14èmes

Journées Cancéropôle Grand Sud-Ouest

21 au 23 Novembre 2018

Palais des Congrès / La Grande Motte

SEMINAR BOOKLET

Cancéropôle Grand Sud-Ouest

www.canceropole-gso.org

INSTITUT NATIONAL DU CANCER

L'équipe du Cancéropôle Grand Sud-Ouest remercie vivement

les coordonnateurs et les membres des Comités de Pilotage des Axes,

les membres du Comité de Pilotage Scientifique,

pour leur participation et leur implication dans l'élaboration du programme de ces 14èmes Journées.

Comité de pilotage Scientifique

JC. Bernhardt, JP. Bleuse, K. Bystricky, P. Clavère, P. Cordelier, P. Denèfle, A. Evrard, D. Fisher, A.M Gué, B. Jacques, L. Karayan-Tapon, M. Khatib, S. Krouri, F. Lalloué, G. Laurent, V. Moreau, J. Pannequin, P. Rochaix, C. Sardet, P. Soubeyran, D. Tougeron

Comités de pilotage des Axes

Axe 1 - Signalisation cellulaire et Cibles thérapeutiques
S. Britton, O. Coux, Y. Denizot, K. Durand, JP. Hugnot, L. Karayan-Tapon, C. Laurent, N. Larmonier, **J. Pannequin**

Axe 2 - Dynamique du Génome et Cancer
JC. Andrau, **K. Bystricky**, F. Chibon, J. Dejardin, E. Julien, **M. Lutzmann**, D. McCusker, S. Millevoi, E. Pinaud

Axe 3 - Recherche translationelle, de la biologie à la clinique

E. Assénat, N. Bakalara, P. Barthélémy, JP. Brouillet, T. Chardès, E. Chatelut, M. Dufresne, A. Evrard, V. Gigoux, N. Houédé, **M. Khatib**, F. Lalloué, **N. Meyer**, MA. Poul, J. Robert, I. Soubeyran, D. Tougeron, N. Tubiana-Mathieu

Axe 4 - Cancers : enjeux individuels et collectifs
D. Alabarracin, C. Bellera, F. Cousson-Gélie, C. Delpierre, P. Gorry, S. Gourgou, **B. Jacques**, A. Sasco, F. Sordes, B. Trétarre

Axe 5 - Technologies pour la santé
A. Bancaud, M. Bardiès, S. Bégu, M. Busson, L. Cognet, A. Collin, P. Cordelier, P. Fernandez, A. Ferrand, R. Ferrand, JL. Feugeas, M. Gary-Bobo, **AM. Gué**, **G. Kantor**, D. Kouamé, S. Lecommandoux, C. Llacer, D. Pagnoux, S. Papot, A. Pothier, JP. Pouget, MP. Rols, O. Sandre, H. Seznec, V. Sol

Bienvenue à la Grande Motte pour cette 14ème édition des Journées Annuelles du Cancéropôle Grand Sud-Ouest.

A nouveau, les Axes scientifiques du Cancéropôle Grand Sud-Ouest se sont largement impliqués dans la construction du programme de ces Journées Annuelles, tant au niveau des sessions des Axes que pour l'organisation des plénières, et je les en remercie.

Ce programme est riche en interventions, de la part des chercheurs et des cliniciens de notre interrégion. Il reflète ainsi le dynamisme de la recherche sur le cancer dans le Grand Sud-Ouest et le tissu dense de relations, de collaborations et de projets, créé depuis 15 ans par notre communauté.

Nos Journées sont aussi comme chaque année l'occasion d'accueillir des conférenciers invités de grande qualité que nous remercions vivement.

Je vous remercie d'être présents et réunis pour ces Journées, que j'espère riches en informations et en discussions. Je suis sûr qu'elles seront aussi l'occasion de rencontres informelles et de moments de convivialité, pour poursuivre la dynamique qui nous anime depuis plusieurs années et envisager de nouvelles perspectives de collaboration.

Je vous souhaite à tous de très bonnes Journées du Cancéropôle Grand Sud-Ouest !

Gilles Favre
Directeur du Cancéropôle Grand Sud-Ouest

LE PROGRAMME DE SOUTIEN A L'EMERGENCE DU CANCEROPOLE GSO

NOUVEAU CALENDRIER : AAP OUVERT DU 7 JANVIER AU 7 FEVRIER 2019 – 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 20k€ par projet (maximum)

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 20k€ par projet (maximum)

EMERGENCE DE CONSORTIUM

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 Initiation d'un nouveau consortium au sein du GSO (pas de publication ni de co-financement préalable). Inscription dans une dynamique de mutualisation des expertises (trans ou inter axes).

FINANCEMENT 20k€ par projet (maximum)

EMERGENCE DE COLLABORATIONS - *uniquement ouvert à l'Axe 4 Cancers : enjeux individuels et collectifs*

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

CRITERES Exploration de thématiques encore peu développées, nécessitant des collaborations interdisciplinaires. Les attendus sont l'identification des équipes clés dans le domaine, la pertinence des collaborations présentées, la possibilité de rassembler les équipes.

FINANCEMENT 3k€ par projet (maximum)

LES PROGRAMMES DE SOUTIEN DU CANCEROPOLE GRAND SUD-OUEST

MOBILITE

OBJECTIF Acquérir une technologie originale non présente dans le GSO.

PUBLIC ELIGIBLE Statutaires (chercheurs, ingénieurs, médecins, pharmaciens, odontologistes et vétérinaires) et post-doctorants.

SEJOUR 3 mois maximum FINANCEMENT 4k€ maximum

SOUMISSION EN LIGNE (AUTOMNE ET PRINTEMPS)

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

SOUMISSION EN LIGNE (AUTOMNE ET PRINTEMPS)

CANDIDATS ERC "STARTING GRANT" ET "CONSOLIDATOR GRANT"

OBJECTIF Améliorer le dossier de candidature.

PUBLIC ELIGIBLE Candidats classés A en 1ère phase puis B après l'audition par le jury ERC

FINANCEMENT 20k€ (maximum) destinés à financer des travaux ou de la mobilité

SOUMISSION EN LIGNE AU FIL DE L'EAU

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 40k€ par projet (maximum)

LES FORMATIONS DU CANCEROPOLE GRAND SUD-OUEST

LES TRANSLATIONNELLES DU GSO

Les Translationnelles réunissent de jeunes médecins (internes et chefs de cliniques) et de jeunes chercheurs (fin de thèse et post-doctorants) afin de les former à la recherche translationnelle sur une thématique donnée et de les inciter aux échanges transversaux. Elles bénéficient du soutien institutionnel d'entreprises du médicament.

PRECEDENTES EDITIONS :

- **Oncodermatologie** (ROCHE) en 2014 sur le mélanome et 2015 sur le carcinome épidermoïde
- **Immuno-oncologie** (BMS) en 2016
- **Métastases hépatiques des cancers colorectaux** (SANOFI) en 2016
- **Oncologie thoracique** (BOEHRINGER INGELHEIM) en 2016
- **Immuno-Oncologie : l'immunothérapie anti-cancéreuse** (BMS) en 2018

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

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

OBJECTIFS :

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

PROCHAINE EDITION EN JUIN 2020 A TOULOUSE. DEBUT DES INSCRIPTIONS A L'AUTOMNE 2019.

DEVELOPPEMENT D'UN MEDICAMENT

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

PRECEDENTES EDITIONS :

- **2015 : Développement d'un médicament, de la biologie à la clinique**
- **2017 : Développement d'un médicament : les anticorps thérapeutiques et l'immunothérapie**

WORKSHOP JEUNES CHERCHEURS

Le Workshop Jeunes Chercheurs a objectif d'améliorer la qualité des travaux et des publications de jeunes chercheurs. Il réunit des experts de renom et des jeunes chercheurs (post-doctorants seniors 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.

PRECEDENTES EDITIONS :

- **2014 : Genomic instability in Cancer**
- **2017 : Nanomedicine in Cancer**
- **2018 : Signaling in Cancer**
- **2015 : Signaling in Cancer**
- **2017 : Genome dynamics and Cancer**

PROCHAINEMENT

13 DECEMBRE 2018 : NEW MASS SPECTROMETRY APPROACHES TO STUDY CANCER GENOME FUNCTIONS AND BEYOND

Le **Cancéropôle GSO** et le **SIRIC Montpellier Cancer** vous convient à ce workshop qui se déroulera à **Montpellier**.

Des spécialistes reconnus partageront leur expertise et des projets initiés au sein du Cancéropôle GSO et du SIRIC Montpellier Cancer seront présentés et discutés. La journée vise ainsi à présenter à la communauté scientifique quelques projets en cours et permettre le partage d'expertises et outils sur les approches de protéomiques et autres analyses par Spectrométrie de Masse en particulier l'analyse de la structure et des fonctions du génome.

Contact GSO : Karine MARENDZIAK

24 & 25 JANVIER 2019: JOURNEES SMAC « RECENT ADVANCES IN JOINT MODELS FOR CANCER AND THE NEW STATISTICAL CHALLENGE OF IMMUNOTHERAPY CLINICAL STUDIES »

The 8th edition of the SMAC club scientific days will be held in **Bordeaux**, January 24th-25th and will adress two important topic for biostaticians and statisticians involved on oncology research : the *recent advances in joint models for cancer* (day one) *and the new statistical challenge of immunotherapy clinical studies* (day two).

The program will leave ample room for recognized international experts such as **Michael Sweeting** (George Davies Centre, Leicester), **Dimitris Rizopoulos** (Erasmus University Medical Center, Rotterdam), **Emilio Bria** (U.O.C. Medical Oncology, Fondazione Policlinico Universitario A. Gemelli, Roma), **Ruwanthi Kolamunnage-Dona** (Medical Statitics Institute of Translational Medicine, Liverpool), **Anna Konstorum** (Uconn Health, Center for Quantitative Medicine, Farmington, Connecticut)

Contact GSO : Olivier CLAVERIE

1-2 AVRIL 2019 : 3EME EDITION DU SYMPOSIUM « METABOLISM&CANCER »

This 3rd edition of the "Cancer and Metabolism" symposium will be held in **Marseille**, April 1st-2nd 2019 and will cover various topics including the impact of environmental disruptors on metabolic reprogramming, signaling associated with metformin/biguanides treatments, the role of microenvironment on the tumor metabolic switch as well as new metabolic approaches for translational strategy. Four main sessions will be organized to highlight recent discoveries of recognized experts in their respective fields through lectures and selected abstracts for oral communications. This 3rd edition will be under the auspices of the Cancéropôles PACA, GSO, and CLARA.

Contact GSO : Karine MARENDZIAK

16-17 MAI 2019 : 3RD SUNRISE MEETING « NEW ADVANCES IN CANCER STEM CELLS »

The **SUNRiSE** network (**Solid tumor cancer stem cell network**) will organize its 3rd meeting in Nice. Confirmed guest speakers are **John Dick** (University Health Network, Toronto, Ontario) and **Julio A. Aguirre-Ghiso** (Icahn School of Medicine at Mount Sinai, New York).

Contact GSO : Karine MARENDZIAK

Program

Wednesday 21st November

13h45 – 14h00

Opening ceremony. **Gilles FAVRE**, Scientific director Cancéropôle Grand Sud-Ouest

14h00 – 16h00

with the institutional support of Bristol-Myers Squibb

Chairs: Gilles FAVRE and Nathalie BONNEFOY

Lecture: **Immunotherapy 2.0: Current challenges and perspectives** - **Aurélien MARABELLE** - *Gustave Roussy Institute (Paris)*

- Tumor Necrosis Factor α blockade in melanoma: from basic research to the clinic and back - **Bruno SEGUI** - *Cancer Research Center of Toulouse (Toulouse)*
- Development of first-in-class humanized blocking antibody targeting CD39 ectonucleotidase for combined cancer immunotherapy - **Nathalie BONNEFOY** – *Montpellier Cancer Research Institute (Montpellier)*
- Single cell transcriptomics unveils the distinct cytotoxic profiles of human TCRVδ1 and TCRVδ2 γδ T lymphocytes - **Jean-Jacques FOURNIE** - *Cancer Research Center of Toulouse (Toulouse)*
- Multiplexed-epitope-based tissue imaging and single cell analysis using mass cytometry - **Henri-Alexandre MICHAUD** - *Montpellier Cancer Research Institute (Montpellier)*

16h00 – 17h00 Coffee break and Poster session

17h00 – 19h00

Chairs: Karine DURAND and Sébastien BRITTON

Lecture: **Role of the microenvironment in cancer invasion and therapy response** - **Eric SAHAI** - *The Francis Crick Institute (London)*

- Inhibition of ATR overcomes resistance to oxaliplatin and promotes anti-tumour immunity in colorectal cancer - **Céline GONGORA** - *Montpellier Cancer Research Institute (Montpellier)*
- TRIM proteins act as a molecular rheostat to regulate the ubiquitination and anti-apoptotic activity of BCL2A1 in melanoma cells - **Jérôme KUCHARCZAK** - *Institute of Molecular Genetics of Montpellier (Montpellier) and Université Lyon 1 (Lyon)*
- Targeting the early steps of adaptive resistance to EGFR tyrosine-kinase inhibitors in lung cancer - **Olivier CALVAYRAC** - *Cancer Research Center of Toulouse (Toulouse)*
- Targeting DNA Repair Mechanisms to Overcome Drug Resistance in Diffuse Large B Cell Lymphoma - **Julie DEVIN** - *Institute of Human Genetics (Montpellier)*
- Targeting SUMOylation to overcome resistance of Acute Myeloid Leukemia to chemotherapies and differentiation therapies - **Guillaume BOSSIS** - *Institute of Molecular Genetics of Montpellier (Montpellier)*

Chairs: Kerstin BYSTRICKY and Malik LUTZMANN

Lecture: **The organization of genome duplication is a critical determinant of the landscape of genome maintenance** - **Jenny WU** - *Rennes Institute of Genetics and Development (Rennes)*

- Evaluation of the anti-proliferative role of the miR-34 miRNA in mammalian cells - **Hervé SEITZ** - *Institute of Human Genetics (Montpellier)*

Thursday 22nd November

08h30 – 10h30

Chairs: Daniel FISHER and David SANTAMARIA

Lecture: **An integrative view of cellular senescence and reprogramming** – **Manuel SERRANO** – *Institute for Research in Biomedicine (Barcelona)*

- Novel insights of KRAS dimerization as an essential oncogenic requirement - **David SANTAMARIA** - *Actions for onCogenesis understanding and Target Identification in Oncology (Bordeaux)*
- Ki-67 promotes cell plasticity and tumourigenesis by regulating global gene expression - **Karim MROUJ** - *Institute of Molecular Genetics of Montpellier (Montpellier)*
- Cellular Plasticity in Gliomas - **Jean-Philippe HUGNOT** - *Institute for Neurosciences of Montpellier (Montpellier)*
- Metabolic and mitochondrial flexibility in acute myeloid leukemia - **Jean-Emmanuel SARRY** - *Cancer Research Center of Toulouse (Toulouse)*

Modération : Nathalie BLANC et Aude MICHEL

Conférence: **La Réalité Virtuelle: quel enjeu dans les soins psychologiques en oncologie ? - Anne-Marie ETIENNE** - *Université de Liège (Liège)*

- "Dessine moi une réalité plus belle" : quelles perceptions du dispositif de réalité virtuelle pour les patientes atteintes d'un cancer du sein ? - **Nathalie BLANC et Aude MICHEL** – *Laboratoire Epsylon - Université Paul Valéry (Montpellier)*
- La réalité virtuelle au service des patients en oncologie dans le cadre de la prise en charge de l'anxiété pré-opératoire - **Christine LAURENT** – *Centre Léon Bérard (Lyon)*
- Prêt à porter un casque ? Modeler le réel grâce à la réalité virtuelle – **Nancy RODRIGUEZ** – *Laboratoire d'Informatique, de Robotique et de Micro-électronique de Montpellier (Montpellier)*
- Utilisation de casque aéro-audio-olfactif dans la gestion du stress en aéronautique – **Sarah GRIVOT** – *Laboratoire de Chimie Agro-Industrielle, INRA (Toulouse)*

10h30 – 11h00 Coffee break

11h00 – 12h30

Chairs: Julie PANNEQUIN and Fabrice LALLOUE

Lecture: **Cellular pliancy and breast cancer genetics - Alain PUISIEUX** - *Lyon Cancer Research Center (Lyon)*

- Modulation of macroH2A1 isoforms during EMT process drives the metastastic potential of human prostate cancer cells - **Anne-Claire LAVIGNE** - *Laboratory of Eukaryotic Molecular Biology / Integrative Biology Center (Toulouse)*
- Dynamic changes in chromatin regulate the highly dynamic changes in alternative splicing observed during the EMT - **Reini LUCO** - *Institute of Human Genetics (Montpellier)*
- RNA epigenetic and FTO activity steer cancer cell fate - **Sébastien RELIER** - *Institute of Functional Genomics (Montpellier)*

Modération : Béatrice JACQUES

- Bilan des projets financés par l'axe 4 – **Olivier CLAVERIE** – *Cancéropôle GSO*
- Parolothèque - **Virginie WOISARD** - *Octogone-Lordat (Toulouse)*
- Des innovations biomédicales issues de l'aéronautique et du spatial ? Contribution à une analyse des processus translationnels en cancérologie - **Pascal RAGOUET** - *Centre Emile Durkheim (Bordeaux)*
- Règles d'enregistrement des tumeurs évolutives - **Laetitia DAUBISSE MARLIAC** - *Registre des cancers du Tarn (Albi)*

12h30 – 14h30 Lunch break and Poster session

14h30 – 16h30

Chairs: Urszula HIBNER and Violaine MOREAU

Lecture: **Genomics of liver tumors: new mechanisms of carcinogenesis** - **Jessica ZUCMAN-ROSSI** - *Functional Genetics of Solid Tumors (Paris)*

- New landscape in HCC treatment: TKI and Immunotherapies - **Eric ASSENAT** - *Institute of Molecular Genetics of Montpellier and University Hospital (Montpellier)*
- Deciphering the dual role of ß-catenin in hepatocellular carcinoma - **Violaine MOREAU** - *Bordeaux Research in Translational Oncology (Bordeaux)*
- Tumor-Antagonizing Fibroblasts in hepatocellular carcinoma - **Bilguun ERKHEM OCHIR** - *Montpellier Cancer Research Institute / Gunma University Graduate School of Medicine (Gunma, Japan)*
- CDK8 kinase acts as an oncogene in hepatocellular carcinoma - **Damien GREGOIRE** - *Institute of Molecular Genetics of Montpellier (Montpellier)*

Modération : Anne-Marie GUE

- Un programme de recherche intégré et pluridisciplinaire en SHS sur une innovation, la radiologie interventionnelle : les points de vue du sociologue des sciences, de l'économiste et du sociologue de la santé – **Béatrice JACQUES, Pascal RAGOUET et Philippe GORRY** – *Centre Emile Durkheim et Gretha (Bordeaux)*
- Présentation et discussions d'innovations en développement au sein de l'axe 5
  - L'électrochimiothérapie : comment faire passer le courant entre la recherche et le milieu médical ? - **Marie-Pierre ROLS** - *Institut de Pharmacologie et de Biologie Structurale (Toulouse)*
  - Nanoparticules dans l'alimentation humaine : existe-t-il un lien avec l'augmentation du nombre de cancers colorectaux ? - **Audrey FERRAND** - *Institut de Recherche en Santé Digestive (Toulouse)*

16h30 – 17h00 Coffee break

17h00 – 18h30

Chair: Philippe GORRY

Lectures: **Open Science & Publishing Models - how to share reproducible data - Andrea LEIBFRIED** - *Life Science Alliance (Germany)*

The transformation of the scientific paper : from knowledge to accounting unit - Yves GINGRAS – *Quebec University (Canada)* & **Johan GIRY** - *Strasbourg University (Strasbourg)*

- Economics of Scientific Edition - **Philippe GORRY** - *Gretha (Bordeaux)*

18h30 – 19h15

Session 7 – Artificial intelligence and cancer 87

Chair: Claude SARDET

Lecture: **Omics data in cancer: No more humans ! – William RITCHIE** – *Institute of Human Genetics (Montpellier)*

Friday 23rd November

08h30 – 10h15

organized with SIRIC MONTPELLIER CANCER

Chairs: David AZRIA and Malik LUTZMANN

Lecture: **Radiotherapy from classical DNA damage to immunotherapy** - **Eric DEUTSCH** - *Gustave Roussy Institute (Paris)*

- Lymphocyte apoptosis and individual radiosensitivity - **David AZRIA** - *Montpellier Cancer Institute (Montpellier)*
- Therapeutic efficacy of ^{177}Lu-lilotomab satetraxetan in non-Hodgkin B-cell Lymphoma is controlled by G2/M cell cycle progression - **Jean-Pierre POUGET** - *Montpellier Cancer Research Institute (Montpellier)*
- Repair proteins in quest of the Ku ring: molecular insights into the first steps of DNA double-strand breaks repair by end-joining - **Patrick CALSOU** - *Institute of Pharmacology and Structural Biology (Toulouse)*

Chairs: Julie PANNEQUIN and Thibault MAZARD

Lecture: **Intestinal tuft cells: novel regulators of the immune micro-environment - Philippe JAY** - *Institute of Functional Genomics (Montpellier)*

- The HSP90 co-chaperone RPAP3 plays an essential role in intestinal homeostasis - **Bérengère PRADET-BALADE** - *Montpellier Cell Biology Research Center (Montpellier)*
- H-1 parvovirus inhibits both primary tumor and metastatic growth of human pancreatic tumors - **Pierre CORDELIER** - *Cancer Research Center of Toulouse (Toulouse)*
- miR-148a sensitizes colon cancer stem cell to chemotherapy by targeting Pregnane X- Receptor signaling - **Jean-Marc PASCUSSI** - *Institute of Functional Genomics (Montpellier)*
- MAGI1 regulates anchorage-independent growth in breast and colon cancers by modulating the interaction between the HIPPO pathway regulators AMOT and YAP - **Lisa HERON-MILHAVET** - *Montpellier Cancer Research Institute (Montpellier)*

10h15 – 10h45 Coffee break

10h45 – 12h30

Chairs: Philippe JAY and Philippe LEHOURS

Lecture: **Microbiota and its involvment in pathology** - **Joël DORE** - *Micalis Institute "Food and Gut Microbiology for Human Health" (Jouy-en-Josas)*

- Characterisation of bioactive lipid molecules produced by bacteria: role in intestinal homeostasis - **Nicolas CENAC** - *Digestive Health Research Institute (Toulouse)*

Lecture: **Remote control of antitumoral immunity by the gut microbiota** - **Mathias CHAMAILLARD** - *Lille infection and immunology center and Pasteur Institute (Lille)*

- Impact of *Helicobacter sp* infection on gastric lymphomagenesis and microbiota - **Philippe LEHOURS** - *Bordeaux Research in Translational Oncology (Bordeaux)*

12h30 – 12h45 Poster award session

Session 1 – The future of immunotherapy in oncology

With the institutional support of

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Immunotherapy 2.0 : Current challenges and perspectives

Aurélien MARABELLE

Institut Gustave Roussy, Villejuif

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Tumor Necrosis Factor α blockade in melanoma: from basic research to the clinic and back

Bruno SEGUI[1,2]

[1] Centre de Recherche en Cancérologie de Toulouse

[2] Université Toulouse 3 Paul Sabatier

Melanoma is a highly immunogenic cancer, the progression of which is likely associated with immune escape mechanisms. Immune Checkpoint Inhibitors (ICI) are monoclonal antibodies targeting immune checkpoints such as CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) and PD-1 (Programmed Cell Death-1) and have demonstrated significant efficacy in the treatment of metastatic melanoma. However, about 40% of patients do not display therapeutic responses, and a significant proportion of responders experience tumor relapse within 2 years following treatment induction. Moreover, patients treated with ICI develop severe immune-related adverse events such as colitis, which can be cured with one bolus of anti-Tumor Necrosis Factor α (TNF) antibodies (infliximab). In this context, whether anti-TNF antibodies affect the anti-cancer immune response remains unknown.

Our recent work has highlighted that TNFR1-dependent TNFα signaling impairs the accumulation of CD8+ tumor-infiltrating T lymphocytes (CD8+ TIL) in mouse melanoma (Bertrand et al., Cancer Res. 2015). Our more recent data indicate that in mice TNF or TNFR1 blockade enhances anti-PD-1 efficacy on anti-cancer immune response towards solid cancers.

Mechanistically, TNF blockade prevents anti-PD-1-induced TIL cell death as well as PD-L1 and TIM-3 expression. As a matter of fact, TNF expression positively correlates with expression of PD-L1 and TIM-3 in human melanoma specimens (Bertrand, Montfort et al., Nat. Commun., 2017). This study provides a strong rationale to develop a combination therapy based on the use of anti-PD-1 and anti-TNF in cancer patients. An ongoing phase 1b clinical trial (TICIMEL, NCT03293784; P.I.: Prof. N. Meyer) aims at evaluating the safety and tolerance of the combination of immune checkpoint inhibitors and anti-TNF in metastatic melanoma patients in our institute (Institut Universitaire du Cancer of Toulouse; IUCT). Our laboratory at the Cancer Research Center of Toulouse (CRCT) is in charge of the exploratory part of TICIMEL to evaluate how anti-TNF antibodies modulate the immune response under ICI in advanced melanoma patients.

Our project illustrates the interest of the Toulouse Oncopole structure, which facilitates the transfer of basic research (from the CRCT) to the clinic (at the IUCT) and back (to the CRCT) to develop innovative treatment combinations of immunotherapies and discover novel biomarkers to predict clinical responses in patients.

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Development of first-in-class humanized blocking antibody targeting CD39 ectonucleotidase for combined cancer immunotherapy

Nathalie BONNEFOY[1], Ivan PERROT[2], Henri-Alexandre MICHAUD[1], Aurélie DOCQUIER[3], Laurent GROS[1], Cécile DEJOU[3], Carine PATUREL[2], Yannis MOREL[2], Eric VIVIER[2]

[1] Institut de Recherche en Cancérologie de Montpellier

[2] Innate Pharma, Marseille

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Immuno-oncology has revolutionized cancer treatment, particularly through Immune Checkpoint Inhibitors (ICIs). However, as many cancers are resistant to ICIs, the targeting of additional inhibitory signals is a promising approach for limiting tumor evasion. The production of adenosine at the tumor bed via the sequential activity of the CD39 and the CD73 ectoenzymes participates to the generation of an immunosuppressive tumor microenvironment.

We demonstrated that *in vivo* blockade of ATP/adenosine pathway in CD39KO mice resulted in improved anti-tumor efficacy of immunogenic chemotherapy and of ICIs. We further described here the discovery and preclinical development of a first-in-class CD39-blocking antibody, IPH52, that specifically binds with high affinity to human CD39 protein and potently inhibits enzyme activity under its soluble and membrane-associated form, without inducing down-modulation. Besides its efficacy to inhibit adenosine-mediated T cell suppression in vitro, the anti-CD39 antibody maintains high concentration of extracellular ATP that further enhances dendritic cell activation and subsequent T cell proliferation *in vitro*.

These results support the clinical development of the anti-CD39 mAb IPH52 and its combination with ICIs and chemotherapies to improve cancer treatments.

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Single cell transcriptomics unveils the distinct cytotoxic profiles of human TCRVδ1 and TCRVδ2 γδ T lymphocytes

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The γδ T lymphocytes are unconventional and infrequent CD4- CD8- T lymphocytes infiltrating most tissues and organs of vertebrates, representing ~1% of circulating mononuclear cells in human adult's blood. Although most γδ T lymphocytes have anti-cancer functions and their presence among tumour-infiltrating γδ T lymphocytes constitute a strong biomarker of good outcome in cancer patients, the gene expression profile of γδ T cells has not been characterized at the single cell level. Hence despite their biological importance, not only γδ T lymphocytes are never spotted or identified as such in scRNASeq of PBMC and healthy tissues and tumor biopsies, but whether they display heterogeneity according to TCR is unknown. Here we present an approach for antibody-free detection of γδ T lymphocytes from bulk PBMC scRNASeq, and report the single cell gene expression profile of purified TCRVδ1 and TCRVδ2 γδ T lymphocytes cell sorted from healthy blood donor. This study reveals that high resolution t-SNE plots of large scRNA-Seq data sets are necessary to delineate the infrequent γδ T lymphocytes among human PBMC. As a whole, the γδ T lymphocytes map in a single cytotoxic region bridging T CD8 and NK cells from PBMC t-SNE plots. However, the TCRVδ1 and TCRVδ2 γδ T lymphocytes form two different clusters with distinct cytotoxicity gene expression profiles in both cases. Finally, pseudo-time reconstruction of the single cell maturation trajectories for each subset showed strikingly parallel trajectories from naïve to terminally differentiated cells, including TEMRA cells with mitotic activity. This landmark study will enable the spotting of γδ T lymphocytes in further mapping of cellular composition of tissues samples.

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Multiplexed-epitope-based tissue imaging and single cell analysis using mass cytometry

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Recent progresses for tumor therapy are mostly the results of technologic advances that allowed a more comprehensive analysis of the tumoral microenvironment (TME), mainly through the use of flow cytometry for single cell in suspension (SCS) analysis and immunohistochemistry or immunofluorescence for tissue analysis. Together with transcriptomic approaches, those conventional methods allowed spectacular breakthrough in cancer therapy field with the discovery, for instance, of the immunosuppressive pathways B7.1/2/CTLA-4 and PD-L1/2/PD-1 and the immunotherapies that target those immune breaks. Such discovery deeply modified our understanding of the TME and underlined the importance to integrate all the different cellular actors (tumor cells, immune cells, cancer-associated fibroblasts, endothelial cells etc.), their cellular state or sub cellular groups/compartments, their interactions and their localization within the TME.

The constant increase of biological markers (cluster of differentiation, cytokine, transcription factors, etc.) tends to invalidate the conventional technics. Indeed, the number of markers that can be simultaneous used are limited because of spectral overlap, auto fluorescence, dye instability or photobleaching which represent today significant limitations regarding the complexity and the heterogeneity of the TME.

The ICM and IRCM just acquired the first and unique in France Hyperion Imaging System (HIS). Developed by Fluidigm, the HIS is an imaging module associated to the Helios, the 3rd generation of CyTOF, which allows SCS analysis and tissue imaging using the mass spectrometry technology. Mass-based cytometry and imaging methods overcome many of the above limitations. Tissue or fresh cells in suspension are incubated with metal-labeled primary antibodies and specific isotopes are then visualized using mass spectrometry. Mass cytometry supports high multiplexing (current instrumentation allows 135 simultaneous channels. Actual limitations come from the limited available reagents) in absence of background signal with a very low signal leak (<3%). The combination of the SCS analysis together with the tissue imaging allows three level of information:

1. The identification of cell types, biological processes (functionality, proliferation, apoptosis) and their particular distribution report on the spatial composition of the TME
2. Cell segmentation and single cell unsupervised-analysis (Principal Component Analysis, span tree, clustering) allow the discovery of unexpected cell subtypes and heterogeneity in an unbiased manner. Subcellular compartment and biological activities can be assigned based on the presence or absence of markers
3. The spatial view and cell segmentation allow to put into their environmental context each cell type and its functional state. Those states can be related to cell types, states and neighborhoods and eventually reconstitute the cellular social network of populations of interest.

The applications of mass-based SCS analysis and tissue imaging are numerous and varied. Beyond a deep and comprehensive study of the TME, biomarker and drug discovery, pharmacokinetics of drugs into the tumor, therapeutic assessment of drug combination are also feasible. Furthermore, data generated can be compared against or integrated to data generated with 'omics' data such as genotype, transcriptome, proteome, metabolome or imaging.

Session 2A – Resistance and signaling

2A / 1

Role of the microenvironment in cancer invasion and therapy response

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We will present data on the mechanism of cooperation between cancer cells and stromal fibroblasts. Many tumors show an initial response to targeted therapies before genetic resistance emerges, however little is known about how tumor cells tolerate therapy before genetic resistance dominates. We show how the ECM generates a 'safe haven' in which melanoma cells can tolerate targeted therapy. This supports the population of cancer cells from which genetically resistance emerges. These data argue fibroblast - cancer cell cross-talk via the ECM. We have recently uncovered a novel mechanism of tumour - stroma cross-talk involving a pathological heterotypic cell-cell contact. In normal skin, epithelial cells and fibroblasts do not contact because they are separated by a basement membrane. However, a signature feature of tissue damage and invasive squamous cell carcinoma is breakdown of the basement membrane, epithelial cells and fibroblasts can then contact each other. This heterotypic can transmit force and enable invasion. More crucially, it triggers dramatic changes in chemokine, cytokine, and other inflammatory modulators triggering anti-microbial and anti-viral responses. We propose that this represents a tissue level damage sensing mechanism analogous to molecular DAMPs.

2A / 2

Inhibition of ATR overcomes resistance to oxaliplatin and promotes anti-tumour immunity in colorectal cancer

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To identify molecular targets of oxaliplatin resistance in colorectal cancer (CRC), we performed a shRNA-based loss of function genetic screen using kinome library. We found that the silencing of ataxia-telangiectasia mutated and RAD3-related (ATR), a serine/threonine protein kinase involved in the response to DNA stress, restored oxaliplatin sensitivity in oxaliplatin resistant cellular model. Moreover, the combined application of the ATR inhibitor VE-822 and oxaliplatin had a strong synergistic effect in six different CRC cell lines and notably their oxaliplatin-resistant sub-clones. The combination of oxaliplatin and VE-822 promoted DNA single- and double-strand break formation, growth arrest and apoptosis. It also increased replicative stress, cytoplasmic DNA and signals related to immunogenic cell death, such as calreticulin exposure as well as HMGB1 and ATP release. Importantly, the combined administration of VE-822 and oxaliplatin significantly increased survival in a syngenic CRC mouse model by promoting anti-tumor T cell responses supporting the rationale to use this drug combination for treatment. Finally, we identified a DNA repair-gene signature discriminating the sensitive from drug resistant CRC patients. Our results highlight the strong potential of ATR inhibition combined to oxaliplatin to sensitize cells to chemotherapy, creating dramatic DNA damages and stimulating ICD. This drug combination may become a new therapeutic option for CRC patients facing therapeutic failure.

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TRIM proteins act as a molecular rheostat to regulate the ubiquitination and anti-apoptotic activity of BCL2A1 in melanoma cells

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BCL2A1 is an anti-apoptotic member of the BCL-2 family that contributes to chemoresistance in a subset of tumors including melanoma. Ubiquitination followed by proteasomal degradation is a major tumor-suppressor mechanism regulating BCL2A1 function. However, the enzymes involved in the regulation of BCL2A1 protein stability are unknown. Here we present evidence that TRIM28 is an E3 ubiquitin-ligase for BCL2A1 and that TRIM17 stabilizes BCL2A1 by blocking TRIM28 from binding and ubiquitinating BCL2A1 at the mitochondria. Finally, overexpression of TRIM28 or knock-out of TRIM17 by inducible CRISPR/Cas9 technology reduced BCL2A1 endogenous protein levels and restored sensitivity of melanoma cells to BRAF-targeted therapy. Therefore, our data describe the first molecular rheostat in which two proteins of the TRIM family of E3 ubiquitin-ligases antagonistically regulate BCL2A1 stability and apoptotic activity.

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Targeting the early steps of adaptive resistance to EGFR tyrosine-kinase inhibitors in lung cancer

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Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) are effective therapies for advanced lung cancer patients bearing EGFR-activating mutations, but are not curative due to the invariable apparition of resistances. Recent in vitro studies have suggested that TKI-resistance might not only be explained by a drug selection of pre-existing resistant sub-clones as it what was generally assumed, but may also arise de novo from a small population of drug-tolerant cells (DTC) that initially resists the treatment by entering a slow cycling state. How these cells can survive and how they can acquire genetic alterations that allow them to fully recover proliferative capacities are two crucial questions that remain unsolved to date. Targeting these DTC should thus be a new promising approach to hamper the emergence of secondary resistance, however we still lack an accurate phenotypic and molecular characterization of this particular state, which are a prerequisite to the development of new therapeutics.

Our previous work identified the RHOB/AKT axis as a key determinant of resistance to targeted therapy in EGFR-mutated lung cancer patients and recent data strongly suggest that this pathway could be a common adaptive mechanism to ERK pathway inhibition and hence a strong candidate to drug-tolerant state acquisition. We have also characterized in vitro a new phenotype associated with drug tolerance in response to EGFR-TKI that shares similarity to a known process of Therapy-Induced Senescence. Understanding the mechanisms underlying this senescent-like phenotype but also the molecular events associated with senescence escape could provide new therapeutic approaches to eliminate the reservoir of drug-tolerant cells and to prevent emergence of resistance mutations responsible for the relapse of patients.

2A / 5

Targeting DNA Repair Mechanisms to Overcome Drug Resistance in Diffuse Large B Cell Lymphoma

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Diffuse large B-cell lymphoma (DLBCL) accounts for 40% of adult non-Hodgkin lymphomas. Most DLBCL patients achieve long-term remission after treatment, but a third relapse after conventional Rituximab (R)-based chemotherapy regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) (Siegel, *Cancer J Clin* 2012). Cancer cells are exposed to chronic replication stress, which impedes DNA replication and induces mitotic catastrophe (Shaheen, *Blood* 2011). Functional DNA repair pathways are therefore important for the survival of cancer cells. This dependence can be to exacerbate DNA damage induced by chemotherapy. Furthermore, high-risk DLBCL patients overexpress genes potentially involved in resistance to CHOP-based regimens, such as genes of the nucleotide excision repair (NER) pathway (Bret, *Oncotarget* 2012, *Cell Cycle* 2013).

We developed GEP-based DNA repair scores that allow to identify high-risk patients that could benefit from treatment with DNA repair inhibitors (Bret, *BJH* 2015). DLBCL treatments include cyclophosphamide an alkylating agent that induces interstrand crosslinks (ICL), and doxorubicin, a DNA topoisomerase inhibitor II that induces DNA double-strand breaks, DNA adducts and ICL formation. Inhibiting DNA repair is a promising strategy to improve the efficacy of genotoxic drugs and overcome drug resistance. Our data support the view that inhibitors of DNA damage signaling and DNA repair have potential therapeutic interest in DLBCL. We characterized the drug-response of 16 DLBCL cell lines to 8 DNA repair inhibitors including PJ34 (PARP inhibitor), NU7441 (DNAPK inhibitor), KU55933 (ATM inhibitor), PF477736 (CHK1 inhibitor), AZD6738 (ATR inhibitor), MK8776 (CHK1 inhibitor), AZD1775 (Wee1 inhibitor), MP-470 (Rad51 inhibitor) and genotoxic agents used in DLBCL treatment (Cyclophosphamide, Gemcitabine, Doxorubicin and Etoposide). All drugs induced significant apoptosis (PARP cleavage) and significant inhibition of proliferation (BrdU incorporation) in the different DLBCL cell lines tested ($P<0.05$). CHK1 inhibitor, Wee1 inhibitor, Cyclophosphamide, Gemcitabine and Doxorubicin induced DNA damages monitored by H2AX phosphorylation. Correlating drug response of each compounds with our GEP-based DNA repair scores (Bret et al, *BJH* 2015), we identified a significant correlation between FANC score and response to ATR inhibitor (AZD6738) and HRR score/BER score and response to Etoposide ($P<0.05$). High-risk DLBCL patients identified with GEP-based FANC, HRR and BER scores may benefit from treatment by ATR inhibitors or Etoposide respectively. Since DNA repair pathways play a role in drug resistance, we sought to identify new synthetic lethal combinations associating IC_{20} of DNA repair targeted treatments with conventional genotoxic agents in DLBCL. Applying a standard threshold of 2 SDs below the IC_{50} of the genotoxic agent alone, a total of 3 synthetic lethal combinations have been identified including cyclophosphamide with CHK1 inhibitor (PF477736) or with ATR inhibitor (AZD6738) and doxorubicin with DNAPK inhibitor (NU7441). These combinations significantly decrease IC_{50} of genotoxic agents ($P<0.05$) and combination indexes (CI) were strongly <1. Furthermore, we identified new potent synergistic combinations (CI <1) including CHK1 inhibitor (PF477736), ATR inhibitor (AZD6738) and ATM inhibitor (KU55933) with etoposide. Despite overall improvements in the treatment of DLBCL, including the use of rituximab, approximately one-third of patients fail to achieve complete remission or experience relapse. This remains a major cause of morbidity and mortality.

The DNA repair scores could be useful to identify high-risk patients and define the best synthetic lethal approach combining DNA repair inhibitors with conventional chemotherapy. These results open new perspectives to improve the treatment of DLBCL patients and provide new strategies to overcome drug resistance.

2A / 6

Targeting SUMOylation to overcome resistance of Acute Myeloid Leukemia to chemotherapies and differentiation therapies

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Acute Myeloid Leukemias are severe haematological malignancies with very poor prognosis, largely due to a high rate of relapse and the acquisition of resistance to chemotherapeutic treatments. We have shown that SUMOylation, a post-translational modification of the ubiquitin family, plays an important role in Acute Myeloid Leukemias (AML) response to chemotherapies combining the nucleoside analogue cytarabine (Ara-C) with an anthracyclin, such as daunorubicin (DNR). One of their early effects is the ROS-dependant deconjugation of SUMO from its targets, in particular various transcription factors and co-regulator bound to chromatin. This participates in the rapid transcriptional reprogramming occurring in chemosensitive AML cells upon chemotherapeutic treatment. In chemoresistant AML, this ROS/SUMO axis is not activated but its targeting can reactivate pro-apoptotic transcriptional programs and help eliminate the resistant cells.

