDZIAK (Montpellier)
Dynamique et expression du génome (Axe 2)	karine.marendziak@canceropole-gso.org
Cancers : enjeux individuels et collectifs (Axe 4)	Jeanne RAMBAUD (Toulouse)
	jeanne.rambaud@canceropole-gso.org

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Bureau Toulouse
Oncopole – Bât. Maison Commune - rdc
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
www.canceropole-gso.org

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