All-trans-retinoic acid (ATRA) is successfully used for differentiation therapy of Acute Promyelocytic Leukemia (APL), a minor subtype of Acute Myeloid Leukemia (AMLs). However, its clinical efficacy, if any, is very limited in the case of non-APL AMLs, largely due to epigenetic repression of ATRA-responsive genes. Using cell lines and patient samples in both in vitro and in vivo settings, we have shown that SUMOylation represses the differentiating effects of ATRA on non-APL AML cells. Pharmacological or genetic inhibition of SUMOylation both increases ATRA-induced cell differentiation and death regardless of resistance or sensitivity to the genotoxics currently used in the clinic whereas enhancing SUMOylation by overexpressing the SUMO conjugating enzyme Ubc9 reduces differentiation. At the molecular level, inhibiting SUMOylation primes AML cells for differentiation by facilitating the expression of myeloid differentiation-associated genes, including CEBPa and RARa.

Altogether, our work suggests that targeting the SUMO pathway could constitute a new approach in the treatment of AMLs, a cancer with dismal prognosis.

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Session 2B – Genome dynamics and cancer

2B / 1

The organization of genome duplication is a critical determinant of the landscape of genome maintenance

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The mechanisms regulating genome duplication are highly conserved, and they give rise to a spatiotemporal organization of replication initiation along the chromosomes referred to as the replication program. However, the biological importance of this program for cellular physiology remains largely unexplored. We have addressed this fundamental question in the context of genome maintenance upon challenge to DNA synthesis. For our studies, we have taken advantage of the inappropriate origin firing that occurs when fission yeast cells lacking the ATR/Rad3 checkpoint kinase are subjected to replication stress. Using this model, we demonstrate that the replication program quantitatively dictates the extent of origin deregulation and the clustered localization of these events. Strikingly, aberrant initiation results in local accumulation of single-stranded DNA and the Rad52 repair protein. These loci constitute a defining source of the overall ssDNA and Rad52 hotspots in the genome and delineate the overall pattern of genome instability. We then induced a genome-wide reprogramming of origin usage and evaluated its consequences in our experimental system. Remarkably, this led to a complete redistribution of the sites of both inappropriate initiation and associated Rad52 recruitment. We therefore conclude that the organization of genome duplication governs the checkpoint control of origin-associated hotspots of instability and plays an integral role in shaping the landscape of genome maintenance.

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Assessment of miRNA-controlled phenotypes from a functional perspective: the example of miR-34-guided control of cell proliferation

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microRNAs ("miRNAs") have attracted a lot of attention over the past 17 years: their role as post-transcriptional gene regulators, together with the poor specificity of their target recognition rules, have suggested that they control the expression of more than 60% of human coding genes (Friedman *et al.*, 2009). In particular, the miR-34 miRNA family was the first proposed anti-tumorigenic miRNA family; it was shown to inhibit cell proliferation in various cell types in human and in mouse (He *et al.*, 2007). Yet, a decade of intense research efforts has failed to identify the miR-34 targets that are responsible for that phenotype. MiR-34 based anti-cancer drugs have also proved disappointing, with the most advanced project (the "MRX34" synthetic miR-34) triggering serious secondary effects, leading to a premature closure of the clinical phase I trial.

These difficulties are due to our current inability to predict accurately the physiological effects of a given miRNA. Current target identification methods (both experimental and computational) are contaminated with large numbers of false positives (Pinzón *et al.*, 2017; Seitz, 2017). Long lists of experimentally-identified miRNA interactors (*e.g.*, with CLIP methods), or of computationally-predicted targets, now need to be replaced with functionally validated targets. We are thus using CRISPR to mutate miR-34 miRNAs in cultured cells and probe their actual cellular effects. We will also set up a CRISPR screen to measure precisely the contribution of every possible miR-34 target to the proliferation phenotype in an unsupervised manner. Using mathematical modeling, we will derive quantitative information about the relative role of each potential target in cell proliferation control.

These experimental procedures can be generalized to every other instance of miRNA-mediated control of cell proliferation. We expect such functional assessment to improve our understanding of miRNA-guided control of gene expression, which is currently too imprecise to be useful in clinical settings.

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2B / 3
p57/Kip2 acts as a transcriptional regulator in colorectal cancer

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p57/Kip2 is a cyclin/CDK inhibitor and a putative tumor suppressor. In fact, p57 inactivation occurs in several type of carcinomas and p57 is a significant prognostic marker in many type of cancers, including intestinal and colorectal cancers. p57 is also mutated or silenced in Beckwith-Wiedemann syndrome (BWS), characterized by multiple developmental defects and predisposition to tumor development during childhood. Molecular and genetic evidence indicate that p57 also has CDK independent roles. To characterize the CDK independent roles of p57 in vivo, a knock-in mice expressing a mutant p57 (p57CK-) that cannot bind to cyclins and CDKs has been developed. Comparative study of p57CK- and p57KO mice has confirmed this idea and also revealed that p57 is required for normal intestinal development in a CDK independent manner.

Our results indicate that p57 plays a critical role in the regulation proliferation and maintenance of intestinal stem cell. Two populations of stem cells have been described in the intestine: proliferative crypt base columnar cells (CBCs) and +4 reserve stem cells. Several studies have shown that most intestinal cancers originate from genetic transformation or deregulation of the intestinal stem cell compartment and that CBCs act as cancer stem cells in colorectal cancer. Our data suggest that p57 plays a critical role in maintaining the balance between these two stem cell populations and p57 loss results in a massive enlargement of the proliferating stem cell pool. We are currently investigating the molecular mechanism by which p57 controls intestinal stem cell proliferation and found that p57 can bind Ascl2, a transcription factor critical for intestinal stem cell specification and maintenance. Finally, our results show that p57 can inhibit Ascl2 transcriptional activity, and we identified new p57 partners involved in this transcriptional repressor complex. This work provides novel mechanistic insight into the role of p57 in intestinal tumorigenesis.

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Transcriptional repression of interferon-stimulated genes by the TRRAP transcriptional co-activator and its chaperone TTT

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Gene expression regulation is essential for cells to respond to signaling cues. Transcription represents a crucial regulatory step and involves several factors with multiple distinct activities. One such factor, TRRAP (Transformation/transcription domain associated protein), was first discovered as an interacting partner for the MYC oncogenic transcription factor. TRRAP was then shown to be part of two co-activator complexes, SAGA and TIP60. Interestingly, TRRAP is the sole pseudokinase of the PIKK family, which encompasses five kinases playing critical roles during key cellular processes. The PIKKs are folded and assembled into their active complexes by a dedicated co-chaperone of HSP90, namely TTT. We used CRISPR-Cas9 to construct fast, inducible degron alleles of both TRRAP and the TTT co-chaperone in colorectal cancer cells. Transcriptomic analysis revealed a significant overlap between genes which expression depends on TRRAP and TTT. Remarkably, most of these genes are MYC and E2Fs targets, suggesting that TTT has an important role in sustaining the activities of these oncogenic transcription factors in colorectal cancer cells. Surprisingly, TTT and TRRAP depletion also induced a common Type I Interferon gene expression signature. Antibody-targeted chromatin profiling (CUT&RUN) and kinetic analyses revealed that TRRAP directly represses the expression of IRF9, which acts as a master regulator for the expression of interferon stimulated genes. To conclude, we have uncovered an unexpected repressive role of TTT and TRRAP at interferon-stimulated genes in colorectal cancer cells, revealing a previously unidentified mechanism by which TRRAP contributes to tumorigenesis.

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JMJD6 participates in the maintenance of rDNA integrity in response to DNA damage

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Genome integrity is constantly disrupted by exogenous and endogenous sources producing DNA damages. If not repaired, they could promote genetic instability and thus diseases such as cancer. To prevent such deleterious effects, repair mechanisms are crucial and occur in a chromatin context which is regulated by histone post-translational modification. Among them, histone methylation has been shown to be important for DNA repair and other processes due to a dynamic control by histone demethylase and histone methyltransferase. After the screening of a siRNA library, we identified a histone demethylase JMJD6 whose depletion in U2OS cells alters DNA damage response and cell survival to ionizing radiation. Moreover, we observed JMJD6 recruitment at DNA damage site in nucleolus by live cell laser tracking. Nucleolus is composed of ribosomal RNA genes in tandem repeats which are highly transcribed and subject to frequent DNA damages. In response to rDNA damages, rDNA transcription silencing occurs and is exacerbated in JMJD6 depleted cells. Furthermore, in JMJD6 depleted cells we observed genetic instability characterized by increased loss of rDNA copies after irradiation. Here we identified JMJD6 as component of the DNA damage response occurring at rDNA regions and participating to maintain its integrity.

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Rad18: a novel target to sensitize cancer stem cells to therapy

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Rad18 is a non-essential gene coding for an E3 ubiquitin ligase that has been so far mainly implicated in DNA damage tolerance, by facilitating the progression of DNA replication in the presence of DNA damage. Rad18 is also involved in the two major double strand break repair pathways, non-homologous end joining and homologous recombination. We have previously shown that high levels of Rad18 are sufficient to shut down the DNA damage checkpoint and induce resistance to DNAdamagingagents in mammalian cells. In addition, we have shown that Cancer Stem Cells (CSCs) of the radiation-resistant brain cancer glioblastoma express a high level of Rad18 compared to the their differentiated counterparts, and that Rad18down regulationsensitizes glioblastoma to cisplatin (Kermi et al., Dev Cell 2015). Here we report an unexpected essential role for Rad18 in the proliferation of CSCs of diverse origins. Rad18 down regulation strongly affects the growth and self-renewal of glioblastoma CSCs and reduces the fraction of the stem cells population, resulting in cell cycle arrest in the absence of external damage. Exposure to DNA damaging agents additionally exacerbated this phenotype. Further, tumor growth of glioblastoma xenografts under expressing Rad18 in mice was severely reduced and survival was increased. Consistent with these results, high Rad18 expression in glioblastoma is correlated with a bad patient prognosis. Conversely, ectopic Rad18 expression provided a proliferation advantage and induced loss of cell-to-cell contact inhibition.

Altogether these results show that Rad18 is an essential gene required for CSCs proliferation and put forward this gene as a novel target to sensitize CSCs.

Session 2C – Translational research, from biology to the clinic

2C / 1

Cathepsin D-targeting antibodies for triple-negative breast cancer therapy

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Triple-negative breast cancer (TNBC) treatment is currently restricted to chemotherapy. Hence, tumor-specific molecular targets and/or alternative therapeutic strategies for TNBC are urgently needed. The aspartic protease cathepsin-D (cath-D), a marker of poor prognosis in breast cancer (BC), is overproduced and hypersecreted by human BC cells.

Many studies indicated that extracellular cath-D displays oncogenic activities, suggesting it could represent a novel therapeutic target in TNBC. In order to block its oncogenic actions, we generated human IgG1 antibodies against extracellular cath-D by phage display.

We showed that elevated CTSD mRNA levels correlated with shorter recurrence-free survival. Using proteomics analysis and anti-cath-D immunohistochemistry performed on Tissue Micro-Array, we observed that extracellular cath-D was detected in the tumor microenvironment of TNBC, but not in matched normal breast stroma samples. Our results thus indicate that cath-D is a tumor cell-associated extracellular biomarker and a potent target for antibody-based therapy in TNBC. We found that anti-cath-D human antibodies, F1 and E2, accumulated in TNBC MDA-MB-231 tumor xenografts in athymic mice by SPECT-CT (Single Photon Emission Computed Tomography) and biodistribution analysis. F1 and E2 antibodies inhibited tumor growth of MDA-MB-231 tumor xenografts and improved mice survival without apparent toxicity. F1, the best antibody candidate, inhibited tumor growth of TNBC patient-derived xenografts.

Together, our results indicate that antibody-based targeting of cath-D may have therapeutic efficacy for TNBC treatment.

2C / 2

Inhibiting integrin β8 to differentiate and radiosensitize Glioblastoma-initiating Cells

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Glioblastomas (GB) are malignant brain tumors with dismal prognosis despite standard treatment which includes maximal surgical resection followed by fractionated radiotherapy with concomitant and adjuvant chemotherapy (Temozolomide). This severe outcome could partly be explained by the presence into the tumor of Glioblastoma-Initiating Cells (GIC), characterized by their ability to self-renew, their higher expression of specific GIC markers, their pluripotent aptitude to differentiate (neurons, astrocytes or oligodendrocytes), and their high tumorigenic potential. In addition, GIC are particularly chemo-radioresistant and involved in tumor recurrence. So, current research focuses on developing potential GIC-targeted therapies in order to improve GB treatment.

Regarding current literature but also transcriptomic results obtained in our lab, integrin Beta 8 (ITGB8) emerged as a potential selective target in GIC. We then hypothesized that ITGB8 could be involved in stemness maintenance but also radioresistance in GIC.

We first demonstrated, with several primocultures from patients, that ITGB8 is overexpressed in GIC in comparison to their differentiated progeny. Moreover, this integrin could be associated with characteristics and features unique to these cells, including self-renewal ability, viability, stemness status and radioresistance. Indeed, the selective inhibition of ITGB8 in GIC by shRNA resulted in a decreased neurosphere formation associated with an increase of differentiation patterns and cell death, this one being potentiated after irradiation.

These results could eventually allow to identify ITGB8 as a new membrane marker of GIC but also to evaluate its targeting potential as a new therapeutic radiosensitizing strategy in these quite aggressive and invasive brain tumors.

2C / 3

Role of PXR (Pregnane X Receptor) and its target genes on the sentivity of prostate cancer cells to tyrosine kinase inhibitors

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Clinical trials to evaluate KIs efficacy in prostate cancer gave disapointing results depsite the presence of KIs pharmacological targets in prostate tumors (VEGF, EGFR, CMET...), suggesting that inefficiency of these drugs would be at least in part linked to the inhibitor itself or its pharmacodynamics/pharmacokinetics parameters. Indeed KIs are metabolized and transported via phase I and II enzymes that are mainly controlled by the xenoreceptor PXR (Pregnane X Receptor, gène NR1I2). It is mainly expressed in liver and gastro-intestinal tract but also in epithelial tumors. PXR is also involved in the resistance to chemotherapies by increasing the catabolism and the efflux of these anticancer agents.

To date only one study evaluated PXR expression in prostate cancer without evaluating its impact on treatment efficacy. In collaboration with Pr G. Fromont we analyzed a cohort of 449 prostate tumors and observed that PXR was more frequently detected in castration resistant or metastatic tumors as compared to clinically localized forms in which PXR expression was significantly correlated with TNM and ISUP Score. These results confirmed the interest to study the potential role of PXR and its target genes in the sensitivity to kinase inhibitors in prostate cancer models. We measured the expression of PXR and its target genes in prostate cancer cell lines 22RV1, LnCap, PC3 and DU145. The results showed that enzymes and transporters involved in KI detoxification was significantly expressed in these cells whereasPXR was poorly expressed due to hypermethylation of NR1I2 in our cells. This lead us to develop specific prostate cancer cell models stably overexpressing PXR in which transcriptional activity of PXR can be induced by its known agonist SR12813 further indicating that prostate cancer cells are metabolically competent. Using these models, we showed that PXR overexpression modulates the sensitivity of 22RV1 cells to erlotinib, dasatinib, dabrafenib and afatinib, demonstrating that PXR plays a functional role in the sensitivity to KIs. We also demonstrated that several KIs were PXR agonists, including dabrafenib that displayed enhanced agonistic properties as compared to SR12813, a result that was never published before. This original finding led us to engage the cristalization of PXR/dabrafenib complex and to test whether induction of PXR could lead to an alteration of metabolism and transport of other drugs that are coadministered. In this line we have observed that in 22RV1 cells the additive effect of the combination of dabrafenib with trametinib that is already approved in the treatment of melanomas, became antagonistic when PXR was overexpressed in these cells. This result is supporting our hypothesis though we still need to demonstrate that this effect is linked to a change in drugs metabolism, which is currently under investigation by the measurement of the known metabolites of these KIs.

Altogether, our data could serve as rational basis for the choice of kinase inhibitors or their potential combinations that could be tested in further clinical trials alone or in association with hormone therapies or with chemotherapies that are currently prescribed in the treatment of advanced prostate cancers, in order to potentiate tumor response.

2C / 4

Hydroxychloroquine as a novel therapeutic approach in mast cell activation diseases

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Mast cell activation diseases (MCAD) include benign and malignant pathologic mast cell (MC) states. MCAD are classically divided in aberrant MC activation disorders classified as mast cell activation syndromes (MCAS) and in proliferation and/or abnormal accumulation of MC in various organs, classified as mastocytosis. No treatment is specifically approved for Cutaneous mastocytosis and MCAS. H1 anti-histamines are recommended by international guidelines for the treatment of clinical manifestations associated with MCAD. Interestingly, we observed that hydroxychloroquine (HCQ) can improve clinical symptoms and signs present in MCAD patients. Our in vitro study shows that this molecule reduces the long-term survival of primary human mast cells, interferes with lysosome function and leads to the accumulation of non-functional tryptase in the mast cell granules. Furthermore, hydroxychloroquine decreases the production of pro-inflammatory mediators.

2C / 5

Development of New Mice Models of Patient Derived Orthotopic Xenograft for Studying Cancer Stem Cells Driving Gastric Cancer Metastasis

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Gastric cancer is the third leading cause of cancer mortality in the world. Recent literature accuses the sub-population of gastric cancer stem cells (CSC) to be at the origin of tumor formation, relapse and metastasis. However, there is a lack of mouse models that allow the dissemination of gastric CSC. To this end, patient-derived xenograft (PDX) cells-encoding luciferase were injected into the stomach wall of NGS mice. Primary tumors and metastases development were followed by bioluminescence imaging. Gastric CSC content was evaluated in primary tumors and distant metastases by analyzing CD44 expression, testing the ability of cells to initiate tumorsphere and to be invasive in collagen-coated transwell. Here we show that eight to ten weeks after orthotopic xenograft, 3 in-house PDX cases among 4 initiated primary tumors and distant metastases into the liver, the lung or the peritoneum cavity. Metastases consisted of more CSC than the primary tumors, and cells are more tumorigenic and invasive, *in vitro*. The development of these preclinical models offers a unique opportunity to decipher the basic mechanism of CSC dissemination and to study the efficiency of new drugs that target invasive gastric CSC, which at the end, may block metastatic spread.

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Towards a screening test for cancer by circulating cell-free DNA analysis

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Circulating DNA (cfDNA) has emerged as a potential biomarker, particularly in cancer, and is the subject of extensive studies in translational and clinical research. It presents a great potential in diagnosis, detection of residual disease, monitoring of recurrence and control of therapeutic response, solely through a non-invasive blood draw. A few groups, including ours, are evaluating its potential for screening and the early detection of cancer.

We developed a screening test (MNR: Multi normalized ratio), based on various cfDNA parameters determined by a specific q-PCR based method, on both nuclear and mitochondrial sequences in the supernatant of cell lines in culture, and in the plasma of healthy individuals (n= 132) and patients with colorectal cancer (CRC) (n= 351).

When applied to the supernatant of cell culture, the MNR had a discriminative potential of 100% between normal and cancer cell lines. In plasma samples, the MNR showed a high potential with an AUC of 0.88, an 86% sensitivity and a 76% specificity. When combined to the total nuclear cfDNA concentration, these two parameters together showed a sensitivity of 74% with a 95% specificity for early stage CRC.

Targeting cfDNA sequences of mitochondrial and nuclear origin, without targeting specific genetic alterations, enables the discrimination between cancerous and healthy individuals. The MNR could be a potent biomarker for tumor detection and could potentially be used to screen for asymptomatic or undiagnosed individuals. At this time, more than 1000 individuals have been tested. Work is currently ongoing to enlarge the cohort and apply this test to almost 2000 patients with different types of cancer (breast, pancreas, lung and others) in comparison to healthy individuals.

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Prognostic significance of MEOX2 in gliomas

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Introduction

Gliomas are the most common malignant primary tumors in the central nervous system and have variable predictive clinical courses. Glioblastoma (GBM), the most aggressive form of glioma, is a complex disease with unsatisfactory therapeutic solutions and a very poor prognosis. During the last decade, some processes at stake in gliomagenesis have been discovered and biomolecular markers i.e. IDH1/2 mutations and 1p19q co-deletion, are now integrated in WHO classification 2016. However, despite extended time of molecular investigation of glioma profile, little is known about the role of homeobox genes, even though they are highly expressed in gliomas, particularly in GBM. Among them, the transcription factor Mesenchyme Homeobox 2 (MEOX2) has previously been associated with malignant progression and clinical prognosis in lung cancer and hepatocarcinoma but never studied in glioma. The aim of our study was to investigate the clinical significance of MEOX2 in gliomas.

Methods

We assessed the mRNA expression of MEOX2 according to IDH molecular profile and patient survival among three different public datasets: The Cancer Genome Atlas (TCGA), The Chinese Glioma Genome Atlas (CGGA) and the US National Cancer Institute Repository for Molecular Brain Neoplasia Data (Rembrandt). We then evaluated the prognostic significance of MEOX2 protein expression on 112 glioma clinical samples including; 56 IDH1-wildtype (wt) GBM, 7 IDH1wt lower grade gliomas (LGG), 49 IDH1-mutated LGGs. Survival rates were estimated by the Kaplan-Meier method followed by uni/multivariate analyses.

Results

In this study, we identified a new transcription factor of interest in glioma, MEOX2. We showed that MEOX2 is correlated with IDH mutational status in public datasets and local clinical data sets. We demonstrated that MEOX2 is a potent prognostic factor of patient outcome in all gliomas and in LGG alone. Moreover, it appeared to be a robust prognostic marker of survival in the LGG IDHwt subpopulation, independent of the combination of chr7 gain/chr10 loss. Finally, we highlighted replication, recombination and mitosis pathways positively correlated with MEOX2 in GBM.

Discussion

Our results may be the first to provide insight into the clinical significance of MEOX2 expression in gliomas, which is a factor closely related to patient outcome. MEOX2 could constitute an interesting prognostic biomarker, especially for LGG.

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Déterminants psychosociaux des trajectoires de fatigue chez des patients suivis en chimiothérapie pour un cancer colorectal métastatique

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Introduction. La fatigue associée au cancer est un symptôme subjectif et envahissant, en lien avec la maladie et ses traitements, qui peut être autant physique qu'émotionnelle et qui impacte considérablement la qualité de vie des patients. Cette étude a deux objectifs fondamentaux : (1) identifier différentes trajectoires de fatigue chez des patients suivis en chimiothérapie pour un cancer colorectal métastatique (2) identifier certains déterminants psychosociaux de ces trajectoires de fatigue.

Méthode. Au total, 169 patients (99 hommes, 70 femmes, âge moyen : 64 ans) ont été évalués sur leur niveau de fatigue dès l'initiation d'un nouveau cycle de chimiothérapie, puis ont été suivis toutes les deux semaines sur une période de 6 mois. Les variables psychosociales telles que l'anxiété, la dépression, le contrôle perçu, les stratégies de coping et le soutien social ont été mesurées dès l'inclusion.

Résultats. Quatre trajectoires de fatigue physique ont été identifiées : 1) une trajectoire de « fatigue intense » (6,51% des patients) qui présente un niveau de fatigue élevée qui se maintient durant les six mois de traitement, 2) une trajectoire de « fatigue moyenne » (48,52%) qui présente un niveau de fatigue moyen et stable au cours du temps, 3) une trajectoire de « fatigue en augmentation » au cours du temps caractérisée par des patients non fatigués à l'inclusion (11,83%), et enfin 4) une trajectoire de patients résilients qui ne rapportent « pas de fatigue » durant les traitements (33,14%). S'il apparait que la fatigue physique et la dépression soit fortement associée, les résultats montrent également qu'une mauvaise adaptation (coping centré sur l'émotion) et peu de contrôle sur l'évolution de la maladie contribuent à l'intensité et l'augmentation de la fatigue au cours du temps. Nous retrouvons également quatre trajectoires de fatigue psychologique mais avec des patterns différents (lassitude intense et en augmentation avec des niveaux élevés dès l'inclusion, lassitude moyenne, et pas de lassitude), qui sont expliquées par les mêmes déterminants psychologiques (coping centré sur le problème et contrôle perçu) mais également par le niveau d'anxiété des patients.

Conclusion. Les résultats de ce travail doctoral ont montré que plusieurs évolutions différentielles caractérisent la fatigue associée au cancer. L'identification de variables transactionnelles dans l'explication d'un tel symptôme permet d'envisager des prises en charge psychosociales adaptées, tournées vers une médecine plus personnalisée.

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Involvement of TrkB transfer through exosomes in glioblastoma tumor progression

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Glioblastoma is the most frequent brain tumor during adulthood. The commonly used treatment consists in a combination of radiotherapy and temozolide, known as the Stupp protocol. However, this type of cancer shows a high rate of recurrence due to therapeutic resistance.

Previous studies showed the involvement of a specific neurotrophin receptor, TrkB (or NTRK2) as a key player in survival and proliferative processes within glioblastoma stem cells. TrkB has been characterized in exosomes derived from highly aggressive tumor cells and exert a control on the tumor microenvironment. These extracellular vesicles and their specific content are able to transfer aggressiveness properties to less aggressive neighboring tumor cells. This transfer induces a CSC transformation in targeted cells, which adopt stem cell characteristics.

To explore the function of TrkB transfer, we established a stable cell models overexpressing TrkB V5-tagged within glioma cell lines: U87-MG and LN18. First, we will validate TrkB overexpression in transfected cells and its function analyzing changes regarding survival pathways and proliferation rate. According to our preliminary works, we will study the impact of TrkB overexpression on the expression of specific CSC markers (Oct4, Sox2, Nanog, Nestin…). To pursue the study, we should examine the impact of TrkB overexpression on the release of extracellular vesicles and on their composition. These highly expressing-TrkB extracellular vesicles will be used to treat native glioblastoma cell lines in order to determine whether TrkB-V5 transfer through exosomes might be involved in the acquisition of an aggressive phenotype related to CSC phenotype. The analysis of exosomes-derived TrkB functions will be achieved by studying survival pathways, proliferation rate and stemness properties in recipient cells. The function of exosomes-derived TrkB in glioblastoma tumor progression and proliferation in recipient cells would like to explore the putative role of this neurotrophin receptor in tumor aggressiveness and for its prospective use as a diagnostic and / or prognostic biomarker in liquid biopsy for a better understanding of glioblastoma tumors and a better patient handling.

Session 2D – Bases de données médico-administratives: utilisations en recherche en épidémiologie et sciences sociales

Les chercheurs et les cliniciens peuvent désormais avoir accès à de nouvelles bases riches en données médico-administratives, tout en ayant l'obligation de respecter une législation qui se met actuellement en place dans le cadre de la recherche en santé.

En effet, de nouvelles bases médico-administratives ont vu le jour ces dernières années, susceptibles d'être utilisées à des fins de recherche, d'études et d'évaluations dans le domaine de la santé. C'est le cas de la base SNIIRAM (Système National d'Information Inter-Régimes de l'Assurance Maladie) qui porte sur l'ensemble des remboursements de l'assurance maladie tous régimes confondus et du SNDS (Système National des Données de Santé) qui rassemble les données du PMSI national, de la base SNIIRAM, du Cépi-dc et de la MDPH. Ces bases médico-administratives pourraient représenter des sources de données potentiellement très intéressantes en cancérologie, notamment dans l'analyse des prises en charge et de parcours de soins. Mais que contiennent vraiment ces bases de données ? Quelles personnes y ont accès ? Quelles démarches doit-on faire pour y avoir accès ? Doit-on avoir une formation préalable pour les utiliser ? Quel intérêt pour quelles études ? Quelles sont leurs limites d'utilisation ?

Par ailleurs, les chercheurs et les structures qui hébergent des données médicales sensibles sont appelés à respecter des nouvelles règlementations (loi Jardé sur les recherches impliquant la personne humaine, décret CNIL MR, règlement européen sur la protection des données personnelles…), mais ne savent pas toujours, concrètement, dans quel cadre ils se situent et comment ils doivent désormais gérer légalement chaque nouveau projet.

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Le SNIIRAM et le SNDS : contenu et conditions d'accès juridiques et techniques

Hélène CAILLOL

Caisse nationale d'assurance maladie

2D / 2

La Cohorte cancer issue des données SNIRAM / PMSI : construction et données mobilisées

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2D / 3

Estimation Départementale De L'Incidence Des Cancers : Comment Utiliser Les Données Médico-administratives De Manière Valide ?

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Introduction: La surveillance des cancers est assurée en France par les registres des cancers, qui ne couvrent qu'une partie du territoire. Afin de prédire l'incidence des cancers sur l'ensemble des départements français, il est nécessaire de recourir à des proxys issus de données disponibles sur l'ensemble du territoire, et de les calibrer à partir des données de registres. Dans ce contexte, l'utilisation de données médio-administratives issues de l'assurance maladie (ALD) et/ou des hospitalisations (PMSI) apparait a priori intéressante.

Cependant, la validité de l'utilisation d'un proxy pour cet objectif n'est pas garantie et doit être évaluée pour chaque localisation cancéreuse. Une méthode a ainsi été développée afin de calibrer le proxy pour estimer l'incidence, de quantifier les erreurs commises avec cette estimation et de s'assurer que ces erreurs restent acceptables. La calibration repose sur la modélisation du rapport proxy/incidence (proxy/I) dans la zone registre. La précision des estimations dépend principalement de la variabilité du rapport entre les départements. Cette présentation vise à décrire la méthode, évaluer la validité des prédictions selon la localisation cancéreuse étudiée, et illustrer son utilisation pour fournir des prédictions d'incidence au niveau des départements et des régions français.

Méthodes: Le rapport entre le proxy et les cas incidents est modélisé selon l'âge dans les départements couverts par des registres par un modèle de Poisson à effets aléatoires. Ce modèle fournit i) un rapport par âge proxy/I lissé f(a) et ii) une estimation de la variabilité du rapport entre les départements. Pour un département non couvert, les prédictions sont calculées par âge en utilisant le proxy divisé par f(a). Les intervalles de prédictions tiennent compte de la variabilité du rapport. La validité des prédictions départementales a été évaluée pour 24 localisations cancéreuses chez l'homme et 26 chez la femme sur la période 2007-2014. Les proxys d'incidence utilisés étaient le nombre d'hospitalisations (et sans hospitalisations pour le même caner dans les 2 années précédentes), de mises en ALD, et un indicateur construit sur la réunion de ces deux sources.

Résultats: Les résultats de l'évaluation montraient que les erreurs de prédictions d'incidence étaient acceptables à partir d'au moins un des proxys (localisation dite éligible) pour la majorité des tumeurs solides (28 couples sexe*localisation), alors que les erreurs de prédictions étaient majeures pour la plupart des hémopathies malignes (13 couples sexe*localisation sur 16). Pour les localisations éligibles, les prédictions départementales d'incidence permettaient de visualiser les gradients spatiaux de l'incidence sur le territoire, et de rendre compte des particularités régionales de l'incidence de ces localisations.

Conclusion: Notre approche permet de prédire sans biais l'incidence et d'évaluer correctement les erreurs commises, confirmant qu'il s'agit d'un outil adéquat pour estimer l'incidence départementale des cancers à partir de données externes et des données des registres. Cependant, en fonction des localisations cancéreuses et de la source de donnée, les erreurs de prédictions peuvent s'avérer trop importantes pour fournir des prédictions informatives. Ces résultats montrent que pour ces localisations, les proxys étudiés ne permettent pas d'estimer de façon fiable l'incidence des cancers. Pour les localisations éligibles, le modèle de calibration permet de fournir des informations fiables sur les disparités territoriales d'incidence des cancers et ainsi servir d'appui à la mise en œuvre de politiques de santé publique. Deux illustrations des résultats obtenus au dans les régions Occitanie et Nouvelle aquitaine font l'objet de communications affichées.

2D / 4

Un exemple d'utilisation des bases de données du SNIIRAM à des fins d'étude épidémiologique : proposition d'une méthode pour identifier les bénéficiaires de la CMU/CMU-C des patients inclus dans un registre des cancers

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Cette étude a pour objectif de déterminer l'impact de la CMU sur la prise en charge des malades atteints de lymphomes non hodgkiniens. Il s'agit en partant de la base de données IsoLymph qui décrit précisément le parcours de soins des patients atteints de LNH diffus à grandes cellules B et folliculaires en population générale, de développer une méthode pour identifier les bénéficiaires de la CMU ou de la CMU-C. De cette manière il sera possible de procéder à l'analyse épidémiologique relative à l'impact de ces statuts sur la prise en charge et la survie des malades diagnostiqués en Gironde entre 2006 et 2008.

Dans le cadre de cette communication, nous détaillerons les différentes étapes règlementaires et techniques qui nous ont permis de retrouver dans les bases du SNIIRAM les informations d'intérêts. Nous discuterons également des limites d'utilisation de ces informations et des améliorations attendues.

2D / 5

Identification des patients avec un cancer de la prostate résistants à la castration et métastatiques (mCRPC) dans la base du SNDS : étude CAMERRA

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Identifying patients with metastatic Castration-Resistant Prostate Cancers (mCRPC) in the SNDS database: CAMERRA study

Introduction & objectives: Management of mCRPC has evolved significantly since 2011. Identifying mCRPC patients is a key step to better assess the evolving treatment patterns. SNDS is the nationwide healthcare insurance system database covering 99% of the French population. In the absence of a direct marker, the identification of prevalent mCRPC patients within the SNDS in 2014 relies on the construction of a complex algorithm.

Materials & methods: An algorithm for identifying mCRPC patients was built from an extraction of men aged 40 and over with an indicator of prostate cancer (Long-term disease and diagnosis codes, hospitalizations and procedures, treatments) and having a 5-years healthcare history. The identification of mCRPC patients relies on two indicators: 1) the date of first management of metastases based on specific acts (radiotherapy, specific hospitalizations for chemotherapy, treatments targeting metastases (denosumab, zoledronic acid, radioisotopes, radiofrequencies, etc.), or drugs specific to mCRPC (abiraterone acetate, enzalutamide, docetaxel and cabazitaxel) associated with imaging procedures; 2) the date of castration resistance based on switch between sequences of anti-androgens and GnRH analogs, surgical procedures (orchiectomy and pulpectomy), or first dispensing of specific treatments for mCRPC. A patient was considered as having mCRPC when a date of first management of metastases and a date of castration resistance were identified in his medical history.

Results: 3 192 patients with prevalent prostate cancer in 2014 were identified in the 1/97th sample of the SNDS database (EGB), including 273 metastatic and 187 castration-resistant. Of these 3 192 patients, 111 were identified as having a mCRPC in 2014. By extrapolation, 468 142 prevalent prostate cancer patients are expected in the SNDS database in 2014 [95%CI: 456 873 - 480 055], with a partial prevalence at 5 years of 191 057 [95%CI: 186 887 - 195 439]. This estimate concurs with the one of the French National Cancer Institute, 508 699 in 2008. Among these prevalent prostate cancers, 16 314 [95%CI: 15 923 - 16 726] should be mCRPC, representing about 3.5% of all prostate cancers.

Conclusion: This functional algorithm for identifying mCRPC patients has been constructed according to complex elements and their sequences. It will help to better understand the chronology of mCRPC and gives rise to a first estimate of its prevalence in the French population based on SNDS data.

Session 2E – Health technologies

2E / 1

Biological fate of silica based nanoparticles: physicochemistry and membranes interactions

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Understanding the interactions of nanoparticles (Nps) with biological systems is clearly multidimensional. Combinations of surface decoration are now described leading to high sophisticated nanocarriers that combines stealth property, imaging, targeting and controlled or triggered release. The chemical composition of the Nps surface influences their stability in biological fluids, their interaction with proteins, and their attraction to the cell membranes. We have developed standardized synthetic routes to achieve the production of different Nps presenting magnetic properties. Core-shell magnetic mesoporous silica Nps (Fe3O4@MSN), that are considered as potential theranostic candidates, were coated with polyethyleneglycol (PEG) or 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) lipid bilayer. Their biological fate was studied in comparison to the native Nps. The surface composition of Nps strongly influences their dispersion in biological fluids mimics, protein binding and their interaction with cell membrane. Moreover, lipid bilayers constitute a steric barrier that diminished proteins adhesion at the nanoparticle surface. While none of these types of Nps was found to be toxic on mice, their surface coating nature influences their in vivo biodistribution. Importantly, Nps coated with DMPC exhibit a strong accumulation in liver and a very low accumulation in lung in comparison with nude or PEG ones.

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Nanosized Prussian blue analogues as theranostic agents

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Nanoscale Prussian blue and its analogous are exciting nano-objects whose origin is the infinite bulk molecule-based networks, which present tuneable size- and shape- dependent properties, a high surface area to volume ratio and tailored functionalized surfaces. Therefore, they exhibit unique physical and chemical properties which are interesting not only on the fundamental aspect, but also because of their intended use in various potential applications with a great potential in biology and medicine.[1]

This lecture will present the synthesis and investigation of Prussian Blue nanoparticles for different types of imaging including Magnetic Resonance Imaging (MRI), SPECT/CT scintigraphy or as therapeutic agents for photo-thermal therapy or radioactive Cs+ decontamination.[2-7]

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Biodegradable polymeric nano-systems, anti-cancer agent, intra-cellular uptake

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These last few years, numerous controlled drug delivery systems have been developed and among them, polymeric nano-systems. [1, 2] In this context, this project aims at synthesizing a new graft amphiphilic and totally biodegradable copolymeric structure, poly(ε-caprolactone)-g-oligosaccharide. Nano-systems based on this new copolymer have been prepared and loaded with anti-cancer agents to carry them into tumoral cells for further intra-cellular release. The first interest of this copolymeric structure is its versatile lipophilic-hydrophilic balance (LHB) allowing to prepare various polymeric drug loaded-nano-carriers with adaptable drug release kinetics. Moreover, the biodegradability of the polymer structure is of particular interest to avoid any problems concerning the future of nano-systems in the organism and their potential toxicity. Actually, the copolymer bears various chemical functions allowing further coupling of biomolecules such as fluorescent probes or targeting molecules, to improve the nano-carrier properties. As part of this project, anti-cancer agents will be encapsulated into the polymeric nano-system to be uptaken into colon tumoral cells. [3]

The syntheses of amphiphilic copolymers with various LHB have been realized as well as the synthesis of fluorescent copolymers. Then nano-objects based on these polymeric structures have been prepared and characterized. Different anti-cancer drugs have been encapsulated into the polymeric nano-carriers to assess the most efficient system for intracellular uptake and further release. Biological studies have been performed and showed cyto-compatibility and intra-cellular uptake of these new nanosystems.

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Development of versatile biological models to study nanodevices biomedical potential.

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The development of personalized and non-invasive therapies based on new nanodevices is a major challenge in medecine. The design of multifunctional nanomaterials with controlled physico-chemical properties thanks to the chemistry expertise allow to the biologists to demonstrate their nanomaterials biomedical potential. In this context, we studied different nanomaterials with two therapeutic applications concerning inflammation or cancer. Nanoparticles can transport important quantity of therapeutic bioactive molecules to precise target in the body (e.g. tumor or inflammation site) in order to have a higher treatment efficacy and significantly decrease side effects.

Firstly, we analyzed the biological efficiency of ionosilicas nanoparticles. These are original Periodic Mesoporous Organosilica (PMO) based materials containing covalently anchored ionic groups. These ionosilicas nanoparticles were used to load diclofenac, an anionic non-steroidal anti-inflammatory drug, which has been used to perform in vitro / in vivo and biodistribution investigations in order to demonstrate their biocompatibility and their potential to be used as drug carrier vehicles to treat inflammation. Moreover, the nanomaterials can be employed in the cancer treatment. Indeed, nanoscience has grown considerably in the fight against cancer with nanoparticles of different categories and activated with different stimuli as Mn2+-doped Prussian blue nanoparticles. They are many advantages as their flexible molecule-based structure, adjustable composition, tunable physico-chemical properties, porosity, high stability in aqueous media and biocompatibility. Moreover, Prussian blue has been approved by the Food and Drug Administration for human. For these reasons Prussian blue nanoparticles have a huge biomedical potential. We have demonstrated for the first time that Mn2+-doped Prussian blue nanoparticles act as efficient agents for photothermal therapy under two-photon excitation and induce an almost eradication of malignant cells.

Finally, in order to go further in the biomedical proof of concept of therapeutic nanodevices, we are currently developing an animal model as Danio rerio (zebrafish) to study different diseases. As an example, we have already implanted fluorescent human cancer cells in zebrafish larvae in order to establish an easily detectable tumor xenograft. Then, we have intravenously injected soluble photosensitizers in zebrafish and irradiated the tumor site during few seconds with a pulsed laser. The strong and rapid decrease in tumor size let us imagine to develop such model to test the biomedical potential of different nanoparticles.

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HSP70 inhibition and Magnetic Intra-Lysosomal Hyperthermia: a promising synergistic combination for cancer therapy.

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The cholecystokinin receptor (CCK2R) is over-expressed in a collection of human endocrine tumors. Our team showed that this receptor is massively internalized and directed by its ligand to the lysosomes. In this context, we developed a Magnetic Intra-Lysosomal Hyperthermia (MILH) approach, which occurs without perceptible temperature rise. We showed that minute amounts of iron oxide magnetic nanoparticles targeting the gastrin receptor (CCK2R) are internalized by cancer cells through CCK2R-dependent physiological process, accumulated into their lysosomes and kill cancer cells, upon a high frequency alternating magnetic field (AMF) application, through a lysosomal cell death. However, since MILH induced cell death by 20-30%, we hypothesize that certain mechanisms of resistance could inhibit this effect. Interestingly, Heat Shock Protein 70 (HSP70) is present in lysosomes of cancer cells but is rarely found in lysosomes of normal cells, and its over-expression in cancers is correlated with poor prognosis and treatment resistance. Additionally, in cancer cells, HSP70 has been described as a guardian of lysosomal integrity and its downregulation or inhibition leads to the destabilisation of lysosomal membranes and induces lysosomal membrane permeabilization (LMP), thereby promoting cancer cell death by activating an apoptotic signaling pathway.

Based on these results, we hypothesized that HSP70 inhibition could enhance the efficacy of MILH in cancer cells. First, we showed that HSP70 overexpression prevent cells against LMP and cell death induced by MILH. Then, the effect of HSP70 inhibition was evaluated on cell death and LMP in combination with MILH using a subletal dose of 2-phenylethynesulfonamide (PES or Pifithrin-µ), an HSP70 specific inhibitor. Our results show that combination of MILH with PES increases the efficiency of eradication of cancer cells with synergism. Indeed, PES/MILH combined treatment kills 51% of cancer cells, whereas MILH eradicates 20% of cancer cells and sublethal dose of PES does not affect cell viability. Furthermore, this result was associated with an increase in LMP and PES treatment potentiates the activation of an original and non-apoptotic cell death mechanism induced by MILH, which depends on Caspase-1 but not on apoptotic Caspase-3. Currently, we are deciphering the molecular and cellular mechanism of the cell death induced by this combined treatment.

All together, these results show that HSP70 exerts a protective role in MILH-induced LMP and cell death and emphasize the benefit of targeting HSP70 for combinatorial treatments, with the prospects of overcoming treatment failure and therapeutic resistance.

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Towards multifunctional peptide-based nanoparticles for cell-delivery of siRNAs in tumors.

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Small interfering RNAs (siRNAs) present a strong therapeutic potential because of their ability to inhibit specifically the expression of any desired protein. However, siRNAs show a very weak propensity to cross the plasma membrane on their own. We recently developed a series of new cell-penetrating peptides able to form stable peptide-based nanoparticles (PBNs) once incubated with a given ratio of siRNA.1 With regard to future in vivo applications, we also studied recently the influence of the polyethylene glycol (PEG) grafting onto the PBNs on their in vitro and in vivo siRNA delivery properties.2 We also planed to address specifically PBNs to tumor sites upon the incorporation of peptide-targeting sequences on PBNs. Thanks to strategies offered by peptide chemistry, we designed, prepared and studied new PBNs made of several different peptides blocks (siRNA complexation, siRNA cellular transfer, targeting and prolonged blood-circulation) in order to improve significantly the cell-specific delivery of siRNAs.

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Combination of photodynamic therapy and gene silencing in cancer cells with porphyrin-siRNA complex.

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To overcome the limitations of single therapy, photodynamic therapy (PDT) has been combined with gene silencing. To achieve this dual therapy, we explored the supramolecular self-assembly of a cationic porphyrin (H2PG) with siRNA with the hypothesis that porphyrin aggregates should be capable of complexing siRNA through multivalent interactions and thus contribute to its intracellular delivery.

First, we have studied the PDT efficiency of H2PG porphyrin alone. For this, human breast cancer cell line (MDA-MB-231) was incubated with this porphyrin. The irradiation of culture cells treated with H2PG porphyrin at 405 nm wavelength induced a strong cell death that is not the case when cells are treated but not irradiated and when cells are only irradiated without any treatment. This demonstrated the specificity of PDT mechanism induced by irradiation of H2PG porphyrin.
Secondly, the ability of H2PG porphyrin to complex nucleic acids such as siRNA-Luc (directed against luciferase) was analysed.

By using agarose gel-shift electrophoresis, we have demonstrated the formation of H2PG-siRNA complexes from N/P* ratio of 5. The biological activity of this complex was studied on MDA-MB-231 genetically modified to express luciferase. In the absence of irradiation, MDA-MB-231 cancer cells incubated with the complex did not exhibit any cytotoxicity. Interestingly, the siRNA-Luc complexed to the H2PG porphyrin induced an inhibition of the luciferase activity, without any irradiation, thereby demonstrating that H2PG acts as a delivery vehicle for siRNA. In summary, the irradiation of MDA-MB-231 incubated with the H2PG porphyrin-siRNA-Luc complex generated (i) photo-induced cell death and (ii) luminescence decrease.

In conclusion, this study shows that dual therapy (PDT and gene silencing) can be achieved using a small molecule self-assembly and may thus represent an improvement for cancer therapies.

*: N: positive charges of porphyrin and P: negative charges of siRNA

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Fluorescent soft molecular nanoparticles as nanocarrier for hydrophobic drugs. Towards novel prodrugs for glioblastoma chemotherapy

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Nanovectorization of anticancer agents is a recent therapeutic strategy to improve drug targeting and delivery of conventional chemotherapy. In particular, several classes of nanoparticles have been explored in recent years as nanocarriers of cytotoxic drugs. Among them Paclitaxel (PTX) is one of the most useful and effective antineoplastic agents for treatment of many solid cancers. Glioblastoma multiforme is the most frequent and invasive primary tumor of the central nervous system. Despite current treatments which combine surgery, radio- and chemotherapy, the median survival is about 15 months. Furthermore, most of drugs are not able to cross the blood-brain barrier (BBB), which is one of the major difficulties in glioblastoma treatment. Hence, novel therapeutic approaches are required and paclitaxel-bound nanoparticles could offer a new perspective to treat brain tumors.

In this context, we have developed soft organic nanoparticles which combine high solubility in aqueous media, remarkable fluorescence properties, biocompatibility and which present a high density of surface groups for further immobilization and masking of PTX by covalent grafting. We have selected fluorescent carbon-based nanodots (FCNDs) as nanocarriers. FCNDs can be prepared using simple pyrolysis or hydrothermal treatments from small, accessible and usually biosourced molecular precursors [1]. By optimizing the synthesis protocol, we were able to prepare soft, small nanoparticles (DTEM < 30 nm) which show intense blue fluorescence and high solubility in water. In addition, by tuning the experimental conditions, high fluorescence quantum yield and high two-photon absorptivity in the NIR region could be achieved, allowing for two-photon imaging of internalization FCNDs in cells [2]. The safety and internalization of the free FCNDs was demonstrated on different cell lines, making them suitable candidate for use as drug delivery systems [2]. With this aim in mind, post-functionalization andactivation of the surface of these nanoparticles was successfully achieved leading to high density of reactive groups (-NH2 and -CO2H) which then permitted subsequent grafting of PTX leading to FCNDs@PTX which retain excellent solubility and reasonable stability in water [2]. The antitumoral activity of the FCNDs@PTX was tested in vitro on 2D and 3D culture. On different cell lines, FCNDs@PTX shows similar anticancer activity as PTX alone [2]. The pharmacological effects of PTX on microtubules were observed by immunofluorescence experiments (presence of bundles, pseudo-asters and mitotic block), which confirms that PTX is released from its binding to FCNDs in active form after cell internalization, thanks to the chemical nature of the surface functionalization [2].

These results demonstrate that hydrophilic FCNDs@PTX are promising as prodrug formulation to improve paclitaxel therapeutic index. In addition, our FCNDs offer interesting promises as theranostics nanotools thanks to their versatile surface functionalization, tunable luminescence properties and high water solubility.

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Glioblastoma Cancer Stem like Cells discrimination by UHF-Dielectrophoresis Crossover Frequency

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Cancer Stem Cells or CSCs appear as major biological and therapeutic targets, in particular for Glioblastoma (GBM). Heterogeneity of tumor cell populations, leads to optimize characterization and sorting methods. Actually, analysis are based on targeting of a set of biological markers, which are efficiently used to validate the stemness properties. Besides the biological properties, biophysical properties of CSCs are expected to be a potential way to discriminate and sort CSC populations. Our data summarize first's results glioblastoma cell lines' characterization; measuring their crossover frequencies by dielectrophoresis (DEP) technics in the UHF frequency range (above 50 MHz). We cultured GBM cell lines following different conditions, in order to achieve an enrichment of cancer stem cells (CSCs). Based on DEP electrokinetic method, CSCs were discriminated from the differentiated cells. In this study, we used microfluidic lab-on-chip systems implemented on Bipolar-Complementary Oxide Semiconductor (BiCMOS) technology, allowing single cell handling and analysis. Based on measurements of their own intracellular specificities, the enriched CSCs population, cultured in dedicated define medium, have shown clear differences of DEP crossover frequency signatures of CSC enriched populations compared to differentiated cells cultured in normal medium. That demonstrates the concept and validates the technique efficiency for CSCs discrimination, confirming a high potential of the lab-on-chip (LOC) platform in the diagnosis and development of new glioblastoma therapeutics.

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Multiplex digital PCR for the diagnostic of pilocytic astrocytoma and glioneuronal tumors

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Background:
A new classification for CNS tumors released by the WHO in 2016 considers histopathology and molecular information to establish an integrated diagnostic that should lead a better characterization of CNS tumors. This diagnostic approach for CNS plays a crucial role in determining the subsequent treatment plan, so must be carry-out with the most accurate techniques.
Regarding techniques used for this molecular characterization, many of them require high amount of DNA and RNA, need highly purified DNA, parameters that could not always be achieve using FFPE sample. In addition, most techniques cannot answer to all questions, and force laboratories to use various approaches. However, digital PCR (dPCR) is getting more interest in oncology, as it is highly sensitive, works in presence of inhibitors, allows copy number variation and gene rearrangement detection using only DNA sample.
We decide to develop a dPCR multiplex panel for the molecular characterization of pediatric CNS tumors by detecting mutations on BRAF; FGFR1 and PIK3CA along with KIAA-BRAF fusion; FGFR1 duplication by using only DNA.

Methods:
DNA sample were isolated from FFPE sample of various CNS tumors prior to be tested by classical approaches (NGS; FISH; QPCR) then by dPCR. A total of 60 samples were tested for the detection of mutation. The dPCR panel for the mutations listed above is a 3-well assay with a sensitivity down to 0.1% fractional abundance.

Results:
All sample were well characterized by dPCR, with 100% specificity and sensitivity. Concordance for each molecular alteration was 100%. Sample with low concentration gave expected results, as the biopsy was enriched in cancer cells. The assay efficiently detects KIAA-BRAF fusion and FGFR1 duplication using a CNV approach using DNA as sample.

Conclusions:
The use of multiplexed dPCR panel allows to get molecular characterization of brain tumors in 1 day, with high sensitivity and specificity. The assay can be performed by using DNA with no need of RNA for fusion transcript detection. dPCR allow laboratories get access to affordable diagnostic tools. We believe that multiplex dPCR approach will allow every patient to get access to high quality diagnostics. Other studies will be performed on cell-free DNA.

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Exploring Multi-Cellular Tumor Spheroids in Virtual Reality

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Goal: Exploring cells inner dynamics of 3D biological models is of central interest. It is particularly the case for Multi Cellular Tumor Spheroids (MCTS) to design new efficient therapeutic protocols. However, exploring them*in vitro* is technically challenging. Nowadays, computer science can help by providing increasingly realistic digital models and accessible means of visualization and interaction, especially also relying on virtual reality (VR) approaches.

Experimental Design: To this end, we have developed a 3D *in silico* model of the growth of *in vitro* MCTS. The model of the cell cycle considers and offers the possibility to manipulate four checkpoints: "R", the restriction point in the G1 phase, the G1/S and G2/M checkpoints, and the intra-mitotic (iM) checkpoint in the M phase. In this model, we used Bernoulli processes, a mathematical tool that allows a discretization of time and the regulation of the cell cycle advancement speed based on sequences of probabilistic draws. Intercellular variability is modelled by randomly choosing the duration of each phase following a log-normal law [Sherer et al., Biotechnol BioEng 2008] every time a new cell is created. The representation of the cell cycle we used is generic enough to integrate additional external events. Under optimal condition, draw probabilities are all equal to one, leading to cell cycling as fast as they can. Taking into consideration environmental modifications requires modifying the draw probabilities accordingly. Cells are interacting in a 3D virtual environment based on a mass-spring-damper system. Oxygen gradients are simulated using finite differences. Using a diffusion and consumption model of oxygen proposed by [Grimes et al., J. Royal Soc. 2014] applied to experimental data based on proliferation marker (i.e. EdU), we were able to correlate cell cycle elongation in depth to oxygen concentration decay. This allows to calculate during the simulation the elongation of the cell cycle of the cells in the MCTS. To improve our understanding of the inner dynamics of the system, we have developed a VR set up in which the simulated growing MCTS can be visualized in real-time. We paid particular attention to the visualization of the virtual cells. We have simulated the effects on cell cycle dynamics, on proliferation markers (i.*e.* EdU) or hypoxia markers (*i.e.* pimonidazole) to evaluate the realism of the virtual MCTS based on data biologists are used to analyze. Our markers are calculated for each time step, therefore reflecting model changes ad-hoc, during the simulation. As the simulation provides access to additional data, users can also color cells with regards to their cell cycle duration, the oxygen concentration, etc. Finally, the VR room (it is a room-scale simulation relying on HTC's Vive device) also contains a virtual board for plotting data such as the population size, phase repartition, or FACS analysis. Using VR allows users to naturally interact with the visualized MCTS, for instance by cutting it to explore its inner structures. Users can also easily navigate in the simulation both in time (using a handheld controller) and space (by moving and reorienting in the room).

Results: Here we report on a new application that allows the exploration of simulated MCTS in VR. The agent-based model used is reproducing the inner proliferation dynamics of the MCTS. We have developed a set of VR tools aimed at improving the comprehension of the complex spatiotemporal dynamics exhibited. In the future, we plan the tool to be usable to explore and evaluate new therapeutic strategies by allowing biologists to visualize and pre-analyze possible outcomes of treatment protocols before actually running them in the wet lab.

Session 3A – Plasticity

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An integrative view of cellular senescence and reprogramming

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Reprogramming of differentiated cells into pluripotent cells can occur in vivo, but essentially nothing is known about the mechanisms, processes, and mediators involved. We have generated mice where we can induce ubiquitous expression of the four Yamanaka reprogramming factors. These factors, when expressed continuously during 1 week, produce widespread de-differentiation in multiple tissues. Upon switching off the reprogramming factors, de-differentiated tissues re-differentiate and homeostasis is restored. We have found that senescence participates in the process of in vivo reprogramming. Senescence is a cellular response to damage characterized by an abundant production of cytokines and other extracellular factors, which recruit inflammatory cells and can orchestrate tissue remodeling. I will present an integrated view of tissue repair whereby tissue injury, through senescence, primes surviving cells to undergo partial reprogramming and initiate tissue repair.

3A / 2

Novel insights of KRAS dimerization as an essential oncogenic requirement

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Recent evidences suggest the transient formation of dimers and possibly higher order KRAS nanoclusters in the cell membrane. Furthermore, structural data indicate that KRAS dimers result in a conformational orientation that is optimal for its interaction with downstream effectors and productive signalling. Yet, it was unknown to what extent KRAS dimers were functionally relevant. We have recently confirmed that dimerization is an essential requirement for the oncogenic activity of mutant KRAS (1). Indeed, our data indicate that KRAS monomers on the membrane are functionally inert and that dimerization is an essential requirement for the activation of downstream signalling and the establishment of an oncogenic output. I will present an on-going genetic approach designed to further substantiate this oncogenic feature and discuss how our findings can be reconciled with other recent studies demonstrating that full length KRAS lacks intrinsic dimerization. Finally I will comment on how these findings could potentially translate into novel therapeutic treatments.

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3A / 3

Ki-67 promotes cell plasticity and tumourigenesis by regulating global gene expression

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Ki-67 is a vertebrate nuclear protein highly expressed only in proliferating cells and is a customary cancer biomarker. However, it is dispensable for cell proliferation and Ki-67 mutant mice are viable, raising the question of why cancer cells express Ki-67. Here, we use mouse cancer models to show that by regulating global transcriptional states, Ki-67 promotes tumour initiation, growth and metastasis, and determines anti-tumour immune and drug responses. Genetic Ki-67 ablation prevents cellular transformation in vitro and protects against induction of intestinal tumourigenesis in vivo. In a syngeneic breast cancer model, Ki-67 knockout disrupts intrinsic tumour growth and metastasis as well as the immune response. Mechanistically, Ki-67 loss promotes extensive changes in gene expression programmes coupled to an abolition of the epithelial-mesenchymal transition (EMT). Several genes required for antigen presentation are abrogated, disrupting MHC1 functions. This renders cancer cells insensitive to attack by cytotoxic T cells. Oppositely, decreased cell stemness characteristics translate into reduced metastasis despite a higher primary tumour burden. Further inactivation of the PRC2 complex by disrupting Suz12 or Ezh2 genes partially restored the EMT but not the loss of metastatic capacity. Finally, extensive downregulation of drug metabolism genes triggered increased sensitivity to a wide range of drug classes. Thus, Ki-67 expression in cancer cells is not required for cell proliferation but promotes tumourigenesis and drug-resistance, along with a potential Achille's heel: maintenance of anti-tumour immunity.

3A / 4
Cellular Plasticity in Gliomas

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Gliomas are most frequent brain tumors comprising high and low grades of malignity. Glioblastomas (GBM) represent the most aggressive and frequent form of gliomas. GBM are highly vascularized tumors which contain subpopulations of glioblastoma stem cells (GSC). We and others have recently reported that GSCs could transdifferentiate into endothelial-like and pericyte-like cells both in vitro and in vivo. The Notch1 and TGFβ signaling pathways were identified as major regulators of this vascular transdifferentiation. The EMT transcription factor SLUG as well as the hematopoietic transcription factor TAL1/SCL were found to be strongly induced by Notch1 activation in GSC. Vascular cells derived from GBM cells were also observed directly in patient samples. This cellular plasticity of GSC may account for the cellular heterogeneity observed in GBM tumors and should be considered for designing original therapeutic approaches against gliomas (Guelfi S, et al, Stem Cells Int. 2016).

3A / 5
Metabolic and mitochondrial flexibility in acute myeloid leukemia

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Metabolic reprogramming is now considered one of the major characteristics of cancer cells as they must adapt their metabolism to fuel energetic and biosynthetic needs for proliferation[1,2,3,4]. Changes in intermediary and energy metabolism are also a key hallmark of acute myeloid leukemia (AML), and targeting glycolysis, glutaminolysis, fatty acid β-oxidation or mitochondrial oxidative phosphorylation (OxPHOS) are promising anti-leukemic approaches[5,6,7,8,9,10]. Others and we have shown that drug-resistant cancer cells rely on High OxPHOS and mitochondrial function[11,12,13,14]. However, the role of the cell metabolism into the mitochondrial-driven drug resistance remains largely unknown. Furthermore, recurrent mutations in genes of two crucial metabolic enzymes, isocitrate dehydrogenase 1 and 2, have been discovered in more than 15% of AML patients[15,16,17,18] and represent new therapeutic targets[19,20,21]. Whereas wild-type IDH1 catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG) generating NADPH in the cytosol, mutant IDH1 catalyzes a neomorphic enzyme activity that produces the oncometabolite R-2-hydroxyglutarate (2-HG) from α-KG[22,23], thereby limiting the availability and utilization of this latter key metabolite central to intermediary metabolism, and oxidizes NADPH. The impact of IDH mutation and its oncometabolite have been well documented on the alteration of DNA and histone methylation and imbalance in myeloid/erythroid differentiation through 2-HG-dependent allosteric competitive inhibition of multiple α-KG-dependent dioxygenases and other enzymes[24,25,26,27,28]. However, the contribution of IDH mutation to cell intermediary metabolism and α-KG homeostasis is not fully understood in AML and its chemoresistance.
Here we will discuss about the role of the metabolic reprogramming in the drug resistance in cancer, especially in mutant IDH1-driven tumor models, providing a strong scientific rationale for clinical trials of innovative combinatory targeted therapies to selectively treat this subset of patients, especially those insensitive to newly-FDA approved IDH mutant-specific inhibitors. In conclusion, we will speculate about the notion that leukemia and cancers are metabolic and bioenergetic (oncogenetic-driven?) syndromes that could form the basis of precision metabolic medicine.

1- Boroughs and DeBerardinis, 2015. 2- Léhuédé et al. 2016. 3- Martinez-Outschoorn et al. 2016. 4- Vander Heiden and DeBerardinis, 2017. 5- Samudio et al. 2010. 6- Skrtic et al. 2011. 7- Scotland et al 2013. 8- Jacque et al. 2015. 9- Matre et al. 2016. 10- Poulain et al. 2017. 11- Kuntz et al. 2017. 12- Farge et al. 2017. 13- Lee et al. 2017. 14- Bosc et al. 2017. 15- Mardis et al. 2009. 16- Abbas et al. 2010. 17- Marcucci et al. 2010. 18- Paschka et al. 2010. 19- Rohle et al. 2013. 20- Wang et al. 2013. 21- Yen et al. 2017. 22- Dang et al. 2009. 23- Ward et al. 2010. 24- Figueroa et al. 2010. 25- Sasaki et al. 2012. 26- Losman et al. 2013. 27- Kats et al. 2014. 28- Boutzen et al. 2016

Session 3B – Réalité virtuelle et cancer

Initialement conçue à des fins de divertissements, les possibilités qu'offre la réalité virtuelle s'étendent aujourd'hui à de nombreux autres secteurs comme l'architecture, la formation, le marketing et la publicité pour n'en citer que quelques-uns.

Son utilisation a été récemment élargie au domaine de la santé avec des bénéfices majeurs sur le plan purement technique et pédagogique (e.g., applications permettant de simuler des actes chirurgicaux avant une opération) mais aussi dans le traitement de nombreuses pathologies (e.g., phobies, addictions et certaines formes de dépression).

La RV présente un atout fundamental : son pouvoir de distraction. Ce pouvoir représente un véritable bénéfice dans le domaine médical et particulièrement en oncologie puisqu'il permet de détourner l'attention du patient lors des soins ou d'actes chirurgicaux tout en réduisant l'anxiété et la douleur ressenties.

Les progrès technologiques récents ont entraîné des réductions considérables dans les coûts de l'équipement de RV si bien que les chercheurs et les cliniciens ont plus facilement accès à ces nouvelles technologies et sont de plus en plus nombreux à mettre en place des études utilisant la RV dans diverses situations médicales.

Dans quelle mesure ces prouesses technologiques associées à la RV peuvent être mises au service du bien-être des patients en oncologie ? Quelles sont les conditions pour une application optimale de ces technologies en cancérologie ?

3B / 1

La Réalité Virtuelle : quel enjeu dans les soins psychologiques en oncologie ?

Anne-Marie ETIENNE

Université de Liège

3B / 2

« Dessine-moi une réalité plus belle » : quelles perceptions du dispositif de réalité virtuelle pour les patientes atteintes d'un cancer du sein ?

Aude MICHEL, Emmanuelle BRIGAUD, Florence COUSSON-GELIE, Jullien VIDAL, Nathalie BLANC

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La réalité virtuelle (RV) gagne à être considérée en cancérologie en particulier pour accompagner les patientes confrontées à des situations médicales stressantes ou douloureuses. Pourtant, aucune étude n'a sondé auprès des patientes concernées la pertinence de l'utilisation d'un tel dispositif. Nous avons réalisé une enquête auprès de 300 femmes atteintes d'un cancer du sein qui a permis d'examiner leur intérêt pour la RV, les modalités d'immersion préférées ainsi que leurs attentes vis-à-vis de ce dispositif. Les résultats seront discutés et permettront d'ouvrir vers les lignes de recherches déjà prometteuses dans ce domaine.

3B / 3

La réalité virtuelle au service des patients en oncologie dans le cadre de la prise en charge de l'anxiété pré-opératoire

Christine LAURENT

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Au Centre Léon Bérard, depuis Septembre 2016 nous accueillons les patients attendus pour leur geste interventionnel au sein d'une même structure (accueil J0). Ainsi, les patients entrent le jour de leur geste interventionnel (chirurgie, radiologie interventionnel, chirurgie ambulatoire…), et après les différentes vérifications sécuritaires réalisées par l'équipe soignante, ils sont installés dans une salle d'attente dite de « détente », pensée de façon à « libérer la pensée » et s'appuyant du concept « snoezelen » (colonnes à bulles, ciel étoilé…). Le projet d'auto hypnose par la réalité virtuelle s'inscrit tout à fait dans ce concept de prise en charge, en effet, il est communément admis qu'il y a des niveaux d'anxiété majeur chez les patients atteints de cancer (60 à 80 %). Cette anxiété est majorée par les gestes interventionnels.

Par ailleurs, il existe un lien récurent entre anxiété préopératoire et douleur postopératoire. La prémédication anxiolytique médicamenteuse est discutée pour ses effets négatifs sur la récupération rapide en postopératoire . La tendance actuelle est de la rendre moins systématique, au profit du développement de techniques non médicamenteuses telles que l'hypnose. L'autohypnose à l'aide de la réalité virtuelle ou casque3D permet une anxiolyse non médicamenteuse. Cette méthode utilise les technologies les plus récentes, en utilisant des images 3D et des ambiances musicales relaxantes. Elle permet une immersion quasi constante et une adhésion importante des patients. Elle fait chuter les valeurs des échelles d'anxiété de moitié et permet à différentes étapes de la prise en charge une aide réelle à la relaxation, à la diminution des antalgiques et psychotropes. Le conditionnement positif induit par cette technique d'hypnose rend possible une récupération mieux vécue.

L'équipe soignante en chirurgie propose ces séquences de relaxation hypnotique aux patients dès leur admission. L'utilisation de cette technologie ne nécessite pas de formation spécifique autre que celle de la mise en place du casque. C'est un outil complémentaire au service du soignant pour améliorer la prise en charge du patient. Dans un contexte budgétaire très contraint, où la gestion des ressources humaines doit être ajustée, il est néanmoins possible d'optimiser la prise en charge des patients. L'autohypnose à partir de la réalité virtuelle soulage le patient en le rendant acteur, sans mobiliser l'équipe soignante.

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Prêt à porter un casque ? Modeler le réel grâce a la réalité virtuelle

Nancy RODRIGUEZ

LIRMM, Montpellier

3B / 5

Utilisation de casque aéro-audio-olfactif dans la gestion du stress en aéronautique

Thierry TALOU, **Sarah GRIVOT**

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Session 4A – Plasticity

4A / 1
Cellular pliancy and breast cancer genetics

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The plasticity of cancer cells underlies their capacity to adapt to the selective pressures they encounter during tumor development. Aberrant reactivation of the epithelial-mesenchymal transition (EMT), a latent embryonic transdifferentiation program, promotes cancer cell plasticity and fuels tumor development and metastatic spread1. Consistent with a prominent role in tumorigenesis, we have shown that EMT-inducing transcription factors of the TWIST and ZEB families act as genuine oncoproteins, fostering cell transformation and primary tumor growth by alleviating key oncosuppressive mechanisms and by providing cells with self-renewal properties2,3. Recently, we have further demonstrated that EMT inducers are expressed in normal mammary stem cells and that their expression influences the entire natural history of breast tumorigenesis4. In contrast with differentiated cells, human mammary stem cells have the innate capacity to withstand an aberrant mitogenic activation. This property is based on an antioxidant program driven by the ZEB1 EMT inducer and the methionine sulfoxide reductase MSRB3. This pre-emptive program prevents the formation of oncogene-induced DNA damage, a major cause of genomic instability, and influences the emergence of cancer-associated events. Overall, our data suggest that malignant transformation of mammary stem cells does not hinge on genomic instability and indicate that intrinsic properties of the cell-of-origin determine the susceptibility to malignant transformation when subjected to an oncogenic insult, an emerging notion referred to as "cellular pliancy" 5. Cellular pliancy is defined as the intrinsic capacity of a cell to adapt to a private oncogenic event. We propose that each discrete differentiation state within a given lineage is associated with a unique level of pliancy, which is epigenetically determined. This level relies upon the dynamic cooperation between the molecular and metabolic networks of the cell and the oncogenic event, and dictates the genomic landscape of human cancers.

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4A / 2

Modulation of macroH2A1 isoforms during EMT process drives the metastastic potential of human prostate cancer cells.

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Epithelial-to-Mesenchymal Transition (EMT) is an outstanding example of developmental cellular plasticity which can be reactivated in pathological processes, such as metastatic dissemination of cancer cells. EMT is rarely fully activated in tumor cells, giving rise to a whole range of partial EMT phenotype and must be reversible. Partial EMT in cancer cells is thought to enhance their invasive properties, generate cancer stem cells, and promote resistance to anti-cancer drugs. Reversion of EMT (MET) would be expected to facilitate the growth of disseminated tumor cells into clinically-relevant metastases. All these features have made emerge the concept of Epithelial Mesenchymal Plasticity (EP) enclosing full and partial EMT processes.

In relevant EP transformation pathways genes are regulated by post-transcriptional mechanisms, including alternative splicing and epigenetic reprogramming, with widespread changes in chromatin modifications including the reprogramming of specific chromatin domains. Hence, chromatin reorganization could contribute to the regulation of epithelial plasticity. To date however, even if changes in histone marks start to be identified, the presence of histone variants has not been clearly investigated with respect to the phenomena of EP.

We have shown that expression of the histone variant macroH2A1.1 correlates with the claudin-low intrinsic subtype in breast cancer cell lines and molecular characteristics of the EMT process. Moreover, untreated Triple Negative Breast Cancers presenting a high macroH2A1.1 mRNA ratio exhibit a poor outcome.

Henceforth, we show that the relation between the EP process and a preferential expression of macroH2A1.1 is not only correlative but that these two processes are functionally nested. First, in the context of multiphasic TGFβ-dependent EP models of mammary epithelial cells (HMEC and MCF10A), the generation of partial states of EP induced a preferential expression of macroH2A1.1. Second, in the context of cancer cell lines, the multiphase appearance of EMT under TGFβ treatment is lost. Even if the expression of macroH2A1.1 is unaffected by TGFβ in this cellular context, cancer cell lines with fixed high macroH2A1.1 expression levels are able to enter in an engaged and maintained EP in contrast to cancer cell lines with a low level of macroH2A1.1 expression. Finally, knock-down of the histone variant macroH2A1.1 in tumor cells decreases tumorigenicity and drastically limits tumor dissemination in a spontaneous metastasis xenograft model of human prostate cancer. In particular, macroH2A1.1-depletion specifically abrogates pulmonary metastasis.

All of these results might reflect a potential role of macroH2A1.1 in cellular plasticity, required for the establishment and/or development of metastasis.

4A / 3

Epigenome editing of alternatively spliced exons relevant for the EMT is sufficient to change the splicing outcome and the cell faith

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Alternative splicing is a key mechanism to increase the complexity of our genome that has been involved in a variety of biological processes and diseases. In the past few years, chromatin has increasingly been shown to play an important role in the regulation of splicing. However to what extent histone modifications can impact alternative splicing in a physiological context still remains unknown. To address this question, we have taken advantage of the epithelial-to-mesenchymal transition (EMT), an inducible and highly dynamic model system of cell reprogramming, in which splicing is highly involved.

We first correlated in time, during the onset of the EMT, the changes in alternative splicing and histone mark enrichment levels along genes essential for the EMT, such as FGFR2 and CTNND1. Surprisingly, we observed that marks, such as H3K27me3 and H3K27ac, changed very early in time, even before the first changes in splicing could be detected. Whereas marks, such as K4me1, changed much later when the changes in splicing were well established. To address the causative role of these histone marks on alternative splicing, we adapted the CRISPR/dCas9 system to edit exon-specifically the levels of H3K27me and H3K27ac at the studied alternatively spliced exons and test the effect on exon inclusion. For the first time, we could induce a change in the splicing outcome by just changing the levels of a histone mark specifically at the alternatively spliced exon, proving that those histone marks are sufficient to trigger the highly dynamic changes in alternative splicing observed during the EMT.

Together, our results prove a new role for chromatin in orchestrating highly dynamic changes in alternative splicing and that locus-specific changes in histone modifications precisely at the regulated exon are sufficient to induce this change. Further studies will bring light into how these two features are tightly bridged and which regulators are involved in its regulation.

4A / 4
RNA epigenetic and FTO activity steer cancer cell fate

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Following decades of near-dormancy, the field of RNA modification is experiencing a rebirth, mostly thanks to recent progress in detection techniques such as high throughput sequencing. This study stems from a transdisciplinary research endeavor that seeks to evaluate the role of RNA modifications in colorectal cancer progression and more specifically in the acquisition of Cancer Stem Cell (CSC) phenotype. CSC represents a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity which can escape from both conventional and targeted therapies, disseminate and seed metastasis. For that reason, **understanding the molecular mechanisms that bestow CSC phenotype has become a major goal to design new therapeutic routes that may prevent tumor relapse and metastasis**.

N6-methyladenosine (m6A), the most frequent epigenetic modification that occurs on mRNA, is involved in all step of gene expression (splicing, transport, stability and translation) and plays a role in major cellular pathways and processes such as stem cell differentiation. m6A is a dynamic, reversible chemical modification deposited by the METTL3 - METTL14 - WTAP "writer" complex and removed by the "erasers" ALKBH5 and FTO. While recent studies have connected m6A dynamic with cancer progression, **the role of this RNA modification in colorectal cancer evolution remains unknown**. Combining ALDH activity (CSC marker) based cell sorting with MeRIP-sequencing (collaboration with Tao Pan, Chicago U.), we have mapped and compared m6A distribution across the transcriptomes of CSC-enriched and CSC-depleted cell samples and shown significant differences. Then, selective silencing of m6A actors, has uncovered a **specific role of FTO, an m6A demethylase, in regulating CSC abilities**: FTO inhibition (expression or activity) increases substantially self-renewal, chemoresistance and tumor initiation in vivo (xenograft mouse model). While this observation holds true for all colorectal cancer cell lines tested, FTO level has no impact on breast cancer cell line, suggesting some sort of "tissue-specificity". Finally, recent data suggest that FTO expression may vary throughout the course of cancer progression, mostly decreasing along with the acquisition of invasive/metastatic properties.

Altogether, FTO activity seems capable of shaping colorectal cancer cell phenotype and might play a role in tumor evolution. Ongoing RNA-seq experiments followed by cross-analysis with m6A mapping data should enable us to identify RNA targets of FTO.

Session 4B – Projets émergents financés au sein de l'axe 4

4B / 1
Parolothèque

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La Parolothèque est issue d'un projet soumis en 2013 à l'appel Soutien à l'émergence du Cancéropôle Grand Sud-Ouest financé à 10000 Euros. Le travail mené pendant 2 ans a permis de déterminer :
1/ sa définition : Par analogie aux tumorothèques, une Parolothèque est une banque d'échantillons de parole enregistrés, obtenus à partir de bilans de trouble de la parole ou du langage ou à partir d'entretiens ou d'interviews de personnes concernées par les pathologies tumorales. Son objectif principal est à d'étudier les corpus de parole des patients atteints de cancer autant du point de vue de son contenant (parole) que de son contenu (discours) et de permettre le développement d'axes de recherches variés dans divers domaines (sciences humaines et sociales: SHS, épidémiologie, linguistique, informatique…).
2/ les partenaires : Université de Toulouse (Jean Jaurès & Paul Sabatier), Université Aix Marseille, Université d'Avignon & CNRS

Il a débouché sur un Groupement d'Intérêt Scientifique (GIS) dont la signature par l'ensemble des partenaires reste incomplète.
Mais à l'issu de la 1ère année de travail, plusieurs projets ont été soumis. Le projet «Carcinologic Speech Severity index C2SI» a trouvé un financement par l'appel libre InCA SHS en 2014 permettant au groupe de concrétiser une première collaboration. Celle-ci se termine avec la production d'un indice automatique capable de mesurer les résultats fonctionnels sur la parole après traitement. Ce travail a permis aux partenaires d'obtenir un financement par l'ANR pour le projet RUGBI : Recherche d'unités linguistiques pertinentes pour améliorer la mesure de l'intelligibilité de la parole altérée par des troubles de production pathologique et un financement par l'Union Européenne Horizon H2020 MSCA-ITN-ETN : TAPAS Training Network on Automatic Processing of PAthological Speech. Les axes psycho-social et épidémiologie n'ont pas encore décroché de fonds pour leur développement.

4B / 2

Des innovations biomédicales issus de l'aéronautique et du spatial? Contribution à une analyse des processus translationnels en cancérologie

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Depuis une dizaine d'années, la question de la diversification et du transfert de technologie se pose à l'industrie aéronautique et spatial en raison notamment de la crise qu'a traversée le secteur (aux alentours de 2006) et la croissance de la concurrence (la création de nouvelles entreprises dans le domaine spatial notamment qui gagnent des parts de marché et font concurrence aux entreprises traditionnelles du secteur). Aussi, pour faire face aux transformations récentes du secteur et à la concurrence croissante plusieurs instances de soutien et de structuration du secteur aéronautique et spatial se sont lancées dans des programmes de diversification et de transfert de technologie. En quoi consistent le transfert de technologie et la diversification industrielle ? Existe-t-il des contraintes spécifiques à ce mode de développement technologique ?

La littérature sur le transfert de technologie est relativement éparse. Les travaux menés dans le courant des études sur les relations Université-Industrie (UIR) portent essentiellement leur attention sur le transfert technologique de type académique. Il s'agit par là d'un processus de valorisation des résultats de la recherche scientifique, c'est-à-dire un mouvement par lequel des résultats de recherche, des connaissances et des dispositifs techniques passent de la sphère académique, universitaire à la sphère industrielle où ils seront transformés en produits, procédés ou technologies commercialisables.
Une représentation du transfert de technologie exclusivement fondé sur la valorisation académique ne permet toutefois pas de saisir pleinement les mécanismes à l'œuvre dans la démarche de diversification engagée par les acteurs du secteur aéronautique et spatial. Les processus de transfert classique fondés sur un cheminement linéaire peinent notamment à saisir les possibilités d'innovation par transposition d'un domaine d'application à un autre. D'autres formes de circulation et de transfert de technologie sont visibles et permettent d'appréhender les ajustements techniques et normatifs nécessaires au passage d'un domaine technique à un autre. En proposant des technologies aéronautique ou spatiale au domaine de la santé, les acteurs ne sont-ils pas contraints de questionner, d'adapter et de retravailler les cadres de fonctionnements ? De quelle manière ces transferts de technologie conduisent-ils à la production de nouvelles connaissances ?
A partir de plusieurs marchés de diversification, nous avons pu repérer quelques-uns des freins au transfert de technologie d'un secteur à l'autre : des freins cognitifs, des controverses techniques, des freins financiers, des questions liées à la propriété Intellectuelle.

La réalisation de cette étude a nourri, sur les plans méthodologiques et conceptuels, l'élaboration d'un projet sur les processus translationnel. Ce projet intitulé « Analyse comparée de trois processus translationnels : les cas de la radiofréquence, des ultrasons hautement focalisés (HIFU) et de l'hyperthermie magnétique » a été soumis dans le cadre de l'AAP « Projets libres de recherche en Sciences Humaines et Sociales, Épidémiologie et Santé Publique » de l'INCa qui l'a retenu pour un financement de 198 992 euros.

4B / 3

Description des délais de prise en charge du cancer du sein en région Midi-Pyrénées

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Introduction: Le cancer du sein est une maladie fréquente qui bénéficie de stratégies qui font l'objet aujourd'hui de recommandations nationales et internationales. Leur mise en œuvre, complexe, nécessite une bonne coordination entre les multiples acteurs et les délais de prise en charge sont de bons indicateurs de cette coordination. Leur importance a justifié des recommandations émises, entre autres, en France par l'Institut National du Cancer, au Royaume-Uni par le National Health Service et en Europe par l'European Society for Medical Oncology. Nous avons souhaité étudier ces délais de prise en charge du cancer du sein à l'échelle de l'ex-région Midi-Pyrénées et les comparer aux recommandations disponibles.

Matériel et méthode: Il s'agit d'une étude descriptive rétrospective, incluant les patientes nouvellement diagnostiquées pour un cancer du sein et sélectionnées à partir de leur présentation en RCP au cours du 1er semestre 2015 dans l'ex-région Midi-Pyrénées. Les délais de prise en charge des cancers infiltrants localisés ont été définis à partir du référentiel régional, des critères nationaux et de l'expertise des animateurs du groupe de travail régional « sénologie ». Le recueil des dates a été réalisé dans les dossiers médicaux. Chez les femmes primo-opérées, la description (médiane en jours (j) et écart interquartile []) concernait les délais biopsie-chirurgie (CG), CG-chimiothérapie (CT), CG-radiothérapie (RT) en l'absence de CT, CG-hormonothérapie (HT) et fin de la CT-début de la RT. En cas de traitement néoadjuvant, les délais entre diagnostic-premier traitement médical et fin du traitement néoadjuvant-CG ont été calculés. Les résultats ont été pondérés pour tenir compte des différences de probabilité d'inclusion des RCP dans l'échantillon.

Résultats: 652 femmes (âge moyen 61 ans +/- 14) ont été incluses, dont 561 (88%) présentaient un stade infiltrant localisé. Parmi elles, 507 ont été opérées d'emblée et 37 ont reçu un traitement néoadjuvant. Chez les femmes primo-opérées, les délais médians d'accès étaient de 35 j [26-48] pour la CG, 41,5 j [35-50] pour la CT adjuvante, 52,5 j [43-65] pour la RT adjuvante en l'absence de CT et 230 j [207-246] pour l'HT adjuvante. En cas de traitement néoadjuvant par chimiothérapie, le délai médian d'initiation du traitement médical était de 35 j [26-49] et la chirurgie était ensuite réalisée dans un délai médian de 35 j [28-44].

Conclusion: Les résultats de cette étude fournissent un état des lieux régional des délais de prise en charge initiale des cancers du sein localisés. En comparaison avec les recommandations actuelles, ces délais semblent élevés. La recherche de facteurs associés, comme notamment l'âge au moment du diagnostic ou le fait d'être pris en charge sur plusieurs structures de soins, fera l'objet d'une analyse complémentaire. Enfin, les résultats de ces analyses seront transmis aux Centres de coordination en cancérologie de la région dans le cadre de leurs démarches qualité.

Session 5A – Hepatocellular carcinoma

5A / 1

Genomics of liver tumors: new mechanisms of carcinogenesis

Jessica ZUCMAN-ROSSI

Functional Genetics of Solid Tumors, Paris

5A / 2

New landscape in HCC treatment: TKI and Immunotherapies

Eric ASSENAT

Montpellier Molecular Genetics Institute and University Hospital

5A / 3
Deciphering the dual role of ß-catenin in hepatocellular carcinoma

Violaine MOREAU

Bordeaux Research in Translational Oncology

Tumor development and progression are mainly driven by oncogenic mutations but are also strongly influenced by physical factors. Indeed, intra- and inter-cellular communications coordinate various cellular activities that direct proliferation and migration through signal transduction pathways. β-catenin is a key effector of these inside-out and outside-in mechanotransduction events. β-catenin is part of the cell-cell adhesion complex, where it plays a structural role but is also the key effector of the Wnt pathway, where it is endowed with a transcriptional regulatory activity.

In hepatocellular carcinoma (HCC), which is the main primary malignancy of the liver, oncogenic mutations of ß-catenin are present in 18-41% of tumors. In most HCCs, β-catenin mutations are present at the heterozygous state meaning that mutated and wild-type alleles co-exist in tumor cells.

We have devised a RNA interference strategy in HepG2 cells that allows uncoupling of the two functions of ß-catenin in the same cellular background: nuclear/transcriptional activity, a function almost exclusively mediated by the mutated β-catenin, and membrane/structural activity, which is mediated by the degradable WT β-catenin.

This "dual β-cat HepG2 model" allowed us to:
1- Identify Fascin 1 as a β-catenin target involved in bile canaliculi formation, a feature of differentiated hepatocytes
2- Characterize the small Rho GTPase, Rnd3/RhoE as a novel atypical target of β-catenin, in HCC.

Thus, we believe that this simple cellular model may help deciphering the dual role of β-catenin in tumor hepatocytes.

5A / 4
Tumor-Antagonizing Fibroblasts in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is world's sixth most common and third most deadly malignancy. The clinical management of HCC is difficult. Apart from liver transplantation in a minority of operable patients, there is currently no effective treatment to eradicate HCC. Two distinct compartments, malignant cells and the tumour stroma in general compose tumors. Cancer associated fibroblasts (CAF) are the most versatile cells in the tumor stroma. While numerous studies have found CAF as key supportive element in tumoral progression, emerging evidence suggests that this cannot be assumed per default. Recent clinical failures resulting from systemic depletion of CAF, suggests a more subtle relationship between tumor and host microenvironment that yet remains to be understood.

In the present work we profile CAF-derived proteins in human HCC in order to understand their tumor supportive and tumor-suppressive aspects. Fresh biopsies were first soaked in biotinylation reagent (Sulfo NHS-SS biotin), followed by isolation of soluble proteins using streptavidin affinity columns. The isolated proteins were further identified and quantified using mass spectrometry. The analysis identified over 200 soluble/extracellular proteins, of which at least 20 targets were uniquely expressed in HCC. Bioinformatic evaluation focusing exclusively on fibroblast-derived proteins identified several novel targets that warranted functional analysis.

Of the different CAF-derived proteins we have characterized one major tumor-suppressive factor that has previously never been reported in the context of cancer. This soluble protein has demonstrated a remarkable ability to bind and block the activity of many tumor growth-factors. However, in aggressive HCC, the stability of this pan-growth factor inhibitor was negatively affected, notably reducing its activity and thus favoring tumor progression. In conclusion our data show the need to revisit the concept of CAF in tumor biology, highlighting the fact that not all CAF are the same. CAF-reprogramming, rather than depletion, should in the future be considered as the new innovative therapeutic approach for treating cancer.

5A / 5
CDK8 kinase acts as an oncogene in hepatocellular carcinoma

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CDK8 is a cyclin-dependent kinase that is an integral part of the Mediator complex, which modulates the transcriptional output of many oncogenic pathways. CDK8 has been proposed to act as an oncogene in melanoma and in colorectal cancer and is considered to be a promising target for anticancer treatments, a notion reinforced by the recent development of potent and specific inhibitors.

CDK8 impacts on pathways frequently altered in hepatocellular carcinoma (HCC): it modulates the Wnt/β-catenin signaling and participates in the control of expression of p53 target genes. In addition, CDK8 has been reported to regulate two major hepatic metabolic pathways: lipogenesis and glycolysis. These observations prompted us to further investigate the role of CDK8 in liver physiology and hepatic carcinogenesis.

We generated a genetically modified mouse carrying floxed Cdk8 gene and crossed it with Alb-Cre transgenic animals to obtain hepato-specific CDK8 knockout (CDK8Δhep). The CDK8Δhep animals are protected from chemically induced liver carcinogenesis (diethylnitrosamine protocol), suggesting an oncogenic function of CDK8 in liver tumours. Importantly, our analysis of Cdk8 expression in a cohort of HCC patients indicated that it is overexpressed in tumours, and that strong expression of Cdk8 is associated with poor prognosis.

To better characterize the role of CDK8 in liver carcinogenesis, we isolated hepatic progenitor (BMEL) cells from Cdk8F/F mouse. The ex vivo deletion of CDK8 either by Cre recombinase or by CrispR/Cas9 gene editing allowed us to compare transformation of wild-type and CDK8 KO cells. Strikingly, CDK8 inactivation fully prevented transformation by a potent oncogene H-RasG12V. The tumour suppressive phenotype of CDK8 KO is not a particularity of the BMEL cell lines, as it was confirmed in the human hepatoblastoma HepG2 cell line.

Using the BMEL cell lines as well as in vivo hydrodynamic gene transfer technology, we have further shown that the oncogenic activity of CDK8 is dependent on the p53 status. RNAseq analyses aimed to elucidate the molecular mechanisms involved in CDK8 oncogenic function in hepatocellular tumorigenesis are underway.

Session 5B – Etudes d'innovations en santé

5B / 1

Un programme de recherche intégré et pluridisciplinaire en SHS sur une innovation, la radiologie interventionnelle: les points de vue du sociologue des sciences, de l'économiste et du sociologue de la santé

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5B / 2

L'électrochimiothérapie : comment faire passer le courant entre la recherche et le milieu médical ?

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Sersa, G., J. Teissie, et al. (2015). "Electrochemotherapy of tumors as in situ vaccination boosted by immunogene electrotransfer." Cancer Immunol Immunother.

Electroporation is a platform technology for drug and gene delivery. When applied to cell in vitro or tissues in vivo, it leads to an increase in membrane permeability for molecules which otherwise cannot enter the cell (e.g., siRNA, plasmid DNA, and some chemotherapeutic drugs). The therapeutic effectiveness of delivered chemotherapeutics or nucleic acids depends greatly on their successful and efficient delivery to the target tissue. Therefore, the understanding of different principles of drug and gene delivery is necessary and needs to be taken into account according to the specificity of their delivery to tumors and/or normal tissues. Based on the current knowledge, electrochemotherapy (a combination of drug and electric pulses) is used for tumor treatment and has shown great potential. Its local effectiveness is up to 80 % of local tumor control, however, without noticeable effect on metastases. In an attempt to increase systemic antitumor effectiveness of electrochemotherapy, electrotransfer of genes with immunomodulatory effect (immunogene electrotransfer) could be used as adjuvant treatment. Since electrochemotherapy can induce immunogenic cell death, adjuvant immunogene electrotransfer to peritumoral tissue could lead to locoregional effect as well as the abscopal effect on distant untreated metastases. Therefore, we propose a combination of electrochemotherapy with peritumoral IL-12 electrotransfer, as a proof of principle, using electrochemotherapy boosted with immunogene electrotransfer as in situ vaccination for successful tumor treatment.

Yarmush, M. L., A. Golberg, et al. (2014). "Electroporation-based technologies for medicine: principles, applications, and challenges." Annu Rev Biomed Eng 16: 295-320.

When high-amplitude, short-duration pulsed electric fields are applied to cells and tissues, the permeability of the cell membranes and tissue is increased. This increase in permeability is currently explained by the temporary appearance of aqueous pores within the cell membrane, a phenomenon termed electroporation. During the past four decades, advances in fundamental and experimental electroporation research have allowed for the translation of electroporation-based technologies to the clinic. In this review, we describe the theory and current applications of electroporation in medicine and then discuss current challenges in electroporation research and barriers to a more extensive spread of these clinical applications.

Autres références de l'auteur:

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5B / 3

Nanoparticules dans l'alimentation humaine : existe-t-il un lien avec l'augmentation du nombre de cancers colorectaux ?

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Le cancer colorectal (CRC) est la 3ème cause de mortalité par cancer dans les pays industrialisés. Les facteurs environnementaux favorisant et/ou aggravant l'inflammation colique ou affectant le processus de renouvellement des cellules épithéliales sont une source majeure de préoccupation concernant le risque tumoral. En effet, les cellules de la muqueuse intestinale se renouvellent tous les 5 jours, soumettant le tractus digestif à un stress important dans le contrôle de la prolifération, la différenciation et l'organisation cellulaire, et donc à un risque sérieux de conversion maligne. Le tractus digestif est une interface entre l'environnement extérieur et notre organisme, permettant l'absorption des nutriments et l'exclusion des composés nocifs. Sa capacité à contrôler l'absorption et à protéger contre les substances nocives est définie comme étant la fonction de barrière intestinale (IBF). Un défaut d'induction de l'IBF en période périnatale est associé à diverses pathologies comme les allergies, les maladies inflammatoires chroniques de l'intestin, les maladies auto-immunes ou encore le CRC.
L'utilisation de nanoparticules (NP) dans l'alimentation humaine s'est généralisée. Bien que les NP de silice (SiO2, additif alimentaire E551) soient largement utilisées dans les aliments, leur utilisation est controversée puisque certaines entreprises les ont interdites.

Notre hypothèse est que les NP de SiO2 dans l'alimentation humaine pourraient altérer la mise en place de l'BF, favorisant à l'âge adulte, l'inflammation et la carcinogénèse colique. L'objectif principal de ce projet est d'étudier l'impact des NP de SiO2 sur l'IBF menant à l'inflammation et la carcinogenèse sur deux modèles originaux : les souris déficientes pour l'IL10 et NOX1et les organoïdes.

Ce projet devrait apporter un réel bénéfice pour la santé des populations exposées à ces E551 et servir de modèle expérimental pour étudier les effets délétères d'autres additifs alimentaires.

Session 6 – New publishing models

6 / 1
Open Science & Publising Models - how to share reproductible data

Andrea LEIBFRIED

Life Science Alliance Journal, USA / Germany

The peer reviewed research paper remains the main conduit for the exchange of research discoveries. The exponential global research growth in the life sciences (with 1.3 million papers on Pubmed in 2017) puts the peer review system under strain.

I will discuss how journals and citation metrics are increasingly employed as surrogates for quality in research assessment, increasing the pressure to publish. My talk will provide an overview of the current peer review system and alternative ways of reviewing and sharing research results, and of the aims of the Open Science movement. Finally, I will present a number of policies that are already in place at the open access journal Life Science Alliance and at its sister journals at EMBO, Rockefeller University and Cold Spring Harbor Laboratory Presses to reduce the burden on reviewers and authors and to ensure a fast, fair and informed editorial process.

6 / 2

The transformation of the scientific paper: from knowledge to accounting unit

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Policies governing scientific research have changed dramantically over the last 30 years. This conference will present those changes and their effects on scientific research. Not only are government policies more constraining and more open to citizen demands but the "evaluation fever" that emerged in the 1990s also contributed to detoriate the conditions of research: the uses of flawed indicators for evaluation like Impact factors and h-index, the growth of the number of published papers and so-called "predatory journals", the rise of 'corrected' and retracted papers, all these phenomena are the effects of the transformation of the scientific paper from "unit of knowledge" to an "accounting unit".

6 / 3
Economics of Scientific Edition

Philippe GORRY

Research Group in Theoretical & Applied Economics UMR CNRS 5113, University of Bordeaux

As the number researchers increase, growth in scholarly publishing is exploding. A the same time, academic publishing has undergone major changes, by making the transition from the print to the electronic format. Digital technology in academic publishing has rendered old business models obsolete. Nowadays, the academic publishing is a oligopolistic market over $25.2 billion with double-digit annual price increases rising faster than inflation and profit margins to rival GAFA. This profitable business is no longer sustainable for library budgets and, therefore, it endanger knowledge diffusion. The welfare of society is sub-optimal and the potential for market failure is very high. In theory, an open-access market could drive down costs, but that might not happen. Indeed, OA journals raise questions about the value publishers add for their money. I will discuss the two current business models, 'subscriber-pays' and 'author-pays' from an economic stand point of view.

Session 7 – Artificial intelligence and cancer

7

Omics data in cancer : No more humans !

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Institut de Génétique Humaine, Montpellier

A large portion of the information contained in biological data is potentially lost through classical bioinformatics analysis. This is especially true in cancer studies where patient transcriptomes or genomes may vary from their references. In addition, each type of experiment is analysed through a specialized set of pipelines and statistical procedures that require a full time bioinformatician. The aim of my talk is to demonstrate how artificial intelligence can be used to automatically process data and help in developing novel hypotheses.

Session 8A – Radiotherapy and DNA damage

organized with

8A / 1

Radiotherapy from classical DNA damage to immunotherapy

Eric DEUTSCH

Institut Gustave Roussy, Villejuif

8A / 2
Lymphocyte apoptosis and individual radiosensitivity

David AZRIA

Institut du Cancer de Montpellier

8A / 3

Therapeutic efficacy of 177Lu-lilotomab satetraxetan in non-Hodgkin B-cell Lymphoma is controlled by G2/M cell cycle progression

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[5] Nordic Nanovector ASA, Oslo, Norway

We aimed at determining the molecular mechanisms involved in the therapeutic efficacy of ^{177}Lu-labeled lilotomab satetraxetan (Betalutin®) directed against the CD37 receptor expressed by non-Hodgkin lymphoma (NHL) B-cells.

Materials and methods. In vitro, Ramos, Raji and rituximab resistant Raji (Raji2R, all Burkitt lymphoma), DOHH2 (transformed follicular), Rec-1 (mantle), U2932 and OCILy8 (diffuse large B-cell) lymphoma cell lines were exposed for 18 hours to increasing activities (0-6 MBq/mL) of 177Lu-lilotomab, of the non-specific ^{177}Lu-cetuximab or to unlabelled mAbs (0-40µg/mL). Clonogenic survival, proliferation, expression level of phosphorylated CDK1, cell cycle progression and apoptosis were investigated. In vivo, mice bearing subcutaneous Ramos, DOHH2, Raji, Raji2R or OCILy8 tumour xenografts, were treated with ^{177}Lu-mAbs, with rituximab or lilotomab and tumour growth was monitored.

Results. We showed in all lymphoma cell lines that unlabelled rituximab was more cytotoxic than lilotomab. When lilotomab was radiolabeled, ^{177}Lu-lilotomab was more cytotoxic than rituximab in the so determined radiosensitive DOHH2 cells while its cytotoxicity in Ramos cells was less pronounced. The higher response to ^{177}Lu-lilotomab in DOHH2 cells than in Ramos cells was mainly mediated by lack of G2/M cell cycle arrest in DOHH2 cells followed by strong induction of apoptosis. Inhibition of CDK1 Tyr15 phosphorylation using MK1775 or PD166285 drugs radiosensitized Ramos cells. These results were supported by in vivo data. In Ramos tumour xenograft models, 250 MBq/kg (1.25 mg/kg) ^{177}Lu-lilotomab and 10 mg/kg rituximab could not delay tumor growth compared with untreated mice. ^{177}Lu-lilotomab significantly delayed tumour growth compared with rituximab (used at the same concentration) only if injected activity was increased up to 500 MBq/kg. Conversely, in DOHH2 tumour xenografts, 100 MBq/kg (0.5 mg/kg) ^{177}Lu-lilotomab was more efficient than rituximab. The in vivo use of MK1775 was shown to radiosensitize Ramos tumour xenografts to ^{177}Lu-lilotomab. Experiments analysis is ongoing for OCILy8, Raji and Raji2R cell lines.

Conclusion: These results indicate that ^{177}Lu-lilotomab is an efficient therapeutic tool for NHL, particularly for tumors showing reduced inhibitory CDK1 phosphorylation.

8A / 4

Repair proteins in quest of the Ku ring : molecular insights into the first steps of DNA double-strand breaks repair by end-joining

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Radiotherapy is a critical tool in cancer treatment that is prescribed in one in two cases. The high-energy rays delivered destroy cancer cells by fragmenting their DNA but cells can resist treatment in part by repairing the DNA breaks. To increase the effectiveness of radiotherapy, for instance by inhibiting DNA repair within the tumour, we first need to get a detailed understanding of how these repair mechanisms work.

In irradiated cells, a ring-shaped protein known as Ku that is conserved from bacteria to humans quickly encircles the ends of DNA breaks. After assembly on Ku of various specialized proteins that are necessary to process the DNA ends, the repair reaction ends with the joining of the breaks ends together. Although many Ku partners are known, the molecular details of their interactions are still elusive. We studied recently the first phase of this protein choreography with Ku at the centre, and particularly how come on stage two proteins that work with Ku at DNA breaks to build the repair protein complex (1). This work combined the view of protein complexes at an atomic scale by X-ray crystallography in the group of Jean-Baptiste Charbonnier with live cell imaging and cellular assays in our group. Based on the precise position of the protein-protein interactions sites on Ku from crystallography snapshots, we challenged with protein mutants the consequences of impaired interactions on protein recruitment to damaged DNA, DNA breaks repair and cell survival to irradiation.

(1) Nemoz, C.*, V. Ropars*, P. Frit*, A. Gontier, P. Drevet, J. Yu, R. Guerois, A. Pitois, A. Comte, C. Delteil, N. Barboule, P. Legrand, S. Baconnais, Y. Yin, S. Tadi, E. Barbet-Massin, I. Berger, E. Le Cam, M. Modesti, E. Rothenberg, P. Calsou#, and J.B. Charbonnier#. 2018. XLF and APLF bind Ku80 at two remote sites to ensure DNA repair by non-homologous end joining. Nat Struct Mol Biol. 25:971-980.

Session 8B – New mechanisms in gastro-intestinal oncology

8B / 1

Intestinal tuft cells: novel regulators of the immune micro-environment

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Gut homeostasis relies on a tight regulation of inflammation according to luminal clues. Although the intestinal epithelium is in direct contact with the luminal content, including microbes, parasites and potentially allergenic and toxic compounds, little is known about its contribution in transmitting luminal signals to stroma-located immune cells and in regulating their behaviour. We characterized the intestinal epithelial tuft cells, a neglected cell type of the mammalian intestinal epithelium, and demonstrated their essential role in initiating immune defence responses against helminth parasites by producing the IL25 alarmin cytokine. This represents an example of a critical cooperation between epithelial and haematopoietic cell compartments to maintain tissue homeostasis. Tuft cells are also present in several digestive cancers where they may play similar roles in mediating interactions between tumor cells and their immune microenvironment.

8B / 2

The HSP90 co-chaperone RPAP3 plays an essential role in intestinal homeostasis

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RPAP3 was initially characterized as a co-chaperone for HSP90 (Zhao et al., 2005). RPAP3 assembles with three other proteins: RUVBL1, RUVBL2, PIH1D1 to form the R2TP. R2TP recruits the chaperone HSP90 to fold newly-synthesized proteins and assemble them into functional complexes. R2TP assembles a variety of substrates, including snoRNPs, telomerase RNP, the nuclear RNA polymerases and PIKKs, a family of proteins which include mTOR and TRRAP. All these substrates play key functions in cellular proliferation and tumorigenesis. Indeed, mRNAs encoding RPAP3 and its interactants are significantly overexpressed in colon tumours. Using a proprietary antibody, RPAP3 expression was assessed by immunohistochemistry in 177 paraffin-embedded, archival primary colorectal cancer (CRC) tissues obtained from patients without pathological evidence of nodal involvement and distant metastasis. RPAP3 appears to be a significant prognostic parameter influencing disease relapse (HR = 2.7: 95% CI, 1.2-6.5; P= 0.023) together with tumor stage.

We first addressed the role of RPAP3 in the intestine, a tissue with continual differentiation and proliferation, using a conditional murine knock-out model. Invalidation of *RPAP3* in the adult intestine led to a rapid loss of weight of the animals as early as 6 days post-induction, and death of most animals after 10 days. *RPAP3* invalidation compromises the proliferation and the survival of the progenitors (constituting the Transient Amplification compartment), which normally ensures the continuous renewal of the intestinal epithelium. As a result, the epithelium of the small intestine rapidly deteriorates, explaining the observed lethality.

We then assessed the role of RPAP3 in a murine genetic model of intestinal cancer. In this model, invalidation of one copy of the tumour-suppressor gene APC (which is mutated the vast majority of human colorectal cancers) induces intestinal dysplasia within 12 weeks. Unexpectedly, invalidation of one copy of RPAP3 in this model (*VilCreER^{T2}; APC$^{flox/+}$; RPAP3 $^{flox/+}$* mice) diminished the incidence of colic tumours but increased the size of the lesions. We are now investigating how the interplay between the different substrates of RPAP3/R2TP can explain this phenomenon.

In conclusion, our work highlights the crucial role of RPAP3 in the small intestine. We are now investigating how down-regulation of RPAP3 interferes with colorectal tumorigenesis, to address its potential as a therapeutic target.

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H-1 parvovirus inhibits both primary tumor and metastatic growth of human pancreatic tumors.

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Pancreatic cancer is a disease with no cure that ranks second worldwide in cancer-related death. Oncolytic virotherapy is an attractive new therapeutic strategy to help fight this disease. Among candidate viruses, H-1 parvovirus has shown great promise for inhibiting cancer cell growth, including pancreatic cancer cells, and is shown to be safe in early phase clinical trial. However, its therapeutic potential has not been fully explored and exploited in human preclinical models of pancreatic tumors.

In this study, we found that H-1PV inhibits cell proliferation using, longitudinal, real-time noninvasive monitoring of cell growth, and induces massive cell death of pancreatic cancer cell lines and patient-derived primary cells. Using qPCR, we found that H-1PV replicates efficiently in pancreatic cancer cells but failed to form plaques, strongly suggesting minimal propagation ability in this model. We next engrafted pancreatic cancer cells in the pancreas of immunodeficient mice. Tumor growth was monitored non-invasively using ultrasonography. Mice with exponentially growing pancreatic tumors received intracardiac injection of H-1PV, as we found this was the best route of administration for systemic distribution of the virus. We found that H-1PV injection is well tolerated, and strongly inhibit the growth of primary tumors. Surprisingly, H-1PV treatment also diminishes the numbers of circulating tumoral cells (CTC) and the size and number of hepatic metastasis. Mice receiving H-1PV survived longer as compared to mock treated mice.

Collectively, our results confirm that H-1PV replicates and kills pancreatic cancer cells, but fails to propagate in cell cultures. Consequently, our next objective is to generate tumor-adapted, H-1PV variants using serial passaging that will successfully spread in vitro and in vivo. In addition, we demonstrate for the first time that H-1PV systemic administration inhibits both human preclinical primary pancreatic tumors and metastases, but may also target CTCs, a unique feature in the field of virotherapy. The role of the immune system in H-1PV mediated antitumoral effect is currently under investigation.

Taken together, our study describes novel aspects of H-1PV therapeutic activity and may stem for future, rationally-designed, clinical trials in patients suffering from pancreatic cancer.

8B / 4

miR-148a sensitizes colon cancer stem cell to chemotherapy by targeting Pregnane X- Receptor signaling

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Therapeutic failure seen in patients with colorectal cancer (CRC) frequently involves post-treatment tumor recurrence, due to the enhanced resistance of cancer stem cells (CSCs). We previously reported that the nuclear receptor Pregnane X- Receptor (PXR, NR1I2) behaves as a key driver of CSC-mediated tumor recurrence where it drives the expression of a large network of genes involved in CSCs chemoresistance (Planque C et al. Oncotarget, 2016). In order to determine the molecular mechanisms that define PXR enrichment in CSCs, we investigated the role of miR-148a on PXR expression and CSC phenotype. The miR-148a has been reported to post-transcriptionally regulate PXR in human liver (Takagi S et al. J Biol Chem, 2008) and has been proposed as a predictive biomarker in patients with advanced CRC (Takahashi M et al. PLoS One 2012). The present study demonstrates that miR-148a is down-regulated in chemoresistant CSC. Accordingly, transfection of miR-148a-3P in CRC cell lines and in patient-derived CRC cells decreases both PXR and PXR target genes expression. In addition miR-148a-3P overexpression decreases CSC proportion and impairs chemotherapy-induced enrichment of CSCs after chemotherapy treatment both in vitro and in vivo. In conclusion, we propose that the deficiency of miRNA-148a-3P is associated with the preferential activation of PXR expression and signalling in colon CSCs. In addition, our findings highlight miR-148a as a promising therapeutic agent that may reduce cancer relapse by selectively sensitizing CSC to chemotherapy.

8B / 5

MAGI1 regulates anchorage-independent growth in breast and colon cancers by modulating the interaction between the HIPPO pathway regulators AMOT and YAP

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MAGIs are a family of apical protein scaffolds whose expression is frequently impaired in different cancers, including colon or breast cancers, and which have been proposed to function as tumour suppressors. However, the mechanisms by which they exert their role remains largely unknown.

To better understand the role of MAGI scaffolds, we performed MS/MS mass-spec analysis on the interactome of MAGI1 in colon and luminal breast cell lines, revealing that MAGI1 interacts with many members of the tumour suppressive HIPPO pathway, such as LATS or AMOTs. In polarised cells, MAGI1 colocalises at the level of the tight-junctions with AMOTs. AMOTs are a family of actin-cytoskeleton modeller which bind and retain in the cytoplasm the Hippo pathway terminal transcriptional activator and potent oncogene YAP. Performing detailed biochemical analyses, we have mapped the domains of interaction between MAGI1 and AMOTs and shown that MAGI1 competes with YAP for AMOT binding. Consistent with these observations we observe that in MAGI1-depleted cells, the accumulation of YAP and p-YAP in the cytoplasm and a down-regulation of the YAP transcriptional targets CTGF, BIRC2 and BIRC5, suggesting that MAGI1 prevents the AMOT-mediated retention of YAP, a role that appears to contradict its proposed tumour-suppressive function.

Strikingly, MAGI1 depleted cells show an increased ability to grow in 3D and in anchorage-independent growth both in vitro and in xeno-grafted mice, a function that appears to depend on cytoplasmic YAP activity, since this effect could be suppressed by YAP inhibition. Confirming the antagonistic interaction between MAGI1 and AMOTs, we observe that opposite to AGI1, AMOTL2-depleted cells show poor 3D and anchorage-independent growth, leading us to propose a model in which the tumour suppressive function of MAGI1 lies in its modulation of the cytoplasmic AMOT-YAP interaction and its effect on adhesion and anchorage dependent growth both in luminal breast and colon cancers.

Session 9 – Microbiota and cancer

9 / 1
Microbiota and its involvment in pathology

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9 / 2

Characterisation of bioactive lipid molecules produced by bacteria: role in intestinal homeostasis

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Numerous studies have highlighted the importance of intestinal microbiota in the physiology and physiopathology of the host. Bacteria contribute to the maintenance of intestinal homeostasis by regulating several essential functions ranging from the protection of the intestinal barrier to the development of the immune system. Impairment in the composition and diversity of this microbiota have been observed in pathologies of digestive tract such as inflammatory bowel disease and colon cancer. In order to restore intestinal homeostasis, therapies using probiotic bacteria were used. Among probiotic bacteria tested, Escherichia coli Nissle 1917 (E. coli Nissle 1917) has been used for its anti-diarrheal, analgesic and anti-inflammatory properties. Nevertheless, the mechanisms of action involved in these therapeutic effects remain unknown. In order to study them, we used two approaches in mass spectrometry to analyse bacterial lipids. A first untargeted approach, allowed us to highlight the production of lipopeptides such as the C12AsnGABAOH composed by a fatty acid of 12 carbons, an asparagine and GABA. These lipopeptides are able to cross the intestinal barrier. The C12AsnGABAOH decreased neuronal activation in sensory neuron primary cultures via the GABAB receptor and inhibited visceral hypersensitivity in vivo. In a second study, we carried out a mass spectrometry targeted approaches looking for hydroxylated long chain fatty acids (LCFA) in bacteri. We highlighted several LCFA of 10 to 18 carbons with a hydroxylation on their third position. These LCFA were not able to cross the intestinal barrier and accumulated in the epithelium where they activated PPAR-γ and PPAR-γ receptor.

These works allowed us to demonstrate that bacteria from the microbiota could signal to host cells by secreting lipopeptides and LCFAs. These lipid compounds could be involved in the maintenance of intestinal homeostasis exerted by the microbiota.

9 / 3

Remote control of antitumoral immunity by the gut microbiota

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Instability in the composition of gut bacterial communities, referred as dysbiosis, has been associated with common human intestinal disorders such as Crohn's disease and colorectal cancer. However, it remained to be determined whether dysbiotic states may be sufficient to instigate disease or may be solely a consequence of the underlying disorder. Recent studies, including ours, shed lights on several mechanisms whereby the host protect from a communicable risk for intestinal inflammation and tumorigenesis by regulating the assembly of the gut microbial communities in mice. Future clinical and metagenomic studies should now i) determine the role of the gut microbiota on the efficiency of biologics and chemotherapies and ii) investigate which microbial genes contribute to the overall disease risk. Such knowledge should advance the development of more efficient anti-tumoral therapeutic approaches that reroute the response to the microbiota before it leads to development of advanced neoplasia.

9 / 4

Impact of Helicobacter sp infection on gastric lymphomagenesis and microbiota

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La bactérie Helicobacter pylori est un pathogène capable de coloniser l'estomac humain et d'induire une inflammation chronique nommée gastrite, souvent asymptomatique mais qui peut évoluer vers des pathologies plus graves telles que l'ulcère gastrique et duodénal, l'adénocarcinome et, dans 0,1% des cas, un lymphome gastrique de type MALT (LGM). Les mécanismes physiopathologiques conduisant au LGM notamment les réponses inflammatoires, immunologiques et cellulaires sont encore peu étudiés.
Le LGM est un lymphome B à petites cellules qui va se développer dans ce contexte de MALT acquis dans la zone marginale des follicules lymphoïdes réactionnels et s'étend dans la muqueuse, détruisant les structures épithéliales. La prolifération des LB néoplasiques est activée par les LT CD4+ non néoplasiques via la costimulation CD40L-CD40.

Pour reproduire cette pathologie en modèle murin, afin de pallier à la difficulté d'accès à des prélèvements humains associés à cette pathologie, différents hôtes tels que la souris BALB/c, la souris C57BL/6 ont été infectés par différentes espèces du genre Helicobacter comme H. pylori, H. felis ou H. heilmannii. H. felis est une espèce fortement inductrice de LGM en modèle murin. Ces modèles ont apporté des éléments intéressants sur la réponse inflammatoire et le rôle des miR dans cette pathologie.

Un nouveau modèle de LGM basé sur des infections, par H. pylori ou H. felis, de souris C57BL6 transgéniques pour la forme humaine de la cytokine APRIL a récemment été décrit. L'infection par Helicobacter dans ce modèle, notamment à H. felis, influence la richesse et la diversité microbienne. L'infection par H. felis est associée à une augmentation de l'abondance relative en E. coli au niveau gastrique et au niveau intestinal. Ces résultats indiquent que les co-infections gastriques H. felis/E. coli mériterait être explorée afin d'évaluer une éventuelle synergie en terme de capacité à induire la lymphomagenèse gastrique.

Posters – Axis 1 “Cell signaling and Therapeutic Targets”

P101
Characterization of BRAFV600E cell in colorectal cancer

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10 % of colorectal cancer (CRC) patients bear the BRAF mutation (BRAFV600E) leading to a constitutive activation of the MAPK pathway resulting to tumor progression. It has been shown that these patients are refractory to any approved treatment for CRC

Preliminary data from our team suggest that CRC tumors with BRAFV600E mutation have an important percentage of cancer stem cells (CSC) compare to other CRC tumors with various mutational statuses. Because chemoresistance is one of the CSC hallmarks, **we hypothesized that BRAFV600E mutation could promote CSC phenotype**.

To validate this hypothesis we propose to characterize BRAFV600E mutated cells from CRC tumors on different models by using strategies aiming at introducing or inhibiting this mutation
This project focuses on a clinical question concerning the poor prognosis of patients with BRAFV600E mutation CRC tumors to potentially propose alternative therapies for these patients in the future.

P102
Negative regulation of STING activation: impact on tumorigenesis

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Chronic inflammation favors tumorigenesis, negatively influencing patient prognosis. Yet, the underlying molecular mechanisms are poorly understood. Recently, it has been described that cytosolic nucleic acids are potent triggers for tumor-associated inflammatory responses. These molecular species are recognized by the cGAS-STING pathway to sustain chronic inflammation. However, the outcome of this inflammatory response varies depending on several parameters, including the type of nucleic acid involved, the cell type from which the tumor originates and the tumor microenvironment. Furthermore, while several activators of STING have been described and proposed to be used as therapeutic adjuvants, no natural STING inhibitor has been described up to date.

Here, we have identified a new negative regulator of the cGAS-STING pathway that orchestrates the inflammatory response in the presence of cytosolic nucleic acids. We show that this pathway operates through a second messenger that can block the activation of STING, impairing the production of inflammatory cytokines. This finding is crucial for our current understanding of the STING-cGAS pathway and its role in tumor immunology. Furthermore, this pathway is druggable and bear important therapeutic implications.

P103

Characterization of cancer-associated mutations reveals a new mode of regulation for p190RhoGAP

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A tight spatio-temporal regulation of Rho GTPases is required to achieve proper cell migration. The GTPase-activating protein, p190RhoGAP (p190A), the main negative regulator of RhoA, localizes to membrane protrusions such as lamellipodia and invadopodia. ARHGAP35, the gene encoding p190A, was found mutated in 15% of endometrial tumors and 2% of global cancers.

In order to get insight into the impact of cancer-associated mutations on p190A, we performed a structure/function analysis of the protein. This approach led to the identification of a sequence sufficient to ensure proper targeting of p190A to lamellipodia and invadopodia. A construct of p190A deleted of the identified "protrusion localization sequence" (p190AΔPLS) cannot target to these actin-based structures. We further pointed out cancer-associated mutations in PLS (S866F and Δ865-870), that alter p190A subcellular localization. In addition, we identified S866F and Δ865-870 mutations as gain of function mutations, favoring tumor cell migration (Binamé et al. JCB. 2016).

The present work focuses on the molecular and the functional characterization of these mutations. We found that alteration of the PLS (p190AΔPLS construct or p190A mutants) increased the RhoGAP activity of the protein. This result is in favor of an intramolecular folding of the molecule, involving the PLS and masking the GAP domain. Co-immunoprecipitation experiments demonstrate that PLS is able to interact with the C-terminal part of the protein that contains the GAP domain. We demonstrated that this interaction is lost if PLS harbors S866F and Δ865-870 mutations, given a molecular explanation to the gain of function mutations. Indeed, our work suggests that p190A exist in two forms in the cell, an inactive closed conformation with a masked GAP domain and an open conformation allowing p190A GAP function. Altogether, our data unveil a new mechanism of regulation of p190A.

P104

Involvement of discoidin domain receptor 1 and 2 in resistance to the targeted bi-therapy during melanoma

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The melanoma skin, a malignant transformation of melanocytes, is the most aggressive form of skin cancer. The most common type of cutaneous melanoma is the Superficial Spreading Melanoma (SSM). The BRAF mutation p.V600E is observed in almost 60% of the cases. The combination therapy anti B-RAF plus anti-MEK is used in patients who have metastatic melanoma and p.BRAF V600E somatic mutation. Unfortunately, the major problem of this treatment is the acquisition of cellular resistance to the targeted bi-therapy. This resistance is associated with an increase of metastasis formation due to a hyper activation of MAP and PI3 kinase activity. Previous reports have indicated that the Discoidin Domain Receptors 1 and 2 (DDRs) can activate MAP and PI3 kinase pathways. The DDRs are members of the tyrosine kinase receptor family and have been found overexpressed in several number of cancers subtypes where they are associated to bad prognosis. Interestingly, a transcriptional study has shown that the DDRs expression is induced in Vemurafenib-treated melanoma cells lines. Therefore, the DDRs could participate to therapeutic resistance mechanisms. The aim of the project is to study the role of the DDRs in melanoma cells resistance to the combined therapy. Firstly, at protein level, we determined that the DDRs are overexpressed in Vemurafenib resistant cells compared to sensitive cells. We hypothesized that resistant cell lines, despite the bi-therapy, are able to activate MAP and PI3 kinase pathways through the activation of DDRs. When we depleted the DDRs or when the kinase activity of the DDRs is inhibited, there is a decrease of MAP kinase pathway activity in resistant cell. Consequently, all those data suggest that the activation of the DDRs could induce an activation of MAP kinase pathway in resistant cells. We have shown that the depletion of the two receptors or DDRs inactivation decreases cell proliferation. Finally, by using melanoma skin samples (before and after treatment), we will study if the results obtained in vitro are also observed at the clinical level. A preliminary data, in one biopsy before and after treatment, has shown an increase of DDRs expression after the treatment. This result has to be confirmed in a larger cohort. Altogether, our results suggest that DDRs may play a role in melanoma resistance. Thus, our aim is to fully determine if DDRs could be therapeutically targeted, especially in case of resistance to BRAF and MEK inhibitors which occurs in most patient.

P105

Cell surface exposed calnexin and ERp57 mediate extracellular collagen degradation

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Extracellular matrix (ECM) and collagen degradation is necessary for tissue organization in health and during tumor growth. We have shown previously that collagen cleavage mediated by the matrix metalloprotease MMP14 is stimulated by O-glycosylating GALNTs Activation (GALA) pathway. Is peptidic bond cleavage the only enzymatic activity required for collagen degradation? Here, we show that GALA also leads to O-linked glycosylation of ER resident protein Calnexin (Cnx), which along with oxidoreductase ERp57 traffics to the cell surface and accumulate at sites of ECM degradation called invadosomes. We show that Cnx/ERp57 complex in the presence of secrete glutathione reduces abundant disulfide bonds in collagen fibrils, a process that is essential for collagen degradation. The Cnx/ERp57 complex functions independent of MMP14. These findings highlight the coordination of two distinct activities by O-linked glycosylation in controlling the extracellular levels of collagens.

P106
MDM2 and Metabolism: new therapeutic strategies for liposarcoma

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Liposarcomas (LPS) are soft tissue sarcomas of mesenchymal origin for which there are still very few therapeutic options. The most common LPS subtypes, well-differentiated and de-differentiated LPS (WD- and DD-LPS), are characterized by a systematic amplification of the MDM2 oncogene. However, the molecular mechanisms underlying this very strong selective pressure for MDM2 overexpression in LPS remain completely unknown. Although MDM2 oncogenic functions have been mainly attributed to its role as a negative regulator of the p53 tumor suppressor, growing evidence indicates that MDM2 activities extend beyond p53. We recently reported that MDM2 is recruited to chromatin independently of p53 wherein it regulates a transcriptional program involved in amino acid metabolism and in the control of the redox status of both normal and cancer cells (Riscal et al., Mol Cell). Our recent data suggest that MDM2-mediated control of serine metabolism plays a major role in LPS pathogenesis. Our project aims at furthering our understanding of MDM2 metabolic functions in LPS and at investigating whether these functions can be targeted to design efficient anti-cancer therapies. We take advantage of a unique biobank and humanized mouse models (Patient-derived xenograft models) that we generated over the past years, to assess the clinical relevance of new therapeutic strategies based on the pharmacological inhibition of MDM2 metabolic functions.

P107
Role of E4F1 in melanocyte homeostasis and melanoma development

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The multifunctional protein E4F1 is an essential regulator of normal skin homeostasis through both the regulation of the Bmi1-Arf-p53 pathway but also through the regulation of pyruvate metabolism. Indeed, E4F1 transcriptionally regulates the expression of components or regulators of the pyruvate dehydrogenase (PDH) complex, which metabolizes pyruvate into acetyl-CoA to fuel the TCA cycle. Consistently, E4F1 inactivation in basal keratinocytes result in impaired PDH activity and in a metabolic reprogramming, redirecting the glycolytic flux towards lactate production. This lead to remodeling of their microenvironment and alterations of the basement membrane of the skin, resulting in the definitive exhaustion of the epidermal stem cell pool. However, E4F1 function in skin seems to extend beyond its implication in keratinocyte and also impact melanocytic lignage. We recently observed that mice lacking E4f1 specifically in melanocytes exhibit hair graying and skin pigmentation defects. In order to decipher the molecular mechanisms underlying the hair and skin whitening, I used human and murine pigmented melanoma cell lines and showed that E4F1 depletion induces melanogenesis alteration suggesting that pigmentation defects occur in a cell autonomous manner. Considering the role of E4F1 in pyruvate metabolism, I am currently analysing the contribution of the PDH in melanin synthesis. In addition, based on growing evidences linking pyruvate metabolism to cancer development, I also investigate the implication of E4F1 in melanomagenesis.

P108

Study of the Hippo/TAZ pathway in gastric carcinogenesis induced in response to Helicobacter pylori infection

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Background. *Helicobacter pylori* is the main risk factor for gastric cancer. We reported that *H. pylori* infection leads through an epithelial mesenchymal transition (EMT) to the emergence of CD44+ cells with cancer stem cell (CSC) properties. The YAP/TAZ co-transcription factors of the Hippo pathway control cancer initiation and progression in many cancers, but their regulation in the context of *H.pylori* mediated gastric carcinogenesis has not been described. We hypothesized that TAZ could be involved in the EMT process and CSC-like cells generation observed during *H. pylori* infection.

Aim. To investigate the consequences of TAZ inhibition on the EMT/CSC-like induction in gastric epithelial cells in response to *H. pylori* infection.

Methods. The effect of TAZ inhibition was studied by a siRNA strategy in MKN45 and NCI-N87 gastric epithelial cell lines infected or not with different strains of *H. pylori*. The expression of TAZ and Hippo pathway related genes was assessed by RTqPCR, western blot and immunofluorescence. The expression level of EMT markers was determined by RTqPCR. EMT/CSC properties were evaluated by functional invasion and tumorsphere assays.

Results. *H.pylori* transiently stimulates TAZ nuclear translocation and co-transcriptional activity. TAZ inhibition reduced EMT markers expression, which correlated with a decrease of invasive properties induced upon *H. pylori* infection. Moreover, this inhibition affects spheroid formation which involves the CSC sub-population. The Hippo/TAZ pathway is activated upon *H. pylori* infection in gastric epithelial cells and TAZ appears to be involved in the regulation of EMT and CSC properties.

Key words: Hippo; TAZ; *Helicobacter pylori*; epithelial-mesenchymal transition; gastric cancer.

P109

Role of immunogenic nucleic acids and IL-17 family cytokines in cancer related inflammation and chemoresistance.

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The goal of this project is to study the contribution of chronic inflammation to chemoresistance in pancreatic cancer (PDAC). There is growing evidence that cytosolic nucleic acids can initiate cancer-promoting inflammation and Interferon (IFN) responses through stimulation of the cGAS-STING pathway. However, the role of cytosolic nucleic acids in promoting resistance to treatment is unknown. In recent years, a contribution of the IL-17 cytokine family to chemoresistance has been proposed and several studies suggest their involvement in the development of PDAC. Our preliminary data indicate that immunogenic nucleic acids drive cell-intrinsic and chemotherapy-induced type I IFN and IL-17B and C inflammatory responses in PDAC and that cytosolic nucleic acids have an impact on PDAC response to genotoxic stress. Furthermore, our data suggest the existence of a nucleic acid-dependent pathway that acts alongside the cGAS-STING pathway to regulate type I IFN and IL-17B/C expression in PDAC. We thus hypothesize that modulating cytosolic nucleic acid levels and/or the cGAS-STING pathway will affect PDAC chemoresistance. To test this hypothesis, we are exploring the molecular mechanisms governing the onset of IL-17 family cytokines production in PDAC and assessing the impact of type I IFN and IL-17B/C signalling on tumour cells and the tumour microenvironment in the context of chemotherapy treatment.

P110
Stromal alteration and colorectal cancer initiation

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Colorectal cancer (CRC) is the third most common cancer in men and the second one in women. The incidence of this cancer remains important with nearly 45,000 new cases on 2017 in France (INVS, health monitoring institute). These data can be explained by the high turnover rate of the renewal process of the colonic epithelium. Indeed, this renewal is maintained by the intestinal stem cells (ISC), located at the bottom of colonic crypts, within only 3 to 5 days putting them under great demands and consequently to a significant risk of malignant conversion. Indeed, Bakers et al,. describe that alterations induced in the colonic stem cells (or progenitors) lead to CRC initiation and development showing that when an oncogenic event impacts ISC, they acquire a tumor initiating cell (TIC) phenotype. This is why under physiological condition, these cells are highly controlled by a specific environment called "niche". The stroma surrounding the colonic crypt participates actively to this niche, and more specifically the fibroblasts that represent the major stromal cell population.

Our hypothesis claims that alterations of the niche, creating a pro-tumoral microenvironment, can induce a phenotype switch from normal ISC to TIC phenotype; and can thus promote CRC initiation.

This hypothesis is based on the fact that patients with chronic inflammatory bowel disease (IBD) present an increased risk (X7) to develop CRC. An explanation could be the alterations of their intestinal epithelium (permeability, oxidative stress, ect.) and more importantly of the stromal compartment. Indeed, fibroblasts from IBD or CRC patients show a morphological phenotype and secretory profile (pro-inflammatory, pro-angiogenic cytokines) different from the one observed under physiological condition.

In order to study a potential reprogramming of normal stem cell (ISC) to tumor-initiating stem cells (TIC) by fibroblasts according to their (physio)pathological origin, we co-culture human normal, inflammatory or cancerous colonic fibroblasts with organoids resulting from normal colic resections, and then perform morphological analyzes and phenotypic characterization using microscopic, cytofluorometric and transcriptomic approaches.

P111

Rnd3, a novel atypical target of ß-catenin, is involved in the regulation of entosis in hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is the major type of primary liver cancer in adult. It is the 6th most frequent cancer worldwide and the 2nd leading cause of cancer-related death. Thus, the prognosis of HCC remains very poor. Late diagnosis and the lack of efficient therapies account for this statement. Our project aims to better characterize liver carcinogenesis in order to identify novel therapeutic targets and treatments. Our study focuses on Rnd3/RhoE, which is a member of the RhoGTPase family. Previous work from the lab identifies Rnd3 as a potential metastasis suppressor in HCC. Indeed, our group demonstrated that Rnd3 expression is downregulated in most HCC patients and HCC-related cell lines and is significantly lower in invasive HCC samples with satellite nodules. Moreover, our recent study identified β-catenin, a well-known oncogene in the liver, as a repressor of Rnd3 expression.

Interestingly, we found that both the transcriptional and structural activities of β-catenin repress Rnd3 expression in HCC cells. We further demonstrated that Rnd3 expression favored acquisition of invasive capacity but surprisingly attenuation of cell proliferation. It has been widely documented that Rho proteins contribute to cell proliferation by regulating cell cycle proteins. The present project aims to understand how Rnd3 is involved in a switch between proliferation and invasion in HCC cells. Our results demonstrated that Rnd3 silencing induces Hep3B cell growth arrest in vitro and in vivo, due to significant reduction of cell percentage entering on G0/G1 phase and an arrest of cell cycle at the G2/M level. Screening of cell cycle proteins revealed that Rnd3 silencing in Hep3B cells led to a decrease in the protein expression levels of cyclin D1. On the other hand, the continuous observation of HCC cell lines rounded phenotype induced by Rnd3 silencing and the inhibition of cell cycle progression suggested the possibility of cell death induction. We did not detect any modification in pro- and anti-apoptotic genes after silencing Rnd3 protein in Hep3B cells. However, fluorescence microscopy analysis reveals a significant increase of "cell-in-cell" (CIC) structures frequencies upon knockdown of Rnd3. The CIC phenomenon, or entosis, describes an active invasion of a living cell into another cell's cytoplasm. Since entosis has been described to promote aneuploidy and tumor progression, we will further aim to focus on the involvement of Rnd3 in this mechanism.

P112
Characterization of Diffuse Low Grade Gliomas in vivo and in vitro

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Introduction: Diffuse Low-Grade Gliomas (DLGG) are second grade glial tumors affecting astrocytes and oligodendrocytes of the brain. They are characterized as silent, slow growing tumors with fewer mitotic activities. However, they diffuse and invade the healthy brain via blood vessels and nerve fibres. These, over a period of years develop to malignant Glioblastoma, where the affected has an average life span of around 12-15 months. Indefinite phenotypic and molecular characterization of DLGG poses serious limitation to treatment and prevention at the early stage. Ambiguous cellular origin also adds to tumoral heterogeneity observed in patients.
My PhD project aims to characterize the low-grade gliomas in vivo and in vitro by dissecting out the underlying cellular heterogeneity of these tumors. We also focus on understanding the molecular players and key signalling pathways involved in their proliferation in vitro.

Material and Methods: Patient tumor resections obtained immediately after the surgery are fixed, embedded and cryo-sectioned to perform Immunofluorescence to study the in vivo cellular compositions. For in vitro studies, we isolate the various cell populations by flow cytometry and magnetic antibody purifications. Immunostainings are performed on the samples to identify various subpopulations of cells and the signalling molecules. Viability assays are also performed under different molecule treatments.

Results: Immunostainings on tissue sections reveals cellular heterogeneity of the tumor cells, which includes stem/progenitor cells, astrocytes and oligodendrocytes. We have identified that there are two main populations of cells expressing Sox9 or Olig1 in astrocytomas and oligodendrogliomas. Subsequently, to isolate these various subpopulations and study them in details, we have standardised methods to dissociate the tumor mass to obtain single cell suspensions. We use various cell-type specific surface markers to isolate stem/ progenitor cells astrocytes and oligodendrocytes. Currently, we have identified cell populations expressing A2B5, O4, PSA-NCAM, GLAST, CD44 and CD24 surface markers. We could successfully purify and culture A2B5 and O4 cells in vitro. Isolated A2B5 cells have been used to study its responsiveness to various cytokines and inhibitor molecules. We also observe changes in the cellular identities of these purified cells in response to cytokines and media conditions. Studies to identify various signaling molecules involved in the identity and proliferative potential of these cells are on going.

Conclusion: We have identified two main cellular populations, which represent the astrocytic and oligodendrocytic cells in DLGG irrespective of their tumor type. These main populations of cells are highly heterogenic in terms of the other markers that they express. Flow cytometry revealed cells with various surface markers specific to astrocytes and oligodendrocytes. We could study the responsiveness of the purified cells to different cytokines in vitro.

P113
Identification of new CTC common markers

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In order to discovered new common markers, our first established CTC line was injected into lamas in the nanobody platform of Marseille-Luminy. Llama's plasmocytes generated special antibodies composed only by a single chain. Nanobodies are the top fragment of the single chain antibodies of camelid species. These fragment have a number of advantages over the whole antibodies, such as antigen accessibility, solubility and du to their structure simplicity, they can be produced by prokaryotes. Briefly, after the CTC injection, we obtained a nanobody library, all targeting a CTC antigen. We screened our library to select nanobody candidates targeting all our CTC lines and now we try to characterize the target of our candidates.

P114

SLAP displays tumor suppressor functions in colorectal cancer via inhibition of mTORC2 signaling

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Metastatic colorectal cancer (CRC) is one of the leading causes of malignancy-related death worldwide and as such, development of effective anti-metastatic therapies is of major concern. Consistently signaling pathways promoting metastatic progression are currently subjected to intense investigation. Particularly, tyrosine kinases (TK) have emerged as important determinants of this malignant process. Among them, the TK Src is well documented as a driver of intestinal stem/progenitor cell proliferation and tumorigenesis in animals; indeed high level of Src activity is a marker of poor clinical prognosis in CRC patients and a potent driver of colon metastasis. How Src induces such a prominent tumor activity is still a matter of debate as Src is rarely mutated in CRC. Interestingly, we found that its oncogenic activity is under the control of its negative regulator SLAP, which displays strong tumor suppressor function in CRC. Mechanistically, SLAP promotes destabilization of critical Src substrates, upon their aberrant phosphorylation, to dampen oncogenic signaling. For instance, SLAP attenuates CRC cell dissemination via destabilization of the adhesive receptor EPHA2 (Naudin et al, Nat Commun 2014). By proteomics, we found an additional SLAP target in CRC, the serine/threonine kinase and metastasis inducer mTORC2. We now show that SLAP controls the capacity of mTORC2 to promote CRC cells invasion and growth properties. Consistently, the level of SLAP expression predicted the tumor cell response to mTOR catalytic inhibitors in these CRC cells. We are currently addressing the mechanism by which SLAP controls mTORC2 signaling, with the idea that it counteracts a Src-dependent mechanism. Collectively, these data will uncover an additional important mechanism by which SLAP may control Src tumor activity and unveil SLAP as a potential biomarker for Src and mTOR kinase inhibitors in CRC.

P115

Resistance to Midostaurin (PKC 412) of FLT3-ITD acute myeloblastic leukemia (AML): CRISPR-Cas9 functional genomic screening approach in culture condition modeling hematopoietic microenvironment.

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Acute myeloid leukemia (AML) is a malignant hematological disease characterized by bone marrow invasion of immature myeloid hematopoietic progenitors associated to a blockage of differentiation. The prognostic factors are related to cytogenetic or molecular abnormalities. One-third of normal karyotype AML harbor "internal tandem duplication" (ITD) mutations of the FMS-like tyrosine kinase 3 (FLT3) resulting in the constitutive activation of FLT3 and its downstream pathways. Correlated to a particularly pejorative prognosis, ITDs seem to confer to the leukemic stem cell, advantages in terms of survival and resistance to chemotherapy. With this in mind, tyrosine kinase inhibitors (TKIs) have been developed and tested over the past 20 years alone or in combination with conventional treatments. Nevertheless, despite these therapeutic advances, the treatment of AML remains a real challenge, primarily due to persistent relapses.

The objective of this project is to decipher by functional CRISPR genomic screening the resistance mechanisms set up by FLT3-ITD AML blasts during exposure to conventional or targeted therapy (TKI).
The importance of the bone marrow microenvironment in the initiation and development of the AML neoplastic process has been highlighted over the last 10 years. Therefore, we will carry out this study using a model mimicking the "hematopoietic niche": co-culture of FLT3-ITD AML cell lines with a mat of stromal cells at low oxygen concentration (O2).
We will identify the resistance mechanisms developed with respect to the TKI: Midostaurin (PKC412) in combination or not with conventional chemotherapy: the Aracytin (AraC).

To date, PKC412 is the first approved TKI for AML treatment. A real improvement in the overall survival of patients with AML has been observed for PKC412 in combination with standard chemotherapy. We will use Cellecta Inc.'s guide RNA (gRNA) library for the genomic screen. After being transduced with a lentivirus expressing an inducible Cas9, FLT3-ITD AML cell lines MV4; 11 and MOLM14 will be infected with lentiviral pool expressing the different gRNAs. After treatment (PKC412 ± AraC, AraC alone, DMSO (control)), the resistant clones will be analyzed by NGS sequencing. The most relevant candidate genes will then individually validate by conventional approaches (overexpression or invalidation). Their role in resistance to new targeted therapies will be evaluated*in vitro*, as well as in patient's blasts, and then *in vivo* in immunodeficient murine models.

These results could lead to the discovery of potential therapeutic targets, specific to FLT3-ITD AML cells within their microenvironment, this, under the pressure of PKC412 with or without AraC in combination. *In fine*, the development of inhibitory strategies for these pathways could prevent resistance of FLT3-ITD blasts to new targeted therapies.

P116

The comparison of syk signaling networks reveals potential molecular determinants of its tumor promoter or suppressor functions depending on the cell type

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Tyrosine-protein kinases are involved in the regulation of cell growth and invasion and are frequently associated with tumor formation and progression. They therefore represent interesting druggable targets. In hematopoietic malignancies, the non-receptor spleen tyrosine kinase (Syk) exerts a mainly pro-survival and pro-proliferation function. Conversely, we and others demonstrated that Syk mechanistically behaves as a tumor suppressor in breast, other carcinomas and melanoma. We recently developed a bioinformatics pipeline for the reconstruction and analysis of the Syk signaling network built from vast phospho-proteomics data obtained in breast cancer cells (Naldi 2017, PLoS Comput Biol). In the present study, we applied the same strategy to Syk signaling in Burkitt lymphoma cells and compared the resulting pro-oncogenic with the breast cancer cell anti-oncogenic signaling networks. We detect few shared Syk targets between the different cancer cell types, leading to signaling pathways from KEGG database that are differentially enriched between Burkitt lymphoma and breast cancer cells. As previously described, we bootstrapped the reconstruction of Syk networks with the elements of these pathways. The analysis of the global topological parameters using the Network Analyzer module of Cytoscape software showed no differences between lymphoma and breast cancer cell networks and Syk played a comparable central role in the connectivity of those networks. However, by aligning the reconstructed networks using the DyNet plugin, we detected nodes with a rewiring of their connections, meaning proteins that did not display the same protein interactions. We are currently focus on small regulatory protein networks that could explained Syk impact on cell adhesion, survival and invasion. We are refining the analysis of the differential Syk signal propagation to particular targets involved in cell adhesion, motility, growth and death. Identification of the molecular determinants accounting for the apparent contradictory pro- and anti-oncogenic activities of Syk is a public health issue as pharmacological Syk inhibitors are starting to be used in the clinics for treating auto-immune diseases, lymphoma and leukemia.

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P117

Function of sortilin in non-small cell lung cancer progression

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Non-small lung cancer is the main type of lung cancer. It is the most common cause of death by cancer with a poor survivalrate. The epidermal growth factor receptor (EGFR) deregulations play a key role in cancer progression. EGFR generates extra- and intracellular signals through various pathways leading in oncogenic signals promoting the tumor aggressiveness. Our previous report showed that sortilin, a member of the VPS10P sorting proteins, is associated with EGFR to allow its regulation in non-small cell lung cancer (NSCLC) cells. Indeed, a high level of sortilin expression in NSCLC cell induces the internalization of EGFR. Conversely, a low level of sortilin expression leads to the membrane retention of EGFR and its expression negatively correlated with tumor grade. This work suggests that sortilin limits EGFR signaling by promoting its internalization. In the order to better understand the exact function of sortilin in lung cancer cells, we developed two cell models permitting to overexpress (1) or to get inducible expression of sortilin (2).

(1) The NSCLC cell line H1975 was modified to constitutively overexpress sortilin in order to study in vitro the function of sortilin regarding the invasiveness and its capacity to regenerate tumor mass or organoids. In vivo, xenograft experiments allow assessing the role of sortilin in tumor growth and progression.

Preliminary in vitro results demonstrate that sortilin limits invasive mechanisms and cell growth. Previous xenograft experiments have shown that sortilin depletion dramatically accelerates the tumor growth in vivo.

(2) The second model is based on the NSCLC cell line H1975 modified to express sortilin under the control of tetracycline inducible promoter. The capacity of sortilin to limit tumor progression was studied by xenograft of NSCLC cells. Cells were grafted on NOD-SCID mice. Following tumor development, we induced sortilin expression by treating the mice with doxycycline. Tumor growth was evaluated twice a week to see the effect of sortilin expression on tumor development. After sacrificing the mice, sortilin expression was checked in tumours.

In vivo, induction of sortilin expression after tumor development limits tumor growth.

All together our results suggest that sortilin overexpression may represent an attractive prospect for preventing tumor growth and confirm that sortilin could be a useful biomarker in lung cancer.

P118

Study of autophagy induced by Cytolethal Distending Toxin-secreting bacteria

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Humans are often exposed to Cytolethal Distending Toxin (CDT), a bacterial genotoxin secreted by many pathogenic Gram-negative bacteria of the microbiota (Helicobacter, Campylobacter, ⋯) often associated with digestive pathologies. CDT is a toxin composed of three subunits: CdtA, CdtB and CdtC. The CdtA and CdtC subunits allow the internalization of the active subunit CdtB in the cells. CDT exerts cytopathic effects (DNA damage, nuclear and cellular distension as well as actin cytoskeleton remodeling) via its active CdtB subunit. Recently, we described that CDT can induce the formation of nucleoplasmic reticulum rich in messenger ribonucleoprotein particles associated to cell survival. As autophagy is a mechanism that can be involved in cell survival, we studied the effect of the CDT on the autophagic process. Coculture experiments with CDT-secreting bacteria and hepatic and intestinal cells, as well as xenograft mouse-derived models, were used to assess the nuclear remodeling and autophagy in vitroand in vivo. We showed that the CDT genotoxin, via its CdtB subunit, triggers cellular autophagy in vitroand in vivo. The presence of this toxin induces an increase in the formation of autophagosomes, these effects being obvious in the giant distended cells presenting nucleoplasmic reticulum, suggesting that CDT-induced autophagy is associated to cell survival. Inhibitors are currently being evaluated.

P119
Streptomycin, a Potent Inhibitor of Cancer Stem Cells Growth.

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Cancer stem cells (CSC) represent a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity which can escape from chemotherapies, disseminate and seed metastasis. Understanding the molecular mechanisms that underlie CSC abilities is a major goal to design new strategies that may prevent both tumor relapse and metastasis formation, which coincide with poor prognosis and increased mortality.

Streptomycin (SM), a potent bactericidal antibiotic, is generally administered for the treatment of individuals with moderate to severe infections such as tuberculosis. Based on our preliminary data, we postulate that this antibiotic interferes with stem-like properties, such as self-renewal, inherent to CSC phenotype. This effect has been observed with cell lines derived from colorectal cancer and other cancers (breast, lung), suggesting a "pan-cancer" effect. More recently, we have shown that SM triggers increased production of mitochondrial reactive oxygen species in CSC, causing oxidative stress and leading to cell apoptosis. Because SM is an aminoglycoside endowed with RNA-binding ability, we believe that the underlying mechanism involves targeting of CSC-specific RNAs and subsequent alteration of their processing or function.

Based on the literature and these preliminary results, our main objective is to further study the impact of SM on CSC and validate this antibiotic as a potential adjuvant chemotherapy agent in advanced and metastatic colorectal cancer. From a molecular perspective, by connecting the association of SM with certain(s) RNA(s) to inhibition of stem-like properties, we might discover unexpected mechanisms or pathways involved in acquisition or maintenance of these properties. This may in particular lead to the identification of new RNA(s) target for cancer therapy.

P120

Involvement of Neurotensin and Neurotrophins pathways in human colorectal cancer cells 5-Fluorouracil treatment resistance

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Introduction: Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths. Surgical resection is the only curative treatment. Depending on disease stage, chemotherapies and targeted therapies are available. Despite considerable progress, recidive cases remain frequent. Studies lead in our laboratory on different cancer models, such as CRC, highlighted the importance of neuropeptides in cancer cells survival and progression : neurotrophines (NT) and neurotensin (NTS). NT is a family of four growth factors, BDNF, NT4/5, NT3 and NGF respectively binding a specific Tropomyosin Receptor Kinase (Trk A, B or C), tyrosin kinase receptors, with a strong affinity. NT can all bind another receptor, p75NTR, with low affinity, as well as the Sortilin, a TRK co-receptor, a NT and NTS intracellular trafficking regulator and also known as Neurotensin Receptor 3 (NTR3). Neurotensin can also bind two other receptors: NTR1 with strong affinity and 2 with low affinity ; both are G protein coupled receptors. Very few is known about NT and NTS pathways in CRC cells resistance to chemotherapies, 5-Fluorouracil (5FU) being the backbone of any chemotreatments. The aim of my project is to understand if and how these pathways could be involved in 5FU CRC cell resistance.

Material and Methods: Two human CRC cell lines from different disease stages (WiDr, SW620) were treated with 8µM of 5FU to obtain stably 5FU resistant cell lines. Both cell lines were also xenografted in Nude mice which were treated with 5FU. Protein expressions were assessed by western blot. Cell activation was assessed by flow cytometry. Stable knockdown cell lines (NTR3) were obtained by shRNA transfection.

Results and Discussions: Preliminary results show that NTSR3 protein expression is increased after 5FU treatment both in whole cell lysates and exosomes especially in the most agressive cell line (SW620). The same results were obtained in vitro and in vivo. Moreover, 5FU treatment induces a decrease of tumor size only for the least agressive line (WiDr). Indeed, the 5FU induces a quiescence state of these cells.

Conclusion: It is the first time that, in CRC, the NTSR3 seems to be overexpressed in 5FU-resistant tumor cells (from primary and advanced stages), in vitro and in vivo. This receptor could constitute a new potential therapeutic target.

P121

A recycling anti-transferrin receptor 1 antibody inhibits tumor growth by iron deprivation and antibody dependent cytotoxic effector functions

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The transferrin receptor 1 (TfR1) is the major receptor involved in cellular iron uptake. Tumor cells show higher iron needs concomitant with an overexpression of the TfR1. Targeting TfR1 with monoclonal antibodies is thus a promising strategy in cancer. We have re-engineered six anti-human TfR1 single-chain variable fragment (scFv) antibodies into fully human scFv2-Fcγ1 and IgG1 antibodies. After characterization of these antibodies, H7 antibody was selected. It displayed the most efficient ability to inhibit TfR1-mediated iron loaded transferrin internalization on the Raji B-cell lymphoma cell line. Invitro, H7 at low concentrations (IC50 0.1 µg/ml) inhibited the growth and induced apoptosis of erythroleukemia and B cell lymphoma cell lines. Moreover, apoptosis was also observed by H7 on the Im9 B cell lymphoma cell line which is resistant to rituximab (anti-CD20 antibody). Also, unlike other anti-TfR1 antibodies, iron deprivation by H7 was accompanied with increased TfR1 cell surface expression. In vivo, tumor regression was observed by H7 IgG1 treatment in nude mice bearing ERY-1 erythroleukemia cell xenografts through iron deprivation and antibody dependent cytotoxic functions. Lower effects were observed using the non glycosylated variant of H7, defective for cytotoxic effector functions. Therefore, targeting TfR1 using H7 represents a promising tool in the treatment of leukemia and lymphoma.

P122

Deciphering a new role for the transcriptional coregulator RIP140 in acute myeloid leukemia chemoresistance

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Cancer stem cells and treatment resistance are one of the challenges of modern oncology research. Indeed, cancer cell resistance is one of the causes of relapse that beget a lower overall survival for patient. This is the case for acute myeloid leukemia (AML) where the 5-year overall survival is only of 40% for patients under 60 years of age and only 15% for patients older than 60 years of age, due to relapses. There are more and more evidences that oxidative metabolism and energetic flexibility take a part in chemotherapy resistance. Indeed, manipulations of high mitochondrial OxPhos status in resistant leukemic clones significantly enhanced anti-AML effects of AraC treatment in vitro and in vivo. RIP140 is a transcriptional coregulator that interacts with nuclear receptors and transcription factors in order to regulate gene expression. We have shown that RIP140 regulate glucose metabolism in solid tumors. Interestingly, the analysis of 3 independent AML patient cohorts showed that a high RIP140 expression is associated with a bad prognostic. Moreover, RIP140 is overexpressed in patient samples at relapse when compared with samples at diagnosis. Therefore, we decided to investigate the role of RIP140 in acute myeloid leukemia chemoresistance and metabolic flexibility. We first measure RIP140 expression in various AML cell lines and could discriminate two groups: the high RIP140 expressing cells, such as OCI-AML 2, OCI-AML 3 and HL-60, and the low RIP140 expressing cells, such as U937, Molm14 and KG1α. Then, we have developed some techniques in order to obtain AML stable cell lines with modified RIP140 expression level, which are known to be hard to transfect. Using those cell lines we observed that RIP140 seems to have a pro-proliferative effect and that RIP140 KD cells are more sensitive to AraC, suggesting that RIP140 plays a role in AML cellular response to chemotherapy treatment. Interestingly, we also have observed that RIP140 is mainly cytoplasmic in AML cells, which is not usually the case in other cancerous cell lines. This cytoplasmic localization could be explained by a localization of RIP140 at mitochondria as shown by our preliminary results. We now want to identify the role of RIP140 at mitochondria by first identifying its domain responsoble for this localization using truncated recombinant proteins. We will study the function of RIP140 mitochondria localization in AML cells proliferation and chemoresistance by generating knock-in stable cells. We also plan to validate our results by using in vivo AML grafts. On the other hand, we want to perform transcriptomic analysis to highlight RIP140 target genes and also metabolic and metabolomics analysis to see if RIP140 takes parts in energetic flexibility of AML. This project could characterize a new factor involved in chemoresistance that could later be used as biomarker of AML response.

P123

Cell models for high throughput screening of inhibitors of the Wnt/ß-catenin signaling pathway.

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At least 90% of colorectal cancers display a constitutive activation of the Wnt/β-catenin signaling pathway, a trigger event of carcinogenesis. This constitutive activity is mainly due to mutations of the APC tumor suppressor which cause the accumulation of β-catenin in the nucleus where it interacts with TCF transcription factors to activate the transcription of target genes such as the c-myc oncogene. To date, very few molecules targeting the Wnt pathway have been discovered and none have yet been approved for clinical practice. The luciferase reporter gene technique is widely used to study the regulation of gene expression at the transcriptional level. We used this technique to develop a high-throughput screening assay for Wnt/β-catenin signaling pathway inhibitors. DLD-1 cells were stably transfected with a luciferase-expressing plasmid under the control of the TCF4 transcription factor, the effector of this signaling pathway. Besides, this kind of approach requires adequate control. Thus, we have developed a model of DLD-1 cell line expressing luciferase under the control of the promoter E2F1, a promoter independent of the WNT pathway. Two types of available inhibitors have been used to validate the model: XAV939, IWR-1 and WIKI4 tankyrase inhibitors (TNKS) and the ICRT14 and PNU-74654 compounds both described as likely to destabilize the TCF/β-catenin complex. TNKS acts as an activator of Wnt/β-catenin signaling by producing ADP-ribosylation of Axine1 and 2, two key components of the β-catenin destruction complex. Inhibition of TNKS increases the degradation of β-catenin and thus inhibits Wnt/β-catenin signaling. We found that XAV939, IWR-1 and WIKI4 specifically inhibit the activity of Wnt/β-catenin signaling, with IC50s of 0.13 µM, 0.21 µM and 0.28 µM, respectively. In contrast, ICRT14 and PNU-74654 behaved as nonspecific inhibitors since they also inhibit the luciferase activity of the control cells. In addition, the inhibitory effect of PNU-74654 was very inefficient with an IC50 greater than 50 µM. Furthermore, we showed that ICRT14 has no effect on cell viability, indicating that the observed inhibitory effect of ICRT14 on the Wnt-independent luciferase activity is not due to toxicity. Many authors have concluded their studies by claiming that the biological activity they were looking at was regulated by the Wnt/β-catenin pathway with respects to the use of believed specific inhibitors of the Wnt pathway. In this study, we clearly demonstrate that ICRT14 and PNU-74654 are not specific for the Wnt/β-catenin pathway. It turns out that testing the implication of the Wnt pathway in a biological mechanism rationally requires the use of at least one of the three specific inhibitors XAV939, IWR-1 or WIKI4. Furthermore, this work provides an assay perfectly suitable for high throughput screening of new inhibitors of the Wnt/ß-catenin pathway.

P124

Stimulation, a new strategy to target PKCα in the fight of colorectal cancer

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Background: whether Serine/Threonine Protein Kinase C (PKC) family members act as oncogenes or tumour suppressors has long been the subject of debate and this is probably why PKC is still not considered as a prime target for cancer treatment.

Methods: we used both *in vitro* and *in vivo* PKCα knock in models in order to investigate the relevance of stimulating PKCα against colorectal cancer (CRC).

Results: we provide evidence that PKCα fulfills key criteria of a relevant target to be stimulated for fighting CRC:

- PKCα is infrequently mutated in CRC;
- stimulating PKCα in the intestine epithelium is neither deleterious nor oncogenic;
- stimulating PKCα in CRC cells disrupts cell morphology, induces growth arrest and promotes cell death;
- natural PKCα activators successfully tested in clinical trials can potently inhibit colon cancer cell growth.

Conclusion: stimulating PKCα is a promising approach to fight CRC.

P125

miR-148a sensitizes colon cancer stem cell to chemotherapy by targeting Pregnane X- Receptor signaling

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Therapeutic failure seen in patients with colorectal cancer (CRC) frequently involves post-treatment tumor recurrence, due to the enhanced resistance of cancer stem cells (CSCs). We previously reported that the nuclear receptor Pregnane X- Receptor (PXR, NR1I2) behaves as a key driver of CSC-mediated tumor recurrence where it drives the expression of a large network of genes involved in CSCs chemoresistance (Planque C et al. Oncotarget, 2016). In order to determine the molecular mechanisms that define PXR enrichment in CSCs, we investigated the role of miR-148a on PXR expression and CSC phenotype. The miR-148a has been reported to post-transcriptionally regulate PXR in human liver (Takagi S et al. J Biol Chem, 2008) and has been proposed as a predictive biomarker in patients with advanced CRC (Takahashi M et al. PLoS One 2012). The present study demonstrates that miR-148a is down-regulated in chemoresistant CSC. Accordingly, transfection of miR-148a-3P in CRC cell lines and in patient-derived CRC cells decreases both PXR and PXR target genes expression. In addition miR-148a-3P overexpression decreases CSC proportion and impairs chemotherapy-induced enrichment of CSCs after chemotherapy treatment both in vitro and in vivo. In conclusion, we propose that the deficiency of miRNA-148a-3P is associated with the preferential activation of PXR expression and signalling in colon CSCs. In addition, our findings highlight miR-148a as a promising therapeutic agent that may reduce cancer relapse by selectively sensitizing CSC to chemotherapy.

P126

Multiplexed-epitope-based tissue imaging and single cell analysis using mass cytometry

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Recent progresses for tumor therapy are mostly the results of technologic advances that allowed a more comprehensive analysis of the tumoral microenvironment (TME), mainly through the use of flow cytometry for single cell in suspension (SCS) analysis and immunohistochemistry or immunofluorescence for tissue analysis. Together with transcriptomic approaches, those conventional methods allowed spectacular breakthrough in cancer therapy field with the discovery, for instance, of the immunosuppressive pathways B7.1/2/CTLA-4 and PD-L1/2/PD-1 and the immunotherapies that target those immune breaks.

Such discovery deeply modified our understanding of the TME and underlined the importance to integrate all the different cellular actors (tumor cells, immune cells, cancer-associated fibroblasts, endothelial cells etc.), their cellular state or sub cellular groups/compartments, their interactions and their localization within the TME.

The constant increase of biological markers (cluster of differentiation, cytokine, transcription factors, etc.) tends to invalidate the conventional technics. Indeed, the number of markers that can be simultaneous used are limited because of spectral overlap, auto fluorescence, dye instability or photobleaching which represent today significant limitations regarding the complexity and the heterogeneity of the TME.

The ICM and IRCM just acquired the first and unique in France Hyperion Imaging System (HIS). Developed by Fluidigm, the HIS is an imaging module associated to the Helios, the 3rd generation of CyTOF, which allows SCS analysis and tissue imaging using the mass spectrometry technology. Mass-based cytometry and imaging methods overcome many of the above limitations. Tissue or fresh cells in suspension are incubated with metal-labeled primary antibodies and specific isotopes are then visualized using mass spectrometry. Mass cytometry supports high multiplexing (current instrumentation allows 135 simultaneous channels. Actual limitations come from the limited available reagents) in absence of background signal with a very low signal leak (<3%).

The combination of the SCS analysis together with the tissue imaging allows three level of information:

1. The identification of cell types, biological processes (functionality, proliferation, apoptosis) and their particular distribution report on the spatial composition of the TME
2. Cell segmentation and single cell unsupervised-analysis (Principal Component Analysis, span tree, clustering) allow the discovery of unexpected cell subtypes and heterogeneity in an unbiased manner. Subcellular compartment and biological activities can be assigned based on the presence or absence of markers
3. The spatial view and cell segmentation allow to put into their environmental context each cell type and its functional state. Those states can be related to cell types, states and neighborhoods and eventually reconstitute the cellular social network of populations of interest.

The applications of mass-based SCS analysis and tissue imaging are numerous and varied. Beyond a deep and comprehensive study of the TME, biomarker and drug discovery, pharmacokinetics of drugs into the tumor, therapeutic assessment of drug combination are also feasible. Furthermore, data generated can be compared against or integrated to data generated with 'omics' data such as genotype, transcriptome, proteome, matabolome or imaging.

Posters – Axis 2 “Genome Dynamics and Cancer”

P201

Comprehensive characterization of the mutational landscape in multiple myeloma cell lines reveals potential drivers and pathways associated with tumor progression and drug resistance

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Human multiple myeloma tumor cell lines (HMCLs) have been a cornerstone of research in multiple myeloma (MM) and have helped to shape our understanding of molecular processes that drive tumor progression. A comprehensive characterization of genomic mutations in HMCLs will provide a basis for choosing relevant cell line models to study a particular aspect of myeloma biology, or to screen for an antagonist of certain cancer pathways.

We performed whole exome sequencing on a large cohort of 30 HMCLs, representative of the broad molecular heterogeneity of MM, and 8 control samples (EBV-immortalized B-cells obtained from 8 different patients). We evaluated the sensitivity of HMCLs to nine drugs.

We identified a high confidence list of 240 protein-coding genes with mutations affecting the structure of the encoded protein. 83% of the mutations identified in HMCLS were also present in primary MM cells from patients. Among the most frequently mutated genes, there were known MM drivers such as TP53, KRAS, NRAS, ATM and FAM46C, as well as, novel mutated genes including NCOR2, KMT2D, FANCG, MSH3 and PMS1. We next generated a comprehensive map of altered key pathways in HMCLs. These include cell growth pathways (MAPK, JAK-STAT, PI(3)K-AKT and TP53 / cell cycle pathway), DNA repair pathway and chromatin modifiers. Interestingly, variant allele frequency analysis of mutated genes revealed that HMCLs present two to four subclones, a range that we also found in primary tumor samples. This result suggests that HMCLs can be used to study the effect of Multiple Myeloma treatments on the subclonal evolution, which is critical to understand drug resistance. Importantly, we found a significant association between the mutation of several genes and the response to the conventional drugs used in MM, as well as, targeted inhibitors.

Taken together, this first comprehensive exome-wide analysis of the mutational landscape in HMCLs provides unique resources for further studies and identifies novel genes potentially associated with MM pathophysiology, some of which may be targets for future therapeutic intervention.

P202
Role of condensin complex in response to a replicative stress

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The condensin is a hetero-pentameric complex very conserved through Eukaryotic organisms. This complex is a member of the highly-conserved Structural Maintenance of Chromosome (SMC) complex family. Condensin was identified in mitotic chromosome condensation and segregation, and its loss leads to abnormal chromosome segregation and subsequent cell death. From mammals, condensin includes two complexes, condensin I and condensin II. In *Saccharomyces cerevisiae* there is only one condensin complex and it is strictly nuclear and associates to chromatin throughout the cell cycle.

The faithfull duplication of the genetc material is essential to ensure the maintenance of genome integrity. However, the genome of eukaryotic cells is continuously exposed to replicative stress (RS) which impedes fork progression and leads to fork stalling. The activation of the S-phase checkpoint and of homologous recombination (HR) mechanisms is essential to resume DNA synthesis. Both processes depend on the presence of single-strand DNA (ssDNA) at stalled forks. It is generated through the controlled resection of nascent DNA strands and recruits the heterotrimeric replication protein A (RPA), which promotes checkpoint activation and fork restart. The presence of RPA-coated ssDNA at stalled forks represents therefore a reliable readout of the replication stress response. Hydroxyurea (HU) is commonly used to induce RS in budding yeast by depleting dNTP pools.

Here we found that condensin associates to paused replication forks under HU treatment, and this association is dependent on MRX. Furthermore condensin is recruited to early-replicating regions and promotes fork progression in the presence of HU, arguing that condesin plays a role in DNA replication in budding yeast. We found that condensin mutants show an increase of RPA at HU-arrested forks. One possibility is that condensin prevents hyper-resection at stalled forks or it is required for the eviction of RPA-coated ss-DNA and then for fork recovery. In the opposite, we show that mammal condensin II complex is required for fork resection.

P203
New regulators of Notch during tumorigenesis

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The team is interested in understanding the mechanisms by which Notch signalling triggers epithelial tissue growth. Using unique highly tractable genetic models in the fruit fly *Drosophila melanogaster* and combining genome-wide analyses (RNA-Seq and ChIP-on-chip), the lab identified the direct Notch targets during hyperplastic growth (activated Notch), dysplastic growth (*scribble* mutants) and neoplastic growth (the combination of the two). Further differential expression analyses highlighted a neoplastic specific program.

Many of these *Drosophila*genes found have clear human orthologues that could help us understand the progression of cancer cells from hyperplastic to neoplastic growth and that could therefore represent new potential tumour suppressors or oncogenes in the context of activated Notch. My PhD project is to study the role of a new Notch pathway regulator: mxc/NPAT.

Our studies in Drosophila revealed important fluctuations of Histone levels and of several genes controlling the amount of Histone loci transcription, between hyperplasia and neoplasia, suggesting that Histone regulation and the transcriptional machinery regulating Histone genes expression could cooperate with Notch to command specific transcriptional programs. Therefore, I will study the role of NPAT, a key histone transcription activator and major target of the CyclinE during G1/S transition, on Notch pathway activity, and on the acquisition of invasive behaviours in lung adenocarcinoma Notch addicted cell lines.

Our results suggest that NPAT, in addition to its role in regulating histones genes transcription, controls the localisation of the NOTCH1 receptor in the cell, and the activity of NOTCH signalling by affecting the levels of the NICD (Notch Intracellular Domain) and the expression levels of its target genes.

P204
Clonal population dynamics in hepatocellular carcinoma

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Tumor heterogeneity and interactions between distinct tumor clones, tumor cell and their microenvironment contribute to the development of hepatocellular carcinoma (HCC), the main primary liver cancer. Genome-wide analysis of human tumor samples defined the most common oncogenic drivers and tumor suppressors associated with HCC development, but also revealed the complex genetic landscape of this tumor. Our laboratory focuses on understanding how oncogenic cooperation affects hepatocellular carcinoma development. The cooperation acts at the single cell level (cell autonomous) and also can trigger ecological interactions between tumoral subpopulations or the tumor cells and their microenvironment (non-cell autonomous).

To study population dynamics and intercellular interactions during tumor growth and dissemination, we have developed a murine model of hepatocellular carcinoma that combines intrahepatic injection of cells and lineage tracing. Hepatic progenitors (BMEL cells) are transformed ex vivo by a combination of genetic events (overexpression of oncogenes, inactivation of tumor suppressors). Combinatorial expression of fluorescent proteins gives rise to distinct multi-color bar-coding of tumor subpopulations. Injection of transformed cells in the liver parenchyma generates orthotopic tumors, whose growth is analyzed, notably in terms composition of clonal subpopulations.

We initiated our inter-clonal interaction study with a simplified model of cells expressing a single oncogene, RasG12V. Our results show that cells expressing an optimal level of oncogenic Ras are preferentially selected for tumor growth in vivo. To better apprehend this mechanism, we generated BMEL cell lines for which the expression level of RasG12V is correlated with the fluorescence intensity of two reporter proteins. Population dynamics of Ras HIGH vs Ras LOW cells during the in vivo tumor growth have been studied following co-injection of mixed populations into the livers of recipient mice.

P205

Modeling of intertumoral heterogeneity of liver carcinogenesis: impact of NASH on tumour-microenvironment interactions

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Hepatocellular carcinoma (HCC) tumours are highly heterogeneous, both in terms of their genetic composition and the accompanying degradation of the hepatic parenchyma. Recent advances in HCC genomics have allowed the identification of numerous driver oncogenic events, resulting in a classification that considers the mutational landscape, the gene expression profile and pathophysiological features of the tumour. The observed association of the genetic composition of the tumour with defined features of the pathological tissue environment suggests specific interactions between the tumour and its microenvironment that are largely defined by the tumours molecular characteristics. However, the molecular aspects of such crosstalk have not been fully elucidated. Our project aims at clarifying the mechanisms implicated in the interplay between the tumour genomic alterations and the tumour microenvironment, notably in the context of NASH.

Methods: Hepatocytes were stably transfected in vivo using the technique of hydrodynamic gene delivery (HGD). Sleeping Beauty mediated transposition ensured insertion of the mutated genes into cellular genome. We used two different combinations of oncogenes and tumour suppressor genes: a mutant form of RAS (N-RAS^{G12D}) or MYC (c-MYC^{T58A}) together with a CrispR targeting p53. To mimic the NASH hepatic environment, C57/Bl6 mice were fed with high-fat choline-deficient diet (HF-CD), reported to reproduce the main features of human NASH. Tumours and surrounding environment were analyzed by qPCR, histology, immunofluorescence and immunohistochemistry. Tumours were also dissociated to generate cell line cultures, which were then orthotopically injected in mice submitted or not to CD-HF diet for three months.

Results: We obtained tumors with both genetic combinations of oncogenes, 4 to 12 weeks after the hydrodynamic tail vein injection. Histologically, tumours obtained with RAS had a more aggressive, poorly-differentiated phenotype, whereas MYC tumours were well differentiated. Cell line cultures obtained from RAS tumours injected orthotopically resulted in large tumours with histopathological characteristics similar to the original neoplasms. Mice fed with the CD-HF diet developed features of human NASH such as glucose intolerance and steato-hepatitis. We will present further data on characterization of tumours developping in control and NASH conditions.

P206

E4F1 a key player in the Response to anticancer treatments in Triple Negative Breast Cancer cells

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The multifunctional protein E4F1 (transcription factor and ubiquitin ligase) was originally identified as a cellular target of the E1A adenoviral oncoprotein in mouse embryonic fibroblasts. E4F1 directly controls genes involved in mitochondria functions, metabolism and cell-cycle checkpoints/DNA Damage Response (DDR), including Chek1, a major component of the DDR. Moreover we showed that E4F1 is essential for the survival of p53-deficient transformed cells. (Le Cam et al, Cell 2006, Lacroix, Caramel et al. PNAS 2010, Hatchi et al. J Exp Med 2011, Rodier, Lacroix et al. Cell Reports 2015, Rodier, Lacroix et al. PNAS 2016, Goguet-Rubio et al. PNAS 2016).

Patients expressing high levels of E4F1 in triple negative breast (TNBC) cancer tumors appeared to have a lower probability of relapse free survival compared to those expressing low E4F1 levels. In these cancers our present work shows that E4F1 is involved in the cellular DDR to genotoxic stresses.

E4F1 depletion in TNBC cells (SUM159) strongly sensitized these cells to Gemcitabine, a potent DNA synthesis inhibitor and replicative stress inducer. Upon this treatment cells failed to arrest in S-phase, and underwent massive cell death. Transcriptomic analyses showed that the expression of 38 DDR-associated genes involved in the cellular response to Gemcitabine, are significantly down-regulated upon E4F1 depletion compared to control. Surprisingly, E4F1-depletion also resulted in a strong down-regulation of checkpoint kinases ATR and ATM protein levels, without impacting on ATR and ATM transcripts levels. Finally, we confirmed in these TNBC cells that E4F1 protein both controls directly the transcription of the CHEK1 gene, and interacts physically with the CHK1 protein. Aiming at understanding how E4F1 controls ATM/ATR stability, we discovered that E4F1 directly controls the transcription of the TTI2 and TELO2 genes that code for components of the TTT-complex, a multi subunit HSP adaptor essential for the folding and stability of the ATM, ATR, DNAPK protein family. Altogether, these results reveal that E4F1 controls the TTT complex-ATM/ATR-CHK1 stress checkpoint pathway at both the transcriptional and post-transcriptional levels.

In both SUM159 cells and in a primary derived xenograft (PDX) model of TNBC, this E4F1 program is stimulated upon Gemcitabine treatment, suggesting that, E4F1 is a key player of the response of TNBC to anticancer treatments.

P207

A new era in cancer biomarkers: multivariate analysis of RNA epigenetics by mass spectrometry

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Recent advances in RNA modifications detection by high throughput sequencing and the role of these modifications in gene expression regulation have giving rises to the emerging field of epitranscriptomics. To date, more than 140 RNA modifications have been identified, they are found in all organisms from bacteria to vertebrate and in all types of RNA (tRNA, rRNA, mRNA and ncRNA). They comprise addition of functional groups (e.g. base or ribose methylation) as well as substitution (e.g. uridine conversion into 4-thiouridine), isomerization (e.g. uridine conversion into pseudouridine, Ψ) and reduction (e.g. conversion of uridine to dihydrouridine). RNA modifications are known to be involved in all step of gene expression regulation and an increase number of diseases have been associated with changes in specific RNA modification. Therefore, correlating alteration of RNA epigenetic marks with disease occurrence or progression represent a significant challenge for therapeutic management. Widely used for identifying and quantitating proteins, mass spectrometry has been recently adapted to detect nucleic acid modifications.

The SMART project gathers three teams from distinct disciplinary horizon and seeks to design and optimize mass spectrometry analysis (LC-MS/MS) of RNA modifications. So far, we successfully calibrated identification and quantification of 7 of them, including the most prevalent of them in mRNA: the N6-methyladenosine (m6A). Several studies are currently exploiting this setup, the first of its kind in France. Our goal is to design multivariate analysis of RNA modifications as biomarker for personalized medicine. In the future, we plan to detect the whole RNA epigenome and, in concert with SIRIC Montpellier cancer, analyze patient samples such as tumor and liquid biopsies.

P208
RNA epigenetic and FTO activity steer cancer cell fate

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Following decades of near-dormancy, the field of RNA modification is experiencing a rebirth, mostly thanks to recent progress in detection techniques such as high throughput sequencing. This study stems from a transdisciplinary research endeavor that seeks to evaluate the role of RNA modifications in colorectal cancer progression and more specifically in the acquisition of Cancer Stem Cell (CSC) phenotype. CSC represents a minor subpopulation of tumor cells endowed with self-renewal and multi-lineage differentiation capacity which can escape from both conventional and targeted therapies, disseminate and seed metastasis. For that reason, **understanding the molecular mechanisms that bestow CSC phenotype has become a major goal to design new therapeutic routes that may prevent tumor relapse and metastasis**.

N6-methyladenosine (m6A), the most frequent epigenetic modification that occurs on mRNA, is involved in all step of gene expression (splicing, transport, stability and translation) and plays a role in major cellular pathways and processes such as stem cell differentiation. m6A is a dynamic, reversible chemical modification deposited by the METTL3 - METTL14 - WTAP "writer" complex and removed by the "erasers" ALKBH5 and FTO. While recent studies have connected m6A dynamic with cancer progression, **the role of this RNA modification in colorectal cancer evolution remains unknown**. Combining ALDH activity (CSC marker) based cell sorting with MeRIP-sequencing (collaboration with Tao Pan, Chicago U.), we have mapped and compared m6A distribution across the transcriptomes of CSC-enriched and CSC-depleted cell samples and shown significant differences. Then, selective silencing of m6A actors, has uncovered a **specific role of FTO, an m6A demethylase, in regulating CSC abilities**: FTO inhibition (expression or activity) increases substantially self-renewal, chemoresistance and tumor initiation in vivo (xenograft mouse model). While this observation holds true for all colorectal cancer cell lines tested, FTO level has no impact on breast cancer cell line, suggesting some sort of "tissue-specificity". Finally, recent data suggest that FTO expression may vary throughout the course of cancer progression, mostly decreasing along with the acquisition of invasive/metastatic properties.

Altogether, FTO activity seems capable of shaping colorectal cancer cell phenotype and might play a role in tumor evolution. Ongoing RNA-seq experiments followed by cross-analysis with m6A mapping data should enable us to identify RNA targets of FTO.

P209

JMJD6 participates in the maintenance of rDNA integrity in response to DNA damage

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Genome integrity is constantly disrupted by exogenous and endogenous sources producing DNA damages. If not repaired, they could promote genetic instability and thus diseases such as cancer. To prevent such deleterious effects, repair mechanisms are crucial and occur in a chromatin context which is regulated by histone post-translational modification. Among them, histone methylation has been shown to be important for DNA repair and other processes due to a dynamic control by histone demethylase and histone methyltransferase. After the screening of a siRNA library, we identified a histone demethylase JMJD6 whose depletion in U2OS cells alters DNA damage response and cell survival to ionizing radiation. Moreover we observed JMJD6 recruitment at DNA damage site in nucleolus by live cell laser tracking. Nucleolus is composed of ribosomal RNA genes in tandem repeats which are highly transcribed and subject to frequent DNA damages. In response to rDNA damages, rDNA transcription silencing occurs and is exacerbated in JMJD6 depleted cells. Furthermore, in JMJD6 depleted cells we observed genetic instability characterized by increased loss of rDNA copies after irradiation. Here we identified JMJD6 as component of the DNA damage response occurring at rDNA regions and participating to maintain its integrity.

P210

Transcriptional repression of interferon-stimulated genes by the TRRAP transcriptional co-activator and its chaperone TTT

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Gene expression regulation is essential for cells to respond to signaling cues. Transcription represents a crucial regulatory step and involves several factors with multiple distinct activities. One such factor, TRRAP (Transformation/transcription domain associated protein), was first discovered as an interacting partner for the MYC oncogenic transcription factor. TRRAP was then shown to be part of two co-activator complexes, SAGA and TIP60. Interestingly, TRRAP is the sole pseudokinase of the PIKK family, which encompasses five kinases playing critical roles during key cellular processes. The PIKKs are folded and assembled into their active complexes by a dedicated co-chaperone of HSP90, namely TTT. We used CRISPR-Cas9 to construct fast, inducible degron alleles of both TRRAP and the TTT co-chaperone in colorectal cancer cells. Transcriptomic analysis revealed a significant overlap between genes which expression depends on TRRAP and TTT. Remarkably, most of these genes are MYC and E2Fs targets, suggesting that TTT has an important role in sustaining the activities of these oncogenic transcription factors in colorectal cancer cells. Surprisingly, TTT and TRRAP depletion also induced a common Type I Interferon gene expression signature. Antibody-targeted chromatin profiling (CUT&RUN) and kinetic analyses revealed that TRRAP directly represses the expression of IRF9, which acts as a master regulator for the expression of interferon stimulated genes. To conclude, we have uncovered an unexpected repressive role of TTT and TRRAP at interferon-stimulated genes in colorectal cancer cells, revealing a previously unidentified mechanism by which TRRAP contributes to tumorigenesis.

P211

Real-time dynamics of estrogen receptor clustering at a transcribing gene in human mammary tumor cells

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The three-dimensional structure of the mammalian genome is highly organized and in constant motion during biological processes. Chromatin dynamics are necessary to regulate all nuclear events. However, to date we do not know how one of the major cellular function such as transcriptional activity, affects motion of the underlying chromatin fiber. The transcription process in the eukaryotic nuclei involves several activities including epigenetic modifications, binding of transcription factors, binding of RNA polymerase 2 (RNA pol2) protein-complex as well as mRNA synthesis. To clarify the mechanisms and kinetics of chromatin and its relationship to the transcription, the chromatin needs to be followed over time at the single cell level.

We use human breast cancer cell lines as a model system, to characterize chromatin dynamics of specific estrogen receptor alpha (ERα)-dependent gene loci in relationship with the transcription factor ERα and RNA pol2. Rapid transcription activation of ERα-sensitive genes is stimulated by hormone - estradiol (E2) within 5 minutes. To follow chromatin in living cells, we developed the non-invasive ANCHOR method for DNA labeling. We generated cell lines in which endogenous loci are specifically inserted in the genome to visualize a single gene and to confront its dynamic behavior to transcription actors clustering and mRNA formation during 60 minutes after transcription activation.

Our observations that transcription initiation confines chromatin locally within minutes indicate that existing chromatin conformation reorganizes to facilitate enhancer promoter contacts. Using confocal and structured illumination microscopy (SIM) in 3D and in living cells, we show that transcription actors undergo rapid (within few minutes) phase transition and cluster formation around the transcribed chromatin loci.

P212

Translation initiation factor INT6/eIF3e is a target for human glioma cell radio-sensitization through regulation of specific mRNA translation.

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Glioblastomas (GBM) are malignant grade IV astrocytomas and very aggressive tumors, with frequent relapses despite an appropriate treatment combining surgery, chemo-radiotherapy. Developing new therapeutics is critical to improve the treatment of these invasive brain tumors. The malignant phenotype is often the result of alterations within the translational machinery as protein abundance and overall rate of protein synthesis are major determinants of cell and tissue functions. Recently, deregulation of translation initiation and eukaryotic translation initiation factors (eIFs) has been shown to contribute to oncogenic transformation and growth by providing an increase in protein synthesis necessary for cancer cell proliferation and selective mRNA translation involved in cell survival, metastases and resistance to treatment. Altered expression of eIF3e has been described in various types of human cancer, but the nature of its involvement in GBM tumorigenesis and resistance to treatments is not yet clear. Using polysomal profiling, we found that eIF3E can act as either a positive or negative regulator of translation of distinct sets of mRNAs. Functional classification showed a marked enrichment of genes involved in the DNA damage response pathways, including those controlled by p53. We showed that eIF3e silencing potentiates radiation response in GBM cells and that the eIF3e-dependent inhibition of HIF mRNA translation could potentially explain our cell death phenotype. Importantly, low or negative expression of eIF3e in GBM correlate with a better survival of these patients, reinforcing a potential prognostic value and role for eIF3e in human GBM progression. Taken together, our work suggests that eIF3e regulates the translation of mRNAs involved in key aspects of cancer cell biology and radio-sensitization and could represent a new therapeutic option for GBM patients.

P213

Role of the RNA-binding protein hnRNP HF in the link between translational control and glioblastoma outcome

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Glioblastoma (GBM) is one of the most lethal primary brain tumors. Treatment options have remained limited in part because of the still incomplete understanding of the basic biology of GBM. Although it is well known that deregulation of protein synthesis contributes to GBM progression and response to current therapeutic treatments, the molecular mechanisms and therapeutic targets remain to be fully elucidated. Accumulating evidences from others and us (Cammas Oncotarget 2016), demonstrated that RNA-binding proteins are abnormally expressed in cancer cells and play a critical role in the link between protein synthesis and cancer by impacting both global and mRNA specific translation. In this study we focused on the RNA-binding protein hnRNP HF, a post-transcriptional regulator that is highly expressed in GBM. Here, we uncovered a novel role for hnRNP HF in translational regulation. hnRNP HF silencing impacts GBM processes known to underpin the spread/relapse of GBM, and regulates tumor growth and response to GBM treatments (temozolomide and irradiation). Together, our results suggest that hnRNP HF is an essential regulatory hub in GBM networks that drives translational control of genes contributing to GBM outcome.

P214

New insights into structural features and optimal detection of circulating DNA determined by single strand DNA analysis.

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Circulating Cell free DNA (cfDNA) has received increasing interest as an apparent breakthrough approach in diagnostics, personalized medicine and tumor biology. However, the structural features of cfDNA are poorly characterized. Specifically, the literature has discrepancies with regards to cfDNA size profile. We performed a blinded study of the distribution of cfDNA fragment sizes in cancer patient plasma (n=11), by various ultra-deep sequencing approaches and Q-PCR. Whole genome sequencing of single-stranded DNA library preparation (SSP-S) revealed that nearly half of the total cfDNA fragment number are below 120 nucleotides (nt) which are not readily detectable by standard double-stranded DNA library preparation (DSP) protocols. cfDNA fractional size distribution was very similar using both SSP-S- or Q-PCR-based methods. These extra small detected cfDNA fragments may mostly result from nicks occurring in blood circulation in one or both DNA strands which are subsequently revealed through the denaturation step of the SSP and Q-PCR procedures. Detailed analysis of the data suggested that most of the detectable cfDNA in blood has a nucleosome footprint (~10-bp periodicity repeats). The nucleosome is thus the most stabilizing structure of DNA in the circulation. cfDNA molecules, which are initially packed in chromatin, are released from cells and are then dynamically degraded in blood both within and between nucleosomes or transcription factor-associated subcomplexes. . While this study provides new insights into cfDNA size profiles harmonizing sequencing and Q-PCR findings, our data validate the use of a specific Q-PCR method and SSP-S for obtaining an optimal qualitative and quantitative analytical signal. As sensitivity is clearly a limitation of cfDNA applications, delineating the structural features of cfDNAs may help adapt optimal analytical approaches to study cancer progression or tumor biology, as well as diagnostic test for monitoring cancer patient and screening which are under investigation in clinical trials.

P215

RNAseq to identify new fusion transcripts in Chronic Myelomonocytic Leukemia

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Chronic myelomonocytic leukemia (CMML) diagnosis is based on cellular biology, recurrent mutations and lower cytogenetic abnormalities. However, the pathology is very heterogenous and patients can develop rapidly acute myeloid leukemia while others present long overall survival with remaining chronic leukemia. RNAseq screening represent an alternative approach to identify new molecular biomarkers to attempt refining risk group stratification or identifying molecular target. This approach would also be beneficial for the establishment of more adapted medical treatment. To this aim we apply RNAseq technology on peripheral blood mononuclear cells and CD14 purified ones from 20 CMMLs donors and run a previously developed pipeline to identify new fusion transcripts (New chimeric RNAs in acute myeloid leukemia *Rufflé et al F1000Res 2017,* RNA-seq analysis to detect abnormal fusion transcripts linked to chromotripsis, *Bougé et al Methods Mol Biol.2018*).Sorted chimeric RNA (chRNA) were classified according to their origins and annotated with genomic informations (as already described). QPCR and resequencing combined with *in silico* approaches were used to check the predicted chRNA candidates as well as their tumor specific expression. Interestingly our work revealed the presence of some recurrent and tumor specific chRNA such as a new RXRA-CCNG2 fusion transcript presents in some samples, which seems to be correlated with CMML status.

Posters – Axis 3 “Translational Research, from Biology to Clinics”

P301
Quantifying circulating cell-free DNA in humans

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Background: To our knowledge, this is the first comprehensive study on the influence of pre-analytical and demographic parameters that could be a source of variability in the quantification of nuclear and mitochondrial circulating DNA.

Methods: We developed an optimal calculation of the simultaneous and independent quantification of nuclear and mitochondrial circulating DNA genome copies based on a very reproducible, linear and sensitive clinically validated q-PCR method. We report data from a total of 222 subjects, 104 healthy individuals and 118 metastatic colorectal cancer (mCRC) patients. Univariate analyses were performed using Mann-Whitney U test or Kruskal-Wallis rank test for continuous variables. Moreover, multivariate analyses were carried out using logistic regressions.

Results: Approximately 50,000 and 3,000-fold more mitochondrial than nuclear genome copies were found in the plasma of healthy individuals and mCRC patients, respectively. In healthy individuals, nuclear circulating DNA concentration was statistically influenced by age ($p=0.009$) and gender ($p=0.048$). Multivariate analysis with logistic regression specified that age over 47 years-old was predictive to have higher nuclear circulating DNA concentration ($OR=2.41$; $p=0.033$). Mitochondrial circulating DNA concentration was independent of age and gender in healthy individuals. In mCRC patients, nuclear and mitochondrial circulating DNA levels were independent of age, gender, food intake and plasma aspect, either with univariate or multivariate analysis. Nonetheless, ad hoc study suggested that menopause and blood collection time might have tendency to influence cirDNA quantification. In addition, high significant statistical differences were found between mCRC patients and healthy individuals for nuclear circulating DNA ($p<0.0001$), mitochondrial circulating DNA ($p<0.0001$) and mitochondrial circulating DNA/nuclear circulating DNA ratio ($p<0.0001$).

Conclusions: Nuclear and mitochondrial circulating DNA levels do not vary in the same way with regards to cancer vs healthy status, pre-analytical and demographic factors. Our observations could serve as a guideline for standard operating procedures and for transposing cirDNA analysis into clinical practice.

P302

Expansion of allogeneic NK cells with efficient antibody-dependent cell cytotoxicity against multiple tumors

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Monoclonal antibodies (mAbs) have significantly improved the treatment of certain cancers. However, in general mAbs alone have limited therapeutic activity.

One of their main mechanisms of action is to induce antibody-dependent cell-mediated cytotoxicity (ADCC), which is mediated by natural killer (NK) cells. Unfortunately, most cancer patients have severe immune dysfunctions affecting NK activity. This can be circumvented by the injection of allogeneic, expanded NK cells, which is safe. Nevertheless, despite their strong cytolytic potential against different tumors, clinical results have been poor.

Methods: We combined allogeneic NK cells and mAbs to improve cancer treatment. We generated expanded NK cells (e-NK) with strong *in vitro* and *in vivo* ADCC responses against different tumors and using different therapeutic mAbs, namely rituximab, obinutuzumab, daratumumab, cetuximab and trastuzumab.

Results: Remarkably, e-NK cells can be stored frozen and, after thawing, armed with mAbs. They mediate ADCC through degranulation-dependent and -independent mechanisms. Furthermore, they overcome certain anti-apoptotic mechanisms found in leukemic cells.

Conclusion: We have established a new protocol for activation/expansion of NK cells with high ADCC activity. The use of mAbs in combination with e-NK cells could potentially improve cancer treatment.

P303
The involvement of PXR in the resistance of KI combinations in cancer cells

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Proliferation of cancer cells is usually due to the deregulation of signalling pathways implicating tyrosine or serine/threonine kinases that are constitutively activated. Therefore, series of Kinase Inhibitors (KI) have been developed in order to specifically target these kinases and have been approved in the treatment of several types of cancers. However, as for chemotherapies, various mechanisms of resistance have limited their clinical efficacy, including enhanced metabolism that could explain treatment failures. Indeed, KIs are known to be metabolized in hepatocytes by the CYP 450 and are the substrates of both influx pumps from the solute carrier family (SLCOs) and efflux pumps from the ABC transporters family. The majority of these genes are also expressed at the tumour level and their expression are regulated by the nuclear receptor PXR (NR1I2), suggesting that PXR could play a major role in drug resistance by modulating the pharmacokinetics of kinase inhibitors.

Preliminary results from our group have shown that overexpression of PXR could sensitize 22RV1 prostate cancer cells to specific kinase inhibitors in vitro including dabrafenib (BRAF inhibitor), erlotinib (EGFR inhibitor), or afatinib (EGFR, HER2 inhibitor). We then wanted to investigate the mechanisms of such a sensitization, and started to study whether it could be due to a change in drug transport. We then measured intra and extracellular concentrations of drugs in control and PXR-overexpressing cells using a mass spectrometry approach, starting with afatinib that is not subject to metabolization. We found that cells overexpressing PXR that are treated with afatinib for 72h showed a 4-fold increase in intracellular concentration of the drug as compared to control cells transfected by an empty vector, suggesting a role of PXR in the modulation of drug transporters in 22RV1 cells. These results are in accordance with a previous study demonstrating that PXR activation was correlated with the expression of the SLCO1A2 influx pump. Measurements of SLCO1A2 and other drug transporters is under evaluation in our models.

We also demonstrated that the B-RAF inhibitors vemurafenib and dabrafenib were agonists of PXR, dabrafenib showing even a higher potency than the reference agonist SR12813. Because these inhibitors are currently approved in the treatment of metastatic melanomas in combination with MEK inhibitors, we wanted to evaluate the effect of PXR activation by B-RAF inhibitors on the sensitivity of A375 melanoma cells or cells overexpressing PXR to B-RAF or MEK inhibitors used alone or in combinations. Our preliminary results confirmed that overexpression of PXR also sensitized A375 melanoma cells to dabrafenib, vemurafenib, trametinib, and cobimetinib. The evaluation of the effect of PXR expression on the sensitivity to vemurafenib/trametinib and dabrafenib/cobimetinib combinations is underway using a specific methodology of synergy matrix developed in our group. We hypothesized that PXR agonist property of B-RAF inhibitors could impair drug response to B-RAF/MEK combinations or associations of B-RAF inhibitors with other chemotherapies, further suggesting that PXR levels could be used as a relevant marker to predict the clinical response to these associations.

P304

Hepatocellular adenomas proteomic intratumoral heterogeneity.

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Hepatocellular adenomas (HCA) are rare benign tumors that represent a heterogenous entity divided into several groups based on patho-molecular features ((1) HCA with inactivating mutations of HNF1A, (2) Inflammatory HCA with diverse mutations leading to the activation of STAT3, (3) HCA with activating beta-catenin, (4) and the unclassified HCA). Recently, a new subgroup among UHCA has recently been described and was characterized by the activation of the sonic hedgehog pathway and named shHCA (Nault et al, Gastroenterology 2017).
Previously we developed a new approach combining laser microdissection and mass spectrometry analysis compatible with FFPE tissue sections to explore proteomic profile of tumor tissue that allowed us to propose ASS1 as a new surrogate biomarker for UHCA (Henriet et al, Hepatology, 2017).

In this study we focused on beta-Catenin-mutated HCA (b-HCA). Different types of b-catenin mutations have been identified by molecular analysis, occurring in exons 3 or 7/8 with different levels of b-cat pathway activation correlated with variable risk of malignant transformation. An immunohistological analysis of the Glutamine Synthetase (GS) patterns validated it as a surrogate marker of the different levels of b-catenin activation and establish a genotype-phenotype correlation. During this study, we observed a very frequent GS positive border in all type of b-HCA, indicating a protein expression heterogeneity into tumors. Thanks to laser microdissection, we compared proteomic profiles of non tumoral tissue with the center of the tumor and the GS positive border of 5 cases of each type b-HCA (exon 3, exon S45, exon 7/8). Thus, we confirmed an intratumoral heterogeneity of HCA with specific pathways deregulated in this GS positive border and investigated their implication in tumor transformation.

P305

Involvement of TrkB transfer through exosomes in glioblastoma tumor progression

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Glioblastoma is the most frequent brain tumor during adulthood. The commonly used treatment consists in a combination of radiotherapy and temozolide, known as the Stupp protocol. However, this type of cancer shows a high rate of recurrence due to therapeutic resistance.

Previous studies showed the involvement of a specific neurotrophin receptor, TrkB (or NTRK2) as a key player in survival and proliferative processes within glioblastoma stem cells. TrkB has been characterized in exosomes derived from highly aggressive tumor cells and exert a control on the tumor microenvironment. These extracellular vesicles and their specific content are able to transfer aggressiveness properties to less aggressive neighboring tumor cells. This transfer induces a CSC transformation in targeted cells, which adopt stem cell characteristics.

To explore the function of TrkB transfer, we established a stable cell models overexpressing TrkB V5-tagged within glioma cell lines: U87-MG and LN18. First, we will validate TrkB overexpression in transfected cells and its function analyzing changes regarding survival pathways and proliferation rate. According to our preliminary works, we will study the impact of TrkB overexpression on the expression of specific CSC markers (Oct4, Sox2, Nanog, Nestin…). To pursue the study, we should examine the impact of TrkB overexpression on the release of extracellular vesicles and on their composition. These highly expressing-TrkB extracellular vesicles will be used to treat native glioblastoma cell lines in order to determine whether TrkB-V5 transfer through exosomes might be involved in the acquisition of an aggressive phenotype related to CSC phenotype. The analysis of exosomes-derived TrkB functions will be achieved by studying survival pathways, proliferation rate and stemness properties in recipient cells. The function of exosomes-derived TrkB in glioblastoma tumor progression and proliferation in recipient cells would like to explore the putative role of this neurotrophin receptor in tumor aggressiveness and for its prospective use as a diagnostic and / or prognostic biomarker in liquid biopsy for a better understanding of glioblastoma tumors and a better patient handling.

P306

Role of integrin Beta8 in stemness maintenance and radioresistance of glioblastoma-initiating cells

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Glioblastomas (GB) are malignant brain tumors with dismal prognosis despite standard treatment which includes maximal surgical resection followed by fractionated radiotherapy with concomitant and adjuvant chemotherapy (Temozolomide). This severe outcome could partly be explained by the presence into the tumor of Glioblastoma-Initiating Cells (GIC), characterized by their ability to self-renew, their higher expression of specific GIC markers, their pluripotent aptitude to differentiate (neurons, astrocytes or oligodendrocytes), and their high tumorigenic potential. In addition, GIC are particularly chemo-radioresistant and involved in tumor recurrence. So, current research focuses on developing potential GIC-targeted therapies in order to improve GB treatment. Regarding current literature but also transcriptomic results obtained in our lab, integrin beta8 emerged as a potential selective target in GIC. We then hypothesized that this integrin could be involved in stemness maintenance but also radioresistance in GIC. We first demonstrated, with several primocultures from patients, that this Beta8 integrin is overexpressed in GIC in comparison to their differentiated progeny. Moreover, this integrin could be associated with characteristics and features unique to these cells, including self-renewal ability, viability, stemness status and radioresistance. Indeed, the selective inhibition of this integrin beta8 in GIC by shRNA resulted in a decreased neurosphere formation associated with an increase of differentiation patterns and cell death, this one being potentiated after irradiation. These results could eventually allow to identify integrin beta8 as a new membrane marker of GIC but also to evaluate its targeting potential as a new therapeutic radiosensitizing strategy in these quite aggressive and invasive brain tumors.

P307
Rational development of drug combination treatments in prostate cancer

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Prostate cancer is the most frequently diagnosed cancer in men and its progression is tightly associated with the androgen signals. The current initial treatment of advanced prostate cancer is the androgen deprivation therapy either through surgical or chemical castration. Most patients respond to these therapies but within two years, they develop a castration-resistant prostate cancer which leads to a poor prognosis. This late stage of prostate cancer is dependent of the androgen receptor activation. Consequently, the treatment strategy focused on inhibiting the active androgen receptor in prostate cancer cells. The enzalutamide molecule is used in hormonotherapy in order to inhibit the androgen receptor interaction with its ligand and the DNA. Even though enzalutamide treatment has participated to enhance patient survival benefit, there is still drug resistance that arises and leads to a considerable therapeutic challenge.

The main objective of this project is to identify new proteins, that could be targeted in combination with standard hormonotherapy, to overcome drug resistance to prostate cancer treatment. In our study, we supposed that enzalutamide treatment could induce the activation of specific signaling pathways, either involved in the drug sensitivity or in the drug resistance. In order to confirm this assumption, we have done phosphokinome profiling that led to the identification of the p38 MAP kinase as a potential target. Our results indicate that the combination of enzalutamide with a p38 inhibitor has a good synergistic effect *in vitro* and *in vivo*. So we are, now, looking for the mechanism underlying this synergistic effect that may have implications in overcoming the resistance to anti-androgen therapy.

P308
MiniSOX9 is a potential biomarker in colorectal cancer

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Background: MiniSOX9 has been first described as a splice variant of the much well known SOX9 transcription factor (Abdel-Samad *et al.*, Oncogene, 2011). This work relies on a long-term experience on this member of the superfamily of High Mobility Group (HMG) domain transcription factors that evidenced the dose-dependent effect of SOX9 and its incidence in colorectal cancer (CRC) (Prévostel and Blache, Eur J Cancer, 2017). More precisely SOX9 inhibits the activity of the canonical Wnt/β-catenin signaling pathway and was shown to be a tumor suppressor gene in the intestine (Prévostel *et al.*, Oncotarget 2016, Jay et*al.*, Cancer Res, 2005, Zalzali *et al.*, Oncogene, 2008). Our previous data clearly indicate that MiniSOX9 expression is low in healthy tissues while being significantly highly expressed in the adjacent colorectal tumors where it potentiates the activity of the oncogenic Wnt/β-catenin signaling pathway. In addition, MiniSOX9 is a dominant negative of SOX9 (Abdel-Samad*et al.*, Oncogene, 2011). Altogether, these observations point out MiniSOX9 as a potential new biomarker for colorectal cancers.

Cohort and Methods: To further investigate the clinical relevance of these findings, we carried out a retrospective study on an annotated cohort of 174 total RNAs, extracted from fresh frozen colon tissue samples (ICM-CORT-2017-25), divided in 7 groups constituted of healthy tissues (n=30), adenomas (n=10), stages I (n=24), stages II (n=22), stages III (n=33), stages IV (n=25) and metastasis (n=30) in order to quantify the expression of MiniSOX9 by quantitative RT-PCR.

Results: We first validated that the expression of MiniSOX9 is significantly higher in pre-neoplasic and neoplasic samples compared to healthy tissues whatever the stages *(mean: 0,56 vs. 0,27; p<0,0001)* as well as in metastasis *(mean: 0,53 vs. 0,27; p<0,0001)*. We further observed that MiniSOX9 is significantly more expressed in pre-neoplasic and early stages of CRC i.e. stages I compared to healthy tissues *(mean: 0,72 vs. 0,27; p<0,0001*).

Conclusions and perspectives: Our data show that MiniSOX9 is expressed in adenomas and early stages of CRC and that this expression is maintained in all stages. So we can hypothesize that MiniSOX9 is at least a witness of colorectal oncogenesis or an active participant considering our previous data that MiniSOX9 arbors several oncogenic properties (Abdel-Samad et al., Oncogene, 2011). Now, taking into account these results, we want to address the potential impact of MiniSOX9 on patient prognosis especially in stages II and III where it could help to guide adjuvant chemotherapy prescription.

P309

Determination of the mechanism of action of diazepinones targeting melanoma

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Because of its aggressiveness and high resistance rate, Malignant Melanoma (MM) is the most lethal skin cancer. Recently, progress brought by targeted therapy and by immunotherapy has significantly improved the median overall survival and the safety profile. However, in order to overcome the onset of acquired resistances, development of new compounds against MM remains a public health priority. Our project aims to develop a new series of active compounds, based on the diazepinone scaffold, active against resistant MM 1,2. In 2014, these new compounds were tested by the NCI against the 60 cancer cell line panel. One of our compounds, JMV5038, had an *in vitro* anti-cancer activity on several cancer lines and more particularly on MM (IC50 on MDA-MB-435 cell line < 1,5 µM)3,4. This activity was confirmed on A375 cells, another MM cell line, while no significant cytotoxicity was found on the "healthy" fibroblast NIH3T3 cells (IC50 > 100 µM). Moreover, transcriptomic studies using Affymetrix arrays strongly suggested that this compound may have an original mechanism of action (MOA) compared to other chemotherapies (both classic and targeted) used for the treatment of MM. Indeed, a fully original mRNA expression pattern was evidenced in JMV5038-treated A375 cells.
Currently, our goal is to determine the MOA of JMV5038 along three different axes. Firstly, we are studying the intracellular localization of JMV5038 to determine its site of action. For this, we use Raman and multiphoton imaging, in collaboration with the laboratory of Bioengineering and Nanosciences (EA4203) and the Charles Coulomb Institute of Montpellier. Our preliminary results in A375 cells showed a peri-membranous accumulation of JMV5038. Secondly, we are conducting a functional proteomic study to find the pharmacological target(s) of our active compound. To achieve this goal, two different fishing strategies can be used. The classic direct fishing strategy which has required a strong modification of JMV5038 by adding a biotin residue, has led to its loss of activity. we thus focused on the indirect fishing strategy in synthesizing "clickable" analogues of our hit bearing one alkyne or one azide function on its structure. A probe that retains the initial activity of JMV5038 was selected. We will then use click chemistry to biotinylate the active derivative directly in melanoma cell lines. After immobilization of the associated proteins on streptavidin beads, proteomic analysis using mass spectrometry will be performed to identify proteins that bind specifically to the active compound. Finally, we continue our functional studies to explore altered signaling or oncogenic pathways using phospho-proteins blots and arrays.
In addition to these three axes, we are trying to show *in vivo* activity of JMV5038 and our first results are promising. We evidenced, on chicken embryo chorioallantoic membrane (CAM) model, the anti-cancer potential of our compound by showing a significant decrease in the surface of A375 cell xenografts after injection of JMV5038 and the absence of toxicity on these models (at ≅ 200 µM). We will soon be testing JMV5038 on resistant cells and also on xenografts with patient biopsies in collaboration with the Cancer Research Institute of Montpellier and the CHU of Nîmes.

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P310

Ongoing studies coordinated by IRCM/ICM on circulating DNA analyses for CRC management care

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Circulating cell-free DNA (cfDNA) analysis constitutes a hopeful approach to provide a non-invasive molecular test for cancer patients. Analyzing this new biological source may have important implications in a shift towards personalized medicine for diagnosing and/or monitoring malignancies. In this context we developed a novel multi-marker assay called IntPlex® and validated for detecting *RAS* and *BRAF* point mutations in the blood of metastatic colorectal cancer (mCRC) patients and can be adapted to all mutations. In order to validate the use of IntPlex® method for cfDNA analysis as a cancer biomarker of prognosis, theranostic, detection of the minimal residual disease (MRD) and the outcome of relapse, three independent studies are conducted by our group to address these specific issues.

<u>STUDY N°1: ANDcirc: Diagnostic and Prognosis Value of Circulating DNA for CRC Patients' Surveillance after Curative Treatment. (INCA PRTK-DGOS).</u>
ADNcirc is an open, prospective and multicenter study of which the primary endpoint is to evaluate the prognostic value of cfDNA analysis at the inclusion for the early detection of recurrences within the 3 years of follow up in patients curatively treated for stage II-III CRC. Secondary endpoints are to determine the rates of total cfDNA and mutational DNA and to compare their rate lead times with the changing carcino embryonic antigen rate leadtime, the relapse detection lead time, the 2-years disease-free survival and the 2-years overall survival; To detect and analyze the evolution of cfDNA during adjuvant chemotherapy and to detect RAS, BRAF, PIK3CA and EGFR mutations in case of recurrence.

<u>STUDY N°2: THRuST: Early detection of relapses in stage III colon cancer patients by longitudinally following a personalized molecular signature from a blood test: (Transcan-2 ERANET European grant).</u>
The primary objective of this study is to determine in stage III MSS CC patients the proof of concept of cfDNA detection for the identification of post-surgery recurrence. The cfDNA will be longitudinally analyzed for the presence of a personalized molecular signature by NGS analyses. Secondary objectives are the longitudinal examination of tumor recurrence by quantitative analysis of cfDNA in stage III MSS CC patients, the clinical feasibility of the real-time clonal evolution assessment of the recurrent tumor with a personalized molecular signature under standard patient management care in stage III MSS CC patients, and the evaluation of the feasibility of the post-surgery detection of MRD from an individualized molecular signature.

<u>STUDYN°3: PANIRINOX: A randomized phase II study comparing FOLFIRINOX + Panitumumab vs mFOLFOX6 + Panitumumab in mCRC patients selected by*RAS/BRAF* status from cfDNA analysis. (AMGEN).</u>
By selecting patients with IntPlex® method, we aim to investigate response rate and outcomes reached with Panitumumab in combination with a standard or an intensified chemotherapy regimen in *RAS/BRA*F WT mCRC patients. 209 *RAS/BRAF* WT patients will be randomized 2:1 to either FOLFIRINOX- Panitumumab or mFOLFOX6-Panitumumab. Primary objective is the evaluation of complete response rate on treatments. Secondary objectives are to assess the overall survival, progression free survival and the diagnostic performance of cfDNA analysis as compared to the tumor-tissue analysis. On-treatment, an ancillary study assesses appearance of RAS mutations in ctDNA detected by Intplex® method. PANIRINOX is the first interventional multicenter open-label randomized phase II study with selection of *RAS/BRAF* WT mCRC patients according to analysis of cfDNA.

Thus, by addressing key clinical questions (detection of MRD, treatment selection, noninvasive monitoring of patients), the impact of the expected results of the three studies presented here will evaluate the clinical utility of cfDNA measurement and allow its implementation in CRC management care.

P311
Prognostic significance of MEOX2 in gliomas

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Introduction

Gliomas are the most common malignant primary tumors in the central nervous system and have variable predictive clinical courses. Glioblastoma (GBM), the most aggressive form of glioma, is a complex disease with unsatisfactory therapeutic solutions and a very poor prognosis. During the last decade, some processes at stake in gliomagenesis have been discovered and biomolecular markers i.e. IDH1/2 mutations and 1p19q co-deletion, are now integrated in WHO classification 2016. However, despite extended time of molecular investigation of glioma profile, little is known about the role of homeobox genes, even though they are highly expressed in gliomas, particularly in GBM. Among them, the transcription factor Mesenchyme Homeobox 2 (MEOX2) has previously been associated with malignant progression and clinical prognosis in lung cancer and hepatocarcinoma but never studied in glioma. The aim of our study was to investigate the clinical significance of MEOX2 in gliomas.

Methods

We assessed the mRNA expression of MEOX2 according to IDH molecular profile and patient survival among three different public datasets: The Cancer Genome Atlas (TCGA), The Chinese Glioma Genome Atlas (CGGA) and the US National Cancer Institute Repository for Molecular Brain Neoplasia Data (Rembrandt). We then evaluated the prognostic significance of MEOX2 protein expression on 112 glioma clinical samples including; 56 IDH1-wildtype (wt) GBM, 7 IDH1wt lower grade gliomas (LGG), 49 IDH1-mutated LGGs. Survival rates were estimated by the Kaplan-Meier method followed by uni/multivariate analyses.

Results

In this study, we identified a new transcription factor of interest in glioma, MEOX2. We showed that MEOX2 is correlated with IDH mutational status in public datasets and local clinical data sets. We demonstrated that MEOX2 is a potent prognostic factor of patient outcome in all gliomas and in LGG alone. Moreover, it appeared to be a robust prognostic marker of survival in the LGG IDHwt subpopulation, independent of the combination of chr7 gain/chr10 loss. Finally, we highlighted replication, recombination and mitosis pathways positively correlated with MEOX2 in GBM.

Discussion

Our results may be the first to provide insight into the clinical significance of MEOX2 expression in gliomas, which is a factor closely related to patient outcome. MEOX2 could constitute an interesting prognostic biomarker, especially for LGG.

P312

Exploring the potential of mesenchymal stem cells small extracellular vesicles as bio-inspired delivery systems

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Extracellular vesicles (EVs) are nano-vesicles produced by cells and present in biological fluids. They are key players of intercellular communication. Given their natural cell internalization capabilities, they have a strong potential as drug-delivery systems (DDS). They could be an alternative to synthetic vesicles, such as modified liposomes, which have proved effective but flawed (cargo leakage, allergic reactions). However, the rationale of using EVs still requires numerous improvements especially for fine characterization to deal with heterogeneity of such vesicles, drug loading control and plasma stability. In this context, our team aims at overcoming these hurdles by using its pharmaceutical and physico-chemical skills to perform EV modifications, in order to create a potent DDS.

We proved able to produce and isolate the EVs from murine mesenchymal stem cells by differential centrifugation and characterize them: dynamic light scattering and nanoparticle tracking analysis (NTA) (size and concentration), protein quantification, western blot and proteomics (presence of specific proteins), cryoTEM (structure), lipidomics (lipid content). EVs were 94±10nm (NTA, n=20) with a production yield of 10±4 .108 particles / 106 cells (n=20) and 23±6 µg protein / 1010 EVs (n=20). The western blot and proteomics analysis evidenced the presence of small EV-specific markers such as TSG101, CD81 and ADAM10. With concern regarding their clinical use, we evaluated EV conservation protocols by monitoring concentration evolution by NTA, as opposed to evaluating protein markers as often performed in previous studies. Freezing EVs at -80°C in trehalose, a cryoprotectant, supplemented with protease inhibitors allowed optimal EV conservation, with a minimal 11±10 % loss (n≥3) in concentration after 14 days. This protocol was a significant improvement over freezing in PBS, which resulted in a 41±12 % loss (n≥3) under the same conditions. After fluorescent labeling, EVs were incubated with the parent cells or foreign cells (NIH3T3), in the presence of cellular intake inhibitors, and tracked by flow cytometry. All experiments were also performed on liposomal commercial standards as a comparison. EVs were internalized to a significantly greater extent than their liposomal counterparts in both target cells (n=4). Our data suggest they follow different endocytic routes, involving caveolae for liposomes and caveolae/cholesterol for EVs (n=4). Among the processes evaluated for drug loading (extrusion, sonication, freeze-drying), EVs were extruded through 50 nm membranes and freeze-dried without significant damage (n≥5), EV diameter and structure remained unchanged (NTA, cryoTEM), and EVs still expressed small EV markers. Moreover, these modifications did not affect EV internalization (n=3).

In summary, our team has been able to reproducibly isolate, characterize and label mMSC-derived EVs. EVs show increased internalization in vitro compared to liposomes currently used as DDS, and follow a different endocytic route than liposomes. Live imaging will be carried out to state the intracellular fate of such vesicles. Moreover, physico-chemical modifications (extrusion and freeze-drying) did not compromise EV integrity or impact their internalization: they are currently explored as protein-loading processes. Overall, our work provides evidence that EVs hold promise for the delivery of exogenous biomolecules, especially in a field were no reference exists, such as intracellular protein delivery.

P313

The « macrotrabecular » variant of hepatocellular carcinoma is associated with a poor prognosis

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Introduction: Hepatocellular carcinoma (HCC) is found in Europe and North America mainly in men over 50 years of age. The WHO describes histological forms of poor prognosis, including sarcomatoid and giant cell variants. Recently, Calderaro et al. have described a new variant of poor prognosis: massive macrotrabecular variant.
Endpoints: Analyze in a peruvian cohort with HCC treated with hepatectomy the overall survival and the clinico-pathological characteristics related to this variant.
i) the prevalence of this new variant, ii) its clinical and biological characteristics and iii) its prognosis.

Methods: The population consisted of all the patients operated for HCC at the National Cancer Institute (Lima, Peru) between 2010 and 2015. A prospectively collected database was used to obtain clinico-pathologic factors. Histopathologic observations were obtained from H&E slides and analyzed according the WHO classification, Massive Macrotrabecular variant was obtained as well. The diagnostic criterion is the existence of thick trabeculas (more than 10 cells) in more than 50% of the tumor. This analysis was performed by two pathologists (LC and BT).
An immunohistochemical study was carried out with the antibodies: for stem cells (EpCAM, CD117, CD133, CK19), for the cell cycle (P53, B-Cathenine) and Gluthamine Syntethase (GS) by establishing a difference between the different histological patterns.
Survival curves were analyzed by the Kaplan-Meier method, all data were analyzed using R software.

Results: The population consisted of 120 patients. It was divided into two subgroups: young (n = 63, 26 +/- 7.83) and elderly (n = 57, 65 +/- 12.93) patients. Among this population, 16 patients presented the new variant. This variant is found in both subgroups: young subjects = 10/65 and elderly subjects = 6/55. The size of the tumor was higher for this new variant (17.75 +/- 8.04) compared to other histological forms (17.8 +/- 8 vs 13.1 +/- 5.4, p = 0.02). Histologically, the cell population within the spans is not homogeneous because there is a peripheral palisade surrounding a central population of clearer cytoplasm cells. This new pattern is not different from others in term of expression of immunohistochemical markers. The survival of patients with this form of HCC is lower compared to that of conventional forms (p = 0.0018). This difference is found in the two age subgroups: median (in weeks): young = 229 vs 62; aged = 59 vs 20 (p <0.0001).

Discussion: The present study demonstrates that this new variant initially described in a European population is present in this Peruvian cohort as well. The morphological aspect is particular compared to that described by Calderaro et al. and Ziol et al. because the spans have two cell subpopulations mimicking that of adamantimomas.
Immunohistochemical markers are not expressed differently between all patterns. In particular we have not found the nuclear expression of B-catenin described by Calderaro et al.

Conclusion: This new histological form of HCC also exists in the Peruvian population and is associated with reduced survival.

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Targeting DNA Repair Mechanisms to Overcome Drug Resistance in Diffuse Large B Cell Lymphoma

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Diffuse large B-cell lymphoma (DLBCL) accounts for 40% of adult non-Hodgkin lymphomas. Most DLBCL patients achieve long-term remission after treatment, but a third relapse after conventional Rituximab (R)-based chemotherapy regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) (Siegel, *Cancer J Clin* 2012). Cancer cells are exposed to chronic replication stress, which impedes DNA replication and induces mitotic catastrophe (Shaheen, *Blood* 2011). Functional DNA repair pathways are therefore important for the survival of cancer cells. This dependence can be to exacerbate DNA damage induced by chemotherapy. Furthermore, high-risk DLBCL patients overexpress genes potentially involved in resistance to CHOP-based regimens, such as genes of the nucleotide excision repair (NER) pathway (Bret, *Oncotarget* 2012, *Cell Cycle* 2013). We developed GEP-based DNA repair scores that allow to identify high-risk patients that could benefit from treatment with DNA repair inhibitors (Bret, *BJH*2015).

DLBCL treatments include cyclophosphamide an alkylating agent that induces interstrand crosslinks (ICL), and doxorubicin, a DNA topoisomerase inhibitor II that induces DNA double-strand breaks, DNA adducts and ICL formation. Inhibiting DNA repair is a promising strategy to improve the efficacy of genotoxic drugs and overcome drug resistance. Our data support the view that inhibitors of DNA damage signaling and DNA repair have potential therapeutic interest in DLBCL. We characterized the drug-response of 16 DLBCL cell lines to 8 DNA repair inhibitors including PJ34 (PARP inhibitor), NU7441 (DNAPK inhibitor), KU55933 (ATM inhibitor), PF477736 (CHK1 inhibitor), AZD6738 (ATR inhibitor), MK8776 (CHK1 inhibitor), AZD1775 (Wee1 inhibitor), MP-470 (Rad51 inhibitor) and genotoxic agents used in DLBCL treatment (Cyclophosphamide, Gemcitabine, Doxorubicin and Etoposide). All drugs induced significant apoptosis (PARP cleavage) and significant inhibition of proliferation (BrdU incorporation) in the different DLBCL cell lines tested ($P<0.05$). CHK1 inhibitor, Wee1 inhibitor, Cyclophosphamide, Gemcitabine and Doxorubicin induced DNA damages monitored by H2AX phosphorylation. Correlating drug response of each compounds with our GEP-based DNA repair scores (Bret et al, *BJH* 2015), we identified a significant correlation between FANC score and response to ATR inhibitor (AZD6738) and HRR score/BER score and response to Etoposide ($P<0.05$). High-risk DLBCL patients identified with GEP-based FANC, HRR and BER scores may benefit from treatment by ATR inhibitors or Etoposide respectively.

Since DNA repair pathways play a role in drug resistance, we sought to identify new synthetic lethal combinations associating IC_{20} of DNA repair targeted treatments with conventional genotoxic agents in DLBCL. Applying a standard threshold of 2 SDs below the IC_{50} of the genotoxic agent alone, a total of 3 synthetic lethal combinations have been identified including cyclophosphamide with CHK1 inhibitor (PF477736) or with ATR inhibitor (AZD6738) and doxorubicin with DNAPK inhibitor (NU7441). These combinations significantly decrease IC_{50} of genotoxic agents ($P<0.05$) and combination indexes (CI) were strongly <1. Furthermore, we identified new potent synergistic combinations (CI <1) including CHK1 inhibitor (PF477736), ATR inhibitor (AZD6738) and ATM inhibitor (KU55933) with etoposide.

Despite overall improvements in the treatment of DLBCL, including the use of rituximab, approximately one-third of patients fail to achieve complete remission or experience relapse. This remains a major cause of morbidity and mortality. The DNA repair scores could be useful to identify high-risk patients and define the best synthetic lethal approach combining DNA repair inhibitors with conventional chemotherapy. These results open new perspectives to improve the treatment of DLBCL patients and provide new strategies to overcome drug resistance.

P315

Development of New Mice Models of Patient Derived Orthotopic Xenograft for Studying Cancer Stem Cells Driving Gastric Cancer Metastasis

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Gastric cancer is the third leading cause of cancer mortality in the world. Recent literature accuses the sub-population of gastric cancer stem cells (CSC) to be at the origin of tumor formation, relapse and metastasis. However, there is a lack of mouse models that allow the dissemination of gastric CSC. To this end, patient-derived xenograft (PDX) cells-encoding luciferase were injected into the stomach wall of NGS mice. Primary tumors and metastases development were followed by bioluminescence imaging. Gastric CSC content was evaluated in primary tumors and distant metastases by analyzing CD44 expression, testing the ability of cells to initiate tumorsphere and to be invasive in collagen-coated transwell. Here we show that eight to ten weeks after orthotopic xenograft, 3 in-house PDX cases among 4 initiated primary tumors and distant metastases into the liver, the lung or the peritoneum cavity. Metastases consisted of more CSC than the primary tumors, and cells are more tumorigenic and invasive, *in vitro*. The development of these preclinical models offers a unique opportunity to decipher the basic mechanism of CSC dissemination and to study the efficiency of new drugs that target invasive gastric CSC, which at the end, may block metastatic spread.

P316

Towards a screening test for cancer by circulating cell-free DNA analysis

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Circulating DNA (cfDNA) has emerged as a potential biomarker, particularly in cancer, and is the subject of extensive studies in translational and clinical research. It presents a great potential in diagnosis, detection of residual disease, monitoring of recurrence and control of therapeutic response, solely through a non-invasive blood draw. A few groups, including ours, are evaluating its potential for screening and the early detection of cancer.

We developed a screening test (MNR: Multi normalized ratio), based on various cfDNA parameters determined by a specific q-PCR based method, on both nuclear and mitochondrial sequences in the supernatant of cell lines in culture, and in the plasma of healthy individuals (n= 132) and patients with colorectal cancer (CRC) (n= 351).

When applied to the supernatant of cell culture, the MNR had a discriminative potential of 100% between normal and cancer cell lines. In plasma samples, the MNR showed a high potential with an AUC of 0.88, an 86% sensitivity and a 76% specificity. When combined to the total nuclear cfDNA concentration, these two parameters together showed a sensitivity of 74% with a 95% specificity for early stage CRC.

Targeting cfDNA sequences of mitochondrial and nuclear origin, without targeting specific genetic alterations, enables the discrimination between cancerous and healthy individuals. The MNR could be a potent biomarker for tumor detection and could potentially be used to screen for asymptomatic or undiagnosed individuals. At this time, more than 1000 individuals have been tested. Work is currently ongoing to enlarge the cohort and apply this test to almost 2000 patients with different types of cancer (breast, pancreas, lung and others) in comparison to healthy individuals.

Posters – Axe 4 “Cancers: enjeux individuels et collectifs”

P401
Incidence et mortalité des cancers en Nouvelle-Aquitaine

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Contexte : En, France, les données d'incidence et de mortalité par cancers sont généralement fournies à l'échelle nationale. Cependant, des estimations à une échelle plus fines sont nécessaires pour évaluer les disparités régionales et territoriales et les besoins spécifiques d'intervention. Dans le cadre d'un partenariat entre les registres de cancers (Francim), SpFrance et l'InCa, une étude a été initiée afin d'estimer l'incidence régionale et départementale des cancers.

Méthode : En Nouvelle-Aquitaine, cette étude concerne les 12 départements pendant la période 2007-2016. Elle a consisté en une estimation des nouveaux cas à partir des données des registres existant dans cette région et des données médico-administratives (PMSI et ALD). La mortalité a été estimée à partir des causes médicales de décès fournies par le CépiDC. La méthodologie d'analyse précise fera l'objet d'une présentation dédiée au cours de ce congrès.

Résultats : Sur la période 2007-2016, environ 37 000 nouveaux cas de cancers sont diagnostiqués en moyenne chaque année en Nouvelle-Aquitaine (dont 56% chez l'homme), soit 10% des nouveaux cas incidents en France métropolitaine. Comme au niveau national, les principales localisations impliquées sont les cancers de la prostate chez l'homme, le sein chez la femme, le poumon et le colon-rectum-anus dans les deux sexes. Le nombre moyen de décès est estimé à 16 300 (période 2007-2014). L'incidence et la mortalité régionales sont comparables à la France métropolitaine. Deux localisations sont beaucoup moins fréquentes qu'au niveau national : le cancer du foie chez l'homme et de l'estomac chez la femme. La mortalité est également plus faible pour les cancers hépatiques et oro-pharyngés chez l'homme et les cancers thyroïdiens et de l'oesophage chez la femme. Malgré cette situation favorable, on observe une sur-incidence des cancers thyroïdiens et une sur-mortalité des cancers du système nerveux central dans la région quel que soit le sexe. Au niveau territorial, les résultats sont plus hétérogènes. Certains départements présentent une situation favorable par rapport à la France métropolitaine alors que d'autres ont des niveaux d'incidence et mortalité relativement plus élevés et pour plusieurs cancers, notamment pour les localisations pulmonaires et colorectales.

Conclusion : Globalement, les estimations de l'incidence et de la mortalité des cancers semblent favorables en Nouvelle-Aquitaine par rapport au niveau national. En effet, les cancers les plus agressifs (lèvre-bouche-pharynx, œsophage, estomac, foie, poumon, pancréas, sein et ovaire) sont soit en sous-incidence ou en sous-mortalité. Cependant on note des disparités de répartition des cas au niveau infrarégional qui seront décrites dans le poster, notamment pour les cancers de la thyroïde et du SNC dont les déterminants seront discutés.

P402

Méthode d'identification d'événements médicaux survenant pendant le suivi de patients atteints d'hémopathies malignes à l'aide des bases médico-administratives : applications à la leucémie myéloïde chronique

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Contexte : L'amélioration constante de la survie de certains cancers entraîne de façon mécanique une augmentation de la prévalence de sujets atteints. Ce phénomène est peu ou pas décrit pour des cancers dont la survie s'est améliorée de façon récente. C'est le cas de la leucémie myéloïde chronique (LMC) qui, avec l'avènement des inhibiteurs de tyrosine kinase à partir de 2001, a vu une augmentation de la survie nette standardisée à 5 ans, passant de 49 % dans les années 1989-1993 à 83 % dans les années 2005-2010.
Objectifs, hypothèses : Les personnes atteintes de LMC ont aujourd'hui une espérance de vie qui s'approche de la population générale. Ces sujets sont à risque de développer des pathologies subséquentes à leur LMC, telles que des 2nd cancers ou des pathologies psychiques, mais aussi des événements toxiques liés aux traitements ou encore des pertes de réponses. Comment alors surveiller et évaluer l'apparition de ces événements secondaire durant le suivi ?
Nous proposons de répondre à ces problématiques par l'étude de la consommation de soins de cette population. Ainsi notre 1er objectif consistera à enrichir les données d'une cohorte issue de registres de cancers avec les données de consommation de soins issue des bases de données médico-administrative de l'assurance maladie française (SNDS). Nous porterons notre intérêt sur plusieurs types d'événements (rechute, toxicité...).
De façon plus générale, ce travail permettra la création d'outils et de méthodes pouvant être utilisés à d'autres populations d'intérêts (croisement de bases de données et identification d'événements intercurrents survenant au cours la prise en charge).

Méthodes : Notre population sont des sujets atteints de LMC diagnostiqués dans une zone couverte par les registres des hémopathies malignes entre 2006 et 2013. Le croisement des données de registre avec les bases médico-administratives sera effectué à partir d'algorithme probabiliste utilisant des données individuelles telles que le lieu où la date de prise en charge, le mois et l'année de naissance. À chacun des sujets de la population d'études seront alors rattachés des informations démographiques et cliniques. Alors, l'identification des pathologies secondaires sera rendue possible par l'analyse de données de consommation de soins à l'aide d'algorithmes adéquats.

Résultats : Entre 2006 et 2013 363, sujets ont pu être identifiés, l'âge médian au diagnostic était de 61,5 ans. Au 1er janvier 2017, 64 (18 %) décès ont été dénombrés.
À leur dernière visite médicale 23 % de la population (n = 85) n'avait pas de réponse optimale au traitement. Ces sujets, par rapport à la population d'étude, étaient plus âgés (médiane : 71,3 ans), peu inclus dans un essai clinique (6 % vs 21 %) et souffrait de comorbidité d'intensité modérée à sévère (40 % vs 20 %). Les caractéristiques de cette sous-population s'opposent aux 55 patients (16 %) qui étaient en stratégie d'arrêt de traitement : ils étaient plus jeunes (médiane : 56,8 ans) préférentiellement inclus dans un essai clinique (24 %) et étaient 3 % à souffrir de comorbidité d'intensité modérée à sévère. Également, 41 % des sujets ont nécessité au moins un changement de ligne de traitement. La raison principale de changement de ligne était liée à un effet toxique (59 %).

Ouverture : Nous décrivions plusieurs profils de sujets possédants différentes prises en charges, mais peu de données longitudinales les précisent. Un nombre de sujets importants ont nécessité un changement de ligne de traitement présumant l'apparition de toxicités ou d'absences de réponse satisfaisante au cours de la prise en charge. Ces éléments peuvent être plus profondément investigués via l'évolution de la consommation de soin. La suite de notre projet consistera à la création d'un outil méthodologique permettant le croisement des bases de données citées précédemment et l'identification et la caractérisation des déterminants de l'apparition de ces événements médicaux.

P403

La prise en charge en sus à l'hôpital de certains médicaments anticancéreux

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CONTEXTE : La prise en charge des patients anti-cancéreux pose la problématique des thérapeutiques particulièrement onéreuses. En 2004 a été mis en place en France, un mode de financement spécifique des hôpitaux : la tarification à l'activité définie notamment à travers des GHS; mais pour certains médicaments ou produits très onéreux, il existe un autre mode de financement appelé « liste en sus », présenté comme permettant à tout hôpital de pouvoir se procurer ces traitements particulièrement coûteux. Les médicaments anticancéreux représentent une part importante de cette liste : 51,1% des dépenses totales en 2016, soit près de 1,7 milliard d'euros facturées en sus des prestations d'hospitalisation de court séjour. Plusieurs rapports et études soulignent non seulement le dynamisme de la croissance de cette liste, mais aussi, la part des médicaments anticancéreux dans cette croissance. Compte tenu de l'impact budgétaire des médicaments anticancéreux sur la liste en sus et de l'évolution du cadre juridique des conditions d'éligibilité visant une gestion transparente de cette liste, nous nous intéressons à la dynamique des inscriptions et des radiations.

MÉTHODES : Les médicaments anticancéreux ont été extraits de la liste établie par le ministère par code ATC. Pour chaque DCI ont été identifiés les indications thérapeutiques, les niveaux du service médical rendu (SMR) et de l'amélioration du service médical rendu (ASMR) disponibles dans la base de données publique des médicaments du Ministère de la Santé. En ce qui concerne les motifs d'inscription et de radiation, nous avons étudié par chaque DCI les arrêtés disponibles sur le site Légifrance jusqu'en septembre 2018.

RÉSULTATS ET DISCUSSION : Parmi la totalité des DCI (n=155) figurant sur la liste en sus, 57 ont été identifiées comme anticancéreuses (50 inscrites et 32 radiées). En 2005, nous retrouvions 35 DCI anticancéreuses inscrites ; 7 DCI s'y sont rajoutées jusqu'en 2010. La même année, les premières radiations (n=5) ont été publiées, conformes aux recommandations du Conseil de l'Hospitalisation- CH (instance chargée de donner son avis au ministre). Malgré l'inaccessibilité des motifs des radiations, nous supposons qu'ils pouvaient être liés à l'arrivée de génériques, comme ce fut le cas en 2011. C'est à partir de 2012 que le CH a mis à disposition toutes les recommandations concernant les inscriptions/radiations et refus d'inscription sur la liste en sus. En 2013, les principaux motifs de radiation (n=3) ont été l'usage marginal en établissement de santé et la baisse des prix rendant le financement compatible avec les tarifs des GHS. Pour la première fois, en 2013/2014, les indications thérapeutiques ont été associées aux avis de la commission de la transparence de la Haute Autorité de Santé pour justifier les cinq inscriptions. Les années 2015/2016 ont été marquées par un nombre important de radiations (n=14) avec des justifications plus robustes, basées notamment sur l'indication thérapeutique associée à l'ASMR, ainsi que sur la fréquence de l'utilisation à l'hôpital. Cette étude de l'évolution des anticancéreux sur la liste en sus suggère une augmentation de la transparence des critères utilisés pour la prise de décision. Par ailleurs, depuis le Décret n° 2016-349 du 24 mars 2016, le contenu de l'arrêté d'inscription/radiation se base directement sur les avis de la commission de la transparence.

INTÉRÊT ET PERSPECTIVES :

- Action 5.8 du Plan cancer 2014-2019 « Faire évoluer les dispositifs de valorisation des médicaments anticancéreux » et Décret n° 2016-349 du 24 mars 2016 : un effort vers la qualité de la gestion de la liste en sus.
- Évaluation de l'influence des lobbyings sur la maintenance des certaines molécules sur la liste en sus, basée sur la lecture des avis de transparence et compte-rendu des réunions à la HAS.
- Estimation de l'impact des incitations aux biosimilaires dans le marché hospitalier sur la radiation des anticancéreux de la liste en sus

P404

Déterminants psychosociaux des trajectoires de fatigue chez des patients suivis en chimiothérapie pour un cancer colorectal métastatique

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Introduction. La fatigue associée au cancer est un symptôme subjectif et envahissant, en lien avec la maladie et ses traitements, qui peut être autant physique qu'émotionnelle et qui impacte considérablement la qualité de vie des patients. Cette étude a deux objectifs fondamentaux : (1) identifier différentes trajectoires de fatigue chez des patients suivis en chimiothérapie pour un cancer colorectal métastatique (2) identifier certains déterminants psychosociaux de ces trajectoires de fatigue.

Méthode. Au total, 169 patients (99 hommes, 70 femmes, âge moyen : 64 ans) ont été évalués sur leur niveau de fatigue dès l'initiation d'un nouveau cycle de chimiothérapie, puis ont été suivis toutes les deux semaines sur une période de 6 mois. Les variables psychosociales telles que l'anxiété, la dépression, le contrôle perçu, les stratégies de coping et le soutien social ont été mesurées dès l'inclusion.

Résultats. Quatre trajectoires de fatigue physique ont été identifiées : 1) une trajectoire de « fatigue intense » (6,51% des patients) qui présente un niveau de fatigue élevée qui se maintient durant les six mois de traitement, 2) une trajectoire de « fatigue moyenne » (48,52%) qui présente un niveau de fatigue moyen et stable au cours du temps, 3) une trajectoire de « fatigue en augmentation » au cours du temps caractérisée par des patients non fatigués à l'inclusion (11,83%), et enfin 4) une trajectoire de patients résilients qui ne rapportent « pas de fatigue » durant les traitements (33,14%). S'il apparait que la fatigue physique et la dépression soit fortement associée, les résultats montrent également qu'une mauvaise adaptation (coping centré sur l'émotion) et peu de contrôle sur l'évolution de la maladie contribuent à l'intensité et l'augmentation de la fatigue au cours du temps. Nous retrouvons également quatre trajectoires de fatigue psychologique mais avec des patterns différents (lassitude intense et en augmentation avec des niveaux élevés dès l'inclusion, lassitude moyenne, et pas de lassitude), qui sont expliquées par les mêmes déterminants psychologiques (coping centré sur le problème et contrôle perçu) mais également par le niveau d'anxiété des patients.

Conclusion. Les résultats de ce travail doctoral ont montré que plusieurs évolutions différentielles caractérisent la fatigue associée au cancer. L'identification de variables transactionnelles dans l'explication d'un tel symptôme permet d'envisager des prises en charge psychosociales adaptées, tournées vers une médecine plus personnalisée.

P405

Résistance à la circulation des savoirs scientifiques : l'effet Warburg en cancérologie

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A l'heure actuelle, les notions d'innovation et de recherche translationnelle sont très fréquemment utilisées. Elles renvoient souvent à la nécessité de contribuer à une circulation de connaissances scientifiques nouvelles dans une logique de valorisation. Pourtant, la nouveauté n'est pas exclusivement liée à des découvertes : des travaux peuvent rester très longtemps ignorés, avant d'être reconnus. Ce phénomène de reconnaissance tardive connaît un regain d'intérêt avec l'analyse en scientométrie des « belles au bois dormant » (ou « sleeping beauties »), et de leur prévalence et importance en histoire et sociologie des sciences (Gorry & Ragouet, 2016 ; El Aichouchi & Gorry, 2018). Cette notion introduite par Van Raan (2004) désigne un article très peu cité pendant une période initiale de plus de 10 ans (période du « sommeil »), qui reçoit au cours des années suivantes beaucoup de citations (période du « réveil ») du fait de son utilisation dans la publication d'un chercheur (le « baiser du Prince »). Le travail présenté se propose d'explorer les dimensions scientométriques, historiques et sociologiques du sommeil et du réveil des travaux d'Otto Warburg.
Ce chercheur allemand du début du XXe siècle a été récompensé du prix Nobel en 1931 « pour sa découverte de la nature et du mode d'action de l'enzyme respiratoire », dans les plantes et les cellules cancéreuses. Il postulera l'hypothèse que les cellules tumorales n'ont pas besoin d'un milieu riche en oxygène pour se développer. Fort de ses résultats, il ira même plus loin dans ses conclusions, et recommandera un régime nutritionnel pour prévenir et guérir du cancer. Ces propos déclencheront alors une forte polémique. Le métabolisme des cellules cancéreuses décrit par Warburg est devenu depuis un éponyme associé au cancer : l'« effet Warburg », et constitue depuis ces dernières années une nouvelle piste thérapeutique.

Sur le plan bibliométrique, l'article fondateur de Warburg à propos du lien entre métabolisme et cancer, publié en 1956 dans la prestigieuse revue Science, remplit les critères de Van Raan. Cet article a traversé un sommeil de près de 45 ans avec moins de 10 citations annuelles avant d'être réveillé à partir de l'année 2006 pour atteindre rapidement en 2016 un pic maximum de 686 citations, marquant la reconnaissance étendue des travaux de Warburg.

Afin de comprendre la dynamique du réveil, nous avons eu recours à une analyse du réseau des citations de ce travail afin d'identifier les « Princes », ces chercheurs ayant contribué significativement à la reconnaissance de l'importance des travaux de Warburg. Cela nous a permis ainsi d'identifier des chercheurs en activité ayant participé à ce réveil, ce afin de mener une série d'entretiens semi-directifs portant, d'une part, sur leur trajectoire et, d'autre part, sur le contexte dans lequel ils ont été amenés à citer le travail d'Otto Warburg, les raisons qui les ont poussés à redécouvrir sa contribution. Les entretiens portent notamment sur la façon dont les chercheurs qui citent le travail de Warburg plus ou moins longtemps après son réveil se représentent cette contribution, sur ce qu'ils considèrent comme ses apports, sur l'importance de ce que l'on appelle maintenant l'« effet Warburg », sur le caractère éventuellement controversé de la thèse et, le cas échéant, sur les échanges que ces chercheurs ont eus avec des cliniciens à propos du travail de Warburg. Le travail proposé ici et qui repose sur des méthodes mixtes vise par conséquent à explorer, au sein de la recherche française, les facteurs explicatifs de la reconnaissance tardive du travail de Warburg et d'amorcer, à partir de cette étude de cas, une exploration des mécanismes qui pourrait expliquer la résistance à la circulation de résultats et savoirs scientifiques et à leur transformation en pratiques diagnostiques et thérapeutiques dans le domaine de la cancérologie.

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Déterminants du recours aux prises en charge palliatives pluridisciplinaires des patients atteints de cancer du sein métastatique de la cohorte ESME-CSM : Analyses préliminaires

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Introduction : Le cancer du sein est la tumeur la plus fréquente chez la femme. Ces cancers peuvent être métastatiques, soit de novo soit après rechute de tumeurs primitives. Les cancers du sein métastatiques (CSM) entraînent des situations palliatives, c'est-à-dire de maladies non guérissables. La survie est alors diminuée et les patients nécessitent souvent une prise en charge pluridisciplinaire pour améliorer leur qualité de vie. Les recommandations préconisent alors d'intégrer précocement les prises en charge palliatives pluridisciplinaires (PECPP) dans le parcours de soins mais peu d'études existent sur le profil des patients qui y ont recours.
Objectif : L'objectif de cette étude était de rechercher les déterminants carcinologiques du recours aux PECPP des patients atteints d'un CSM en tenant compte du risque de décès.
Méthodes : Pour cela, les données de la cohorte de données de vie réelle ESME-CSM ont été utilisées. Cette cohorte inclut des patients de plus de 18 ans, homme ou femme, en primo-traitement d'un CSM dans un des 20 centres de lutte contre le cancer français participants entre 2008 et 2015. Pour cette analyse, un échantillon a été tiré au sort. Le critère de jugement principal était le délai entre le diagnostic du CSM et la première PECPP, codée Z515 par le PMSI (en diagnostic principal ou associé du résumé standardisé des séjours des centres). Les variables explicatives étaient le profil moléculaire (statut hormonal + surexpression protéine HER2), le grade, la réalisation d'une chimiothérapie adjuvante, les antécédents d'autres cancers, le statut de novo ou rechute du CSM, le nombre de sites métastatiques et la présence d'un cancer synchrone. Les rapports de risques (HR) associés aux caractéristiques carcinologiques au diagnostic des CSM ont été estimés à l'aide d'un modèle de Cox cause-spécifique basé sur la fonction de risque cause-spécifique cumulée afin de prendre en compte le risque compétitif de décès. Les HR ont été estimés ajustés sur l'âge, le centre, la période.
Résultats : La population d'analyse comptait 2490 patients et était représentative de la population ESME globale. L'âge médian aux diagnostics de tumeur primitive et du CSM était respectivement de 54 et 61 ans. Un tiers des tumeurs étaient de grade élevé, 15% de profil moléculaire triple négatif et près de la moitié avaient été traitées par une chimiothérapie adjuvante. Un quart des CSM étaient métastatiques d'emblée dont 42% avaient au moins deux sites métastatiques. Près de 40% des patients ont eu une PECPP. Dans le sous-groupe des patients décédés, 61% ont eu une PECPP dont 77% dans les trois derniers mois de vie. Le délai médian de PECPP après diagnostic était de 1,7 ans. La médiane de survie était de 3,7 ans et le suivi médian de 3,8 ans. En analyse multivariée, les caractéristiques de mauvais pronostic (profil moléculaire triple négatif, grade élevé, chimiothérapie adjuvante, rechute métastatique) étaient associées à un risque plus élevé de recours aux PECPP. Concernant le profil triple négatif, l'association était statistiquement significative uniquement chez les patients sans antécédent d'autre cancer, avec un HR plus important chez les plus jeunes. Enfin, en cas de sites métastatiques multiples, le risque de recours aux PECPP était plus élevé dans les premières années après le diagnostic de CSM.
Conclusion : Une maladie cancéreuse de mauvais pronostic au diagnostic était associée à une PECPP plus fréquente. Néanmoins, malgré les recommandations, ces prises en charge sont intervenues tardivement. Ces résultats sont transposables à une population légèrement plus jeune que la population française avec cancer du sein. Ils restent à confirmer sur l'ensemble de la cohorte ESME-CSM. D'autres analyses pourraient préciser les déterminants du non recours précoce aux prises en charge palliatives pluridisciplinaires, du risque de décès avec ou sans PECPP ou les facteurs spécifiques au sous-groupe de patients avec CSM d'emblée.

P407

Estimations régionales et départementales de l'incidence et de la mortalité en Occitanie

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Contexte : L'incidence et la mortalité par cancers sont des indicateurs épidémiologiques indispensables à connaitre à l'échelon régional et départemental pour la mise en œuvre de politiques de santé. Cette étude réalisée, dans le cadre d'un partenariat Francim/HCL/SpFrance/INCa, et analysée localement en partenariat avec les registres du Tarn et de l'Hérault, vise à produire des indicateurs d'incidence et de mortalité pour 24 localisations cancéreuses sur la période 2007-2016 dans la région Occitanie et dans les 13 départements qui la constituent.

Méthodologie : Les prédictions régionales et départementales d'incidence sont basées sur une modélisation du rapport entre les données médico-administratives (ALD et/ou PMSI) et les données d'incidence observées dans les registres du réseau Francim. Les données de mortalité sont issues du CépiDc. La méthodologie précise de cette étude fait l'objet d'une présentation spécifique lors de ce congrès.

Résultats : Au total 33 487 nouveaux cas sont diagnostiqués chaque année dans la région (18 664 cas masculins et 14 823 cas féminins) et on enregistre parallèlement 14 165 décès par cancer chaque année (8 232 chez l'homme et 5 933 chez la femme). La région Occitanie est comparable à la France métropolitaine en termes d'incidence et de mortalité pour toutes les localisations cancéreuses confondues, avec néanmoins une faible sous-incidence de 4 % chez l'homme et de 2 % chez la femme, ainsi qu'une sous-mortalité encore plus marquée, de 8 % chez l'homme et de 4 % chez la femme.

A l'échelle régionale chez l'homme, une sous-incidence par rapport à la moyenne française s'observe pour 4 cancers liés à la consommation d'alcool et de tabac (lèvre-bouche-pharynx, œsophage, estomac, foie) et pour le cancer de la prostate. Chez la femme il existe une sous-incidence pour les cancers de l'œsophage, de l'estomac, du sein et de l'ovaire. Quelques cancers sont toutefois en sur-incidence dans la région, tels que le cancer du poumon, du col utérin et de la vessie chez la femme, ainsi que les cancers de la vessie, du rein, du système nerveux central et de la thyroïde chez l'homme.

Pour presque tous les cancers, la mortalité en Occitanie est inférieure à la moyenne nationale. Seul le cancer du poumon chez la femme présente une surmortalité de 4 %.

Au niveau départemental, nous enregistrons deux grandes particularités en Occitanie :

- Sur l'arc méditerranéen il existe une sur-incidence de certains cancers associés à des facteurs de risque connus et fortement prévalant dans cette zone géographique (tabac, alcool, précarité). Nous observons ainsi une sur-incidence des cancers du poumon chez la femme dans les 4 départements bordés par la mer Méditerranée par rapport à la moyenne nationale: le Gard, l'Hérault, l'Aude et les Pyrénées Orientales avec une surmortalité dans les 3 derniers départements. Dans l'Aude et les Pyrénées Orientales, il existe aussi une sur-incidence des cancers de la vessie chez l'homme. Dans le Gard et l'Hérault les cancers du col de l'utérus sont de 15 % supérieurs à la moyenne nationale.

Nous notons par ailleurs que les 4 départements les plus au Nord-Ouest de la région (l'Aveyron, le Lot, le Tarn et le Tarn-et-Garonne) ont plusieurs localisations avec des taux inférieurs à la moyenne nationale et aucune sur-incidence ou surmortalité.

- Enfin une sur-incidence et une surmortalité des tumeurs du système nerveux central sont observées dans le Gers et les Hautes-Pyrénées. Ces deux départements forment avec les Pyrénées-Atlantiques et les Landes une zone de sur-incidence et de surmortalité pour ces tumeurs, méconnue à ce jour.

Conclusion : même si l'on dénombre de nombreux cas de cancers du fait de la taille de sa population, l'Occitanie est une région relativement protégée par rapport au reste de la France. Toutefois, quelques particularités départementales en termes de prévalence de facteurs de risque, de sur-incidence et de surmortalité, justifient des actions de prévention ciblées.

P408

Exhaustivité, qualité et déterminants de passage en réunions de concertation pluridisciplinaire des cancers dans l'Hérault

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Introduction

Les RCP ont été initiées par le plan cancer 2003-2007 qui préconisait de faire bénéficier à 100% les nouveaux patients atteints de cancers d'une concertation pluridisciplinaire autour de leur dossier. Le registre des tumeurs de l'Hérault recueille de manière exhaustive tous les cancers du département. L'objectif principal de ce projet était d'évaluer l'exhaustivité et les déterminants du passage en RCP des patients atteints d'un cancer primitif.

Matériel et méthodes

Tous les cancers survenus chez les patients résidant dans l'Hérault et diagnostiqués entre 2009 et 2014 ont été croisés avec les données RCP (disponibles au sein du réseau OncoLR) . Le taux d'exhaustivité a été calculé en divisant les cas de cancer ayant bénéficié d'une RCP par l'ensemble des cas du registre. Nous avons analysé le lien entre le passage en RCP et différents facteurs disponibles dans cette base. L'adéquation entre le traitement préconisé en RCP et celui effectivement réalisé a été analysée.

Résultats

Sur l'ensemble des cancers diagnostiqués entre 2009 et 2014, 58,5% ont bénéficié d'un passage en RCP. Le taux de passage en RCP a significativement augmenté en fonction des années de diagnostic. 47,3% des cancers diagnostiqués en 2009 ont bénéficié d'une RCP contre 62,1% en 2014. La présentation en RCP est moins fréquentepour les cancers survenus: chez les femmes, les moins de 39 ans et plus de 75 ans et pour les tumeurs in-situ. Le passage en RCP est plus fréquent pour les cancers de la thyroide et du sein. Des disparités ont été relevées entre le traitement recommandé et celui réellement réalisé en fonction du type de traitrement et de la topographie de la tumeur.

Conclusion

Le taux de passage en RCP augmente au cours du temps mais reste éloigné de celui fixé par le plan cancer. L'âge élevé reste un facteur de non présentation en RCP malgré les recommandations du plan pour la promotion d'une meilleure prise en charge du sujet âgé.

P409

Cancers colorectaux des personnes déficientes intellectuelles : fréquence augmentée, dépistage mal suivi et retards diagnostiques

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Les personnes avec déficience intellectuelle (DI) qui ont globalement une incidence similaire des cancers à celle dans la population générale montrent une répartition particulière des cancers. Les tumeurs digestives sont en excès, et plus particulièrement les cancers du côlon et du rectum. Les études épidémiologiques sur l'incidence du cancer (Patja et al 2001, Sullivan et al 2004) et sur la mortalité par cancer (Lauer 2016, Glover et al 2017), ainsi que l'expérience des institutions (Cooke 1997, Bourgarel et al 2015) abritant des personnes déficientes intellectuelles montrent une plus grande fréquence de ces tumeurs en comparaison de la population générale. Des cas cliniques rapportés dans la littérature indiquent des patients DI dont la tumeur colique ou rectale a été diagnostiquée tardivement, parfois après le décès. Les facteurs de risque des cancers du côlon et du rectum sont plus importants chez les personnes avec DI puisqu'elles sont plus à risque d'être en surpoids ou obèses (30%), puisqu'elles sont plus souvent sédentaires (60%) et que leur alimentation peut être mal équilibrée (17%). Cependant les études sur le dépistage du cancer colorectal dans différents pays montrent systématiquement une participation faible des personnes DI (de 18.5 à 34%), toujours inférieure à celle dans la population générale. Les symptômes de cancer colorectal sont semblables aux symptômes chez les personnes sans handicap mental : rectorragies, douleurs abdominales, perte de poids, et sont souvent mal repérés.

Comme il n'existe pas de données publiées sur les caractéristiques des cancers colorectaux chez les personnes avec DI, nous avons utilisé l'étude CHAID (Cancer-Hérault-Adults-Intellectual-Disability) pour évaluer ces caractères sur une population bien délimitée géographiquement et dans le temps, en utilisant les données du Registre des Tumeurs de l'Hérault. Parmi 10 cancers du côlon (7) et du rectum (3) diagnostiqués chez des personnes DI au cours des années 2008-2018 l'âge moyen au diagnostic était de 63,3 ans contre 72,5 ans dans la population générale. Il est important de noter que 9/10 (90%) de ces tumeurs avaient été découvertes à un stade avancé (3-4) au lieu d'un stade plus précoce (1-2), alors que seulement 47% des mêmes cancers dans la population générale étaient à un stade avancé au diagnostic. Trois patientes ont souffert d'une autre tumeur avant (carcinome du sein, carcinome de la thyroïde), ou après, (tumeur cérébrale) la découverte de leur carcinome colique ou rectal.

L'effectif de cette étude est petit, cependant c'est la seule et donc la plus grande série rapportée chez les personnes DI actuellement. Elle montre que la participation au dépistage est moins bonne et que les diagnostics sont effectués plus tardivement que dans la population générale. Comme les cancers colorectaux sont plus fréquents chez ces personnes que dans la population générale, il convient de développer les actions de prévention. Comme les personnes avec déficiences intellectuelles manifestent peu et de façon particulière leurs symptômes, des efforts importants doivent être faits pour réduire les délais diagnostiques du cancer colique en accroissant la participation au dépistage et en prêtant une particulière attention aux symptômes digestifs chez les personnes avec déficience intellectuelle.

Posters – Axis 5 “Health Technologies”

P501

Development of versatile biological models to study nanodevices biomedical potential

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The development of personalized and non-invasive therapies based on new nanodevices is a major challenge in medecine. The design of multifunctional nanomaterials with controlled physico-chemical properties thanks to the chemistry expertise allow to the biologists to demonstrate their nanomaterials biomedical potential.

In this context, we studied different nanomaterials with two therapeutic applications concerning inflammation or cancer. Nanoparticles can transport important quantity of therapeutic bioactive molecules to precise target in the body (e.g. tumor or inflammation site) in order to have a higher treatment efficacy and significantly decrease side effects. Firstly, we analyzed the biological efficiency of ionosilicas nanoparticles. These are original Periodic Mesoporous Organosilica (PMO) based materials containing covalently anchored ionic groups. These ionosilicas nanoparticles were used to load diclofenac, an anionic non-steroidal anti-inflammatory drug, which has been used to perform in vitro / in vivo and biodistribution investigations in order to demonstrate their biocompatibility and their potential to be used as drug carrier vehicles to treat inflammation.

Moreover, the nanomaterials can be employed in the cancer treatment. Indeed, nanoscience has grown considerably in the fight against cancer with nanoparticles of different categories and activated with different stimuli as Mn2+-doped Prussian blue nanoparticles. They are many advantages as their flexible molecule-based structure, adjustable composition, tunable physico-chemical properties, porosity, high stability in aqueous media and biocompatibility. Moreover, Prussian blue has been approved by the Food and Drug Administration for human. For these reasons Prussian blue nanoparticles have a huge biomedical potential. We have demonstrated for the first time that Mn2+-doped Prussian blue nanoparticles act as efficient agents for photothermal therapy under two-photon excitation and induce an almost eradication of malignant cells.

Finally, in order to go further in the biomedical proof of concept of therapeutic nanodevices, we are currently developing an animal model as Danio rerio (zebrafish) to study different diseases. As an example, we have already implanted fluorescent human cancer cells in zebrafish larvae in order to establish an easily detectable tumor xenograft. Then, we have intravenously injected soluble photosensitizers in zebrafish and irradiated the tumor site during few seconds with a pulsed laser. The strong and rapid decrease in tumor size let us imagine to develop such model to test the biomedical potential of different nanoparticles.

P502

Towards multifunctional peptide-based nanoparticles for cell-delivery of siRNAs in tumors

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Small interfering RNAs (siRNAs) present a strong therapeutic potential because of their ability to inhibit specifically the expression of any desired protein. However, siRNAs show a very weak propensity to cross the plasma membrane on their own. We recently developed a series of new cell-penetrating peptides able to form stable peptide-based nanoparticles (PBNs) once incubated with a given ratio of siRNA.1 With regard to future in vivo applications, we also studied recently the influence of the polyethylene glycol (PEG) grafting onto the PBNs on their in vitro and in vivo siRNA delivery properties.2 We also planed to address specifically PBNs to tumor sites upon the incorporation of peptide-targeting sequences on PBNs. Thanks to strategies offered by peptide chemistry, we designed, prepared and studied new PBNs made of several different peptides blocks (siRNA complexation, siRNA cellular transfer, targeting and prolonged blood-circulation) in order to improve significantly the cell-specific delivery of siRNAs.

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P503

HSP70 inhibition and Magnetic Intra-Lysosomal Hyperthermia: a promising synergistic combination for cancer therapy.

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The cholecystokinin receptor (CCK2R) is over-expressed in a collection of human endocrine tumors. Our team showed that this receptor is massively internalized and directed by its ligand to the lysosomes.

In this context, we developed a Magnetic Intra-Lysosomal Hyperthermia (MILH) approach, which occurs without perceptible temperature rise. We showed that minute amounts of iron oxide magnetic nanoparticles targeting the gastrin receptor (CCK2R) are internalized by cancer cells through CCK2R-dependent physiological process, accumulated into their lysosomes and kill cancer cells, upon a high frequency alternating magnetic field (AMF) application, through a lysosomal cell death. However, since MILH induced cell death by 20-30%, we hypothesize that certain mechanisms of resistance could inhibit this effect. Interestingly, Heat Shock Protein 70 (HSP70) is present in lysosomes of cancer cells but is rarely found in lysosomes of normal cells, and its over-expression in cancers is correlated with poor prognosis and treatment resistance. Additionally, in cancer cells, HSP70 has been described as a guardian of lysosomal integrity and its downregulation or inhibition leads to the destabilisation of lysosomal membranes and induces lysosomal membrane permeabilization (LMP), thereby promoting cancer cell death by activating an apoptotic signaling pathway.

Based on these results, we hypothesized that HSP70 inhibition could enhance the efficacy of MILH in cancer cells. First, we showed that HSP70 overexpression prevent cells against LMP and cell death induced by MILH. Then, the effect of HSP70 inhibition was evaluated on cell death and LMP in combination with MILH using a subletal dose of 2-phenylethynesulfonamide (PES or Pifithrin-µ), an HSP70 specific inhibitor. Our results show that combination of MILH with PES increases the efficiency of eradication of cancer cells with synergism. Indeed, PES/MILH combined treatment kills 51% of cancer cells, whereas MILH eradicates 20% of cancer cells and sublethal dose of PES does not affect cell viability. Furthermore, this result was associated with an increase in LMP and PES treatment potentiates the activation of an original and non-apoptotic cell death mechanism induced by MILH, which depends on Caspase-1 but not on apoptotic Caspase-3. Currently, we are deciphering the molecular and cellular mechanism of the cell death induced by this combined treatment.

All together, these results show that HSP70 exerts a protective role in MILH-induced LMP and cell death and emphasize the benefit of targeting HSP70 for combinatorial treatments, with the prospects of overcoming treatment failure and therapeutic resistance.

P504

Fluorescent soft molecular nanoparticles as nanocarrier for hydrophobic drugs. Towards novel prodrugs for glioblastoma chemotherapy

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Nanovectorization of anticancer agents is a recent therapeutic strategy to improve drug targeting and delivery of conventional chemotherapy. In particular, several classes of nanoparticles have been explored in recent years as nanocarriers of cytotoxic drugs. Among them Paclitaxel (PTX) is one of the most useful and effective antineoplastic agents for treatment of many solid cancers. Glioblastoma multiforme is the most frequent and invasive primary tumor of the central nervous system. Despite current treatments which combine surgery, radio- and chemotherapy, the median survival is about 15 months. Furthermore, most of drugs are not able to cross the blood-brain barrier (BBB), which is one of the major difficulties in glioblastoma treatment. Hence, novel therapeutic approaches are required and paclitaxel-bound nanoparticles could offer a new perspective to treat brain tumors.

In this context, we have developed soft organic nanoparticles which combine high solubility in aqueous media, remarkable fluorescence properties, biocompatibility and which present a high density of surface groups for further immobilization and masking of PTX by covalent grafting. We have selected fluorescent carbon-based nanodots (FCNDs) as nanocarriers. FCNDs can be prepared using simple pyrolysis or hydrothermal treatments from small, accessible and usually biosourced molecular precursors [1]. By optimizing the synthesis protocol, we were able to prepare soft, small nanoparticles (DTEM < 30 nm) which show intense blue fluorescence and high solubility in water. In addition, by tuning the experimental conditions, high fluorescence quantum yield and high two-photon absorptivity in the NIR region could be achieved, allowing for two-photon imaging of internalization FCNDs in cells [2]. The safety and internalization of the free FCNDs was demonstrated on different cell lines, making them suitable candidate for use as drug delivery systems [2]. With this aim in mind, post-functionalization andactivation of the surface of these nanoparticles was successfully achieved leading to high density of reactive groups (-NH2 and -CO2H) which then permitted subsequent grafting of PTX leading to FCNDs@PTX which retain excellent solubility and reasonable stability in water [2]. The antitumoral activity of the FCNDs@PTX was tested in vitro on 2D and 3D culture. On different cell lines, FCNDs@PTX shows similar anticancer activity as PTX alone [2]. The pharmacological effects of PTX on microtubules were observed by immunofluorescence experiments (presence of bundles, pseudo-asters and mitotic block), which confirms that PTX is released from its binding to FCNDs in active form after cell internalization, thanks to the chemical nature of the surface functionalization [2]. These results demonstrate that hydrophilic FCNDs@PTX are promising as prodrug formulation to improve paclitaxel therapeutic index. In addition, our FCNDs offer interesting promises as theranostics nanotools thanks to their versatile surface functionalization, tunable luminescence properties and high water solubility.

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P505

Combination of photodynamic therapy and gene silencing in cancer cells with porphyrin-siRNA complex.

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To overcome the limitations of single therapy, photodynamic therapy (PDT) has been combined with gene silencing. To achieve this dual therapy, we explored the supramolecular self-assembly of a cationic porphyrin (H2PG) with siRNA with the hypothesis that porphyrin aggregates should be capable of complexing siRNA through multivalent interactions and thus contribute to its intracellular delivery.

First, we have studied the PDT efficiency of H2PG porphyrin alone. For this, human breast cancer cell line (MDA-MB-231) was incubated with this porphyrin. The irradiation of culture cells treated with H2PG porphyrin at 405 nm wavelength induced a strong cell death that is not the case when cells are treated but not irradiated and when cells are only irradiated without any treatment. This demonstrated the specificity of PDT mechanism induced by irradiation of H2PG porphyrin.

Secondly, the ability of H2PG porphyrin to complex nucleic acids such as siRNA-Luc (directed against luciferase) was analysed.

By using agarose gel-shift electrophoresis, we have demonstrated the formation of H2PG-siRNA complexes from N/P* ratio of 5. The biological activity of this complex was studied on MDA-MB-231 genetically modified to express luciferase. In the absence of irradiation, MDA-MB-231 cancer cells incubated with the complex did not exhibit any cytotoxicity. Interestingly, the siRNA-Luc complexed to the H2PG porphyrin induced an inhibition of the luciferase activity, without any irradiation, thereby demonstrating that H2PG acts as a delivery vehicle for siRNA. In summary, the irradiation of MDA-MB-231 incubated with the H2PG porphyrin-siRNA-Luc complex generated (i) photo-induced cell death and (ii) luminescence decrease.

In conclusion, this study shows that dual therapy (PDT and gene silencing) can be achieved using a small molecule self-assembly and may thus represent an improvement for cancer therapies.

*: N: positive charges of porphyrin and P: negative charges of siRNA

P506

WRAP & Roll: Understanding the internalization mechanism of siRNA-loaded WRAP nanoparticles.

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Nanotechnology has emerged as a major field in academic research with direct impact on human health. Among the different nanomaterials used to vectorize therapeutic agents, peptide-based nanoparticles (PBNs) have gained popularity in recent years due to its simplicity and programmability [Boisguerin 2015]. The PBN efficiency for the cellular delivery of therapeutic molecules has been several times highlighted during the last two decades with an impressive number of examples [Jafari 2015, Lehto 2016] including those designed in our group [Konate 2016, Vaissière 2017, Aldrian 2017].

Recently, we have conceived a new family of amphipathic peptides called **WRAP** (**W**- and **R**-rich**A**mphipathic **P**eptides). WRAP peptides show an out-standing ability to form immediately PBNs when mixed with siRNAs and to trigger specific and efficient desired gene knockdown.

It is nowadays largely admitted in the scientific community, that two major mechanisms are employed by cell penetrating peptides or PBNs: direct translocation or endocytosis. Here, we depict the internalization mechanism of our siRNA-loaded WRAP nanoparticles (NP). First, we evaluate the knock-down efficacy of the WRAP NP under energy-depletion and in the presence of different endocytosis inhibitors. Results are confirmed by co-localization experiments with endocytosis markers. Finally, we use different scavenger receptor (SCARA) inhibitors to analyze their effect of the silencing property of the WRAP NPs. All these results allow us to conclude that our NPs are internalized via direct cellular translocation independently from any endocytosis- or SCARA-dependent pathway.

Understanding the mechanisms of WRAP NPs internalization represents a complementary approach for the rational design of efficient NPs with improved cell specific delivery.

P507

Glioblastoma Cancer Stem like Cells discrimination by UHF-Dielectrophoresis Crossover Frequency

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Cancer Stem Cells or CSCs appear as major biological and therapeutic targets, in particular for Glioblastoma (GBM). Heterogeneity of tumor cell populations, leads to optimize characterization and sorting methods.

Actually, analysis are based on targeting of a set of biological markers, which are efficiently used to validate the stemness properties. Besides the biological properties, biophysical properties of CSCs are expected to be a potential way to discriminate and sort CSC populations.

Our data summarize first's results glioblastoma cell lines' characterization; measuring their crossover frequencies by dielectrophoresis (DEP) technics in the UHF frequency range (above 50 MHz). We cultured GBM cell lines following different conditions, in order to achieve an enrichment of cancer stem cells (CSCs). Based on DEP electrokinetic method, CSCs were discriminated from the differentiated cells.

In this study, we used microfluidic lab-on-chip systems implemented on Bipolar-Complementary Oxide Semiconductor (BiCMOS) technology, allowing single cell handling and analysis. Based on measurements of their own intracellular specificities, the enriched CSCs population, cultured in dedicated define medium, have shown clear differences of DEP crossover frequency signatures of CSC enriched populations compared to differentiated cells cultured in normal medium.

That demonstrates the concept and validates the technique efficiency for CSCs discrimination, confirming a high potential of the lab-on-chip (LOC) platform in the diagnosis and development of new glioblastoma therapeutics.

P508
New peptide-based nanoparticles to "Wrap and Roll" siRNA into cells

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Although chemotherapies constitute the main treatment for most cancers, they are often limited by their lack of selectivity, rapid clearance and important side effects. In this context, new therapeutic agents such as small interfering RNAs (siRNAs) [Burnett 2012] specifically targeting molecular abnormalities of certain cancers have been developed. Although these molecules have great potential, their use remains limited by their low metabolic stability, cell selectivity and their inability to cross biological barriers. Therefore identification of tools enabling their intracellular delivery has become the keystone of future therapeutic agents.

The peptide-based nanoparticles (PBNs) have been extensively developed for intracellular transport of molecules. In our laboratory several PBNs have been developed for the specific transfer of siRNA [Konate 2016, Vaissière 2017, Aldrian 2017]. Moreover, the flexible nature of these nanoparticles can serve as a basis for functionalization allowing their specific targeting to certain organs or tissues.

Recently, we designed a new family of amphipathic peptides, called WRAP (for W- and R- rich Amphipathic Peptide), in order to obtain PBNs for in vivo applications. WRAP were able to self-assemble with siRNA in homogeneous nanoparticles smaller than 100 nm as characterized by biophysical methods. A rapid luciferase screening was used to determine the best nanoparticle formulations and transfection conditions in vitro before validating the siRNA interference efficiency on specific endogenous proteins by Western blot. The knock-down efficiency induced by PBNs was characterized on different cell lines and also after several repeated doses. A significant gene silencing (90 %) was usually obtained with a 20 nM siRNA concentration. In addition, analysis of the cellular internalization of PBNs indicated a rapid siRNA delivery process, independent on the main endocytosis pathways. Finally a first in vivo investigation revealed an effective knock down in a mouse xenograft model and multi-grafted PBNs (e.g. PEGylation or targeting sequence) were also evaluated.

Considering datas collected with WRAP peptides, our studies clearly show the importance of modular drug delivery systems as new therapeutic approach.

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P509

Targeting Cancer-associated fibroblasts by magnetic nanoparticles and magnetic field exposure to disrupt tumor microenvironment

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Efficacy of anti-cancer treatments is limited by low drug concentration at the tumor site and development of resistance to treatments. Cancer progression is not only determined by the genotype of cancer cells, but also by their interactions with tumor microenvironment. The extracellular matrix (ECM) constitutes a barrier limiting the penetration of chemotherapeutic agents into the tumor; Cancer-associated fibroblasts (CAFs) secrete collagen increasing ECM density and factors promoting tumor growth and resistance acquisition of cancer cells.

Thus, CAFs eradication constitutes an interesting strategy to inhibit cancer progression. In this context, the development of targeted magnetic nanoparticles (MNPs), known to release thermal energy or mechanical forces when exposed to a high or low frequency alternating magnetic field (AMF) respectively, represents a real new opportunity. As a proof-of-concept, we previously showed that MNPs targeting the gastrin receptor (CCK2R) are internalized by tumoral cells, accumulated into their lysosomes and killed tumoral cells upon a high frequency AMF application through lysosomal cell death. We take advantage of these results to propose new therapeutic solutions to overcome the physical barrier and decrease the resistance to conventional anti-cancer treatments. The main objectives were to develop MNPs targeting the pancreatic CAFs and to evaluate the effect of local release of thermal energy or mechanical forces on their survival. Recently, the CCK2R was shown to be expressed on pancreatic CAFs and its inhibition decrease collagen secretion.

We synthesized MNPs decorated with gastrin to target CAFs (Gastrin-MNPs). We have analyzed Gastrin-MNPs binding, internalization on pancreatic CAFs and studied the effects of a high or low frequency AMF application. Gastrin-MNPs bound and internalized in CAFs. High and low frequency AMF application both induced the death of 30% of CAFs-containing Gastrin-MNPs. We currently study the mechanism involved in CAF death. This project will establish the proof-of-concept that targeted MNPs can eradicate CAFs and disrupt tumor microenvironment.

P510

Combined treatments of magnetic intra-lysosomal hyperthermia with Doxorubicin promotes synergistic anti-tumoral activity

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Cancer is a leading cause of death with millions of new people diagnosed with cancer every year. The conventional cancer therapies include surgery, radiotherapy and/or chemotherapy. Doxorubicin belongs to the anthracylin chemotherapeutic drugs and is one of the commonly used anticancer drugs. For decades, Doxorubicin is a cytotoxic drug used for the treatment of many cancer types including breast, lung, stomach, bone cancers and endocrine tumors. However, one major difficulty in anti-cancer therapy is the multidrug resistance that appears during treatments. Moreover, Doxorubicin may be hampered by its significant dose-related adverse effects, including cardiotoxicity, myelosuppression, gastrointestinal distress, alopecia, stomatitis… which lead to dose-limited of Doxorubicin use. Hyperthermia has been recently introduced as an adjuvant therapy for cancer and presents promising opportunities to treat cancers, especially in combination with chemotherapy or radiotherapy. Indeed, many clinical experiments have demonstrated that the addition of hyperthermia to radiotherapy or chemotherapy significantly improves tumor control and patient survival rates. Among hyperthermia methods, magnetic hyperthermia is a promising way for site-specific heating that reach deeper tissue, in which magnetic nanoparticles (MNPs) play an important role to relay the externally delivered high frequency alternating magnetic field (AMF). Indeed, direct injection of MNPs into solid tumors, followed by AMF exposure, has been shown to induce tumor regression. However, conventional hyperthermia methods including standard magnetic hyperthermia do not thermally discriminate between the target and the surrounding normal tissues, and this non-selective tissue heating can lead to side effects.

In this context, nanotherapy based on Magnetic Intra-Lysosomal Hyperthermia (MILH) generated by MNPs that are grafted with ligands of receptors overexpressed in tumors appears to be a very promising therapeutic option. Strikingly, in such approach, no perceptible temperature rise in the cell medium occurred during AMF exposure. Thus, MILH differs from standard magnetic hyperthermia whereby tumor eradication is achieved with large doses of MNPs which cause a temperature elevation of the whole tumor. As a proof-of-concept, we previously showed that minute amounts of iron oxide MNPs (Gastrin-MNPs) targeting the gastrin receptor (CCK2R) are internalized by tumoral cells through a CCK2R-dependent physiological process, accumulated into their lysosomes and killed tumoral cells upon AMF application through lysosomal cell death [1,2,3]. The aim of this study was to analyze whether combination of MILH with chemotherapy could increase the efficiency of eradication of cancer cells. Endocrine tumoral cells were incubated with Gastrin-MNPs, treated with Doxorubicin, the commonly used drug to treat endocrine tumors, and exposed to AMF. The impact of combined treatments was analyzed on cell viability and cell death, comparatively to individual treatments. Mechanisms of cell death were also studied following the different treatments. Here, we report that combination of MILH with Doxorubicin increased the efficiency of eradication of endocrine tumor cells with synergism or additivity, according to Doxorubicin concentrations used. We demonstrated that these two treatments activated two different cell death pathways that were respectively dependent on Caspase-1 and Caspase-3 activation.

Finally, these findings suggest that MILH can decrease required dose of chemotherapy drugs such as Doxorubicin and thereby reduce their side effect.

P511
Impact of mitotic arrest on breast cancer cells clustering

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Metastasis is the leading cause of cancer mortality. Recently, it has been shown that clusters of circulating tumor cells (CTCs) have a higher metastatic potential compared to single CTCs. Indeed, the presence of CTC clusters in patients correlates with poor prognosis. Misregulation of cell cycle progression, under the control of cyclin dependent kinases (CDKs), is one of the hallmarks of tumor cells and several pharmacological anti-tumor therapies are based on targeting cell cycle. However, the relationship between the cell cycle progression and tumor cell clustering is not yet elucidated.

In order to study the mechanisms that control and regulate cluster formation, we developed an original live microscopy-based methodology allowing quantifying anchorage-independent clustering of tumor cells. Using this assay, we investigated the effect of mitotic arrest on breast cancer cell aggregation, independently of cell substrate adhesion. The MCF-7 cells were treated for 20 hours with nocodazole (200ng/ml), then for 2 hours with the proteasome inhibitor MG-132 (25µM) to arrest cells in metaphase. We showed that, metaphase-arrested MCF-7 cells have a decreased ability to form clusters. We then analysed at a low cell density, thanks to dedicated micro-devices and time-lapse microscopy, the dynamic of tumor cell clustering by using MCF-7 cells stably expressing the Life Act-mCherry protein. This strategy allowed showing the formation of highly dynamic membrane protrusions in MCF-7 cells in anchorage-independent clustering conditions. These protrusions are absent in metaphase-arrested cells which also lead to the formation of loose clusters.

These results suggest that pharmacological treatments that alter progression through mitosis affect the ability of cells to form cluster, thereby potentially modulating their metastatic potential.

P512
Exploring Multi-Cellular Tumor Spheroids in Virtual Reality

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Goal: Exploring cells inner dynamics of 3D biological models is of central interest. It is particularly the case for Multi Cellular Tumor Spheroids (MCTS) to design new efficient therapeutic protocols. However, exploring them*in vitro* is technically challenging. Nowadays, computer science can help by providing increasingly realistic digital models and accessible means of visualization and interaction, especially also relying on virtual reality (VR) approaches.

Experimental Design: To this end, we have developed a 3D *in silico* model of the growth of *in vitro* MCTS. The model of the cell cycle considers and offers the possibility to manipulate four checkpoints: "R", the restriction point in the G1 phase, the G1/S and G2/M checkpoints, and the intra-mitotic (iM) checkpoint in the M phase. In this model, we used Bernoulli processes, a mathematical tool that allows a discretization of time and the regulation of the cell cycle advancement speed based on sequences of probabilistic draws. Intercellular variability is modelled by randomly choosing the duration of each phase following a log-normal law [Sherer et al., Biotechnol BioEng 2008] every time a new cell is created. The representation of the cell cycle we used is generic enough to integrate additional external events. Under optimal condition, draw probabilities are all equal to one, leading to cell cycling as fast as they can. Taking into consideration environmental modifications requires modifying the draw probabilities accordingly. Cells are interacting in a 3D virtual environment based on a mass-spring-damper system. Oxygen gradients are simulated using finite differences. Using a diffusion and consumption model of oxygen proposed by [Grimes et al., J. Royal Soc. 2014] applied to experimental data based on proliferation marker (i.e. EdU), we were able to correlate cell cycle elongation in depth to oxygen concentration decay. This allows to calculate during the simulation the elongation of the cell cycle of the cells in the MCTS. To improve our understanding of the inner dynamics of the system, we have developed a VR set up in which the simulated growing MCTS can be visualized in real-time. We paid particular attention to the visualization of the virtual cells. We have simulated the effects on cell cycle dynamics, on proliferation markers (i.*e.* EdU) or hypoxia markers (*i.e.*pimonidazole) to evaluate the realism of the virtual MCTS based on data biologists are used to analyze. Our markers are calculated for each time step, therefore reflecting model changes ad-hoc, during the simulation. As the simulation provides access to additional data, users can also color cells with regards to their cell cycle duration, the oxygen concentration, etc. Finally, the VR room (it is a room-scale simulation relying on HTC's Vive device) also contains a virtual board for plotting data such as the population size, phase repartition, or FACS analysis. Using VR allows users to naturally interact with the visualized MCTS, for instance by cutting it to explore its inner structures. Users can also easily navigate in the simulation both in time (using a handheld controller) and space (by moving and reorienting in the room).

Results: Here we report on a new application that allows the exploration of simulated MCTS in VR. The agent-based model used is reproducing the inner proliferation dynamics of the MCTS. We have developed a set of VR tools aimed at improving the comprehension of the complex spatiotemporal dynamics exhibited. In the future, we plan the tool to be usable to explore and evaluate new therapeutic strategies by allowing biologists to visualize and pre-analyze possible outcomes of treatment protocols before actually running them in the wet lab.

P513

PEG free topical formulations towards an effective antioxidant treatment to prevent skin cancer

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The exposure of the skin to ultraviolet radiation and to certain environmental pollutants results in excess generation of reactive oxygen species (ROS), which can cause skin cells damage and potentially leading to skin cancer[1]. To address the specific challenge of enhanced oxidative stress in human skin, topical delivery of antioxidants must be improved in order to scavenge the excess reactive oxygen species in the epidermis. Thus, our research work intends to prevent premature skin cancer by focusing on the development of innovative phospholipid-based formulations loaded with natural lipophilic antioxidant such as quercetin.

Our formulations are designed for penetration enhancement through the stratum corneum and the epidermis by means of unsaturated phospholipids and amphiphilic polymers called polyoxazolines (POx) acting as chemical penetration enhancers. POx are bioinspired polymers presenting similar properties to poly(ethylene glycol) (PEG)[2]. Considering the clinical awareness of PEG overuse leading to potential toxicity[3], POx also constitute a suitable candidate as a PEG alternative. Therefore, our research also strives to prove POx value to topical formulations by its capacity to enhance the formulation stability and the skin penetration.
One of the main dermal delivery systems designed was the lipid nanocapsules (LNC) stabilized by POx. The amphiphilic POx used in the LNC are constituted by a hydrophobic alkyl chain and a hydrophilic POx chain of various repeating units. Four POx of interest were synthesized: C16(POx)15, C16(POx)35, C18:2(POx)15 and C18:2(POx)35 enabling new DDS formulations for both architectures. The LNC are characterized by a size of 40-50 nm, demonstrating low dispersity (PDI<0.3) and good stability. The POx and the LNC were evaluated for their penetration capacity using a preliminary evaluation method developed in our team. To do so, the affinity for lipid bilayer, membrane fluidization, interaction with the bilayer, and the depth capacity were analyzed by means of fluorescence spectroscopy, isothermal titration calorimetry and Raman microscopy. The antioxidant effect of the DDS loaded with quercetin were measured on NiH3T3 mice cells and with the DPPH assay[4].

Promising preliminary penetration results are currently confirmed with in vivo tests on mice ears.

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P514

Confocal Raman microscope for the study of paclitaxel resistance in MCF7 cancer cells

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Background: Paclitaxel has been reported to induce apoptosis in several experimental models including breast carcinoma cell lines grown in vitro. Significant differences were observed between sensitive and resistant cell lines after exposure to paclitaxel. Raman microscopy with its high spatial resolution and sensitivity is used as a unique label-free tool to trace drugs and cellular components. Paclitaxel uptake and intracellular localization in addition to the drug-induced apoptosis were studied using analytical methods by confocal Raman microscopy, and confirmed by several cytotoxicity and viability assays. The objective of our study is to compare two cell lines, the MCF7 and the MCF7TAX19 paclitaxel-resistant subline exposed to paclitaxel, to determine the relevance of drug uptake to the reduction of sensitivity to anticancer drug, and to investigate the paclitaxel-induced effects in both types. This understanding is aimed to employ targeted therapy that overcomes chemotherapy resistance.

Methods: Cytotoxicity and viability during a 7-day assay were performed allowing to highlight the resistance of the subline to paclitaxel. Subsequently, cells were studied by confocal Raman spectroscopy to determine the concentration and location of the drug within the cells. Moreover, we have traced different cellular/ phenotypic biomarkers, pre and post-treatment. By software supervised Raman analysis, we were able to detect and measure the cytochrome c translocation from mitochondria to the cytosol.

Results: We were able to calculate the resistance index as the ratio of mean viability achieved in taxol-resistant to that of the parental taxol-sensitive MCF7 cell line. The results achieved in sensitive MCF7 cells confirmed, qualitatively and quantitatively, a percentage amount of intracellular PTX representing 2.3% of the whole cell surfaces. In the paclitaxel-resistant subline, 4% of drug in cells, was achieved after same time incubation, indicating there is more drug uptake in the resistant cells. Paclitaxel is localized within the cytoplasm of both cell lines. Apoptosis measurement by translocation of cytochrome c from mitochondria showed, as expected, signs of apoptosis after 6h of treatment of the normal MCF7. As for the treated resistant subline, there was lesser translocation of cytochrome c with no inverse correlation. Therefore, there is fewer apoptosis in resistant cancer cells and, unlike sensitive cells, mortality is lower. Results confirm switching from apoptotic cell death in resistant cells to other means such as autophagy, indicated in other studies.

Conclusion: In this study, we investigated the effects of paclitaxel treatment on sensitive and established-resistant cell line. Taken together, our results show that the higher paclitaxel uptake does not induce apoptosis in resistant cells but does induce other phenotypic changes, leading to another pathway of cell death. Biochemical imaging techniques have been developed to understand the molecular dynamics underpinning the fundamental cellular processes such as proliferation or apoptosis. Label-free drug tracing using confocal Raman microscope would help to have a better understanding of drugs mechanism of action and cellular behavior, including intracellular drug distribution and cell-drug interaction mechanisms.

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Posters – “Technological facilities & Industrial partnerships”

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Preclinical nuclear imaging core facility of Montpellier

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Preclinical imaging facilities of Montpellier offer different imaging modalities that are complementary, and allow support for various programs in life science such as oncology, immunology, cardiology, neurobiology, embryonic development, etc. Altogether, imaging equipment provides functional, anatomical and molecular information. They allow noninvasive longitudinal in vivo studies required for monitoring the development and progression of pathologies together the long-term effect of drugs.

Montpellier nuclear preclinical imaging: IRCM core facility is dedicated to nuclear preclinical imaging based on the administration of radionuclides emitting particles that can be further detected by suitable cameras. The advantage of using radionuclides is that particles emitted are not attenuated by traversed tissues, which can be a limitation of other modalities. Radionuclides are usually label to vectors of interest to form a radiotracer. Two complementary dual imaging systems are then available: the nanoScan SPECT/CT (single photon emission computed tomography/computed X tomography; Bioscan®) and the recently acquired nanoScan PET/CT (positron emission tomography/Computed tomography; Mediso®). SPECT system allows the detection of gamma/x rays such as those emitted by indium 111 (111In) or iodine 125 (125I) that are usually label to peptides or mAbs. PET allows the detection of beta+ particles such as those emitted by fluorine 18 (18F) or zirconium 89 (89Zr), gallium 68 (68Ga). 18F-FDG (2-[(18)F]fluoro-2-deoxyglucose) is one of the main PET tracers which is devoted to glucose metabolic assessment of normal or pathological tissue but 18F-FMISO (18F-Fluoromisonidazole) detecting tissue hypoxia, 18F-annexin-V detecting apoptosis, 18F-FNa exploring bone metabolism, 18F-Choline exploring cell membrane metabolism, 18F-DOPA (3,4-dihydroxy-6-[18F]fluoro-L-phénylalanine) a tracer of amino acid synthesis can be also used. Moreover, peptides and mAbs can also be radiolabeled with 68Ga or 89Zr.

The two systems also include a low dose, high resolution and high speed computed tomography (CT) with real time reconstruction such they both allow the acquisition and superposition of functional molecular (SPECT or PET) and of morphological images (CT). Vital functions monitoring are performed during anesthesia of the animal. The choice between the two systems depends on the required sensitivity (10-10-10-11 mol/l for SPECT, 10-11-10-12 mol/l for PET), spatial resolution (300µm-1mm for SPECT vs 1-2mm for PET) and on radiolabelling. Mice, rats, microcebs can be imaged by SPECT or PET systems.

Both post-processing programs of InterViewTM FUSION and VivoQuantTM are able to co-register and analyze multiple images across all modalities of the platform. All animals are housed in a pathogen-free restricted area that will be soon compatible with other preclinical imaging core facilities (MRI, photo-acoustic, multi-photon..). Multimodal preclinical imaging is particularly valuable, as it results in an increase in the statistical quality of the data (subjects can act as their own control) and substantially reduces the numbers of animals required for a given study (3R rule).

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Evolution d'un système de traçabilité vers une organisation permettant gestion, traçabilité et interrogation en ligne de la BioBanque Expérimentale du RHEM

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Les modèles animaux de maladies humaines sont utilisés en recherche pour modéliser, comprendre et tester des hypothèses diagnostiques et thérapeutiques. En 2008, le Réseau d'Histologie Expérimentale de Montpellier (RHEM) a été créé pour répondre aux besoins des chercheurs répartis sur 5 instituts. Cette organisation en réseau a mis en exergue des contraintes de traçabilité, de confidentialité et de gestion des plateaux techniques, que seule l'utilisation d'un système informatique pouvait pallier. En collaboration avec une société montpelliéraine, le RHEM a développé en 2008 un logiciel de gestion et de traçabilité d'une plateforme d'histologie expérimentale. En 2016, plus de 50 000 blocs de paraffine étaient enregistrés.

Objectif: En 2016, nous avons décidé de générer une nouvelle version de notre logiciel pour améliorer l'interface chercheur et l'interface technique, et pour valoriser les ressources biologiques générées. Un autre objectif est de créer un module d'interrogation en ligne pour permettre l'accès de chercheurs extérieurs non affiliés au RHEM, à toutes ces ressources, regroupées dans la BioBanque Expérimentale du RHEM.

Méthode: En 2016, une concertation étroite a été réalisée entre les responsables du RHEM et la responsable informatique du logiciel. L'amélioration des interfaces chercheur et technique ont d'abord été ciblées. Une réponse à un appel d'offres GEPETOs a été effectuée pour financer ce travail. Ensuite, le module d'interrogation en ligne de la BioBanque Expérimentale a été généré.

Résultats: Une nouvelle version de ce logiciel est développée et installée début 2017. Les chercheurs sont formés à l'utilisation de ce nouveau logiciel et depuis janvier 2017 enregistrent leurs échantillons dans cette nouvelle application. La migration de leurs données restantes sur l'ancienne version est en cours. La traçabilité des actes techniques réalisés est affinée, permettant au RHEM de s'impliquer dans l'amélioration du système management qualité et dans une procédure de certification qualité. Le module d'interrogation en ligne de la BioBanque Expérimentale est en cours de finalisation et sera implémenté au printemps 2019.

Conclusion: De nombreux blocs issus de souris génétiquement modifiées, de xénogreffes issues de biopsies de patients ou de lignées tumorales humaines, seront ainsi rendus accessibles à la communauté scientifique via l'interrogation en ligne de la BioBanque Expérimentale. Cet outil devrait permettre d'un point de vue scientifique, d'augmenter le potentiel des blocs générés par les chercheurs en favorisant contacts et collaborations, et d'un point de vue éthique, de réduire le nombre d'animaux utilisés en recherche.

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